**Alternate Healthy Eating Index 2010, Dietary inflammatory index and risk of mortality: Results from the Whitehall II cohort study and meta-analysis of previous DII and mortality studies.**

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**Running Title:** Association between DII, AHEI-2010 and mortality risk in Whitehall II Study

**Abstract:**

We aimed to examine the association between the Alternative Healthy Eating Index updated in 2010 (AHEI - 2010), the Dietary Inflammatory Index (DII$^{TM}$) and risk of mortality in the Whitehall II study. We also conducted a meta-analysis on the DII-based results from previous studies to summarize the overall evidence. Data on dietary behavior assessed by self-administered repeated food frequency questionnaires and on mortality status were available for 7627 participants from the Whitehall II cohort. Cox proportional hazards regression models were performed to assess the association between cumulative average of AHEI-2010 and DII scores and mortality risk. During 22 years of follow-up, 1001 participants died (450 from cancer, 264 from cardiovascular disease). Both AHEI-2010 and DII were associated with all-cause mortality. After adjustment for a large range of potential confounders, for each increment of dietary indices z-score, hazard ratio (HR)=0.82, 95 % CI: 0.76-0.88 for AHEI-2010 and HR= 1.18, 95 % CI: 1.08-1.29 for DII were observed. Significant associations were also observed with cardiovascular and cancer mortality risk. For DII, a meta-analysis (using fixed effects) from this and 4 previous studies showed a positive association of DII score with all-cause (HR=1.04, 95 % CI: 1.03-1.05, n=28,891deaths), cardiovascular (HR=1.05, 95 % CI: 1.03-1.07, n=10,424 deaths) and cancer mortality (HR=1.05, 95 % CI: 1.03-1.07, n=8269).The present study confirms the validity to assess overall diet through AHEI-2010 and DII in the Whitehall II cohort and highlights the importance of considering diet indices related to inflammation when evaluating all cause, cardiovascular and cancer mortality risk.

**Keywords**: Dietary indices; mortality risk; Whitehall II cohort Study; meta-analysis;

## INTRODUCTION

Various studies have been conducted exploring diet and dietary components in relation to, both from all-cause and cause-specific mortality [1]. There has recently been a shift in the focus from individual nutrient and food studies to dietary pattern studies because dietary components are consumed in combination and are correlated with one another [2]. With the dietary pattern approach overall quality of takes into account the complexity of the diet and the potentially synergistic or antagonistic effects of individual dietary components [3].

Chronic inflammation is known to be associated with a variety of chronic health conditions including arthritis, diverticulitis, cardiovascular disease, diabetes [4; 5; 6], and common epithelial cancers, with colorectal cancer [7; 8; 9] being the most extensively studied. Dietary factors can contribute to an individual's underlying state of chronic inflammation [10; 11] and there is growing evidence that specific dietary components influence inflammation [12; 13; 14], potentially influencing risk of all-cause, cancer and cardiovascular mortality [15; 16; 17; 18]. We previously showed in the Whitehall II cohort that a high score in Alternative Healthy Eating Index (AHEI) score was associated both with inflammatory markers and mortality risk.

The Dietary Inflammatory Index (DII) was developed to characterize an individual's diet on a continuum from maximally anti- to pro-inflammatory [19]. Thus far, the DII has been found to be associated with C-reactive protein (CRP) [20; 21], interleukin-6 [22; 23; 24], and tumor necrosis factor (TNF)-alpha [23]. Until now, the DII has been applied to mortality outcomes only in four cohort studies and no overall evaluation of this evidence exists. Since the creation of the AHEI in 2002 which was based on foods and nutrients predictive of chronic disease risk, substantial evidence has emerged to support a role of additional dietary factors in the development of chronic disease and a new measure of diet quality that incorporates current scientific evidence on diet and health has been proposed: the AHEI-2010 [25]. In this analysis, we assessed the association between the DII, the AHEI-2010 and all-cause, cardiovascular, and cancer mortality risk in a population-based prospective cohort of British men and women participating in the Whitehall II cohort. A secondary objective was to summarize the overall evidence of the association between DII and mortality from the Whitehall II study and all previous studies using meta-analysis.

## METHODS

**Study population**

Participants of the Whitehall II study were London-based office staff, aged 35–55 years, who worked in 20 civil service departments at study inception [26]. Baseline screening (phase 1: 1985–1988, n = 10,308) consisted of a clinical examination and a self-administered questionnaire. Subsequent phases of data collection alternated between a clinical examination along with a questionnaire survey (Phase 3: 1991/93, n = 8815; Phase 5: 1997/99, n=7263; Phase 7: 2002/04, n=6943; Phase 9: 2007/09) and a postal questionnaire alone (Phases 2, 4, 8 and 10). After the study was described to each participant, written informed consent was obtained. The University College London Ethics Committee approved the study. Phase 3 (1991–1993) was considered the baseline for the purpose of this study, because it was the first assessment of the AHEI-2010 and DII. Analyses were carried out on the 7627 participants alive at phase 3 with information on vital status and with complete data on dietary indices and covariates at phase 3.

**Dietary assessment**

Dietary intake at phase 3 was assessed with the use of a semi-quantitative food-frequency questionnaire (FFQ) with 127 food items, as described previously [27; 28]. The validity and the reliability of the FFQ in terms of nutrient and food consumption have been documented in detail both in our cohort and in another independent UK cohort [28; 29]. The selected frequency category for each food item was converted to a daily intake. Nutrient intakes were computed by multiplication of the consumption frequency for each food by its nutrient content (for specified portions), and then the nutrient contributions from all foods were summed. Frequency of consumption for multivitamin supplements was also collected. Nutrient values were calculated with the use of a computerized system developed for the Whitehall II dietary data.

*Alternative Healthy Eating Index 2010 (AHEI- 2010)*

Scoring criteria for AHEI-2010 are described in detail elsewhere [25]. The AHEI-2010 is based on 11 components: six components for which the highest intakes were supposed to be ideal (vegetables, fruit, whole grains, nuts and legumes, long chain omega-3 fats (docosahexaenoic acid and eicosapentaenoic acid), and

polyunsaturated fatty acids ), one component for which moderate intake was supposed to be ideal (alcohol), and four components for which avoidance or lowest intake were supposed to be ideal (sugar sweetened drinks and fruit juice, red and processed meat, trans fat, and sodium). Each component is given a minimal score of 0 and a maximal score of 10, with intermediate values scored proportionally, and has the potential to contribute 0-10 points to the total score. All the component scores are summed to obtain a total AHEI-2010 score, which ranges from 0 to 110, with a higher score representing a healthier diet (see online supplementary material for the distribution of the baseline score).

### *Dietary Inflammatory Index (DII)*

The DII is based on literature published through 2010 linking diet to inflammation. Developing the DII involved reviewing and scoring nearly 2000 scientific articles on diet and six inflammatory markers [i.e., CRP, interleukin (IL)-1β, IL-4, IL-6, IL-10, and TNF-α] based on cell culture and laboratory animal experiments, and cross-sectional, longitudinal and intervention trials in humans. Individual intakes of food parameters on which the DII is based have then been compared to a world standard database of dietary intake based on datasets from 11 different regions worldwide. A complete description of the DII is available elsewhere. Briefly, to calculate DII scores for participants in this study, the dietary data at phase 3 were first linked to the world database that provided a robust estimate of a mean and standard deviation for each parameter [19]. These then become the multipliers to express an individual's exposure relative to the "standard global mean" as a z-score. This is achieved by subtracting the "standard global mean" from the amount reported and dividing this value by the standard deviation. To minimize the effect of "right skewing," we converted this value to a centered percentile score. The centered percentile score for each food parameter for each individual was then multiplied by the respective food parameter-specific inflammatory effect score, which was derived from the literature review, in order to obtain a food parameter-specific DII score for an individual. All of the food parameter-specific DII scores were then summed to create the overall DII score for each participant in the study [19]. A description of validation of the DII, including comparing hs-CRP values to DII derived from both dietary recalls and a structured questionnaire similar to an FFQ, is available elsewhere [19]. More negative values represent more

anti-inflammatory diets. The DII score when calculated from all 45 food parameters could range from a global minimum of − 8.87 (maximally anti-inflammatory) to a global maximum +7.98 (maximally pro-inflammatory), though the typical observed range in most studies where DII is calculated from an average of 27 food parameters is from about -5.5 to +5.5 [24; 30; 31]. Details regarding the construct validation of the DII have been detailed elsewhere [19]. In the present study, a total of 27 of 45 food parameters were available from the FFQ and were used to calculate the DII. These include energy, carbohydrate, protein, total fat, alcohol, fiber, cholesterol, saturated fat, MUFA, PUFA, omega-3, omega-6, trans-fat, niacin, thiamin, riboflavin, vitamin B12, B6, iron, magnesium, zinc, selenium, vitamin A, vitamin C, vitamin D, vitamin E, folic acid. Steps involved in the DII calculation are described in Online Supplementary Figure A. DII scores were calculated from nutrients derived only from dietary items.

We compute the AHEI-2010 and the DII scores from each FFQ administrated in phase 3 (1991-93), phase 5 (1997-99) and phase 7 (2002-2004). To reduce measurement errors and to represent long-term dietary intake, we calculated the cumulative average of AHEI-2010 and DII.

**Mortality assessment**

The Whitehall II study is linked to the National Health Services death and electronic patient records with the use of the National Health Services identification number assigned to all British citizens. A total of 10,297 participants (99.9%) were successfully traced and have been followed through these registries. Mortality data, which included the date and cause of death, were available through the National Health Services Central Registry until 28 February 2015. Death certificates were coded with the use of the 9th or 10th revision of the International Classification of Diseases (ICD) (http://www.who.int/classifications/ icd/en/). We analyzed all-cause mortality and mortality from specific causes, such as CVD (ICD-9 codes 390.0–458.9 and ICD-10 codes I00–I99) and cancer (ICD-9 140.0–209.9 and ICD-10 C00–C97). Non cancer/non-CVD mortality includes all remaining deaths that are classified neither as cancer nor CVD, and included deaths from diseases of the

respiratory system (most common other cause of death), digestive system, or nervous system; injuries; poisoning; and external causes.

**Covariates**

Sociodemographic variables consisted of age, sex, ethnicity (White/South Asian / Black), marital status (married or cohabiting versus living alone) and occupational position with the use of current (or last, for retired participants) British civil service employment grade, defined on the basis of salary and grouped into 3 categories: high (senior administrators) / intermediate (executives, professionals, and technical staff) / low (clerical and office support staff) grades.

Health behaviors included in the analysis were smoking (current / former / nonsmoker), total energy intake estimated from the food frequency questionnaire (in kcal/day), alcohol intake patterns [none : 0 glass per day, moderate: <2 (3) glasses per day for women (men), and heavy consumption: ≥2 (3) glasses per day for women (men)] and physical activity assessed via questionnaire data and categorized into 3 groups (high, intermediate, low) according to frequency of participation in "vigorous" (e.g., running, hard swimming, playing squash), "moderately energetic" (e.g., dancing, cycling, leisurely swimming), and "mildly energetic" physical activity [32]. Health status was ascertained with the use of a number of measures: prevalence of cardiovascular diseases on the basis of clinically verified events, which included non-fatal myocardial infarction, definite angina, self-reported stroke or transient ischemic attack; hypertension (systolic or diastolic blood pressure ≥140 or ≥90 mm Hg, respectively, or use of hypertensive drugs); concentration of high density lipoprotein (HDL) cholesterol (in mmol/L), use of lipid-lowering drugs; type 2 diabetes (diagnosed with the use of the World Health Organization (WHO) definition); body mass index (BMI; in kg/m$^2$) and self-reported longstanding illness (participants responded to a question asking  if they had a longstanding illness: yes/no).

Covariates were obtained from the baseline questionnaire (phase 3) and updated every 5 years (at phase 5 and phase 7). All variables (other than sex and ethnicity) included time-varying covariates.

**Statistical analysis**

Characteristics of participants as a function of mortality status were first described and tested using chi-square tests for categorical variables and Student t-test for continuous variables. Next, comparison of characteristics associated with DII and AHEI-2010 tertiles were performed using chi-square tests for categorical variables and ANOVA for continuous variables. Associations between AHEI-2010 and DII tertiles were assessed using chi-square tests.

The main analyses consisted of exploring the association between the risk of mortality and the cumulative average of AHEI-2010 and DII scores in the Whitehall II cohort. Stratified proportional Cox hazard models analyses were used to calculate hazard ratios (HRs) and 95% confidence intervals (95% CIs) for death. In these analyses the AHEI-2010 and DII were first considered as continuous variables by using z -score. Then AHEI-2010 and DII were categorized into tertiles, with the lowest tertile serving as the reference group for both indices. We calculated a test for trend across the tertiles of the AHEI-2010 and DII score by treating the categories as an ordinal variable in a proportional hazards model. We used three multivariable models, In model 1 we adjusted age, sex and ethnicity; in model 2 we additionally adjusted for occupational grade, living alone, smoking habits, alcohol consumption (only for DII), physical activity; and model 3 was further adjusted for health status factors including body mass index (BMI), antecedent of CVD, use of lipids lowering drugs, HDL cholesterol, hypertension, type 2 diabetes and longstanding illness. These time-varying covariates were chosen *a priori* as they previously had been shown to be strong risk factors for mortality in this cohort. To minimize the effect of missingness, we replaced missing data on these covariates with the last valid values. These analyses of the association between DII, AHEI-2010 and overall mortality were repeated for cause-specific mortality including cardiovascular and cancer mortality. Stratified analyses also were carried out by tertiles of energy intake. Analyses were performed using SAS statistical software, version 9.4.

A second analysis consisted for the DII of meta-analysis results from Whitehall II and all four previous studies. To date, there were four other studies [33; 34; 35; 36] that have been published on the DII and mortality. We synthesised this evidence by pooling effect estimates from those studies and the current study. As the number of studies was modest [37] fixed-effects meta-analysis was used. For comparison, we repeated the analysis using an

alternative approach, random-effects meta-analysis. We used continuous DII score as the exposure because results for that variable were available from all five studies. Mortality analyses were restricted to deaths from all-causes, cancer and cardiovascular disease. Heterogeneity in study-specific estimates was evaluated using $I^2$ statistics. All meta-analyses were performed using Stata, version MP 13.1 with the "metan" command (Online Supplementary Material Table F).

## RESULTS

Analyses from the Whitehall II study were carried out on the 7627 participants alive at phase 3 with information on vital status and with data on dietary indices and covariates as described in the Flow chart mapping the selection of participants (Online supplementary Figure B). Characteristics of these participants as a function of mortality status are detailed in Table 1. Distribution of AHEI-2010 and DII score are presented in Online Supplementary Material- Table A. DII had a mean ± SD value of 0.37 ±1.41, with a range from -3.28 (most anti-inflammatory score) to +4.54 (most pro-inflammatory score). AHEI had a mean ± SD value of 48.7±10.0, with a range from 15.5 (least healthy diet) to 85.5 (healthiest diet). Participants in the highest tertile of AHEI-2010 (reflecting a healthier diet) compared to those in the lowest tertile (reflecting an unhealthier diet) were less likely to be men, white with a low socioeconomic position and more likely to be younger, with higher occupational grade, to be married, and to have healthy behaviors (smoking habits, alcohol consumption and physical activity). Their average mean of total energy intake was also higher. Regarding health factors, the group of participants in the highest tertile of AHEI-2010 were less likely to have hypertension, they showed higher means of HDL cholesterol and lower means of BMI and.  Similar pattern of socio-demographic, health behavior and health status factors associated with DII tertiles were observed.

The correlation coefficient between AHEI-2010 and DII was -0.41. In Table 2 we show that 54.4% of participants in tertile 1 of DII; i.e., with the most anti-inflammatory diets, are in tertile 3 of AHEI-10 (corresponding to the healthiest diet) and 51.9 % of participants in tertile 3 of DII i.e., with the most pro-inflammatory diets, are in tertile 1 of AHEI (corresponding to the unhealthiest diet). However, there is some

discordance, 18.1% of participants in the most anti-inflammatory group (tertile 1) of DII are in the unhealthiest diet group for AHEI-2010

In total, 1001 total deaths were identified during the 22 years of follow-up; 450 cancer deaths, 254 cardiovascular deaths. As illustrated in Figure 1 and Figure 2, both AHEI-2010 and DII were associated with all-cause mortality. Whatever the model, for each SD increment of AHEI-2010 (9.8 points) a 20% reduced risk of mortality was observed, and for DII, one increment of 1SD (1.3 points) was associated with an increased by 20% of mortality hazard ratio. Results of the analyses in which AHEI-2010 and DII scores were categorized in tertiles are concordant with these findings (results are presented in Online Supplementary Material- Table C). In sex-, age- and ethnicity-adjusted model, participants in the 3rd and 2nd tertiles of AHEI-2010 showed, respectively, 30% and 40% reduced risk of all-cause mortality risk over the 22 years of follow-up. Further adjustment for health behaviors (occupational grade, living alone, smoking habits, physical activity and total energy intake) in model 2 and health status factors (body mass index, antecedent of CVD, use of lipids lowering drugs, HDL cholesterol, hypertension, type 2 diabetes and long-standing illness) in model 3) did not substantially attenuate the association. Online Supplementary Material- Table C shows that cumulative average of AHEI score tertiles remained significantly associated with mortality risk after full adjustment (Model 3) ($HR_{\text{Tertile3 versus Tertile1}}$ = 0.73, 95% CI: 0.69 to 0.87; HR Tertile 2 versus Tertile1 = 0.79, 95% CI: 0.66 to 0.93 ; $P_{\text{trend}}$<0.001 ). Regarding DII, participants in tertile 3 (most pro-inflammatory group) had 47% higher risk of all-cause mortality compared to participants in tertile 1 (most anti-inflammatory group) ($HR_{\text{Tertile3 versus Tertile1}}$ = 1.47, 95% CI: 1.19 to 1.82; $P_{\text{trend}}$ <0.001). Regarding the important differences in total energy intake average means across DII tertiles, we carried out an additional analysis to describe the DII –all cause mortality association across total energy intake tertiles. Results (Online Supplementary Material- Table B) showed that the DII was significantly associated with all-cause mortality only among participants in the lowest tertile of total energy intake ($HR_{\text{Tertile3 versus Tertile1}}$ = 1.72, 95% CI: 1.08 to 2.72; $P_{\text{trend}}$=0.02).

Over the 22 years of follow-up, 264 death caused by cardiovascular diseases occurred. Results of the association between cumulative average of AHEI-2010 and DII scores and risk of cardiovascular mortality are

detailed in figures 1 and 2 and in Online Supplementary Material- Table D. Higher AHEI-2010 score was consistently associated with lower risk of cardiovascular mortality whatever the level of adjustment considered (in full adjusted model, HR=0.80, 95% CI: 0.69 to 0.93). Similar results were observed when tertiles of AHEI-2010 and DII were considered (AHEI-2010HR$_{\text{Tertile3 versus Tertile1}}$ = 0.68, 95% CI: 0.48 to 0.95; P$_{\text{trend}}$ =0.03); and (DIIHR $_{\text{Tertile3 versus Tertile1}}$ = 1.46, 95% CI: 1.00 to 2.13; P$_{\text{trend}}$ 0.05).

Regarding cancer mortality, 450 death occurred over the follow-up. Figures 1 shows that AHEI-2010 was significantly associated with lower risk of cancer mortality (HR=0.87, 95% CI=0.78 to 0.98). Online Supplementary Material- Table E confirms that in sex-, age- and ethnicity-adjusted models, participants in higher tertiles of AHEI-2010 showed a lower risk of cancer mortality compared to those in the bottom tertile. However further adjustment for health behavior and health status factors substantially attenuate the association. Participants with high DII score showed a significant higher risk of cancer mortality and this association remains statistically significant whatever the way DII was analysed and the level of adjustment (Figure 2 and Online Supplementary Material- Table E).

To our knowledge four other previous studies investigated the DII –mortality risk (all cause, and caused by cardiovascular diseases or by cancer). A full description of these studies is provided in Table 3. DII for the IWHS in the US was calculated from FFQ that was adapted from the 126-item instrument developed by Willett et al, in total there were 27 food parameters that were used for DII calcultion and this study had information on supplement use [35]. DII for SMC in Sweden was calculated using a 96-item food frequency questionnaire from 27 food parameters without supplements [36]. In the NHANES III study in the US, DII was calculated using 24 hour recall without supplements from 27 food parameters [34]. In the SUVIMAX study conducted in France, DII was calculated using multiple 24-hour records from 37 food parameters [33]. We combine these results with those from the Whitehall II study. We then conducted a meta-analysis on data from the total of 91,520 participants across the five studies. Figures 3, 4 and 5 show positive associations between DII score and all-cause, cardiovascular and cancer mortality, respectively. The pooled hazard ratios from fixed and random effect models were 1.04 (95 % CI: 1.03 to 1.05) and 1.05 (95 % CI: 1.03 to 1.07) for all cause

mortality (28,891 deaths), 1.05 (95 % CI: 1.03 to 1.07) and 1.05 (95 % CI: 1.03 to 1.08) for cardiovascular mortality (10,424 deaths); and 1.05 (95 % CI: 1.03 to 1.07) and 1.06 (95 % CI: 1.02 to 1.09) for cancer mortality (8269 deaths). Thus, no differences were observed in summary estimates between the two methods of meta-analysis.

## DISCUSSION

In this prospective cohort study of 7627 British men and women, adherence to healthy diet assessed by the AHEI-2010 was associated with lower risk of all cause, cardiovascular mortality and in a lesser extent to cancer mortality while participants with higher DII– reflecting a consumption of a pro-inflammatory diet– showed higher risk of all-cause, cardiovascular and cancer mortality. Meta-analyses of the DII –mortality risk reported in this study along with those from previous cohort studies, consisting of a total of 91,520 participants, confirmed a higher risk of overall, cardiovascular and cancer mortality in individuals with a high DII score.

We observed concordance between the two dietary indices, DII and AHEI-2010. More than 50% of the participants in the healthiest group of AHEI-2010 were in the most anti-inflammatory group and similar results were observed for the least healthy and most pro-inflammatory groups of AHEI-2010 and DII, respectively. This is along expected lines because components, such as vegetables and fruits, which contribute to healthier AHEI-2010 scores, also contribute to anti-inflammatory DII scores. Both adherence to diet high in AHEI-2010 score and diet low in DII scores constitutes healthy diet. We did observe some discordance between the two indices. The importance of dietary features common to all: higher intakes of whole grains, vegetables, fruit and plant-based components which contribute a range of phytochemicals with potential to impact disease risk through different mechanisms working at different stages of cancer initiation and development. Differences between different indices and outcomes may reflect how other items such as fruit juice, green leafy vegetables and low-fat dairy were considered differently by the different indices. The DII is based on the idea that many disease-determining mechanisms operate in a pro-inflammatory environment [31], whereas the AHEI 2010 is based on foods and nutrients predictive of chronic disease risk [25]. The most anti-inflammatory diets are likely to include foods that feature prominently in other 'high-quality diets'.

AHEI-2010 was found to predict all cause, cardiovascular and cancer mortality. These results fall in line with a recent meta-analysis conducted by Onvani et al. [38] investigating how diet quality indices as assessed by Healthy Eating, Alternative Healthy Eating Index relate to all-cause and specific causes of mortality (cardiovascular mortality, cancer mortality). Conversely previous studies examining the DII-mortality association produced mixed findings. In the Swedish Mammography study, DII was positively associated with all-cause and digestive cancer mortality but not with overall cancer mortality [36]. In the Iowa Women's Health Study, increasing DII was associated with greater risk of all-cause, CVD, digestive tract cancer, coronary heart disease and chronic obstructive pulmonary disease mortalities [24]. Among digestive-tract cancers, colorectal cancer (CRC) is known to be strongly related to inflammation [39; 40; 41; 42] and represents the majority of digestive-tract cancers [20; 43]. The DII has been shown to be associated with various digestive tract cancers including CRC [31; 44; 45; 46; 47; 48] and with CVDs [49; 50; 51]. In a couple of other studies, the DII was shown to be associated with increased prostate cancer mortality [33; 52]. Our meta-analysis including all data available confirm an association between DII, all-cause mortality, CVD mortality and overall cancer mortality. Participants with higher DII score showed lower mean of total energy intake compared to participants with high DII score. Conversely participants in the highest tertile of AHEI-2010 were more likely to have higher total energy intake. One possibility is that the overall higher intake of food (contributing to higher overall energy intake) would encompass many anti-inflammatory dietary components amongst WII participants who consume higher amounts of food in general.

Although the mechanisms of how a healthy diet reduces mortality are not known, a plausible pathway is that a pro-inflammatory diet increasing systemic inflammation also increases insulin resistance [53; 54]. Higher consumption of food items such as meat and butter and lower consumption of food items like vegetables and fruits has been shown to increase systemic inflammation by increasing levels of high-sensitivity CRP, E-selectin and soluble vascular cell adhesion molecule-1 [53], which are then responsible for increasing insulin resistance [54]. Insulin resistance caused by increasing circulating levels of insulin, triglycerides, and non-esterified fatty acids [55; 56] is associated with an increased risk of chronic diseases, such as cardiovascular

diseases, which can be fatal. On the other hand, the cardio-protective role of higher scores on the AHEI-2010 could be explained by other biological mediators such as arrhythmia, thrombosis, and insulin resistance [57].

Our study has several strengths. First, it is population-based and employs a prospective design. It also, benefits from complete ascertainment of deaths through the National Health Services Central Registry until 31 August 2014, and detailed information on diet. This study also had a long follow-up for the outcomes studied. Although DII has been used to predict mortality in a European; i.e., Swedish cohort [36], this is the first time the DII has been used in a cohort study in Britain whose population and dietary habits are more diverse than in Sweden [58; 59]. The main limitation of this study was that information on diet was self-reported, which can lead to a potential misclassification of the exposure. Classification errors in our prospective study, however, were non-differential with respect to the occurrence of death and most likely led to an attenuation of the results. Dietary data were available only at one-time point. Participants' dietary habit might have changed during the follow-up period. However, previous studies have reported that dietary pattern classification is moderately stable over long periods of time during adulthood [60; 61; 62; 63; 64; 65]. Another important limitation of the study includes non-availability of information on the remaining 18 food parameters for DII calculation, Britain with a diverse population which include several Asians availability of information on food parameters like spices would have modified the results.

In conclusion, diet indices –the AHEI-2010 and DII- that possibly reflect pro / anti -inflammatory properties of diet are associated with long-term all-cause, cardiovascular and cancer mortality in the UK Whitehall II study. Future steps might include investigating how these dietary indices are related to chronic inflammation and their biomarkers.

**Acknowledgements**

**Data Sharing**: Whitehall II data, protocols, and other metadata are available to the scientific community. Please refer to the Whitehall II data sharing policy at https://www.ucl.ac.uk/whitehallII/data-sharing.

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TABLES

Table 1 : Characteristics of the 7627 Whitehall II participants according to survival status over 22-y of follow-up.

| Characteristics at baseline | | All N= 7627 | Alive N= 6626 | Deceased N= 1001 | P value |
|---|---|---|---|---|---|
| | | (%) or m± sd | **%** | **%** | |
| **Socio demographic** | | | | | |
| Sex | Men | 5308 (69.6) | 69.7 | 68.8 | 0.57 |
| | Women | 2319 (30.4) | 30.3 | 31.2 | |
| Age, years | | 50.1 ± 6.0 | 49.5 ± 5.9 | 53.7 ± 5.8 | |
| Ethnicity | White | 6968 (91.4) | 91.5 | 90.1 | 0.29 |
| | South Asian | 405 (5.3) | 5.2 | 5.9 | |
| | Black | 254 (3.3) | 3.2 | 4.0 | |
| Occupational Grade | Low | 1233 (16.2) | 15.3 | 22.0 | <0.001 |
| | Intermediate | 3460 (45.4) | 45.7 | 43.2 | |
| | High | 2934 (38.5) | 39.0 | 34.9 | |
| Marital status | Married cohabited | 5856 (76.8) | 77.1 | 74.9 | 0.13 |
| | Living alone | 1771 (23.2) | 22.9 | 25.1 | |
| **Health behaviours** | | | | | |
| Total energy intake, kcal/day | | 2094 ± 634 | 2096 ± 624 | 2081 ± 695 | 0.52 |
| Smoking Status | Non smoker | 3844 (50.4) | 51.7 | 41.8 | <0.001 |
| | Ex-smoker | 2636 (36.6) | 34.7 | 32.9 | |
| | Current smoker | 1147 (15.0) | 13.6 | 24.4 | |
| Alcohol intake | None | 1460 (19.1) | 18.6 | 22.9 | <0.001 |
| | Moderate | 4849 (63.6) | 64.5 | 57.2 | |
| | Heavy | 1318 (17.3) | 16.9 | 19.9 | |
| Physical activity | Low | 1538 (20.2) | 19.5 | 24.5 | <0.001 |
| | Intermediate | 2156 (28.3) | 28.2 | 28.5 | |
| | High | 3933 (51.6) | 52.2 | 47.0 | |
| **Health Status** | | | | | |
| Body mass index, kg/m² | | 25.3 ± 3.7 | 25.2 ± 3.6 | 26.0 ± 4.2 | |
| Hypertension | No | 6168 (80.9) | 82.3 | 71.2 | <0.001 |
| | Yes | 1459 (19.1) | 17.7 | 28.9 | |
| Type 2 diabetes | No | 7390(96.9) | 97.3 | 93.9 | <0.001 |
| | Yes | 237 (3.1) | 2.7 | 6.1 | |
| Antecedent of CVD | No | 7390 (96.9) | 97.5 | 92.8 | <0.001 |
| | Yes | 237 (3.1) | 2.5 | 7.2 | |
| HDL cholesterol, mmol/L | | 1.43 ± 0.41 | 1.44 ±0.41 | 1.38 ±0.42 | <0.001 |
| Use of lipids lowering drugs | No | 7571 (99.3) | 99.3 | 99.3 | 0.88 |
| | Yes | 56 (0.73) | 0.74 | 0.70 | |
| Longstanding illness | No | 5053 (66.2) | 67.3 | 59.3 | <0.001 |
| | Yes | 2574 (33.7) | 32.7 | 40.7 | |
| **Dietary exposure** | | | | | |
| AHEI-2010 | T1 | 2640 (34.6) | 33.5 | 41.8 | <0.001 |
| | T2 | 2332 (30.6) | 30.9 | 28.1 | |
| | T3 | 2655 (34.8) | 35.5 | 30.2 | |

| DII | | | | | |
|---|---|---|---|---|---|
| | T1 | 2542 (33.3) | 33.6 | 31.4 | <0.001 |
| | T2 | 2543 (33.3) | 33.8 | 30.3 | |
| | T3 | 2542 (33.3) | 32.6 | 38.4 | |

CVD: Cardiovascular disease; AHEI-2010: Alternative Healthy Eating Index 2010; DII: dietary inflammatory Index; T : Tertile

Occupational position with the use of current (or last for retired participants) British civil service employment grade, was defined on the basis of salary and grouped into 3 categories: high (senior administrators) / intermediate (executives, professionals, and technical staff)  / low (clerical and office support staff) grades.

Alcohol intake categories were defined as none : 0 glass per day ;  moderate:< 2 (3) glasses per day for women (men);  and heavy consumption : ≥ 2 (3) glasses per day for women (men).

Physical activity was categorized into 3 groups (high, intermediate, low) according to frequency of participation in "vigorous" (eg, running, hard swimming, playing squash), "moderately energetic" (eg, dancing, cycling, leisurely swimming), and "mildly energetic" physical activity.

Table 2:  Relationship between Alternative Healthy Eating Index 2010 (AHEI-2010) and Dietary Inflammatory Index (DII)

| | DII   tertiles | | |
|---|---|---|---|
| **AHEI-2010  tertiles** | Tertile 3 (Most pro-inflammatory) | Tertile 2 | Tertile 1 (Most anti-inflammatory) |
| Tertile 1 (Unhealthy diet) | 1319 (51.9) | 860 (33.8) | 461 (18.1) |
| Tertile 2 | 809 (31.8) | 825 (32.4) | 698 (27.5) |
| Tertile 3 (Healthiest diet) | 414 (16.2) | 858 (33.7) | 1383 (54.4) |

| | Sample size | Follow up (years) | Dietary Assesment tool used | Number of food parameters used for DII calculation | Mean and standard deviation of DII | DII included information from supplements | Assessment of mortality | Total number of deaths | Adjustment |
|---|---|---|---|---|---|---|---|---|---|
| Table 3: Characteristics of included studies | | | | | | | | | |
| Whitehall II | 7622 | 22 | 127 item FFQ | 27 | 0.37 ±1.41 | No | Deaths were identified by linkage to the National Health Services death and electronic patient records with the use of the National Health Services identification number assigned to all British citizens | 1001 | adjusted for age, sex, ethnicity, occupational grade, living alone, smoking habits, alcohol consumption, physical activity, total energy intake, body mass index, antecedent of CVD, use of lipids lowering drugs, HDL cholesterol, hypertension, type 2 diabetes and longstanding illness |
| NHANES III | 12366 | 18 | 24-Hour recalls | 27 | 0.73±2.20 | No | death were identified through | 2795 | adjustment was made for age, BMI, |

| | | | | | | | linkage to National Death Index records through December 31, 2006, by the National Center for Health Statistics | | smoking status, sex, race/ethnicity, diabetes status, hypertension status, physical activity, medical history of CVD, and poverty index (PI). |
|---|---|---|---|---|---|---|---|---|---|
| Swedish Mammography Cohort | 33747 | 15 | 96 item FFQ | 27 | 0.64 ± 1.45 | No | death were identified through linkage to the Swedish Cause of Death Registry at National Board of Health and Welfare. | 7095 | Adjusted for age, energy intake, BMI , education, smoking status, physical activity, and alcohol intake |
| Iowa Women's Health Study | 37525 | 24 | adapted from the 126-item FFQ developed by Willett and group at Harvard | 27 | −0.87± 2.02 | Yes | Deaths were identified through the State Health Registry of Iowa or the National Death Index for women who did not respond to the last | 17793 | Adjusted for age , BMI , smoking status, pack-years of smoking, HRT use , education, prevalent diabetes, prevalent hypertension, |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | follow-up questionnaire (2004) or who emigrated from Iowa. | | prevalent heart disease, prevalent cancer, total energy intake |
| SUVIMAX | 8089 | 13 | 24-Hour dietary records | 37 | $0.6 \pm 1.7$ for women and $0.8 \pm 1.5$ for men | No | Death were identified from relatives or physicians during follow-up. At the end of follow-up, vital status of all subjects of the cohort and causes of death were verified with the national death registry (CépiDC). | 207 | Adjusted for age , sex, intervention group of the initial SU.VI.MAX trial, number of 24-h dietary records, BMI, physical activity, smoking status, educational level, family history of cancer in first-degree relatives, family history of CVD in first-degree relatives, energy intake without alcohol, and alcohol intake |