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Running Title: DII and cardiometabolic risk factors and diseases

The Dietary Inflammatory Index, Obesity, Type 2 Diabetes and Cardiovascular Risk Factors and Diseases

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Abstract

Unhealthy diet is a recognised risk factor in the pathophysiology of numerous chronic non-communicable diseases (NCD), including obesity, type 2 diabetes (T2DM) and cardiovascular diseases (CVD). This is, at least in part, due to unhealthy diets causing chronic low-grade inflammation in the gut and systemically. To characterize the inflammatory potential of diet, we developed the Dietary Inflammatory Index (DII®). Following this development, around 500 papers have been published which examined the association between the DII, energy-adjusted DII (E-DII™) and the children's DII (C-DII™) and many chronic NCDs including obesity and cardio-metabolic diseases. Although a previous narrative review published in 2019 briefly summarized evidence in this area, there was a significant increase in papers on this topic since 2020. Therefore, the purpose of this narrative review is to provide an in-depth updated review by including all papers until July 2021 on DII and its relationship with obesity, T2DM and CVD. Furthermore, we aim to identify potential gaps in literature and provide future direction for research. Most studies found that DII was associated with increased risk of obesity, T2DM and CVD with some relationships being sex specific. However, we identified the paucity of papers describing associations between dietary inflammation and T2DM and its risk factors. Few studies used gold-standard measures of cardiometabolic risk factors. We also identified the lack of interventional studies designed to change inflammatory potential of diets and study its effect on cardiometabolic

risk factors and diseases. We recommend that such interventional studies are needed to assess if changes in DII, representing inflammatory potential of diet, independently of changes in body composition can modulate cardiometabolic risk factors and diseases.

1. Introduction

According to the latest Global Burden of Disease data, non-communicable diseases (NCD) account for 72.3% of mortality worldwide[1]. Of these, cardiovascular diseases (CVD), specifically ischaemic heart disease and stroke, were the top two causes of death, claiming 15.2 million lives annually [2]. The main risk factors for CVD include obesity, diabetes, hypertension, and dyslipidaemia [3-6]. Obesity has tripled worldwide since 1975 with 1.9 billion adults currently being overweight and 650 million with obesity [7]. Obesity and overweight are causing a public health crisis; the numbers of deaths and disability-adjusted life years (DALY) attributable to overweight and obesity doubled between 1990 and 2017 [8]. During the same period, obesity was the cause of 39 deaths per every 100,000 CVD deaths and 9.6 per 100,000 diabetes deaths [8]. The prevalence of diabetes in the world is projected to rise to 10.2% (578 million) by 2030 from an estimated 9.3% (463 million people) in 2019, largely due to increasing rates of obesity [9]. In 2017, it was estimated that diabetes has claimed 4 million lives globally which resulted in economic costs of US$ 727 billion on households, a figure predicted to increase to US$ 776 billion by 2045 [9].

Unhealthy diet is an important contributor to many NCDs [10, 11]. In 2017, 11 million deaths and 255 DALYs were attributed to unhealthy diet [12]. Unhealthy diet plays a significant role in the pathophysiology of obesity, diabetes and CVD, in part due to low-grade, chronic inflammation [13]. Diet can effectively influence inflammation, independent of weight change [13, 14]. For example, the typical Mediterranean diet, rich in whole grains, vegetables and healthy fats was associated with lower inflammation and reduced risk of diabetes and CVD as well as other chronic diseases such as cancers, depression, anxiety, and cognitive decline[15, 16]. In

contrast, diets with high saturated fat and red meat may significantly increase inflammation and increase the risk of obesity, type 2 diabetes (T2DM), CVD as well as other non-communicable diseases [17, 18].

In 2014, we developed the Dietary Inflammatory Index (DII®) based on a review of literature exploring associations between various dietary components (foods, nutrients and flavonoids) and biomarkers of inflammation [19]. The DII aims to quantify the inflammatory potential of people's diets on a continuum from maximally pro-inflammatory to maximally anti-inflammatory [19]. A high DII score, reflecting a more pro-inflammatory diet, has been linked to increased risk of obesity, T2DM, CVD and other chronic diseases [20-23]. In 2019, we briefly summarized in a narrative review of literature the evidence on DII and obesity, diabetes, cardiovascular disease, cancers, respiratory and musculoskeletal disorders, as well as impaired neurodevelopment and adverse mental health [24]. There has been a significant increase in new publications since 2020, including new meta-analysis (Supplementary Table 1). These new findings enhance the understanding of the role of pro-inflammatory diet in development of cardiometabolic risk factors and diseases, hence the new review on this topic was warranted.

This review aims to present updated evidence on DII and obesity, T2DM and CVD.

2. Overview of the Development of Dietary Inflammatory Index

The development of the DII commenced with our extensive literature search [19]. We included all studies (observational and intervention; human, animal and tissue/cell) which investigated the relationship between dietary components and measured at least one of 6 selected markers of inflammation; interleukin 1 beta (IL-1β), interleukin 6 (IL-6), tumour

necrosis factor (TNF-α), interleukin 4 (IL-4), interleukin 10 (IL-10) and C-reactive protein (CRP)[19]. Each food parameter identified in the study was then scored as a food parameter specific inflammatory effect score based on the relationship between the food parameters and inflammatory biomarkers, specifically the number of papers reporting that relationship, and the strength of dose [19]. We then developed a global database, based on data from 11 countries, consisting of means and standard deviations of intakes of the 45 food parameters in the DII. For each individual, dietary data was scored for DII and the intake of all available DII food parameters was compared to the global mean and a z-score calculated by first subtracting the global mean from the individual mean then dividing by the global standard deviation. The z-score was converted to a percentile and then centred by doubling the percentile and subtracting one. To achieve the overall inflammatory potential of a food parameter, the centred percentile value was multiplied by the specific inflammatory effect of each dietary parameter. The methods used to estimate an individual's DII score has been described by us elsewhere [19]. The DII is sometimes adjusted for energy intake. Energy-adjusted DII (E-DII™) is computed when food intake is expressed per 1,000 kcal of energy intake using the energy-standardized version of the global database [25]. Although 45 whole foods, nutrients and other bioactive dietary components were identified in the development of the DII, most studies do not assess all components and DII can be estimated from minimum 25 DII parameters. A version of DII developed for children, known as children's DII (C-DII™) also has been used in several settings. Unlike the original version, this version is based on 25 food constituents including carbohydrate, protein, fat, alcohol, fibre, cholesterol, saturated fat, mono-unsaturated fat, poly-unsaturated fat, energy, niacin, thiamine, riboflavin, magnesium, zinc, selenium, beta-carotene,

vitamin A, vitamin C, vitamin B12, vitamin B6, iron, vitamin D, vitamin E and folic acid [26]. The calculation of DII for children (C-DII) uses similar methods as for adults [19] with only 25 food parameters compared to 45 used in the adult calculation. Similarly, C-DII can also be adjusted for energy intake [26].

The performance of the DII/E-DII/C-DII in predicting chronic low-grade inflammation (detected as increase in plasma concentration of inflammation markers) has been evaluated in several studies [27-31] through statistically significant relationships between DII scores and inflammatory biomarkers. For example, in a study of 928 elderly Scottish people, higher E-DII scores were positively associated with circulating CRP and IL-6 [27]. Another study in 329 Portuguese adolescents found that DII was significantly associated with circulating IL-6, complement component C4 but not CRP after adjusting for covariates [28]. *Kanauchi et al.* determined that higher DII scores were associated with higher inflammatory ageing [30]. The Healthy Lifestyle in Europe by Nutrition in Adolescence (HELENA) study conducted in 532 mixed Northern and Southern European adolescents showed that after adjusting for covariates, higher DII scores were positively associated with TNF-α, IL-1, IL-2, IFN-γ and sVCAM but not CRP, IL-1, 4, 6, 10 and ICAM[29].

3. Methods

Medical Subject Headings (MeSH) terms focused on the DII and keywords related to obesity, diabetes and CVD risk factors and diseases. The following search terms were used: “Dietary Inflammatory Index”, “DII”, “E-DII”, “Energy adjusted dietary inflammatory index”, “C-DII”, “Inflammatory Index”, “cardiovascular disease”, “obesity”, “body weight”,

"overweight", "insulin resistance", "insulin secretion", "insulin sensitivity", "diabetes" "metabolic syndrome", "cardiovascular risk", "mortality", "morbidity", "adiposity", "fat mass", "fat free mass", "body composition", "BMI", "glucose intolerance", "lipids", "dyslipidaemia", "cholesterol", "triglycerides", "high density lipoprotein (HDL-c)", "low density lipoprotein (LDL-c)", "blood pressure". A comprehensive search was conducted in PUBMED, Medline, Web of Knowledge and Google scholar up to July 2021 with appropriate Boolean operators to connect the MeSH terms.

From this search, a study was included in our review if:

- it was an observational, interventional study or a systematic review.
- it used DII, E-DII or C-DII [19, 25, 26] to measure inflammatory potential of diet.
- it investigated associations of the DII, E-DII or C-DII and obesity, T2DM or CVD and its risk factors which are known to be influenced by diet such as insulin resistance, insulin secretion, hypertension, dyslipidaemia.

The application of these inclusion criteria implied that all academic commentaries, case reports or unpublished evidence was excluded from this review.

4. Pathophysiology of pro-inflammatory diet in the development of obesity, diabetes, and cardiovascular diseases

The exact mechanisms by which an inflammatory potential of diet affects the development of obesity, T2DM and cardiovascular diseases has not been fully understood. Some hypothesised pathways are discussed below.

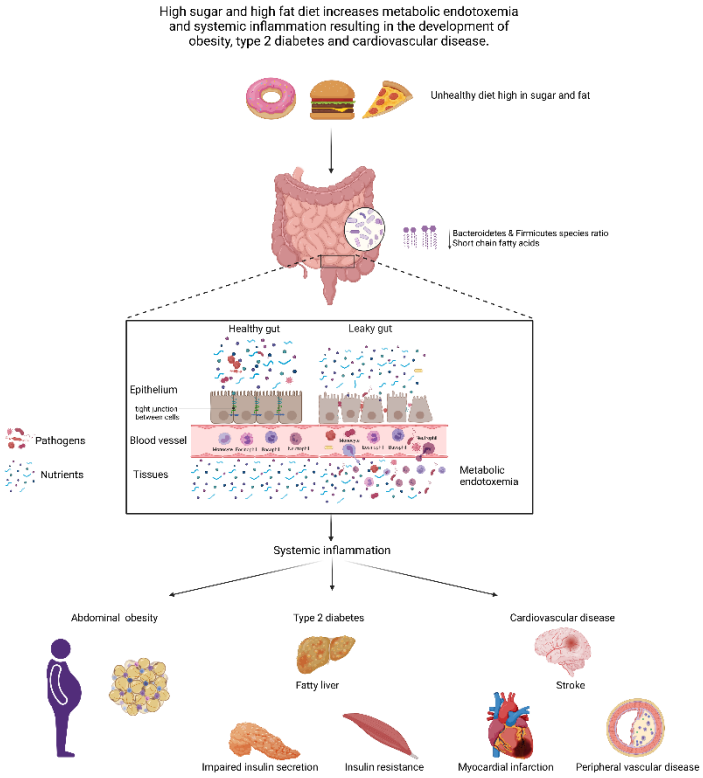

Figure 1: High sugar diet and high fat diet increases metabolic endotoxemia and systemic inflammation resulting in development of obesity, type 2 diabetes, and cardiovascular disease.

Diet plays an important role in shaping gut microbiome, which consists predominantly of gram positive Firmicutes and gram negative Bacteroidetes. The microbiome contributes to host health through biosynthesis of vitamins, essential amino acids, and generation of metabolites from undigested dietary components in the small intestine [32]. Short-chain fatty acids (SCFA), especially butyrate, propionate, and acetate, function as important energy sources for intestinal epithelial cells and may therefore strengthen the mucosal barrier [33]. This may result in a less "leaky gut" and therefore cause less systemic inflammation [33]. Microbiota also directly promote

local intestinal immunity through their effects on toll-like receptor (TLR), antigen presenting cells, T and B cells [34, 35]. Studies examining the composition and the role of the intestinal microbiome in different disease states have uncovered associations with obesity, T2DM and CVD [36-39]. Specifically, studies involving microbiota transplantation from obese to lean mice have shown that the obese and insulin resistant phenotype is transmissible via microbiota and their ability to harvest more or less energy from the host diet [39, 40]. Obesity is characterized by a lower ratio of intestinal Bacteroides: Firmicutes [38]. We and others have previously shown that the gut microbiome is associated with insulin resistance and impaired insulin secretion, which is essential for development of T2DM [38, 41]. A proposed mechanism underpinning this relationship is that lipopolysaccharides from Gram negative bacteria in the gut have pro-inflammatory properties and stimulate TLR expression and activation promoting release of pro-inflammatory cytokines and chemokines [41]. Risk of atherosclerosis has also been linked to gut microbiota due to enhanced metabolism of choline and phosphatidylcholine that produces the proatherogenic compound, trimethylamine-N-oxide [42].

Adipose tissue functions as an active metabolic tissue producing and releasing several adipokines and cytokines that contribute significantly to chronic low-grade inflammation [43, 44]. Overconsumption of food rich in lipids results in "overloaded" adipocytes and proteopathy in the endoplasmic reticulum (ER), resulting in accumulation of misfolded proteins. Proteopathy in the ER lumen activates several pathways for unfolded protein response (UPR) [45]. Increased ER volume due to accumulation of misfolded proteins facilitates increased membrane lipid production via IRE1/XBP1 UPR pathway which is associated with changes in the ER membrane resulting in apoptosis signalling [46]. Moreover, dimerization of IRE1 as a result of

this derangement, increases the likelihood of further activation of UPR pathways and therefore UPR not only affects protein homeostasis within the ER but is also coupled with a significant effect on lipid compositions of the ER membrane [46]. Inversely, increased dietary fat also activates IRE1/XBP1 pathways leading to protein synthesis errors and inducing apoptosis [46]. Independent of UPR, there is also an increase in c-Jun N-terminal kinases (JNK), nuclear factor κB (NFκB)/inhibitor of IκB (IKK-β) pathways [47], TLR4 and macrophages [48], all of which induce inflammation [49, 50] and contribute to the development of chronic diseases including T2DM and CVD. In addition, consumption of unhealthy foods such as those high in saturated fat cause fatty acid infiltration of macrophages which can activate cytotoxic T-cells, perpetuating inflammatory responses [51].

In summary, consumption of pro-inflammatory diets leads to an activation of pro-inflammatory pathways and release of cytokines and adipokines which are worsened by obesity and contribute to the development of T2DM and CVD [13, 52].

5. Dietary Inflammatory Index and Obesity

In this section, we present the evidence of the relationship between the DII, obesity and adipokines. The previous review in 2019 [24] described only 3 studies (2 cross-sectional and 1 intervention) and results of meta-analyses investigating effects of DII on BMI cross-sectionally (n=22) and a risk of development of obesity (n=4). It concluded that there was a paucity of data on DII and a risk of obesity in men and high levels of heterogeneity for results of meta-analyses. The authors noted that pro-inflammatory foods are more energy dense hence adjustment for energy intake is necessary to separate the effect of pro-inflammatory diet from energy dense

diet [24]. In this review, we updated the evidence of the relationship between DII and obesity which we split by study design.

5.1 Observational Studies

5.1.1 Cross-sectional studies

Several cross-sectional studies reported a positive relationship between DII and different measures of obesity including BMI, waist circumference (WC), waist-hip-ratio (WtHR) with few reporting on body composition. *Mazidi et al.* [53] found that after controlling for confounders, E-DII was positively associated with BMI in 17,689 participants of the US National Health and Nutrition Examination Survey (NHANES). These findings are in congruence with recent findings from other large studies such as the Primary Prevention of Cardiovascular Disease with a Mediterranean Diet trial (PREDIMED) (n=7,236)[54], the Brazilian Cohort of Universities of Minas Gerais (CUME) (n=3,151)[55], the Seguimiento University of Navarra (SUN) Cohort (n=7,027)[56], the Supplementation en Vitamines et Minéraux Antioxydants (SU.VI.MAX) study (n=3,726)[57] and the Ravansar Cohort Study (n= 6,538)[58]. In the PREDIMED study, Spanish female participants in the 5th DII quintile (most pro-inflammatory diet), had higher waist circumference, WHR and BMI than those in the first quintile (least pro-inflammatory diet). In men, there was an association between the DII, WC and WHR but not BMI [54] . The CUME study found, among 945 Brazilian men and 2197 women, the most pro-inflammatory quartile of DII had higher prevalence of obesity [55]. Likewise, in the SUN cohort of Spanish university graduates, the risk of obesity/overweight was higher among participants in the most pro-inflammatory DII quartile [56]. In 20,823 Italian adults (age ≥35 y; 48% male) of Moli-sani

study, participants in quintile 5 of DII (pro-inflammatory diet) had surprisingly, lower BMI but higher abdominal obesity than those from quintile 1. A higher DII score also was positively associated with each single biomarker of inflammation [59].

In the study of 1,352 European adult participants (51% men) from the Observation of Cardiovascular Risk Factors in Luxembourg study, a nationwide, cross-sectional survey based in Luxembourg, individuals in the highest tertile of DII was associated with a lower body mass index and waist circumferences compared to the lowest tertile, although the highest tertile group were significantly younger [60]. A study in 21,649 participants (7% of participants had chronic kidney disease (CKD)) from National Health and Nutrition Examination Survey found that participants with higher E-DII had a higher BMI [61]. In 631 pregnant American women from NHANES cohort, *Shin et al.* found that an increased consumption of pro-inflammatory diets (higher DII scores) was associated with a higher pre-pregnancy BMI and CRP concentrations [62]. In 1,992 adults (49% male) from Cork and Kerry Diabetes and Heart Disease Study, E-DII above median was associated with 2.8 cm higher waist circumference compared to E-DII below median. There was no association with BMI [63].

In a cross-sectional study of Croatian workers (n = 366, men and women), of whom 25% have metabolic syndrome, a consumption of a diet in 3rd and 4th quartiles of DII were associated with elevated waist circumference [64]. In 3,862 Polish participants from PONS study (aged 45-64 years; 33% male), pro-inflammatory DII was associated with higher WHR and waist circumference (in men only; odds ratio 1.6) compared to anti-inflammatory DII. There was no association between DII and metabolic syndrome [65].

There were several studies investigating the relationship between DII and obesity in Iranian population. The Ravansar study of 6,538 Iranian men (n=2,931) and women (n=3,607), found a relationship between the pro-inflammatory DII and waist circumference [58]. Another study in 199 Iranian women with overweight (mean age 37 years) found also that, a high DII was associated with waist circumference but not BMI, WHtR, WHR or weight after controlling for age, level of education, smoking status, and physical activity [66]. An Iranian study of 151 healthy participants with central obesity [67] calculated DII and identified three dietary patterns using principal component analysis: healthy dietary pattern (anti-inflammatory diet), traditional diet (relatively balanced in terms of inflammatory potential) and westernised diet (maximally pro-inflammatory). They found that western dietary pattern was associated with higher BMI and fat mass [67]. In a study in 171 Iranian participants with abdominal obesity, a higher DII was associated with BMI before and after adjustment for age, sex, physical activity, and level of energy intake [68]. In 301 Iranian women with overweight or with obesity (age 18-56 years, BMI 31 kg/m^2), DII was associated with fat free mass (bioimpedance) but not (%) body fat, waist circumference or WHR[69].

Several studies investigated the relationship between DII and body composition. A study in 190 South African women, the E-DII was associated with waist circumference, WHR and visceral adipose tissue (VAT) estimated from dual energy absorptiometry, but not BMI or total body fat [70]. The Korea National Health and Nutrition Examination Survey data showed that higher dietary inflammatory score was associated with both osteopenic and osteosarcopenic obesity in 1,344 post-menopausal women in Korea [71]. The pro-inflammatory DII was associated with increased odds of being overweight in 197 adults after adjustment for height,

fat mass, blood pressure and total energy intake [72]. In the same study, there was a correlation between high DII scores and fat mass (bioimpedance), BMI and waist circumference before and after adjusting for sex, height, and energy intake [72]. In 651 Pakistani men (age 54–95 years), DII score was positively associated with weight, BMI, WHR and (%) body fat [73].

Two studies investigated the relationship of DII and obesity in children. A cross-sectional study among Brazilian children (boy and girls) recruited from the PASE (Pesquisa de Avaliação da Saúde do Escolar) survey investigated the relationship between C-DII scores, adiposity via dual energy x-ray absorptiometry (DEXA) and serum adipokines (adiponectin leptin, retinal-binding protein 4 (RBP4) and chemerin) [74]. After controlling for confounders, mean C-DII score was not associated with adiposity but was inversely related to adiponectin and RBP4 levels and positively associated with chemerin [74] before and after adjustment for body fat [74]. This may suggest that a pro-inflammatory diet is associated with deranged adipokine levels even before development of obesity. DII was associated with weight-to-height ratio (WHtR) in a cross-sectional study of 428 Spanish schoolchildren aged 12-14 [75]. The authors reported that DII as a continuous variable was positively correlated with WHtR, even after adjustment for age, sex, total energy intake and pubertal staging [75].

Few cross-sectional studies, however, showed no association between DII and obesity. A study of 503 adults in Indonesia showed no association between DII and body weight, BMI, body fat, or waist circumference [76]. Among 300 women with obesity in Southern Tehran, the waist circumference in the fourth DII quartile was not different from those in the first quartile [77]. In another cross-sectional study on 266 Iranian women with overweight or obesity, DII scores were not associated with body composition measured by bioimpedance scale [78]. In 331 adults

who participated in the Nutrition and Non-Communicable Diseases Risk factors cross-sectional survey (part of National WHO Stepwise survey) conducted in Lebanon, DII was not associated with waist circumference [79]. In a cohort of 90 adults (men and women) with overweight and sedentary from Colombia, DII was not associated with BMI, waist or any of the body composition variables measured by DEXA [80].

One study reported an inverse relationship between high DII and obesity. A study in 249 Iranian women, investigated the inflammatory potential of diet and its effect on sleep and obesity [81]. The authors found that high DII (as a continuous variable) was significantly negatively associated with BMI, weight, and waist circumference, although these did not to reach significance in the adjusted model [81]. Interestingly, individuals in the fourth quartile (most inflammatory diets) had significantly greater intakes of monosaturated fatty acids and saturated fats compared to individuals with the most anti-inflammatory diets (low DII scores) [81].

In our updated review, we included several new studies which further strengthened evidence from 2019 [24], in particular, in men and several large studies adjusted the relationships between DII and obesity for energy intake. Most studies employed BMI and body weight as obesity measures rather than adiposity. In two studies using body composition (DEXA), there were no associations between DII and adiposity. However, it should be noted two studies in children had smaller sample sizes. Overall, pro-inflammatory DII categories appear to be associated with measures of both total and abdominal obesity in most studies with predominance of studies showing an association with central/abdominal obesity. Additional larger studies using DEXA in both adults and children of both sexes are needed.

5.1.2 Longitudinal studies

We have recently reported on the Australian population-based Melbourne collaborative cohort study of 11,030 men and 16,774 women aged 40-69 years at baseline that DII (5th vs 1st quintile) was associated with higher BMI and WHR at follow-up [82]. We found, however, that the Alternative Healthy Eating Index performed better than DII or Mediterranean Diet Score, other indices of healthy eating, in predicting future obesity [82]. In the Korean Genome and Epidemiology Study, a prospective study of 157,812 adults in Korea, *Khan et al.* showed that consuming diets in highest DII quintile (pro-inflammatory) was associated with developing abdominal obesity (measured as waist circumference) [83]. In a study of 132 Brazilian women who underwent bariatric surgery, a more pro-inflammatory diet (high DII) pre-operatively was associated with smaller weight and fat mass loss than women consuming an anti-inflammatory diet (low DII) at 6 months post-surgery [84]. A major limitation of this study was its inability to capture dietary data at follow-up. In a study of 399 participants followed for 13 years as part of the Health Workers Cohort study, the highest DII quartile was associated with increased incidence of abdominal obesity and metabolic syndrome compared to the lowest DII quartile [85]. In a case-control study (214 incident cases and 200 controls) conducted in Esfahan, Iran, DII in third tertile was associated a higher body fat and lower lean body mass over 5 years follow-up compared to first tertile [86].

A study in 726 Mexican children studied at 5, 7 and 11 years investigated the association between C-DII scores and adiposity [87]. In this study, positive associations between C-DII score and adiposity (measured as BMI z-score, skinfold sum and abdominal circumference) was seen

in girls but not in boys [87]. There was also an association between C-DII score and serum adipokines. In a subgroup for whom inflammatory markers and adipokines were available, C-DII score was associated with an increase in CRP, leptin concentrations and a decrease in adiponectin/leptin ratio by -38% at the age of 11 years [87]. This finding highlights that pro-inflammatory diet promotes obesity and results in systemic chronic low-grade inflammation in girls [87]. *Wallace et al.* followed 49 women with overweight or obesity during pregnancy from 13-16 weeks to 34-36 weeks and utilised E-DII to measure the effect of diet on BMI and inflammation (IL-6) [88]. Diet during first trimester of the pregnancy and BMI measured at the same time were the strongest predictors of IL-6 levels later in pregnancy [88]. This evidence suggests an effect of early gestational pro-inflammatory diet on inflammation later in gestation which has been associated with pregnancy complications such as preeclampsia, gestational diabetes, and preterm birth [88].

Several studies have looked at effects of DII across generations. A recent study in 1459 mother-child pairs found that women in the highest DII quartile had children with higher BMI than those women in the lowest DII quartile [89]. The authors report that children born of mothers with high DII scores (those in the highest quartile of DII) had higher BMI-z growth rates between the ages of three to ten and had higher BMI z- scores from seven to ten [89]. A sub-study of the Lifeways Cross-Generation Cohort study followed 1082 mother-child pairs, 333 index-child's fathers and 707 grandparents to investigate the association between maternal and paternal grandparents' DII scores and childhood adiposity [90]. Mothers that had higher E-DII scores had a higher risk of low-birth-weight babies [90]. Furthermore, higher paternal E-DII and paternal grandmother E-DII scores were associated with an increased risk of childhood obesity

and overweight [90]. Another sub-study of 551 children and index-child's mothers, fathers and grandparents from the Lifeways Cross-Generation Cohort Study found higher C-DII scores among children associated with greater risk of childhood obesity at five years and overweight and obesity at five and nine years [91]. The authors posit that length of exposure to a high DII diet is an important contributor to development of obesity in children [91]. Higher maternal, not paternal E-DII scores during pregnancy and at 5-year follow-up were associated with greater pro-inflammatory diet at age 5 [91]. These findings reflect The Project Viva study in 992 mother-child pairs [92] which found that higher maternal DII during pregnancy was associated with bigger offspring size (BMI z-score, fat free mass, fat-free and fat mass in mid-childhood (median age 7.7 years) in both girls and boys [92]. The relationships were attenuated after adjustment for maternal BMI and sociodemographic status [92]. Higher (pro-inflammatory) DII in early childhood (median age 3.1 years) was associated with higher waist circumference and BMI-z in boys, but not in girls at mid-childhood (7.7 years) even after adjusting for co-variates. The association with fat free mass was not significant after adjustment for socioeconomic status [92]. In addition, DII in early childhood was not associated with offspring hsCRP in mid-childhood. This study indicates that a pro-inflammatory diet in pregnancy and early childhood could influence the development of adiposity later in life [92]. An analysis from 1,078 mother-neonate pairs in Healthy Start, a prospective US pre-birth cohort, found that high DII among pregnant women was associated with higher neonatal birth weight by 53g, fat mass by 20g and percentage fat by 0.5% [93]. It should be noted that the diet of mothers might have not changed significantly pre-, during and post pregnancy, therefore offspring may have been exposed to the same diet during their childhood as their mothers were eating during pregnancy; hence the

direct effects of pre-pregnancy DII cannot be separated from the effect of the mother's influence on children's diet.

Previous review [24] included only 4 longitudinal studies. This review expands the evidence in both sexes and several studies which adjusted DII for energy intake (n=3). Collectively, limited evidence from longitudinal studies supports that diets with high inflammatory potential assessed by DII are associated with development of obesity in adults and children. High pre-pregnancy DII and DII during early gestation were associated with increased risk of childhood adiposity in offspring.

5.2 Interventional Studies

Two randomised controlled trials assessed changes in the DII and its association with weight changes in adult women [64, 94]. In the first randomised case-control trial, 74 women were allocated to receive 6-month intervention with either the anti-inflammatory diet intervention or control diet. Both groups were provided an energy restricted diet. The control group was provided diet which had a lower DII score than a typical Westernised diet but higher than the anti-inflammatory diet [64]. An anti-inflammatory diet with low DII resulted in a reduction in BMI, waist circumference, total and visceral fat and an increase in lean mass [64]. In another trial in 365 women with overweight or with obesity, healthy or post-menopausal were randomized to a caloric-restricted diet with a goal of 10% weight-loss, moderate-to-vigorous activity aerobic-exercise, combination diet+exercise, or control group; and DII and pro-inflammatory and angiogenic biomarkers were measured [94]. The restricted diet+exercise group resulted in the greatest weight loss and change in E-DII at 12 months [94]. Weight change had a more

pronounced effect than E-DII change on biomarkers at 12-months. Associations between E-DII and biomarkers were attenuated after adjustment by weight change [94].

Another intervention study in 45 Brazilian adolescents (14-19 years old) with obesity examined the effect of a long-term interdisciplinary therapy including clinical, nutritional, psychological counselling and exercise training on body weight, BMI, waist circumference, neck circumference, hip circumference, fat mass [95]. The study resulted in change in DII and an improvement of all parameters. The subgroup of individuals that decreased their E-DII showed a significantly greater decrease in BMI, fat mass, leptin and an increase fat free mass and adiponectin/leptin ratio [95].

5.3 Systematic Reviews and Meta-analysis

There have been 2 systematic reviews and 4 meta-analyses of observational studies exploring DII and obesity. A systematic review of three cross-sectional and three longitudinal studies among children and adolescents (n=8,259, ages 3-18 years) concluded that there is a significant positive correlation between DII/C-DII and measures of obesity such as BMI, waist and hip circumference, waist-to-height ratio and fat mass index [96] as well as pro-inflammatory biomarkers suggesting that a pro-inflammatory diet during childhood results in chronic low-grade inflammation and increases risk for development of obesity early in a child's life. This review was recently updated to include a wider population of 103,071 participants across 32 studies (30 cross-sectional and 2 cohort studies) [97] who were healthy participants or participants with obesity. The meta-analysis reported that DII score was positively associated with waist circumference [98]. In subgroup analysis, the continent, dietary assessment tool and gender were the heterogeneity sources.

Two studies pooled individual participant data (IPD) and performed meta-analyses of multiple studies. IPD were pooled from 16,295 mother-child pairs in seven European birth cohorts and the relationship between maternal, pre-, early-, late-, and whole-pregnancy (any time during pregnancy) E-DII and childhood overweight and obesity, skinfold thickness, fat mass index and fat-free mass index were assessed. Higher early-pregnancy E-DII scores (more pro-inflammatory diet) was associated with a higher odds of late-childhood overweight and obesity, although interestingly, an inverse association for late-pregnancy E-DII score and early-childhood overweight and obesity was observed [99]. In addition, higher whole pregnancy E-DII was associated with a lower late-childhood fat-free mass index in males and a higher mid-childhood fat mass index in females [99]. In another study, pooled individual participant data from up to 24,861 mother–child pairs were analysed from 7 European mother–offspring cohorts from UK, France, Netherlands, Poland, and Ireland [100]. Maternal diets were assessed pre-conceptionally (n = 2 cohorts) and antenatally (n = 7 cohorts). Mean age of mother was 30 years and BMI 23 kg/m^2. Higher maternal pre-pregnancy E-DII score was associated with lower birth weight and shorter birth length, whereas higher pregnancy E-DII score was associated with a shorter birth length and higher risk of small-for-gestational-age births. In male infants, higher maternal pre-pregnancy E-DII was associated with lower birth weight, and higher risk of small-for-gestational-age births, which has been previously linked with cardiometabolic diseases. E-DII was not associated with macrosomia and large-for-gestational-age births [100].

In summary, most studies show that DII and E-DII are associated with total and/or central obesity. Few studies adjusted for changes in energy intake which is a major limitation when

assessing the effect of pro-inflammatory energy dense diets on the development of obesity. Future studies investigating body composition data by gold-standard methods such as dual energy X-ray absorptiometry, magnetic resonance imaging (MRI) and computer tomography are needed to delineate the associations between DII/E-DII and adiposity. Some evidence indicates that there are differences in the relationship between DII and obesity among different ethnic groups and genders which needs to be further investigated. More longitudinal studies in both children and adults are warranted. In the future, the interventional studies need to be designed to change DII independently of energy intake to assess if lowering DII through dietary intervention can improve obesity.

6. Dietary Inflammatory Index, Insulin Resistance, Insulin secretion and T2DM

Given the role of inflammation in the pathogenesis of T2DM [13], it is important to consider the relationship between DII (pro-inflammatory diet) and insulin resistance, insulin secretion, hepatic glucose output and T2DM. The previous 2019 review [24] identified only 3 studies on DII and T2DM or gestational diabetes (GDM). All 3 studies were cross-sectional or case-control, of small sample sizes and set in developing countries [24]. Here, we present further evidence on the relationship between DII and risk factors of T2DM and T2DM/GDM to date.

6.1 Observational Studies

6.1.1 Cross-sectional studies

A previously mentioned cross-sectional study of 151 healthy Iranian participants with central obesity [67] found that those in the highest tertile of traditional diet (lower inflammatory potential than pro-inflammatory diets) had lower Homeostatic Model Assessment of Insulin Resistance

(HOMA-IR) scores (less insulin resistance) than those in the lowest tertile of traditional diet [67], and was inversely associated with DII. This indicates that consuming the traditional diet, rich in a fresh fruits, green leafy vegetables and poultry may have reduced insulin resistance. In another previously mentioned Iranian study in 171 participants (50% male) with abdominal obesity, higher DII was associated with fasting glucose but not insulin resistance or insulin secretion (both measured by HOMA) suggesting that hepatic glucose output may be impaired in these individuals. In 2,975 adults from the Tehran Lipid and Glucose Study (44% male), DII was weakly associated only with 2-hour glucose after oral glucose tolerance test but not fasting glucose, insulin, QUICKI, HOMA-IR and HOMA-B [101]. In 606 participants aged 18–64 years from East-Azerbaijan, Iran, 4th quartile of DII was associated with more than 2-fold higher odds of fasting glucose and metabolic syndrome, after adjustment for smoking status, physical activity, sex, age, BMI, lipid lowering medication use, glucose lowering medication and hypertension medications use, compared to first quartile [102]. Similarly, another study in 190 South African women found that DII was positively associated with fasting and 2-hour glucose, fasting insulin, glycated haemoglobin (HbA1c %) and HOMA-IR [70]. *King* and *Xiang* [103] also reported that in 4,434 participants with T2DM in the NHANES study, a one-unit increase in DII score was associated with 43% greater odds of having HbA1c greater than 9%. Another cross-sectional study in 1,174 Mexican adults (48.5% male), the highest quintile of DII was associated with 3-times higher odds of T2DM for participants aged 20-69 years and 9-times higher odds for participants ≥55 years suggesting pro-inflammatory diet might be more detrimental at older ages when T2DM risk increases [104]. A previously mentioned study in 21,649 participants (50% male; 7% of participants had CKD) from National Health and

Nutrition Examination Survey found that participants with higher E-DII had a higher fasting blood glucose and were more likely to have T2DM [61]. Participants with higher DII had also higher circulating chemerin but not omentin levels. The models were adjusted for age, sex, physical activity, and level of energy intake [68]. A study of survivors of childhood leukaemia (PETALE study, n=241 with median age of 22 years) in Canada found that individuals with greater E-DII scores (highest vs. lowest tertile), indicating a pro-inflammatory dietary pattern were associated with increased insulin resistance (HOMA-IR), elucidating the increased risk of developing T2DM [105]. In the previously mentioned Cork and Kerry Diabetes and Heart Disease Study in 1,992 adults (49% male), E-DII above median was associated with non-clinically but statistically significantly higher (0.04 mmol/l) fasting glucose compared to E-DII below median. There was an association between DII and fasting insulin and HOMA-IR (both 0.06) but not QUICKI [63]. In 9,291 Korean adults (aged 19–65 years, 3,682 men and 5,609 women) from Korea National Health and Nutrition Examination Survey, highest DII quartile (Q4) was positively associated with prevalence of metabolic syndrome in men and postmenopausal women. The top DII quartile was also positively associated with the prevalence of hyperglycaemia in men and the prevalence of central obesity in postmenopausal women. There were no association found between DII and the features of metabolic syndrome for women [106]. In a previously mentioned cohort of 90 adults with overweight and sedentary from Colombia, a lower DII score was associated with lower fasting glucose and Hb1Ac [107]. An Iranian study in 454 candidates of coronary artery bypass graft (CABG) aged 35-80 years found that high DII scores were associated with higher prevalence of diabetes [59]. In 1,024 participants (men and women) from the following 2 Dutch cohorts (the Cohort study on

Diabetes and Atherosclerosis Maastricht (CODAM) and the Hoorn study), a higher E-DII was associated with a higher insulin resistance (HOMA-IR), fasting glucose and post-load glucose but not with glycated haemoglobin (HbA1c) [108].

A cross-sectional study in 133 pregnant Chinese women from the Tongji Maternal and Child Health Cohort, found that women in the highest tertile of DII during second trimester had a higher prevalence of gestational diabetes (GDM; 1.43 times higher) at 24-26 weeks of pregnancy than women in the lowest tertile even after adjusting for confounders [109].

Several studies reported no associations with measures of glucose metabolism. In a study on 266 Iranian women with overweight or obesity, DII scores were not associated with fasting glucose, insulin concentration and HOMA-IR [78]. Another study in 7,085 mostly Caucasian (88%) women (aged 65–79 years) recruited from 39 sites across USA as a part of Women's Health Initiative Memory Study (WHIMS), DII was not associated with presence of T2DM [110]. In a study of Croatian workers (n = 366 men and women), DII was not associated with fasting glucose [111]. In 331 adults from the previously mentioned Nutrition and Non-Communicable Diseases Risk factors cross-sectional survey conducted in Lebanon, DII was not associated with hyperglycaemia [79]. In 3,862 Polish participants (men and women) from previously mentioned PONS study, pro-inflammatory DII was not associated with glucose levels compared to anti-inflammatory DII [65]. In Buffalo Cardio-Metabolic Occupational Police Stress study of 447 police officers (mean age 42 years), DII was not associated with glucose, insulin, adipokines or inflammatory markers [112]. In the previously mentioned Observation of Cardiovascular Risk Factors in Luxembourg study of 1,352 adult Europeans (51% male), DII

score was also not associated with any glycaemic parameters including fasting glucose, insulin, and HOMA-IR [60].

Two studies reported inverse association between DII and prevalence of T2DM. Interestingly, in 20,823 adults (age ≥35 y; 48% male) of Moli-sani study, participants in quintile 5 of DII had lower prevalence of T2DM than those from quintile 1 despite being more likely to smoke, be male, and have low levels of physical activity [59]. In 8,847 women from the previously mentioned SUN cohort, high DII was associated with lower prevalence of T2DM at baseline [113]. In both studies the participants with pro-inflammatory diets were significantly younger (7 and 4 years younger, respectively) compared to those eating anti-inflammatory diets [113]. One explanation for these inverse relationships may be that older individuals with chronic diseases may have also adopted a healthier anti-inflammatory diet.

In summary, some cross-sectional studies showed a positive association between high DII and T2DM and its risk factors (insulin sensitivity and secretion), several other studies reported no associations and 2 studies reported inverse associations. There was only 1 study in GDM from China. New evidence in this review includes several large-scale studies in both men and women.

6.1.2 Longitudinal studies

Few large cohort studies have described the relationship between DII and T2DM or GDM. In 70,991 women from the Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale (E3N) study, an anti-inflammatory DII score was associated with a lower risk of developing T2DM over 20 years after adjustment for family history of T2DM, smoking

status, mentally taxing work, physical activity, education level, hypercholesterolemia and hypertension, although statistical significance disappeared when adjusting for BMI [114]. The authors further highlighted the moderate mediation effect of BMI on the relationship between the pro-inflammatory diet and a risk of T2DM [114]. In a previously mentioned Iranian case-control study (214 incident cases and 200 controls, 47% male), DII in the third tertile was associated with 19 times higher odds of developing pre-diabetes over 5-year follow-up compared to first tertile after adjusting for co-variates [86]. Subjects in tertile 3 versus tertile 1 of DII had also significantly higher fasting plasma glucose, oral glucose tolerance and HbA1c [86].

In pregnant Iranian women aged 18-40 years (n=388; 122 GDM cases and 266 controls) who were hospitalized for acute non-neoplastic diseases, higher DII scores before pregnancy were associated with an increased risk of gestational diabetes before and after adjustment for BMI and other confounders [115]. In another prospective cohort study, 812 Iranian pregnant women aged 20–40 years, DII in the first trimester was not associated with GDM at 24–28 weeks of gestation before and after adjustment for age and weight gain [116].

In the previously mentioned study of 992 mother-child pairs, higher maternal DII during pregnancy was associated with higher offspring fasting insulin levels at a median age of 7.7 years in both girls and boys but was not associated with increased metabolic risk score consisting of systolic blood pressure, triglycerides, waist circumference, high density lipoprotein-cholesterol, and insulin resistance measured as HOMA-IR [92].

In summary, all longitudinal/case-control studies on DII and the development of T2DM except one were conducted in women or children. All identified studies showed a positive relationship between DII and development of T2DM or measures of glucose metabolism. One study (case-

control) showed positive relationship between DII and GDM and another one (prospective study) showed no relationship. Additional longitudinal large-scale studies investigating the relationship between DII and development of T2DM or GDM are needed in general and, particularly, in men.

6.2 Interventional Studies

A randomized controlled intervention trial in 81 Croatian participants with obesity [117], who underwent a 6 -month dietary intervention based on an energy-reduced anti-inflammatory diet or control isocaloric diet, examined the relationship between E-DII and insulin resistance (HOMA-IR) and HBA1c. Anti-inflammatory diet resulted in improvement of fasting glucose, insulin, HOMA-IR and HBA1c [117]. A previously mentioned intervention study in 45 Brazilian adolescents with obesity [95] which examined the effect of a long-term interdisciplinary therapy found an improvement in DII, fasting glucose, insulin resistance (HOMA-IR and QUICKI) [95]. The subgroup of individuals that decreased their E-DII showed a significantly greater decrease in fasting plasma glucose, and insulin sensitivity (QUICKI) [95], although the study did not adjust for reduction in body weight, BMI and (%) body fat which occurred as a result of the therapy [95].

6.3 Systematic Reviews and Meta-analysis

Only one systematic review and meta-analysis (10 studies) has investigated the association between DII and hyperglycaemia, reporting no significant association [98]. In the same review 13 studies were identified, investigating DII and mean fasting glucose and glycated

haemoglobin (HBA1c). The highest DII category was associated with 1.08 mg increase in glucose compared with lowest DII. Three studies included in this meta-analysis investigated an association between DII and HBA1c, showing 0.62% increase in HBA1c in the highest vs. the lowest DII category. There were 6 studies that investigated relationships between DII and insulin and insulin resistance. This revealed a 0.83 uU/ml increase in insulin concentrations and 0.19 increase in HOMA-IR value for the highest DII group versus the lowest DII group [98]. Significant heterogeneity was a noticeable limitation of this meta-analyses.

Taken together, there has been a significant increase in studies investigating DII and T2DM including its risk factors. Most studies reported weaker but positive relationships between higher DII and T2DM or its risk factors. There is no evident distinction between results from studies which adjusted and those which did not adjust for energy intake. Future studies should endeavour using gold standard methods of measurement of insulin sensitivity, secretion, and hepatic glucose output. Furthermore, intervention studies should be designed to investigate if changing DII, independent of energy intake, can improve T2DM and its risk factors.

7. Dietary Inflammatory Index and Cardiovascular Risk Factors and Diseases

The previous review [24] from 2019 found that DII was associated with higher risk of myocardial infarction but not other types of CVD. The relationships were stronger in women and certain geographical regions (Europe and North America versus Japan and Australia). Two studies found DII to be associated with cardiovascular mortality independently of BMI, smoking and physical activity. We present the current evidence of the relationship between DII and other cardiovascular risk factors (CVD-RF), including systolic (SBP) and diastolic blood

pressure (DBP), blood lipids and albumin/creatinine ratio, renal function, and CVD including cardiovascular morbidity and mortality.

7.1 Observational Studies

7.1.1 Cross-sectional studies

Several large-scale studies investigated the relationship between DII and CVD-RF in adults. *Tyrovolas et al* [118] found that American adults (n=7,880) who consumed pro-inflammatory diets (Q4) of DII were 1.4 times more likely to have one or more CVD-RF (including obesity, T2DM, hypertension, hypercholesterolemia). In the previously mentioned PETALE study of survivors of childhood leukaemia, a greater E-DII score was associated with hypertension and an increased risk of having two or more cardiovascular risk factors (CVD-RF) [105]. In a study of 105 Spanish women with systemic lupus erythematosus, which poses an increased risk of CVD due to its inflammatory nature, there was a positive relationship between DII and total cholesterol but no other CVD-RFs (HDL-cholesterol, LDL-cholesterol, triglycerides, high-sensitivity C-reactive protein and homocysteine levels) [119]. In a cross-sectional study of 266 Iranian women with overweight or obesity, DII scores were significantly associated with lower HDL and higher triglyceride levels [78]. In the above mentioned Cork and Kerry Diabetes and Heart Disease Study of in 1,992 adults (49% male), E-DII above median was associated with 2 mmHg increase in systolic but not diastolic blood pressure as well as small but significant changes in LDL-cholesterol, HDL-cholesterol and triglyceride levels [63]. Logistic regression showed increased likelihood of large VLDL-cholesterol (very low density lipoprotein) , small

HDL-cholesterol, small LDL-cholesterol particle sizes and high lipoprotein-associated insulin resistance scores in those with a pro-inflammatory diet after adjustment for age, gender, BMI and medication use [63]. In the previously mentioned Observation of Cardiovascular Risk Factors of 1,352 adult Europeans, the highest tertile for DII was associated with a lower systolic blood pressure and a low high-density lipoprotein (HDL) cholesterol compared with the lowest tertile, but there was no association with diastolic blood pressure, CRP and other lipid parameters [120]. In the previously mentioned Women's Health Initiative Memory Study (WHIMS) which included 7,085 predominantly Caucasian women (aged 65–79 years), DII was associated with presence of hypercholesterolemia but not hypertension [110]. In a previously mentioned cohort of 90 adults with overweight and sedentary from Colombia, a lower DII score was associated with higher HDL-cholesterol and flow-mediated dilation (FMD), and lower triglycerides, pulse wave velocity (PWV) and a cardiometabolic risk score (MetScore)[107]. A previously mentioned study using National Health and Nutrition Examination Survey investigated the effect of DII on prevalent chronic kidney disease (CKD) (eGFR <60ml/min per 1·73m 2or urinary albumin/creatinine ≥ 30mg/g) in adult Americans [61]. They included 21,649 participants, with 1,634 (7%) having CKD. Participants with high E-DII scores had higher systolic blood pressure and were more likely to be hypertensive compared with those with lower E-DII scores [61]. Mean eGFR decreased and urinary albumin/creatinine ratio increased across increasing quartiles of E-DII. In multivariable-adjusted logistic regression models, the odds of prevalent CKD were 29% higher in the highest compared with the lowest E-DII quartile [61]. A cross-sectional study in 454 patients aged 35-80 years who were candidates of CABG at Tehran Heart Centre found that high DII scores were associated with higher prevalence of myocardial infarction [121]. Male

patients in 4th and 3rd quartile of DII had significantly higher total cholesterol, triglyceride, creatinine, and hsCRP concentrations and lower high density lipoprotein cholesterol concentrations compared with male patients in lower quartiles [121], while in female patients, only lipoprotein (a) concentrations differed between quartiles.

Three studies found that pro-inflammatory diet is associated with CVD risk factors in children and adolescents. A previously mentioned study (PASE), which investigated the inflammatory potential of diet on atherosclerotic risk in Brazilian adolescents [122], found a positive association between a pro-inflammatory diet assessed as quintiles of C-DII scores and dyslipidemia [122]. In American adolescents (n=6,101) with mean age of 15 years (range 12-18years) from NHANES study, quartile 4 of C-DII (most pro-inflammatory) compared to quartile 1 (most anti-inflammatory) was positively associated with albuminuria [123]. After stratifying by weight status, C-DII quartile was associated with albuminuria and dyslipidemia in adolescents who were overweight. Among adolescents (aged 12-18 years) with obesity from NHANES study, C-DII was associated with higher SBP and lower DBP [123]. Only one cross-sectional study has investigated the association between DII and atherosclerosis. In a group of 378 children and adolescents of both sexes (48% girls, 68% with obesity and 83% in pubertal stage), participants in the highest DII tertile had 2.46 times greater odds of having carotid artery intima-media thickness (CCA-IMT) greater than 0.43mm versus those individuals in the lowest DII tertile. This indicates that pro-inflammatory diet may influence sub-clinical atherosclerosis [124].

Two cross-sectional studies which investigated the relationship between DII and blood pressure, reported no association between DII and CVD-RF/CVD. A study in 404 Iranian adults [125] and in 428 Spanish children and adolescents found no association between DII and

blood pressure [75]. In addition, in a previously mentioned cross-sectional Buffalo Cardio-Metabolic Occupational Police Stress study of 447 police officers, DII was not associated with dyslipidaemia or metabolic syndrome [112]. In 1,712 participants from eight cities in China (582 males and 1,130 females, age of 50 ± 17 years) who participated in Chinese Urban Adults Diet and Health study, there was no significant association between DII and the prevalence of metabolic syndrome (MetS) or its individual components, except for the blood pressure after adjustment for age, gender, city, education level, family monthly expenditure on food, smoking status and BMI [126]. In 3,862 Polish participants from the previously mentioned PONS study, pro-inflammatory DII was associated with higher diastolic blood pressure but not associated with lipid levels [65].

Two previously mentioned large scale studies [59, 113] reported inverse associations between DII and CVD risk which was likely due to larger proportion of younger individuals in high DII group.

In summary, most of the cross-sectional studies showed a positive relationship between higher DII and CVD/CVD-RF with only a few studies of smaller sample sizes reporting otherwise. Only one study evaluated the relationship between DII and atherosclerosis, finding no significant relationships after adjusting for confounders. The relationship between DII and blood pressure seems to be more prominent than dyslipidaemia.

7.1.2 Longitudinal studies

In a large Japanese cohort (n=58,782), participants in the highest DII quintile were 1.3 times more likely to develop CVD, stroke and coronary heart disease mortality compared to participants in the lowest quintile [127]. The Spanish PREDIMED study (n=7,216) found that after adjusting for covariates, participants in the 5th quintile of DII had 1.76 times higher incidence of CVD (myocardial infarction, stroke, or cardiovascular death) compared to those in the 1st quintile [128]. The Spanish SUN cohort study (n=18,794) found a progressively increasing incidence of cardiovascular events (myocardial infarction, stroke, or cardiovascular death) with each increasing quartile of DII [129]. We studied 12,366 Americans from NHANES study and found that participants in 3rd DII tertile (the most pro-inflammatory group) were 1.4 times more likely to die from CVD compared to those in the 1st tertile [130]. In 3,733 Jordanian adults with obesity and overweight, DII score (3rd vs 1st tertile) was associated with 3.3 times higher CVD mortality in the metabolically unhealthy (defined as high BMI and presence of other metabolic risk factors) and 5.5 times higher in participants with obesity [131]. There was no association in metabolically healthy participants (defined as high BMI without metabolic risk factors)[131]. We previously compared DII with Mediterranean Diet Score, another healthy eating dietary index, in 41,513 men and women who participated in the Melbourne Collaborative Cohort Study [132]. This study found that both dietary indices performed well in predicting CVD mortality with DII categories in quintile 5 versus quintile 1 increasing risk by 1.30 times [132]. We also investigated the association between the Alternative Healthy Eating Index updated in 2010 (AHEI-2010) and DII and risk of CVD mortality in 7,627 participants from the Whitehall II cohort and found both indices were associated with CVD mortality [133]. This suggests that DII captures similar information from diet as other healthy eating indices. In a previously

mentioned longitudinal study of 399 individuals from the Health Workers Cohort followed for 13 years, individuals in highest DII quartile showed significantly increased risk of developing CVD-RF including hypertriglyceridemia, hypertension and abdominal obesity compared with individuals in the lowest DII quartile [85]. When findings of some of the studies are stratified by sex, there were differences in the relationships between DII and CVD-RF. In the Korea National Health and Nutrition Examination Survey, among 4,185 Korean participants, in the 3rd and 4th quartiles of DII, the risk of atherosclerotic CVD was 1.20 and 1.34 greater, respectively, compared to the 1st quartile in men but not in women. Authors, however, did not formally test for interaction based on sex [134]. In a prospective case–control study of 1,389 verified cases of first myocardial infarction (MI) and 5,555 matched controls nested within the population-based cohorts of the Northern Sweden Health and Disease Study and over a median follow-up of 6.4 years, male participants with the pro-inflammatory DII had an increased risk of myocardial infarction before and after adjustment for potential confounders [135]. No association was found between DII and myocardial infarction in women [135]. The cohort study which included 1,304 Australian women aged 70 and over and followed up to 15 years, reported that an increase of 1 SD of DII score (at 3 year follow up) represented 0.013 mm higher mean carotid artery intima-media thickness (CCA-IMT) [136]. The women in the highest DII quartile had significantly higher CCA-IMT than participants in the lowest DII quintile even after adjustment for age, BMI, energy intake, energy expenditure on physical activity, socioeconomic status, low-dose aspirin use, statin use, anti-hypertensive use and smoking [136]. Furthermore, women in the highest DII quartile were also at two times greater risk of atherosclerotic vascular disease, cerebrovascular disease and ischemia heart disease compared

with women in the lowest DII quartile even after adjustment for the above-mentioned confounders [136]. In a previously mentioned Iranian case-control study (214 incident cases and 200 controls), pro-inflammatory DII in third tertile was associated with higher LDL-cholesterol and triglycerides and lower HDL compared with the first tertile [86].

In contrast to the above findings, two studies reported no associations between DII and CVD. The Iranian Mashhad Stroke and Heart Atherosclerotic Disorder (MASHAD) study (n=4,672) found no significant association between DII and incidence of atherosclerotic heart disease [137]. There was also no association between DII and total CVD, ischemic heart disease, myocardial infarction or stroke in women aged 50-55 years in the Australian Longitudinal Study on Women's Health (n= 6,972), again highlighting that sex-specific differences may exist in the relationship between DII and CVD [138]. Another study by *Park et al* [131] examined the relationship between DII and CVD mortality in one of the largest longitudinal studies to date with 150,405 participants from diverse ethnic backgrounds (African Americans, Native Hawaiians, Japanese Americans, Latinos, and Whites). In the whole group, the highest DII quintile group had 1.3 times higher CVD mortality compared with the lowest DII quintile group [131]; however, the relationship was not present in Native Hawaiians. Native Hawaiians have the highest prevalence of obesity, smoking and more pro-inflammatory diets (measured by the DII) compared with other ethnic groups. The authors suggest that this may explain the lack of a relationship between DII and CVD mortality in this group [131]. Nevertheless, ethnic differences should be explored further.

The three studies described below suggest that sex and ethnic differences may interact with the relationship between DII and CVD risk. A large cohort study in Korea (n =162,773) found that

DII was associated with higher risk of developing CVD in men but not in women [139]. Similarly, in the previously mentioned study by Park et al. [132], DII was associated with CVD mortality in men across all ethnic groups, whereas in women the relationship was present only in Caucasian and Japanese Americans but not Hawaiian, Latino or African Americans [132]. In contrast, the DII was also associated with a higher risk of self-reported hypertension in the Australian Longitudinal Study on Women's Health (n=7,169) [138].

In summary, most longitudinal studies found DII was associated with development of CVD or its risk factors, however, ethnic and gender differences may exist which needs further exploration.

7.2 Interventional Studies

A previously mentioned intervention study in 45 Brazilian adolescents with obesity [95] which examined the effect of a long-term interdisciplinary therapy found an improvement in DII, triglycerides and HDL in the intervention group [95].

7.3 Systematic Reviews and Meta-analysis

Six systematic reviews and meta-analyses have explored the relationship between DII and CVRFs, CVD and CVD mortality [20, 22, 23, 98, 133]. The first meta-analysis (n=57,781) in 2017 comprising of cohort and cross-sectional studies, reported a positive association between DII and CVD risk and CVD [22]. The small number of studies included in this review may be a limitation. Another meta-analysis, using fixed effects models (n=91,260) (5 studies) also reported a positive relationship between DII and CVD mortality [133]. A recent review and meta-

analysis confirmed these findings although significant heterogeneity is a noticeable limitation [21]. Another systematic review and meta-analysis included 15 cohort studies (n= 427,853) reporting that higher DII scores correlated with a higher risk of CVD and CVD mortality [23]. A systematic review and meta-analyses by Farhangi et al. [98] confirmed a significant relationship between higher DII scores and incidence of hypertension (9 studies). The most recent meta-analysis by Marx et al [140], stratified their results based on p-values. A method that provided a clearer approach in understanding associations between DII and cardiometabolic risk. This meta-analysis investigated 15 meta-analyses on 38 health outcomes with a total of 4,360,111 subjects and found that a pro-inflammatory diet measured as DII had a significant positive association with 27 (71%) of the included health outcomes. Moreover, when stratified by p-value, the study found strong (Class 1) evidence of the association between high DII scores and myocardial infarction and moderate (Class 2) evidence of an increase in risk of all-cause mortality [140].

In summary, most studies point to a significant association between DII and CVD-RF, CVD and CVD mortality. There is no clear distinction between results from studies which adjusted or did not adjust for energy intake. Most studies were longitudinal with only one interventional study. In the future, the interventional studies need to be designed to primarily change DII and investigate if changing DII independent of energy intake can improve cardiovascular risk factors or CVD.

8. Critical Appraisal

The presented evidence largely supports the relationship between DII and obesity, CVD and less with T2DM with some possible differences between ethnicities and genders which need

further investigation. Several studies demonstrate that DII is associated with indirect measures of obesity such as BMI and WHR (cross-sectionally and longitudinally). Very few studies use DEXA, MRI or CT to measure adiposity. Furthermore, the evidence from large scale studies showed that the associations between DII and surrogate measures of adiposity persist after adjusting for confounders and energy intake. We found that high DII predicts CVD and CVD mortality though there was less studies investigating DII and T2DM and its risk factors. None of the studies investigated gold-standard measures of glucose metabolism.

Apart from already mentioned limitations of the literature, we list below other limitations to the whole body of literature. Compared to 2019 review [24], our review shows an increase in both cross-sectional and longitudinal studies. Furthermore, some studies were conducted with small sample sizes, implying that these studies may have been underpowered. Underpowered studies threaten external validity, precluding them from drawing population-level generalizations [141]. Several studies had a shorter follow-up period or retrospective designs (for cohort studies). From these studies, it can be difficult to delineate the point in time when continuous exposure to pro-inflammatory diet resulted in development of the outcomes under study. Only one intervention study was designed to primarily change DII.

Method of collecting dietary data could have also been a source of discrepancies between studies: Food Frequency Questionnaires (FFQ) versus 24-hour dietary recalls (Supplementary Table 1). While most studies used an FFQ, the rest of studies used 24-h dietary recall which could be misleading and may not represent long term habitual dietary intake of study participants [142, 143] (Supplementary Table 1). Almost all studies compute DII with less than the 45 food parameters used in the original DII calculation [19].

9. Conclusions and future considerations

Evidence from this review suggests that DII scores corresponding to a pro-inflammatory diet are associated with increased risk of obesity, T2DM and CVD. Other adapted DII versions such as the C-DII and E-DII also were positively associated with risk of both childhood and adult obesity including visceral obesity. It would be important to design studies where change in DII was a primary intervention with energy intake maintained to understand the impact of anti-inflammatory diet independent of energy intake on cardiometabolic parameters.

Practical tools for assessing inflammatory potential of diet may be useful in clinical and community settings. However, given that most of these studies were observational and unable to confirm causality, RCTs studying the effect of changing DII are needed before DII can be recommended as a tool for reducing obesity, T2DM and CVD.

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10.1 Author Contributions

ENO searched, reviewed, and summarized the literature; wrote the first draft of the manuscript. RH searched, reviewed, and summarized the literature and drafted the submitted manuscript. DS, NS, JRH and AH critically revised and edited the manuscript. BdC conceptualised the scope of the review, supervised the review process and revised and edited the manuscript. All authors provided substantial intellectual input to the work in line with ICMJE criteria for authorship and approved the final manuscript for publication. Figure 1 created with Biorender.com

10.2 Ethics Statement

This review article is based on already published literature. No additional human or animal subjects were contacted in any way for the production of this article and therefore no ethics committee approval was required for this study.

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10.4 Conflicts of Interest

All authors declare no conflicts of interest.

Disclosure: Dr. James R. Hébert owns controlling interest in Connecting Health Innovations LLC (CHI), a company that has licensed the right to his invention of the dietary inflammatory index (DII®) from the University of South Carolina in order to develop computer and smart phone applications for patient counselling and dietary intervention in clinical settings. Dr. Nitin Shivappa is an employee of CHI.

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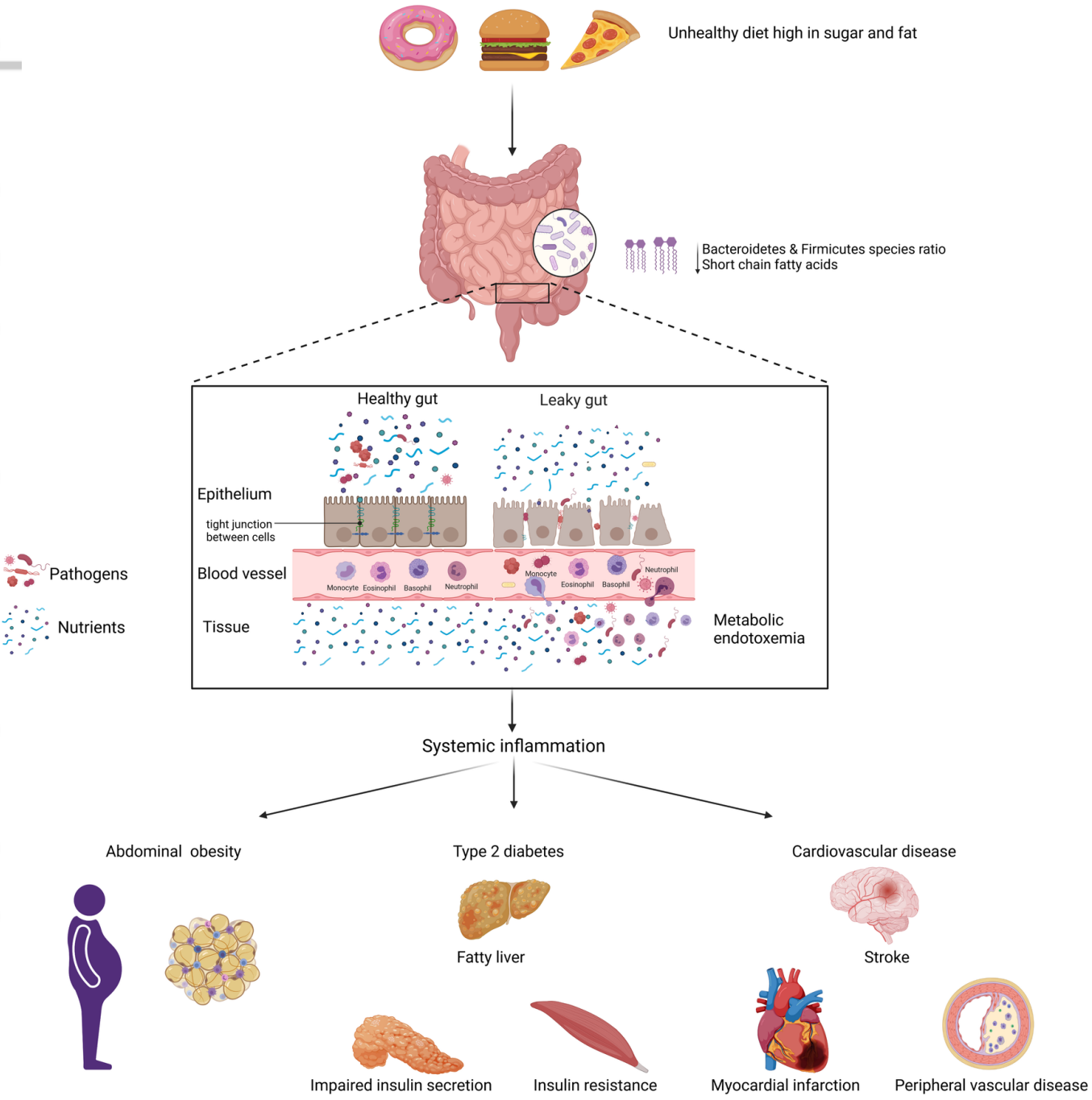
Figure Legends:

Figure 1: High sugar diet and high fat diet increases metabolic endotoxemia and systemic inflammation resulting in development of obesity, type 2 diabetes, and cardiovascular disease

Supplementary Table 1: Characteristics of studies reviewed (latest to oldest)

High sugar and high fat diet increases metabolic endotoxemia and systemic inflammation resulting in the development of obesity, type 2 diabetes and cardiovascular disease.



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