The Inflammatory Potential of the Diet at Midlife Is Associated with Later Healthy Aging in French Adults

Karen E Assmann,1 Moufidath Adjibade,1 Nitin Shivappa,2,3 James R Hébert,2,3 Michael D Wirth,2,3 Mathilde Touvier,1 Tasnime Akbaraly,4,5 Serge Hercberg,1,6 Pilar Galan,1 Chantal Julia,1,6 and Emmanuelle Kesse-Guyot1

1Paris 13 University, Nutritional Epidemiology Research Team (EREN), Epidemiology and Statistics Research Center, U1153 National Institute of Health and Medical Research (INSERM), U1125 National Institute for Agricultural Research (INRA), National Conservatory of Arts and Crafts (CNAM), Sorbonne Paris Cité COMUE, Bobigny, France; 2Cancer Prevention and Control Program, and Department of Epidemiology and Biostatistics, Arnold School of Public Health, University of South Carolina, Columbia, SC; 3Connecting Health Innovations LLC, Columbia, SC; 4MMDN, Univ. Montpellier, EPHE, INSERM, U1198, Montpellier, France; 5University College London, Department of Epidemiology and Public Health, London, United Kingdom; and 6Department of Public Health, Hôpital Avicenne (AP-HP), Bobigny, France

Abstract

Background: While low-grade chronic inflammation has been suggested as a major modulator of healthy aging (HA), no study has yet investigated the link between the inflammatory potential of the diet and multidimensional concepts of HA.

Objective: We aimed to evaluate the association between the inflammatory potential of the diet at midlife, as measured by the Dietary Inflammatory Index (DII), and HA assessed 13 y later.

Methods: We analyzed data from 2796 participants in the French Supplémentation en Vitamines et Minéraux Antioxydants (SU.VI.MAX) study aged 45–60 y at baseline (1994–1995) and initially free of diabetes, cardiovascular disease, and cancer. During the trial phase of the study (1994–2002), participants received either a placebo or a daily nutritional dose of antioxidant supplement (120 mg vitamin C, 6 mg β-carotene, 30 mg vitamin E, 100 μg Se, 20 mg Zn). HA was assessed in 2007–2009, and defined as having no major chronic disease, good physical and cognitive functioning, independence in daily activities, no depressive symptoms, good social health, good overall self-perceived health, and no function-limiting pain. The DII was calculated based on repeated baseline 24-h dietary records. Its association with HA was assessed by robust-error-variance Poisson regression, providing RR estimates.

Results: After adjustment for potential confounders, higher DII scores (reflecting a more proinflammatory diet), were associated with a decreased likelihood of HA: RRtertile 3/tertile 1 = 0.85 (95% CI: 0.74, 0.99); P-trend = 0.03. Secondary analyses revealed that this association was only significant among participants who had been in the placebo group during the trial phase: RRtertile 3/tertile 1 = 0.80 (95% CI: 0.64, 1.00); P-trend = 0.04.

Conclusions: This study suggests that a proinflammatory diet may lower the probability of overall HA. The SU.VI.MAX trial was registered at www.clinicaltrials.gov as NCT00272428.


Keywords: dietary inflammatory index, dietary score, healthy aging inflammation, nutrition

Introduction

While the incidence of most chronic diseases and functional disability increases with age, a substantial variation in the risk of chronic disease, pain, and impairment is observed across individuals of similar age (1). This may be attributed to differences in genetic factors, but also to heterogeneity in environmental factors such as diet (1).

Among other features, biological aging is characterized by telomere attrition, mitochondrial dysfunction, and cellular senescence (2). Furthermore, it has been suggested that inflammatory processes may be responsible for a large portion of these features associated with aging (3).

Recently, inflammation has been defined as 1 of the 7 pillars of aging (4) and the concept of “inflammaging,” referring to low-grade chronic systemic inflammation occurring during the physiological aging process, has emerged (5). In addition, inflammatory processes appear to contribute to the pathogenesis of most chronic age-related diseases such as cancer, cardiovascular diseases, and type 2 diabetes (5).
Furthermore, the nutritional epidemiology literature suggests a detrimental role of unhealthy dietary patterns concerning several age-related outcomes (6); and the underlying mechanisms evoked include oxidative stress and inflammatory processes. Based on the existing knowledge on the role of dietary constituents in the regulation of inflammatory conditions, the Dietary Inflammatory Index (DII) was recently developed as a means of estimating the inflammatory potential of the overall diet (7). This index has been associated with inflammatory biomarkers in several cohort studies (8–11) and has also been associated with age-related diseases including cardiometabolic disorders, cancer (12–15), cognitive impairment (24), and with mortality in several studies (16–20) including the Supplémentation en Vitamines et Minéraux Antioxydants (SU.VI.MAX) study (21–23). In light of the strong interrelations between age-related diseases and their potential common pathways involving inflammatory processes, we aimed to examine the association between the DII and aging in a holistic manner, based on the "successful aging" or "healthy aging" (HA) concept of Rowe and Kahn (1). This concept defines HA as presenting a low risk of disease or disability, and maintaining elevated cognitive and physical functioning as well as an active engagement with life. Our objective was to investigate whether high scores on the DII (reflecting a more proinflammatory diet) decrease the likelihood of HA in a middle-aged French cohort. A further objective was to test to what extent supplementation with antioxidant nutrients tested during the trial-phase of the SU.VI.MAX study would modulate the association between the DII and HA.

Methods

Study population. This analysis was based on data from the SU.VI.MAX study. This study was initially a randomized double-blind, placebo-controlled trial (1994–2002), designed to test the efficacy of a daily supplementation with nutritional doses of antioxidant vitamins and minerals (120 mg vitamin C, 6 mg β-carotene, 30 mg vitamin E, 100 μg Se, 20 mg Zn) on the risk of cancer, ischemic heart disease, and mortality. The specific doses of the different vitamins and minerals were chosen to be high enough to be potentially efficient, but within the range of dietary plausible intakes, to mimic adequate intake. The period of daily supplementation corresponded to the entire study period of the SU.VI.MAX trial: 1994–2002. Details on the study’s design are available elsewhere (24, 25). Briefly, a total of 13,017 volunteers living in France (women aged 35–60 y and men aged 45–60 y), meeting all eligibility criteria (25) were randomly assigned and included in the study. At the end of the trial phase, participants who agreed to participate (n = 6830) in a postsupplementation follow-up were included in the observational SU.VI.MAX 2 study (2007–2009).

The SU.VI.MAX2 study included 6850 participants, among whom 5583 were >45 y of age at baseline. Among these participants, we selected those with available dietary data (i.e., with ≥3 valid 24-h dietary records at baseline, n = 4174). Next, we excluded 257 participants with prevalent diabetes, cardiovascular disease, or cancer at baseline, and 905 with missing values of ≥1 of the variables that were necessary to determine HA status. Finally, 216 participants with missing values of ≥1 covariable were also removed. The final sample included 2796 men and women.

Ethics. The SU.VI.MAX and SU.VI.MAX2 studies were conducted according to the guidelines in the Declaration of Helsinki, and were approved by the ethics committees for studies with human subjects of the Paris-Cochin Hospital (Comités de Consultation pour la Protection des Personnes se prêtant à la Recherche Biomédicale, CCPRB no. 706 and no. 2364, respectively) and the Commission Nationale de l'Informatique et des Libertés (CNIL no. 334,641 and no. 907,094, respectively). Written informed consent was obtained from all participants.

Health data and HA definition. Incident cases of cancer and cardiovascular diseases were recorded during follow-up, and were validated by an external committee of medical doctors (25). At the SU.VI.MAX2 examination, tests of physical and cognitive functioning were administered in visit centers and self-administered questionnaires were completed by the participants. Using these different measures, we developed a binary HA indicator that was mostly based on the concept proposed by Rowe and Kahn (25). HA was defined as follows: absence of incident major chronic disease (cancer, cardiovascular disease, or diabetes) during follow-up concomitantly with the absence of limitations in instrumental activities of daily living, function-limiting pain, depressive symptomatology, and health-related limitations in social life, as well as the presence of good physical and cognitive functioning and good overall self-perceived health.

Cancer was defined as cancer of any kind, except for basal cell carcinoma. Cardiovascular disease was defined as codes I20-I25, I63, I65, I66, I70, I71, and I74 from the 10th International World Health Organization Classification of Diseases. Incident diabetes was defined as having a fasting blood glucose value ≥1.26 g/L, antidiabetic medication use, or self-reported diabetes at the end of follow-up.

Independent in instrumental activities was defined as <1 limitation on the Lawton instrumental activities of daily living scale and the absence of depressive symptoms was defined by a score <16/60 on the Center for Epidemiological Studies Depression scale. The absence of function-limiting pain and of health-related limitations in social life, as well as good overall self-perceived health, were assessed based on responses to 5 different items of the Medical Outcome Study Short-Form 36 questionnaire.

Good physical functioning was defined as a score ≥11/12 on the Short Physical Performance Battery. Finally, good cognitive functioning was considered as present when a participant presented good overall cognitive functioning (defined as a score ≥27/30 on the Mini-Mental State Examination), good verbal episodic memory (defined as a score ≥19/48 on the rappel indexé–étal item test), and good mental flexibility (defined as a Delis-Kaplan Trail-making test scaled score ≥5.5).

A participant was considered to present overall HA when all of the above criteria were met. Otherwise (i.e., if ≥1 of the above binary criteria was “no”) the participant was considered not to present HA. More details are presented in Supplemental Table 1.
**Dietary data and the DII.** During the trial phase, participants were asked to provide a 24-h dietary record every 2 mo, corresponding to 6 records/y and thus covering most days of the week and all seasons to account for intraindividual variability in dietary intake. Participants were assisted by an instruction manual presenting validated photographs of over 250 generic food items represented in 3 main, 2 intermediate, and 2 extreme portion sizes (26). A validated French food composition table was used to estimate nutrient intakes (27). Daily food intake refers to average consumptions across all 24-h dietary records completed during the first 2 y of follow-up, as a proxy of usual diet in midlife.

The DII score was used to estimate the inflammatory potential of the diet. The computation of the DII score based on dietary data from the SU.VI.MAX study has been extensively described previously (7, 23, 28). Briefly, the DII was computed using data for 36 of the possible 45 parameters (nutrients, specific food items, and bioactive compounds). Energy intake, carbohydrate, protein, total fat, cholesterol, saturated fatty acids, vitamin B-12, and iron intake were considered as proinflammatory factors, whereas MUFAs, PUFAs (ω-3, ω-6), niacin, thiamin, riboflavin, vitamin B-6, magnesium, vitamin A, vitamin C, vitamin D, vitamin E, folic acid, β-carotene, anthocyanidins, flavan-3-ol, flavonols, flavonones, flavones, isoflavones, alcohol, fiber, garlic, ginger, pepper, onion, and tea were computed as anti-inflammatory factors. Dietary intakes were first standardized using means and SDs listed in a database that included food consumption data from 11 populations around the world. The resulting values were then converted to centered percentile scores. Next, the centered percentile scores for each nutritional parameter were multiplied by parameter-specific coefficients derived from a literature review (7). Finally, all resulting parameter-specific values were summed to define the overall DII score for each individual. Higher DII values reflect a more proinflammatory diet. In our study sample, the range of the calculated DII score was −5.31 to 5.98 points (first quartile: −0.92, third quartile: 1.67). The range of the DII score found in the present subsample of the SU.VI.MAX study is roughly comparable to that found in other studies, such as a subsample of the Whitehall II study (−3.35 to 4.23) (29) and a nested case-control study within the Northern Sweden Health and Disease Study (−4.16 to 5.04) (20).

**Covariates.** At inclusion, information on sex, date of birth, educational level (primary, secondary, or university), living arrangement (living alone or cohabiting), socioprofessional category (unemployed, manual worker, employee or support staff, or white-collar worker), physical activity (irregular, <1 h or ≥1 h walking/d), and smoking status (never, former, or current) were collected using self-administered questionnaires.

**Statistical analysis.** Baseline characteristics were presented as means ± SDs or percentages across tertiles of DII scores. P values were estimated by linear contrast tests or by Cochran-Mantel-Haenszel tests (i.e., χ²-square trend tests). For these descriptive analyses, all nutritional intakes except intakes of the main macronutrients (carbohydrates, proteins, lipids, alcohol) were adjusted for energy intake using the residual probability weighting method (31). The probability of inclusion into our analysis, using multivariable logistic regression. We considered as “eligible” all participants of the initial SU.VI.MAX study (n = 12,741) who were within the desired age range at baseline and had available dietary data at baseline (n = 6371). The inverse of the probability of inclusion was then multiplied by the sampling proportion (n Included/n Eligible, i.e., 2796/6371) to obtain stabilized weights which were used as weights in Poisson regression models.

Two secondary analyses were performed to test the robustness of our findings. First, we restricted our analyses to participants with at least six 24-h records. The rationale behind this sensitivity analysis was that DII scores obtained on data from ≤5 dietary records may have been less accurate, and that an analysis restricted to participants for whom the most precise nutritional estimates were available may thus be less prone to any bias related to measurement error (notably for nutritional components with high intraindividual variability, and whose intake is particularly season dependent, such as the different types of polyphenol components).

Second, we investigated a potential interaction between the DII and intervention group status during the trial phase (antioxidant supplementation compared with placebo). We hypothesized that antioxidant supplementation could modify the relation of the inflammatory potential of the diet (which is related to, amongst other things, pathways that influence oxidative stress) with HA. Although we did not find a significant formal interaction in the present study (P = 0.29), the strong rationale for a potential effect modification by a long-term daily antioxidant supplementation led us to conduct stratified analyses nonetheless.

All statistical analyses were conducted using SAS version 9.4 (SAS institute Inc.) with a significance level of 0.05 for 2-sided tests.

**Results**

The present analysis included 2796 participants. Our study sample’s mean age at baseline was 51.9 ± 4.5 y and the mean follow-up time was 13.3 ± 0.7 y. In our sample, 41% of men and 35% of women met all criteria of our HA definition.

The characteristics of the participants were presented across tertiles of the DII (Table 1 for main characteristics and Table 2 for diet-related characteristics). Participants with higher DII scores (reflecting more proinflammatory diets) were younger, less educated, more often women, and less often physically active. Of note, no association was detected between DII tertiles and smoking status or BMI. Nutritionally, participants with a higher DII showed a lower intake of overall energy. In addition, in terms of contributions of the different macronutrients to overall energy intake, they had higher intakes of lipids and proteins—and lower intakes of carbohydrates. As expected by virtue of how the DII is constructed, those with a higher DII had lower intakes of n−3 and n−6 PUFAs, fiber, vitamin E, vitamin C, β-carotene, and folates.

The association between DII scores at midlife and HA is presented in Table 3.

In the main model (model 2), adjusted for sociodemographic and lifestyle factors as well as energy intake, higher DII scores were negatively associated with HA. This association was not substantially modified when further adjusted for BMI. Comparing the 3rd tertile of the DII to the 1st, the observed relative risk was 0.85 (95% CI: 0.74, 0.99), and the P value for a linear trend across tertiles was 0.03.

In the secondary analysis (Table 4) with the selection of a subsample with at least six 24-h records, the magnitude of the association was very similar, although the results were no longer statistically significant due to reduced statistical power. Next, models stratified by supplementation group during the trial phase (1994–2002) of the study showed that while there was a significant association in the placebo group with a reduction in the probability for HA of 20%, no significant
findings were observed in the antioxidant supplementation group.

Discussion

In this longitudinal study carried out among French middle-aged men and women from the SU.VI.MAX trial, higher scores on the DII—a dietary index built to capture the proinflammatory potential of the diet—were associated with a lower probability of multidimensional HA assessed 13 y later.

In the present study, analyses stratified according to antioxidant supplementation yielded different RR estimates in the 2 strata (i.e., a significant association in the placebo group only) but no statistically significant formal interaction test. Yet, a previous analysis of data from the SU.VI.MAX study and from other studies have found an association between the DII and diverse age-related chronic conditions: metabolic syndrome (16, 17, 23), cardiovascular diseases (16, 18–20, 22), and various types of cancers (12–15). Moreover, a more anti-inflammatory or less pro-inflammatory potential of the diet, as measured by the DII, has been related to a lower all-cause mortality (16, 21), higher levels of cognitive functioning (28), and to fewer depressive symptoms or a lower risk of depression (29, 33, 34).

While, to the best of our knowledge, no study has investigated the DII in relation to a multidimensional model of HA, our findings are consistent with previous studies on the link between the proinflammatory potential of the diet and specific components of aging phenotypes (12–23, 28, 29, 33, 34). Indeed, previous analyses based on data from the SU.VI.MAX cohort and from other studies have found an association between the DII and diverse age-related chronic conditions: metabolic syndrome (16, 17, 23), cardiovascular diseases (16, 18–20, 22), and various types of cancers (12–15). Moreover, a more anti-inflammatory or less pro-inflammatory potential of the diet, as measured by the DII, has been related to a lower all-cause mortality (16, 21), higher levels of cognitive functioning (28), and to fewer depressive symptoms or a lower risk of depression (29, 33, 34).
and vegetables (35, 36). To our knowledge, 7 studies have investigated the relation between the overall quality of the diet and multidimensional concepts of HA. These studies have notably shown a beneficial role of high adherence to the French and Australian national dietary guidelines (37, 38), empirically derived dietary patterns high in fruits and vegetables (39, 40), and to the Mediterranean diet (41, 42). In addition, 1 study indicated a detrimental role of adherence to an empirically derived pattern high in “Western” foods such as red meat and refined grains (43).

Both chronic low-grade inflammation and oxidative stress have been advanced as key mediators of biological aging (5, 44)—and both phenomena are interrelated, since oxidative stress can be both a cause and a consequence of inflammation (44). Inflammatory processes involve the production of reactive oxygen species that help combat pathogens in a physiologic context, but can also contribute to tissue damage in a pathophysiologic context. In turn, damage to macromolecules and/or to tissues caused by oxidative stress can also induce an inflammatory response. As stated above, our finding that the inflammatory potential of the diet was not significantly related to HA among participants who had received daily antioxidant supplementation is of great interest in that context. It can be hypothesized that the negative role of a proinflammatory diet can be partially counterbalanced by a sufficient supply of antioxidant nutrients. In this context, we would, however, like to emphasize that meeting antioxidant needs with dietary sources such as fruits and vegetables is widely suggested to be highly advantageous compared with meeting antioxidant needs with supplements (45).

TABLE 3  Association between the DII and healthy aging in the SU.VI.MAX study (n = 2796)1

<table>
<thead>
<tr>
<th>Model 12</th>
<th>Model 23</th>
<th>Model 34</th>
</tr>
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<tbody>
<tr>
<td>1 (−)</td>
<td>0.04 (0.93, 1.17)</td>
<td>0.08 (0.77, 1.00)</td>
</tr>
<tr>
<td>1 (−)</td>
<td>0.02 (0.91, 1.15)</td>
<td>0.08 (0.74, 0.99)</td>
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<tr>
<td>1 (−)</td>
<td>0.03 (0.92, 1.16)</td>
<td>0.08 (0.74, 0.99)</td>
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1Values are RR (95% CI), estimated through robust-error-term Poisson regression models. DII, Dietary Inflammatory Index; SU.VI.MAX, Supplémentation en Vitamines et Minéraux Antioxydants.

2P for trend obtained by contrast.

3Model 1 is adjusted for sex, supplementation group, age, follow-up duration.

4Model 2 is adjusted as for Model 1 + number of 24-h records, daily energy intake, education level, occupational status, living arrangement, smoking status, and physical activity.

5Model 3 is adjusted as for Model 2 + BMI.
Growing evidence suggests that inflammatory processes have a detrimental effect on the various components of our HA concept, notably the avoidance of age-related chronic disease and the avoidance of functional decline (5, 46–48). In addition to mechanisms related to oxidative stress, it has been suggested that low-grade chronic inflammation may trigger insulin resistance, notably via activation of TNF-α (49). In addition, inflammatory processes in the endothelium of blood vessels, including the promotion of monocyte adherence and migration as well as smooth muscle cell proliferation, have been suggested to play an important role in the development of cardiovascular diseases (44).

Recent epidemiologic evidence confirms the hypothesis that chronic low-grade inflammation may be detrimental to the maintenance of good overall health during aging. An investigation based on data from the British Whitehall II study showed that a repeatedly high blood level of the proinflammatory marker IL-6 during a 10-y follow-up was related to a marked decrease in the probability of multidimensional “successful aging” (defined as not developing major chronic disease and “optimal physical, mental and cognitive functioning”) (50). These results are thus well in line with the findings of our study—although our study’s results do not allow us to make any direct conclusions on the role of oxidative stress and inflammatory processes for HA, since we did not measure any serum markers of oxidative stress or systemic inflammation.

Some limitations of this study should be acknowledged. First, the participants included in our analysis were volunteers participating in a nutritional intervention study. As such, they had a higher educational attainment than the general population. Although we attempted to limit selection bias by using inverse probability weighting, this may not have been sufficient to remove all biases related to the fact that information on HA status was available only for those participants of the initial SU.VI.MAX trial who had been willing to participate in the SU.VI.MAX 2 observational follow-up, and who completed all questionnaires and tests related to our HA definition. Next, information on HA status (or its components) was available only at follow-up, limiting the potential for causal inference. However, participants were initially middle-aged adults free of chronic diseases, which supports our working hypothesis that only a few participants were, in reality, not in good overall health at baseline.

The strengths of the present study include its large sample size and its longitudinal design, allowing us to assess the association between the inflammatory potential of the diet at midlife and later HA over a period of 13 y. Moreover, the analyzed dietary data are characterized by a high level of accuracy, because on average ten 24-h dietary records were available per participant. Finally, the dietary index used to measure the inflammatory potential of the diet has been designed based on an extensive review of the literature.

In conclusion, our results indicate that a proinflammatory diet may lower the probability of aging healthily. Hence, our study is in agreement with suggestions that the promotion of a healthy lifestyle, in particular a healthy diet, may contribute to reducing “inflammaging” and the burden of age-related pathologies.

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| TABLE 4 Association between the DII and healthy aging, secondary analyses$^1$ |
|----------------------------------|------------------|------------------|------------------|------------------|
|                                  | T1DII            | T2DII            | T3DII            | P-trend$^2$      |
| ≥6 dietary records$^3$           | Model 1$^4$      | Model 2$^5$      | Model 3$^6$      | Placebo group$^7$|
|                                  | 1 (–)            | 1 (–)            | 1 (–)            | Model 1$^4$      |
|                                  | 1.09 (0.96, 1.23) | 1.08 (0.95, 1.22) | 1.08 (0.96, 1.22) | 0.99 (0.83, 1.18) |
|                                  | 0.87 (0.76, 1.00) | 0.86 (0.74, 1.01) | 0.87 (0.74, 1.01) | 0.81 (0.66, 0.98) |
|                                  | 0.04             | 0.06             | 0.07             | 0.03             |
|                                  | 0.97 (0.94, 1.00) | 0.97 (0.94, 1.00) | 0.97 (0.94, 1.00) | 0.97 (0.93, 1.02) |
|                                  | 0.06             | 0.21             | 0.27             | 0.26             |
| Active group$^8$                 | Model 1$^4$      | Model 2$^5$      | Model 3$^6$      | Placebo group$^7$|
|                                  | 1 (–)            | 1 (–)            | 1 (–)            | Model 1$^4$      |
|                                  | 1.07 (0.92, 1.26) | 1.06 (0.90, 1.24) | 1.07 (0.91, 1.26) | 0.99 (0.83, 1.12) |
|                                  | 0.94 (0.79, 1.12) | 0.91 (0.75, 1.10) | 0.92 (0.76, 1.11) | 0.46             |
|                                  | 0.03             | 0.33             | 0.39             | 0.99 (0.96, 1.03) |
|                                  | 0.97 (0.92, 1.02) | 0.98 (0.94, 1.02) | 0.99 (0.95, 1.03) | 0.66             |
|                                  | 0.43             | 0.50             |                  |                  |

$^1$Values are RRs (95% CIs), estimated through robust-error-term Poisson regression models. DII, Dietary Inflammatory Index; T, tertile.
$^2$P for trend.
$^3$At least six 24-h records: n = 2445. T1: n = 815; T2: n = 815; T3: n = 815.
$^4$Model 1 is adjusted for sex, supplementation group (except in analyses stratified according to supplementation group), age, follow-up duration.
$^5$Model 2 is adjusted as for Model 1 + number of 24-h records, daily energy intake, education level, occupational status, living arrangement, smoking status, and physical activity.
$^6$Model 3 is adjusted as for Model 2 + BMI.
$^7$Placebo group: n = 1313. T1: n = 437; T2: n = 438; T3: n = 438.
$^8$Active group: n = 1483. T1: n = 494; T2: n = 495; T3: n = 494.
References


