

**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

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Glossary

AHEI: Alternative Healthy Eating Index

CES-D : Center for Epidemiologic Studies Depression Scal

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

1 ABSTRACT

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

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

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

12 **Results:** After adjustment for potential confounders, AHEI score was inversely associated
13 with recurrent depressive symptoms in a dose-response fashion in women (p for trend < 0.001 ;
14 for 1SD in AHEI score, OR: 0.59; 95% CI: 0.47, 0.75) but not in men. Women who
15 maintained high AHEI score or improved their score during the 10-year measurement period
16 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
17 of subsequent recurrent depressive symptoms compared to women who maintained low AHEI
18 score. Amongst the AHEI components, vegetable, fruit, trans-fat and ratio of polyunsaturated
19 fat vs. saturated fat components were associated with recurrent depressive symptoms in
20 women.

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

23

24

25

26 INTRODUCTION

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

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

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

49 However, the cross-sectional design of most of these studies (7-10) inevitably preclude any
50 conclusion as to the direction of the association (12-14). To understand if poor diet indeed

51 constitutes a risk factor for depression and not only the reverse, studies with longitudinal
52 design are needed.

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

61

62

63 MATERIAL AND PARTICIPANTS

64 **Study population**

65 Data were drawn from the Whitehall II Study, a large-scale, on-going, prospective cohort
66 study of 10308 (3413 women) UK civil servants (government employees) aged 35 to 55 years
67 at study induction (15). The baseline examination (phase 1) took place during 1985-1988 and
68 involved a clinical examination and self-administered questionnaire. Subsequent phases of
69 data collection have alternated between postal questionnaire alone (phases 2 (1988-1990), 4
70 (1995-1996), 6 (2001), and 8 (2006)), and postal questionnaire accompanied by a clinical
71 examination (phase 3 (1991–1993), n=8104; phase 5 (1997–1999), n=7263; phase 7 (2003–
72 2004), n=6943, and phase 9 (2008-2009), n=6354). After describing the study to the
73 participants, written informed consent was obtained; the University College London ethics
74 committee approved the study.

75 After excluding those on antidepressant treatment at phase 3 or phase 5, analyses were
76 restricted to participants with dietary assessment and covariates at phase 7 and complete data
77 on depressive symptoms at phases 7 and 9, resulting in a total of 4215 participants. Amongst
78 them, 4053 participants had complete data on the 10-y change in AHEI between phases 3 and
79 7 (Figure 1).

80

81 **Data Collection**

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

83 Dietary intake at phases 3 and 7 was assessed using a semi-quantitative food-frequency
84 questionnaire (FFQ) with 127 food items, as described previously (16, 17). The validity and
85 the reliability of the FFQ in terms of nutrient and food consumption have been documented in
86 detail both in our cohort and others(17, 18). The AHEI score (19) was created (On-line
87 supplemental table S1) by summing its 9 component scores (1: fruit, 2: vegetable, 3: ratio of
88 white meat (seafood and poultry) to red meat, 4: trans fat, 5: ratio of PUFA to saturated fat

89 (SatF), 6: total fiber, 7: nuts and soy, 8: alcohol consumption and 9: long-term multivitamin
90 use). Higher values corresponded to a healthier diet. At phase 3, the mean score of AHEI was
91 50.6 ± 11.9 points at phase 3 and 51.4 ± 12.3 at phase 7. The Pearson correlation coefficient
92 between AHEI score at phase 3 and phase 7 was 0.59, p-value $<10^{-4}$.

93

94 *DepS at phases 7 and 9*

95 Depressive symptoms (DepS) were assessed using the Center for Epidemiologic Studies
96 Depression Scale(20) first introduced at phase 7. At both phases 7 and 9, DepS was defined
97 by Center for Epidemiologic Studies Depression Scale score of 16 or higher(20), self-reported
98 use of antidepressant medications, or both. After excluding participants under antidepressant
99 treatments before phase 7, “recurrent DepS” cases were defined as having DepS at both phase
100 7 and phase 9; “No recurrent DepS” was defined by the absence of DepS at phase 7 or /and at
101 phase 9.

102

103 *Covariates assessed at phases 3 and 7*

104 Socio-demographic variables included sex, age (years), ethnicity (White/ South Asian/
105 Black), living alone (yes/no), a 3-level measure of socioeconomic status (SES)
106 (low/intermediate /high) related to salary, social status and level of responsibility, and
107 retirement status (yes/no). Health behaviors were smoking habits (never/former/current), total
108 energy intake (kcal per day), and physical activity assessed by a questionnaire, that included
109 20 items on frequency and duration of participation in different activities of different intensity
110 (e.g., walking, cycling, and sports). Participants were classified as ‘active’ (>2.5 hours per
111 week of moderate physical activity or >1 hour per week of vigorous physical activity),
112 ‘inactive’ (<1 hour per week of moderate physical activity and <1 hour per week of vigorous
113 physical activity), or ‘moderately active’ (neither active nor inactive) (21). Health status
114 covariates included prevalent coronary heart disease (CHD) - (denoted by clinically verified

115 non-fatal myocardial infarction or definite angina); hypertension (defined by systolic or
116 diastolic blood pressure ≥ 140 or ≥ 90 mm Hg, respectively, or use of antihypertensive drugs);
117 serum high density lipoprotein (HDL) cholesterol measured in mmol/L, use of lipid-lowering
118 drugs, central obesity (waist circumference >102 cm in men and >88 cm in women), and
119 cognitive impairment (≤ 27 score on the Mini Mental State Examination (MMSE)) (22).

120 Except for HDL-cholesterol, all the health status covariates were dichotomized as yes/no

121

122 **Statistical Analysis**

123 Characteristics of men and women according to the recurrent DepS were compared using the
124 Chi-squared test for categorical covariates and ANOVA for continuous covariates. Logistic
125 regression analyses were used to compute odds ratios (OR) with 95% confidence intervals
126 (95%CI) to assess the association between AHEI score at phase 7 and recurrent DepS. AHEI
127 score was first categorized into tertiles (lowest tertile as the reference) to assess whether
128 AHEI score was linearly associated with DepS. We then derived a continuous standardized
129 variable (z-score; mean=0, standard deviation (SD) =1) to compute the odds ratio for
130 recurrent DepS per 1 SD increment in dietary score.

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

139 Similar logistic regression models were performed to estimate the association of each AHEI
140 component z-scores with recurrent DepS. To assess whether the AHEI component- recurrent

141 DepS association was independent of other components, a third model was also computed
142 which incorporated all other AHEI components in addition to potential confounders (Model
143 3). Further analyses were performed to examine the contribution of AHEI components to the
144 association between AHEI and DepS. For each component (component i), we computed a
145 modified AHEI score based on the total AHEI score without the component i (modified AHEI
146 score $i = \text{Total AHEI score} - \text{score of the component } i$).

147 To analyze the 10-y change in AHEI score, scores of AHEI at phases 3 and 7 were
148 categorized as high or low according to the median value of AHEI score at phase 3 equal to
149 51.5 points. Four categories in 10-y change of AHEI were then defined: participants who
150 maintained a high score (Phase 3 and 7 scores ≥ 51.5), those who maintained a low score over
151 the 10-y exposure period (Phase 3 and 7 scores < 51.5), participants who improved their AHEI
152 score (Phase 3 score < 51.5 and Phase 7 score ≥ 51.5) and those who decreased their score
153 (Phase 3 score ≥ 51.5 points and Phase 7 score < 51.5 points). Similar procedures were applied
154 to categorize the 10-y change in AHEI components. Median values at phase 3 for AHEI
155 components were : [6] for vegetable, [6] for fruits, [3] for nuts and Soy, [5] for the ratio of
156 white to red meat, [10] for fiber, [10] for trans Fat, [5] for the ratio of PUFA to saturated fat,
157 [2.5] for multi-vitamin use and [5] alcohol. Similar adjustments as in Models 1 and 2
158 described above were made, but including in the models covariates assessed at phase 3. Some
159 covariates were not included: prevalent CHD and lipid lowering drugs (due to small number
160 of cases in stratified analyses) and cognitive impairment (as not assessed at phase 3).

161 We also examined if the diet-DepS association was mediated by CHD. To do so, similar
162 analyses were repeated after excluding CHD cases. Three other sets of analyses were
163 performed to assess the direction of the diet-DepS relationship. First we examined the
164 association between the AHEI score at phase 3 and subsequent recurrent DepS assessed 10-y
165 later (phases 7 and 9) after adjustment for potential confounders assessed at phase 3. Second,
166 the main analyses were repeated after excluding participants who met the definition for

167 General Health Questionnaire “depression” (GHQ-Dep) at phase 3 - based on the 4-item
168 General Health Questionnaire depression subscale (23). We also performed linear regression
169 models estimating the linear regression coefficient (Beta and its standard error (SE)) of diet
170 score to assess whether the GHQ-Dep cases at phase 3 showed significant differences in
171 subsequent AHEI score assessed at phase 7 or in the 10-y change in AHEI score between
172 phase 3 and phase 7 compared to GHQ-Dep non-cases.

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

175

176

177 RESULTS

178 *Participant characteristics*

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

184

185 *AHEI score at phase 7 and 5-year DepS*

186 The associations between AHEI at phase 7 and recurrent DepS are presented in Table 2.
187 Irrespective of adjustments, analyses in which AHEI were categorized in tertiles showed that
188 this measure of dietary quality was associated with recurrent DepS in a dose-response fashion
189 in women (p for trend <0.001) but not in men (p for trend =0.81), (**p-value for the sex
190 interaction=0.004**). In women, each 1 SD increase (12 points) in AHEI score was associated
191 with a 40% lower odds of recurrent DepS (OR=**0.59**, 95 % CI: 0.47, 0.75, **p<0.001**) after
192 adjustment for potential confounders. In men, such relationship was not found (Table 2).
193 Further analyses were performed in women to identify which of the AHEI components
194 contributed most to the reduce odds of DepS. As shown in Figure 2, high consumption of
195 vegetable and fruits, high intake of fiber, elevated PUFA/SatF ratio, and low intake of trans
196 fat were all associated with lower odds of recurrent DepS after adjustment for potential
197 confounders (Figure 2, Model 2). Of these AHEI components, only vegetable, fruit and trans
198 fat components revealed independent effects (Figure 2, Model 3). In addition, when AHEI
199 was computed without each of AHEI components, the modified AHEI-recurrent DepS
200 association remained statistically significant suggesting that no single AHEI component was
201 responsible for generating the total AHEI-DepS association (results not shown). **In men None**

202 of the AHEI components were found to be significantly associated with recurrent DepS after
203 adjustment for potential confounders (On-line supplemental Figure S1).

204

205 *10-year change in AHEI score and subsequent 5-year DepS*

206 Table 3 show that women who maintained a high score of AHEI (≥ 51.5 points at
207 phases 3 and 7) as well as those who improved their AHEI score (Phase 3 score < 51.5 and
208 Phase 7 score ≥ 51.5 points) over the 10-y measurement period had a 65 % (OR:0.35; 95% CI:
209 0.19, 0.64) and 68 % (OR:0.32; 95% CI:0.13, 0.18) lower odds of subsequent recurrent DepS
210 compared to participants who maintained a low AHEI score at both phases 3 and 7
211 (scores < 51.5 points). Women whose AHEI score decreased over time (Phase 3 score ≥ 51.5
212 and Phase 7 score < 51.5 points) had 2-fold increased odds of developing subsequent recurrent
213 DepS compared to women who maintained high AHEI score over the 10-y exposure period
214 (OR: 2.15; 95%CI: 1.09, 4.22). In men, no evidence of an association between the 10-y
215 change in total AHEI score and subsequent recurrent DepS was observed (On-line
216 supplemental table S2).

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

228

229 *Sensitivity analyses*

230 With an association only observed in women, sensitivity analyses were confined to
231 this group. First, in a subgroup excluding women with prevalent CHD (n=55), both AHEI at
232 phase 7 and the 10-y change in AHEI remained significantly associated with recurrent DepS
233 (AHEI z-score at phase 7: OR: 0.56; 95% CI: 0.43, 0.73; z-score of the 10-y change: OR:
234 0.75; 95% CI: 0.59, 0.96). This suggests that the association was not driven by the effects of
235 CHD on diet and DepS. Second, the association between AHEI score assessed at phase 3 and
236 recurrent DepS 10 years later was examined. We found that after adjustment for socio-
237 demographic, health behavior, hypertension, HDL-cholesterol and central obesity assessed at
238 phase 3, adherence to AHEI at phase 3 among participants who were not taking
239 antidepressant treatment at phases 3 was associated with lower odds of developing recurrent
240 DepS 10 years later (per 1 SD of AHEI score at phase 3, OR: 0.77; 95% CI: 0.60, 0.97).
241 Third, while participants treated with antidepressive drugs before phase 7 were already
242 excluded from the present analyses, we conducted further sensitivity analyses to explore the
243 effects of existing mental health problems on dietary intake (reverse causality). Thus,
244 supplementary analysis in which women who met the definition for GHQ-Depression,
245 (n=134) and those with missing values on GHQ-Depression (n=35) at phase 3 were
246 additionally excluded. Similar trends between AHEI score at phase 7 (OR: 0.57 ; 95% CI:
247 0.42, 0.78), 10-y change in AHEI score (OR: 0.77; 95% CI: 0.58, 1.03, p=0.075) and
248 subsequent recurrent DepS were found in this subsample of 891 women. Fourth, an additional
249 test to assess the direction of the association included the 1494 women for whom data on
250 GHQ-Depression at phase3, use of antidepressive drugs, AHEI score at phases 3 and 7 were
251 available. Results from linear regression models provided no evidence of differences between
252 GHQ cases (n=230) and GHQ non-cases (n=1264) in subsequent AHEI score assessed at
253 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.**

256 DISCUSSION

257 This study sought to examine the longitudinal association between overall diet and the
258 development of recurrent DepS. To do so, the association between adherence to the AHEI, its
259 10-year change and recurrent DepS at two consecutive follow-ups over 5 years was examined.
260 We found that that adherence to healthy dietary recommendations such as those provided by
261 the AHEI reduced the likelihood of developing recurrent DepS, in women but not in men.
262 These effects were independent of socio-demographic, behavioral, metabolic and health status
263 factors such as cognitive performance and vascular diseases. Those women who maintained
264 or improved their AHEI score over the 10-y measurement period had 65 % lower odds of
265 subsequent recurrent DepS compared to those who maintained low AHEI scores, while
266 women whose AHEI score decreased had twice the odds of recurrent DepS. These
267 prospective results add to the modest evidence base concerning the temporality of the diet-
268 DepS association in middle-aged people.

269 The prospective association between adherence in AHEI and lower risk of recurrent DepS
270 reported here accords with the results of studies that have investigated the cross-sectional
271 relationship between overall diet and depression in adults (7-11), including the present study
272 (4). One type of those studies assessed diet using dietary patterns (4, 7, 8, 10). Across diverse
273 samples there is a suggestion that patterns characterizing healthier eating behavior were
274 inversely associated with DepS. Because dietary patterns are derived through statistical
275 modeling of dietary data without *a priori* hypothesis, dietary patterns closely matched those
276 of the population samples considered but not necessarily those of other populations. Another
277 group of studies assessed overall diet by building dietary indices based on dietary
278 recommendations (7-9, 11) such as the AHEI as used herein. Poor adherence to several
279 healthy dietary recommendations, including the HEI-2005 (24) and the Diet Quality Score (7)
280 has been associated with depressive symptoms in cross-sectional data (7, 9). Only one study
281 additionally assessed the temporal direction of the diet-depression association. Investigators

282 on a large Spanish cohort study showed, consistent with our findings, that a high
283 Mediterranean Diet (Med-Diet) score was associated with a 30 % reduced risk of self-reported
284 depression (11). The Med-Diet index shares several components with AHEI, but in contrast to
285 the AHEI, the thresholds used for computing the Med-Diet score are defined according to the
286 median of the food /nutrient intakes in the specific population studied. Even though the Med-
287 Diet score has been associated with improvements in health (25, 26), the use of a dietary
288 index with population-specific cut-points may be problematic for quantitative diet
289 recommendations and for comparisons of results between Mediterranean and non-
290 Mediterranean countries.

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

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

302 Our study highlights the importance of specific dietary components in the AHEI-DepS
303 association. We found that, in women, vegetables, fruits, trans fat and an elevated ratio of
304 PUFA/SatF were independently associated with reduced odds of recurrent DepS over 5 years.

305 Our study also showed that maintaining or improving the scores for these components over
306 adult life was associated with recurrent DepS. Be it the high amounts of folate and other
307 vitamin B and antioxidants provided by vegetables and fruits or the vascular protective and

308 anti-inflammatory properties of the PUFA (conversely to trans fat properties) they all prove
309 compatible with the hypothesis of a long-term beneficial impact of adherence to AHEI to
310 prevent DepS (On-line supplemental table S1). By showing that the AHEI-DepS association
311 was not completely generated by any individual AHEI components, our study suggest that the
312 effects are likely to be due to the cumulative and synergic effect of nutrients from different
313 sources of foods rather than from the effect of single nutrient. However, at this stage, further
314 investigations are needed to identify the potential underlying mechanisms by which overall
315 diet may act on depression processes.

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

334 associated with DepS assessed at phase 7, this makes this possibility, as sole explanation for
335 our findings, unlikely.

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

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350

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352

353 Authors' contributions

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

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

Characteristics at Phase 7 ²	Recurrent DepS ¹ over 5 years of follow-up					
	Men (n=3155)			Women (n=1060)		
	No	Yes	p- value‡	No	Yes	p-value*
	2991	(164)		(964)	(96)	
% or mean±SD	% or mean±SD		% or mean±SD	% or mean±SD D		
Socio-demographic factors						
Age (years)	61.0 ± 5.9	59.7± 5.8	0.01	61.0±5.91	60.8±6.2	0.77
Ethnicity, (White)	96.7	89.0	<0.001	93.1	86.5	<0.001
SES (low)	2.3	6.7	<0.001	22.8	28.1	0.02
Retired (yes)	51.1	48.8	0.56	54.7	57.3	0.62
Living alone (yes)	15.4	26.2	<0.001	39.7	52.1	0.02
Health behaviors factors						
Smoking habits (current smokers)	6.1	10.4	0.09	8.6	11.5	0.40
Physical activity (low)	20.7	32.9	<0.001	26.8	38.5	0.03
Total Energy intake (kcal/day)	2258±634	2340±788	0.19	1996±594	2121±732	0.11
Health status factors						
Type 2 Diabetes (yes)	8.3	11.0	0.23	9.1	10.4	0.68
Central obesity (yes)	22.2	29.3	0.03	43.9	46.9	0.57
History of CHD (yes)	7.0	10.4	0.11	4.7	10.4	0.01
Hypertension (yes)	35.7	39.0	0.33	36.4	37.5	0.83
HDL-C (mmol/l)	1.49±0.39	1.45±0.38	0.23	1.86±0.48	1.72±0.46	0.009
Use of lipids lowering drugs (yes)	11.6	14.6	0.24	9.1	10.4	0.68
Cognitive impairment (yes)	10.9	18.9	0.001	12.7	18.7	0.09

AHEI scores (points)						
At phase 7	50.5±11.9	50.0±14.1	0.66	54.6±12.6	49.0±11.9	<0.001
At phase 3	49.68±11.5	49.3±12.2	0.75	53.9±12.9	51.4±12.6	0.06
Absolute 10-y change	0.90±10.9	0.60±12.2	0.77	-0.75±11.3	-3.0±9.7	0.002

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’ (> 2.5hours 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’ (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-

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 women¹.

AHEI at Phase 7 ²	Men			Women		
	OR	95% CI	<i>P value</i>	OR	95% CI	<i>P value</i>
Model 1						
Tertile 1	1	ref		1	ref	
Tertile 2	0.80	0.54, 1.19	0.28*	0.56	0.33, 0.94	0.02*
Tertile 3	0.85	0.57, 1.26	0.42*	0.31	0.18, 0.54	<0.001*
AHEI z-score	0.89	0.75, 1.05	0.18	0.56	0.44, 0.70	<0.001
Model 2						
Tertile 1	1	ref		1	ref	
Tertile 2	0.89	0.59, 1.32	0.55*	0.61	0.35, 1.04	0.07*
Tertile 3	0.95	0.64, 1.42	0.81*	0.36	0.20, 0.64	<0.001*
AHEI z-score	0.95	0.80, 1.13	0.57	0.59	0.47, 0.75	<0.001

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

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

²Results 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 women¹

10-y change category in AHEI ²	n	OR	95% CI	P
Model 1 (n=1024)				
Maintaining a high AHEI score (Phases 3&7 scores \geq 51.5)	477	0.32	0.18, 0.57	<i>0.001</i>
vs. low score (Phase 7 and Phase 3 scores $<$ 51.5)	251	1	ref	
Improving AHEI score (Phase 3 score $<$ 51.5 and Phase 7 score \geq 51.5)	148	0.40	0.18, 0.87	<i>0.02</i>
vs. maintaining low score	251	1	ref	
Decreasing AHEI score (Phase 3 score \geq 51.5 and Phase 7 score $<$ 51.5)	148	2.34	1.24, 4.42	<i>0.009</i>
vs. maintaining high score	477	1	ref	
Model 2 (n=968)				
Maintaining a high AHEI score (Phases 3&7 scores \geq 51.5)	449	0.35	0.19, 0.64	<i><0.001</i>
vs. low score (Phase 7 and Phase 3 scores $<$ 51.5)	233	1	ref	
Improving AHEI score (Phase 3 score $<$ 51.5 and Phase 7 score \geq 51.5)	142	0.32	0.13, 0.78	<i>0.01</i>
vs. maintaining low score	233	1	ref	
Decreasing AHEI score (Phase 3 score \geq 51.5 and Phase 7 score $<$ 51.5)	144	2.15	1.09, 4.22	<i>0.03</i>
vs. maintaining high score	449	1	ref	

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

SD: standard deviation

¹Results 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.

²Four 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 \geq 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 \geq 6) and those who decreased their score (Phase 3 score \geq 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.