Infection and food combine to cause atherosclerotic coronary heart disease – Review and hypothesis

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ABSTRACT

Hypothesis: It is hypothesised that a combination of childhood and later life infections and excess food consumption, particularly of Western style food, initiates and contributes to atherosclerotic coronary heart disease. To consider this hypothesis we have conducted a brief review of the role of childhood infections, food, and their combined influence on atherosclerosis.

Evidence: (i) Studies of populations with high prevalence of infections and low “hunter gather” like food consumption, have extremely low prevalence of atherosclerosis, (ii) there are consistent associations between infections in childhood and adult atherosclerotic coronary heart disease, (iii) there is an association between increased body weight, (an indication of excess eating), and atherosclerotic heart disease, and (iv) there is evidence that a combination of increased body weight and infections influences the development of atherosclerotic coronary heart disease.

Infections do not appear to act independently to cause atherosclerosis. A combination of both food and infection appears to be required to cause atheroma.

Conclusion: The hypothesis that infections when combined with excess eating initiate atherosclerosis, is plausible.

Action: Action aimed at prevention of atherosclerotic heart disease is possible. There are three safe approaches to prevention (i) encouragement of Mediterranean like diets, (ii) avoidance of overeating and (iii) vigorous control of infections among all age groups. There is a need to monitor patients with a history of serious childhood infections and poor nutrition. In addition, for high risk subjects, cholesterol lowering statins are of proven and safe value.

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Abbreviations: BMI, body mass index; CVD, cardiovascular disease; HDL, high density lipoproteins; HPV, human papilloma virus; CI, 95% confidence interval.

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1. Introduction

The risk factors for atherosclerotic coronary heart disease include: tobacco use, diabetes, hypertension, abnormal blood lipids, obesity and lack of exercise [1]. However, early signs of atherosclerosis can develop in up to 50% or more of teenagers and young soldiers, few of whom have these risk factors [2,3]. Accordingly it is likely that different risk factors initiate atherosclerosis in childhood and young adults. We hypothesise that a combination of childhood and teenage infections and excess food consumption, initiates and contributes to atherosclerotic coronary heart disease.

To develop this hypothesis we have conducted a review of (i) the role of childhood and teenage infections, (ii) the role of food, and (iii) the evidence that a combination of food and infections contributes to atherosclerosis.

There is sound evidence that atherosclerosis is an inflammatory process which involves the decades long progression of early age lesions to advanced plaques in adulthood whose rupture can ultimately lead to acute myocardial infarction – best known as a heart attack [4]. There is high quality evidence that food consumption patterns, lipids, infections, gut microbiota composition and early life psychosocial factors all contribute to atherosclerosis, the underlying disease leading to coronary heart disease [4,5,6]. Atheromatous lesions may develop in infancy and childhood [7].

While there is no direct longitudinal evidence which tracks the development of atherosclerosis from childhood to young adulthood and finally to middle and old age, abnormal arterial lesions can be observed in children and adolescents at the same sites at which advanced atheroma subsequently develop [7]. The earliest feature of atherosclerosis in children is vascular intimal thickening [7].

2. Methods and materials

Data for this hypothesis were identified by searches of PubMed from 1950 to 2021 using the search terms food, diet, weight, infectious agents, atherosclerosis, ischaemic heart disease, myocardial infarction and heart attacks. References listed in articles were also reviewed.

2.1. Associations between childhood infection, early and later age atherosclerosis

In 1978 Fabricant et al demonstrated that Marek’s herpes virus could cause atherosclerosis in chickens [8]. Fabricant et al also demonstrated that infections with these herpes viruses alter intracellular lipid metabolism [8]. These observations of atherosclerosis in chickens closely resemble atherosclerosis in humans. Experimental evidence supporting the pro-atherosclerotic nature of various bacterial and viral infections have since confirmed these pioneering studies [9,10]. In addition, studies on experimental animals have shown that both viral and bacterial infections can lead to inflammation of arterial blood vessels [11,12].

The results of 13 studies in which childhood infections, early signs of atherosclerosis and subsequent coronary heart disease are shown in Table 1. Several of these studies indicate there is thickening of the vascular endothelium associated with acute common childhood infections [13,14,15]. This vascular thickening can be considered as an early sign of atherosclerosis [7]. In 11 of the 13 studies, there were significant associations between infectious conditions in infancy and childhood and subsequent increases in risk of early age and later age atherosclerotic coronary artery disease. Based on autopsies of 175 children aged between 0 and 15 years of age, who had died due to viral or bacterial infections, Pesonen et al observed that there was thickening of the coronary intima which may predispose coronary arteries to atherosclerosis [16]. Overall, the findings are consistent that childhood infections are associated with an increased prevalence of atheromatous heart disease.

There is limited evidence implicating specific viral or bacterial infections in the initiation of atherosclerosis in childhood. However, chlamydia infections have been repeatedly shown to be correlated with atherosclerosis in Western communities [17]. Chlamydia infections have the ability to stimulate arterial thickening by changes in vascular smooth muscle cells, especially under hyperlipidemic conditions. In experimental mice toll-like receptor 2 (TLR2) and C-X-C motif chemokine receptor 4 (CXCR4) when combined, have been shown to be involved in Chlamydia pneumoniae infection-induced atherosclerosis [18]. An Australian based study has shown that previous exposure to Chlamydia pneumoniae is associated with increased coronary heart disease risk factors [19]. An increase in body mass index (BMI) appears to underlie these associations [19]. In addition, porphyromonas gingivalis, a major causative agent of periodontitis, has been linked to atherosclerosis [20].

Twelve of these 13 studies of infections in childhood and associated development of early signs of atheroma, have been conducted in economically developed populations, all of whom consume Western type diets. The exception is a small (153 cases and 153 controls) retrospective study of childhood infections and adult cardiovascular disease which was conducted in urban Indonesia [21]. The subjects in this study were not typical of most Indonesian populations. The average body mass index was 24.4 for both adult cardiovascular cases and controls, 36% of cases and 41% of controls were obese (BMI equal or over 25). In this Indonesian study early childhood infections were associated with a three fold increase in coronary heart disease.

Although these observations are based on correlations, it appears that bacteria and viruses, are both associated with increased risk of atheromatous coronary heart disease if these infections occur in subjects who consume Western diets [10]. The common factor appears to be infection induced inflammation. The combination of infection and food as risk factors for atheromatous coronary heart disease is considered in more detail later in this narrative.

Autopsy based studies of young US subjects (15–19 year old teenagers), who were killed between 1987 and 1994 because of accidental trauma or homicide, have demonstrated that over 50% had atheromatous lesions in their coronary arteries [2]. Many Western children may have early and even advanced atherosclerosis at ages 12–14 years [21-24]. It is relevant that few, if any, of the key
Autopsies of young (average age 22 years) German and US soldiers who were killed in World War I, Korea, Vietnam, Iraq and Afghanistan, also had coronary atherosclerosis [3]. The dramatic rise and equally dramatic fall in the prevalence of coronary atherosclerosis over a period of 100 years in these young soldiers,

| Study                        | Childhood infectious condition                      | Positive childhood infections. | Negative childhood infections. | Follow up               | Coronary heart disease risks                                                                 |
|------------------------------|-----------------------------------------------------|-------------------------------|--------------------------------|-------------------------|---------------------------------------------------------------------------------------------|
| Pesonen 1999 [16] Finland    | Pneumonia. Viral infections influential.             | 76 Age 0–15 years             | 99 Age 0–15 years              | Based on autopsies. 0–15 year age.             | Coronary artery thickening with increased age. No infection 10% increased thickening. Positive infection up to 32% increased thickening. |
| Liuba 2003 [13] Sweden        | Respiratory, urinary, gastro-enteritis. Viral infections most influential. | 28 Age 5 years (mean)         | 20 Age 5 years (mean)          | 3 months post infection             | Positive infection – increased carotid thickening. 3 months after clinical recovery. (0.48 mm versus 0.41 mm, p = 0.01) |
| Charakida 2005 [51] United Kingdom | Mainly respiratory assumed viral infections       | 135 Age 10 years (specific age) | 299 Age 10 years (specific age) | 12 months post infection             | Impaired brachial artery vasodilation associated with infections. Positive infection - dilation 6.3%. Negative infection - dilation 9.7% |
| Pesonen 2007 Finland [52]    | Bacterial & viral infections – varicella, measles, rubella, mumps | 335 adults with CHD Childhood age not defined. | 335 adult controls negative CHD Childhood age not defined | Retrospective study of adults | Past infections with enteroviruses, herpes simplex and chlamydia pneumoniae [serological assessment] significantly associated with CHD. Common childhood infections gave protection against CHD. |
| Jansky 2011 [53] Sweden      | Tonsillitis Presumed viral and bacterial infections | 27,284 Tonsillectomy before age 20 years | 136,401 No tonsillectomy | 23.5 years post tonsillectomy | Increased risk factors for CHD associated with tonsillectomy (hazard ratio 1.44 95% CI, 1.04–2.01)). |
| Burgner 2015a [15] Finland   | Hospital admissions - respiratory, gastroenteritis presumed viral and bacterial infections. | 181 Infections before age 5 years | 1196 No hospital admissions | 20 to 35 years | Hospitalised group / non hospitalised. Increased body mass index (BMI) (p = 0.02), increased waist circumference, increased triglycerides and blood pressure (p = 0.03) interval: 1.03–2.35; p = 0.03. |
| Burgner 2015b [54] Australia | Respiratory, urinary, gastroenteritis. Presumed viral and bacterial infections. | 631 Cardiovascular related adult hospital admissions. Infections before age 18 years. | 6310 No adult hospital admissions. Infections before age 18 years. | Greater than 12 years | Increased adult cardiovascular disease associated with prior child hood infections. Three childhood infections associated with 2.2 (95% CI 1.7–2.9) times increased cardiovascular risk. |
| Dratva 2015 [14] Switzerland | Bronchitis, pneumonia, tonsillitis, otitis, mononucleosis, meningitis, appendicitis, and scarlet fever viral and bacterial infections. | 178 boys and girls aged 8 to 21 years | 79 boys and girls aged 8 to 21 years | Cross sectional study. | Infected group / non infected group. Increased carotid artery intima thickness in infected boys by 0.046 mm - girls 0.011 mm. |
| Burgner 2015c [55] Finland   | Hospital admissions - mainly respiratory and urinary viral and bacterial infections. | 141 Age 0 to 5 years         | 902 Age 0 to 5 years           | 27 years follow up | Early childhood infection associated with lower carotid distensibility levels (1.95 vs. 2.09 mmHg, p = 0.02) No difference in carotid artery intima thickness |
| Qanitha 2016 [21] Indonesia  | Severe typhoid, respiratory, measles, varicella, tuberculosis, malaria, dengue, gastro-enteritis | 153 Age less than 21 years | 153 Age, sex matched controls. | Retrospective study of adults average age 47 years | Early childhood infections associated with 3 fold increased coronary heart disease (odds ratio of 2.67 (95% CI 1.47–4.83, p = 0.001). |
| Liu 2016 [56] Finland        | Hospital admissions - childhood infections not defined | 1015 participants age range 3–18 years at baseline | age 30–45 years at follow-up | Increased cardiovascular risk factors as adults among low socio-economic study participants. Childhood infections significantly associated with higher adult BMI (p = 0.008), waist circumference p = 0.004), and reduced brachial artery dilatation (P = 0.002). |
| Prins-van Gingel 2018 [57] Netherlands | Respiratory, varicella, pertussis. Virus and bacterial infections. | 221 participants Age 3 months to 4 years at baseline | 12 years follow up at age 16 years | Overall no association between childhood infections at ages 0 to 4 years and carotid artery thickness at 16 years of age. There were positive associations among participants of low socio-economic status. |
| Pussinen 2019 [58] Finland   | Oral, dental infections. Fungal and bacterial infections | 694/755 92% | 33/755 4.5% | 27 year follow up | Childhood oral infection associated with increased carotid intima media thickness (relative risk of 1.87 (CI, 1.25–2.79) at 27 year follow up. |

risk factors for atheromatous heart disease, which includes tobacco use, obesity, hypertension, diabetes, high non-HDL cholesterol, and high waist to hip ratios, are commonly present in infants, children and teenagers. However overnutrition cannot be excluded in these studies.
is shown in Fig. 1. The rise and fall in US deaths due to coronary heart disease is also shown in Fig. 1. We speculate that the fall in the prevalence of atherosclerotic coronary heart disease may be due to increasingly successful prevention and control of viral and bacterial infections that developed in the post 1945 world war years. This speculation is based on a study of children who experienced thickening of the carotid artery intima 3 months after a severe infection as compared to controls. The thickening of the carotid intima in the infection group was less in those who were treated with antibiotics during their acute illness than those who did not receive antibiotics (0.055 ± 0.02 versus 0.112 ± 0.015 mm, respectively; p < 0.05) [13].

2.2. The role of food in atherosclerotic coronary artery disease

There have been a huge number of studies into the role of food in the initiation of atherosclerosis. It can be argued that the most important and certainly the most influential of these studies, has been the Seven Countries Studies initiated by Ancel Keys during the 1950s [25]. A positive association between deaths due to coronary heart disease and increased consumption of saturated fats and processed sugar was observed in these studies (saturated fats are present in dairy fats, red meats and plant oils). This data is not readily available and therefore has been included as Table 2.

Recently Salim Yusef and his colleagues have conducted a series of prospective studies (PURE) involving 21 low, moderate and high income countries and 155,722 participants [1,26]. They demonstrated that increased consumption of all types of fat (saturated, monounsaturated, and polyunsaturated) was not associated with higher risk of coronary heart disease.

It is of interest to consider the reasons why the outcomes of the Seven Countries Studies are so different from these recent studies. The Seven Countries Studies showed there were significant correlations between Seven Countries food components and 25 year coronary heart disease death rates are all significant (hard fats p = 0.029, meat p = 0.322, sweet products p = 0.004). Similarly, correlations between the Mediterranean Index and serum cholesterol and 25 year death rates are significant (Mediterranean index p = 0.020, serum cholesterol p = 0.008). There are no significant correlations between food components, Mediterranean index and serum cholesterol and 2017 coronary heart disease whole country age adjusted death rates (hard fats p = 0.713, meat p = 0.402, sweets p = 0.958, Mediterranean index p = 0.473, serum cholesterol p = 0.687).

A 50 year follow up of the Seven Countries study is available but coronary heart disease death rates are calculated by a different method. The trends and correlations are the same for the 25 and 50 year follow up data.
cholersterol (0.008) and deaths due to coronary heart disease at the 25 year follow up [25]. There were no correlations between consumption of meats (not defined), total calories and deaths due to coronary heart disease (meats p = 0.322, calories p = 0.102). The only consistent factor between the Seven Countries Studies conducted over 60 years ago and the recent studies, is the significant correlation between consumption of processed sugar products and coronary heart disease.

While there is no sound evidence to support conclusive explanations for the differences between the outcomes of the Seven Countries Studies and the recent PURE studies, a probable reason is that deaths due to coronary artery disease have dramatically fallen in most countries since the mid 1960s. Accordingly, the comparisons between the Seven Countries Studies, and the PURE studies are not “like with like”.

Bechtold et al have conducted a recent review of the intake of specific food groups and the risk of coronary heart disease [27]. This data is shown in Table 3. The data is based on meta-analyses of each food group. The main harmful food group includes drinks with refined sugar. Processed meats may also be harmful but the confidence interval is wide and suggest caution. This confirms the original observation by Keys et al that sweet sugar products were associated with coronary heart disease [25]. Prospective studies among US men and women indicate that high intakes of sugar sweetened beverages increase the risk of coronary heart disease by 20% [28,29].

Weight. Based on observational studies, there is high quality evidence that increased weight is associated with increased prevalence of coronary heart disease [130]. There are relationships between excess eating, increased weight, obesity, abnormal lipids, inflammation and atheromatous cardiovascular diseases [131]. A direct consequence of obesity is the development of low grade inflammation which induces atherosclerosis [31].

Excess weight is an indication of excess food consumption. Although body mass index (BMI – kg/m²) is only a broad guide, it is well documented that a BMI equal or over 30 is associated with an almost doubled risk of cardiovascular disease [32]. Not so well known is that a BMI below 18.5 is associated with an increased death rate due to accidents and suicide but not cardio-

It is reasonable to conclude that food consumption patterns influence the risk of atheromatous coronary heart disease. Western diets with high levels of fats, meat and sweet products lead to high risks of coronary heart disease. Traditional Mediterranean and Japanese diets lead to lower risks of heart attacks.

The role of infections has been an important omission from almost all studies on the influence of food on atheromatous coronary heart disease. We have identified only one study in which the combined influence of both infections and food has been considered. This is the recent study of Korean women which showed that this combination increased the risk of cardiovascular disease [33].

2.3. Atherosclerosis in populations with high burdens of infections and low food consumption

Studies conducted over 50 years ago in “economically developing” countries, clearly demonstrated that despite a heavy burden of infectious diseases, populations who had low body mass (an indication of low food consumption compared to Western populations) and low total serum cholesterol, had an extremely low prevalence of atheromatous coronary heart disease. Selected studies are shown in Table 4.

Kaplan et al have conducted detailed studies of the Tsimane, a forager-horticulturalist (hunter gatherer) population of the Bolivian Amazon [34]. Despite a high infection burden, the Tsimane, who have few coronary heart disease risk factors, have the lowest reported levels of coronary heart disease of any population recorded to date. Respiratory and gastrointestinal infections are common and the cause of over half the deaths in infancy until middle adulthood [34]. The Tsimane have reduced low density lipoproteins, low blood pressure, low blood glucose, normal body-mass index, almost no smoking, and plenty of physical activity.

It must be noted that two thirds of Tsimane adults are infected by intestinal helminths which probably have some protective influence against atherosclerosis [35,36,37]. Intestinal helminths include Ascaris lumbricoides (roundworm), Trichiuris trichiurias (whipworm), and Necator americanicus (hookworms).

These findings complement studies of other hunter gather populations. Lemogoum et al have compared the carotid femoral pulse

Table 3
Risk of coronary heart disease according to intake of specific food groups. Meta-analyses. (Relative risk is the comparison of an event – coronary heart disease, between groups – low compared to high consumption of specific food groups). Based on Bechtold et al. [27].

| Food group          | Number of cases in meta-analyses | Over-all intake range. Grams per day. | Relative risk of coronary heart disease |
|---------------------|----------------------------------|--------------------------------------|----------------------------------------|
| **Beneficial association** |                                  |                                      |                                        |
| Whole grains        | 6834                             | 0–220                                | 0.95 (CI 0.92–0.98)                     |
| Vegetables          | 19,402                           | 0–1300                               | 0.97 (CI 0.96–0.99)                     |
| Fruits              | 17,827                           | 0–1820                               | 0.89 (CI 0.84–0.93)                     |
| Nuts                | 5,480                            | 0–28                                 | 0.67 (CI 0.43–1.05)                     |
| Legumes             | 8,228                            | 0–230                                | 0.91 (CI 0.84–0.99)                     |
| Dairy               | 15,790                           | 0–3000                               | 0.99 (CI 0.92–1.07)                     |
| Fish                | 16,732                           | 0–320                                | 0.88 (CI 0.79–0.99)                     |
| **No association**  |                                  |                                      |                                        |
| Refined grain       | 3286                             | 15–540                               | 1.11 (CI 0.99–1.25)                     |
| Eggs                | 14,370                           | 0–75                                 | 0.99 (CI 0.94–1.05)                     |
| Red meat            | 6659                             | 0–205                                | 1.15 (CI 1.08–1.24)                     |
| **Harmful association** |                                 |                                      |                                        |
| Sugar sweetened drinks | 8740                         | 0–650                                 | 1.17 (CI 1.11–1.25)                     |
| Processed meat      | 7038                             | 0–150                                 | 1.27 (CI 1.09–1.49)                     |
wave velocity of two groups of Cameroon pygmies, one living a traditional hunter-gatherer existence in a rural setting and one in a more Westernized, semiurban environment [38]. On average, aortic stiffness was approximately 20% lower in the rural individuals but did not differ between the semin urban pygmies and other ethically unrelated individuals in the same environment. The authors suggest that their findings concerning arterial stiffness provide evidence that the hunter-gatherer lifestyle of the traditional pygmies is associated with a lower risk of atherosclerosis.

Because atheroma has been identified in ancient Egyptians and indigenous people of the Americas, there are some doubts that the virtual absence of atheroma in the Tsimane may not be due to their restricted diets [39,40]. While it is possible that genetic, gut microbiota and the protective influence of intestinal helminths, may be involved in the Tsimane, in our view this is unlikely. The reasons include (i) chemical studies of hair indicate that contents of food include (i) chemical studies of hair indicate that contents of food were similar in ancient, compared to modern, peoples [40], and (ii) as shown in Table 3 many different peoples with restricted diets have a low prevalence of atheroma.

2.4. Combined influences of food and infections on the development of atherosclerotic coronary heart disease.

There are three studies which are of particular relevance to the hypothesis that infections combined with excess food consumption are the underlying causes of atheromatous coronary heart disease (and other forms of atherosclerotic arterial diseases) [19,33,41]. In each of these studies it was shown that there was an increased prevalence of cardiovascular disease when the combined influences of both infection and weight are considered. This is shown in Table 5.

The most comprehensive of these investigations is by Joo et al who conducted a prospective study of 63,411 Korean women without cardiovascular disease (CVD) and who had cervical screening for high risk for cancer human papilloma viruses (HPV) [33]. They were followed up for 4 years. The prevalence of high risk HPV infection was 7.6%. There was a significant association between high risk HPV infection and the onset of cardiovascular disease with a hazard ratio of 1.69 (CI 1.19–2.51). The prevalence of CVD increased in parallel with increased weight. Cardiovascular disease was not separated into coronary heart disease and stroke in this study.

170 Australian women were investigated for the presence of antibodies to Chlamydia pneumoniae and angina [19]. Patients who were positive for Chlamydia antibodies were significantly heavier. In a retrospective study of 76 US patients, all of whom had bacterial blood stream infections, those with higher body mass index (BMI) more frequently developed cardiovascular failure [41].

3. Mechanisms

Trained immunity. “Trained immunity” is an emerging concept describing a prolonged hyperactivation of the innate immune system after exposure to specific stimuli, leading to an immune response to a secondary stimulus. Uncontrolled persistent innate immune activation causes chronic inflammatory diseases. The long-term over-activation of the innate immune system conferred by trained immunity has been hypothesized to serve as a link between non-resolving vascular inflammation and atherosclerosis.
3.1. Lipopolysaccharides (LPS) and infections

LPS are part of the outer membranes of Gram negative bacteria such as Escherichia coli, salmonella and porphyromonas gingivalis. When LPS enter the blood stream they can cause widespread inflammation which in turn can lead to atherosclerosis by increasing production of cytokines (proteins that affect the growth of cells and initiate inflammation) [47,48].

An example is Porphyromonas gingivalis periodontitis which causes high levels of LPS to enter the blood stream where it leads to systemic inflammation [47].

3.2. Lipopolysaccharides (LPS) and diets

High intakes of overall energy and specifically high fat diets leads to significant increases in serum LPS levels [49,50]. In a 10 year prospective study of 2,452 Finnish subjects high intakes of dietary energy was associated with high serum LPS and significantly high coronary heart disease [50].

4. Conclusions

Overall, the evidence is compatible with the hypothesis that (i) infections acting in isolation probably do not promote atherosclerosis, (ii) excess food, particularly excess refined sugars, acting in isolation can probably promote atherosclerosis and (iii) infections in combination with “excess” eating, contribute to the development of atherosclerosis in childhood and its continued development into adult life.

These findings add to the classic risk factors for atherosclerosis.

4.1. Limitations

There is only one prospective observational study of the combined influence of infections and food (as implied by increased BMI) as risk factors for cardiovascular disease, namely the Joo et al study of Korean women which considered human papilloma virus, weight and metabolic disorders [33]. This study did not distinguish between coronary heart disease and stroke.

By current standards many of the old studies, particularly those conducted over 50 years ago in Africa, lack relevant data.

There are no randomised trials available which test this hypothesis.

4.2. Strengths

The evidence that excess weight (BMI 25 or above) is associated with increased risk of coronary heart disease is consistent.

The evidence is consistent that infections (associated with inflammation of the arteries) in infancy and childhood in economically developed countries whose populations consume abundant food, are associated with early atherosclerosis.

The evidence is consistent, that despite the high prevalence of infections, atheroma and coronary heart diseases are rare in “indigenous” populations, consuming “traditional” diets.

4.3. Action

Despite this review being an hypothesis, action aimed at prevention of atherosclerotic coronary heart disease is possible. There are three safe approaches to prevention (i) encouragement of Mediterranean like diets, (ii) avoidance of overeating and (iii) vigorous prevention and treatment of infections among all age groups. There is also a need to monitor patients with a history of serious childhood infections and poor nutrition. In addition, for high risk subjects, cholesterol lowering statins are of proven and safe value in lowering the risk of heart attacks.
R.C. Thompson, A.H. Allam, G.P. Lombardi, L.S. Wann, M.L. Sutherland, J.D. I. Janszky, K.J. Mukamal, C. Dalman, N. Hammar, S. Ahnve, Childhood David P. Burgner, Matthew A. Sabin, Costan G. Magnussen, Michael Cheung, M.D. Carroll, D.A. Lacher, P.D. Sorlie, J.I. Cleeman, D.J. Gordon, M. Wolz, S.M. J. Amar, R. Burcelin, J.B. Ruidavets, P.D. Cani, J. Fauvel, M.C. Alessi, B. Dong D. Wang, Long H. Nguyen, Yanping Li, Yan Yan, Wenjie Ma, Ehud Rinott, Jacob J.E. Koopman, David van Bodegom, J. Wouter Jukema, Rudi G.J. G.M Edington, Cardiovascular disease as a cause of death in the Gold Coast A.C. Prins-van Ginkel, P.C.J. Bruijning-Verhagen, A.H. Wijga, M.L. Bots, U. K. A. Elisa Kallio, Katja A. Hätönen, Markku Lehto, Veikko Salomaa, Satu R.M. Maizels, Parasitic helminth infections and the control of human allergic M.K. Jones, D.E.G. Briggs, G. Eglington, E. Hagelberg, Stephen A. Macko, Michael D. Lemogoum, W. Ngatchou, C. Janssen, M. Leeman, L. Van Bortel, P. Bryan D. Lizza, Nathaniel J. Rhodes, John S. Estey, Carolyn Toy, Jenna Lopez, Marc H. Scheetz, Impact of body mass index on clinical outcomes in patients with gram-negative bacteria bloodstream infections. J. Infect. Chemother. 22 (10) (2016) 671–676.

C. Zhong, X. Yang, Y. Feng, J. Yu, Trained Immunity: An Underlying Driver of Inflammatory Atherosclerosis. Front. Immunol. 21 (11) (2020 Feb) 284.

Jenneke Leentjens, Sirono Bekkerking, Leo A.B. Joosten, Robert E.M. Hedges. Documenting the diet in ancient human populations through stable isotope analysis of hair. Philos. Trans. R. Soc. Lond. B Biol. Sci. 354 (1379) (1999) 65–76.

Bryan D. Lizza, Nathaniel J. Rhodes, John S. Estey, Carolyn Toy, Jenna Lopez, Marc H. Scheetz. Impact of body mass index on clinical outcomes in patients with gram-negative bacteria bloodstream infections. J. Infect. Chemother. 22 (10) (2016) 671–676.

C. Zhong, X. Yang, Y. Feng, J. Yu, Trained Immunity: An Underlying Driver of Inflammatory Atherosclerosis. Front. Immunol. 21 (11) (2020 Feb) 284.

M. Wilson, Biological activities of lipopolysaccharides from oral bacteria and their relevance to the pathogenesis of chronic periodontitis. Sci. Prog. 78 (Pt 1) (1995) 19–34.

Marta Serrano, José María Moreno-Navarrete, Josep Puig, Maria Moreno, Estrella Guerra, Francisco Ortega, Gemma Xifra, Wilfredo Ricart, José Manuel Fernandez-Real. Serum lipopolysaccharide-binding protein as a marker of atherosclerosis. Atherosclerosis 230 (2) (2013) 223–227.

J. Amar, R. Burcelin, J.B. Ruidavets, P.D. Cani, J. Fauvel, M.C. Alessi, B. Chamontin, J. Ferriéres, Energy intake is associated with endotoxemia in apparently healthy men. Am. J. Clin. Nutr. 87 (5) (2008) 1219–1223.

K. A. Elisa Kallo, Katja A. Hätönen, Markku Lehto, Veikko Salomaa, Satu Mannistö, Pirskko J. Pussinen, Susanna Paju, Jaana Koponen, Jorma S.A. Viikari, Leena Taittonen, Tomi Laitinen, David P. Burgner, Mika Kähönen, Nina Nutri-Kähönen, Terho Lehtimäki, Eero Jokinen, Tomu Laitinen, Jorma S.A. Viikari, M. Ka ho nen, M. Ka ho nen, T. Lehtimäki, E. Jokinen, T. Laitinen, L. Taittonen, T. Dywer, J.S.A. Viikari, M. Kiviina, K. Raitakari, M. Juonala, Juonala M Childhood infections, socioeconomic status, and adult cardiometabolic risk. Pediatrics 137 (6) (2016) e20160236.

A.C. Prins-van Ginkel, P.C.J. Bruijning-Verhagen, A.H. Wijga, M.L. Bots, U. L. H. Howland, Diet, atherosclerosis, and helmintic infection in Tsimane, Lancet 390 (10107) (2017) 2034, https://doi.org/10.1016/S0140-6736(17)31955-4.

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