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The risk associated with ultra-processed food intake on depressive symptoms and mental health in older adults: a target trial emulation

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Abstract

Background Longitudinal cohort studies across the lifespan suggest an association between ultra-processed food (UPF) and depression. However, the effect of UPF on depression and mental health in older adults has not been determined. Therefore, this study investigated the effect of UPF on depressive symptoms and mental health in community-dwelling older adults.

Methods A pragmatic target trial was designed and emulated using the ASPirin in Reducing Events in the Elderly longitudinal data. Participants were community-dwelling older adults (≥ 70 years) in Australia. We specified and emulated the protocol of a two-arm randomised pragmatic clinical trial using the level of UPF consumption as the intervention. Greater than or equal to 4 servings of UPF per day was considered the intervention, with less than 4 servings per day the control. Dietary consumption was assessed using a mail-based diet screening questionnaire, and the level of food processing was classified based on the NOVA classification. The study outcomes were depressive symptoms, defined as a score of ≥ 8 on the Center for Epidemiological Studies Depression 10-item scale, and general mental health, defined by the mental component summary score of the Short Form-12. We applied inverse probability treatment weighting to balance confounders. Marginal structural models were employed to estimate the population-level average effect of intervention using generalised estimated equations.

Results A total of 11,192 participants (3415 intervention and 7777 control) were eligible for the emulation. High UPF consumption at time zero was associated with an increased risk of depressive symptoms at follow-ups (RR: 1.10; CI: 1.04–1.18). The finding was consistent with sensitivity analyses; after excluding participants on antidepressants at time zero, the risk of depressive symptoms in the intervention group was increased by 11% compared to the control (RR: 1.11; 95% CI: (1.04–1.20)). Consumption of UPF adversely affected the mental component quality of life (β: − 0.40; CI: − 0.65 to − 0.15).

Conclusions A higher level of UPF consumption was associated with a higher risk of depressive symptoms and adversely affected mental health among older adults.

Keywords Depression, Mental health, Target trial emulation, Ultra-processed food

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Background

Given the rapid rise of the older population, mental disorders are a major public health concern for this population. According to a recent World Health Organisation (WHO) report, approximately 14% of older adults live with mental disorders, contributing to 10.6% of the total years lived with disability worldwide [1]. Although depression affects individuals at any stage of life, late-life depression is a common mental health condition, often under-recognised and undertreated [1], associated with several adverse health outcomes [2]. Its pathophysiology and risk pathways remain incompletely understood [3].

Diet is a modifiable factor for health. Consumption of a low-quality diet contributes to several health and health-related conditions in older adults including functional disability [4], sarcopenia [5, 6], frailty [7], depression [8], cognitive decline [9, 10], and chronic diseases [11, 12]. The mechanism by which diet is associated with these health outcomes is complex and multifaceted, but diet impacts many pathways implicated in mood [13].

According to the NOVA classification, a widely used food grouping system noting the nature, extent, and purpose of industrial processing, food can be classified into four groups: (i) unprocessed or minimally processed food; (ii) processed culinary ingredients; (iii) processed food; and (iv) ultra-processed foods (UPF) [14]. UPF are manufactured foods generally characterised by high energy and poor nutritional profiles, containing a mix of additives to give long shelf life and to make them attractive and palatable, which include confectionary sweets, sweetened beverages and packaged/ready-meals [14, 15].

UPF is typically nutritionally unbalanced in terms of nutrient composition with high added sugar, fat and trans-fat constructed from extracted, refined, fractionated and low-cost ingredients [16, 17]. Moreover, processing techniques such as artificialisation (use of colourants, flavours, artificial sweeteners, emulsifiers, cosmetic additives, and synthetic food products) as well as a transformation of food attributes to include non-nutritious products [17].

The dietary pattern of the global population is changing with an increase in UPF consumption. In high-income countries, including the United States of America (USA) and Australia, over half of the total energy intake is through UPF [17, 18]. A study among older adults in the Netherlands reported that 37% of total energy intake was from UPF [19].

Extant literature demonstrates that UPF is associated with a range of adverse health outcomes, including dementia [15], mental health disorders [20], cardiovascular diseases, cancer, type 2 diabetes, frailty, chronic inflammation and all-cause mortality [18, 21, 22].

An umbrella review on UPF and adverse health outcomes indicated that UPF is associated with adverse mental health outcomes such as sleep-related problems, anxiety and incident depression [23]. The review classified the level of evidence for UPF consumption on depression as low. Similarly, a systematic review and meta-analysis showed that a higher UPF consumption was associated with increased odds of common mental disorders (depressive and anxiety symptoms) [24]. Moreover, in a recently published cohort study among British adults ($n=4554$, 1183 females, mean age of 61 ± 5.9 years), a higher intake of UPF was associated with a 34% higher likelihood of recurrent depressive symptoms [25].

Although these studies have found an association between UPF and depressive symptoms, the effect of UPF on the development of depressive symptoms among older adults has not been thoroughly investigated. Given the prevalence of late-life depression and a globally ageing population, assessing the effect of diet on mental health outcomes in older adults considering potential effect modifiers and confounders, including socio-demographics, comorbidities, and biomarkers, is crucial to enhance healthy ageing. Conducting randomised controlled trials (RCTs) to investigate the effect of diet on health outcomes is not straightforward due to the feasibility of large-scale RCTs, challenges in dealing with information bias, expectation bias due to the knowledge of which study participants are receiving intervention or control [26, 27] and ethical issues [28]. Causal interpretation from observational studies is challenging due to the lack of randomised treatment assignments [29]. Target trial emulation is a framework to apply principles of randomised trials to prospective longitudinal observational studies and uses inverse probability of treatment weighting (IPTW) to control for measured confounders through balancing potential confounders of exposed and unexposed groups [30].

This study aimed to employ a target trial framework to address the methodological limitations of observational studies and to investigate the effect of UPF on depressive symptoms and mental health quality of life in older adults using longitudinal data from the ASPrin in Reducing Events in the Elderly study (ASPREE).

Methods

We designed an emulated two-arm randomised pragmatic clinical trial using the target trial framework to assess the effect of UPF on depressive symptoms in older adults.

Data sources

This study was a secondary analysis of the ASPREE trial. ASPREE was a double-blind randomised

placebo-controlled trial of daily 100 mg enteric-coated aspirin in 19,114 community-dwelling older adults aged 70 + years from Australia and 65 + years from the USA. Participants were males and females willing and able to provide informed consent recruited between 2010 and 2014, and the clinical trial was completed in June 2017. Participants were recruited from primary care in Australia and predominantly through academic and clinical trial centres in the USA. Participants were free from overt cardiovascular disease, dementia, and independence-limiting physical disability at baseline. The design, recruitment, eligibility criteria and baseline characteristics of participants in the ASPREE study have been published in detail [31–33].

The ASPREE Longitudinal Study of Older Persons (ALSOP) is a sub-study of the ASPREE trial among Australian participants ($n = 16,703$) that started in early 2012, where 12,578 participants provided the year 3 medical and lifestyle data including the diet screen survey. The details of the ALSOP study have been previously published [34]. The follow-up of participants after the trial phase continued through the ASPREE-eXTension (ASPREE-XT) study and investigates the long-lasting effects of aspirin and a broad range of factors that contribute to healthy ageing [35].

The longitudinal dataset contains socio-demographic characteristics, social and physical health indicators, anthropometrics, medical diagnoses, medications, laboratory tests and dietary information, among other data [35]. We used ASPREE participants with valid ALSOP diet data and incorporated extended follow-ups beyond the ASPREE trial period from the ASPREE-XT starting from wave 3 of the ASPREE trial (time zero of this study) to ASPREE-XT 04 (wave 11) (Fig. 1).

Study design and approach

A target trial emulation was applied based on the ASPREE longitudinal data. The study protocol for a hypothetical randomised control trial was framed by rigorously defining eligibility criteria, assignment procedures (intervention and control arms), follow-up, outcome ascertainment and analysis plan. The components of the target trial design are summarised in (Table 1).

Eligibility criteria

We included community-dwelling older adults of the ASPREE participants who completed the dietary habits food screening survey as part of the ALSOP sub-study. To be eligible for the target trial, participants had to be assessed for depression endpoints in the ASPREE study and had a valid food screening survey. In sensitivity analyses, we considered the following as exclusion criteria: participants who had depressive symptoms at time zero and participants taking antidepressants and/or antipsychotics at time zero. In this study, wave-3 of the ASPREE trial was considered as a baseline (labelled as time zero in

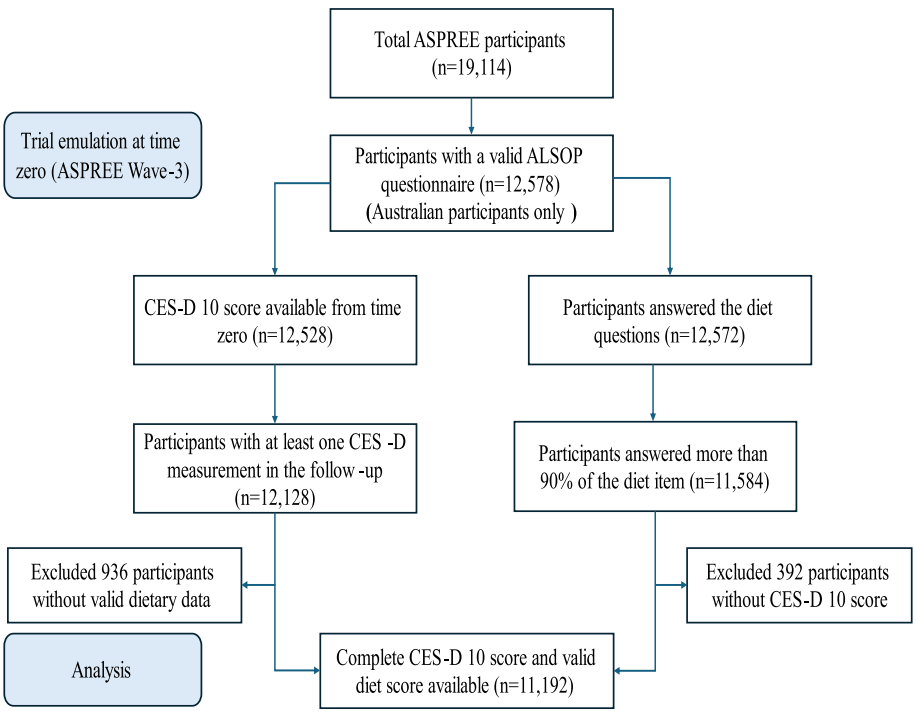

Fig. 1 Flow diagram showing ASPREE and ALSOP participants used in the analysis

Table 1 Summary of a target trial protocol and its emulations to estimate the effect of ultra-processed food on depressive symptoms in older adults using ASPREE data

Protocol component	Target trial	Target trial emulation
Eligibility criteria	**Inclusion:** Community-dwelling older adults (> 70 years) and no upper age limit **Exclusion:** Follow-up commenced when all eligibility criteria were met	Same as the target trial Participants with no valid dietary score were excluded In sensitivity analysis, participants taking antidepressants and/or antipsychotics at time zero and participants with clinically relevant depressive symptoms at time zero were excluded
Intervention strategy	Strategy 1: consume a high level of UPF (intervention) at time zero of the trial Strategy 2: consume a low level of UPF (control) at time zero	Same as the target trial UPF consumption was calculated in servings per day and categorised as high consumption (≥ 4 servings/day) and low consumption (< 4 servings/day) We assumed that the diet habits of older people were stable so that participants maintained the allocation groups
Intervention assignment	Participants were randomly assigned to the intervention at time zero and aware of the group to which they were assigned (randomisation but no blinding)	We assumed random assignment of high or low UPF intake by employing inverse probability weights to balance predefined confounders, a-priori selected from the ASPREE data domains
Outcomes	Onset of depressive symptoms Mental component quality of life	Same as the target trial We defined depressive symptoms as the presence of clinically relevant depressive symptoms measured by a total score of ≥ 8 on the CES-D 10 scale during the follow-up period Mental component quality of life was assessed using the SF-12
Follow-up	We followed participants after randomisation (intervention assignment) until the first episode of depressive symptoms, lost follow-up, or end of follow up whichever occurs first	Same as the target trial Time zero was defined at wave 3 of follow-up, when the diet survey was collected, and ended at the last available follow-up (APREE-XT 04)
Causal contrast	Intention-to-treat	Intention-to-treat effect (effect of intervention as specified in the protocol)
Statistical analysis	Intention-to-treat analysis	Intention-to-treat analysis was applied. We used logistic regression to calculate IPTWs and the marginal structural model to estimate the population average effect of intervention through generalised estimated equations

IPTW Inverse probability treatment weights

the manuscript) as the dietary assessment was conducted at year-3 of the trial period.

Intervention strategies

We compared two dichotomised intervention strategies. The first strategy involved consuming a high level of UPF (intervention) at the initiation of the target trial (i.e. time zero), and the second strategy involved consuming a low level of UPF over the same period (control).

Dietary assessment

Dietary information was assessed using a mail-based diet screening questionnaire. The questionnaire was used to assess the dietary intake of participants that contains food and drink items categorised into food groups such as meat, fish and eggs, snack and convenience foods, dairy (including milk and milk alternatives)), bread, grains and cereals, fruit and vegetables, drinks (soft drinks, cordial, supplements drinks, etc.) and other nutrients (salt, fats and oils, water, and discretionary foods) based on the expert knowledge of dietary patterns of older adults. Consumption frequency was recorded considering the last 12-month diet in the form of scales ranging from never to every day/several times a day.

The level of food processing was determined according to the NOVA food classification system [14]. Foods and drinks of the screener tool were classified into four groups (unprocessed/minimally processed, culinary ingredients, processed food, and ultra-processed food). Then, 21 food and drink items were identified as UPF (NOVA group 4), which includes processed meats (e.g. bacon, ham, corned beef or salami), sausages, potato chips or similar, sweet biscuits/cakes, dark chocolate, milk chocolate, lollies or other sweets, hamburgers/pizza or 'fast' food, meat pies or sausage rolls, ice cream, frozen yoghurt or other dairy desserts, breakfast cereal/oats, crackers/savoury biscuits, mass-produced packaged bread, soy or other non-dairy milk, malt drinks (e.g. Milo or Horlicks), cordial, soft drink (e.g. regular Coke), hot chocolate, diet soft drink (e.g. Diet Coke) and supplement drinks (e.g. Ensure or Sustagen) (Additional file 1: Table S1).

Data from the diet screen were converted to a daily equivalent frequency (DEF) for each food using the reference guide adapted from the Victorian Cancer Council food frequency questionnaire user guide for dietary questionnaires for epidemiological studies. Daily UPF consumption was calculated as serving per day by converting consumption of UPF frequencies from the diet screen response to a daily frequency to make all foods in similar units as; 0 for never or almost never, 0.053 for one to two times a month, 0.21 for one to two times a week, 0.64 for three to six times a week, and 1 for every day of the week. For drinks, we used 0 for never or almost never, 0.14 for once per week or less, 0.57 for several times a week, 1.5 for one to two times a day, and 3 for three or more times a day [36]. Serving per day for each participant was computed by summing the serving score of each UPF item. Then UPF consumption was categorised as high consumption (≥4 servings/day) and low consumption (<4 servings/day) according to a recent study conducted to investigate the association between UPF consumption and risk of depression [37]. Sex-specific quartiles were also computed to stratify UPF consumption (Additional file 1: Table S2).

In addition, an estimated portion size (the amount of food in grams that a person consumed at a particular eating time) of UPF consumption was considered. Age- and sex-specific median portion sizes in grams were estimated (for older adults; 71+years) by multiplying the daily consumption frequencies for each item by its specified portions [38] based on the Australian National Nutrition and Physical Activity Survey report [39]. The estimated portion size for UPF consumption (grams/day) was calculated by summing up portions of each UPF item. The weighted proportion of UPF was calculated as UPF consumed divided by the total amount of food consumed in grams per day using similar methods used by previous studies [40, 41]. Quartiles of portion size as a daily energy percentage contribution of UPF were used for the analysis.

Trial interventions

Eligible participants of the target trial were assumed a random allocation to one of the two dietary intervention strategies: (i) exposed (intervention) group—participants who were consuming high levels of UPF (≥4 servings per day) were taken as the intervention arm and (ii) control group—participants who consumed low levels of UPF (<4 servings per day) were taken as the control arm. We considered the 12-month dietary data a stable dietary pattern [42] and performed an intention-to-treat analysis, assuming participants maintained the assigned intervention strategy for the duration of the study.

Outcomes and follow-up

The primary outcome of the target trial was the risk of depressive symptoms. Participants were followed from time zero of the emulated trial (i.e. wave-3 of the ASPREE study) to 2022 (up to a maximum of wave-11 of ASPREE-XT 04). We followed up with the participants until the onset of depressive symptoms, the last available follow-up, lost to follow-up or 2022 (the time on which wave-11 of ASPREE-XT 04 data were collected) whichever occurred first.

The depression outcome was defined using the Center for Epidemiologic Studies-Depression 10-item (CES-D 10) scale [33, 43]. The CES-D 10 is a self-administered questionnaire of 10 items on depressive symptoms, which range from 0 to 30, with higher scores indicating more severe depressive symptoms. The scale was validated for older adults previously [43, 44]. Depressive symptom was defined as the presence of clinically relevant depressive symptoms measured by a total score of ≥8 on the CES-D 10 scale [45, 46]. The CES-D 10 was administered annually, including the ASPREE-XT 04 visit (2022).

The secondary outcome of interest was mental health quality of life which was measured using the 12-item Short Form Health Survey (SF-12). The SF-12 health survey is a 12-item summary score assessing physical and mental health quality [47]. The Mental Component Score (MCS) score was generated by combining medical outcome short-form items using the US general population-derived item weights [48]. The SF-12 MCS ranges from 0 to 100, with higher scores indicating better mental health functions and being a valid measure of depression [49]. The SF-12 was administered annually through the ASPREE-XT 04 visit.

Covariates

Potential confounders include age, sex, ethnicity (race), years of education, smoking status, alcohol use, living situation (living alone or living with family/in a residential home), self-reported physical activity, social support [50], Body mass index (BMI) in kg/m^2, waist circumference, CES-D score at time zero, global cognitive function (Modified Mini-Mental State examination (3MS) scored out of 100), comorbidities (hypertension, diabetes mellitus, dyslipidaemia, chronic kidney disease (CKD), gastro-oesophageal reflux disease (GORD), pulmonary disease, gout, cancer and Parkinson's disease), multimorbidity (coexistence of two or more chronic health conditions), metabolic syndrome (based on the Adult Treatment Panel III (ATP III) diagnostic criteria [51], polypharmacy (use of five or more prescription medications) and biomarkers such as lipid profiles and fasting blood glucose.

We used causal-directed acyclic graphs (DAGs) to a priori identify the confounders (Additional file 2: Fig. S1).

Statistical analysis

The primary analysis compared the risk of depressive symptoms among participants who consumed high (intervention arm) and low (control arm) UPF. We used descriptive analyses to present participants' characteristics by frequencies with percentages for categorical variables and mean with standard deviation (SD) for continuous variables.

The probability of receiving treatment was predicted using multivariable logistic regression considering UPF consumption as an outcome variable conditional on prespecified covariates, and potential interaction terms were checked.

We applied the IPTW approach to create synthetic populations in which the treatment group is independent of measured baseline confounders. Employing IPTW resulted in an intervention and control arms with a similar probability of receiving a high or low level of UPF, and as such, the target population closely mimics the characteristics of a population in a pragmatic randomised trial [52, 53]. We used stabilised weights (SW) to mitigate the impact of selection bias and maintain the robustness of the estimation [53].

To maintain the exchangeability assumption (i.e. participants in the intervention and control group have the same potential outcomes on average), the distribution of confounders across the trial arms was compared after employing IPTW using standardised mean difference (SMD) [54]. An SMD less than 0.1 indicates a covariate balance between the intervention and control group [55]. Weight truncation was applied at the 1st and 99th percentiles (1%) to prevent the effect of extreme weights [52].

For the primary outcome, inverse probability weights were included in the marginal structural model (MSM) by employing the generalised estimated equations with a log link, CES-D $10 \geq 8$ as the dichotomised outcome, and intervention group as the nominal independent variable using the first-order autoregressive correlation structure. Risk ratio (RR) with its 95% confidence interval was used to estimate the effect of UPF on depressive symptoms.

For the secondary outcome, MSM was fitted using generalised estimated equations assuming a Gaussian distribution with an identity link function and repeated (follow-up) MCS SF-12 scores as a continuous outcome variable using the first-order autoregressive working correlation structure. The estimated between-group mean difference with 95% confidence interval was reported. A two-sided p-value less than 0.05 was used to determine statistical significance.

To evaluate the extent to which unmeasured confounders could affect the findings, E-values were reported [56, 57].

Sub-group analyses were conducted using sex, level of education, BMI category, presence of multimorbidity (coexistence of two or more chronic health conditions), metabolic syndrome and aspirin use as these are known factors associated with depressive symptoms. We performed sensitivity analyses using quartiles of UPF servings and portion size, using CES-D 10 cutoff ≥ 10 as the outcome, excluding participants with clinically relevant depressive symptoms or those taking antidepressants or/and antipsychotics at time zero. The main analysis was replicated using the ASPREE trial duration only (participants followed until 2017, using four waves) to be consistent with previous studies that reported negligible variability in diet patterns in four years [37, 58].

Statistical analyses were conducted using R statistical software (*ipw* and *geepack* packages), version 4.3.3 (R Foundation for Statistical Computing, Vienna, Austria).

Missing data

Participants with missing data in the intervention (no diet data at time zero) and outcomes (those with no records at time zero and at least one of the follow-ups) variables were excluded from the analyses. To handle missing data in covariates, we performed imputation using the Predictive Mean Matching (PMM) approach in the *mice* package in R.

Results

Participants characteristics

Among 12,597 participants enrolled in the ALSOP substudy, 11,192 were eligible for this study.

The mean UPF consumption (servings per day) was 3.4 ± 1.5. UPF use was higher among males than among females (3.7 ± 1.6 for men and 3.2 ± 1.4 for females). Three thousand four hundred fifteen participants (30.5%) had high UPF consumption (≥ 4 servings/day) and were classified as the intervention arm.

At the baseline of the trial, the mean (standard deviation) age of participants was 74.9 (4.07) years and 53.7% were females. In our study, at time zero, most participants ($n = 8490$, 90.1%) had good social support, and 8322 (74.8%) were alcohol users at time zero. Most of the participants had two or more medical comorbidities ($n = 7523$, 81.5%; 81.9% from intervention and 81.4% from the control arm). At time zero, 4665 (41.7%) of participants reported polypharmacy use (Table 2).

The time zero socio-cultural, body composition characteristics, comorbidities, and medication intake of participants in the intervention and control arm were similar. However, as indicated in Table 2, participants

Table 2 Baseline characteristics of ASPREE study participants included in the target trial emulation stratified by intervention strategies before and after IPTW

Covariates	Overall cohort (frequency/%)	Unweighted			Weighted		
		Intervention (frequency/%)	Control (frequency/%)	SMD	Intervention (frequency/%)	Control (frequency/%)	SMD
N	11,192	3415	7777		11,183	11,195	
Age (years): mean ± SD	74.9 ± 4.07	75.3 ± 4.25	74.68 ± 3.97	0.160	74.94 ± 4.02	74.90 ± 4.12	0.010
Sex: female	6017 (53.7)	1466/42.9	4551/58.5	0.316	5988/53.6	6016/53.7	0.003
Education status: > 12 years	4682 (41.8)	1423/41.7	3259/41.9	0.005	4649/41.6	4675/41.8	0.004
Racial: White	11,059/98.8	3386/99.2	7673/98.7	0.052	11,054/98.8	11,055/98.8	0.001
Alcohol: yes	8322/74.8	2435/71.7	5887/76.1	0.102	8321/74.4	8363/74.7	0.007
Smoking: yes	252/2.3	48/1.4	204/2.6	0.087	252/2.2	249/2.2	0.002
Income: low	8855/92.8	2729/93.4	6126/92.5	0.032	10,352/92.6	10,367/92.6	0.001
Social support: good	8490/90.1	2581/89.7	5909/90.2	0.018	10,033/89.7	10,054/89.8	0.003
Living status: living at home with family	7525/67.6	2443/71.9	5082/65.7	0.134	7560/67.5	7561/67.6	0.001
Physical activity: moderate to high	5953 /61.8	1838/62.4	4115/61.6	0.017	6811/60.9	6874/61.4	0.010
BMI, kg/m^2: mean ± SD	27.6 ± 4.5	27.3 ± 4.3	27.8 ± 4.6	0.096	27.67 ± 4.7	27.63 ± 4.5	0.008
Waist circumference, cm: mean ± SD	96.5 ± 12.7	96.9 ± 12.5	96.3 ± 12.8	0.052	96.53 ± 12.55	96.63 ± 13.02	0.008
Total cholesterol, mg/dl: mean ± SD	197.7 ± 38.7	194.9 ± 37.7	198.9 ± 39.1	0.103	197.59 ± 37.96	197.55 ± 39.02	0.001
HDL, mg/dL: mean ± SD	61.6 ± 17.8	59.0 ± 17.0	62.8 ± 18.0	0.215	61.66 ± 18.65	61.55 ± 17.69	0.006
Triglyceride, mg/dl: mean ± SD	116.9 ± 55.5	117.4 ± 57.1	116.7 ± 54.7	0.013	117.71 ± 57.13	117.24 ± 55.36	0.008
Blood glucose, mg/dL: mean ± SD	99.1 ± 17.5	98.7 ± 16.6	99.3 ± 17.8	0.031	99.54 ± 18.40	99.52 ± 18.22	0.002
Metabolic syndrome: yes	5000/54.8	1487/52.5	3513/55.8	0.066	6,148/54.9	6164/55.1	0.004
3MS score: mean ± SD	94.4 ± 4.6	94.1 ± 4.9	94.6 ± 4.5	0.118	94.42 ± 4.7	94.4 ± 4.6	0.004
CES-D score at time zero: mean ± SD	4.1 ± 3.9	4.2 ± 3.9	4.06 ± 3.9	0.048	4.12 ± 3.85	4.12 ± 3.94	< 0.001
Multimorbidity: yes	7523/81.5	2337/81.9	5186/81.4	0.015	9145/81.8	9178/82.0	0.005

Table 2 (continued)

Covariates		Overall cohort (frequency/%)	Unweighted			Weighted		
			Intervention (frequency/%)	Control (frequency/%)	SMD	Intervention (frequency/%)	Control (frequency/%)	SMD
Comorbidities	Hypertension: yes	8734/78.9	2633/78.0	6101/79.4	0.033	8819/78.9	8828/78.9	< 0.001
	Diabetes: yes	949/9.7	258/8.6	691/10.2	0.055	1099/9.8	1083/9.7	0.005
	Cancer: yes	2555/22.9	845/24.8	1710/22.0	0.065	2525/22.6	2556/22.8	0.006
	CKD: yes	2331/23.2	747/24.0	1584/22.8	0.030	2568/23.0	2564/22.9	0.002
	GORD: yes	3627/32.4	1187/34.8	2440/31.4	0.072	3634/32.5	3642/32.5	0.001
	Dyslipidaemia: yes	6487/66.8	1969/65.6	4518/67.3	0.037	7446/66.6	7434/66.4	0.004
	Parkinsonism: yes	152/1.4	50/1.5	102/1.3	0.013	142/1.3	150/1.3	0.006
	Pulmonary disease: yes	1629/14.6	528/15.5	1101/14.2	0.037	1652/14.8	1632/14.6	0.006
	Gout: yes	541/4.8	181/5.3	360/4.6	0.031	550/4.9	544/4.9	0.002
Polypharmacy: yes		4665/41.7	1399/41.0	3266/42.0	0.025	4703/42.1	4678/41.8	0.005

CKD chronic kidney disease, *GORD* gastro-oesophageal reflux disease, *HDL* high-density lipoprotein, *SMD* standardised mean difference, *3MS* Modified Mini-Mental State examination score, *BMI* body mass index in kilogramme/metre square

Physical activity: usual intensity of physical activity in a typical week; low (never, rare or light) and moderate (moderate to vigorous)

Social support: based on the Lubben Social Network Scale (LSNS-6, ≥ 12 out of 30 points was considered as good)

Multimorbidity: coexistence of two or more chronic health conditions (hypertension, diabetes mellitus, dyslipidaemia, chronic kidney disease, gastroesophageal reflux disease, respiratory condition, osteoarthritis, gout, and Parkinson's disease)

Metabolic syndrome: based on the Adult Treatment Panel III (ATP III) diagnostic criteria as a composite measure of 5 variables (waist circumference, blood pressure, triglyceride, HDL, cholesterol level and blood glucose)

Hypertension: SBP ≥ 140 mmHg or DBP ≥ 90 mmHg or on treatment for high blood pressure

Diabetes: self-report of diabetes or fasting glucose ≥ 126 mg/dL or on treatment for diabetes

Cancer: the diagnosis of any cancer during the study period or a history of a cancer diagnosis by self-report

CKD: an estimated glomerular filtration rate of less than 60 mL/min/1.73 m^2

Diabetes: self-report or the use of any drug use for the treatment of diabetes, including insulin, or a fasting blood glucose level of greater than or equal to 7 mmol/L

Medication use: was self-report and drugs were classified according to the Anatomical Therapeutic Chemical (ATC) system, including N05A, N06A, C10 and A10

Polypharmacy: taking ≥ 5 prescription medications daily

IPTW was based on propensity score adjusted for age, sex, education status, racial white, alcohol, smoking, income, social support, living status, physical activity, BMI, metabolic syndrome, cognition status, multimorbidity, and polypharmacy after multiple imputation

Weighted SMD was presented for those covariates included in the propensity score model considering multicollinearity

in the control arm were more frequently females (58.5% vs 42.9%). The baseline characteristics/covariates and potential confounders were fairly similar after employing the IPTWs (Additional file 2: Fig. S2). The two groups were balanced over the intervention strategies (i.e. UPF high vs UPF low) as evidenced by a standardised mean difference of < 0.1 (Fig. 2).

Associated effect of UPF on the risk of depressive symptoms

At time zero, 17.4% and 15.8% of participants had depressive symptoms in the intervention group and the control group, respectively. During the follow-up period (median with interquartile range: 5.8 ± 2.5 years), 4682 (41.8%) participants; 1457 (42.6%) in the intervention group and 3,225 (41.5%) in the control group had depressive symptoms over the follow-up period.

As shown in Table 3, higher UPF consumption was associated with an increased risk of depressive symptoms among older adults; the associated risk of depressive symptoms among older adults who consumed high UPF (4 or more servings per day) was increased by 10% compared to those consumed low UPF (less than 4 serving per day) (RR: 1.10; 95% CI: (1.04–1.18)). A sensitivity analysis after excluding participants taking antidepressant and/or antipsychotic medications at time zero showed the risk of depressive symptoms in the high UPF group elevated by 11% as compared to the low UPF group (RR: 1.11; 95% CI: (1.04–1.20)). Moreover, after excluding participants taking antidepressant and/or antipsychotic medications at time zero and participants with depressive symptoms at time zero, the association remained significant (RR: 1.09; 95% CI: (1.00–1.19)).

The E-value estimate for the main comparison was 1.43, in which unmeasured confounders must be correlated

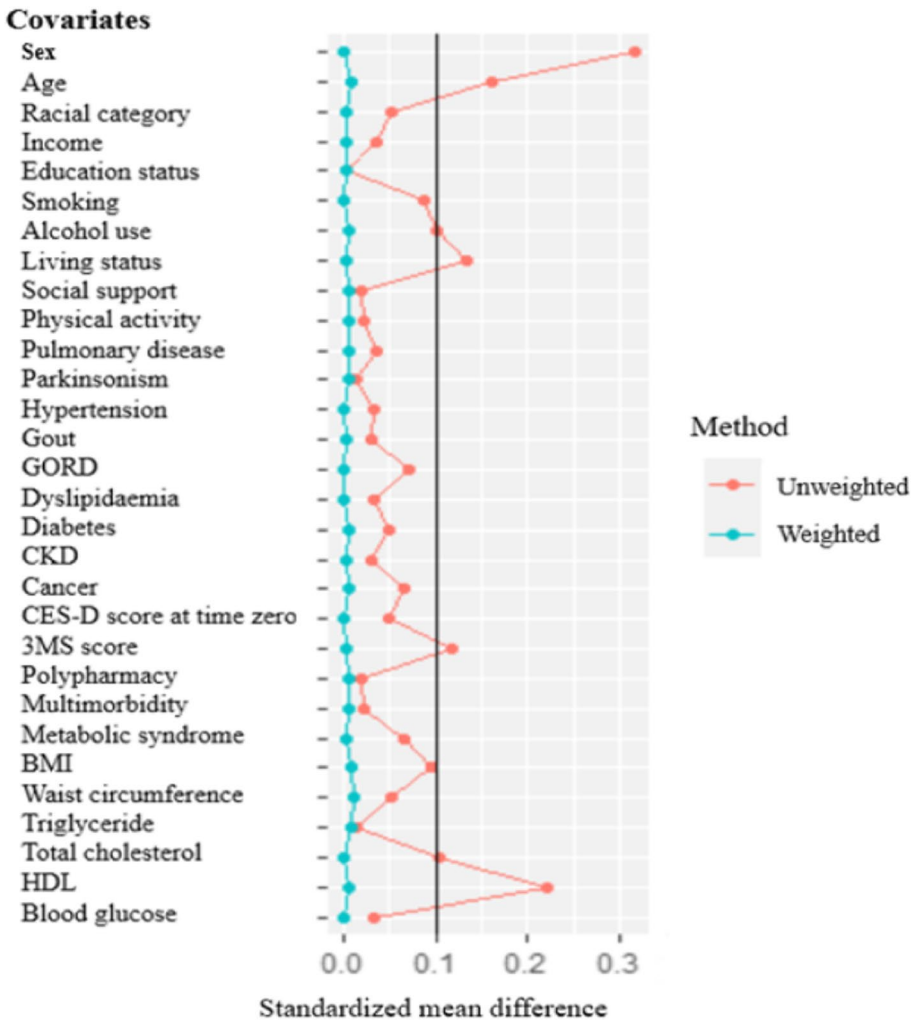

Fig. 2 Absolute standardised mean difference (SMD) for comparisons of baseline characteristics before and after IPTW

Table 3 Model-based risk ratios estimating the risk of depressive symptoms under UPF intervention strategies of the longitudinal cohort study in Australian older adults

Participants	Intervention strategy	Risk of depressive symptoms				
		Model 1		Model 2		
		RR (95%CI)	*p*-value	RR (95%CI)	*p*-value	*E*-value
All sample ($n=11,192$)	Control	1 (reference)	0.003	1 (reference)	0.002	1.43
	Intervention	1.10 (1.03–1.17)		1.10 (1.04–1.18)		
Sub-group one ($n=9560$)	Control	1 (reference)	0.013	1 (reference)	0.004	1.46
	Intervention	1.10 (1.02–1.18)		1.11 (1.04–1.20)		
Sub-group two ($n=8280$)	Control	1 (reference)	0.099	1 (reference)	0.044	1.40
	Intervention	1.09 (0.99–1.17)		1.09 (1.00–1.19)		

Sub-group one: participants on antidepressants/antipsychotics at time zero were excluded

Sub-group two: participants on antidepressants/antipsychotics and participants with depressive symptoms (CES-D 10 ≥ 8) at time zero were excluded

In model 1, covariate age, sex, BMI, smoking, alcohol use and CES-D score at time zero were used for the inverse probability weights. Variable selection was based on the *p*-values in the propensity score model

In model 2, covariates included in model 1 plus race, living status, social support, multimorbidity, baseline cognition, metabolic syndrome, polypharmacy, income, education status, intensity of physical activity, hypertension, diabetes, cancer, CKD, GORD, dyslipidaemia, Parkinsonism, pulmonary disease, gout, waist circumference, total cholesterol, HDL, triglyceride and blood glucose level were included in the inverse probability weights

with both consumption of UPF and risk of depressive symptoms by a risk ratio of at least 1.43 to fully explain away the observed association indicating a substantial effect size for unmeasured confounding would be needed. This suggests that unmeasured confounding was unlikely to alter these findings.

Sub-group analysis

We performed sub-group analyses using sex-specific UPF quartiles of serving and portion size. The associated risk of depressive symptoms among older adults in the fourth UPF serving quartile was increased by 10% as compared to those in the first quartile (RR: 1.10; 95% CI: (1.02–1.20)). Similarly, older adults in the fourth UPF portion size quartile were 1.15 times more likely to develop depressive symptoms as compared to participants in the first quartile (RR: 1.15; 95% CI: (1.04–1.26)). However, no significant relationship was observed among participants in other quartiles (q2 and q3) compared with the first quartile (Additional file 1: Table S3).

Sub-group analyses showed that the association between consumption of UPF and risk of depressive symptoms was significant among females and participants with lower education levels. In addition, sub-group analyses by the presence of multimorbidity and BMI categories (≥ 30 kg/m^2 vs < 30 kg/m^2) showed that the association was stronger among participants without multimorbidity and with higher BMI (Fig. 3).

Replicating the analyses confined to the ASPREE trial period (time zero in 2012 to 2017) indicated that high consumption of UPF adversely impacted the risk of depressive symptoms, similar to the main analysis (RR: 1.12; 95% CI: (1.05–1.20)) (Additional file 1: Table S4). Using CES-D 10 cutoff ≥ 10 (RR: 1.12; 95% CI: (1.03–1.21)) and after excluding participants on antidepressants and/or antipsychotics at time zero (RR: 1.12; 95% CI: (1.02–1.23)) consistent findings were observed with the main analysis (cutoff ≥ 8) (Additional file 1: Table S5).

Associated effect of UPF on the SF-12 Mental Component Score

A total of 11,201 participants had a valid SF-12 score and were included in the analysis. The mean MCS was 55.6 ± SD (55.0 for intervention and 56.9 for control) at time zero and 54.6 ± SD (54.0 for intervention and 55.5 for control) at the last follow-up visit.

The between-group mean difference in MCS was significant, and there was a 0.40-unit decrease in mean MCS in the intervention group (high UPF consumption) compared to the control group (low UPF consumption) (β: −0.40; 95% CI: −0.65 to −0.15).

Analysis using serving quartiles of UPF indicated that the between-group mean difference of MCS in the intervention group (i.e. quartile 4 of UPF serving) decreased by 0.57 units compared to the control group (β: −0.57; 95% CI: −0.89 to −0.25). Further sub-group analysis by sex indicated that the association remains significant in females (Table 4).

Discussion

In this study, we emulated a two-arm randomised pragmatic clinical trial using the ASPREE extended follow-up cohort to evaluate the effect of ultra-processed food use on the risk of depressive symptoms in older adults. We

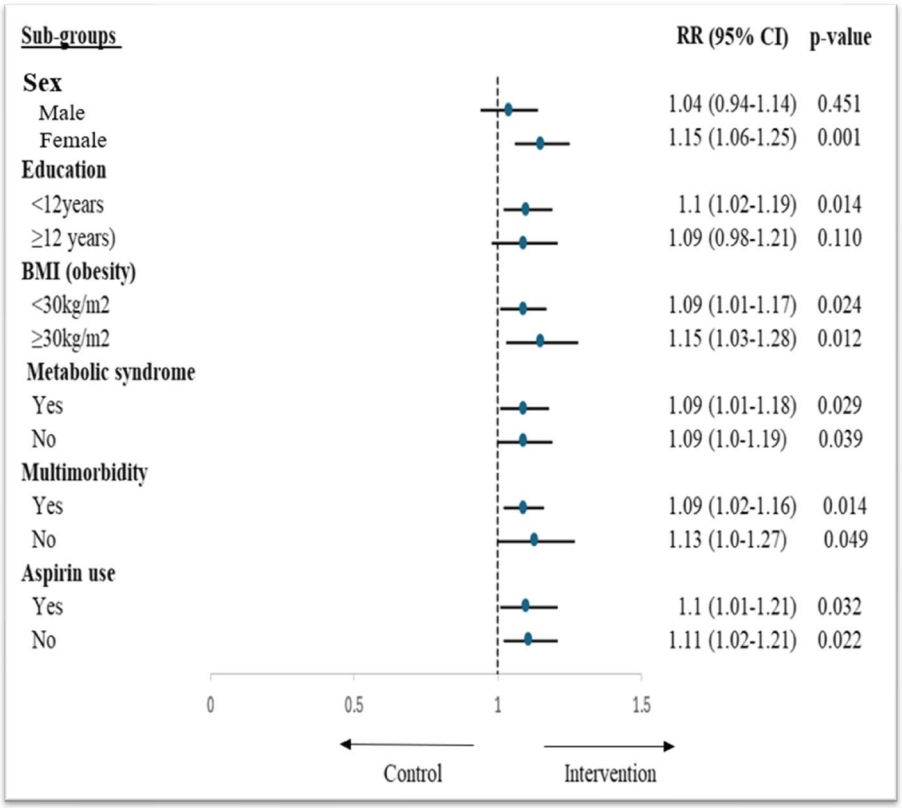

Fig. 3 Sub-group analyses by important characteristics showing the effect of UPF consumption on risk of depressive symptoms among older adults

Table 4 Model-based estimate showing the effect of UPF on mental health quality of life of Australian older adults ($n = 11,201$)

		Category	Coefficient (β) (95% CI)			
			Model 1	*P*-value	Model 2	*P*-value
UPF serving category (high vs low)		high vs low	−0.63 (−0.88 to −0.37)	< 0.001	−0.40 (−0.65 to −0.15)	0.002
UPF serving quartiles		Quartile 2 vs quartile 1	−0.20 (−0.51–0.10)	0.186	−0.14 (−0.45–0.17)	0.387
		Quartile 3 vs quartile 1	−0.28 (−0.58–0.03)	0.072	−0.12 (−0.43–0.19)	0.435
		Quartile 4 vs quartile 1	−0.80 (−1.11 to −0.48)	< 0.001	−0.57 (−0.89 to −0.25)	0.001
Sub-group by sex	Male	High vs low	−0.31 (−0.62–0.00)	0.051	−0.17 (−0.48–0.15)	0.304
	Female	High vs low	−0.92 (−1.30 to −0.54)	< 0.001	−0.61 (−1.00 to −0.23)	0.002

In model 1, covariate age, sex (not for the sub-group), BMI, smoking and alcohol use were used for the inverse probability weights

In model 2, covariates included in model 1 plus race, living status, social support, multimorbidity, baseline cognition, metabolic syndrome, MCS score at time zero, polypharmacy, income, education status, intensity of physical activity, hypertension, diabetes, cancer, CKD, GORD, dyslipidaemia, Parkinsonism, pulmonary disease, gout, waist circumference, HDL, triglyceride and blood glucose level were included in the inverse probability weights

included 11,192 older adults with a median (interquartile range) follow-up of 5.8 ± 2.5 years. In the intention-to-treat analysis, a higher level of ultra-processed food consumption increased the risk of depressive symptoms and adversely affected the SF-12 mental health domain among older adults. The results were robust to challenge in multiple sensitivity analyses, and *E*-value calculation suggested the effect of unmeasured confounders is unlikely to alter the findings. Altogether, the results suggest that greater use of UPF is associated with a higher risk of depressive symptoms and poorer mental health.

Although no randomised trial has investigated the effect of UPF on depressive symptoms and mental health in older adults, prospective cohort studies on the

association between UPF and depressive symptoms in the general adult population using traditional analysis have shown similar findings. The Melbourne Collaborative Cohort Study ($n=23,299$ adults, mean age = 54.2 years) data suggested psychological distress as a marker of depression was adversely associated with UPF consumption [59]. In the Whitehall cohort study of 4554 British adults (mean age 61 years), high intake of UPF was associated with an increased likelihood of recurrent depressive symptoms over 13 years of follow-up [25]. The prospective French NutriNet_Sané study in the adult population aged 18 to 86 years ($n=20,380$) found that an increased proportion of UPF in the diet was associated with an increased risk of depressive symptoms [60]. Although the two studies used similar depression measurement tools, the Whitehall study used the CES-D $20 \geq 16$ or antidepressant use as the endpoint, and the NutriNet_Sané used CES-D $20 \geq 17$ for males and ≥ 23 for females as cutoff points). The short format of the CES-D (CES-D 10), used in this study, has shown good predictive accuracy compared to the 20-item version [43]. Similar findings were observed in studies conducted in the Mediterranean cohort of the SUN project among 14,907 Spanish graduates (mean age = 36.7 years) [38], the Nurses' Health Study prospective study among 31,712 middle-aged females (42–62 years) [37] and a longitudinal study of Brazilian adults ($n=2572$, mean age = 36.1 years) [61]. All these studies were conducted among the general population (younger/ middle-aged adults).

However, a prospective cohort study using the two Brazilian birth cohorts ($n=3165$) reported that no association was observed between quartiles of UPF consumption and incidence of common mental disorders (affective, somatic, and anhedonia symptoms) using a 20-item self-reporting questionnaire [62]. This inconsistent finding may be due to the age difference in the participants, as the latter study was conducted among a younger population (mean age = 20.8 years) in addition to the differences in outcome variables (depression vs common mental disorders). It may be the case that diet quality has a cumulative effect on health and takes several years or decades to manifest.

The main study findings were consistent with a priori sub-group analyses using various participant characteristics. Interestingly, the analysis after excluding participants who were on antidepressants and/or antipsychotics at time zero showed similar findings. We included this segment of the sample in the main analysis because there is evidence of high off-label use of antidepressants [63] and to increase the generalisability of the findings. In the analysis, after excluding participants who were on antidepressants and/or antipsychotics and those with depressive symptoms at time zero, high UPF consumption significantly increased risk of depressive symptoms, although the association was weaker.

In the sensitivity analysis using the CES-D $10 \geq 10$ cutoff score, consistent findings were observed with the main analysis (cutoff ≥ 8). Moreover, the analyses using data during the ASPREE trial period (2012–2017)) and the entire follow-up period to ASPREE-XT (2012–2022) revealed consistent findings. This analysis was conducted to ensure that diet pattern was not altered substantially over time and allows the follow-up period of this study in agreement with the follow-up periods in the previous longitudinal studies that utilised dietary data collected 4 years apart [37, 58].

Sub-group analysis by sex indicated that the association between UPF and risk of depressive symptoms was significant only among females. The non-significant finding among males may be due to insufficient statistical power as more than half of the participants (53.7%) were females. In addition, this could be due to the higher rates of depressive symptoms in females [64] which may increase the likelihood of detecting statistically significant effects in this subgroup. However, further investigation is required to verify the effect of UPF on mental health outcomes across sexes and to explore a possible underlying biological mechanism.

Analyses using quartiles of serving per day as well as portion size indicated that participants in the fourth quartile (higher servings) compared to the first quartile were at a higher risk of developing depressive symptoms over the follow-up period. This finding was in line with the findings of previous longitudinal studies [37, 65]. Although Samuthpongtorn et al.'s study was conducted only on female participants, it also highlighted that higher UPF consumption adversely affects SF-12 mental component quality of life.

Overall, the findings of this study align with existing literature confirming that high UPF consumption adversely affects mental health outcomes. The possible explanation for this relationship could be due to the fact that UPFs are high in added sugar, saturated and trans-fat, low in micronutrients (minerals and vitamins) and contain non-nutritive components such as additives (flavourings, emulsifiers, and sweeteners) [66]. This nutritional composition can lead to chronic inflammation [22, 67] which in turn may contribute to the onset of depressive symptoms [68, 69]. The opportunity cost of a diet high in ultra-processed foods may be lower consumption of nutritionally dense unprocessed foods, which likely convey health and mental health benefits. Inflammatory molecules affect neurotransmitters, neuroendocrine function, and functional brain activity, which are relevant to the physiology of mood that result in changes in emotions and behaviour including low mood, fatigue, anxiety

and sleep disturbances [13, 70]. In addition, added chemicals during food processing and packaging might affect the pathways in the microbiome-gut-brain axis [22]. Moreover, dietary compounds can change antioxidant properties and promote oxidative stress (imbalance of oxidative and antioxidant processes), causing cellular injuries, which is one of the important pathways in mental health disorders including depression [13, 71, 72].

Strengths and limitations

The unique feature of this study is that we emulated a target trial using the core design principles of the target trial methodology and applied advanced statistical techniques. To our knowledge, this is the first target trial emulation that robustly estimated the associated effect of UPF consumption on mental health outcomes and addresses the limitations of previous observational studies. A wide range of known potential confounders (sociodemographics, lifestyle, chronic medical conditions, biomarkers and medication-related factors) were collected and incorporated in balancing off the comparative groups using the IPTW approach. A relatively large sample size with a long follow-up period was another major strength.

While interpreting our findings, we need to consider the following potential limitations. First, although we used the diet screening questionnaire based on the Australian Dietary guideline, questionnaires are prone to measurement errors as a self-reported dietary assessment and risk recall bias, especially given the age of the participants. Given that the NOVA food classification system is a well-established classification system and widely used approach in research, there may still be misclassification bias in UPF labelling, and that magnitude cannot be measured. In addition, in the measurement of UPF, we could not estimate energy intake from our data; instead, we have adjusted for BMI and physical activity in the models as proxies of energy intake. In addition, we conducted a sensitivity analysis using the proportion of UPF or estimated portion size.

Second, the possibility of change in dietary habits and change in UPF use during the follow-ups was not measured. However, we conducted a sensitivity analysis over the first four years of the follow-up period, which showed consistent findings. To assess change in dietary intake over time and its impact on mental health over time, further research incorporating repeated dietary data is warranted. Third, prevalence bias, i.e. participants already adhering to a dietary pattern before study follow-up began, can introduce selection bias if the risk varies with time [73]. In our study, diet was measured at a single time point, and we cannot evaluate the effect of selection bias through a sensitivity analysis that compares those who newly switched to a diet pattern with the long-term users. So, the observed effect could be the impact of long-term habits rather than a diet-based intervention. In addition, the CES-D 10 is a validated self-reported tool to indicate the presence of clinically relevant depressive symptoms rather than a clinical diagnosis of depression.

Lastly, although we considered a comprehensive range of confounders and used the E-value to evaluate the robustness of the findings against unmeasured confounding bias, the issue of unmeasured confounding should be still considered in the interpretation of the findings. The use of trial emulation cannot resolve all potential limitations of observational studies, such as model misspecification and measurement bias.

Conclusions

Our study provides evidence of the real-life association of UPF consumption on the risk of depressive symptoms and mental health quality of life in Australian older adults. The findings from this target trial emulation highlight the importance of reducing UPF consumption in preventing depressive symptoms and improving mental health in older adults. This provides a rationale for developing and evaluating the effectiveness of population-based and public health programmes aiming to reduce dietary UPF intake to improve the mental health of older adults. Interventional studies, such as randomised controlled dietary trials using repeated food frequency questionnaires and clinical depression diagnosis, are needed to confirm these findings and to assess the feasibility and efficacy of dietary changes in reducing depression risk in ageing populations.

Abbreviations

ASPREE	ASPrin in Reducing Events in the Elderly study
ALSOP	ASPREE Longitudinal Study of Older Persons
BMI	Body mass index
CES-D 10	Center for Epidemiologic Studies-Depression 10-item
CKD	Chronic kidney disease
CI	Confidence interval
GORD	Gastro-oesophageal reflux disease
IPTW	Inverse probability of treatment weighting
MSM	Marginal structural model
MCS	Mental Component Score
3MS	Modified Mini-Mental State examination
SF-12	Short Form Health Survey
SMD	Standardised mean difference
RCTs	Randomised controlled trials
RR	Risk ratio
UPF	Ultra-processed food
WHO	World Health Organisation

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-025-04002-4.

Additional file 1: Table S1-S5. Table S1. Classification of food and drink items according to the NOVA food classification system. Table S2.

Characteristics of study participants according to serving quartiles of UPF. Table S3. Sensitivity analyses using UPF quartiles of serving/day and portion size as an intervention strategy. Table S4. Sensitivity analyses using ASPREE trial period. Table S5. Sensitivity analyses using CES-D 10 cutoff ≥ 10.

Additional file 2: Figures S1-S2. Figure S1. Directed acyclic graph showing the relationship of covariates with the intervention and outcome. Figure S2. Distribution of propensity score before and after adjustment.

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Authors' contributions
BM: conceived, conceptualized and designed the study, analysis of data, interpretation of the results and wrote the first draft of the manuscript. ML, JAP, BA: provided guidance and supervision and edited the manuscript. MB, MF, MML, SGO, JR, AJO, RLW and JJM: edited the manuscript. MM: conceived and designed the study, provided guidance, supervision and edited the manuscript. All authors approved the final version of the manuscript.

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Data availability
Data cannot be shared publicly for legal and ethical reasons as data are part of a large ongoing observational cohort. Data are available from Monash University for researchers who meet the criteria at https://aspree.org/aus/for-researchers/. The analysis code can be obtained from the corresponding author upon a reasonable request.

Declarations

Ethics approval and consent to participate
The ASPREE trial was conducted in accordance with the 2008 Declaration of Helsinki and approved by the ethics review board at each participating institution. Monash University Human Research Ethics Committee and the Alfred Hospital Human Research Ethics Committee approved the ALSOP and ASPREE-XT (Monash 4HREC CF11/1935/2011001094 and Alfred HREC 593/17). All participants provided their written informed consent to participation. The current secondary analysis was approved by the Monash University Human Research Ethics Committee.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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