Adherence to Healthy Dietary Guidelines and Future Depressive Symptoms: Evidence for Gender Differentials in the Whitehall II Study

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**Short Running Title:** Overall Diet and Future Depressive Symptoms

The present research is not registered in any clinical trial registry

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**List of last names used by Pubmed for Indexing**

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**Glossary**

AHEI: Alternative Healthy Eating Index
CES-D: Center for Epidemiologic Studies Depression Scale
CHD: coronary heart diseases
CI: confidence interval
DepS: Depressive symptoms
FFQ: food frequency questionnaire
GHQ: General Health Questionnaire
HDL: High density lipoprotein
HEI: Healthy Eating Index
M: Model
Med-Diet: Mediterranean Diet
MMSE: Mini Mental State Examination
OR: Odds ratio
PUFA: polyunsaturated fatty acids
SES: Socio-economic status
SAS: Statistical Analysis Software
SatF: saturated fatty acids
SD: Standard deviation
ABSTRACT

Background: It has been suggested that dietary patterns are associated with the future risk of depressive symptoms. However, there is a paucity of prospective data examining the temporality of this relationship.

Objective: To examine whether adherence to a healthy diet, defined by the Alternative Healthy Eating Index (AHEI), was prospectively associated with depressive symptoms assessed over a 5-year period.

Design: Analyses are based on 4215 participants from the Whitehall II Study. AHEI score was computed in 1991-1993 and 2003-2004. Recurrent depressive symptoms were defined as having a Center for Epidemiologic Studies Depression Scale score ≥16 or self-reported use of antidepressants in 2003-2004 and in 2008-2009.

Results: After adjustment for potential confounders, AHEI score was inversely associated with recurrent depressive symptoms in a dose-response fashion in women (p for trend < 0.001; for 1SD in AHEI score, OR: 0.59; 95% CI: 0.47, 0.75) but not in men. Women who maintained high AHEI score or improved their score during the 10-year measurement period had a 65% (OR: 0.35; 95%CI:0.19, 0.64) and 68% (OR: 0.32; 95%CI:0.13, 0.78) lower odds of subsequent recurrent depressive symptoms compared to women who maintained low AHEI score. Amongst the AHEI components, vegetable, fruit, trans-fat and ratio of polyunsaturated fat vs. saturated fat components were associated with recurrent depressive symptoms in women.

Conclusion: In the present study, there was a suggestion that poor diet is a risk factor for future depression in women.
INTRODUCTION

The potential impact of specific nutrients on the physiological pathways leading to depression(1), allied to the observation that diet is a modifiable behavior, has prompted a series of studies examining the potential etiological role of dietary factors in the development of this mental health problem. However, to date, studies examining the diet-depression relationship have focused primarily on individual foods or nutrients. The most frequently investigated dietary characteristics include long-chain n-3 polyunsaturated fatty acids (PUFA), fish, and nutrients involved in the homocysteine pathway (2), but the findings have been mixed with a recent systematic review of observational studies reporting a lack of consistent evidence linking these dietary factors with depression(2).

Some methodological limitations may have contributed to inconsistencies in the evidence, including reliance on cross-sectional studies, the lack of adjustment for potential confounding factors, or crude assessment of diet or depressive symptoms (2). A further explanation is that, although a potential beneficial effect of some nutrients on the depression disease process may exist, the effect of single nutrients may be too small to be detected (3). Indeed, as people are not eating individual nutrients or individual foods, but meals which consist of complex combinations of nutrients which interact each other (3), it appears that focusing on individual nutrients or food may provide an incomplete understanding of the relationship between diet and depressive symptomatology. Accordingly, more emphasis needs to be given to the influence of dietary pattern on chronic diseases such as depression.

We have previously shown an association between a single baseline measurement of dietary pattern and future depressive symptoms (4) assessed 5 years later. Reports from several other studies have since confirmed this finding in both adolescents (5, 6) and adults (7-11).

However, the cross-sectional design of most of these studies (7-10) inevitably preclude any conclusion as to the direction of the association (12-14). To understand if poor diet indeed
constitutes a risk factor for depression and not only the reverse, studies with longitudinal
design are needed.

By using updated data from the Whitehall II study, including depressive symptoms measured
twice over a 5-year period, we examined the association of overall diet, assessed using the
Alternative Healthy Eating Index (AHEI), and 10-year change in diet, with subsequent
recurrent depressive symptoms. The ability to examine dietary adherence repeatedly is
particularly important: if diet is indeed associated with new-onset of depressive symptoms, it
would be expected that change in diet would precipitate a change in the risk of subsequent
depressive symptoms. These data are rare: to the best of our knowledge, no such study has
been conducted.
**Study population**

Data were drawn from the Whitehall II Study, a large-scale, on-going, prospective cohort study of 10308 (3413 women) UK civil servants (government employees) aged 35 to 55 years at study induction (15). The baseline examination (phase 1) took place during 1985-1988 and involved a clinical examination and self-administered questionnaire. Subsequent phases of data collection have alternated between postal questionnaire alone (phases 2 (1988-1990), 4 (1995-1996), 6 (2001), and 8 (2006)), and postal questionnaire accompanied by a clinical examination (phase 3 (1991–1993), n=8104; phase 5 (1997–1999), n=7263; phase 7 (2003–2004), n=6943, and phase 9 (2008-2009), n=6354). After describing the study to the participants, written informed consent was obtained; the University College London ethics committee approved the study.

After excluding those on antidepressant treatment at phase 3 or phase 5, analyses were restricted to participants with dietary assessment and covariates at phase 7 and complete data on depressive symptoms at phases 7 and 9, resulting in a total of 4215 participants. Amongst them, 4053 participants had complete data on the 10-y change in AHEI between phases 3 and 7 (Figure 1).

**Data Collection**

*Dietary pattern using the Alternative Healthy Eating Index at phases 3 and 7*

Dietary intake at phases 3 and 7 was assessed using a semi-quantitative food-frequency questionnaire (FFQ) with 127 food items, as described previously (16, 17). 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 others(17, 18). The AHEI score (19) was created (On-line supplemental table S1) by summing its 9 component scores (1: fruit, 2: vegetable, 3: ratio of white meat (seafood and poultry) to red meat, 4: trans fat, 5: ratio of PUFA to saturated fat...
(SatF), 6: total fiber, 7: nuts and soy, 8: alcohol consumption and 9: long-term multivitamin use). Higher values corresponded to a healthier diet. At phase 3, the mean score of AHEI was 50.6 ± 11.9 points at phase 3 and 51.4 ±12.3 at phase 7. The Pearson correlation coefficient between AHEI score at phase 3 and phase 7 was 0.59, p-value <10^-4).

DepS at phases 7 and 9
Depressive symptoms (DepS) were assessed using the Center for Epidemiologic Studies Depression Scale(20) first introduced at phase 7. At both phases 7 and 9, DepS was defined by Center for Epidemiologic Studies Depression Scale score of 16 or higher(20), self-reported use of antidepressant medications, or both. After excluding participants under antidepressant treatments before phase 7, “recurrent DepS” cases were defined as having DepS at both phase 7 and phase 9; “No recurrent DepS” was defined by the absence of DepS at phase 7 or /and at phase 9.

Covariates assessed at phases 3 and 7
Socio-demographic variables included sex, age (years), ethnicity (White/ South Asian/ Black), living alone (yes/no), a 3-level measure of socioeconomic status (SES) (low/intermediate /high) related to salary, social status and level of responsibility, and retirement status (yes/no). Health behaviors were smoking habits (never/former/current), total energy intake (kcal per day), and physical activity assessed by a questionnaire, that included 20 items on frequency and duration of participation in different activities of different intensity (e.g., walking, cycling, and sports). Participants were classified as ‘active’ (>2.5hours per week of moderate physical activity or >1 hour per week of vigorous physical activity), ‘inactive’ (<1 hour per week of moderate physical activity and <1 hour per week of vigorous physical activity), or ‘moderately active’ (neither active nor inactive) (21). Health status covariates included prevalent coronary heart disease (CHD) - (denoted by clinically verified
non-fatal myocardial infarction or definite angina); hypertension (defined by systolic or
diastolic blood pressure ≥140 or ≥90 mm Hg, respectively, or use of antihypertensive drugs);
serum high density lipoprotein (HDL) cholesterol measured in mmol/L, use of lipid-lowering
drugs, central obesity (waist circumference >102 cm in men and >88 cm in women), and
cognitive impairment (≤27 score on the Mini Mental State Examination (MMSE)) (22).
Except for HDL-cholesterol, all the health status covariates were dichotomized as yes/no

**Statistical Analysis**

Characteristics of men and women according to the recurrent DepS were compared using the
Chi-squared test for categorical covariates and ANOVA for continuous covariates. Logistic
regression analyses were used to compute odds ratios (OR) with 95% confidence intervals
(95%CI) to assess the association between AHEI score at phase 7 and recurrent DepS. AHEI
score was first categorized into tertiles (lowest tertile as the reference) to assess whether
AHEI score was linearly associated with DepS. We then derived a continuous standardized
variable (z-score; mean=0, standard deviation (SD) =1) to compute the odds ratio for
recurrent DepS per 1 SD increment in dietary score.

Effect modification of the association between AHEI (z-score) and recurrent DepS by socio-
demographic and health behavior was examined. **A significant interaction was found with sex**
(p=0.004), leading us to conduct analyses separately in men and women. No other statistically
significant interactions were found. Models stratified by sex were first adjusted for age,
etnicity and total energy intake (Model 1) and then additionally for SES, retirement, living
alone, smoking behavior, physical activity, HDL-cholesterol, type 2 diabetes, CHD,
hypertension, use of lipid lowering drugs, central obesity and cognitive impairment assessed
at phase 7-the time of exposure (Model 2).

Similar logistic regression models were performed to estimate the association of each AHEI
component z-scores with recurrent DepS. To assess whether the AHEI component- recurrent
DepS association was independent of other components, a third model was also computed which incorporated all other AHEI components in addition to potential confounders (Model 3). Further analyses were performed to examine the contribution of AHEI components to the association between AHEI and DepS. For each component (component i), we computed a modified AHEI score based on the total AHEI score without the component i (modified AHEI score i=Total AHEI score - score of the component i).

To analyze the 10-y change in AHEI score, scores of AHEI at phases 3 and 7 were categorized as high or low according to the median value of AHEI score at phase 3 equal to 51.5 points. Four categories in 10-y change of AHEI were then defined: participants who maintained a high score (Phase 3 and 7 scores ≥51.5), those who maintained a low score over the 10-y exposure period (Phase 3 and 7 scores <51.5), participants who improved their AHEI score (Phase 3 score <51.5 and Phase 7 score ≥51.5) and those who decreased their score (Phase 3 score ≥51.5 points and Phase 7 score <51.5 points). Similar procedures were applied to categorize the 10-y change in AHEI components. Median values at phase 3 for AHEI components were: [6] for vegetable, [6] for fruits, [3] for nuts and Soy, [5] for the ratio of white to red meat, [10] for fiber, [10] for trans Fat, [5] for the ratio of PUFA to saturated fat, [2.5] for multi-vitamin use and [5] alcohol. Similar adjustments as in Models 1 and 2 described above were made, but including in the models covariates assessed at phase 3. Some covariates were not included: prevalent CHD and lipid lowering drugs (due to small number of cases in stratified analyses) and cognitive impairment (as not assessed at phase 3).

We also examined if the diet-DepS association was mediated by CHD. To do so, similar analyses were repeated after excluding CHD cases. Three other sets of analyses were performed to assess the direction of the diet-DepS relationship. First we examined the association between the AHEI score at phase 3 and subsequent recurrent DepS assessed 10-y later (phases 7 and 9) after adjustment for potential confounders assessed at phase 3. Second, the main analyses were repeated after excluding participants who met the definition for
General Health Questionnaire “depression” (GHQ-Dep) at phase 3 - based on the 4-item General Health Questionnaire depression subscale (23). We also performed linear regression models estimating the linear regression coefficient (Beta and its standard error (SE)) of diet score to assess whether the GHQ-Dep cases at phase 3 showed significant differences in subsequent AHEI score assessed at phase 7 or in the 10-y change in AHEI score between phase 3 and phase 7 compared to GHQ-Dep non-cases.

All analyses were conducted using the SAS software, version 9 (SAS Institute, Cary, NC, USA).
RESULTS

Participant characteristics

Among the 4215 participants, 260 (6.2%) developed recurrent DepS. Among the 3955 participants without recurrent DepS (93.8%), 575 (13.6%) had DepS in one measurement at phase 7 (n=310) or 9 (n=265) only and 3380 (80.2%) had no DepS at either phase. Table 1 presents the characteristics of participants according to recurrent DepS status separately in men and women.

AHEI score at phase 7 and 5-year DepS

The associations between AHEI at phase 7 and recurrent DepS are presented in Table 2. Irrespective of adjustments, analyses in which AHEI were categorized in tertiles showed that this measure of dietary quality was associated with recurrent DepS in a dose-response fashion in women (p for trend <0.001) but not in men (p for trend =0.81), (p-value for the sex interaction=0.004). In women, each 1 SD increase (12 points) in AHEI score was associated with a 40% lower odds of recurrent DepS (OR=0.59, 95% CI: 0.47, 0.75, p<0.001) after adjustment for potential confounders. In men, such relationship was not found (Table 2).

Further analyses were performed in women to identify which of the AHEI components contributed most to the reduce odds of DepS. As shown in Figure 2, high consumption of vegetable and fruits, high intake of fiber, elevated PUFA/SatF ratio, and low intake of trans fat were all associated with lower odds of recurrent DepS after adjustment for potential confounders (Figure 2, Model 2). Of these AHEI components, only vegetable, fruit and trans fat components revealed independent effects (Figure 2, Model 3). In addition, when AHEI was computed without each of AHEI components, the modified AHEI-recurrent DepS association remained statistically significant suggesting that no single AHEI component was responsible for generating the total AHEI-DepS association (results not shown). In men None
of the AHEI components were found to be significantly associated with recurrent DepS after
adjustment for potential confounders (On-line supplemental Figure S1).

10-year change in AHEI score and subsequent 5-year DepS

Table 3 show that women who maintained a high score of AHEI (≥51.5 points at
phases 3 and 7) as well as those who improved their AHEI score (Phase 3 score <51.5 and
Phase 7 score ≥51.5 points) over the 10-y measurement period had a 65 % (OR:0.35; 95% CI:
0.19, 0.64) and 68 % (OR:0.32; 95% CI:0.13, 0.18) lower odds of subsequent recurrent DepS
compared to participants who maintained a low AHEI score at both phases 3 and 7
(scores<51.5 points). Women whose AHEI score decreased over time (Phase 3 score ≥51.5
and Phase 7 score<51.5 points) had 2-fold increased odds of developing subsequent recurrent
DepS compared to women who maintained high AHEI score over the 10-y exposure period
(OR: 2.15; 95%CI: 1.09, 4.22). In men, no evidence of an association between the 10-y
change in total AHEI score and subsequent recurrent DepS was observed (On-line
supplemental table S2).

Similar analyses were performed for 10-y change in each of the AHEI components. In
women (Figure 3), improvements in the scores for vegetables, fruits, trans fat and PUFA/
SatF ratio were associated with lower odds of subsequent recurrent DepS compared to those
who maintained a low score in the respective components over the 10-y measurement period.
Women whose score for these components decreased over time had higher odds of recurrent
DepS (this was not the case for the fruit component). Their 10-y changes of the other
components were not related to recurrent DepS. In men, results of the associations between
the 10-y change for each AHEI component score and recurrent DepS are shown in the On-line
supplemental Figure S2. Except for an association between maintained high score in nuts and
soy and multivitamin use components and higher odds of DepS, no AHEI component score
improvement nor decreasing over the 10-y period was associated with DepS in men.
Sensitivity analyses

With an association only observed in women, sensitivity analyses were confined to this group. First, in a subgroup excluding women with prevalent CHD (n=55), both AHEI at phase 7 and the 10-y change in AHEI remained significantly associated with recurrent DepS (AHEI z-score at phase 7: OR: 0.56; 95% CI: 0.43, 0.73; z-score of the 10-y change: OR: 0.75; 95% CI: 0.59, 0.96). This suggests that the association was not driven by the effects of CHD on diet and DepS. Second, the association between AHEI score assessed at phase 3 and recurrent DepS 10 years later was examined. We found that after adjustment for socio-demographic, health behavior, hypertension, HDL-cholesterol and central obesity assessed at phase 3, adherence to AHEI at phase 3 among participants who were not taking antidepressant treatment at phases 3 was associated with lower odds of developing recurrent DepS 10 years later (per 1 SD of AHEI score at phase 3, OR: 0.77; 95% CI: 0.60, 0.97). Third, while participants treated with antidepressive drugs before phase 7 were already excluded from the present analyses, we conducted further sensitivity analyses to explore the effects of existing mental health problems on dietary intake (reverse causality). Thus, supplementary analysis in which women who met the definition for GHQ-Depression, (n=134) and those with missing values on GHQ-Depression (n=35) at phase 3 were additionally excluded. Similar trends between AHEI score at phase 7 (OR: 0.57 ; 95% CI: 0.42, 0.78), 10-y change in AHEI score (OR: 0.77; 95% CI: 0.58, 1.03, p=0.075) and subsequent recurrent DepS were found in this subsample of 891 women. Fourth, an additional test to assess the direction of the association included the 1494 women for whom data on GHQ-Depression at phase3, use of antidepressive drugs, AHEI score at phases 3 and 7 were available. Results from linear regression models provided no evidence of differences between GHQ cases (n=230) and GHQ non-cases (n=1264) in subsequent AHEI score assessed at phase 7 (beta = -0.84, SE=0.83, p=0.31) or in 10-y change in AHEI score between phases 3
254 and 7 (beta = -0.92 SE=0.90, p=0.31), after adjustment for age, ethnicity, SES. These results
255 suggest that reverse causation does not fully explain our findings.
This study sought to examine the longitudinal association between overall diet and the development of recurrent DepS. To do so, the association between adherence to the AHEI, its 10-year change and recurrent DepS at two consecutive follow-ups over 5 years was examined. We found that adherence to healthy dietary recommendations such as those provided by the AHEI reduced the likelihood of developing recurrent DepS, in women but not in men. These effects were independent of socio-demographic, behavioral, metabolic and health status factors such as cognitive performance and vascular diseases. Those women who maintained or improved their AHEI score over the 10-y measurement period had 65 % lower odds of subsequent recurrent DepS compared to those who maintained low AHEI scores, while women whose AHEI score decreased had twice the odds of recurrent DepS. These prospective results add to the modest evidence base concerning the temporality of the diet-DepS association in middle-aged people.

The prospective association between adherence in AHEI and lower risk of recurrent DepS reported here accords with the results of studies that have investigated the cross-sectional relationship between overall diet and depression in adults (7-11), including the present study (4). One type of those studies assessed diet using dietary patterns (4, 7, 8, 10). Across diverse samples there is a suggestion that patterns characterizing healthier eating behavior were inversely associated with DepS. Because dietary patterns are derived through statistical modeling of dietary data without a priori hypothesis, dietary patterns closely matched those of the population samples considered but not necessarily those of other populations. Another group of studies assessed overall diet by building dietary indices based on dietary recommendations (7-9, 11) such as the AHEI as used herein. Poor adherence to several healthy dietary recommendations, including the HEI-2005 (24) and the Diet Quality Score (7) has been associated with depressive symptoms in cross-sectional data (7, 9). Only one study additionally assessed the temporal direction of the diet-depression association. Investigators...
on a large Spanish cohort study showed, consistent with our findings, that a high
Mediterranean Diet (Med-Diet) score was associated with a 30% reduced risk of self-reported
depression (11). The Med-Diet index shares several components with AHEI, but in contrast to
the AHEI, the thresholds used for computing the Med-Diet score are defined according to the
median of the food/nutrient intakes in the specific population studied. Even though the Med-
Diet score has been associated with improvements in health (25, 26), the use of a dietary
index with population-specific cut-points may be problematic for quantitative diet
recommendations and for comparisons of results between Mediterranean and non-
Mediterranean countries.

The association of a repeat assessment of diet with recurrent DepS in women constitutes a
novel finding. By showing that maintaining high AHEI score or improving AHEI score over
the 10-year exposure period was associated with a lower odds of recurrent DepS compared to
maintaining low AHEI score, our findings is consistent with the hypothesized temporal
association between diet on DepS in women.

The reason for this gradient being apparent in women but not men is unclear. One possible
explanation, although non-testable with the present dataset, is that the instrument we used to
assess DepS was less sensitive to male depression; some CES-D items have been shown to
produce biased responses in comparisons of male and female respondents (27). Further
prospective studies using clinical interview or other sensitive measures to detect depression
both in men and women are therefore needed.

Our study highlights the importance of specific dietary components in the AHEI-DepS
association. We found that, in women, vegetables, fruits, trans fat and an elevated ratio of
PUFA/SatF were independently associated with reduced odds of recurrent DepS over 5 years.
Our study also showed that maintaining or improving the scores for these components over
adult life was associated with recurrent DepS. Be it the high amounts of folate and other
vitamin B and antioxidants provided by vegetables and fruits or the vascular protective and
anti-inflammatory properties of the PUFA (conversely to trans fat properties) they all prove compatible with the hypothesis of a long-term beneficial impact of adherence to AHEI to prevent DepS (On-line supplemental table S1). By showing that the AHEI-DepS association was not completely generated by any individual AHEI components, our study suggest that the effects are likely to be due to the cumulative and synergic effect of nutrients from different sources of foods rather than from the effect of single nutrient. However, at this stage, further investigations are needed to identify the potential underlying mechanisms by which overall diet may act on depression processes.

Limitations of the present findings include, first, the use of the CES-D scale to assess DepS. Even if CES-D scale has been shown to be a reliable and valid measurement tool indicating the presence of DepS (28), the two repeated measurements of CES-D did not capture the severity or the chronicity of DepS. We sought to take into account this limitation by considering recurrent DepS defined as participants who met the CES-D criteria at two consecutive measurements. However, our results, which are based on DepS, cannot be extended to major depression. Second, our study was limited by the assessment of dietary intake. We used a semi-quantitative FFQ that only covers specific foods and is recognized to be less precise than dietary assessment by diary records. However, we have shown previously that nutrient intake estimated by the FFQ method is well correlated with biomarker concentrations and with intake estimates from the generally more accurate 7-d diary in this (17). Third, the extent to which our results are generalizable is an important consideration. Whitehall II study participants are mainly white, office-based civil servants and not fully representative of British general population(15). Finally, even with the prospective design, the possibility remains that low AHEI score could be the consequence, rather than the cause, of DepS. Actually, participants who self-reported CES-D DepS at phases 7 and 9 may already have been depressed before phase 7 and then adopted a less healthy diet. By showing that adherence of AHEI at phase 3 (10 years before the assessment of CES-D DepS) was
associated with DepS assessed at phase 7, this makes this possibility, as sole explanation for
our findings, unlikely.

In conclusion, our report provides evidence of an association between adherence to healthy
recommendations as provided by the AHEI and lower risk of recurrent DepS assessed over
five years in women but not men. By showing that long term adherence to AHEI over adult
life was associated with lower odds of DepS in the late middle-aged, the present study is
unique in expanding the evidence on temporality of the diet-DepS association. Our findings
suggest that at least in women existing healthy eating policies might generate additional
benefits for depression.
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Authors’ contributions

TNA, SS, MJS, GDB, and MK developed the research question; TNA and MK conducted research; TNA analyzed the data; TNA and MK drafted the manuscript; and SS, MJS, GDB, MK made a critical revisions of the manuscript for important intellectual content. TNA has primary responsibility for final content.
REFERENCES


Table 1: Characteristics of participants without a history of prior depression according to depressive symptoms (DepS)* over 5 years follow-up (N=4215)

<table>
<thead>
<tr>
<th>Characteristics at Phase 7</th>
<th>Recurrent DepS* over 5 years of follow-up</th>
<th>Men (n=3155)</th>
<th>Women (n=1060)</th>
<th>p-value*</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>No</td>
<td>Yes</td>
<td>% or mean±SD</td>
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<td>Socio-demographic factors</td>
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<tr>
<td>Age (years)</td>
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<td>Health behaviors factors</td>
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<td>Smoking habits (current smokers)</td>
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<td>10.4</td>
<td>0.09</td>
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</tr>
<tr>
<td>HDL-C (mmol/l)</td>
<td></td>
<td>1.49±0.39</td>
<td>1.45±0.38</td>
<td>0.23</td>
</tr>
<tr>
<td>Use of lipids lowering drugs (yes)</td>
<td></td>
<td>11.6</td>
<td>14.6</td>
<td>0.24</td>
</tr>
<tr>
<td>Cognitive impairment (yes)</td>
<td></td>
<td>10.9</td>
<td>18.9</td>
<td>0.001</td>
</tr>
</tbody>
</table>
Abbreviations: AHEI Alternative Healthy Eating Index; CHD, coronary heart disease; DepS, depressive symptoms; HDL-C, High-density lipoprotein cholesterol; SES, socioeconomic status.

1 "Recurrent DepS" were defined as having DepS at both phases 7 and 9 and were compared to “No recurrent DepS” defined by the absence of DepS at both phases 7 or having DepS only once out of the two phases (with DepS defined as having CES-D score ≥16 or using anti-depressive drugs).

2 Characteristics of participants included socio-demographic variables consist of sex, age (years), skin color (White/ South Asian/ Black) living alone (no vs. yes), socio-economic status (SES)(low/intermediate /high) and retirement status (yes/no). Health behaviors considered were smoking habits (never/former/current) and physical activity (inactive/moderately active/active). Physical activity was assessed by a questionnaire including 20 items on frequency and duration of participation in different physical activities (e.g., walking, cycling, and sports) that were used to compute hours per week at each intensity level. Participants were classified as ‘active’ (> 2.5 hours per week of moderate physical activity or >1 hour per week of vigorous physical activity), ‘inactive’ (< 1 hour per week of moderate physical activity and <1 hour per week of vigorous physical activity), or ‘moderately active’ (if neither active nor inactive) (21). Baseline health status was based on coronary Heart Disease (CHD) (clinically verified non-fatal myocardial infarction or definite angina); hypertension (systolic or diastolic blood pressure ≥ 140 or ≥ 90 mm Hg respectively or use of antihypertensive drugs); high density lipoprotein (HDL) cholesterol, use of lipid-

<table>
<thead>
<tr>
<th>AHEI scores (points)</th>
<th>At phase 7</th>
<th>50.5±11.9</th>
<th>50.0±14.1</th>
<th>0.66</th>
<th>54.6±12.6</th>
<th>49.0±11.9</th>
<th>&lt;0.001</th>
</tr>
</thead>
<tbody>
<tr>
<td>At phase 3</td>
<td>49.68±11.5</td>
<td>49.3±12.2</td>
<td>0.75</td>
<td>53.9±12.9</td>
<td>51.4±12.6</td>
<td>0.06</td>
<td></td>
</tr>
<tr>
<td>Absolute 10-y change</td>
<td>0.90±10.9</td>
<td>0.60±12.2</td>
<td>0.77</td>
<td>-0.75±11.3</td>
<td>-3.0±9.7</td>
<td>0.002</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
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<th>50.0±14.1</th>
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<td></td>
</tr>
</tbody>
</table>
lowering drugs, central obesity (waist circumference >102 cm in men and >88 cm in women); and cognitive impairment defined by a score ≤27 in the Mini Mental State Examination (MMSE) (22). Except for HDL-cholesterol (mmol/L) all other health status covariates were dichotomized as yes/no.

*Chi-squared test for categorical variables and ANOVA for quantitative variables were used to compare characteristics according to recurrent, non-recurrent and no DepS.
Table 2: Odds ratios (OR) and 95% confidence intervals (CI) for the association between AHEI score at phase 7 and subsequent recurrent depressive symptoms (DepS) over 5 years of follow-up in men and women.

<table>
<thead>
<tr>
<th>AHEI at Phase 7</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Model 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tertile 1</td>
<td>1</td>
<td>ref</td>
</tr>
<tr>
<td>Tertile 2</td>
<td>0.80</td>
<td>0.54, 1.19</td>
</tr>
<tr>
<td>Tertile 3</td>
<td>0.85</td>
<td>0.57, 1.26</td>
</tr>
<tr>
<td>AHEI z-score</td>
<td>0.89</td>
<td>0.75, 1.05</td>
</tr>
<tr>
<td>Model 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tertile 1</td>
<td>1</td>
<td>ref</td>
</tr>
<tr>
<td>Tertile 2</td>
<td>0.89</td>
<td>0.59, 1.32</td>
</tr>
<tr>
<td>Tertile 3</td>
<td>0.95</td>
<td>0.64, 1.42</td>
</tr>
<tr>
<td>AHEI z-score</td>
<td>0.95</td>
<td>0.80, 1.13</td>
</tr>
</tbody>
</table>
AHEI: Alternative Healthy Eating Index; OR odds ratio; 95% CI Confident interval at 95 %

1 A significant interaction was found with sex (p=0.004), leading us to conduct analyses separately in men and women.

2 Results of logistic regression estimating odds of recurrent DepS according to AHEI tertiles and by one SD of total AHEI score (12 points). Tertile 1: median=39.5, range [10.5-45.5], (35.2 % of men, 24.9 % of women); Tertile 2: median=51.5, range [46.5-56.5], (33.7 % of men, 31.2 % of women); Tertile 3: median=63.5, range [57.5-87.5], (31.1 % of men, 43.9 % of women).

Model 1: Adjusted for age, sex, ethnicity and total energy intake at phase 7.

Model 2: Model 1 + additionally adjusted for SES, retirement, living alone, smoking, physical activity, coronary heart disease, type 2 diabetes, hypertension, HDL-cholesterol, use of lipid-lowering drugs, central obesity, cognitive impairment assessed at phase 7.

* In men, p for trend was 0.41 in Model 1 and 0.81 in Model 2. In women, p for trend was <0.001 in Model 1 and Model 2
Table 3: Odds ratios (95% CI) for the association between 10-year change in AHEI score between phase 3 and phase 7 and the subsequent recurrent depressive symptoms (DepS) over 5 years of follow-up in women

<table>
<thead>
<tr>
<th>10-y change category in AHEI</th>
<th>n</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Model 1 (n=1024)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maintaining a high AHEI score (Phases 3&amp;7 scores≥51.5) vs. low score (Phase 7 and Phase 3 scores&lt;51.5)</td>
<td>477</td>
<td>0.32</td>
<td>0.18, 0.57</td>
<td><strong>0.001</strong></td>
</tr>
<tr>
<td>Improving AHEI score (Phase 3 score&lt;51.5 and Phase 7 score≥51.5) vs. maintaining low score</td>
<td>148</td>
<td>0.40</td>
<td>0.18, 0.87</td>
<td>0.02</td>
</tr>
<tr>
<td>Decreasing AHEI score (Phase 3 score≥51.5 and Phase 7 score&lt;51.5) vs. maintaining high score</td>
<td>148</td>
<td>2.34</td>
<td>1.24, 4.42</td>
<td><strong>0.009</strong></td>
</tr>
<tr>
<td><strong>Model 2 (n=968)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maintaining a high AHEI score (Phases 3&amp;7 scores≥51.5) vs. low score (Phase 7 and Phase 3 scores&lt;51.5)</td>
<td>449</td>
<td>0.35</td>
<td>0.19, 0.64</td>
<td><strong>&lt;0.001</strong></td>
</tr>
<tr>
<td>Improving AHEI score (Phase 3 score&lt;51.5 and Phase 7 score≥51.5) vs. maintaining low score</td>
<td>142</td>
<td>0.32</td>
<td>0.13, 0.78</td>
<td><strong>0.01</strong></td>
</tr>
<tr>
<td>Decreasing AHEI score (Phase 3 score≥51.5 and Phase 7 score&lt;51.5) vs. maintaining high score</td>
<td>144</td>
<td>2.15</td>
<td>1.09, 4.22</td>
<td><strong>0.03</strong></td>
</tr>
</tbody>
</table>

AHEI: Alternative Healthy Eating Index; OR: odds ratio; 95% CI: Confident interval at 95 %.
SD: standard deviation

1 Results of logistic regression estimating odds of recurrent DepS according to the 10-y change in AHEI score.
To analyze the 10-y change in AHEI score, scores of AHEI at phases 3 and 7 were categorized as high or low according to the median value of AHEI score at phase 3 equal to 51.5 points.

Four categories in 10-y change of AHEI were then defined: participants who maintained a high score (Phase 3 and 7 scores ≥ 51.5), those who maintained a low score over the 10-y exposure period (Phase 3 and 7 scores < 51.5), participants who improved their AHEI score (Phase 3 score < 51.5 and Phase 7 score ≥ 51.5) and those who decreased their score (Phase 3 score ≥ 51.5 points and Phase 7 score< 51.5 points).

Model 1: Adjusted for age, ethnicity and total energy intake at phase 3.

Model 2: Model 1 + additionally adjusted for SES, retirement, marital status, smoking, physical activity, hypertension, HDL-cholesterol and central obesity at phase 3.
FIGURE LEGENDS

Figure 1: Derivation of the analytical sample

Figure 1 footnote:
Compared to participants excluded from the present analytic sample (n=2728), those included (n=4215) were more likely to be men, white, younger, with high socio-economic status (all p<0.001), and less likely to report recurrent depressive symptoms (p<0.001). Furthermore, higher mean total energy intake (p<0.001) and AHEI score (p<0.001) were observed in participants included compared to those excluded due to missing data on depressive symptoms or covariates.

Figure 2: Association between AHEI components scores assessed at phase 7 and onset of recurrent depressive symptoms over 5 years in women

Figure 2 footnote:
OR, Odds ratio for development of recurrent depression symptoms associated with an increase of 1 Standard deviation of AHEI components scores at phase 7.
Model 1 (M1): Adjusted for age, ethnicity and total energy intake at phase 7.
Model 2 (M2): M1 + additionally adjusted for SES, retirement status, marital status, smoking, physical activity, coronary heart disease, type 2 diabetes, hypertension, HDL-cholesterol, use of lipid-lowering drugs, central obesity, cognitive impairment assessed at phase 7.
Model 3 (M3): M2 + additionally adjusted for the 8 other AHEI component scores

Figure 3: Association between the change of AHEI components over the 10-y exposure period and subsequent recurrent depressive symptoms over five years in women.

Figure 3 footnote:
To analyse the 10-y change in AHEI component scores, the latter were categorized as high or low according to the median value of AHEI components scores at phase 3. The median values at phase 3 for AHEI components scores were respectively 6, 6, 3, 5, 10, 10, 5, 2.5, 5 for vegetable, fruits, nuts and Soy, ratio of white to red meat, fiber, trans fat, ratio of PUFA to saturated fat, multi-vitamin use and alcohol.

Four categories in 10-y change of AHEI components were then defined: participants who maintained a high AHEI score (Phase 3 and 7 scores ≥ median value at phase 3, i.e. 6 for vegetables), those who maintained a low score (Phase 3 and 7 scores < 6), participants who improved their AHEI score (Phase 3 score < 6 and Phase 7 score ≥ 6) and those who decreased their score (Phase 3 score ≥ 6 points and Phase 7 score < 6 points).

Odds of 5-y recurrent depressive symptoms were estimated for 1) participants who maintained a high AHEI score (compared to those who maintained a low score), 2) participants who improved their score (compared to those who maintained low score) and 3) participants who decreased their score (compared to those who maintained high score).

This procedure was applied to the 9 AHEI components.

Odds ratio were adjusted for age, ethnicity, total energy intake, SES, retirement status, marital status, smoking, physical activity, HDL-cholesterol, hypertension and central obesity assessed at phase 3.