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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2022

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):
Shi, H., Schweren, L. J. S., Ter Horst, R., Bloemendaal, M., van Rooij, D., Vasquez, A. A., Hartman, C. A., & Buitelaar, J. K. (2022). Low-grade inflammation as mediator between diet and behavioral disinhibition: A UK Biobank study. *Brain, Behavior, and Immunity*, *106*, 100-110. https://doi.org/10.1016/j.bbi.2022.07.165
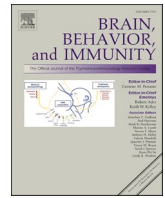
Full-length Article

Low-grade inflammation as mediator between diet and behavioral disinhibition: A UK Biobank study

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A R T I C L E   I N F O

A B S T R A C T

Background: Dietary patterns have been associated with variations in behavior. However, evidence has been limited and mixed, and the underlying mechanism remains unclear.

Objective: Extend a previous study reporting significant associations between food patterns and behavioral disinhibition and explore whether low-grade inflammation is linked to behaviors and mediates the association between diet and behavioral disinhibition.

Design: Among participants of the UK Biobank (UKB) we extracted a single behavioral disinhibition principal component using the UKB touchscreen questionnaire, Mental Health Questionnaire (MHQ), and registered diagnoses. We identified four dietary patterns (prudent diet, elimination of wheat/dairy/eggs, meat-based diet, full-cream dairy consumption) by using the Food Frequency Questionnaire (FFQ). Immune biomarkers and an aggregated inflammation score (INFLA-score) were used to characterize low-grade inflammation. Associations between dietary patterns and immune biomarkers, between immune biomarkers and disinhibition were assessed, with adjustment for demographics, lifestyle factors, and somatic health conditions. Next, mediation analyses were run to examine whether the association between dietary patterns and disinhibition was partially explained by inflammatory levels. We also conducted subgroup analyses to explore whether associations and the mediation effect differed by sex, age, ethnicity/race, body-mass-index (BMI), and socioeconomic status (SES).

Results: The prudent diet was negatively, and the meat-based diet was positively associated with several proinflammatory biomarkers. Most immune biomarkers were positively associated with disinhibition (numbers of lymphocytes ($\beta_{standardized} = 0.082$, $p < 0.001$), monocytes ($\beta_{standardized} = 0.043$, $p < 0.001$), neutrophils ($\beta_{standardized} = 0.071$, $p < 0.001$), platelets ($\beta_{standardized} = 0.022$, $p < 0.001$), leukocytes ($\beta_{standardized} = 0.093$, $p < 0.001$), C-reactive protein ($\beta_{standardized} = 0.051$, $p < 0.001$), and for INFLA-score ($\beta_{standardized} = 0.074$, $p < 0.001$). In the mediation model, the INFLA-score mediated the association between prudent diet and meat-based diet and disinhibition score, with a significant indirect effect of low-grade inflammation for the prudent diet-disinhibition association ($\beta_{standardized} = -0.007$, $p < 0.001$) and for meat-disinhibition association ($\beta_{standardized} = 0.001$, $p < 0.001$)). Although all effects were small, covariates and interaction term adjustments did not attenuate the effects, and neither did most subgroup-only analyses.

Conclusions: The prudent diet was associated with a lower disinhibition score and this effect was partially mediated by the lower inflammation. Reversely, the meat-based diet was linked to more inflammation, which was associated with more disinhibition. Our findings suggest mediating effects of immune function in the

relationship between diet and behavioral disinhibition. However further alternative designs such as interventional trials are needed to establish causal effects.

1. Introduction

Over the last decade, increasing evidence has emerged suggesting a connection between diet and mental health, which gives rise to a burgeoning field that uses food and food supplements as an alternative treatment to intervene in mental health disorders, so-called "nutritional psychiatry" (Sarris et al., 2015; Zepf et al., 2015). Both cross-sectional and prospective studies have demonstrated that certain dietary habits are potential contributors or modifiers of many common mental disorders (Jacka et al., 2014). Recent studies have implied a link between a poor-quality diet (e.g. high-fat Western diet) and an increased risk for poor mental health outcomes both in observational studies (Del-Ponte et al., 2019; Ríos-Hernández et al., 2017) and experimental settings (Steele et al., 2017). Conversely, better diet quality, usually characterized by high consumption of fruit and vegetables, whole grain, nuts, and/or regular fish intake has been revealed to be associated with a lower likelihood of the occurrence and reduced severity of symptoms of mental disorders, such as attention deficit hyperactivity disorder (ADHD) (Lee et al., 2022; Del-Ponte et al., 2019). Similarly, results of an elimination diet study suggested that diet is a key modifiable factor for decreasing ADHD symptoms (Pelsser et al., 2011). A further randomized controlled trial conducted to investigate the effectiveness of dietary improvement as an intervention for ADHD children is ongoing (Bosch et al., 2020).

One of the likely mediators between diet and mental health is the immune system, where the dietary impact on the immune system might have downstream effects on mental functioning. The habitual dietary pattern has been identified as one of the modifiable lifestyle factors that can aggravate or improve low-grade inflammation (Bujtor et al., 2021). In support of this notion are large epidemiological studies which demonstrated that a dietary pattern with a high intake of fruit and vegetables and/or regular fish consumption is associated with reduced systemic inflammation (Ko et al., 2016; Esposito et al., 2004). On the contrary, a high intake of saturated fat and low fiber consumption elicits a pro-inflammatory response and is associated with an elevated level of pro-inflammation biomarkers such as CRP and IL-6 (Nettleton et al., 2006; Anderson et al., 2012). In addition to soluble cytokines, changes in immune cell composition have also been implicated depending on dietary alterations. Mena et al. investigated the association between a Mediterranean diet and circulating immune cells and found an inverse correlation between this dietary pattern and adhesion molecule expression in circulating T lymphocytes and monocyte (Mena et al., 2008). In contrast, the Western dietary pattern was found to have a positive association with the absolute number of monocyte lipopolysaccharide receptor (CD14) and platelets, which are both biomarkers for low-grade inflammation (Nettleton et al., 2010).

In turn, a state of the low-grade inflammatory response, characterized by an overproduction of peripheral pro-inflammatory markers (e.g. C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TFN-α)) while incurring no clinical symptoms, are reported to be associated with several neurological and mental disorders, such as mania (Fond, 2014) and bipolar disorders (Benedetti et al., 2020). Moreover, low-grade inflammatory states including type 2 diabetes (Sharma et al., 2014), rheumatoid arthritis (Charoenngam et al., 2019), and auto-immune diseases (Zhou et al., 2017; Pérez-Vigil et al., 2016) have also been associated with mental disorders, such as ADHD (Zhou et al., 2017), bipolar disorders (Charoenngam et al., 2019), and tic disorders (Pérez-Vigil et al., 2016). In addition to these findings from observational studies, a causal relationship between low-grade inflammation and impaired mental health is further supported by extensive experimental data in animal models (Veniaminova, 2020; Han et al.,

2018). On the other hand, an anti-inflammatory intervention, such as probiotic supplementation, highlighted a beneficial effect on cytokine profiles while resulting in a significant reduction in the severity of ADHD (Skott et al., 2020). Although the pathophysiological mechanism involved in the etiology and course of mental disorders remain elusive, it has been implied that systemic inflammation and the increased production of cytokines by glia may be a plausible pathway (Cunningham, 2013).

A common behavioral trait shared by mental disorders is behavioral disinhibition. This trait reflects the tendency to act in an uncontrolled fashion, without prior risk assessment and/or in disregard of social conventions (Sharma et al., 2014), and is present in disorders like ADHD, obsessive–compulsive disorder, addictions, substance abuse, and mania (McCown et al., 1993). Yet, to date, much of the research on the associations between diet and mental health has focused on the role of diet and the immune system in internalizing disorders and in particular depression (Mac Giollabhui, 2021; Bai et al., 2020). The associations between dietary intake and behavior disinhibition have received comparably less attention. Therefore, this study was designed to address this issue by testing the hypothesis that inflammation would act as a mediator in the effect of diet on behavioral disinhibition.

It is well established that gender differences occur in dietary behaviors, for instance, food preference, food consumption, and eating habits for both physiological and sociocultural factors (Song et al., 2018; Imamura et al., 2015). Not limited to gender, dietary habits also differ by age subgroups (de Boer et al., 2013), ethnicities (Yau et al., 2020), or socioeconomic status (SES) (Foster et al., 2018). Body mass is affected by diet and subsequently may exert an influence on immune response (Ghanim et al., 2004). So far, those subgroup-specific associations between diet, inflammation, and disinhibition and their interplay have rarely been described in prior studies. Therefore, the secondary aim of the current study is to investigate these relations by stratifying the study population by gender, age, ethnicity, body mass index (BMI), and SES.

2. Methods

2.1. Study population

The data for this study came from the UK Biobank (UKB, https://www.ukbiobank.ac.uk/), a large, population-based cohort study comprising approximately 500,000 European ancestry participants, aged 37–73 and recruited between 2006 and 2010 from 22 assessment centers across England, Wales and Scotland (Palmer, 2007). Baseline blood measures were collected, and touch-screen questionnaires were administered at recruitment to collect basic demographics, diet and mental health information (Sudlow et al., 2015). From 2016 to 2017, a subset of the participants (N = 157,354) completed an additional online follow-up concerning symptoms of mental disorders by using mental health questionnaire (MHQ). Compared to all UK Biobank participants, the MHQ samples were in the same age range, but were better educated, of higher socioeconomic status, and reported less long-standing illness or disability (Davis et al., 2020). UKB received ethical clearance from the North West – Haydock Research Ethics Committee (11/NW/0382) to ensure subjects' protection and adherence to the principles expressed in the Declaration of Helsinki. All participants provided written informed consent at study entry. The current study was performed under application number 23668.

2.2. Dietary assessment

All five hundred thousand participants completed a short

touchscreen questionnaire that comprised 29 questions on diet. Most of them assessed the consuming frequency of the main foodstuffs including meat (beef, mutton, pork, processed meat, or poultry), cheese, bread and cereals, fruit (fresh or dried), vegetables (cooked or raw), and fish (oily or non-oily). Typically, the options ranged from "never" to "once or more daily"; for fruit and vegetable items, participants indicated directly their specific serving size (in teaspoons) each day; consumption of bread and cereals was determined with a frequency of slices/bowls per week.

We applied principal component analysis (PCA) to the 29 food items to create the dietary patterns. The number of components retained was based on the scree plot test and empirical interpretability of the components. Loadings were derived by Promax rotation and the naming of the rotated components was derived based on the combination of highest loadings. Component score coefficients were estimated by the regression approach and saved for the individual values.

2.3. Immune measures

To explore the relationship between inflammation and disinhibition, we selected immune parameters which are reported to be involved in different extents in inflammatory processes, including absolute counts of lymphocytes, monocytes, leukocytes, and platelets, level of CRP, red cells distribution width, basophils, eosinophils, percentage of lymphocytes, monocytes, and neutrophils to the total white blood cell (WBC) count, neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR). Immune trait-specific extreme outliers ($<$quartile(Q)1 – 3*interquartile (IQR) or $>$Q3 + 3*IQR) were considered implausible and excluded from all analyses without further imputation.

In addition to single immune biomarkers, we computed the INFLA-score as an aggregated measure of low-grade inflammation. The INFLA-score, which contains CRP, WBC, platelet count, and the NLR, has been reported to be associated with diet and mental health in previous prospective studies (Bonaccio et al., 2016; Gialluisi et al., 2020). Those four components of the INFLA-score are all well-established markers of systemic inflammation and synergistically have a pro-inflammatory role in different biological processes of the immune response (Pounis et al., 2016). To compute the INFLA-score, for all four components, laying in the highest deciles (7th to 10th) were assigned values from +1 to +4; while biomarker levels laying in the lowest deciles (1st to 4th) were given values from −4 to −1. The INFLA-score is thus the arithmetic sum of scores of the four biomarkers with equal weight, ranging between −16 and +16. A higher score indicates a greater level of low-grade inflammation (Pounis et al., 2016).

2.4. Mental health assessment and disinhibition score

To define behavioral disinhibition, we used PCA, aimed at generating an overall score that was based on the items related to disinhibited behaviors in the MHQ and registered clinical diagnoses. Details of the item selection and analyses have been described earlier (Schweren et al., 2020). Briefly, first, we selected all items that were linked to impulsivity, compulsivity, and/or emotional instability, which came from three parts: 1) a touchscreen questionnaire on the lifestyle that covered smoking, mood swings, irritability, and fed-up feelings; 2) online MHQ that included self-reported mental health problems ever diagnosed by a professional addiction behavior; 3) main or secondary ICD-10 diagnoses from hospital inpatient records. Next, a disinhibition score was extracted by applying tetrachoric correlation analysis, a technique of factor analysis to handle ordered categorical data (Schweren et al., 2021). We chose an *a priori* one-factor solution relying on theoretical expectations that impulsivity, compulsivity, and emotional instability have been recognized to share traits of dysfunctional inhibition of thoughts and behaviors (Hollander and Wong, 1995; Matthies and Philipsen, 2014). The principal component score was saved as the individual's disinhibition score. A higher score indicates a stronger tendency for disinhibition.

### 2.5. Subgroups, covariates, and sensitivity analyses

The primary analysis was extended by stratification in five additional ways: by gender/sex (male or female), age (middle adulthood $<$ 60 years or later adulthood $\geq$ 60 years according to WHO's definition (World Health Organization. Ageing and health, 2021), ethnicity/race/region (African, Caribbean, Eastern Asian, Western Asian, White, participants with mixed origins were not included in this analysis), BMI (underweight ($<$ 18.5), healthy (18.5 to $<$ 25.0), overweight (25.0 to $<$ 30.0), obesity ($\geq$ 30.0)), and SES (low, medium, high). The assessment of SES was performed by principal component analysis based on household income before tax ($<$ £18 000, £18 000-£30 999, £31 000-£51 999, £52 000-£100 000, $>$ £100 000), education qualifications (College or University, A levels/AS levels, or equivalent, O levels/GCSEs, or equivalent, CSEs or equivalent; NVQ/HND/HNC or equivalent; other professional qualifications) and current employment status (employed (in paid employment or self-employed, retired, doing unpaid or voluntary work, or being full or part-time students) and unemployed) (Zhang et al., 2021). Below 25th percentile was defined as low SES, 75th above was high SES, and the interquartile range was coded as medium SES. We also tested the potential interaction effect by modeling subgroups-by-dietary patterns in the regression models.

Covariates considered in the analysis included sociodemographic factors (age, sex, ethnicity, and SES), BMI, lifestyle factors (vitamin supplementation, physical exercise, sleep, and other three dietary patterns identified by the current analysis), and chronic somatic diseases (baseline self-reported cardiovascular diseases, diabetes, and cancer). Age, SES, and BMI were classified as described above. Based on current recommendations for physical exercise in adults (Watson et al.,), participants were categorized into two groups: 1 = at least 150 min each week of moderate-intensity aerobic activity or 75 min per week of vigorous aerobic activity, 0 = less. The analyses were also adjusted for sleep by using a binary classification of 1 = daily sleep duration of 7–9 h, 0 = $<$7 or $>$9 h, according to a previously published consensus statement (Watson et al., 2015). More details related to the assessment of all covariates are accessible on the UK Biobank website (https://www.ukbiobank.ac.uk).

2.6. Statistical analysis

All analyses were performed in R version 4.0.2. Dietary information was available within the whole sample, immune measures were available for 454,776 participants (immune subsamples), and the mental health questionnaire was completed by 157,340 participants after excluding the withdrawal. This yielded three subsets: the whole sample, the immune subset, and the mental subset. Baseline characteristics of these subsets are presented as the number (percentage) for categorical variables and the mean (standard deviation) for continuous variables. T-tests or $\chi2$ tests were performed to examine the differences in participant characteristics in immune and mental subsets compared with all samples.

Regression analyses included 4 sets of tests (Fig. 1): (1) associations between diet and behavioral disinhibition (N = 157,354) (Schweren et al., 2021); (2) associations between diet and immune outcomes (N = 454,776); (3) associations between inflammatory measures and behavioral disinhibition (N = 150,548); and (4) statistical mediation analyses of the pathway: Diet—INFLA-score—Disinhibition (N = 150,548). For set (1), detailed analyses have been conducted and presented by Schweren et. al previously (Schweren et al., 2021). For (2), multiple linear regression analyses were performed, given the continuous nature of the dietary component. Sex, age, ethnicity, SES, BMI, use of vitamin supplements, physical exercise, sleep, and somatic diseases (baseline self-reported diabetes, cardiovascular disease, previous cancer) were included as covariates. For (3), multivariable linear regression was used to model the association between immune measures and disinhibition with adjustment for sex, age, SES, physical exercise, sleep, dietary
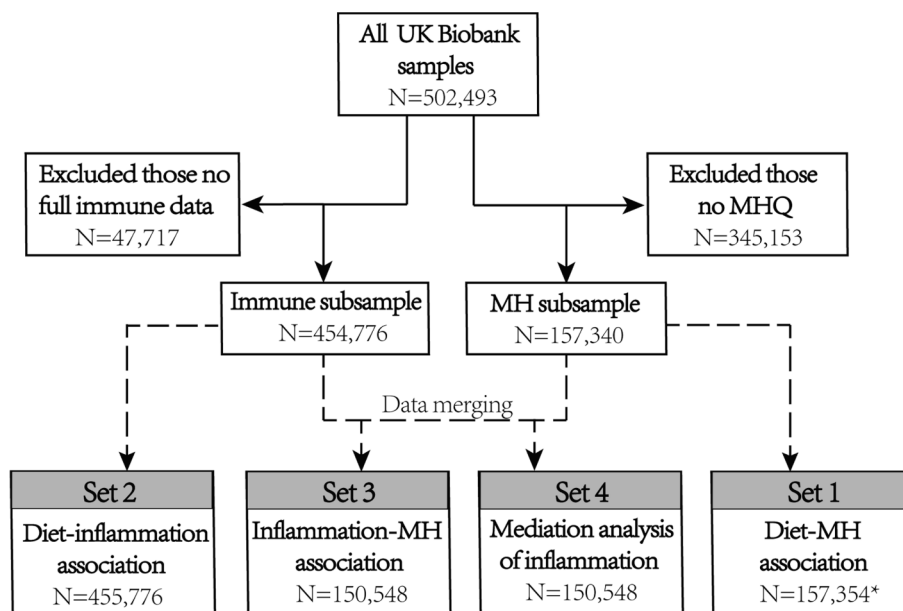
Fig. 1. Flow chart and four sets of the association analyses. MH: mental health; *: The diet-disinhibition association was reported by Lizanne et al. (Schweren et al., 2021) with a sample size of 157,354. In the present study, 14 participants were further excluded due to withdrawal, yielding a sample size of 157,340.

factors, and somatic diseases. For (4), we estimated the direct, indirect, and total effect of diet on behavioral disinhibition and mediation by immune measures with 5000 simulations of non-parametric boot-strapping by using the 'lavaan' package in R (Rosseel, 2021), and adjusted covariates in set (2) and set (3) on corresponding pathways . In addition, sets (2) and (3) of analyses were also run by including sub-group*diet interaction terms and next by separate subgroups and set (4) was additionally run by subgroups. In addition, all variables were standardized before regressing by subtracting the mean and dividing by the standard deviation.

To account for multiple testing, an adjusted p-value was calculated with the Bonferroni procedure (N_{test} = 14 for diet-immune, immune-disinhibition analysis, 0 for mediation analysis), and a threshold of adjusted $p < 0.05$ was considered as statistical significance.

Furthermore, to test the robustness of the results, two sensitivity analyses were conducted: 1) we excluded participants with self-reported somatic diseases (cardiovascular diseases, cancer, or diabetes) and ran analyses within the remaining sample (N = 109,553) and also broken down by sex (N_{men} = 44,821); 2) considering underrepresentation of minor ethnic subgroups, 8024 (equals to numbers of Western Asian) age-, sex- and SES (categories)-matched participants were randomly selected from the white population to replicate the analyses involving ethnicity.

3. Results

3.1. Participant characteristics

Basic characteristics of the whole study population (whole samples) and each subset (immune subsamples, mental health subsamples) are reported in Table 1. Among all 502,494 participants with food frequency data, 54.4 % were women, 56.7 % were in middle adulthood (<60 years), with a mean age of 56.5 years at recruitment. A large part of the cohort was white (94.1 %) and other ethnicities included were 8024 (1.6 %) Western Asian, 1574 (0.3 %) Eastern Asian, 4517 Caribbean (0.9 %), and African 3394 (0.7 %). 144,844 (28.8 %) were of high SES, 232,098 (52.8 %) of medium SES, and 124,641 (24.8 %) of low SES. 162,407 participants (32.3 %) of the sample had a healthy weight, 212,206 (42.2 %) were overweight and 122,150 (24.3 %) were obese. There were no differences in most of the characteristics between the immune subsamples and all samples. Compared to the whole dataset,

the participants of the mental health subset were more often females (56.7 % vs 54.4 %, $p < 0.001$), were generally younger (middle adulthood 61.2 % vs 56.7 %, $p < 0.001$) and had more often a high SES (42.3 % vs 28.8 %, $p < 0.001$). Unlike most assessments (e.g. lab-based measures, registered diagnoses), the mental health symptoms were collected by a questionnaire and in a separate measurement wave, which may potentially explain this underrepresentation of low SES, older people, and males (Davis et al., 2020).

3.2. Dietary patterns

Fig. 2 shows the food items with absolute factor loading > 0.2 in each dietary pattern derived from PCA with Promax rotations. The highest loadings were employed to label the diet patterns, as follows: prudent diet, wheat/dairy/eggs restrictive diet, meat-based diet, and full-cream dairy. More details concerning the description of diet patterns were presented in a prior publication (Schweren et al., 2021). Supplementary Materials 1 present the plot of increased Bayesian information criterion (BIC) Index under different assumed number of dietary patterns, of which four components were optimal. The exact loadings for all food items were presented in Supplementary Materials 2. The pairwise Spearman's correlations between either two dietary patterns and p-values are provided in Supplementary Materials sections 3,4, respectively. Significant differences in food selection exist among subgroups, as displayed in Supplementary Materials 5.

3.3. Overall and subgroup-specific diet-immune associations

The results of regression analysis modelling the relation between the dietary patterns and immune markers are shown in Fig. 3. Among all samples, we observed that prudent diet is negatively correlated with several pro-inflammatory biomarkers (numbers of monocytes: $\beta_{standardized}$ = -0.048, $p < 0.001$; neutrophils: $\beta_{standardized}$ = -0.107, $p < 0.001$; platelets: $\beta_{standardized}$ = -0.069, $p < 0.001$; leukocytes: $\beta_{standardized}$ = -0.107, $p < 0.001$; C-reactive protein: $\beta_{standardized}$ = -0.091, $p < 0.001$; INFLA-score: $\beta_{standardized}$ = -0.133, p < 0.001) after controlling for age, sex, ethnicity, BMI, SES, physical exercise, sleep, vitamin intake, somatic diseases (CVD, cancer, diabetes) and correction for multiple testing (Fig. 3A). Reversely, the analysis of a number of circulating biomarkers of low-grade inflammation revealed significant positive associations

Table 1
Basic characteristics of whole population and two subsamples.

	All samples (N = 502,493)	Immune subsample (N = 454,776)	Mental health subsample (N = 157,340)
Female	273,378 (54.4%)	246,315 (54.2%)	89,086 (56.7%)[2]
Age			
Later adulthood (≥60 years)	217,480 (43.3%)	196,742 (43.3%)	61,033 (38.8%)[2]
Middle adulthood (<60 years)	285,013 (56.7%)	258,034 (56.7%)	96,307 (61.2%)
BMI categories			
Underweight (<18.5)	2,626 (0.5%)	2,315 (0.5%)	896 (0.6%)[2]
Healthy (18.5 to < 25)	162,407 (32.3%)	147,750 (32.5%)	59,962 (38.1%)
Overweight (25.0 to < 30)	212,206 (42.2%)	193,053 (42.5%)	64,962 (41.3%)
Obesity (≥30)	122,150 (24.3%)	109,871 (24.2%)	31,128 (19.8%)
Missing	3,104 (0.6%)	1,791 (0.4%)	392 (0.2%)
Ethnicity			
White	472,684 (94.1%)	429,818 (94.3%)	152,246 (96.8%)[2]
Western Asian	8,024 (1.6%)	7,080 (1.6%)	1,076 (0.7%)
Eastern Asian	1,574 (0.3%)	1,399 (0.3%)	364 (0.2%)
Caribbean	4,517 (0.9%)	3,898 (0.9%)	667(0.4%)
African	3,394 (0.7%)	2,902 (0.6%)	461 (0.3%)
Missing	12,300 (2.4%)	10,596 (2.3%)	2,526 (1.6%)
SES			
High	144,884 (28.8%)	132,933 (29.2%)[2]	66,583 (42.3%)[2]
Medium	232,098 (46.2%)	212,560 (46.6%)	71,034(45.1%)
Low	124,641 (24.8%)	109,739 (24.1%)	19,650(12.5%)
Missing	870 (0.2%)	461 (0.1%)	73 (0.0%)
Lifestyle			
Weekly physical exercise (Meet guideline[1])	271,747 (54.1%)	244,253 (53.6%)	76,341 (48.5%)[2]
Daily sleep duration of 7–9 h (vs <7 or >9 h)	365,789 (72.8%)	332,389 (72.9%)	120,877 (76.8%)[2]
Vitamin intake	157,920 (31.4%)	144,448 (31.7%)	51,092 (32.5%)[2]
History			
Diabetes	26,399 (5.3%)	23,707 (5.2%)	5,235 (3.3%)[2]
CVD	150,603 (30.0%)	136,335 (29.9%)	37,472 (23.8%)[2]
Cancer	38,615 (7.7%)	34,415 (7.6%)	11,101 (7.1%)[2]
Dietary components			
Prudent diet	−0.00 (1.00)	−0.00 (1.00)	0.18 (0.937)[2]
W/d/e restrictive diet	−0.00 (1.00)	−0.00 (0.998)	0.06 (0.939)[2]
Meat-based diet	−0.00 (1.00)	−0.00 (1.00)	−0.01 (0.997)[2]
Full-cream dairy	0.00 (1.00)	0.00 (1.00)	−0.01(1.01)
INFLA-score	−0.07 (4.93)	−0.07(4.93)	−0.65 (4.86)[2]

[1]Guideline: Duration of moderate activity ≥ 150 min or vigorous activity ≥ 75 min per week. [2] Significantly different from all samples (adjusted P-value < 0.05). BMI: Body mass index; SES: Socioeconomic status; CVD: Cardiovascular diseases, including heart attack, angina, stroke, and high blood pressure in the present study; W/d/e: wheat/dairy/eggs.

between meat-based diet and numbers of lymphocytes ($\beta_{standardized}$ = 0.039, $p < 0.001$), monocytes ($\beta_{standardized}$ = 0.023, $p < 0.001$), neutrophils ($\beta_{standardized}$ = 0.024, $p < 0.001$), platelets ($\beta_{standardized}$ = 0.007, $p < 0.001$), leukocytes ($\beta_{standardized}$ = 0.035, $p < 0.001$), C-reactive protein ($\beta_{standardized}$ = 0.017, $p < 0.001$). Similar evidence emerged from the analysis of the INFLA-score, which decreased by 0.133 standardized unit ($p < 0.001$) given an increase of 1 unit in prudent diet and increased by 0.030 for meat-based diet ($p < 0.001$).

Separate analyses for males and females (Fig. 3B) revealed a similar

significantly positive or negative pattern to the analyses within the whole sample for prudent, meat-based diet and immune biomarkers, although the strength of correlations differed. All other subgroup analyses are reported in Supplementary Materials 9 and 10. Analyses of whether the associations between diet patterns and immune measures were moderated by subgroups suggested that subgroup-by-diet interactions also contribute to the heterogeneity of immune function (Supplementary Materials 11). However notably, the prudent diet is consistently negatively associated with pro-inflammatory factors across all diet-immune models indicating a robust association.

### 3.4. Association of immune measures with disinhibition scores

Correcting for the covariates (sex, age, SES, ethnicity, physical exercise, sleep, health conditions), most immune biomarkers were positively associated with the disinhibition score, with individuals carrying higher pro-inflammatory level reporting a higher disinhibition score (see Fig. 4A and Supplementary Materials 14. The following associations with disinhibition were observed for: lymphocytes ($\beta_{standardized}$ = 0.082, $p < 0.001$), monocytes ($\beta_{standardized}$ = 0.043, $p < 0.001$), neutrophils ($\beta_{standardized}$ = 0.071, $p < 0.001$), platelets ($\beta_{standardized}$ = 0.022, $p < 0.001$), leukocytes ($\beta_{standardized}$ = 0.093, $p < 0.001$), C-reactive protein ($\beta_{standardized}$ = 0.051, $p < 0.001$), and INFLA-score ($\beta_{standardized}$ = 0.074, $p < 0.001$).

Tests for interactions were run by adding immune biomarkers, subgroups variables, and subgroups by immune terms (see Fig. 4B and Supplementary Materials 14. Among these, men showed faster-increasing disinhibition scores than women with increasing inflammatory biomarkers including lymphocytes ($\beta_{standardized}$ 0.089 (male) vs 0.075 (female), $p < 0.001$), monocytes (0.054 vs 0.032, $p < 0.001$), CRP (0.073 vs 0.037, $p < 0.001$), and INFLA-score (0.101 vs 0.056, $p < 0.001$).

3.5. Mediation analyses of inflammation

The mediation analyses indicated that INFLA-score mediated the association between the prudent diet , meat-based diet and disinhibition (Fig. 5 and Supplementary Materials 17). In detail, in the analysis of the whole sample, the total effect of prudent diet on disinhibition score was $\beta_{standardized}$ = -0.079 ($p < 0.001$). Dissecting the total effect, the direct effect was $\beta_{standardized}$ = -0.072 ($p < 0.001$), and the indirect effect through INFLA-score was $\beta_{standardized}$ = -0.007 ($p < 0.001$). The latter indirect contribution accounted for 8.9 % of the total effect. For the meat-based diet, the results indicated that the direct effect on the disinhibition score was $\beta_{standardized}$ = 0.019 ($p < 0.001$). The indirect effect via the INFLA-score was $\beta_{standardized}$ = 0.001, which also reached significance ($p < 0.001$). The indirect effect of the meat-based diet on disinhibition explained 6.7 % of the total effect. The mediation through the INFLA-score between prudent diet and disinhibition was similar for males and females, and the mediation effects of inflammation between the meat-based diet, INFLA-score, and disinhibition were also found in both sexes.

Sensitivity analyses after excluding participants with chronic health problems (CVD, diabetes, cancer) showed similar findings regarding the mediation effect. Although attenuation of effects occurred, associations were consistent and largely independent of underlying diseases that may affect immune status (see Supplementary Materials 18 for data and Supplementary Materials 19 for the figure). Likewise, sensitivity analyses after selecting a comparable sample size for the white population to other ethnicity subgroups indicated robust associations between prudent diet/meat-based diet and immune measures, between lymphocytes, neutrophils, leukocytes, INFLA-score and disinhibition (Supplementary Materials 20).
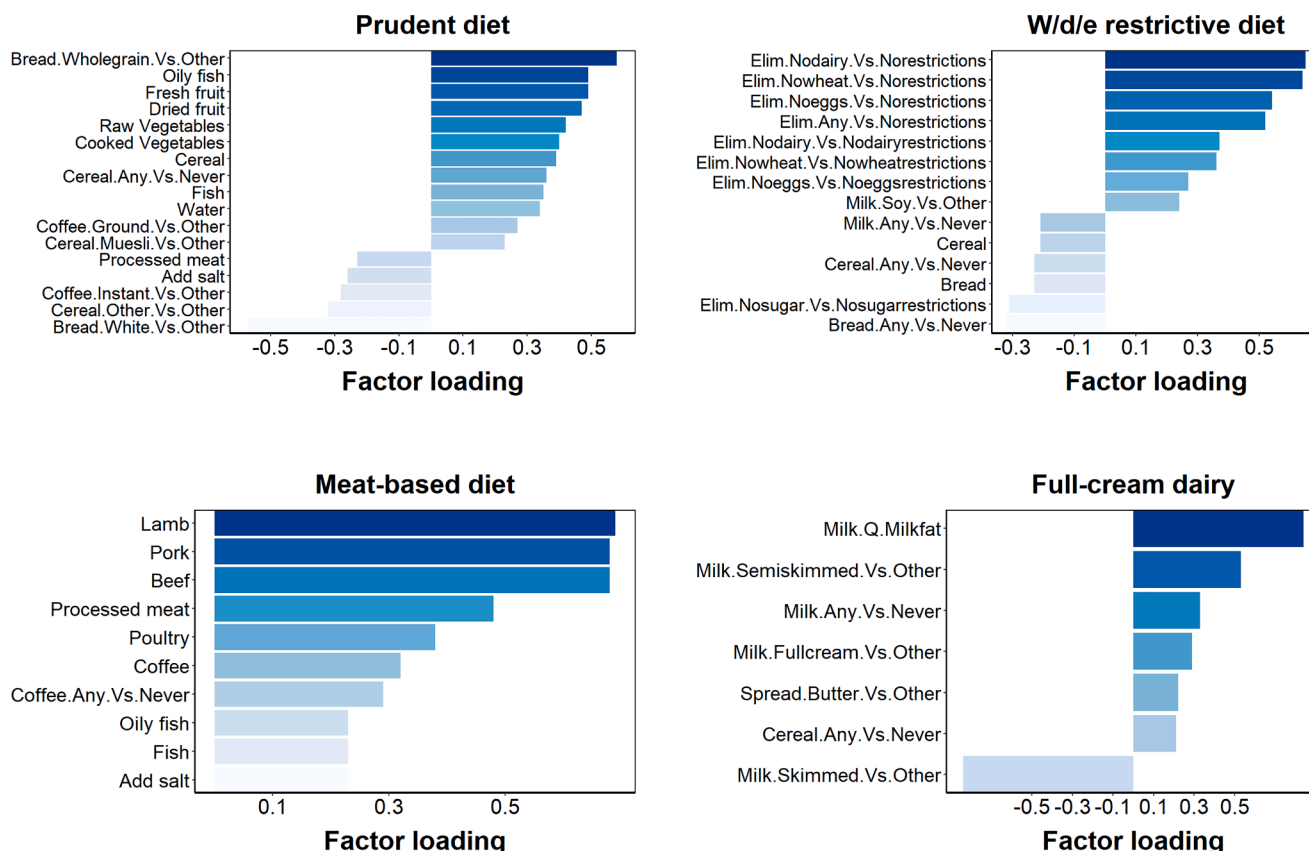
Fig. 2. Dietary patterns identified in this study. Figures show the food items with factor loadings absolute value > 0.2 in each dietary pattern. Results are from principle component analysis with Promax rotation.

4. Discussion

Using this large population-based dataset, our previous study found that adherence to prudent dietary patterns, characterized by high consumption of fruits, vegetables, oily fish, whole grains, and low consumption of processed meat is associated with a reduced level of disinhibited traits (Schweren et al., 2020). We subsequently aimed to identify plausible mechanisms by which diet may influence behaviors. In another previous paper, we reported on mediation by cortical and subcortical brain volumes (van Rooij et al., 2021) and here we focused on immune pathways. We found support for the hypothesis that dietary patterns and low-grade inflammation are associated and additionally revealed that inflammation level mediates, for a small part, the association between the prudent, meat-based diet and behavioral disinhibition. These significant associations and mediation effects were independent of SES, lifestyle, and chronic health conditions. Although in line with expectations, the effects were weak.

Among the four dietary factors identified, the prudent diet is similar to the "healthy/prudent" dietary pattern, which is characterized by high intakes of vegetables, fruit, legumes, and fish (Castelló et al., 2014; Medina-Remón et al., 2018). The meat-based diet is analogous to the "high meat diet" or "Western type of diet" (Steffen et al., 2007; Shi et al., 2022), characterized by high consumption of red or processed meat and lower consumption of fruits and vegetables. The wheat/dairy/eggs restrictive diet represents a food preference as reported in previously published studies (Schweren et al., 2021; Cole et al., 2020), usually due to hypersensitivity to the corresponding food or metabolic diseases. Regular milk and dairy products are also one of the predominant foodstuffs that are frequently consumed, particularly in western industrialized countries (Fontecha et al., 2019). Thus, the extracted dietary factors are generally consistent with earlier literature.

The findings of the associations between dietary patterns and immunological biomarkers are largely in agreement with previous literature that adherence to the prudent diet, Mediterranean diet, or any anti-inflammatory diet lowers markers of inflammation in humans (Ko et al., 2016; Esposito et al., 2004). Conversely, processed and red meats that are high in saturated fat may stimulate immune activation (Ley et al., 2014). Note that the effects observed in our study were weak, with the highest $\beta_{standardized}$ (-0.133) assessed between prudent diet and INFLA-score. However, these effects are comparable to effect sizes of the associations between age and immune biomarkers ($\beta_{standardized}$ ranging from −0.0007 to 0.010), a non-modifiable covariate that is reported to have a significant impact on immunological mediators (ter Horst et al., 2016).

We also observed that the pro-inflammatory immunological biomarkers were positively correlated with disinhibition. Our findings are in keeping with results from prior studies illustrating various mental health conditions, including conditions characterized by disinhibited behaviors, have been linked to heightened inflammation. A prospective study demonstrated that a Western-type of diet at age 14 was significantly positively associated with levels of CRP and leptin at 17, while a healthy diet correlated negatively with these markers; further that the pro-inflammation biomarkers were positively associated with externalizing behaviors characterized as attentional and aggressive problems and rule-breaking at age 17, (Oddy et al., 2018). It is also supported by a longitudinal cohort study that showed an association between the diagnosis of ADHD and asthma, including between late-diagnosed (at either age 18 or 22) ADHD and late-onset asthma in adulthood, which suggests pathophysiological mechanisms underlying the comorbidity between ADHD and inflammatory diseases (Leffa et al., 2021). A recent population-based *trans*-generational study provided evidence demonstrating a link between maternal prenatal inflammatory diseases and
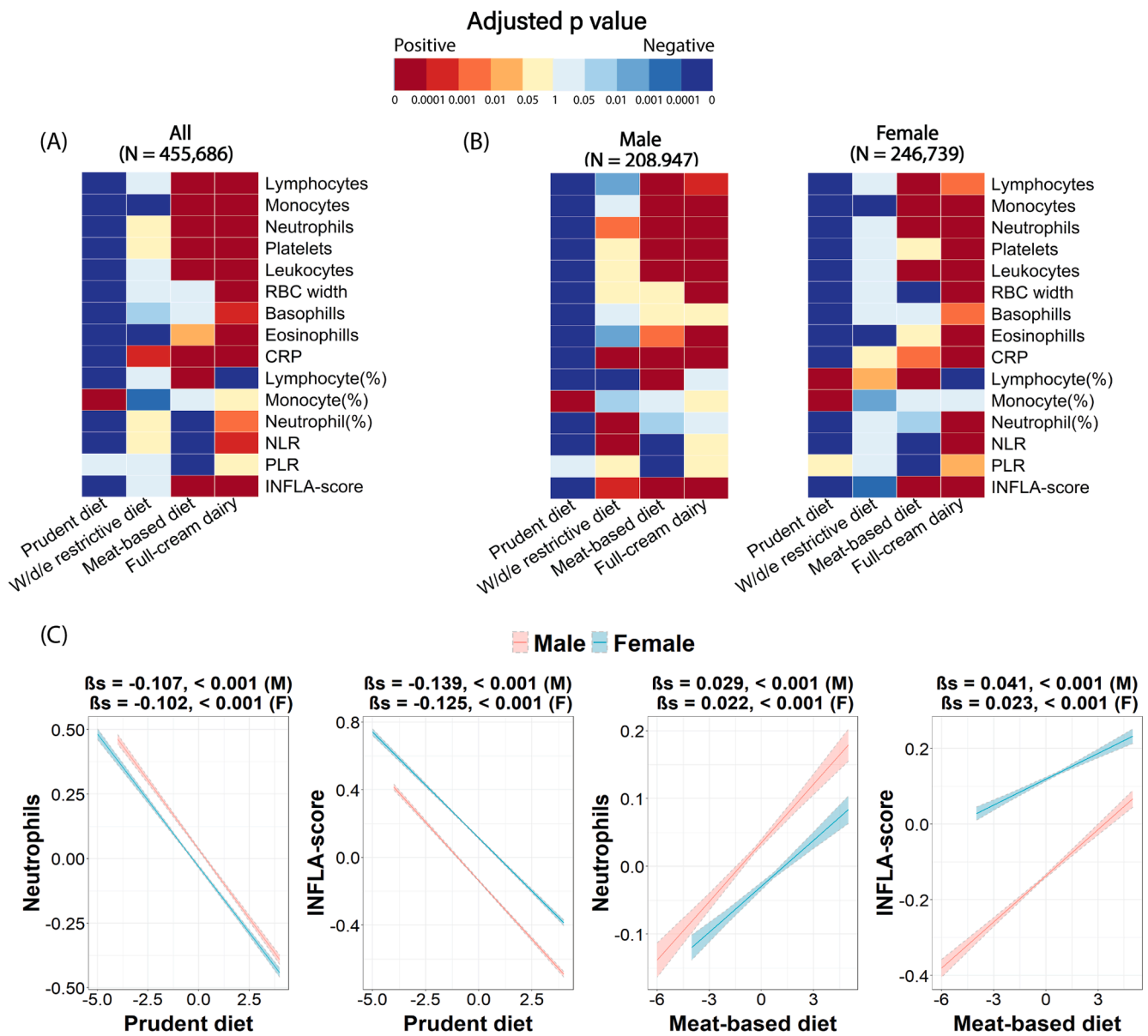
Fig. 3. Association between scores of dietary patterns and immune measures. (A) The *p* values of the regression for all samples. Red blocks indicate a *p* with positive correlation and blue indicates a *p* with negative correlation. CRP: C-reactive protein; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio. W/d/e: wheat/dairy/eggs. (B) Diet-immune regression between each dietary pattern and circulating inflammatory measures split by male and female. All subgroup analyses were presented in Supplementary Materials 9 and 10. (C) Line plots demonstrating the effect of dietary patterns on the inflammatory level with 95 % confidence interval. Red lines indicate male, blue lines indicate female. Both dietary scores and immune biomarkers were standardized before regressing. βs: standardized estimates.

ADHD in offspring, even after controlling for a diagnosis of parental ADHD. This exaggerated maternal inflammatory response linked to offspring brain alterations provides insights into a potential non-negligible role of exposure to environmental factors such as infections, either or not combined with genetic risk factors of the immune system (Instanes et al., 2017). Similar conclusions have been drawn in a meta-analysis of four European cohorts that revealed an association between a pro-inflammatory diet during pregnancy and the child's aggressive behavior and ADHD symptoms (Polanska et al., 2021). There is additional evidence that fits with our findings, for example, heightened plasma CRP levels in youth and adults with ADHD (Leffa et al., 2021) and elevated CRP in patients with obsessive–compulsive disorder (Turna et al., 2020).

Causal effects of inflammation on disinhibition have been explored by animal studies. Several biological pathways have been suggested to

explain a higher risk of behavioral disinhibition with higher levels of low-grade inflammation. Researchers have found ADHD-like symptoms (impulsivity) and an upgrade of Toll-like receptor 4, responsible for activating the innate immune system, in rodents fed with the Western diet for 3 weeks (Strekalova, 2015). A subsequent study replicated this behavioral finding and also found signs of microglia activation and oxidative stress in the prefrontal cortex (Veniaminova, 2020). Administration of medication with anti-inflammatory properties improved symptoms of hyperactivity and impulsivity in spontaneous hypertensive rats, an animal model for ADHD, by suppressing the mitogen-activated protein kinase (MAPK) and nuclear factor (NF)-κB signaling pathways. These play an essential role in regulating immune and inflammatory responses (Song, 2020).

Additionally, we estimated associations and mediation effects of inflammation in the diet-disinhibition relation in pre-specified
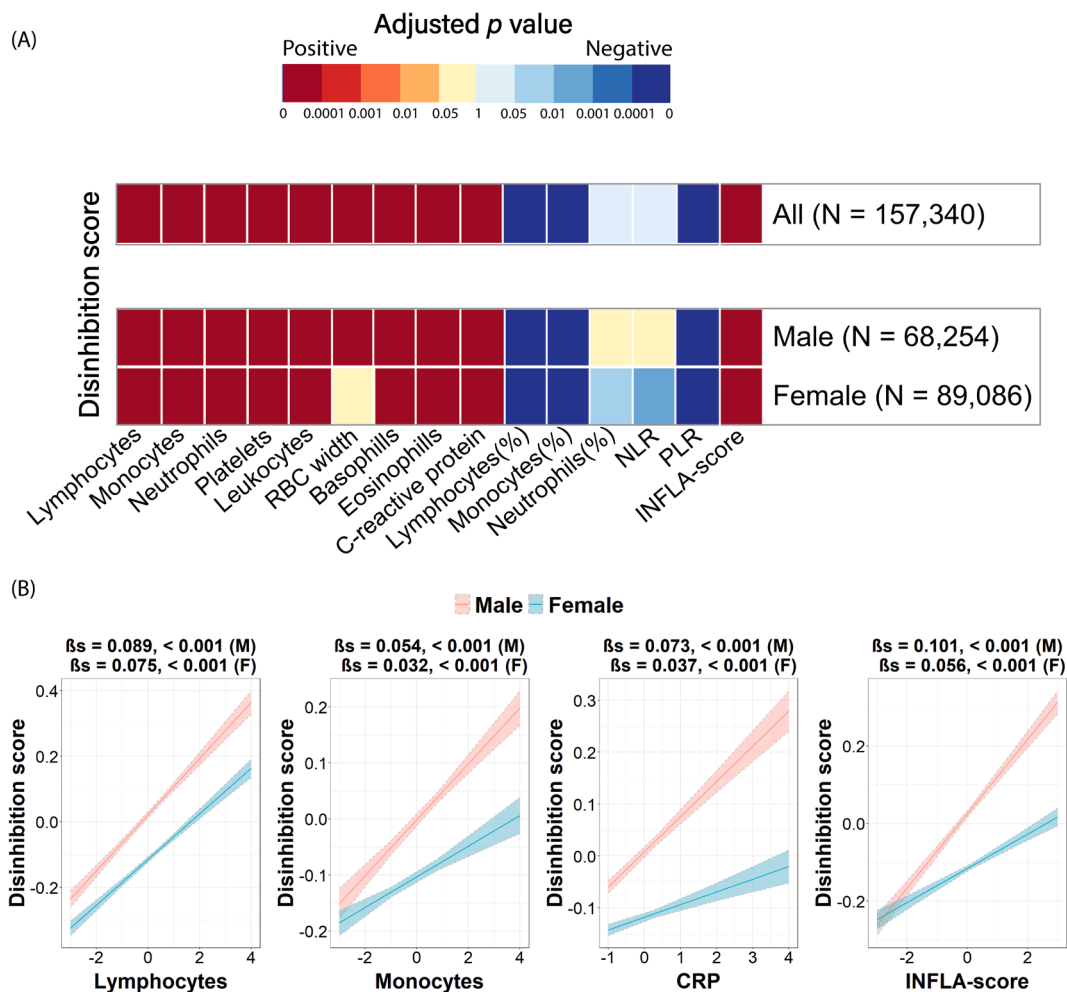
Fig. 4. Associations between immune biomarkers and behavioral disinhibition. (A) The plot shows the *p* values of the regression between immune biomarkers (independent variables) and disinhibition scores (dependent variables) for all samples. (B) Red blocks indicate a *p* with positive correlation and blue indicates a *p* with negative correlation. All estimates, exact *p*, and the results within each subgroup, subgroup*immune interaction analyses were presented in Supplementary Materials 14. CRP: C-reactive protein; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio. (C) Line plots show the effect of immune biomarkers on disinhibition. Both disinhibition scores and immune biomarkers were standardized before regressing. β_s: standardized estimates.

subgroups. Albeit weak, the findings were robust and reproducible across most subgroups, including those based on sex, age, BMI, SES, and in white participants. We noticed a sex-by-prudent diet interaction, reflecting a greater decrease in the inflammation level in men with more prudent diet consumption. Reversely, it could be interpreted as a stronger increased inflammation with lower adherence to the prudent diet. Men also showed a faster increase in disinhibition score as the inflammation level raised, which suggests a different sensitivity in immunoregulation between sexes. It may be owing to differences in sex hormones, considering the bioactivity of estrogen in downregulating myeloid inflammation induced by diet, as argued by previous literature (Varghese, 2021), and may partially explain the weaker mediation effect of inflammation in females.

The present study represents one of the largest population-based investigations linking diet, inflammation and behavioral disinhibition within detailed subgroup analyses including different sexes, ages, ethnicities, BMI categories, and SES categories. Still, some limitations of the current research should be noted. Firstly, since this cross-sectional analysis does not allow establishing causal relationships between inflammation and immune markers, the mediating effects of inflammation require further testing in longitudinal and experimental studies. In a similar vein, we modeled the mediation analysis based on the hypothesis that low-grade inflammation may influence mental health. However, there is also evidence of the bi-directional nature of the

relations between diet, immune system, and mental health, namely that food preferences may also be dependent on mental states. This motivates the need for studies on reverse causation e.g. mendelian randomization, to understand the bi-directional causal pathways between diet, immune system, and mental health.

5. Conclusion

Our results indicate that dietary patterns are associated with levels of low-grade inflammation and that low-grade inflammation is positively associated with behavioral disinhibition among middle to old-aged individuals. Although associations were weak and further replication is needed, our findings suggest mediating effects of immune function in the relationship between diet and behavioral disinhibition.
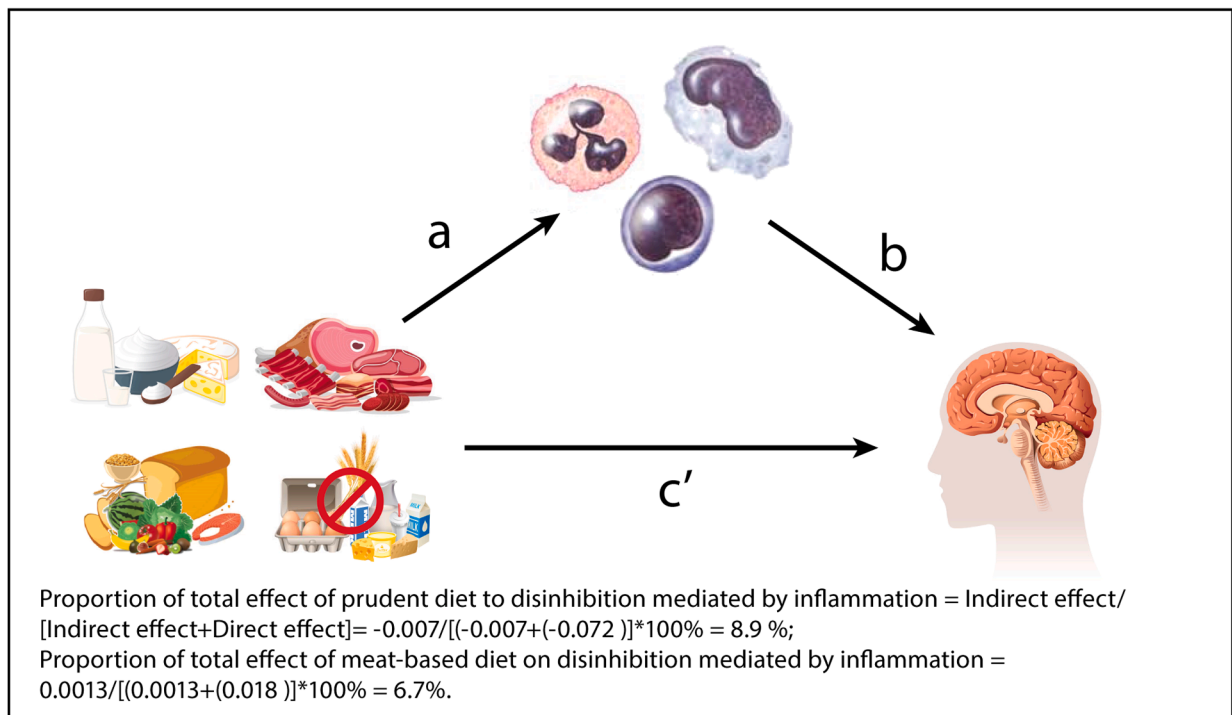
Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

For the data of UK Biobank, please visit https://www.ukbiobank.ac.

(A)

Mediation model

Proportion of total effect of prudent diet to disinhibition mediated by inflammation = Indirect effect/
[Indirect effect+Direct effect]= -0.007/[(-0.007+(-0.072)]*100% = 8.9 %;
Proportion of total effect of meat-based diet on disinhibition mediated by inflammation =
0.0013/[(0.0013+(0.018)]*100% = 6.7%.

(B)

Mediating effects (a*b)

Subgroup	P-value	95%CI
Prudent diet		
All	<0.001	-0.0069 (-0.0077 , -0.0061)
Male	<0.001	-0.011 (-0.012 , -0.0092)
Female	<0.001	-0.0043 (-0.0053 , -0.0034)
W/d/e restrictive diet		
All	0.0014	-0.00051 (-0.00082 , -2e-04)
Male	0.83	-8.2e-05 (-0.00082 , 0.00065)
Female	<0.001	-0.00047 (-0.00074 , -2e-04)
Meat-based diet		
All	<0.001	0.0013 (0.00094 , 0.0016)
Male	<0.001	0.0025 (0.0018 , 0.0032)
Female	<0.001	0.00072 (0.00042 , 0.001)
Full-cream dairy		
All	<0.001	0.0016 (0.0013 , 0.0019)
Male	<0.001	0.0025 (0.0018 , 0.0032)
Female	<0.001	0.001 (0.00073 , 0.0014)

-0.01 -0.005   0   0.005 0.01

Fig. 5. Results of the mediation model. (A) INFLA-score mediates the relationship between dietary patterns and behavioral disinhibition. a, b, c represent the estimates of the pathways. The mediation effect (a*b), which is an indirect effect, demonstrated whether the INFLA-score is on a pathway between dietary patterns and mental health. Total effect referred to the total effect of diet on disinhibition, which is a combination of direct effect (c') and indirect effect (a*b). W/d/e: wheat/dairy/eggs. (B) Standardized estimates of indirect effects within all samples and split by male and female.

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Acknowledgements

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi. org/10.1016/j.bbi.2022.07.165.

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