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# Associations between an energy-adjusted inflammatory diet index and incident depression: a cohort study

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## Abstract

Growing evidence indicates a link between diet and depression risk. We aimed to examine the association between an inflammatory diet index and depression utilising extensive data from UK biobank cohort. The energy-adjusted dietary inflammation index (E-DII) was calculated to quantify the potential of daily diet, with twenty-seven food parameters utilised. The E-DII scores were classified into two categories (low *v.* high) based on median value. To mitigate bias and ensure comparability of participant characteristics, propensity score matching was employed. To ascertain the robustness of these associations, sensitivity analyses were conducted. Subgroup analyses were performed to evaluate the consistency of these associations within different subpopulations. Totally, 152 853 participants entered the primary analyses with a mean age of 56·11 (SD 7·98) years. Employing both univariate and multivariate logistic regression models, adjustments were made for varying degrees of confounding factors (socio-demographics, lifestyle factors, common chronic medical conditions including type 2 diabetes and hypertension). Results consistently revealed a noteworthy positive correlation between E-DII and depression. In the context of propensity score matching, participants displaying higher E-DII scores exhibited an increased likelihood of experiencing incident depression (OR = 1·12, 95 % CI: 1·05, 1·19; $P = 0·000316$). Subgroup analysis results demonstrated variations in these associations across diverse subpopulations. The E-value for the point-estimate OR calculated from the propensity score matching dataset was 1·48. Excluding individuals diagnosed with type 2 diabetes or hypertension, the findings consistently aligned with the positive association in the primary analysis. These findings suggested that consumption of a diet with higher pro-inflammatory potential might associated with an increase of future depression risk.

**Keywords:** **Energy-adjusted inflammatory diet index: Incident depression: Prospective study: UK biobank**

Depression, characterised by the recurrence and chronicity of impaired mood, anhedonia, ruminative thoughts and compromised cognition, stands as a prevalent psychiatric concern[1].

Among the top ten disabling diseases worldwide, depression causes the most losses due to disability and leads the global disease burden list[2]. It profoundly impacts an individual's social and psychological functioning, diminishing their quality of life and imposing notable health and economic burdens. Moreover, depression may increase the risk for various other health issues, such as diabetes and CVD. Significantly, it has also been associated with an elevated risk of mortality[3,4]. The pathophysiological mechanisms of depression are complex and await comprehensive elucidation[5]. Over the past decades, accumulating evidence indicating a correlation between diet and depression[6]. The emergence of depression is frequently accompanied by changes in the inflammatory state[7,8]. Inflammation probably plays a crucial role in modifying diseases, making individuals more prone to developing depression[9]. Furthermore, numerous studies have underscored the pivotal impact of dietary choices on the emergence of chronic inflammation[2,10–12].The diet incorporates

**Abbreviations:** DII, dietary inflammation index; E-DII, energy-adjusted dietary inflammatory index; SMD, standardised mean difference.

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various bioactive components exhibiting either pro- or anti-inflammatory attributes, and increasing evidence suggests an association between dietary inflammatory potential and the manifestation of depression symptoms[12–18].

Diets have the potential to induce either pro-inflammatory or anti-inflammatory effects, determined by the hormonal responses they generate[19]. The dietary inflammation index (DII) was developed as a tool to quantify the inflammatory potential of an individual's diet. Derived from the literature, the DII is a population-based diet quality index that considers the positive or negative effects of forty-five different dietary factors on the serum concentrations of six inflammatory biomarkers[20,21]. Through a series of calculations involving a spectrum of nutrients, the DII offers a comprehensive assessment of inflammation within daily diets[22]. A higher DII score indicates a greater dietary inflammatory potential. The DII has been validated in multiple studies using a variety of inflammatory markers[23–25]. Energy-adjusted dietary inflammation index (E-DII) takes into account an individual's total energy intake and serves as a refined adaptation of the DII[26]. This adjustment enables a more accurate assessment of the inherent inflammatory attributes of the diet. Theoretically, positive DII/E-DII scores indicate food patterns with the most pro-inflammatory potential, whereas negative DII/E-DII values indicate food patterns with the most anti-inflammatory potential, and a higher DII/E-DII score signifies an increased pro-inflammatory potential of the diet.

To our knowledge, the majority of current studies examining the association between inflammatory diet and depression employ a cross-sectional design. This design limits the ability to draw causal inferences, especially when exploring the complex and likely bidirectional relationship between diet and depression. Furthermore, these studies often focus on depression symptoms rather than utilising clinically diagnosed depression as a study outcome. Additionally, they frequently feature small sample sizes, based on a single measurement, and use DII calculation without adjustment for total energy intake. In the present study, we aimed to address these research gaps by conducting a large cohort study with extended follow-up periods to evaluate the prospective association between E-DII and depression risk, utilising the UK Biobank database. We hypothesised that long-term adherence to a pro-inflammatory diet increases the risk of depression compared with adherence to a long-term anti-inflammatory diet. To assess and validate this association, we employed several statistical techniques and explored the potential existence of subpopulations within the study.

## Methods

### Data source

The UK Biobank is a large-scale prospective cohort study, with more than half a million UK participants recruited from 2006 to 2010 from twenty-two health centers. At recruitment, participants completed a detailed touch-screen questionnaire, had physical measurements taken and provided biological samples. More details about the UK Biobank can be found online (http://www.ukbiobank.ac.uk). The UK Biobank received ethical approval from the research ethics committee (11/NW/0382), and all participants signed informed consent. We applied for and were permitted to use UK Biobank data under study number 99709.

### Dietary measures

Dietary data were collected using the Oxford WebQ, a web-based 24-hour dietary assessment tool that gathers information on 206 types of foods and thirty-two types of drinks consumed during the preceding 24 h[27,28]. Participants were invited to complete the questionnaire at baseline and on four separate occasions (from the first instance conducted in the assessment centre (April 2009 to September 2010) to the last instance April 2012 to June 2012). The 24-hour recall questionnaire offers a cost-effective method for measuring dietary intake in large-scale prospective studies, with its reliability well validated in multiple studies. When compared with an interviewer-administered 24-hour recall completed on the same day, Spearman's correlation coefficients for the majority of nutrients calculated from the WebQ ranged between 0·5 and 0·9, with a mean of 0·6[27]. A recent validation study involving 160 participants in London, based on their blood and urine biomarkers, further supports the reliability of the Oxford WebQ[28]. This indicates that repeated use of the Oxford WebQ Online 24-Hour Dietary Questionnaire in large-scale projects such as the UK Biobank can yield high-quality dietary information.

For this study, we included participants who filled in a 24-hour dietary recall questionnaire at least once, and the mean intakes from the five 24-hour recalls were then used in the calculation of DDI. The original DII proposed by Shivappa *et al.* in 2014 included forty-five different dietary factors[20]. Briefly, the scoring algorithm obtained world standard reference values for the forty-five food parameters derived from a comprehensive review and weighted algorithm scoring of nearly 2000 articles on diet and inflammatory markers and eleven food consumption datasets from different countries[14]. This, combined with food parameter-specific inflammatory effect scores, creates an overall DII score for each individual[14]. Following the proposed scoring algorithm, the overall DII in this study was derived based on twenty-seven food or nutrient parameters available in the UK Biobank dataset. These were as follows: alcohol, vitamin $B_{12}$, vitamin $B_6$, beta-carotene, carbohydrate, cholesterol, total fat, fibre, Fe, Mg, MUFA, niacin, *n*-3 fatty acids, *n*-6 fatty acids, protein, riboflavin, SFA, Se, thiamin, trans-FA, vitamin A, vitamin C, vitamin D, vitamin E, Zn, tea and total energy. These twenty-seven food parameter-specific DII scores were summed to obtain the overall DII score. Furthermore, to control for the effect of total energy intake, the energy-adjusted DII (E-DII) scores were calculated by converting all food parameters to the amount of consumed food per 1000 kcal[26]. E-DII adjusts for total energy intake and demonstrates an enhanced predictive ability relative to that of original unadjusted DII[20,26]. The details of E-DII calculations have been described in several published studies[26,29,30]. Briefly, the calculation of the E-DII score involved using procedures identical to those employed in estimating the DII. An energy-adjusted global comparative database was utilised for this calculation. Due to energy's inclusion in the denominator, only twenty-six food parameters

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were used to calculate the E-DII scores. Similarly, higher E-DII scores signify food patterns with a greater pro-inflammatory potential, whereas lower (i.e. more negative) E-DII scores indicate food patterns with a higher anti-inflammatory potential. The E-DII score was used as a continuous variable and classified into two levels using the median value: (i) low E-DII (scores ≤ median) and (ii) high E-DII (scores > median).

### Outcome measures

All incident depression events were defined using the following the International Classification of Disease, 10th Revision codes: F32 (Depressive Episode), F33 (Recurrent Depressive Disorder), F34 (Persistent Mood (Affective) Disorders), F38 (Other Mood (Affective) Disorders) and F39 (Unspecified Mood (Affective) Disorder). These codes were extracted from the first occurrence dataset (Data Category: 1712) in the UK Biobank. This dataset indicates the initial occurrence of a set of diagnostic codes encompassing a broad spectrum of health outcomes, sourced from self-report, primary care, hospital inpatient data and mortality records. Further details can be found at: https://biobank.ndph.ox.ac.uk/ukb/label.cgi?id=2405.

### Covariates

The covariates for this study were selected based on a review of several published studies[15,31–33]. A wide range of factors were taken into account to mitigate the influence of potential confounding, including age at recruitment (years), sex (female or male), ethic (categorised as white and others), smoking status (never, previous, or current), alcohol status (never, previous or current), index of multiple deprivation (used as a proxy for socio-economic status) and education (categorised as high (college or university degree), intermediate (A/AS levels or equivalent, O levels/GCSEs or equivalent) and low (none of the aforementioned)). The multiple deprivation index scores were derived from a UK government qualitative study focusing on deprived areas within British local councils. These studies were conducted separately for England, Scotland and Wales. The scores were compiled from open data published by the UK government. For further information, please refer to the UK Biobank website. Additionally, physical activity was derived from the short-form International Physical Activity Questionnaire, and total physical activity was calculated as the total metabolic equivalent task minutes per week for all activity (divided into high, intermediate and low)[34]. Time spent on TV viewing was self-reported as the number of hours per day. BMI was calculated as weight (kg) divided by height (cm) squared. The history of diabetes and hypertension was determined based on the first-reported date in the first occurrence dataset and the date of attending the assessment center.

### Statistical analysis

Descriptive baseline characteristics by the E-DII levels were presented as means with standard deviations (SD) for quantitative variables and as frequencies and percentages for categorical variables.

Associations between the E-DII groups and incident depression were first investigated using both univariate and multivariate logistic regression analyses. The results were reported as OR and their 95 % CI. Analyses were adjusted for confounding factors based on published literature, using the following four models: model 0 was an unadjusted. Model 1 was adjusted for age and sex. Model 2 was additionally adjusted for socio-demographic factors (deprivation, ethnicity and education). Model 3 was adjusted as per model 1 but additionally included several health-related factors (BMI, smoking, alcohol, TV viewing and physical activity). Model 4 was adjusted per model 3 and also for type 2 diabetes and hypertension.

In addition, to mitigate bias and ensure comparability of participant characteristics, we employed propensity score matching. It is a widely employed technique in observational studies to create a subgroup of participants among whom the covariates were distributed in a balanced fashion and to reduce bias in estimating treatment effect[35,36]. The propensity score represents the conditional probability of a subject receiving a particular exposure given a set of confounders. In our study, the propensity score was calculated using model 4 and individuals with low E-DII scores and high E-DII scores were matched (1:1) by using the nearest neighbour matching with a caliper of 0·02. Standardised mean difference (SMD) was used to assess comparability of covariates between participants with low and high E-DII. SMD > 0·1 is used to imply a significant covariate imbalance.

We further conducted subgroup analyses to examine the heterogeneity by: sex (female or female), age (< or >= 60 years), ethnicity (white or non-white), multiple deprivation (< or >= median), education (low, intermediate or high), physical activity(low, intermediate or high), TV viewing time (< or >= median), smoking(never or previous/current), alcohol (never or previous/current), history of type 2 diabetes (yes or no) and history of hypertension (yes or no).

Finally, to examine the robustness, we performed sensitivity analyses to assess for potential unmeasured or uncontrolled confounding and to examine the robustness of the association between E-DII and incident depression. First, we explored the potential for unmeasured confounding between two groups by calculating E-values[37]. The E-value was used to measure the magnitude of the unmeasured confounding, and a higher E-value suggests less unmeasured confounding in the analyses[38]. Second, we repeated the analysis after excluding participants who had hypertension and type 2 diabetes at baseline.

All statistical analyses and graph plotting in this study were conducted using SAS (version 9.4, SAS Institute Inc.) and R (version 4.2.1). A two-sided *P* value below 0·05 was considered to be statistically significant.

## Results

### Characteristics

Of the 502 368 participants in UK Biobank, 291 432 were excluded for no dietary assessment data. Moreover, a further

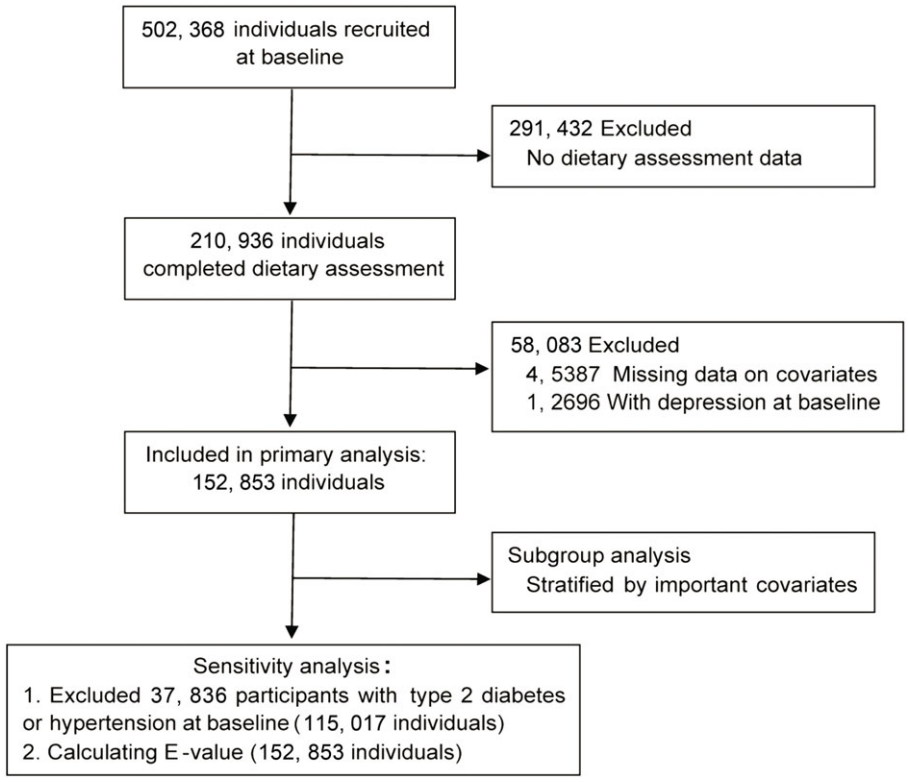



**Fig. 1.** Participant flow diagram.

50 389 were excluded including 45 387 participants missing data on covariates and 1296 participants with baseline depression. Therefore, 152 853 participants entered the primary analyses. In sensitivity analyses, 37 836 were excluded due to having suffered type 2 diabetes or hypertension at baseline, leading to a remaining cohort of 115 017 participants (Fig. 1).

In the primary analysis, the median of total DII in this study was −0·50 with a range of −6·36 to + 5·02. Consequently, 76 426 participants were classified into the low-E-DII group and 76 427 into the high-E-DII group. Within these groups, 2390 individuals (3·13 %) in the low-E-DII group developed depression, whereas 2723 (3·56 %) individuals in the high-E-DII group experienced depression. The baseline characteristics of the study participants are presented in Table 1. In summary, participants in the high E-DII group exhibited a higher likelihood of being male, current smokers, having a higher BMI, experiencing greater socio-economic deprivation and being more inclined to have a lower or intermediate educational background, in contrast to those within the low E-DII group. Additionally, they displayed a propensity for higher TV viewing time and reduced engagement in physical activity. Notably, participants with high E-DII scores displayed a slightly elevated incidence of baseline type 2 diabetes alongside a diminished prevalence of baseline hypertension. Detailed nutrient intakes for the low and high E-DII groups were presented in online Supplementary Table S1. The results indicated significant differences between individuals in the low E-DII and high E-DII groups across all twenty-seven dietary components used to estimate the E-DII.

### *Association of energy-adjusted dietary inflammation index and depression*

Associations between the E-DII groups and incident depression are shown in Table 2.

Consistently, it is shown that participants with higher E-DII scores were at higher risk of incident depression than those with lower E-DII scores. Model 0 was an unadjusted model with the corresponding OR (95 % CI) being 1·14 (1·08, 1·21). When adjusting for sex and age in model 1, the magnitude of the associations was somewhat strengthened (1·20 (1·14, 1·27)). The association was attenuated after adjusting socio-demographic factors in model 2 but remained significant (1·17 (1·10, 1·24)). Additionally, adjusted health-related factors in model 3 and added history of type 2 diabetes and history of hypertension as covariates in model 4 result in similar significant results (1·09 (1·03, 1·16), and 1·10 (1·03, 1·16), respectively). We also included E-DII as a continuous variable in the logistic regression model, and the estimated results were consistent. Specifically, as the E-DII score increases, the risk of future depression also rises (online Supplementary Table S2).

Of all the 152 853 patients included in the primary analysis, 132 908 were PS-matched (66 454 in each group). Figure 2 shows the SMD for the covariates in the unmatched and matched cohort. All variables were within less than 0·1 SMD of each other (SMD < 0·1 was considered to be negligible)[35]. Therefore, baseline covariates were comparable between participants with high E-DII and their matched controls. In the PS-matched cohort, 2337 individuals (3·52 %) in the high-E-DII group had incident depression events compared with 2101 (3·16 %) in the low-E-DII

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**Table 1.** Baseline cohort characteristics

| Characteristics | Total | | Low E-DII | | High E-DII | | *P* value |
|---|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | Mean | SD | |
| No. of participants | 152 853 | | 76 426 | | 76 427 | | |
| Energy, Mean (SD), kJ | 8685·90 | 2527·77 | 8223·41 | 2272·73 | 9148·38 | 2680·71 | < 0·0001 |
| Age, Mean (SD), year | 56·11 | 7·98 | 57·06 | 7·70 | 55·15 | 8·14 | < 0·0001 |
| Multiple Deprivation, Mean (SD) | 14·69 | 12·13 | 14·10 | 11·61 | 15·28 | 12·61 | < 0·0001 |
| | *n* | % | *n* | % | *n* | % | |
| Sex (%) | | | | | | | < 0·0001 |
| Female | 79 757 | 52·18 | 45 467 | 59·49 | 34 290 | 44·87 | |
| Male | 73 096 | 47·82 | 30 959 | 40·51 | 42 137 | 55·13 | |
| BMI, kg/m$^2$ | 26·92 | 4·53 | 26·58 | 4·41 | 27·25 | 4·63 | < 0·0001 |
| Ethnic, *n* (%) | | | | | | | < 0·0001 |
| White | 146 387 | 95·77 | 73 481 | 96·15 | 72 906 | 95·39 | |
| Others | 6466 | 4·23 | 2945 | 3·85 | 3521 | 4·61 | |
| Education, *n* (%) | | | | | | | < 0·0001 |
| Low | 41 895 | 27·41 | 20 081 | 26·28 | 21 814 | 28·54 | |
| Intermediate | 45 128 | 29·52 | 21 964 | 28·74 | 23 164 | 30·31 | |
| High | 65 830 | 43·07 | 34 381 | 44·99 | 31 449 | 41·15 | |
| Alcohol, *n* (%) | | | | | | | 0·2858 |
| Never | 4539 | 2·97 | 2240 | 2·93 | 2299· | 3·01 | |
| Previous | 4198 | 2·75 | 2058 | 2·69 | 2140 | 2·80 | |
| Current | 144 116 | 94·28 | 72 128 | 94·38 | 71 988 | 94·19 | |
| Smoking, *n* (%) | | | | | | | < 0·0001 |
| Never | 86 335 | 56·48 | 44 517 | 58·25 | 41 818 | 54·72 | |
| Previous | 54 896 | 35·91 | 27 759 | 36·32 | 27 137 | 35·51 | |
| Current | 11 622 | 7·60 | 4150 | 5·43 | 7472 | 9·78 | |
| Watching TV, h/d | 2·60 | 1·44 | 2·52 | 1·39 | 2·69 | 1·49 | < 0·0001 |
| MET minutes per week, *n* (%), minutes | | | | | | | < 0·0001 |
| Low | 50 155 | 32·81 | 22 768 | 29·79 | 27 387 | 35·83 | |
| Intermediate | 54 283 | 35·51 | 28 007 | 36·65 | 26 276 | 34·38 | |
| High | 48 415 | 31·67 | 25 651 | 33·56 | 22 764 | 29·79 | |
| Type 2 diabetes, *n* (%) | | | | | | | 0·3245 |
| No | 149 904 | 98·07 | 74 978 | 98·11 | 74 926 | 98·04 | |
| Yes | 2949 | 1·93 | 1448 | 1·89 | 1501 | 1·96 | |
| Hypertension, *n* (%) | | | | | | | 0·0941 |
| No | 115 887 | 75·82 | 57 803 | 75·63 | 58 084 | 76·00 | |
| Yes | 36 966 | 24·18 | 18 623 | 24·37 | 18 343 | 24·00 | |

E-DII, energy-adjusted dietary inflammation index; met, metabolic equivalent task.

**Table 2.** Associations between E-DII groups and incident depression

| | OR | 95 % CI | *P* value |
|---|---|---|---|
| Model 0 (crude model) | 1·14 | 1·08, 1·21 | < 0·0001 |
| Model 1 | 1·20 | 1·14, 1·27 | < 0·0001 |
| Model 2 | 1·17 | 1·10, 1·24 | < 0·0001 |
| Model 3 | 1·09 | 1·03, 1·16 | 0·0031 |
| Model 4 | 1·10 | 1·03, 1·16 | 0·0021 |

E-DII, energy-adjusted dietary inflammation index.
Model 0: crude model.
Model 1: adjusted for age (continuous) and sex (categorical).
Model 2: adjusted for age (continuous), sex (categorical), deprivation index (continuous), ethnicity (categorical) and education (categorical).
Model 3: adjusted for age (continuous), sex (categorical), ethnicity (categorical), education (categorical), deprivation index (continuous), BMI (continuous), smoking status (categorical), alcohol status (categorical), time watching TV (continuous) and physical activity (categorical).
Model 4: as per model 3 and also for type 2 diabetes (categorical) and hypertension (categorical).
A *P* value below 0·05 was considered statistically significant.

group. Of note, participants with high E-DII scores were more likely to experience incident depression (OR = 1·12, 95% CI: 1·05, 1·19; *P* = 0·000316).

The results of subgroup analyses are shown in Fig. 3. Associations of high E-DII and incident depression remained significant in subgroup analyses stratified by sex, age, BMI, smoking and baseline hypertension. Regarding other subgroups, we observed that the E-DII score was significantly associated with incident depression in the participants who were white more deprived, with low or intermediate education level, high level of physical activity, less time on watching TV, previous/current alcohol drinker and have no history of diabetes. Detailed results for the subgroup analysis were shown in online Supplementary Table S3.

We conducted sensitivity analyses to examine the robustness of the association between E-DII and incident depression. We

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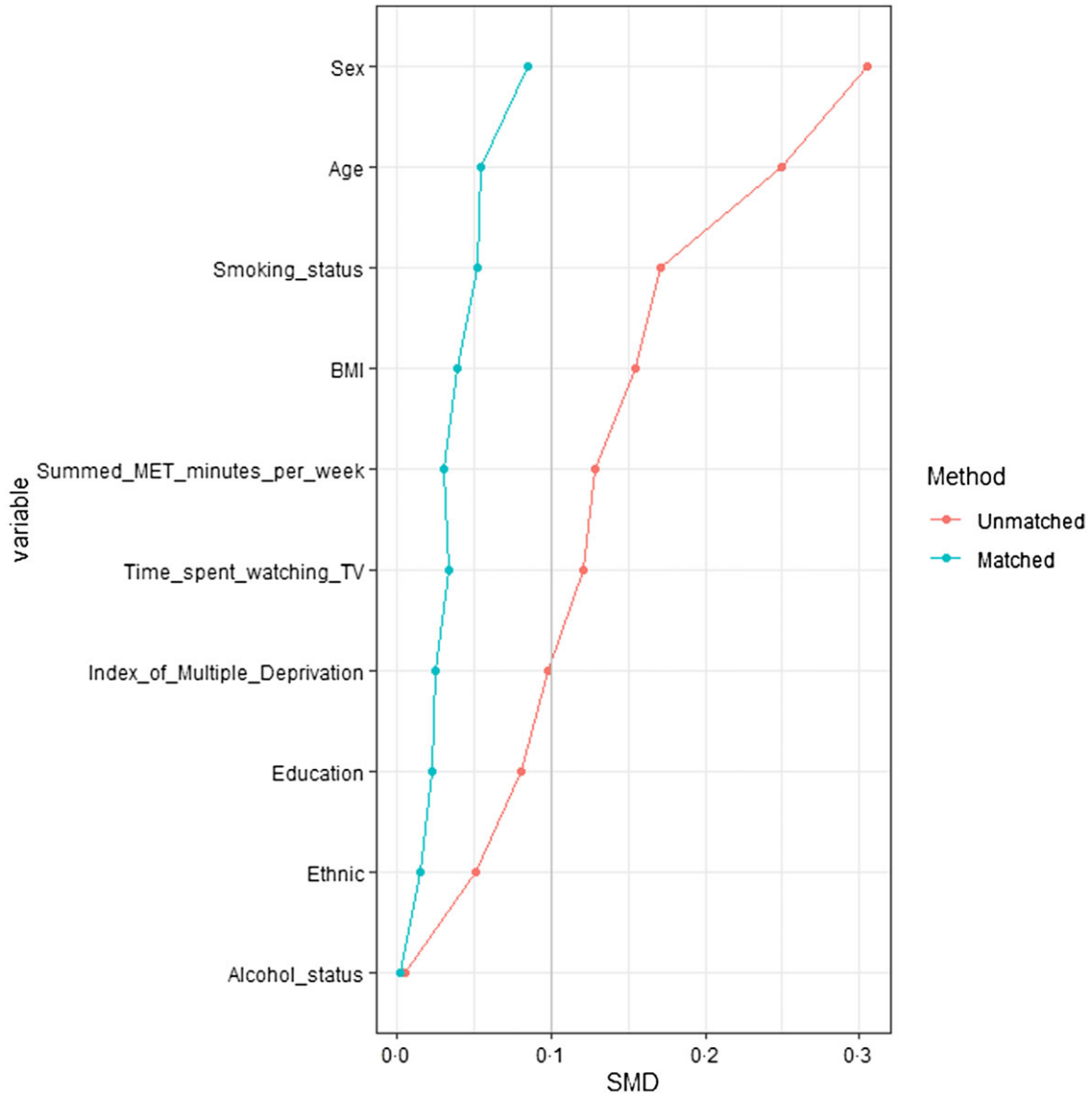



**Fig. 2.** SMD after propensity score matching. SMD, standardised mean difference.

excluded participants with type 2 diabetes or hypertension at baseline and left a remaining cohort of 115 017 participants. The same propensity score matching procedure was applied to resulting a 99 458 matched individuals. A similar positive association was observed in agreement with the primary analysis (OR = 1·13, 95 % CI: 1·06, 1·22; $P = 0{\cdot}000617$). E-values quantify the magnitude required to negate the association between E-DII and incident depression due to unmeasured confounding. We also estimated E-values for the present study. The E-value for the OR calculated from the matched data set was 1·48 for the point estimate and 1·28 for the lower CI bound. Briefly, it means that an unmeasured confounder would need to have a relative risk association >= 1·28 with both the E-DII score and the incident depression to make the observed exposure–outcome association no longer significant, after adjusting for measured covariates[39,40].

## Discussion

In recent decades, there has been a noticeable upwards trend in the occurrence of mental health disorders, highlighting a substantial challenge in the realm of public health[41]. Depression is an important public health problem and is also listed as one of the leading causes of disease burden worldwide[1]. It accounted for the largest proportion of mental disorder disability-adjusted life-years in 2019[42]. In 2008, The WHO ranked major depression as the third cause of the burden of disease worldwide and predicted that the burden of depression will rank first by 2030[43]. While the use of antidepressants can alleviate depressive symptoms, they are often accomplished by several adverse effects. Dietary patterns have been shown to modulate the inflammatory state, thus there is an increasing recognition of the importance of diet patterns, as a potential way of preventing and improving depression. This study examined

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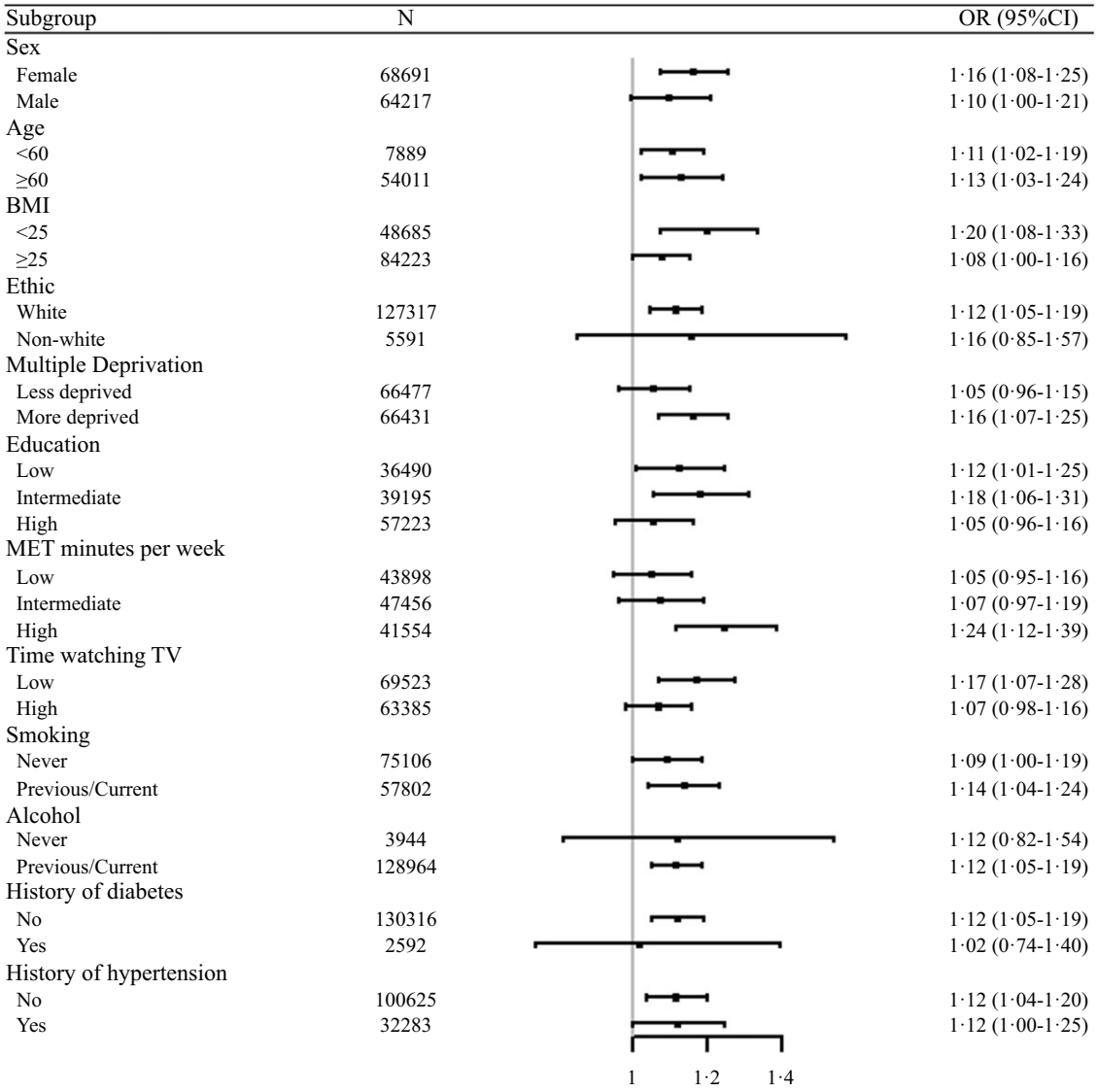



**Fig. 3.** Associations between E-DII and incident depression stratified by covariates. E-DII, energy-adjusted dietary inflammation index.

the prospective association between E-DII and incident depression in a large representative sample of middle-aged and older adults in the UK. Among 152 853 UK Biobank participants, an evaluated risk of incident depression was observed in individuals who consumed a more pro-inflammatory diet, when accounting for an array of potential confounding factors. Subgroup analysis showed that the association between E-DII and depression differed across various subpopulations. The positive correlations remained consistent across age groups (both < 60 and ≥ 60), BMI categories (< 25 and ≥ 25), females and individuals with or without baseline hypertension. Furthermore, the results of the sensitivity analysis also align consistently with those of the primary analysis.

Indeed, increasing evidence suggested an association between dietary inflammatory potential and depression symptoms, and this finding was generally in line with existing meta-analyses in the general population. A meta-analysis has revealed a noteworthy link between a pro-inflammatory diet and a heightened risk of experiencing depression, whether through diagnosis or symptoms (OR: 1·40, 95 % CI: 1·21, 1·62, $P < 0·001$)[14]. Data from the North West Adelaide Health Study cohort and the updated meta-analysis of observational studies also provided further evidence that a pro-inflammatory diet is positively associated with an increased risk of depression symptoms[15]. A more recent meta-analysis synthesised findings from three longitudinal observational studies aimed at evaluating the correlation between the DII and the risk of developing depression over time. The analysis revealed that individuals classified in the highest category of inflammatory diet exhibited elevated odds of experiencing incident depression in comparison with those situated in the lowest category (OR 1·33; 95 % CI 1·04, 1·70; $P = 0·02$)[6]. Moreover, similar findings were also seen in two recent studies based on the National Health and Nutrition Examination Survey focused on specific populations[12,44]. These findings support the hypothesis that the DII is an appropriate tool for measuring dietary inflammatory

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potential and reinforce the role of diets with inflammatory potential in the pathophysiology of depression.

Indeed, the precise mechanisms through which the inflammatory potential of diet relates to depressive are not fully clarified. Inflammation has been implied to play a key role in the occurrence and development of depression. It was implied that a long-term pro-inflammatory diet could lead to constant activation of the immune system, triggering inflammation, leads to overproduction of reactive oxygen species resulting in oxidative stress. The neurons in the brain were susceptible to oxidative stress, leading to depressive symptoms[41]. Furthermore, an additional conceivable pathway by which diet could exert an impact on depression is through the brain–gut-microbiota axis. The intestinal microbiota and dietary factors assume a vital role in these gut–brain interactions, potentially contributing to the development of psychiatric disorders, including depression[45].

Although the exact role of inflammation in depression has not been fully elucidated, the findings of this study indicated anti-inflammatory dietary patterns may offer a new strategy to combat the inflammatory state associated with the onset and development of depression. Specifically, promoting the consumption of anti-inflammatory foods (such as green leafy vegetables like kale, dark yellow vegetables, whole grains and fruits, tea, coffee and wine.) and preventing the intake of pro-inflammatory foods (such as red meat, processed meat, refined carbohydrates and sweetened beverages) may serve as a preventive strategy for reducing depression. Future well-designed randomised clinical trials are imperative for substantiating the connection between E-DII score and the onset of depression, while also shedding light on the underlying mechanisms. Additionally, the relationship between E-DII and the severity of depressive conditions also needs further research. Furthermore, there is also a pressing need for further research to explore the relationship between E-DII and the severity of depressive conditions.

In our subgroup analysis, we observed heterogeneity in the association between E-DII and depression, suggesting that a high-E-DII diet, characterised by a high inflammatory response, may contribute more significantly to depression in specific populations that warrant further attention. For instance, we found a significant association between E-DII and depression in females, whereas no significant association was observed in males. A study indicated that diet may play a less prominent role in the development of depressive in women compared with men[32]. However, the lack of association among males in the present study could be attributed to sex-based differences and requires further validation. Additionally, we identified a significant association between E-DII and depression in more deprived and low-to-intermediate educated populations, which was not evident in less deprived or highly educated populations. This discrepancy suggests that individuals in more deprived and less educated groups may be more vulnerable to depression. Indeed, a previous cohort study indicated that the relationship between DII and major depression diminishes with increasing education levels, implying that education may serve as a protective factor against depression[46]. Interestingly, we observed heterogeneity in the associations based on varying levels of physical activity. Subgroup analysis revealed that a pro-inflammatory diet is a risk factor for depression among individuals with high levels of metabolic equivalent task minutes per week, but not for those with low or intermediate metabolic equivalent task minutes per week. Further research is needed to confirm these findings. Furthermore, no positive association was detected in certain subgroups, such as non-white individuals, those who never consumed alcohol, and those with a history of diabetes. This may be due to the limited sample size in these subgroups.

### *Strength and limitations*

The main strength of this study lies in its utilisation of a substantial sample size sourced from the UK Biobank. The study benefits from both a sizable participant cohort and an extended follow-up duration, allowing for a comprehensive investigation into the relationship between E-DII and the subsequent occurrence of depression. Additionally, our analyses incorporated various levels of confounder adjustment, considering a broad range of essential covariates such as age, sex, socio-demographic variables, and health-related factors. The quality of the dietary data is another strength, based on repeated 24-hour dietary records that reflect participants' food habits. Moreover, using the E-DII score provides a more accurate measure of the inflammatory potential of the overall diet compared with the original DII. Furthermore, our study introduces methodological novelties compared with other research. The large sample size enabled us to employ a combination of statistical methods, including traditional univariate and multivariate logistic regression analyses, propensity score matching and subgroup and sensitivity analyses, to assess the reliability and robustness of our findings

Nonetheless, it is important to acknowledge several limitations inherent to this study. First, despite relying on five repeated rounds of 24-hour dietary recalls to capture food nutrient intake, diet remains susceptible to recall and misclassification bias, and dietary patterns may have evolved over time. Second, the computation of the E-DII in this study relied on a selection of only twenty-seven foods and nutrients for which detailed intake data were available through the UK Biobank. This approach omitted various foods and nutrients, including but not limited to caffeine, onion, garlic, eugenol, ginger, turmeric, oregano, pepper, rosemary and saffron. This selection constraint may preclude a more comprehensive and accurate assessment of the participants' daily dietary inflammatory potential. However, studies also revealed a strong correlation between inflammatory biomarkers and E-DII when it was computed with fewer than 30 food parameters[47,48]. Additionally, participants missing key covariate data were directly excluded from the study, which might have had some impact on the study. Third, it's important to note residual confounding bias could persist even after individuals are matched based on their propensity scores. Although propensity score matching is a valuable way to control for bias and achieve pseudo-randomisation in observation studies, it is still just a mathematical technique and cannot substitute for experimental evidence derived from randomised control trials. Fourth, in the present study, despite we controlled for several key baseline confounders including

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socio-demographic (age, ethic, BMI, index of multiple deprivation and education), lifestyle (smoking status, alcohol status, physical activity and TV viewing) and health-related factors (type 2 diabetes and hypertension), the potential for residual confounding cannot be completely ruled out. Furthermore, owing to incomplete and imprecise dosing information obtained from the UK Biobank data, we opted not to include medication data in our analysis. We must acknowledge the potential presence of residual and unmeasured confounders. To address this concern, we conducted a sensitivity analysis, the results of which yielded an E-value of 1·48.

### *Conclusions*

Using large-scale data from the UK biobank cohort, we reported an extensive evaluation of the associations between E-DII and risk of depression. Our results showed that adherence to a diet with higher pro-inflammatory potential was associated with an overall higher depression risk. It indicates that a prudent approach involving the restriction of pro-inflammatory foods, coupled with the adoption of an anti-inflammatory diet, could serve as a highly effective strategy for preventing depression. Experimental studies are required to further evaluate causality and unveil the mechanism behind.

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The authors declare there are no competing interests.

## Supplementary material

For supplementary material/s referred to in this article, please visit https://doi.org/10.1017/S0007114524002253

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