Long-term Adherence to Healthy Dietary Guidelines and Chronic Inflammation in the Prospective Whitehall II Study

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ABSTRACT

BACKGROUND: Inflammation plays an important role in the cause of cardiovascular diseases and may contribute to the association linking an unhealthy diet to chronic age-related diseases. However, to date the long-term associations between diet and inflammation have been poorly described. Our aim was to assess the extent to which adherence to a healthy diet and dietary improvements over a 6-year exposure period prevented subsequent chronic inflammation over a 5-year follow-up in a large British population of men and women.

METHODS: Data were drawn from 4600 adults (mean ± standard deviation, age 49.6 ± 6.1 years, 28% were women) from the prospective Whitehall cohort II study. Adherence to a healthy diet was measured using Alternative Healthy Eating Index (AHEI) scores in 1991-1993 (50.7 ± 11.9 points) and 1997-1999 (51.6 ± 12.4 points). Chronic inflammation, defined as average levels of serum interleukin-6 from 2 measures 5 years apart, was assessed in 1997-1999 and 2002-2004.

RESULTS: After adjustment for sociodemographic factors, health behaviors, and health status, participants who maintained a high AHEI score (ie, a healthy diet, n = 1736, 37.7%) and those who improved this score over time (n = 681, 14.8%) showed significantly lower mean levels of interleukin-6 (1.84 pg/mL, 95% confidence interval [CI], 1.71-1.98 and 1.84 pg/mL, 95% CI, 1.70-1.99, respectively) than those who had a low AHEI score (n = 1594, 34.6%) over the 6-year exposure period (2.01 pg/mL, 95% CI, 1.87-2.17).

CONCLUSIONS: These data suggest that maintaining and improving adherence to healthy dietary recommendations may reduce the risk of long-term inflammation.

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KEYWORDS: Alternative Healthy Eating Index; Diet quality indices; Inflammatory marker; Interleukin-6; Middle-aged population; Nutritional Epidemiology; Prospective cohort

The impact of an unhealthy diet on the risk of specific age-related diseases, such as cardiovascular disease 1-6 and type 2 diabetes, 7,8 has been shown in various independent studies.

Inflammatory processes have been suggested partly to underlie these associations. 9 In agreement with this hypothesis, a recent study applying Mendelian randomization provided convincing evidence for a causal role of an inflammatory marker interleukin (IL)-6 in coronary heart disease. 10 However, the extent to which modifiable factors, such as a healthy diet, might protect against systemic chronic inflammation remains unclear.

Many observational studies on the overall diet—inflammation association have been based on cross-sectional data 11 that cannot separate the impact of diet on inflammation from possible reverse causation effects (ie, the
impact of chronic inflammation on dietary habits). Of the recent cohort studies with a prospective design, one reported that dietary pattern reflecting a high n-6:n-3 fatty acid intake ratio was associated with higher serum levels of C-reactive protein (CRP) measured 13 years later.12 Another longitudinal study that showed long-term adherence to the Alternative Healthy Eating Index (AHEI), a multicomponent measure of healthy diet, was associated with CRP but not with IL-6 serum levels.13 A major limitation in all these cross-sectional and longitudinal studies is the lack of repeat data on inflammation because the assessment of inflammation at one point in time only precludes distinctions between short-term (acute) and longer-term (chronic) inflammatory processes.

Several randomized controlled trials have been performed to determine the association between diet and inflammatory markers,9,14,23 most of them assessing the beneficial impact of the Mediterranean diet.14,16-22 Results from these trials have shown a positive impact of short-term adherence to healthy dietary guidelines on inflammation15-23 in obese participants,17,19,21 participants with type 2 diabetes,9,15 participants with a high risk of cardiovascular disease,18 participants with the metabolic syndrome,16 and participants with prevalent myocardial infarction.22 On the other hand, when intervention studies have been performed in nonclinical and healthier populations,14,23 no association with CRP or IL-6 serum levels has been observed. However, none of these studies assessed whether long-term adherence to a healthy diet or improvements in diet were associated with subsequent chronic inflammation in a general population.

To address some of these limitations in the current evidence, we analyzed data from a large British occupational cohort, the Whitehall II study, in which adherence to the dietary guidelines provided by the AHEI has been shown to reduce the risk of cardiovascular death24 and increase the likelihood of reversion of the metabolic syndrome in participants with central obesity and high triglyceride levels.25 The aim of the present article is to examine associations of the AHEI score and change in AHEI score over a 6-year exposure period with subsequent chronic inflammation, assessed by average serum levels of IL-6 and CRP from 2 measures 5 years apart.

**CLINICAL SIGNIFICANCE**

- Data from British adults suggest that long-term good and improving adherence to healthy recommendations provided by the Alternative Healthy Eating Index score are associated with lower levels of chronic inflammation assessed by serum interleukin 6.
- Adverse dietary effects on inflammatory markers were observed when adherence to healthy dietary recommendations was poor in the repeated measurements over a 6-year period.

**Data Collection**

**Diet Quality Using the Alternative Healthy Eating Index in 1991/1993 and 1997/1999.** At both examinations, dietary intakes were assessed using a semiquantitative food-frequency questionnaire with 127 food items, as described previously.24 The AHEI was scored on the basis of the intake levels of 9 components (Appendix Table 1, available online): (1) vegetables, (2) fruits, (3) nuts and soy, (4) ratio of white meat (seafood and poultry) to red meat, (5) trans fat, (6) total fiber, (7) ratio of polyunsaturated fat to saturated fat, (8) long-term multivitamin use, and (9) alcohol consumption. Higher scores corresponded to a healthier diet.

**Inflammatory Markers Assessment in 1997/1999 and 2002/2004.** IL-6, a marker of systemic inflammation, was measured using a high-sensitivity enzyme-linked immunosorbent assay (R&D Systems, Oxford, UK).28,29 Procedures are detailed in the Appendix, available online. Long-term inflammation was assessed as the average of 2 IL-6 measures in 1997/1999 and 2002/2004 (n = 3632) or by a single measure if only 1 was available (n = 968). CRP was also measured using a high-sensitivity immunonephelometric assay in a BN ProSpec nephelometer (Dade Behring, Milton Keynes, UK).

**Covariates Assessed at Baseline.** Sociodemographic variables included sex, age, ethnicity (white/South Asian/black), living alone (yes/no), and socioeconomic status (low/intermediate/high). Health behaviors were smoking habits
(never/former/current), total energy intake (kilocalories per day), and physical activity (inactive/moderately active/active).30 Health status covariates included depressive symptoms assessed using the 4-item depression subscale of the 30-item General Health Questionnaire31; prevalent coronary heart disease (denoted by clinically verified nonfatal myocardial infarction or definite angina); hypertension (defined by systolic/diastolic blood pressure $\geq 140/90$ mm Hg, respectively, or use of antihypertensive drugs); type 2 diabetes (diagnosed according to the World Health Organization definition); serum high-density lipoprotein cholesterol measured in millimoles/liter; body mass index (weight in kilograms/height in meters squared); and self-reported use of anti-inflammatory medication (eg, nonsteroidal anti-inflammatory drugs and corticosteroids).

### Statistical Analysis

The distribution of average IL-6 assessed in 1997/1999 or 2002/2004 was normalized by logarithmic transformation. The overall AHEI score and its component scores in 1991/1993 were dichotomized as high and low according to the median value (detailed in Appendix Table 1, available online).

To analyze sustained adherence to a healthy diet and improvements in diet, AHEI scores in 1991/1993 and 1997/1999 were categorized as high or low according to the median AHEI score 1991/1993.32 Thus, 4 categories of change in AHEI score over a 6-year period were defined: participants who maintained a high score (1991/1993 and 1997/1999 scores $\geq 51.5$), participants who maintained a low score (1991/1993 and 1997/1999 scores $< 51.5$), participants whose AHEI score improved (1991/1993 score $< 51.5$ and 1997/1999 score $\geq 51.5$), and participants whose AHEI score deteriorated (1991/1993 score $\geq 51.5$ and 1997/1999 score $< 51.5$ points).

Regression models were used to calculate adjusted geometric mean levels of IL-6 for each AHEI score category and the percentage difference (calculated as exp [regression coefficient] $- 1$)*100) in average levels associated with change in AHEI score. Models were first adjusted for age, sex, socioeconomic status, ethnic group, and use of anti-inflammatory drugs (model 1), and further adjusted for other covariates (model 2), including living alone, smoking status, physical activity, total energy intake, coronary heart disease, hypertension, diabetes, body mass index, and high-density lipoprotein cholesterol (as defined in “Covariates Assessed at Baseline” section).

In subsidiary analyses, we used linear regression to assess the reverse association: whether IL-6 level assessed in 1991/1993 was associated with 6-year change in AHEI score between 1991/1993 and 1997/1999 and the 11-year change in AHEI score between 1991/1993 and 2002/2004. All analyses were conducted using SAS software, version 9 (SAS Institute Inc., Cary, NC).

### RESULTS

#### Participant Characteristics

The present analyses were restricted to participants with complete data on inflammation, change in diet, and covariates ($n = 4600$). Possible cases of acute inflammation and immune activation due to current illness (defined as having CRP values $> 10$ pg/mL) were excluded because these may reflect short-term responses not representative of usual levels of chronic low-grade inflammation. A flow chart depicting participant selection is shown in Figure 1.

Compared with participants excluded from the present analyses, those included were more likely to be men and younger, with higher socioeconomic status and healthy behaviors, and were less likely to have coronary heart diseases or cardiometabolic disorders. Lower average mean IL-6 values were observed in those included (1.63 pg/mL, 95% confidence interval [CI], 1.60-1.66) compared with those excluded (2.10 pg/mL; 95% CI, 2.03-2.14; $P < .001$). In regard to the exposure, the AHEI score in 1991/1993 was higher in those included compared with those excluded (50.7 $\pm$ 11.9 points vs 49.4 $\pm$ 12.7 points, $P < .001$); however, no statistically significant difference was observed for the AHEI score in 1997/1999 or for the 6-year change in the AHEI score.

In the 4600 participants included in the present analyses, the mean (± standard deviation) score of AHEI was 50.7 $\pm$ 11.9 points in 1991/1993 and 51.6 $\pm$ 12.4 points in 1997/1999. The Pearson correlation coefficient between AHEI scores at 1991/1993 and 1997/1999 was 0.62 (95% CI, 0.60-0.64).

Table 1 shows the mean long-term IL-6 over the 5-year follow-up (1997/1999 and 2002/2004) by characteristics of the 4600 participants. Except for depressive symptoms, all other socioeconomic, health behavior, and health status factors were associated with average levels of IL-6 and were then considered as covariates in further multivariable adjusted analyses.

#### AHEI Score at Baseline (1991/93) and Average Levels of IL-6 over the 5-Year Follow-up (1997/99-2002/04)

Compared with having a low AHEI score at baseline (below median value of 51.5 points, $n = 2275$), a high AHEI score (median or greater, $n = 2325$) was associated with lower average levels of IL-6 (regression coefficient, $-0.087$, $P < .001$ in model 1 adjusted for age, sex, ethnicity, socioeconomic status, and use of anti-inflammatory drugs and $-0.066$, $P < .001$ in model 2 further adjusted for health behaviors and health status factors). All the AHEI components, with the exception of vegetable and trans-fat components, were associated with subsequent average levels of IL-6 in model 1. In model 2, only high scores in the fruit, nuts and soy, ratio of polyunsaturated to saturated fat, and moderate alcohol intake remained significantly associated
with lower levels of chronic inflammation (Appendix Figure 1, available online).

Change in AHEI over the 6-Year Exposure Period (1991/93-1997/99) and IL-6 levels over the 5-Year Follow-up (1997/99-2002/04)

The percentage difference in the average of 2 measures of IL-6 according to the AHEI change categories are shown in Table 2 and Figure 2. Compared with participants who maintained a lower AHEI score (n = 1591, 34.6%) over the 6-year exposure period, those who improved their adherence to AHEI guidelines (n = 681, 14.8%) and those who maintained high AHEI scores (n = 1736, 37.7%) over this period had lower average IL-6 values after adjustment for age, sex, ethnicity, socioeconomic status, and use of anti-inflammatory drugs. Further adjustment slightly attenuated but did not remove these associations (Table 2). Among the 2275 participants who had a lower AHEI score in 1991/1993, each 10-point increase in AHEI score over the 6-year exposure period was associated with a reduction of 4.2% in subsequent average levels of IL-6 (P < .001) (results not shown).

As illustrated in Figure 2, there was no significant difference in average IL-6 levels between participants who decreased their AHEI score between 1991/1993 and 1997/1999 (n = 589, 12.8%) and participants who maintained a high AHEI score over the 6-year exposure period, suggesting that the adverse effect of diet on inflammatory markers is detectable only when poor adherence to healthy dietary recommendations is maintained over a long period.

Sensitivity Analyses

As sensitivity analyses, models were repeated in participants for whom measures of IL-6 were available both in 1997/1999 and 2002/2004 (n = 3632), excluding those with a measure at 1 phase only. Similar results were observed (Table 2). Analyses were also repeated after considering different categories of long-term adherence to AHEI. Adherence to a healthy diet and improvements in diet were built according to quartile values (third quartile or greater, 59.5 vs < 59.5 points) of the AHEI score in 1991/1993 (rather than median value). Again, similar trends were obtained (Appendix Table 3, available online).

Furthermore, instead of considering IL-6 measures, we repeated analyses by considering CRP measures; similar associations between change in AHEI score over the 6-year exposure period (1991/1993 to 1997/1999) and average levels of CRP over the 5-year follow-up (1997/1999 to 2002/2004) were observed (Appendix Table 4, available online).

Because IL-6 is involved in physiopathologic processes leading to chronic disease and might modify dietary behaviors, we performed supplementary analyses to assess whether the level of IL-6 assessed in 1991/1993 was related to subsequent 6-year and 11-year change in AHEI score using linear regression models. Although IL-6 levels were cross-sectionally associated with AHEI score at phase 3 (regression coefficient, −0.401; standard error, 0.097; P < .001), they were not associated with subsequent change in AHEI score over follow-up (Appendix Table 2, available online), making it less probable that the diet and inflammation association we reported
might be due to reverse causality, that is, an effect of inflammation on diet.

**DISCUSSION**

The present study examined the association between long-term adherence to dietary guidelines and subsequent chronic inflammation assessed by average levels of IL-6 measured at the beginning and the end of a 5-year follow-up period. The main findings showed that maintaining a healthy diet score or improving adherence to a healthy diet was associated with lower mean levels of IL-6 compared with maintaining a poor dietary score over the 6-year exposure period. This association was independent of socioeconomic factors, health behavior (smoking, physical activity, and total energy intake), and health status (body mass index, use of anti-inflammatory drugs, and cardiometabolic disorders/diseases).

Our analysis of associations between long-term dietary behavior and changes in dietary behavior over time, and subsequent chronic inflammation constitutes a novel approach to the diet and inflammation relationship. In addition to finding that participants who improved or maintained a healthy diet had lower levels of IL-6, we also found that participants whose healthy diet score deteriorated over the 6-year exposure period had subsequent levels of IL-6 similar to those who maintained a high score or improved their score over the same period. This finding suggests that unhealthy dietary behaviors have a deleterious impact on chronic inflammation only when maintained over a long period, a hypothesis that needs to be tested in future studies.

Although previous studies in this field have had methodological limitations, our results are consistent with the diet—inflammation association reported in some previous observational studies. Studies that have assessed overall diet by extracting dietary patterns using statistical methods, mainly principal component analyses, have shown healthy dietary patterns, generally characterized by higher intake of

| Table 1 Characteristics in 1991/1993 of Participants Excluded and Included in the Analyses and Mean Long-term Levels of Interleukin-6 Assessed in 1997/1999 and 2002/2004 of Those Included |

| Variables                  | Category               | N or Mean (SD) * | Mean Long-term IL-6 (95% CI) (pg/mL) or r† | P Value‡ |
|----------------------------|------------------------|------------------|-------------------------------------------|---------|
| Sex                        | Men                    | 3334             | 1.65 (1.62-1.68)                          | .05     |
|                            | Women                  | 1266             | 1.59 (1.55-1.64)                          |         |
| Age                        | Per year               | 49.6 (6.1)       | 0.25                                       | <.001   |
| Ethnicity                  | White                  | 4317             | 1.61 (1.59-1.64)                          | <.001   |
|                            | South Asian            | 185              | 2.07 (1.92-2.23)                          |         |
|                            | Black                  | 98               | 1.63 (1.47-1.81)                          |         |
| Socioeconomic status       | Low                    | 542              | 1.78 (1.70-1.86)                          | <.001   |
|                            | Intermediate           | 2046             | 1.68 (1.64-1.72)                          |         |
|                            | High                   | 2012             | 1.55 (1.52-1.59)                          |         |
| Living alone               | No                     | 3588             | 1.61 (1.58-1.63)                          | .001    |
|                            | Yes                    | 1012             | 1.72 (1.67-1.78)                          |         |
| Smoking habits             | Nonsmokers             | 2402             | 1.55 (1.52-1.59)                          | <.001   |
|                            | Former smokers         | 1657             | 1.64 (1.60-1.68)                          |         |
|                            | Current smokers        | 541              | 1.98 (1.90-2.07)                          |         |
| Total energy intake        | Per kcal/d             | 2124             | 0.05                                       |         |
| Physical activity          | Inactive               | 808              | 1.76 (1.70-1.83)                          | <.001   |
|                            | Moderately active      | 1313             | 1.62 (1.57-1.67)                          |         |
|                            | Active                 | 2479             | 1.60 (1.57-1.63)                          |         |
| General health questionnaire| depression cases       | No               | 4040                                       | .99     |
|                            | Yes                    | 560              | 1.63 (1.61-1.66)                          |         |
| Coronary heart diseases    | No                     | 4487             | 1.63 (1.60-1.65)                          | .01     |
|                            | Yes                    | 113              | 1.84 (1.67-2.02)                          |         |
| Body mass index            | per kg/m²              | 25.0             | 0.32                                       | <.001   |
| Hypertension               | No                     | 3803             | 1.58 (1.55-1.60)                          | <.001   |
|                            | Yes                    | 797              | 1.92 (1.86-2.00)                          |         |
| Diabetes                   | No                     | 4487             | 1.63 (1.60-1.65)                          | .05     |
|                            | Yes                    | 113              | 1.79 (1.63-1.98)                          |         |
| HDL-cholesterol            | per mmol/L             | 1.43 (0.40)      | 0.18                                       | <.001   |
| Use of anti-inflammatory drugs | No | 3939 | 1.59 (1.57-1.62) |         |
|                            | Yes                    | 661              | 1.90 (1.83-1.97)                          |         |

CI = confidence interval; HDL = high-density lipoprotein; IL = interleukin; SD = standard deviation.

* N presented for categoric variables and mean (SD) for continuous variables.
† IL-6 geometric means with its 95% CI (pg/mL) shown for categoric variables and Spearman correlation coefficient for continuous variables.
‡ P value for association with chronic IL-6.
favorable food groups such as fruits, vegetables, fish, white meat, and whole grains, to be associated with lower levels of CRP and IL-6. They have also shown that unhealthy dietary patterns—characterized by sweetened desserts, refined grains, processed/red meat, high fat dairy products, and pizzas—to be associated with higher levels of CRP or IL-6. We did not observe an association between high overall consumption of vegetables and IL-6. Some previous studies have linked use of cruciferous, but not noncruciferous, vegetables to lower IL-6 levels. After full adjustment, the fruit, nuts and soy, polyunsaturated to saturated fatty acids ratio, and moderate alcohol components were associated with subsequent lower average IL-6 levels. The antioxidants contained in fruits and the high levels of polyunsaturated fat provided by nuts and soy products, which will contribute to a favorable polyunsaturated to saturated fatty acids ratio, may contribute synergistically to reducing proinflammatory stimuli and thus prevent inflammation and the induced secretion of inflammatory cytokines. The positive impact of moderate alcohol consumption on low-grade inflammation reported in our study is also concordant with the literature, although the underlying mechanisms are still under debate.

Study Limitations
First, the assessment of dietary intake using a semi-quantitative food frequency questionnaire covered only specific foods. This method is recognized to be less precise than dietary assessment by the food diary method. Second, we assessed long-term inflammation using average IL-6 levels assessed twice over 5 years of follow-up. However, having a high IL-6 level at the beginning and end of the follow-up period is not necessarily an indicator of chronic inflammation because repeated short-term inflammatory responses are possible. To address this issue, we used repeat measures of IL-6 and removed participants with acute inflammatory responses (CRP >10) at each measurement. Third, because most of the Whitehall II study participants were office-based civil servants on recruitment to the study,
our results may not be generalizable to the wider British population.

Finally, as in every observational study, we cannot exclude that possibility that the diet—flammation association observed may have been generated by unmeasured confounders, despite the extensive adjustment for a large range of sociodemographic, health behavior, and health status factors.

CONCLUSIONS

Our study is the first to show that sustained adherence and improved adherence to healthy dietary guidelines, as exemplified by the AHEI, are associated with lower levels of subsequent chronic inflammation assessed as serum IL-6 in a white-collar population of men and women. This study reinforces the recommendations of following dietary guidelines that encourage dietary intake similar to what is assessed in the AHEI.

ACKNOWLEDGMENTS

The authors thank all participating civil service departments and their welfare personnel and establishment officers; the Occupational Health and Safety Agency; the Council of Civil Service Unions; all participating civil servants in the Whitehall II study; and all members of the Whitehall II Study Team. The Whitehall II Study Team comprises research scientists, statisticians, study coordinators, nurses, data managers, administrative assistants, and data entry staff, who make the study possible.

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**Funding:** The Whitehall II study is supported by grants from the British Medical Research Council (MR/K013351/1); the British Heart Foundation (PG/11/63/29011 and RG/13/2/30098); the Economic and Social Research Council (ES/J023299/1); the National Heart, Lung, and Blood Institute (R01HL036310); the National Institute on Aging, National Institutes of Health (R01AG013196 and R01AG034454); and the Agency for Health Care Policy and Research (Grant HS06516). TA is supported by the Economic and Social Research Council (ES/J023299/1), the National Institutes of Health and by the Languedoc-Roussillon Region (Chercheur d’avenir Grant 2011). MJS is partly supported by the British Heart Foundation. MK is supported by the Medical Research Council (MR/K013351/1), the British Heart Foundation (PG/11/63/29011 and RG/13/2/30098), Academy of Finland, and a professorial fellowship from the Economic and Social Research Council (ES/J023299/1). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

**Conflict of Interest:** None.

**Authorship:** All authors had access to the data and played a role in writing this manuscript.
APPENDIX

Supplementary Information on the Procedures of Interleukin-6 Measurement in 1997/1999 and 2002/2004

Interleukin (IL)-6, a marker of systemic inflammation, was measured using a high-sensitivity enzyme-linked immunosorbent assay (R&D Systems, Oxford, UK).1,2 At both the 1997/1999 and 2002/2004 follow-up screenings, blood samples were collected between 8 AM and 1 PM, stored at −80°C, and not thawed or refrozen during storage. Stored serum samples from both phases were analyzed in the same laboratory. Values below the detection limit (0.08 pg/mL) were assigned a value equal to half the detection limit. To examine short-term biological variation and laboratory error, a repeated sample was taken from a subset of 329 participants at phase 7 (average elapse time 24 days; standard deviation, 11.0). Reliability between samples was assessed with Pearson’s correlation coefficients: $r = 0.63$; intra- and inter-assay coefficients of variation were 7.5% and 8.9%, respectively. The correlation coefficient for IL-6 measures at the 2 follow-up screenings was 0.50. Long-term inflammation was assessed as the average of 2 IL-6 measures in 1997/1999 and 2002/2004 (n = 3632) or by a single measure if only 1 was available (n = 968).

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Appendix Figure 1  

Difference in average interleukin-6 levels (1997/1999 and 2002/2004) as a function of high versus low overall AHEI score and AHEI component scores at baseline (1991/1993) in 4600 participants from the Whitehall II cohort. AHEI = Alternative Healthy Eating Index; IL = interleukin; PUFA = polyunsaturated fatty acid; SatF = saturated fat.

* Linear regression models were performed to assess the association between AHEI score at baseline and the average levels of IL-6. The reduction in IL-6 means between AHEI score categories were expressed by the percentage difference in average levels of IL-6 between AHEI score categories. These estimates were calculated using the formula: Percentage difference = (exp(regression coefficient) – 1)*100.

M1: adjusted for age, sex, socio-economic status, ethnic group and use of anti-inflammatory drugs
M2: M1 + living alone, smoking, total energy intake, physical activity, coronary heart disease, hypertension, diabetes, body mass index and HDL-cholesterol.
### Appendix Table 1  Construction of Alternative Healthy Eating Index Scores

| Components* | Criteria for Minimum Scores | Criteria for Maximum Scores | Possible Score Range | AHEI Scores in the Participants in 1991/1993 |
|--------------|----------------------------|-----------------------------|----------------------|---------------------------------------------|
| Vegetable (serving/d) | 0 | 5 | 0-10 | 5.6 (2.7) |
| Fruit (serving/d) | 0 | 4 | 0-10 | 6.1 (3.0) |
| Nuts and soy (serving/d) | 0 | 1 | 0-10 | 3.2 (3.0) |
| Ratio of white to red meat | 0 | 4 | 0-10 | 5.4 (2.8) |
| Trans fat (% of energy) | ≥4 | ≤0.5 | 0-10 | 8.4 (2.8) |
| Total fiber (% of energy) | 0 | 24 | 0-10 | 7.8 (3.0) |
| Ratio of polyunsaturated to saturated fat | ≤0.1 | ≥1 | 0-10 | 5.2 (2.7) |
| Duration of multivitamin use | <5 y | ≥5 y | 2.5-7.5 | 4.2 (2.4) |
| Alcohol serving/d | Men 0 or >3.5 | 1.5-2.5 | 0-10 | 4.8 (3.7)† |
| Alcohol serving/d | Women 0 or >2.5 | 0.5-1.5 | 0-10 | 5† |
| Total score | 2.5-87.5 | | | 50.7 (11.9) |

AHEI = Alternative Healthy Eating Index; SD = standard deviation.

*Each AHEI component contributed from 0 to 10 points to the total AHEI score, except the multivitamin component, which was dichotomous and contributing 2.5 points (for nonuse) or 7.5 points (for use). A score of 10 indicates that the recommendations were fully met, whereas a score of 0 represents the least healthy dietary behavior. Intermediate intakes were scored proportionately between 0 and 10.

†Median score for men and women combined.

### Appendix Table 2  Association between Change* in Alternative Healthy Eating Index Score over the 6-Year Exposure Period and Long-term Interleukin-6 Measured Twice over the Subsequent 5-Year Follow-up Period: Supplementary Analyses

| Change* in AHEI Score over the 6-Year Exposure Period (Between 1991/1993 and 1997/1999) | Participants with IL-6 Measures Available at 1997/1999 or 2002/2004 |
|-----------------------------------------------|---------------------------------------------------------------|
|                                              | % Difference | SE | P Value |
| Maintaining high score vs maintaining low score |              |    |         |
| Model 1                                      | −7.7         | 2.1 | .0001 |
| Model 2                                      | −4.2         | 2.0 | .0311 |
| Improving score vs maintaining low score      |              |    |         |
| Model 1                                      | −7.0         | 2.2 | .0010 |
| Model 2                                      | −5.1         | 2.1 | .0128 |
| Deteriorating score vs maintaining high score |              |    |         |
| Model 1                                      | −4.1         | 3.0 | .1596 |
| Model 2                                      | −4.4         | 2.8 | .1090 |

Model 1: partially adjusted model: adjusted for sex, age, ethnic group, socioeconomic status, and use of anti-inflammatory drugs. Model 2: fully adjusted model: adjusted as in model 1 + living alone, smoking status, physical activity, total energy intake, hypertension, body mass index, diabetes, coronary heart diseases, and high-density lipoprotein cholesterol. % difference (exp[linear regression coefficient] − 1)*100; a negative percentage difference expressed the percentage reduction in IL-6 levels in the relevant exposure group compared with the reference group.

AHEI = Alternative Healthy Eating Index; IL = interleukin; SE = standard error.

*To analyze sustained adherence to a healthy diet and improvements in diet, AHEI scores in 1991/1993 and 1997/1999 were categorized as high or low according to the highest quartile of AHEI score in 1991/1993. Thus, 4 categories of change in AHEI score over a 6-year period were defined: participants who maintained a high score (1991/1993 and 1997/1999 scores ≥59.5, n = 740), participants who maintained a low score (1991/1993 and 1997/1999 scores <59.5, n = 2804), participants whose AHEI score improved (1991/1993 score <59.5 and 1997/1999 score ≥59.5, n = 612), and participants whose AHEI score deteriorated (1991/1993 score ≥59.5 and 1997/1999 score <59.5 points, n = 444).
### Appendix Table 3  Association between Change in Alternative Healthy Eating Index Score over the 6-Year Exposure Period and Long-Term C-reactive Protein Measured Twice over the Subsequent 5-Year Follow-up Period

| Change in AHEI Score over the 6-Year Exposure Period (Between 1991/1993 and 1997/1999) | Participants with CRP Measures | % Difference | SE | P Value |
|---|---|---|---|---|
| Maintaining high score vs maintaining low score | Model 1 | −17.1 | 3.3 | <.001 |
| | Model 2 | −12.4 | 3.1 | <.001 |
| Improving score vs maintaining low score | Model 1 | −12.2 | 4.3 | .0023 |
| | Model 2 | −12.2 | 3.9 | .0010 |
| Deteriorating score vs maintaining high score | Model 1 | 18.6 | 4.5 | .0001 |
| | Model 2 | 13.2 | 4.1 | .0027 |

Model 1: partially adjusted model: adjusted for sex, age, ethnic group, socioeconomic status, and use of anti-inflammatory drugs. Model 2: fully adjusted model: adjusted as in Model 1 + living alone, smoking status, physical activity, total energy intake, hypertension, body mass index, diabetes, coronary heart diseases, and high-density lipoprotein cholesterol. % difference (exp[linear regression coefficient] − 1)*100; a negative percentage difference expressed the percentage reduction in CRP levels in the relevant exposure group compared with the reference group.

AHEI = Alternative Healthy Eating Index; CRP = C-reactive protein; SE = standard error.

### Appendix Table 4  Association between Interleukin-6 Assessed in 1991/1993 and Alternative Healthy Eating Index Score and Its Subsequent Change over the Follow-up

| IL-6 Measured in 1991/1993 | 6-Year Change in AHEI Score between 1991/1993 and 1997/1999 | 11-Year Change in AHEI Score between 1991/1993 and 2002-2004 |
|---|---|---|
| | n | β | SE | P | n | β | SE | P |
| Model adjusted for age, sex, ethnicity, SES, and use of anti-inflammatory drugs in 1991/1993 | 4654 | 0.066 | 0.078 | .40 | 3830 | 0.111 | 0.096 | .25 |

AHEI = Alternative Healthy Eating Index; IL = interleukin; SE = standard error; SES = socioeconomic status.