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High ultra-processed food consumption is associated with elevated psychological distress as an indicator of depression in adults from the Melbourne Collaborative Cohort Study

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ABSTRACT

Background: Few studies have tested longitudinal associations between ultra-processed food consumption and depressive outcomes. As such, further investigation and replication are necessary. The aim of this study is to examine associations of ultra-processed food intake with elevated psychological distress as an indicator of depression after 15 years.

Method: Data from the Melbourne Collaborative Cohort Study (MCCS) were analysed (n = 23,299). We applied the NOVA food classification system to a food frequency questionnaire (FFQ) to determine ultra-processed food intake at baseline. We categorised energy-adjusted ultra-processed food consumption into quartiles by using the distribution of the dataset. Psychological distress was measured by the ten-item Kessler Psychological Distress Scale (K10). We fitted unadjusted and adjusted logistic regression models to assess the association of ultra-processed food consumption (exposure) with elevated psychological distress (outcome and defined as K10 $\geq$ 20). We fitted additional logistic regression models to determine whether these associations were modified by sex, age and body mass index.

Results: After adjusting for sociodemographic characteristics and lifestyle and health-related behaviours, participants with the highest relative intake of ultra-processed food were at increased odds of elevated psychological distress compared to participants with the lowest intake (aOR: 1.23; 95%CI: 1.10, 1.38, p for trend = 0.001). We found no evidence for an interaction of sex, age and body mass index with ultra-processed food intake.

Conclusion: Higher ultra-processed food intake at baseline was associated with subsequent elevated psychological distress as an indicator of depression at follow-up. Further prospective and intervention studies are necessary to identify possible underlying pathways, specify the precise attributes of ultra-processed food that confer harm, and optimise nutrition-related and public health strategies for common mental disorders.

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1. Introduction

There is growing recognition that mental disorders are leading causes of disease burden (Patel et al., 2018), with global burden of disease studies showing that depressive disorders are one of the most prevalent mental disorders and confer the greatest overall burden (Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 2022). Measures of general psychological distress that include questions about depressive symptoms are an appropriate and effective means of identifying 'cases' or current diagnoses of depression in the community, as defined by globally used diagnostic tools such as the International Classification of Diseases – 10th Edition (ICD-10) and Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition (DSM-IV) (Andrews and Slade, 2001).

Poor diet quality has been implicated as one potentially modifiable risk factor for depression (Marx et al., 2021a). The link between poor dietary quality and depression has largely been observed using diet quality indices. Additional studies have used a dietary pattern analysis approach – by defining patterns such as high intakes of 'fast food', red and processed meat, refined grains, sweets, salty snacks and sugar-sweetened beverages – and associated macronutrient content such as saturated fat and sugar intake (Rahe et al., 2014; Jacka et al., 2014; Marx et al., 2021b; Lassale et al., 2019). However, less is known about the role of foods classified according to different degrees of processing as a separate indicator of dietary quality in relation to depression.

A relatively novel tool, known as NOVA (name not acronym), provides a separate measure of diet quality, by classifying and aggregating foods into categories based on the extent and purpose of food processing (Monteiro et al., 2019). NOVA's categories include four incrementally processed groups, namely: 1) unprocessed or minimally processed foods, 2) processed culinary ingredients, 3) processed foods, and 4) ultra-processed foods. Ultra-processed foods are manufactured through various commercial processes and are predominantly comprised of high-yield and inexpensive ingredients (Monteiro et al., 2019). These include components 'never or rarely used in kitchens, or classes of additives whose function it is to make the final product palatable or more appealing' (Monteiro et al., 2019). Recent time-series country-level sales data demonstrate an upward trend in the range and number of ultra-processed foods purchased worldwide, reflecting a 'nutrition transition' to a more processed global diet (Baker et al., 2020; Monteiro et al., 2013).

Our recent systematic reviews and meta-analyses indicate a role for ultra-processed foods in the prevalence, incidence, morbidity and mortality of many chronic non-communicable diseases (Lane et al., 2021; Lane et al., 2022a; Moradi et al., 2021). Indeed, one of our reviews suggested bidirectional associations exist between the intake of ultra-processed food and adverse mental health (Lane et al., 2022a). The strongest evidence, however, was identified through meta-analyses of cross-sectional studies that showed ultra-processed food intake (exposure) was associated with depressive and anxiety symptoms (outcomes). These meta-analyses demonstrated direct associations, both when depressive and anxiety symptoms were assessed together as well as separately (Lane et al., 2022a). Despite these findings, the majority of studies included in this review were conducted cross-sectionally and in one region (Brazil). This does not provide information about possible longitudinal associations of ultra-processed food consumption with common mental disorders such as depression and limits interpretations to the Brazilian population.

Similar generalisability issues are present in our previous meta-analysis of prospective studies (Lane et al., 2022a). Although this meta-analysis demonstrated that greater ultra-processed food intake was associated with increased risk of subsequent depression (hazard ratio: 1.22, 95%CIs 1.16 to 1.28), only two longitudinal studies were available for inclusion at the time of publication (Lane et al., 2022a). Further, the two studies identified were confined to European cohorts from the Mediterranean region (Spain and France). Both studies were subject to key limitations, which do not necessarily make them generalisable to other settings (Adjibade et al., 2019; Gómez-Donoso et al., 2018). For example, the Seguimiento Universidad de Navarra (SUN) cohort was a relatively homogeneous sample of university graduates (n = 14,907) (Gómez-Donoso et al., 2018). The NutriNet-Santé cohort collected depressive symptoms data via a web-based system (n = 26,730) (Adjibade et al., 2019), which may yield different results compared with more direct and traditional methods of data collection, such as face-to-face or pencil-to-paper approaches (van Gelder et al., 2010). Furthermore, the French version of the Center for Epidemiological Studies Depression scale was systematically validated offline (Morin et al., 2011). It therefore remains unclear whether scores obtained via the web can be compared with offline cut-off scores (van Gelder et al., 2010). Moreover, individuals from Mediterranean countries have some of the lowest intake of ultra-processed food (~10 % of total energy), whereas energy intake from ultra-processed food is upwards of 40 % in countries such as Australia, the United States of America, the United Kingdom and Canada (Marino et al., 2021). This again highlights the lack of generalisability of previously published studies.

The Melbourne Collaborative Cohort Study (MCCS) is an Australian prospective cohort study, with aims to investigate associations between diet, lifestyle and chronic non-communicable diseases (Milne et al., 2017). The MCCS is a suitable dataset in which to address the limitations of previous studies given its longitudinal design, broad scope and sampling method. This included deliberately recruiting migrants from Southern Europe (30 %) with distinct dietary and lifestyle differences from the majority of participants who were born in Australia or New Zealand (69 %) (Milne et al., 2017). Thus, we primarily aimed to investigate an association between ultra-processed food intake at baseline and depressive symptoms at 13–17 years follow-up in a sample of individuals with diverse backgrounds and in a region where the intake of ultra-processed food is higher than previously studied cohorts (Lane et al., 2022b; Machado et al., 2019).

2. Methods

2.1. Pre-registration and ethics approval

This study was prospectively registered with Open Science Framework (OSF) registry (internet archive link: https://archive.org/details/osf-registrations-e3cht-v1), and was reported in line with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement and checklist for cohort studies (Vandenbroucke et al., 2007). The study protocol for the original MCCS project was approved by the Cancer Council Victoria's Human Research Ethics Committee, and participants provided written consent to participate and for researcher access to their medical records (Hodge et al., 2016). The current study was approved for exemption from ethical review in accordance with the National Statement on Ethical Conduct in Human Research (2007, updated 2018) Section 5.1.22 by the Deakin University Human Research Ethics Committee (project number: 2020–415).

2.2. Cohort profile

A detailed description of the MCCS main- and case-cohort profiles, as well as methods for data collection, has been published elsewhere (Milne et al., 2017). In brief, 41,513 participants aged between 27 and 76 years were recruited from the Melbourne metropolitan area between 1990 and 1994. Of these, 24,469 were women, and 99 % were aged between 40 and 69 years. Migrants from Southern Europe were deliberately oversampled to expand the range of diet and lifestyle exposures. An initial follow-up was completed between 1995 and 1998 (follow-up 1), with a second follow-up (follow-up 2) completed between 2003 and 2007 and being the follow-up of interest for our current study (Milne et al., 2017). Demographic, lifestyle, drug audit, dietary information, anthropometric measures, and blood samples were collected at baseline

during face-to-face clinical visits. At follow-up 2, participants attended another clinic for face-to-face interviews and physical measurements.

Participants were eligible for this study if baseline dietary and follow-up psychological distress questionnaires were completed (n = 24,674; Fig. 1). Of 41,513 original participants who were initially recruited at baseline (1990–94) and then of 28,240 participants who attended follow-up 2 (2003–07), 24,674 participants completed dietary intake assessments at baseline as well as the psychological distress questionnaire at follow-up 2. After excluding participants who took medication for depression and anxiety at baseline (n = 1047) and participants with total energy intake (kJ/d) below the 1st or above the 99th percentiles (n = 328), 23,299 participants remained for analysis.

2.3. Exposure: Dietary assessment

Dietary data were collected at baseline from participants who attended face-to-face clinics. A self-administered 121-item Food Frequency Questionnaire (FFQ) was used to assess dietary intake (Ireland et al., 1994). This questionnaire was designed specifically for use in the MCCS and was based on a study of weighed food records in 810 Melbournians (Ireland et al., 1994), with validation reported in relation to antioxidant and fatty acid intakes (Hodge et al., 2009; Hodge et al., 2007). The demographic characteristics of the MCCS and these 810 Melbournians were comparable (data not shown).

For the current study, and as per the methods employed elsewhere (Machado et al., 2019), two authors with Australian food and dietary intake knowledge applied the NOVA food classification system to all FFQ food items, and data were classified as ultra-processed foods or non-ultra-processed foods, described below. FFQs have been shown to provide an adequate level of information to categorise food items based on NOVA groups (Khandpur et al., 2021). Cross-sectional data from the National Nutrition Survey 1995–96 (data not published) and Australian National Nutrition and Physical Activity Survey (NNPAS) 2011–12 were used for comparison and decision making when it was not possible to discriminate food items (e.g. food items like 'bread', 'pasta or noodles', 'low fat cheese', 'yoghurt', 'fruit juice') (Machado et al., 2019). In cases where the classification of a food item was unclear, the conservative alternative was chosen (i.e., homemade or processed rather than ultra-processed) and thus disaggregated (for more detailed information, see online supplementary appendices 1 to 2 in (Machado et al., 2019)).

Ultra-processed foods (NOVA group 4) include soft drinks, sweet or savoury packaged snacks, confectionery, packaged breads and buns, margarine, reconstituted meat products and pre-prepared frozen or shelf-stable dishes (Patel et al., 2018). Non-ultra-processed foods, as characterised by NOVA, include unprocessed or minimally processed foods (NOVA group 1) such as rice and other cereals, meat, fish, milk, eggs, fruit, roots and tubers, vegetables, nuts and seeds; processed culinary ingredients (NOVA group 2) such as sugar, plant oils and butter; and, processed foods (NOVA group 3) such as processed breads and cheese, canned fruit and fish, and salted and smoked meats. A more detailed description of the NOVA food classification system can be found elsewhere (Monteiro et al., 2019).

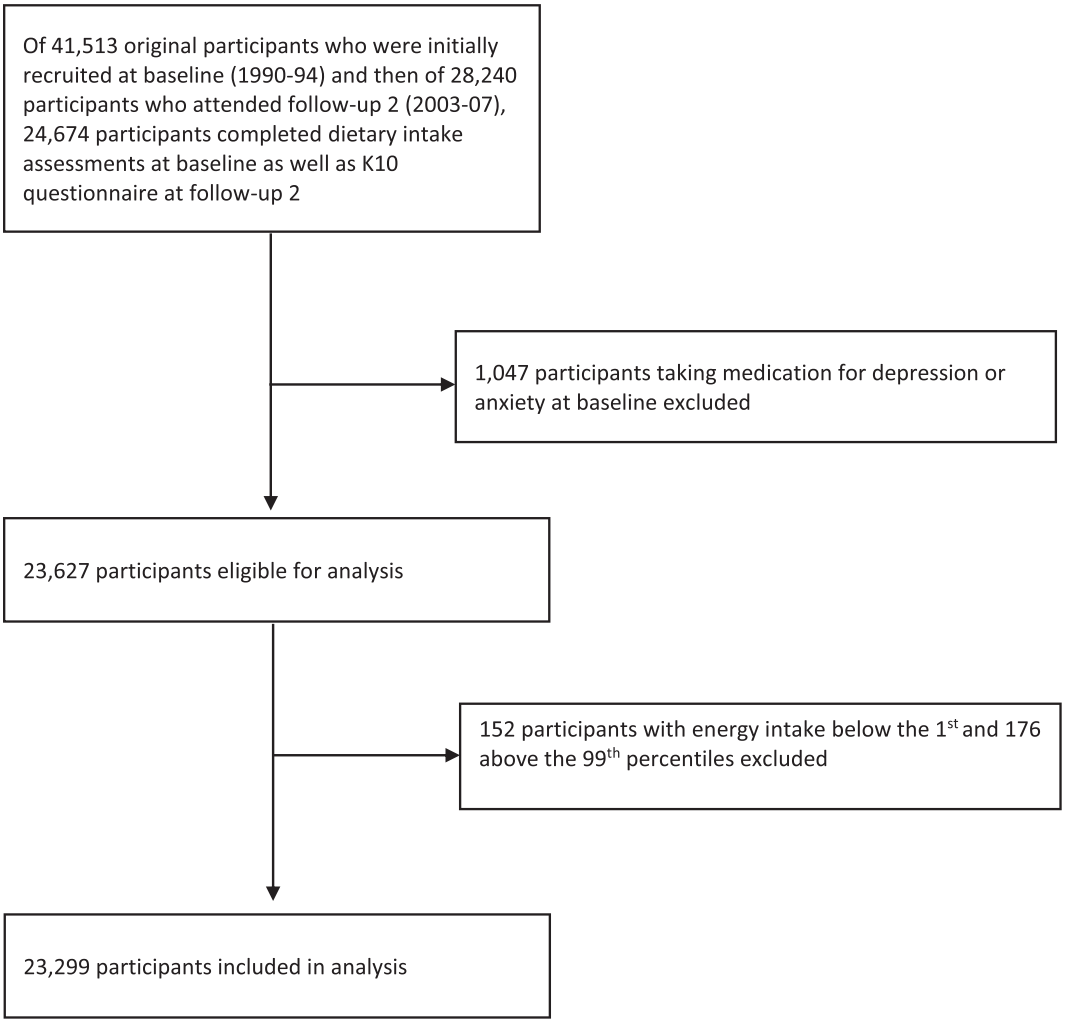

Fig. 1. Flow-chart of participant selection. *MCCS* Melbourne Collaborative Cohort Study, *K10* Kessler Psychological Distress Scale (K10).

The mean daily contribution of ultra-processed foods to intake of total energy (kilojoules) and weight (grams) were calculated by transforming frequencies into grams, based on sex-specific portion sizes of each food, multiplied by the daily equivalent frequency as per previous research (Ireland et al., 1994; The Cancer Council Victoria Epidemiology Centre, 2008; Bassett et al., 2016). Energy was estimated based on the Nutrient Data Table for Use in Australia 1995 (NUTTAB 95). The NUTTAB 95 food composition database contains information for 1800 foods and beverages available in Australia (Lewis et al., 1995).

2.4. Outcome: Psychological distress assessment

Psychological distress at follow-up was measured using the ten-item Kessler Psychological Distress Scale (K10) (Kessler et al., 2002). The K10 is a widely used screening tool to monitor the population prevalence of non-specific psychological distress based on manifestations of behaviour, cognition, emotion and psychophysiology, with symptoms including fatigue, hopelessness, nervousness, sadness and worthlessness (Kessler et al., 2003). It has been used in, and validated across, international (Kessler et al., 2002) and Australian population-based surveys (Andrews and Slade, 2001). The K10 is based on 10 questions that assess anxiety and depressive symptoms during the 30 days prior to the survey. The K10 is scored using a five-level response scale on the frequency of symptoms reported for each item, where 1 is the minimum score for each item (none of the time) and 5 is the maximum score (all of the time). The sum of these scores yields a maximum possible score of 50, with higher scores indicating greater psychological distress.

While the K10 assesses non-specific psychological distress, prior research has reported associations between higher scores on the K10 and the diagnosis of common mental disorders (Australian Bureau of Statistics ABS, 2007). As such, we investigated psychological distress as a marker for depression and used the previously reported cut-off point of at or above 20 to indicate elevated psychological distress (Hodge et al., 2013). This cut-off point also has high sensitivity (0.66) and specificity (0.92) for diagnosis of any current anxiety or depressive disorder in a community sample of Australians, as compared to ICD-10 and DSM-IV (Andrews and Slade, 2001). Symptoms of psychological distress were not assessed at the baseline survey. In line with methods previously used in the ultra-processed food-depression literature (Gómez-Donoso et al., 2018), medication use for depression and anxiety was used to account for elevated psychological distress at baseline. Medication use has been shown to be a valid and reliable proxy method to estimate disease prevalence in the absence of more direct sources or measures, with previous studies reporting high correlations (up to 0.73) between these two methods (Füssenich et al., 2021; Cossman et al., 2010).

2.5. Assessment of covariates

Covariates were identified a priori based on previous literature (Adjibade et al., 2019; Gómez-Donoso et al., 2018; Hodge et al., 2013). They were added to a directed acyclic graph to map hypothesised causal relationships between all relevant variables (Fig. S1). These were measured at baseline via a structured interview and included sociodemographic characteristics, lifestyle and health related factors, and history of non-communicable diseases.

Specifically, the sociodemographic variables of interest included: sex (male, female), age (continuous), education (primary school, high/technical school, tertiary degree or diploma), country of birth (Australia/New Zealand, United Kingdom/Malta, Italy, Greece), marital status (married, de facto, divorced, separated, widow), number of people occupying household (1, 2, 3–4, 5+) and Socio-Economic Indexes for Areas (SEIFA) – Index of Relative Socio-Economic Disadvantage. SEIFA scores are recorded by the Australian Bureau of Statistics about the relative socioeconomic advantage and disadvantage of defined geographical areas (postal code, in this case) (Australian Bureau of Statistics, 2022). We divided these SEIFA scores into quintiles, with the lowest and highest representing the greatest and least disadvantaged, respectively.

We additionally included lifestyle and health related factors such as: smoking status (never smoked, current smoker, and former smoker), alcohol intake (lifetime abstainers, ex-drinkers, and current drinkers (further categorised as up to 19, 20–29, 30–39 and 40+ g/d)), and physical activity over the last 6 months (a score was calculated ranging from 0 to 16 based on the frequency of walking, less vigorous and vigorous activity multiplied by two and this was then divided into categories, namely: 0 [none], >0 and < 4 [low], ≥ 4 and < 6 [moderate], ≥ 6 [high] (Hodge et al., 2016; RJ et al., 2004)). These sociodemographic and lifestyle and health factors were used as covariates in the main effects models. Finally, we excluded participants with history of non-communicable diseases, such as cancer, cardiovascular diseases, diabetes mellitus and body mass index $\geq$30, as part of our sensitivity analysis to reduce the possibility of sampling biases. Body mass index was calculated as kg/m^2 (Milne et al., 2017).

2.6. Statistical analyses

Participant characteristics, including baseline intakes of carbohydrate, protein, fibre and fat (grams per day) as well as intakes of total energy (kilojoules per day), fish (times per week) and fruit and vegetable (times per day), were summarised using mean and standard deviation (SD) for continuous variables and frequency and percentage for categorical variables, respectively. As per previous studies (Srour et al., 2019a; Srour et al., 2019b; Schnabel et al., 2019; Julia et al., 2018), we sought to better account for ultra-processed foods that provided little to no energy (e.g. artificially sweetened beverages). Thus, the total weight of ultra-processed foods in grams per day was adjusted for energy using Willett's residual method (Willett et al., 1997) and used to model our exposure. In this procedure, a linear model was executed to regress participants' ultra-processed food intakes on their total energy intakes (Willett et al., 1997). The residuals from the regression were then included as the main exposure and they represent the differences between participants' actual intake of ultra-processed food and the intake predicted by their total energy intake (Willett et al., 1997). We visually and statistically assessed the linearity of the association between ultra-processed food intake and psychological distress and found some evidence for non-linearity. As such, we categorised the energy-adjusted ultra-processed food variable into quartiles based on the distribution of the dataset. *P* values for trend were estimated by using the quartiles of energy-adjusted ultra-processed food consumption as a continuous ordinal variable and the Wald $\chi 2$ method. We were unable to estimate risk ratios given baseline K10 data were unavailable. As such, we fitted logistic regression models to assess the odds of elevated psychological distress (outcome and defined as K10 $\geq$ 20) associated with quartiles of ultra-processed food (exposure).

Three different sequential models were fitted: energy-adjusted ultra-processed food as the exposure variable (model 1); additionally adjusted for sociodemographic characteristics, such as sex (male, female), age (continuous), education (primary school, high/technical school, tertiary degree or diploma), country of birth (Australia/New Zealand, United Kingdom/Malta, Italy, Greece), marital status (married, de facto, divorced, separated, widow), number of people occupying household (1, 2, 3–4, 5+) and SEIFA scores (quintiles) (model 2); and, a fully adjusted model that further adjusted for lifestyle and health related factors, such as smoking status (never smoked, current smoker, and former smoker), alcohol intake (lifetime abstainers, ex-drinkers, and current drinkers (further divided as up to 19, 20–29, 30–39 and 40+ g/d)), physical activity over the last 6 months (0 [none], >0 and < 4 [low], ≥ 4 and < 6 [moderate], ≥ 6 [high] (Hodge et al., 2016; RJ et al., 2004)) (model 3). Model 3 was considered our main model. As per our pre-registered analysis plan, we had planned additional analyses to investigate the potential mediating effect of hsCRP, but due to sample size restrictions ($n = 912$), this analysis was not possible.

As per previous ultra-processed food-depression studies (Adjibade et al., 2019; Gómez-Donoso et al., 2018), we conducted supplementary analyses to 1) stratify by sex (male, female), age (<60 years, ≥60 years) and body mass index (18.5 to 24.99 kg/m^2, 25 to 29.99 kg/m^2, ≥30 kg/m^2; denoting categories of 'normal weight', 'overweight' and 'obese', respectively), and 2) assess interactions and the potential effect modification by these variables with ultra-processed foods consumption. It is important to highlight here that diseases such as cancer, cardiovascular diseases, diabetes and body mass index at or above 30 kg/m^2 were considered as potential intermediates in any association between ultra-processed food consumption and depression, rather than confounders (see (MacKinnon and Lamp, 2021; Ananth and Schisterman, 2017)). As such, and as per our pre-registered analysis plan, we assessed the possible influence of these diseases by performing sensitivity analyses to exclude people with prevalent cancer (n = 1543), cardiovascular diseases (n = 4439), diabetes (n = 478) and body mass index ≥30 (n = 3879). Sensitivity analyses were also undertaken 1) using the proportion of ultra-processed food consumption in weight as the exposure variable (modelled as quartiles of ultra-processed food/total food, % grams per day), and 2) additionally adjusting for body mass index (continuous) and intakes of fish (times per week) and fruits and vegetables (times per day); that is, in addition to controlling for the sociodemographic characteristics and health related behaviours listed above for model 3. Lastly, the shape of the dose-response association between the consumption of ultra-processed food and the risk of elevated psychological distress was estimated with restricted cubic spline analysis (Desquilbet and Mariotti, 2010).

All analyses were undertaken using R version 3.6.3 (29-02-2020) (R Core Team, 2017).

3. Results

3.1. Participant characteristics

This study included 13,876 women and 9423 men. Table 1 details participants' sociodemographic and lifestyle characteristics at baseline (as well as age both at baseline and follow-up) according to quartiles of ultra-processed food consumption. Participants in the highest quartile of ultra-processed food consumption appeared to be more likely to be born in Australia or New Zealand and live alone. They were also less likely to have a tertiary education, be the least disadvantaged (as per the SEIFA index), be in a married or de factor relationship and to engage in a high level of physical activity. Participants who reported higher ultra-processed food consumption also had a lower intake of protein, fibre and saturated fat (grams per day) as well as lower total energy (kilojoules per day) and fruit and vegetable intake (times per day).

3.2. Primary analysis

Table 2 details the results of the multivariable adjusted models with the categorical exposure variable. In model 1, compared to participants in the lowest quartile, participants in the highest quartile of energy-adjusted ultra-processed food intake had 1.14-fold increased odds of elevated psychological distress (aOR: 1.14; 95%CIs: 1.03–1.27, p for trend = 0.038). After accounting for potential covariates in the main multivariable analysis (model 3), the magnitude of the association increased to 1.23-fold higher odds of elevated psychological distress (aOR: 1.23; 95%CIs: 1.10–1.38, p for trend = 0.001). Across all models, when each category of energy-adjusted ultra-processed food consumption was compared with the reference quartile (first), it was only the top quartile (fourth) that was significantly different. That is, there was an apparent threshold effect, where the direct associations between ultra-processed food consumption and elevated psychological distress were observed only among participants with very high relative consumption of ultra-processed food. Results were consistent between our main models and sensitivity analyses (see Tables S2 and S3). Additionally, the

Table 1
Descriptive characteristics of the study population at baseline according to ultra-processed food consumption.

	Quartiles of energy-adjusted ultra-processed food intake				Overall sample
n (frequency)	Q1 (n = 5825)	Q2 (n = 5825)	Q3 (n = 5824)	Q4 (n = 5825)	Total (n = 23,299)
Age (years) at baseline – Mean (SD)	53.9 (8.3)	54.2 (8.5)	54.6 (8.6)	54.4 (8.6)	54.2 (8.5)
Age (years) at follow-up – Mean (SD)	65.6 (8.6)	65.9 (8.7)	66.3 (8.9)	66.2 (8.9)	66.0 (8.8)
Female	3284 (56.4 %)	3707 (63.6 %)	3732 (64.1 %)	3153 (54.1 %)	13,876 (59.6 %)
At least some tertiary education[a]	2086 (35.8 %)	1871 (32.1 %)	1722 (29.6 %)	1578 (27.1 %)	7257 (31.1 %)
Born in Australian/ New Zealand	3931 (67.5 %)	4365 (74.9 %)	4579 (78.6 %)	4496 (77.2 %)	17,371 (74.6 %)
Top quintile of SEIFA[b] index (least disadvantaged)	1961 (33.9 %)	1865 (32.3 %)	1750 (30.2 %)	1585 (27.4 %)	7161 (30.9 %)
Married/de facto	4324 (76.8 %)	4190 (74.4 %)	4166 (74 %)	4160 (74.3 %)	16,840 (74.8 %)
Lives alone	724 (12.4 %)	784 (13.5 %)	840 (14.4 %)	856 (14.7 %)	3204 (13.8 %)
Current smoker	506 (8.7 %)	507 (8.7 %)	524 (9.0 %)	526 (9.0 %)	2063 (8.9 %)
High physical activity score[c] (≥ 6)	1585 (27.2 %)	1439 (24.7 %)	1342 (23.0 %)	1468 (25.2 %)	5834 (25.0 %)
Alcohol intake of up to 19 g/d	2673 (46.5 %)	2766 (48.0 %)	2762 (48.0 %)	2527 (44.1 %)	10,728 (46.6 %)
Body mass index (kg/m^2) - Mean (SD)	26.2 (4.0)	26.3 (4.2)	26.4 (4.2)	27.2 (4.4)	26.5 (4.2)
Proportion (%) of energy-adjusted ultra-processed food (g/d) - Mean (SD)	15.9 (5.3)	21.0 (5.4)	26.8 (6.1)	37.1 (9.9)	25.2 (10.5)
Proportion (%) of energy-adjusted ultra-processed food (kJ/d) - Mean (SD)	30.8 (9.0)	38.5 (9.1)	44.5 (10.2)	47.3 (11.4)	40.3 (11.8)
Total energy-adjusted ultra-processed food (g/d) - Mean (SD)	282.9 (120.3)	308.1 (125.2)	379.7 (133.4)	649.6 (304.6)	405.1 (237.4)
Total energy-adjusted ultra-processed food (kJ/d) - Mean (SD)	2798.1 (1352.0)	2968.5 (1402.9)	3426.0 (1552.7)	4041.6 (1828.7)	3308.5 (1618.4)
Total energy intake with alcoholic beverages (kj/d) – Mean (SD)	10,166.2 (3114.7)	8711.2 (2884.1)	8739.8 (3011.1)	9654.1 (3303.5)	9317.9 (3143.6)
Total energy intake without alcoholic beverages (kj/d) – Mean (SD)	9718.7 (3072.3)	8310.4 (2832.9)	8374.9 (2942.7)	9282.4 (3233.8)	8921.6 (3082.8)
Carbohydrate (g/d) – Mean (SD)	267.3 (103.1)	233.5 (95.4)	240.0 (96.7)	272.3 (109.4)	253.3 (102.7)
Protein (g/d) – Mean (SD)	112.4 (35.1)	93.6 (28.5)	91.9 (29.8)	99.2 (32.3)	99.3 (32.5)
Fat (g/d) – Mean (SD)	91.6 (32.4)	77.5 (27.8)	77.3 (29.1)	84.1 (31.6)	82.6 (30.8)
Saturated fat (g/d) – Mean (SD)	37.0 (14.6)	31.5 (12.9)	31.5 (13.3)	34.0 (14.4)	33.5 (14.0)

(continued on next page)

Table 1 (*continued*)

	Quartiles of energy-adjusted ultra-processed food intake				Overall sample
n (frequency)	Q1 (*n* = 5825)	Q2 (n = 5825)	Q3 (*n* = 5824)	Q4 (n = 5825)	Total (n = 23,299)
Monounsaturated fat (g/d) – Mean (SD)	33.0 (12.2)	27.5 (9.8)	27.2 (10.2)	29.8 (11.3)	29.4 (11.2)
Polyunsaturated fat (g/d) – Mean (SD)	13.7 (5.8)	12.0 (5.3)	12.3 (5.5)	13.4 (5.8)	12.9 (5.6)
Fibre (g/d) – Mean (SD)	36.4 (12.7)	29.7 (10.4)	28.8 (10.3)	30.7 (11.3)	31.4 (11.6)
Fruit intake (times/d) – Mean (SD)	5.5 (4.0)	3.8 (2.5)	3.5 (2.3)	3.9 (2.8)	4.2 (3.1)
Vegetable intake (times/d) – Mean (SD)	6.3 (3.4)	5.4 (2.8)	5.0 (2.6)	5.1 (3.1)	5.5 (3.1)
Fish intake (times/w) – Mean (SD)	2.2 (2.0)	1.8 (1.4)	1.7 (1.4)	1.8 (1.6)	1.9 (1.6)

[a] Participants who had some study towards a tertiary degree or diploma as well as participants who had completed a tertiary degree or diploma.
[b] SEIFA = Socio-Economic Indexes for Areas.
[c] Ordinal score based on frequency of walking plus frequency of less vigorous activity plus twice the frequency of vigorous activity, and ranging from 0 to 16 (Hodge et al., 2016; RJ et al., 2004).

restricted cubic spline analysis that was used to assess the shape of the dose-response association showed that increasing ultra-processed food consumption was associated with a higher risk of elevated psychological distress; however, and in line with our main models, participants in the top quartile (fourth) had a significantly higher risk of elevated psychological distress compared to participants in the first three quartiles (see Fig. S2).

3.3. Supplementary analyses

We found little evidence for an interaction of ultra-processed food with sex (male, female), age (<60 years, ≥60 years) and body mass index (18.5 to 24.99 kg/m^2, 25 to 29.99 kg/m^2, ≥30 kg/m^2) (all *p*-values >0.05). In addition, stratified associations between higher intake of energy-adjusted ultra-processed food and increased odds of elevated psychological distress appeared generally similar across subgroups of sex, age and body mass index (see Table S1).

4. Discussion

In this Melbourne-based cohort of 23,299 participants, higher consumption of ultra-processed food at baseline was associated with elevated psychological distress, as a marker for depression, at 15 years follow-up. The results of our study build upon previous works that have demonstrated direct associations between the intake of ultra-processed food and the prevalence (Zheng et al., 2020; Werneck et al., 2020; Coletro et al., 2022; Bonaccio et al., 2021) and incidence (Adjibade et al., 2019; Gómez-Donoso et al., 2018) of depression or depressive symptoms (Lane et al., 2022a).

We observed comparable effect estimates in this study (adjusted odds ratio: 1.22; 95%CIs: 1.08–1.37) to the two previously mentioned longitudinal studies in the SUN and NutriNet-Santé cohorts (adjusted hazard ratios: 1.33; 95%CIs: 1.07–1.64 (Gómez-Donoso et al., 2018) and 1.21; 95%CIs: 1.15–1.27, respectively (Adjibade et al., 2019)). However, the dose-response association between ultra-processed food consumption (modelled as quartiles) and incident depressive outcomes was reported as linear in the NutriNet-Santé study (Adjibade et al., 2019). Conversely, the SUN study reported no further increases in risk beyond >400 energy-adjusted grams per day, which was described by the authors as a threshold effect (Gómez-Donoso et al., 2018). Similar findings were observed in our study, where an apparent threshold effect was evident. Although we also had evidence to suggest a dose-response association (i.e., *p* values for trend <0.05 across all models), when each category of energy-adjusted ultra-processed food consumption was compared with the reference level (quartile 1), it appeared that only those participants in the highest quartile had increased risk of elevated psychological distress; we did not observe increases in risk below a very high relative consumption (quartile four; mean of ~650 energy-adjusted grams per day). Further longitudinal studies across high-income countries are needed to better understand whether the association between ultra-processed foods and depressive outcomes is linear across a wide range or not.

Although there are several hypotheses regarding the mechanisms by which ultra-processed food may elicit deleterious mental (and physical) health outcomes, a complete biological understanding is yet to be elucidated (Tobias and Hall, 2021). While NOVA does not account for nutritional composition to classify foods (as it is based on the extent and purpose of food processing), many ultra-processed foods have nutrient-poor profiles (Monteiro et al., 2019). These include high levels of carbohydrate, saturated fat and energy and low levels of protein and fibre (Monteiro et al., 2019). Such nutrient-poor profiles have been implicated in the prevalence, incidence and severity of depression through various complex and interacting pathways, including inflammation, oxidative stress and the gut microbiome (Marx et al., 2021a). Indeed, direct associations have been reported between ultra-processed food consumption and inflammation and oxidative damage in Australian, Brazilian, Portuguese and Iranian populations (Lane et al., 2022b; Lopes

Table 2
Odds ratios and 95%CIs of K10 score < 20/≥20 for quartiles of energy-adjusted ultra-processed food consumption in grams per day (g/d).

	n	Q1 (282.9 g/d)	Q2 (308.1 g/d)	Q3 (379.7 g/d)	Q4 (649.6 g/d)	*p* for trend
Cases	2927	738	697	665	827	
Model 1[a]	23,299	1 (ref)	0.94 (0.84–1.05)	0.89 (0.79–0.99)	1.14 (1.03–1.27)	**0.038**
Model 2[b]	22,365	1 (ref)	0.95 (0.85–1.07)	0.94 (0.84–1.06)	1.25 (1.12–1.40)	**<0.001**
Model 3[c]	22,089	1 (ref)	0.96 (0.85–1.08	0.93 (0.82–1.05)	1.23 (1.10–1.38)	**0.001**

[a] Model 1 = unadjusted
[b] Model 2 = additionally adjusted for sociodemographic characteristics: sex (male, female), age (continuous), education ([in]completed tertiary degree or diploma, completed high/technical school, [in]completed high/technical school, completed primary school, [in]completed primary school) and country of birth (Australia/New Zealand/Other, United Kingdom/Malta, Italy, Greece), marital status (married, de facto, divorced, separated, widow), number of people occupying household (1, 2, 3–4, 5+) and SEIFA quintiles (Q1-Q5)
[c] Model 3 = additionally adjusted for lifestyle and health related behaviours: smoking status (never smoked, current smoker, former smoker), physical activity over the last 6 months (0 [none], >0 and < 4 [low], ≥ 4 and < 6 [moderate], ≥ 6 [high]), alcohol intake (g/d) (lifetime abstainers, ex-drinkers, up to 19, 20–29, 30–39, 40+). Change to N due missing values for confounder alcohol intake.

et al., 2019; Silva dos Santos et al., 2022; Martins et al., 2022; Edalati et al., 2020). Consistent with this, the participants in our study who reported higher relative ultra-processed food consumption appeared to, on average, have lower intakes of protein, fibre and fruits and vegetables. However, when compared to participants in the lowest quartile of ultra-processed food consumption, participants with relative high ultra-processed food intake also appeared to have lower intakes of total energy and saturated fat. This suggests that ultra-processed formulations that do not provide energy or are low in fat or energy (e.g. artificially sweetened beverages), might make up a considerable proportion of food items in participants consuming higher amounts of ultra-processed food. Future studies are encouraged to explore this notion. In addition, our results showed that higher ultra-processed food consumption was associated with elevated psychological distress, despite the lower total energy intake. This reinforces the importance of using the weight of ultra-processed food (i.e. grams per day) to better account for ultra-processed foods that provide little to no energy.

Beyond nutritional composition, certain non-nutritive components used or induced via food ultra-processing have been implicated in the link between ultra-processed food and mental health. Preclinical and clinical studies also suggest that advanced glycation end-products formed during the heat treatment of intensively processed food, coupled with artificial additives that are common to ultra-processed foods (e.g. carboxymethylcellulose (Swidsinski et al., 2009; Chassaing et al., 2015; Chassaing et al., 2021), polysorbate-80 (Chassaing et al., 2015; Singh et al., 2016), saccharin (Bian et al., 2017a) and sucralose (Bian et al., 2017b)), may contribute to the development of gut and metabolic disease (Partridge et al., 2019); both of which have been linked with mental disorders (Zamani et al., 2019; Ghanei Gheshlagh et al., 2016). Limited but consistent evidence implicates the flavour-enhancing food additive, mono-sodium glutamate (a salt form of non-essential glutamic acid), and the artificial sweeteners, aspartame and saccharin, in mood disorders via dysregulation of the hypothalamic pituitary adrenal axis (Quines et al., 2014), and of dopamine, norepinephrine and serotonin synthesis and release (Choudhary and Lee, 2018; Lohner et al., 2017). Preclinical studies show that greater intake of titanium dioxide nanoparticles (white food colourant) may cause neuro-inflammation (Grissa et al., 2016) and destruction of dopaminergic neurons (Heidari et al., 2019). Bisphenol A, a compound common in food packaging may also alter endocrine systems that translate to anxious and depressive states (Wiersielis et al., 2020). However, more mechanistic studies in humans are necessary to better establish causal relations.

Consideration of the following limitations is recommended when interpreting our results. Given K10 scores were not measured at baseline, subsequent reverse causation remains possible. However, and as previously suggested, medication use has been shown to be a valid and reliable proxy method to estimate disease prevalence in the absence of more direct sources or measures (Füssenich et al., 2021; Cossman et al., 2010). This strategy is also comparable to another ultra-processed food-depression study in terms of the definition of cases (Gómez-Donoso et al., 2018). In addition, there was an extended duration of time between baseline measures of ultra-processed food intake and psychological distress at follow-up (>10 years). However, in other nationally representative Australian cohort studies (Davis et al., 2021; Baldwin et al., 2020), diet quality is stable over long periods of time, particularly in the European-Australian population (e.g., up to 15 years (Davis et al., 2021)). Participants who attended follow-up also had higher socio-economic status and were younger and more likely to be born in an English-speaking country on average compared to those who did not (Milne et al., 2017). However, a wide range of explanatory variables were considered and adjusted for, including sociodemographic-related factors. Although we accounted for an array of confounders in our statistical models, causal inference remains somewhat limited as unmeasured factors relevant to depression may have given rise to possible residual confounding. Relatedly, while country of birth was included as a possible sociodemographic confounder, our sample included migrants from the Mediterranean region. If at baseline, a participant's migration was recent, it remains possible that food consumption changed during follow-up. Future studies are encouraged to test whether and at what point people migrating to countries with different levels of ultra-processed food consumption than their country of origin may alter their consumption to be more in-line with the general population or cultural practices of the non-native country or region.

Another limitation is the K10's relatively short reference period covering anxiety and depressive symptoms during the 30 days prior to the survey (Althubaiti, 2016). That is, elevated psychological distress as an indicator of depression, as defined in our study, may have been more representative of an acute versus chronic condition. However, this limitation is not specific to our study, with the NutriNet-Santé ultra-processed food-depression study using the Center for Epidemiological Studies Depression scale, which also comprised a relatively short reference period (i.e., frequency of depressive symptoms in the previous week) (Adjibade et al., 2019).

Finally, the FFQ used in this study was not designed to discriminate different levels of food processing, with misclassification remaining possible (Adjibade et al., 2019). Additionally, given that the FFQ was self-administered and comprised a lengthy recall period that measured participants' usual dietary intakes over the preceding 12 months (Milne et al., 2017), inaccurate self-reporting or recall bias also remains possible (Althubaiti, 2016); such potential error in dietary recall surveys has been shown to lead underestimated risk estimates (Paeratakul et al., 1998). Evidence continues to accumulate, however, for the acceptable validity of FFQs to estimate usual dietary intakes according to the NOVA food classification system (Fangupo et al., 2019; Dinu et al., 2021; Oviedo-Solís et al., 2022). Moreover, FFQs have also been used by the majority of published studies to date to evaluate associations between ultra-processed food intake and mental health outcomes such as depression (Lane et al., 2021; Lane et al., 2022a), suggesting that our results may have reasonable external validity. Related to this, in our study, the FFQ dietary data used to measure ultra-processed food intake were captured over two decades ago and may not reflect more contemporary estimates. However, both the participant characteristics and percent estimate of ultra-processed food consumption reported in our study are comparable to the most recent estimate of ultra-processed food consumption (42 %) in a nationally representative sample of Australians (Machado et al., 2019).

Our study had several notable strengths. These include the use of a validated tool for the assessment of psychological distress, the robustness of associations that were supported by sensitivity analyses and the relatively large sample of individuals with diverse backgrounds. The latter is particularly important given the majority of previous studies assessing the link between ultra-processed food intake and mental health have been limited to one region (Brazil) or relatively homogeneous samples. The results of our study may thus have implications for future research and the development of public health policies and strategies that target ultra-processed food consumption in multicultural societies.

5. Conclusions

The current study demonstrated a direct association between the consumption of ultra-processed food at baseline and elevated psychological distress at follow-up. However, this association was evident only among participants with very high consumption of ultra-processed food; that is, those in the highest quartile. Further prospective (with relevant data at all time-points), mechanistic and intervention research is needed to better identify the harmful attributes of ultra-processed food, and to inform nutrition-related and public health strategies for mental health.

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CRediT authorship contribution statement

MML: Conceptualization, Data curation, Formal analysis, Project administration, Writing - original draft, Writing - review & editing. **ML:** Data curation, Formal analysis, Writing - review & editing. **WM:** Conceptualization, Project administration, Supervision, Writing - review & editing. All remaining authors were involved in Conceptualization, Writing -review & editing. The manuscript has been read and approved by all authors.

Role of the funding source

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Declaration of competing interest

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