Eat2beNICE

Effects of Nutrition and Lifestyle on Impulsive, Compulsive, and Externalizing Behaviours

H2020 - 728018

D1.3: Manuscripts 3a, 3b: how lifestyle may enhance harmful/beneficial effects of diet or cancel these out

Dissemination level	PU
Contractual date of delivery	28.02.2021
Actual date of delivery	09.04.2021
Type	R
Version	1.0
Workpackage	WP1
Workpackage leader	Catharina Hartman, UMCG

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 728018.

Author list

Organisation	Name	Contact information
UMCG	Lizanne Schweren	l.j.s.schweren@umcg.nl
UMCG	Catharina Hartman	c.hartman@accare.nl
ORU	Henrik Larsson	henrik.larsson@ki.se
ORU	Lin Li	lin.li@oru.se
UiB	Berit Skretting Solberg	Berit.Skretting-Solberg@uib.no
UiB	Jan Haavik	jan.haavik@uib.no
RUMC	Jan Buitelaar	jan.buitelaar@radboudumc.nl
RUMC	Daan van Rooij	d.vanrooij@donders.ru.nl

Executive Summary

Within Deliverable 1.3 ("how lifestyle may enhance harmful/beneficial effects of diet or cancel these out "), two manuscripts have been prepared. Both manuscripts report on associations between diet, lifestyle and impulsivity/compulsivity in the general population of adults, manuscript 3a based on reduced cognitive control as measured by a cognitive task and manuscript 3b based on disinhibition based on behavioral and mental health measures.

The role of diet/lifestyle on cognitive control in manuscript 3a was studied by using an executive functioning (EF) task. The study was performed in a large-scale study in Dutch adults taking part in the Lifelines sample. In this study we focused on alcohol intake. It is known that excessive drinking compromises brain health and compromises cognitive functioning. The vast majority of adults, however, drink in moderation. Yet, surprisingly little is known about the effects of moderate alcohol consumption on cognitive functioning and whether there is a dose-dependent effects of non-excessive alcohol consumption on cognitive control. Here, we applied propensity-weighted analyses to investigate associations between habitual drinking patterns and executive functioning in the general population. A community sample of N=78,832 Dutch males and females age 18-65 completed the Ruff Figural Fluency Task of executive functioning (range 1-165; 2007-2015), and provided a detailed report of their past month alcohol consumption frequency and quantity. Participants were stratified according to drinking level (abstinent [22.0%], occasional [<2.5 g/day, 21.4%], light [2.5–14.9 g/day, 42.9%], moderate [15–29.9 g/day, 11.4%], or heavy [>30 g/day, 2.3%]) and binge-drinking (yes [10.6%] vs. no [89.4%]). Groups were equivalised using multinomial propensity score-weighing based on demographic, socioeconomic, health-related and psychosocial factors influencing drinking behaviour. Compared to abstinent participants, task performance was better among light drinkers (β[95%

CI]=0.058[0.035-0.080] or +1.3 points, p<0.0001) and moderate drinkers (β[95% CI]=0.114[0.082-0.147] or +2.6 points, p<0.0001), but not among occasional drinkers (β[95% CI]=0.020[-0.004-0.045], p=0.1053) or heavy drinkers (β[95% CI]=0.044[-0.040-0.128], p=0.3032). No difference in task performance was found between binge-drinkers and non-binge-drinkers (β[95% CI]=0.030[-0.004-0.063], p=0.0822). We conclude that light-to-moderate drinkers performed better on an executive functioning task compared to abstainers. The non-linear association between drinking level and executive functioning is reminiscent of the dose-dependent effect of alcohol consumption on cardiovascular risk. Further studies may determine whether cardiovascular, inflammatory and/or other somatic factors mediate the association between moderate drinking and higher-order cognitive functions. This study addresses a timely and highly relevant topic. Governmental bodies in the UK and the US, among others, have recently revised their dietary guidelines to discourage alcohol consumption, stating that there is no safe level of drinking. In both countries, these changes inspired animated discussions among scientists as well as the general public. Our study adds empirical evidence to these discussions suggesting that the guidelines on safe levels of drinking in relation to cognitive control functions may be premature.

The second manuscript 3b was focused on associations between diet, lifestyle and impulsivity/compulsivity in the general population of adults on behavioural disinhibition and poor self-regulation. These are prominent features of impulsvity/compulsivity of many severe and often persistent psychiatric disorders (e.g. ADHD, OCD, addictions), and important risk-factors for a range of negative long-term health outcomes including obesity and cardiovascular disease. Behavioural disinhibition is also associated with poor dietary habits, with causal pathways likely going in both directions. Very little is known, however, about dietary habits and manifestations of behavioural disinhibition at later age, when somatic poor health becomes increasingly prevalent. Modifiable lifestyle factors including diet and moderate-to-vigorous physical activity (MVPA) may be associated with disinhibition, but their contributions have not previously been quantified among middle-aged/older adults. Here, among N=157,354 UK Biobank participants age 40-69, we extracted a single disinhibition principal component and four dietary components (prudent diet, elimination of wheat/dairy/eggs, meat consumption, full-cream dairy consumption). In addition, latent profile analysis assigned participants to one of five empirical dietary groups: prudent-moderate, unhealthy, restricted, meat-avoiding, low-fat dairy. Disinhibition was regressed on the four dietary components, the dietary grouping variable and self-reported MVPA. In men and women, disinhibition was negatively associated with prudent diet, and positively associated with wheat/dairy/eggs elimination. In men, disinhibition was also associated with consumption of meat and full-cream dairy products. Comparing groups, disinhibition was lower in the prudent-moderate diet (reference) group compared to all other

groups. Absolute βs ranged from 0.02-0.13 indicating very weak effects. Disinhibition was not associated with MVPA. In conclusion, disinhibition is associated with multiple features of diet among middle-aged/older men and women (e.g. diet quality, but also dietary restrictions, meat and dairy consumption), but not with physical activity levels. Our study addresses a timely and highly relevant topic: the complex interplay between mental and somatic health, and the role of modifiable health behaviours therein. We apply advanced statistical methods to derive ecologically valid indicators of complex dietary habits in the general population – an approach with which we hope to inform and inspire nutritional scientists worldwide. In a time where the relationship between nutrition and mental health is heavily debated, our paper provides valuable new insights.

1. Deliverable report

In this deliverable report two manuscripts have been included, as follows:

Manuscript 3a: the role of diety/lifestyle and reduced cognitive control as measured by a cognitive task, and

Manuscript 3b: the role of diety/lifestyle and disinhibition based on behavioral and mental health measures.

***Manuscript 3a**: the role of diety/lifestyle and reduced cognitive control as measured by a cognitive task.*

Title

Alcohol consumption and executive functioning: a propensity score-weighted analysis of 78,832 adults

Authors

Lizanne JS Schweren, PhD [1] (corresponding author), Henrik Larsson, PhD [2], Jan Haavik, PhD [3], Lin Li, MSc [4], Berit Skretting Solberg, MD PhD [5], Alejandro Ariaz-Vasquez [6] & Catharina A Hartman, PhD [7]

Author information

1. Interdisciplinary Center Psychopathology and Emotion regulation, University Medical Center Groningen, UMCG HPC CC72. Hanzeplein 1, 9700 RB Groningen, the Netherlands.
2. School of Medical Sciences, Örebro University. Fakultetsgatan 1, 702 81 Örebro, Sweden. Department of Medical Epidemiology and Biostatistics, Karolinska Institutet. Solnavägen 1, 171 77 Stockholm, Sweden.
3. Department of Biomedicine, University of Bergen. 5007 Bergen, Norway. Bergen Centre of Brain Plasticity, Division of Psychiatry, Haukeland University Hospital. Jonas Lies vei 65, 5021 Bergen, Norway.
4. School of Medical Sciences, Örebro University. Fakultetsgatan 1, 702 81 Örebro, Sweden.
5. Department of Biomedicine, University of Bergen. 5007 Bergen, Norway.
6. Departments of Psychiatry and Human Genetics, Donders Center for Medical Neuroimaging. RadboudUMC; Geert Grooteplein Zuid 10, 6525 GA Nijmegen, The Netherlands.
7. Interdisciplinary Center Psychopathology and Emotion regulation, University Medical Center Groningen, UMCG HPC CC72. Hanzeplein 1, 9700 RB Groningen, the Netherlands.

Corresponding author

Dr. Lizanne JS Schweren

University Medical Center Groningen

Hanzeplein 1, 9700 RB Groningen, the Netherlands

lizanneschweren@gmail.com

Abstract

Excessive alcohol intake compromises cognitive functioning. Little is known, however, about dose-dependent effects of non-excessive alcohol consumption on higher-order cognitive functioning among generally healthy adults. Here, we applied propensity-weighted analyses to investigate associations between habitual drinking patterns and executive functioning in the general population. A community sample of N=78,832 Dutch males and females age 18-65 completed the Ruff Figural Fluency Task of executive functioning (range 1-165; 2007-2015), and provided a detailed report of their past month alcohol consumption frequency and quantity. Participants were stratified according to drinking level (abstinent [22.0%], occasional [<2.5 g/day, 21.4%], light [2.5–14.9 g/day, 42.9%], moderate [15–29.9 g/day, 11.4%], or heavy [>30 g/day, 2.3%]) and binge-drinking (yes [10.6%] vs. no [89.4%]). Groups were equivalised using multinomial propensity score-weighing based on demographic, socioeconomic, health-related and psychosocial factors influencing drinking behaviour. Compared to abstinent participants, task performance was better among light drinkers (β[95% CI]=0.058[0.035-0.080] or +1.3 points, p<0.0001) and moderate drinkers (β[95% CI]=0.114[0.082-0.147] or +2.6 points, p<0.0001), but not among occasional drinkers (β[95% CI]=0.020[-0.004-0.045], p=0.1053) or heavy drinkers (β[95% CI]=0.044[-0.040-0.128], p=0.3032). No difference in task performance was found between binge-drinkers and non-binge-drinkers (β[95% CI]=0.030[-0.004-0.063], p=0.0822). We conclude that light-to-moderate drinkers performed better on an executive functioning task compared to abstainers. The non-linear association between drinking level and executive functioning is reminiscent of the dose-dependent effect of alcohol consumption on cardiovascular risk. Further studies may determine whether cardiovascular, inflammatory and/or other somatic factors mediate the association between moderate drinking and higher-order cognitive functions.

Introduction

Executive functions (EF) refer to a set of higher-order cognitive processes necessary for flexible and goal-directed behaviours, including working memory, planning, inhibitory control, self-monitoring and problem solving [1]. Poor EF shows moderate genetic overlap with alcohol dependence and with continuous measures of alcohol intake [2]. Alcohol-dependent patients and excessive drinkers often present with impaired EF [3], likely reflecting bidirectional effects: while poor EF (e.g. poor response inhibition) may increase the risk of problematic drinking, excessive alcohol consumption may also compromise brain structure and function resulting in impaired task performance.

Little is known about the effects of non-excessive or moderate alcohol intake on higher-order cognitive functioning. The assumption of linear or quasi-linear continuity (i.e. incremental exposure resulting in incremental damage) is well established for some drinking-related outcomes (e.g. accident-related injuries [4]), but not for others. For cardiovascular outcomes, for instance, both abstinence and very heavy drinking have been associated with higher risks compared to moderate drinking [5], [6]. Initial evidence suggests that a similar non-linear dose-dependency might occur between alcohol consumption and EF: in a limited sample of 20-24, 40-44 and 60-64 year olds, Rodgers and colleagues found that light drinkers performed better on a working memory task compared to abstainers, occasional drinkers or harmful/hazardous drinkers [7]. In a second study of N=397 participants, moderate drinkers displayed superior performance over abstainers on an inhibitory control task but not on other EF tasks [8]. To date, however, no adequately powered studies are available. Perhaps more importantly, no studies are available that effectively address the risk of confounding by non-random group allocation, socioeconomic factors and other lifestyle behaviours (e.g. diet quality).

Here, in a community-sample of 78,832 generally healthy adults, we investigated associations between past month alcohol consumption as an indicator of drinking habits and figural fluency task performance as an indicator of EF. We modelled linear and non-linear effects of multiple drinking levels and patterns, applying propensity score-weighing to minimize confounding risks.

Participants and methods

Participants

The Lifelines Study is a multidisciplinary prospective population-based cohort study examining the health of 167,729 persons living in the north of the Netherlands [9]. Baseline data regarding biomedical, sociodemographic, behavioural and psychological factors were collected between 2006 and 2015. Data collection involved (among others) self-administered questionnaires, in-person interviews and physiological measurements at one of the Lifelines locations. Written informed consent was obtained from all participants. The Lifelines Cohort Study is conducted according to the principles of the Declaration of Helsinki and is approved by the medical ethics committee of the University Medical Center Groningen, the Netherlands.

Randomly selected general practitioners (GPs) invited all their listed patients age 25-50 years. Almost all inhabitants of the Netherlands are registered with a local GP. Willing respondents and their family members were asked to participate. General exclusion criteria were: a) severe mental/physical illness, b) unable to visit the GP, c) unable to complete the questionnaires, and d) insufficient understanding of the Dutch language. For the current work, baseline data were used applying the following additional exclusion criteria: e) age <18 or >65 years; f) missing or incomplete data on EF or drinking habits (see below); g) self-reported diagnosis of any neurological disorder; and h) Mini Mental State Examination-score <26. The final sample consisted of N=78,832 participants with an average age of 42.8 (SD=10.8) years of whom N=32,267 (40.9%) male (see flowchart, Supplement 1).

Alcohol consumption

Past-month food and drink intake was assessed using a 110-item semi-quantitative food frequency questionnaire [10]. Participants self-reported a) past month consumption of alcoholic drinks on a seven-point ordinal scale ranging from “never/not this month” to “6–7 days a week”; b) average number of glasses per day on such occasions; and c) how often (never/sometimes/often/always) on such occasions they drank beer, red/rose wine, white wine, fortified wine (e.g. sherry, port), liquor/distilled alcoholic drinks (e.g. rum, whiskey), and other alcoholic drinks. Items were weighted by their alcohol content and summed across drink types to derive alcohol intake in grams per day.

Two indicators of habitual alcohol intake were defined. First, drinking level was categorised as abstinent, occasional (<2.5 g/day or <0.25 Dutch standard unit [SU_{NL}]/day), light (2.5–14.9 g/day or 0.25-1.5 SU_{NL}/day), moderate (15–29.9 g/day or 1.5-3 SU_{NL}/day), or heavy (>30 g/day or >3 SU_{NL}/day). Second, participants were classified as binge-drinker if they reported drinking ≥5 units on a single occasion at least once in the past month (≥4 for females), and non-binge-drinker if they did not [11]. Past month abstinent participants were included in the latter group. For descriptive purposes, we

assessed drinkers' predominant drink type (e.g. beer) as the drink type that constituted >50% of their alcohol intake in grams per day. When no single drink type constituted >50%, drink type was classified as 'mixed'.

Executive functioning

EF was assessed with the Ruff Figural Fluency Test (RFFT). The RFFT is a measure of EF comprising planning, reasoning, mental flexibility, inhibition, strategy generation and regulation of action [12], [13]. The RFFT consists of five parts, each containing 35 five-dot patterns arranged on a five-by-seven grid. Each part uses either different distractors or different patterns. Participants are instructed to draw as many unique designs between the dots as possible during 60 seconds. The total number of unique designs (range 0-175) was used as the dependent variable in the analyses, with higher scores representing better performance. Participants who failed to produce a single design throughout the test were excluded. Due to logistical reasons, the RFFT was administered in all Lifelines participants until April 2012, and in a random half of all participants thereafter.

Confounders

We measured the following potential confounders: *demographic:* age, sex, ethnicity (Caucasian-white/other); *socioeconomic:* neighbourhood socioeconomic status by postcode, monthly household income, monthly household income adjusted for household size, educational attainment (low/middle/high), occupational status (ISEI08 [14]). For participants age<25, all socioeconomic parameters except neighbourhood SES were based on parental data; *lifestyle:* body mass index (BMI) in kg/m^2, smoking (never/former/current), overall diet quality [10], moderate-to-vigorous physical activity in minutes/week, sleep duration relative to age and sex (short/normal/long); *health:* lifetime diagnosis (yes/no) of cardiovascular disease, cancer, diabetes or liver cirrhosis, current diagnosis (yes/no) of depression or anxiety disorder, familial risk (yes/no) of cardiovascular disease, depression/anxiety or addiction; *personality:* NEO personality inventory facet sum scores for impulsivity, excitement-seeking and self-discipline [15], past month estimated number of social contacts; and *stress:* past year number of stressful life events and long-term difficulties. Note that certain confounders might be considered both a potential cause and a potential consequence of drinking.

Propensity models

We applied a multinomial propensity score-weighing approach to increase comparability of participants with different drinking levels, and of binge-drinking and non-binge-drinking participants. Propensity scores, designed to adjust incomplete randomization in intervention studies, have proven effective in reducing selection bias in observational studies [16]. In two propensity models, we predicted drinking level (abstinent/occasional/light/moderate/heavy) and binge-drinking (yes/no) from all covariates listed above and all possible two-way interactions between them. Multinomial propensity score-estimation treats the drinking levels as nominal variables, i.e. does not require linear dependencies between the covariates and alcohol intake. Residual imbalance between any two propensity-weighted groups not exceeding an absolute standardized mean difference (ASMD) of 0.1 or 0.25 was deemed acceptable resp. adjustable [17].

For descriptive purposes, we estimated correlations between each covariate and each propensity score: Pearson's correlations between continuous variable pairs and polyserial correlations between continuous-categorical pairs. The correlation matrix represents the contribution of each individual covariate to each propensity score, as well as the unweighted and unadjusted association between each drinking level and each covariate.

Statistical analyses

All analyses were performed in R version 3.5.2. Missing data points were imputed prior to propensity score-estimation using multivariate imputation by chained equations [18], applying classification tree predictions for categorical variables and regression tree predictions for continuous variables. Categorical values were derived after imputation of the underlying continuous variables.

We compared EF task performance between abstinent participants and participants of the other four drinking levels, and between binge-drinking and non-binge-drinking participants, applying the inverse probability of treatment weights [19]. To address residual confounding while maintaining covariate balance, all covariates included in the propensity score-models were also included in the regression models [17].

Three sensitivity analyses assessed robustness of our findings. First, propensity score-estimation and weighted regression modelling were repeated in participants of white ethnicity only, as ethnicity has been shown a particularly strong predictor of drinking habits in the Dutch population [20]. Second, analyses were repeated in age- and sex-stratified samples, as both EF and drinking patterns differ by age and sex [13], [21]. For this purpose, age was stratified in tertiles (young: age 18-38; middle-age: 39-48; old: 48-65). Finally, analyses were repeated within drinkers of predominantly beer and wine separately, as drinking habits may differ by drink type even if total alcohol intake

remains unchanged [22]. Other drink types were rarely predominant and could not be tested separately.

Associations of β≥0.20 are generally regarded as weak. In our sample of 78,832 participants, provided power=0.9 and Bonferroni-adjusted α=0.010 (conservatively adjusted for testing one predictor with five levels and one binary predictor: 0.05/(5-1)+(2-1)=0.010), associations of β<0.05 may reach significance [23]. In well-powered models predicting complex behaviours, large βs are not expected and small βs can be informative [24]. Consensus regarding denotation of weak associations is lacking. Here, for interpretational purposes, we qualified absolute βs of statistically significant associations (p<0.010) as follows: 0.05-0.19=very weak, 0.2-0.39=weak, 0.4-0.59=moderate, 0.6-0.79=strong and ≥0.8=very strong. Associations with an absolute β<0.05 were considered to be non-informative even if they reached statistical significance.

Results

N=17,373 participants (22.0%) had been abstinent in the past month, compared to n=16,838 occasional drinkers (21.4%), n=33,827 light drinkers (42.9%), n=8,955 moderate drinkers (11.4%) and n=1,839 heavy drinkers (2.3%). N=8,380 participants (10.6%) had engaged in binge-drinking. Among drinkers, red wine was most often the predominant drink type (n=26,999, 43.9%), followed by beer (n=10,993, 17.9%), white wine (n=4,487, 7.3%), and liquor (n=2,858, 4.7%). N=14,100 (22.9%) reported no predominant drink type ('mixed').

Unweighted, unadjusted analyses

The full matrix of unadjusted associations between drinking levels, binge-drinking and covariates is found in Supplement 2. Most prominently, higher drinking levels and binge-drinking were associated with male sex. Socioeconomic status and general health were better (e.g. higher income, lower diabetes risk) in light drinkers compared to other drinking levels and poorer in abstinent participants compared to other drinking levels. Similarly, excitement seeking was highest in light drinkers and lowest in abstainers. Binge-drinking was most strongly associated with younger age, poorer diet quality, smoking and more excitement seeking.

Balance after propensity weighing

Propensity score-weighing reduced all ASMDs between binge-drinkers and non-binge-drinkers to acceptable levels, and all pairwise ASMDs between abstinent and other drinking levels to acceptable or adjustable levels (Supplement 3). Adjustable residual imbalance between groups after weighing involved almost exclusively the abstinent vs. heavy drinking contrast, and ranged from ASMD=0.11

(income: 2499.0 euros among abstinent participants vs. 2580.6 euros among heavy drinkers) to ASMD=0.23 (49% never-smokers among abstinent participants vs. 37% among heavy drinkers). No contrasts showed non-adjustable imbalance after propensity score weighing, indicating that weighing was successful.

Alcohol intake and EF

After propensity score-weighing, light drinkers (2.5-14.9 g/day) scored on average 1.3 points higher (95% CI: 0.8-1.8 points) on the EF task compared to abstinent participants, indicating better performance. Moderate drinkers (15-29.9 g/day) scored on average 2.6 points higher (95% CI: 1.9-3.3 points) than abstinent participants. EF task performance did not differ between abstinent participants and occasional drinkers, or between abstinent participants and heavy drinkers (Table 1). We found no difference in EF task performance between binge-drinkers and non-binge-drinkers.

Sensitivity analyses

Results were attenuated when excluding participants of non-white ethnicity (N=1,137, Supplement 4), but the difference between abstainers and moderate drinkers remained significant. Propensity score-estimation and weighted regression modelling were repeated in age- and sex-stratified samples (Supplement 5). The increased EF task performance in light drinkers compared to abstainers, as seen in the full sample, was observed in all female strata (β ranging from 0.070 to 0.112) and in males of middle-age (β=0.098), but not in younger (β=-0.017) or older males (β<0.001). The increased task performance in moderate drinkers compared to abstinent participants was found in all male and female strata (β=0.054-0.178) except in younger males (β=0.018). Note that a) the young male group contained few abstainers (n=930 or 8.9% of all young males), and b) propensity weighing could not achieve satisfactory balance in all groups, warranting cautious interpretation of age- and sex-stratified findings.

Analyses were also repeated comparing drinkers of predominantly wine (n=39,139) and beer (n=10,993) to abstinent participants (Supplement 6). Better task performance among light drinkers, as found in the full sample, replicated in drinkers of wine (β[CI]=0.067[0.045-0.088]) but not in drinkers of beer (β[CI]=0.041[-0.007-0.089]). Better task performance among moderate drinkers replicated in both groups (beer: β[CI]=0.139[0.066-0.211]; wine: β[CI]=0.120[0.081-0.159]). For light/moderate drinkers of beer, however, satisfactory propensity balance with abstinent participants could not be achieved.

Discussion

In an unprecedented sample of 78,832 generally healthy adults, we investigated associations between habitual alcohol consumption and higher-order cognitive functioning. Applying propensity score-weighing to adjust for a comprehensive set of demographic, socioeconomic, lifestyle, psychosocial and health-related factors influencing drinking behaviour, we found that light (2.5-14.9 g/day) and moderate drinkers (15-29.9 g/day), but not heavy drinkers (≥30 g/day), performed better on an EF task compared to participants who consumed no alcohol. The association of moderate drinking held for men and women and across ages and drink types. Standardised effect sizes in our study never exceeded β=0.2, indicating very weak effects. Yet, the difference between abstainers and moderate drinkers equalled the average covariate-adjusted difference between depressed and non-depressed individuals in our model, and corresponded to the effect of 6.3 years of normal aging. Nonetheless, the weak association strength should be kept in mind while reading the below discussion.

The observed non-linear association between alcohol consumption and EF resembles the inverted J-shaped pattern of the risk of coronary heart disease at various drinking levels compared to abstinence [5], tentatively suggesting that cardiovascular factors might mediate the association between moderate alcohol consumption and better EF. Associations between EF and cardiovascular risk have indeed been shown (e.g. [25]). Cardiovascular effects of moderate alcohol consumption include, among others, lower blood pressure [26] and reduced inflammatory marker C-reactive protein (CRP) [27]. Both lower blood pressure and lower CRP have been associated with better cognitive performance [28], [29]. Alternative study designs are needed to elucidate the potential mediating role of cardiovascular and inflammatory factors.

As an alternative to cardiovascular changes, one may hypothesize that moderate alcohol consumption might cause subtle brain changes that result in better EF task performance. Population-based neuroimaging studies, however, have convincingly shown regional and global brain volume reductions among moderate drinkers compared to abstainers [30]–[33], suggesting detrimental rather than beneficial effects of moderate drinking. The observation of improved (cognitive) outcomes in the presence of unfavourable brain changes has been described as the “alcohol paradox” [34]. We deem the possibility of volumetric brain changes mediating the association between moderate drinking and better EF unlikely. However, other brain parameters (e.g. functional connectivity) may also be of interest.

Finally, we wish to explore two methodological explanations for finding better EF among moderate drinkers. First, it has frequently been proposed that individuals who refrain from drinking for health reasons, including ‘sick quitters’, may drive poorer outcomes in the abstinent group. Former drinking was not assessed in our sample, but our propensity metrics did include somatic and mental

health factors that may persuade individuals to quit drinking. That said, the influence of sick quitters is often overestimated, as they typically make up only a small proportion of abstainers [35]. Second, one might argue that the positive association between drinking and EF may suggest a collider bias. Collider bias occurs when conditioning upon a (measured or unmeasured) third variable, that is influenced by both the predictor and the outcome, causes a spurious association between the two. We exclude the possibility of a measured collider variable, as unadjusted associations similarly produced positive associations between light/moderate drinking and task performance (not shown). Unmeasured colliders can occur through selection bias [36]. Note, however, that our positive findings involved light and moderate rather than heavy drinkers (the latter group being more susceptible to selection bias). Thus, although the sick-quitter- and collider-hypotheses cannot fully be disproved, we conclude that neither hypothesis likely explains our findings.

Three limitations of our work should be mentioned. First, our data is cross-sectional. Balancing drinking groups based on factors predicting alcohol intake (rather than EF) installs a model in which drinking level affects EF task performance rather than the other way around. However, reverse causation cannot fully be eliminated. Specifically, we cannot exclude the possibility that moderate drinkers may not progress into heavy/problematic drinking due to their effective higher-order cognitive skills. Second, EF was assessed using a single figural fluency task, which correlates with – but does not fully capture – other executive domains such as inhibitory control, cognitive flexibility and working memory [37], [38]. Drinking may be differentially associated with other executive domains. Similarly, drinking habits were indexed by past month alcohol consumption, which has limited capacity to capture *habitual* behaviours. Finally, third, due to the observational nature of our study, we cannot exclude the possibility of residual (unmeasured, potentially genetic) confounding.

The potential implications of our findings should be carefully formulated. Recent years have witnessed a shift in alcohol consumption guidelines worldwide, with new guidelines stating that 'there is no safe level of drinking' (e.g. [39], [40]). While our findings do not provide support for such statements, we wish to emphasize that consumption guidelines are formulated balancing all potential positive and negative outcomes of drinking, including the risk of cancer, accident-related injuries and addiction. Our study adds to this balance one potential beneficial outcome of light-to-moderate drinking.

In conclusion, we observed better EF task performance in light and moderate drinkers of alcohol compared to abstainers, but not in heavy drinkers or binge-drinkers. This non-linear association is reminiscent of the dose-dependent effect of alcohol consumption on cardiovascular risks. In the future, identifying (partial) mediators of the association between light-to-moderate drinking and higher-order cognitive functions may advance our understanding of underlying biological mechanisms.

Funding and Disclosure

This work was supported by the European Union's Horizon 2020 Research and Innovation Program under grant agreement No 728018. The funding source has had no involvement in the study design, data collection, interpretation of the findings, or writing of this manuscript. During the past three years, JH has received educational speaking fees from HB Pharma, Biocodex, Medice, Takeda and Shire. H Larsson has served as a speaker for Evolan Pharma and Shire/Takeda and has received research grants from Shire/Takeda; all outside the submitted work. The other authors declare no conflicts of interest. All other authors certify that they have no affiliations with or involvement in any organization or entity with any financial or non-financial interest in the subject matter or materials discussed in this manuscript.

Author contributions

Funding was acquired by Alejandro Arias-Vasquez. All authors contributed to the study conception and design. Data curation and analysis was performed by Lizanne Schweren. The first draft of the manuscript was written by Lizanne Schweren and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

References

[1] Gilbert SJ, Burgess PW. Executive function. Curr Biol. 2008;18(3):142–50.

[2] Hatoum AS, Morrison CL, Mitchell EC, Lam M, Benca-Bachman CE, Reineberg AE, et al. Genome-Wide Association Study of Over 427,000 Individuals Establishes Executive Functioning as a Neurocognitive Basis of Psychiatric Disorders Influenced by GABAergic Processes. bioRxiv. 2020;674515.

[3] Stephan RA, Alhassoon OM, Allen KE, Wollman SC, Hall M, Thomas WJ, et al. Meta-analyses of clinical neuropsychological tests of executive dysfunction and impulsivity in alcohol use disorder. Am J Drug Alcohol Abuse. 2017;43(1):24–43.

[4] Taylor B, Irving HM, Kanteres F, Room R, Borges G, Cherpitel C, et al. The more you drink, the harder you fall: A systematic review and meta-analysis of how acute alcohol consumption and injury or collision risk increase together. Drug Alcohol Depend. 2010;110(1–2):108–16.

[5] Ronksley PE, Brien SE, Turner BJ, Mukamal KJ, Ghali WA. Association of alcohol consumption with selected cardiovascular disease outcomes: A systematic review and meta-analysis. Bmj. 2011;342(7795):479.

[6] Wood AM, Kaptoge S, Butterworth A, Nietert PJ, Warnakula S, Bolton T, et al. Risk thresholds for alcohol consumption: combined analysis of individual-participant data for 599 912 current drinkers in 83 prospective studies. Lancet. 2018;391(10129):1513–23.

[7] Rodgers B, Windsor TD, Anstey KJ, Dear KBG, Jorm AF, Christensen H. Non-linear relationships between cognitive function and alcohol consumption in young, middle-aged and older adults: The PATH through life project. Addiction. 2005;100(9):1280–90.

[8] Bø R, Landrø NI. Inhibitory control and response monitoring are not systematically related to weekly alcohol consumption in the general population. Psychopharmacology (Berl). 2017;234(11):1761–8.

[9] Stolk RP, Rosmalen JGM, Postma DS, De Boer RA, Navis G, Slaets JPJ, et al. Universal risk factors for multifactorial diseases: LifeLines: A three-generation population-based study. Eur J Epidemiol. 2008;23(1):67–74.

[10] Vinke PC, Corpeleijn E, Dekker LH, Jacobs DR, Navis G, Kromhout D. Development of the food-based Lifelines Diet Score (LLDS) and its application in 129,369 Lifelines participants. Eur J Clin Nutr. 2018;72(8):1111–9.

[11] Wechsler H, Austin S. Binge drinking: the five/four measure. J Stud Alcohol. 1998;59(1):122–4.

[12] Ruff R, Light R, Evans R. The ruff figural fluency test: a normative study with adults. Dev Neuropsychol. 1987;3(1):37–51.

[13] Izaks GJ, Joosten H, Koerts J, Gansevoort RT, Slaets JP. Reference data for the ruff figural fluency test stratified by age and educational level. PLoS One. 2011;6(2):1–8.

[14] Ganzeboom HB. A new international socioeconomic index (ISEI) of occupational status for the international standard classification of occupation 2008 (ISCO-08) constructed with data from the ISSP 2002-2007. 2010.

[15] Costa P, McCrae R. Revised NEO Personality Inventory (NEO PI-R) and NEO Five-Factor Inventory (NEO-FFI) Manual. Odessa, Florida: Psychological Assessment Resources; 1985.

[16] Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. Multivariate Behav Res. 2011;46(3):399–424.

[17] Nguyen TL, Collins GS, Spence J, Daurès JP, Devereaux PJ, Landais P, et al. Double-adjustment in propensity score matching analysis: choosing a threshold for considering residual imbalance. BMC Med Res Methodol. 2017;17(1):1–8.

[18] van Buuren S. Multivariate Imputation by Chained Equations (MICE). 2020.

[19] Feng P, Zhou XH, Zou QM, Fan MY, Li XS. Generalized propensity score for estimating the average treatment effect of multiple treatments. Stat Med. 2012;31(7):681–97.

[20] Kuipers MAG, Jongeneel-Grimen B, Droomers M, Wingen M, Stronks K, Kunst AE. Why residents of Dutch deprived neighbourhoods are less likely to be heavy drinkers: The role of individual and contextual characteristics. J Epidemiol Community Health. 2013;67(7):587–94.

[21] Poznyak V, Rekve D. Global status report on alcohol and health 2018. Global status report on alcohol. 2018.

[22] Grønbæk M, Tjønneland A, Johansen D, Stripp C, Overvad K. Type of alcohol and drinking pattern in 56,970 Danish men and women. Eur J Clin Nutr. 2000;54(2):174–6.

[23] Erdfelder E, FAul F, Buchner A, Lang AG. Statistical power analyses using G*Power 3.1: Tests for correlation and regression analyses. Behav Res Methods. 2009;41(4):1149–60.

[24] Nieminen P, Lehtiniemi H, Vähäkangas K, Huusko A, Rautio A. Standardised regression coefficient as an effect size index in summarising findings in epidemiological studies. Epidemiol Biostat Public Heal. 2013;10(4):1–15.

[25] Rostamian S, Van Buchem MA, Westendorp RGJ, Jukema JW, Mooijaart SP, Sabayan B, et al. Executive function, but not memory, associates with incident coronary heart disease and stroke. Neurology. 2015;85(9):783–9.

[26] Tasnim S, Tang C, Musini VM, Wright JM. Effect of alcohol on blood pressure. Cochrane Database Syst Rev. 2020;2020(7).

[27] Sierksma A, van der Gaag MS, Kluft C, Hendriks HFJ. Moderate alcohol consumption reduces plasma C-reactive protein and fibrinogen levels; a randomized, diet-controlled intervention study. Eur J Clin Nutr. 2002;56(11):1130–6.

[28] Forte G, De Pascalis V, Favieri F, Casagrande M. Effects of Blood Pressure on Cognitive Performance: A Systematic Review. J Clin Med. 2019;9(1):34.

[29] Yang Y, Shields GS, Wu Q, Liu Y, Chen H, Guo C. The association between obesity and lower working memory is mediated by inflammation: Findings from a nationally representative dataset of U.S. adults. Brain Behav Immun. 2020;84(November 2019):173–9.

[30] Paul CA, Au R, Fredman L, Massaro JM, Seshadri S, DeCarli C, et al. Association of alcohol consumption with brain volume in the Framingham study. Arch Neurol. 2008;65(10):1363–7.

[31] Fukuda K, Yuzuriha T, Kinukawa N, Murakawa R, Takashima Y, Uchino A, et al. Alcohol intake and quantitative MRI findings among community dwelling Japanese subjects. J Neurol Sci [Internet]. 2009;278(1–2):30–4. Available from: http://dx.doi.org/10.1016/j.jns.2008.11.007

[32] Taki Y, Kinomura S, Sato K, Goto R, Inoue K, Okada K, et al. Both global gray matter volume and regional gray matter volume negatively correlate with lifetime alcohol intake in non-alcohol-dependent Japanese men: A volumetric analysis and a voxel-based morphometry. Alcohol Clin Exp Res. 2006;30(6):1045–50.

[33] Immonen S, Launes J, Järvinen I, Virta M, Vanninen R, Schiavone N, et al. Moderate alcohol use is associated with decreased brain volume in early middle age in both sexes. Sci Rep [Internet]. 2020;10(1):1–8. Available from: https://doi.org/10.1038/s41598-020-70910-5

[34] Davis BJK, Vidal JS, Garcia M, Aspelund T, Van Buchem MA, Jonsdottir MK, et al. The alcohol paradox: Light-to-moderate alcohol consumption, cognitive function, and brain volume. Journals Gerontol - Ser A Biol Sci Med Sci. 2014;69(12):1528–35.

[35] Neafsey EJ, Collins MA. Moderate alcohol consumption and cognitive risk. Neuropsychiatr Dis Treat. 2011;7(1):465–84.

[36] Infante-Rivard C, Cusson A. Reflection on modern methods: Selection bias—a review of recent developments. Int J Epidemiol. 2018;47(5):1714–22.

[37] Ross TP. The reliability and convergent and divergent validity of the ruff figural fluency test in healthy young adults. Arch Clin Neuropsychol. 2014;29(8):806–17.

[38] Kuiper JS, Oude Voshaar RC, Verhoeven FEA, Zuidema SU, Smidt N. Comparison of cognitive functioning as measured by the Ruff Figural Fluency Test and the CogState computerized battery within the LifeLines Cohort Study. BMC Psychol. 2017;5(1):1–12.

[39] Department of Health UK. Alcohol Guidelines Review-Report from the Guidelines development group to the UK Chief Medical Officers. Department of Health. 2016.

[40] USDA Dietary Guidelines Advisory Committee. Scientific Report of the 2020 Dietary Guidelines Advisory Committee: Advisory Report to the Secretary of Agriculture and the Secretary of Health and Human Services. Washington, DC; 2020.

Table 1. Propensity weighted models comparing abstinent participants to each drinking level, and binge-drinkers to non-binge-drinkers

	Non-standardised		Standardised		
	Estimate	95% CI	β	95% CI	p
Occasional (0-2.5 g/day) vs. abstinent	0.457	-0.096 – 1.010	0.020	-0.004 – 0.045	0.1053
Light (2.5-14.9 g/day) vs. abstinent	1.308	0.802 – 1.814	0.058	0.035 – 0.080	<0.0001***
Moderate15-29.9 g/day) vs. abstinent	2.593	1.861 – 3.324	0.114	0.082 – 0.147	<0.0001***
Heavy (30-60 g/day) vs. abstinent	0.996	-0.900 – 2.893	0.044	-0.040 – 0.128	0.3032
Binge-drinking yes vs no	0.673	-0.086 – 1.432	0.030	-0.004 – 0.063	0.0822

*** significant effect at Bonferroni adjusted α=0.010

Supplemental materials belonging to:

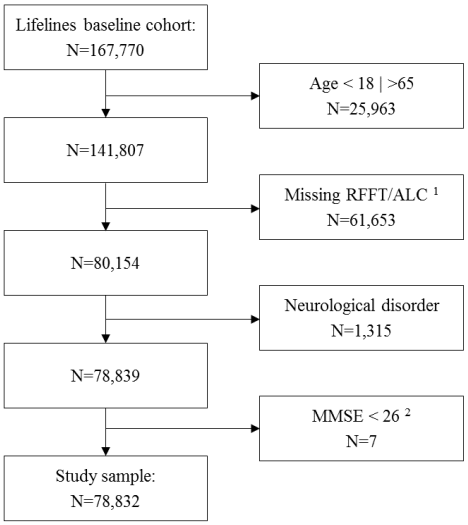
Alcohol consumption and executive functioning: a propensity score-weighted analysis of 78,832 adults

Schweren, Larsson, Haavik, Li, Solberg, Arias-Vasquez & Hartman. 2021

Supplement 1: Participant flowchart

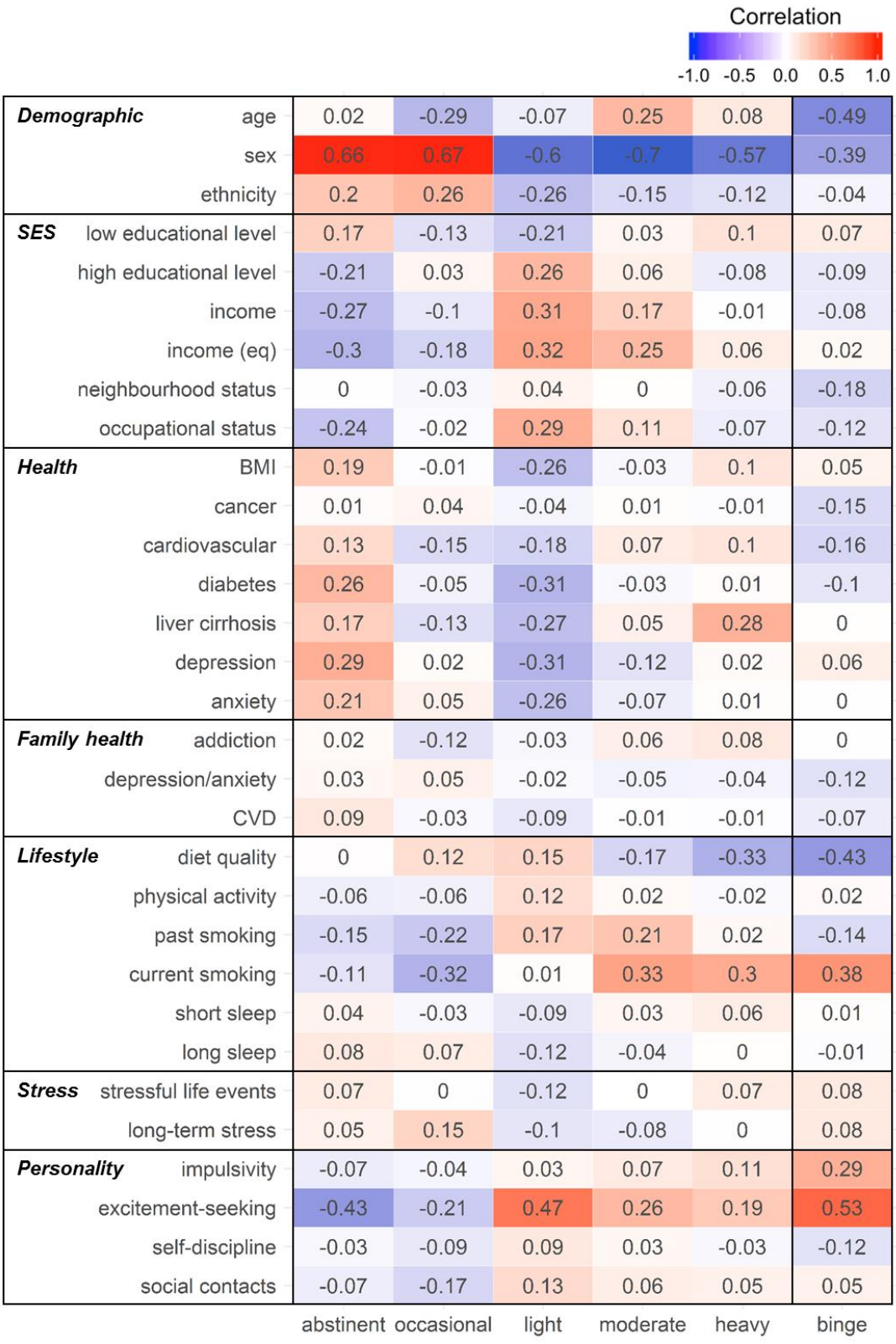
Supplemental Figure S1. Participant flowchart.

RFFT = Ruff Figural Fluency Task; MMSE = Mini Mental State Examination; 1 For logistic reasons, the RFFT was administered in all Lifelines participants until April 2012, and in a random half of all participants thereafter, resulting in a relatively large proportion of missing data; 2 By protocol, the RFFT was not administered in participants with MMSE<26. MMSE was only administered in participants age 65 and older.



Supplement 2: Correlations between propensity scores and all potential confounders

Supplemental Figure S2. Heatmap of correlations between all confounders and each propensity score.



Supplement 3: Balance before and after weighing

Supplemental Table S3.1. Means by drinking level before and after weighing

	Before weighing					After weighing				
	abst.	occ.	light	mod.	heavy	abst.	occ.	light	mod.	heavy
Age	42.9	41.7	42.6	45.1	44.4	43.1	42.8	42.9	43.5	44.7*
Income	2353.5	2492.3	2586.8	2617.9	2506.9	2499.0	2515.2	2524.6	2544.9	2580.6*
Income equivalised	1495.5	1586.2	1665.9	1720.8	1678.7	1604.1	1612.5	1623.6	1645.3	1692.0*
Neighbourhood status	-0.6	-0.6	-0.6	-0.6	-0.7	-0.6	-0.6	-0.6	-0.6	-0.5
Occupational status	42.5	46.5	48.4	48.3	44.0	46.3	46.4	46.7	47.2	46.5
BMI	26.7	26.0	25.7	25.9	26.8	26.1	26.0	26.0	25.9	26.1
Diet quality	23.7	23.9	23.9	23.0	20.4	23.7	23.7	23.7	23.6	23.2
Physical activity	249.3	259.1	275.0	270.2	254.9	258.8	260.5	264.3	257.4	262.3
SLE	1.3	1.2	1.1	1.2	1.4	1.2	1.2	1.2	1.2	1.2
LTD	2.7	2.7	2.5	2.4	2.6	2.6	2.6	2.6	2.6	2.5
Impulsivity	22.1	22.3	22.4	22.6	23.2	22.3	22.3	22.4	22.4	22.5
Excitement seeking	20.5	21.8	22.9	23.2	23.9	22.0	22.1	22.3	22.3	22.5*
Self-discipline	29.2	29.1	29.4	29.4	29.0	29.3	29.3	29.3	29.3	29.5
Social contacts	16.7	16.7	18.1	18.2	18.7	17.3	17.4	17.5	17.4	17.9
Male sex (%)	19.4	31.8	48.3	63.5	82.2	41.4	40.5	42.2	45.4	51.1*
Nonwhite ethnicity (%)	2.1	1.8	1.1	0.9	0.5	1.6	1.5	1.4	1.2	1.0
Low education (%)	34.9	26.6	25.7	29.7	37.5	29.5	28.7	28.4	28.6	29.9
High education (%)	22.8	31.4	34.7	33.3	24.4	29.3	30.7	31.4	32.1	30.7
Cancer (%)	3.7	3.8	3.6	3.7	3.5	3.7	3.8	3.5	3.5	4.8
CVD (%)	34.3	28.5	28.6	32.4	37.1	31.1	30.2	30.3	30.6	33.5
Diabetes (%)	2.9	1.8	1.4	1.7	1.8	2.1	1.9	1.8	2.1	1.7
Liver cirrhosis (%)	2.5	1.8	1.7	1.9	2.2	0.1	0.1	0.1	0.0	0.1
Depression (%)	5.0	3.2	2.5	2.5	3.3	3.4	3.1	3.1	3.1	2.8
Anxiety (%)	10.7	8.3	6.9	7.3	8.1	8.3	8.1	7.9	8.8	7.5
Fam addiction (%)	5.6	4.9	5.3	6.0	7.3	5.8	5.3	5.4	5.7	5.7
Fam dep/anx (%)	27.0	26.8	26.1	25.0	24.1	26.3	26.4	26.2	25.9	27.1
Fam CVD (%)	10.7	9.4	8.9	9.2	8.9	9.8	9.5	9.4	8.9	10.1
Past smoking (%)	25.8	28.1	34.3	40.0	34.5	30.7	31.7	32.1	33.9	37.3*
Current smoking (%)	17.7	17.1	22.1	33.3	44.9	20.5	21.3	22.4	23.5	26.4*
Short sleep (%)	11.0	9.7	9.2	10.9	13.7	10.3	10.1	10.1	10.8	9.9
Long sleep (%)	12.0	10.8	8.8	8.8	10.4	10.3	10.1	9.7	9.3	10.0

* adjustable difference between indicated group and abstinent group after weighing. Abbreviations: abst. = abstinent, occ. = occasional drinker, mod. = moderate drinker.

Supplemental Table S3.2. Means by binge-drinking (yes/no) before and after weighing

	Before weighing		After weighing	
	non-binge-drinking	binge-drinking	non-binge-drinking	binge-drinking
Age	43.5	36.8	42.8	42.5
Income	2525.6	2443.5	2517.9	2526.8
Income equivalised	1616.3	1631.1	1617.8	1634.8
Neighbourhood status	-0.6	-0.8	-0.6	-0.6
Occupational status	46.9	43.9	46.6	46.1
BMI	26.0	26.2	26.0	26.1
Diet quality	24.0	21.0	23.7	23.4
Physical activity	264.2	270.6	264.7	267.7
SLE	1.2	1.3	1.2	1.2
LTD	2.6	2.8	2.6	2.6
Impulsivity	22.2	23.6	22.4	22.5
Excitement seeking	21.9	24.9	22.2	22.5
Self-discipline	29.3	28.7	29.3	29.4
Social contacts	17.4	18.3	17.5	17.2
Male sex(%)	39.0	57.4	40.8	43.3
Nonwhite ethnicity (%)	1.5	1.2	1.5	1.5
Low education (%)	28.2	32.5	28.6	29.3
High education (%)	31.6	26.1	31.0	29.1
Cancer (%)	3.8	2.5	3.7	3.8
CVD (%)	31.2	23.9	30.6	30.2
Diabetes (%)	1.9	1.3	1.9	1.7
Liver cirrhosis (%)	2.0	1.4	0.1	0.1
Depression (%)	3.1	3.7	3.2	3.1
Anxiety (%)	8.1	7.9	8.1	8.1
Fam addiction (%)	5.4	5.5	5.4	5.9
Fam dep/anx (%)	26.8	21.8	26.4	26.1
Fam CVD (%)	9.6	8.0	9.5	9.2
Past smoking (%)	32.6	24.4	31.8	33.8
Current smoking (%)	19.8	39.2	21.8	23.9
Short sleep (%)	10.0	10.3	10.0	9.5
Long sleep (%)	10.0	9.5	10.0	9.9

Supplemental Table S3.3. Adjustable and non-adjustable differences between weighted groups

	Contrast	Confounder	Group 1	Group 2	ASMD
Adjustable	Abstinent vs. moderate	Smoking: never (%)	48.8%	42.6%	0.1248
	Abstinent vs. heavy	Age	43.1	44.7	0.1422
	Abstinent vs. heavy	Sex: male (%)	41.4%	51.1%	0.1935
	Abstinent vs. heavy	Income	2499.0	2580.6	0.1074
	Abstinent vs. heavy	Income equivalised	1604.1	1692.0	0.1781
	Abstinent vs. heavy	Smoking: never (%)	48.8%	37.3%	0.2329
	Abstinent vs. heavy	Smoking: past (%)	30.7%	36.3%	0.1189
	Abstinent vs. heavy	Smoking: current (%)	20.5%	26.4%	0.1410
	Abstinent vs. heavy	Excitement-seeking	22.0	22.5	0.1205
Non-adjustable	*None*				

Supplement 4: Results among participants of white ethnicity only

Supplemental Table S4.1. Adjustable and non-adjustable differences between weighted groups

	Contrast	Confounder	Group 1	Group 2	ASMD
Non-adjustable	*None*				

Supplemental Table S4.2. Propensity weighted models comparing abstinent participants to each drinking level, and binge-drinkers to non-binge-drinkers

	Non-standardised		Standardised		
	Est	95% CI	β	95% CI	p
Occasional (0-2.5 g/day) vs. abstinent	0.243	-0.322 – 0.807	0.011	-0.014 – 0.036	0.3993
Light (2.5-14.9 g/day) vs. abstinent	0.629	0.120 – 1.139	0.028	0.005 – 0.050	0.0154
Moderate15-29.9 g/day) vs. abstinent	1.648	0.929 – 2.368	0.073	0.041 – 0.105	<0.0001
Heavy (30-60 g/day) vs. abstinent	0.159	-1.865 – 2.183	0.007	-0.083 – 0.097	0.8780
Binge-drinking yes vs no	0.169	-0.675 – 1.014	0.007	-0.030 – 0.045	0.6945

Supplement 5: Results stratified by age and sex

Supplemental Table S5.1. Age- and sex-stratified groups

Sex	Age	N	%
Male	Young (18-38)	10,392	13.2
	Middle (39-48)	11,999	15.2
	Old (49-65)	9,876	12.5
Female	Young (18-38)	15,442	19.6
	Middle (39-48)	17,287	21.9
	Old (49-65)	13,836	17.6

Supplemental Table S5.2. Non-adjustable differences between weighted groups

Group	Contrast	Confounder	Group 1	Group 2	ASMD
Male – young	Abst. vs. light	liver cirrhosis	0.3%	<0.1%	0.2514
Male – middle	*none*				
Male – old	*none*				
Female – young	Abst. vs. heavy	Age	30.4	27.6	0.4823
	Abst. vs. heavy	Smoking: never	60.0%	36.1%	0.4780
	Abst. vs. heavy	Smoking: current	21.5%	51.5%	0.6830
	Abst. vs. heavy	Stressful life events	1.2	1.9	0.5406
	Abst. vs. heavy	Excitement seeking	22.9	25.0	0.4824
Female – middle	Abst. vs. heavy	Income (equivalised)	1508.8	1662.7	0.3279
	Abst. vs. heavy	Cancer	3.9%	13.1%	0.4680
	Abst. vs. heavy	Sleep: normal	80.0%	91.5%	0.2929
Female – old	Abst. vs. heavy	Smoking: never	36.9%	21.7%	0.3269

Abbreviations: abst. = abstinent

Supplemental Table S5.3. Fully adjusted models comparing abstinent participants to each drinking level, and binge-drinkers to non-binge-drinkers, in age- and sex stratified groups

		N	β	95% CI	p
Occasional (0-2.5 g/day) vs. abstinent	Full sample	16,838	0.020	-0.004 – 0.045	0.1053
	Male – young Δ	1,710	-0.026	-0.118 – 0.066	0.5788
	Male – middle	2,181	0.048	-0.027 – 0.123	0.2068
	Male – old	1,456	-0.030	-0.113 – 0.053	0.4787
	Female – young	4,487	0.030	-0.016 – 0.076	0.1959
	Female – middle	4,142	0.047	0.006 – 0.088	0.0253
	Female – old	2,862	0.065	0.017 – 0.113	0.0080***
Light (2.5-14.9 g/day) vs. abstinent	Full sample	33,827	0.058	0.035 – 0.080	<0.0001***
	Male – young	5,605	-0.017	-0.099 – 0.066	0.6899
	Male – middle	5,916	0.098	0.031 – 0.165	0.0039***
	Male – old	4,821	<0.001	-0.072 – 0.073	0.9963
	Female – young	5,862	0.070	0.024 – 0.115	0.0025***
	Female – middle	6,095	0.112	0.073 – 0.150	<0.0001***
	Female – old	5,528	0.106	0.063 – 0.149	<0.0001***
Moderate (15-29.9 g/day) vs. abstinent	Full sample	8,955	0.114	0.082 – 0.147	<0.0001***
	Male – young	1,695	0.018	-0.077 – 0.112	0.7157
	Male – middle	1,966	0.178	0.102 – 0.254	<0.0001***
	Male – old	2,030	0.054	-0.026 – 0.133	0.1845
	Female – young	584	0.134	0.021 – 0.247	0.0198
	Female – middle	1,094	0.148	0.071 – 0.225	0.0002***
	Female – old	1,586	0.158	0.094 – 0.221	<0.0001***
Heavy (30-60 g/day) vs. abstinent	Full sample	1,839	0.044	-0.040 – 0.128	0.3032
	Male – young	452	0.022	-0.115 – 0.158	0.7530
	Male – middle	529	0.107	-0.037 – 0.252	0.1446
	Male – old	531	0.039	-0.085 – 0.162	0.5382
	Female – young Δ	40	-0.099	-0.562 – 0.365	0.6767
	Female – middle Δ	122	-0.036	-0.388 – 0.316	0.8420
	Female – old Δ	165	0.119	-0.066 – 0.303	0.2069
Binge-drinking yes vs no	Full sample	8,380	0.030	-0.004 – 0.063	0.0822
	Male – young	2,426	0.023	-0.029 – 0.074	0.3863
	Male – middle	1,534	0.028	-0.031 – 0.088	0.3490
	Male – old	851	-0.066	0.154 – 0.021	0.1372
	Female – young	2,111	0.033	-0.030 – 0.097	0.3024
	Female – middle	909	0.130	0.041 – 0.219	0.0043***
	Female – old	549	0.058	-0.056 – 0.172	0.3177

Contrasts marked with Δ indicate residual non-adjustable differences between group in confounders. P-values marked with *** indicate significant effects ($p<0.01$ and $\beta>0.05$).

Supplement 6: Results stratified by drink type

Supplemental Table S6.1. Non-adjustable differences between weighted groups

Group	Contrast	Confounder	Group 1	Group 2	ASMD
Beer	Abst vs. light	Sex: male	41.8%	52.7%	0.2983
	Abst vs. moderate	Sex: male	41.8%	56.3%	0.3972
	Abst vs. moderate	Smoking: never	52.2%	36.8%	0.3108
	Abst vs. moderate	Smoking: current	21.6%	33.2%	0.2517
	Abst vs. heavy	Sex: male	41.8%	59.7%	0.4914
	Abst vs. heavy	Smoking: never	52.2%	32.6%	0.3972
	Abst vs. heavy	Smoking: current	21.6%	42.5%	0.4555
	Abst vs. heavy	Excitement-seeking	21.7	23.1	0.3015
Wine	Abst vs. heavy	Smoking: never	49.4%	35.1%	0.2889

Abbreviations: abst. = abstinent

Supplemental Table S6.2. Fully adjusted models comparing abstinent participants to each drinking level, and binge-drinkers to non-binge-drinkers, in age- and sex stratified groups

		N	β	95% CI	p
Occasional (0-2.5 g/day) vs. abstinent	Full sample	16,838	0.020	-0.004 – 0.045	0.1053
	Beer	2,369	0.036	-0.015 – 0.087	0.1642
	Wine	11,104	0.022	-0.003 – 0.047	0.0836
Light (2.5-14.9 g/day) vs. abstinent	Full sample	33,827	0.058	0.035 – 0.080	<0.0001***
	Beer [Δ]	5,637	0.041	-0.007 – 0.089	0.0949
	Wine	22,399	0.067	0.045 – 0.088	<0.0001***
Moderate (15-29.9 g/day) vs. abstinent	Full sample	8,955	0.114	0.082 – 0.147	<0.0001***
	Beer [Δ]	2,194	0.139	0.066 – 0.211	0.0002***
	Wine	5,010	0.120	0.081 – 0.159	<0.0001***
Heavy (30-60 g/day) vs. abstinent	Full sample	1,839	0.044	-0.040 – 0.128	0.3032
	Beer [Δ]	793	0.047	-0.069 – 0.162	0.4288
	Wine [Δ]	626	0.029	-0.081 – 0.140	0.6030
Binge-drinking yes vs no	Full sample	8,380	0.030	-0.004 – 0.063	0.0822
	Beer	3,563	0.034	-0.019 – 0.086	0.2127
	Wine	2,958	0.048	-0.005 – 0.101	0.0741

* Residual non-adjustable imbalance (ASMD>0.25) remained after propensity score weighing, rendering this between-group comparison prone to residual confounding.

***Manuscript 3b**: the role of diety/lifestyle and disinhibition based on behavioral and mental health measures*

Article type

Original research article

Title

Diet, physical activity and disinhibition: capturing complex behaviours in middle-aged and older adults

Authors

Lizanne JS Schweren [a] (corresponding author), Daan van Rooij [b], Huiqing Shi [b], Henrik Larsson [c,d], Alejandro Arias-Vasquez [b], Lin Li [c], Liv Grimstvedt Kvalvik [e], Jan Haavik [e,f], Jan Buitelaar [b,g], Catharina A Hartman [a]

Affiliations:

[a)] Interdisciplinary Center Psychopathology and Emotion regulation, University Medical Center Groningen, the Netherlands. [b)] Donders Center for Brain, Cognition and Behaviour, Department of Cognitive Neuroscience, RadboudUMC. Nijmegen, the Netherlands. [c)] School of Medical Sciences, Örebro University. Örebro, Sweden. [d)] Department of Medical Epidemiology Biostatistics, Karolinska Institutet. Stockholm, Sweden. [e)] Department of Biomedicine, University of Bergen. Bergen, Norway. [f)] Bergen Centre of Brain Plasticity, Haukeland University Hospital. Bergen, Norway. [g)] Karakter Child and Adolescent Psychiatry University Centre, RadboudUMC. Nijmegen, the Netherlands.

Correspondence

University Medical Center Groningen, t.a.o. Dr. Lizanne JS Schweren,

Hanzeplein 1, 9700 RB Groningen, the Netherlands

Telephone: +31 6 53 75 22 70

Email: lizanneschweren@gmail.com

Running head

Diet, physical activity and disinhibition

Conflicts of Interest

JH declares that he has in the past 3 years been a paid speaker for Medice, Biocodex, Shire, and Takeda, all unrelated to the work presented in the submitted manuscript. JB has been in the past 3 years a consultant to / member of advisory board of / and/or speaker for Takeda/Shire, Roche, Medice, Angelini, Janssen, and Servier. He is not an employee of any of these companies, and not a stock shareholder of any of these companies. He has no other financial or material support, including expert testimony, patents, royalties. HL has served as a speaker for Evolan Pharma and Shire/Takeda and has received research grants from Shire/Takeda; all outside the submitted work. The companies were in no way involved in the study design or analyses performed in the submitted manuscript, nor in the reporting of results or interpretation of findings. LJSS, DvR, HS, AA, LL, LGK and CAH declare that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

Sources of Funding

This work was supported by the European Union's Horizon 2020 Research and Innovation Program under grant agreement No 728018. The funding source has had no involvement in the study design, data collection, interpretation of the findings, or writing of this manuscript.

Availability of Data and Code

Bona fide researchers can apply to access the UK Biobank research resource to conduct health-related research that is in the public interest. Access to the data was granted to the authors by UK Biobank following registration with their system and approval of our research project (project number 23668). All derived variables will be returned and shared through UK Biobank (http://biobank.ndph.ox.ac.uk/showcase/). The R-scripts to derive these variables are available from the corresponding author upon reasonable request.

Abstract

Background: Behavioural disinhibition is a prominent feature of multiple psychiatric disorders, and has been associated with poor long-term somatic health outcomes. Modifiable lifestyle factors including diet and moderate-to-vigorous physical activity (MVPA) may be associated with behavioural disinhibition, but their contributions have not previously been quantified among middle-aged and older adults.

Methods: N=157,354 UK Biobank participants who completed the online mental health assessment were included (age 40-69, 2006-2010). Using principal component analyses, we extracted a single disinhibition score and four dietary component scores (prudent diet, elimination of wheat/dairy/eggs, meat consumption, and full-cream dairy consumption). In addition, latent profile analysis assigned participants to one of five empirical dietary groups: prudent-moderate, unhealthy, restricted, meat-avoiding, low-fat dairy. Participants self-reported MVPA in minutes/week. Behavioural disinhibition was regressed on the four dietary components, the dietary grouping variable and MVPA.

Results: in men and women, behavioural disinhibition was negatively associated with prudent diet scores, and positively associated with wheat/dairy/eggs elimination. In men only, disinhibition was also associated with consumption of meat and full-cream dairy products. Comparing groups, disinhibition was lower in the prudent-moderate diet (reference) group compared to all other groups. Absolute βs ranged from 0.02-0.13 indicating very weak effects. Disinhibition was not associated with MVPA.

Conclusions: Among middle-aged and older adults, behavioural disinhibition is associated with multiple features of diet. While the observational nature of UK Biobank does not allow causal inference, our findings foster specific hypotheses (e.g. early malnutrition, elevated immune-response, dietary restraint) to be tested in alternative study designs.

Keywords:

Behavioural disinhibition; dietary habits; physical activity; prudent diet; lifestyle

Background

Behavioural disinhibition is the tendency to act in an uncontrolled fashion, without prior risk-assessment and/or in disregard of social conventions. Manifestations of disinhibition may include poor self-regulation, impulsivity, compulsivity, emotional instability, aggression and high-risk behaviours [1]. Extreme manifestations of disinhibition are at the core of severe and often persistent psychiatric disorders, including attention-deficit/hyperactivity disorder (ADHD), mania and addiction. Poor self-regulation and psychiatric disorders related to disinhibition have been associated with a range of negative long-term health outcomes such as obesity [2] and cardiovascular disease [3].

Dietary habits may mediate the association between (extreme manifestations of) disinhibition and poor health. Impulsivity and poor self-regulation have been associated with unhealthy food choices, both in experimental settings [4], [5] and in observational studies [6]. Similarly, overall diet quality is poorer in patients with ADHD [7], mania [8] and addictions [9] compared to unaffected individuals. While a causal pathway running from disinhibition/self-regulation to dietary habits is plausible, dietary intake may also contribute to disinhibited behaviours. Rodents being fed a high-sugar or high-fat diet for a prolonged period of time showed increases in both impulsive [10] and compulsive behaviours [11]. Excessive consumption of palatable foods may evoke lasting changes in cortico-limbic dopamine signalling [12], relevant in impulse control. Others have speculated that disinhibited behaviours such as those seen in ADHD might arise as a result of diet-induced inflammation [13] or hypersensitivity to specific foods/allergens [14].

The available literature has several limitations, however. First, prior studies have primarily focussed on overall diet quality; associations between disinhibition and consumption of other dietary features remain largely unexplored. In the current study, we investigated associations between disinhibition and multiple data-driven dietary patterns, and compared homogenous dietary subgroups. Second, behavioural disinhibition is often studied in the young, especially in boys and young men. Dietary patterns differ by sex and change with age [15], [16], as may manifestations of disinhibition. Here, we studied disinhibition in the unprecedentedly large population of middle-aged and older UK Biobank participants, allowing investigation of its lifestyle correlates at different ages and for men and women separately. Third, dietary habits inevitably cluster together with other health behaviours including physical activity [17]. Lower levels of moderate-to-vigorous physical activity (MVPA) have been associated with poor self-control/disinhibition [18]–[20], and long-term physical activity interventions have been proposed to ameliorate inhibitory control task performance and reduce symptoms of psychiatric outcomes related to disinhibition (e.g. [21], [22]). Prior epidemiological studies, however, focused on either dietary habits or physical activity levels. Here, combined modelling of dietary habits and physical activity allows quantification of their unique and shared contributions.

Methods

The UK Biobank Study

The data underlying this article were provided by UK Biobank. UK Biobank is a prospective cohort study providing detailed characterisation of over half a million UK-based persons aged 40-69 years at recruitment (2006-2010; http://www.ukbiobank.ac.uk/wp-content/uploads/2011/11/UK-Biobank-Protocol.pdf). With linkage to routinely collected data such as those produced by the National Health Service, UK Biobank offers a highly efficient resource for observational epidemiology [23]. UK Biobank has ethical approval from the North West Multi-centre Research Ethics Committee. All participants gave informed consent. For the current study, we included participants who completed the follow-up online mental health questionnaire (MHQ) that was sent to 339,092 participants who had agreed to being contacted by email. Of those, 46% (N=157,354) completed the assessment [24].

Behavioural disinhibition

To assess disinhibition as a unitary construct, we performed a principal component analysis (PCA) on all disinhibition-related items. For details, see Supplemental Digital Content (SDC) section 1. First, all data-fields related to disinhibition, impulsivity, compulsivity and/or emotional instability were selected. Selected data-fields covered addictions including smoking, risk behaviours such as heavy drinking, self-reported and hospital-record diagnoses of selected psychiatric disorders, self-harm behaviours and personality questionnaire items. To ascertain a balanced representation of different manifestations of disinhibition, we defined nine categories of disinhibited behaviours: smoking, addiction (other than smoking), excessive cannabis use, personality factors, self-harm, mania, obsessive compulsive behaviours, externalising behaviours and risk-taking behaviours including binge-drinking. Next, we performed a PCA based on tetrachoric correlations between these behaviours. The single-component model, preferred *a priori*, presented with no interpretational shortcomings: all behaviours loaded positively on the principal component with factor loadings ranging from 0.335 to 0.708 (SDC Table S1.3). For each subject, a factor score was extracted with higher scores indicating a higher tendency for disinhibition.

Diet

Dietary habits were assessed using a 29-item food frequency questionnaire (FFQ) about participants' past-year average diets. Individual FFQ items are highly correlated reflecting underlying dietary patterns [25]. We thus performed two established data-reduction techniques: PCA to detect shared variance between items (i.e. dietary components), and latent profile analysis to detect clusters

of subjects behaving similarly with respect to the dietary components (i.e. dietary groups). For details see SDC Section 2-3.

Raw data included continuous variables (e.g. tablespoons of vegetables), ordinal variables (e.g. cereal intake frequency), food type descriptions (e.g. bread type: brown/white/wholemeal/other), and one tick-box item assessing elimination of specific food groups (eggs/dairy/wheat/sugar). Alcohol-related items were removed, since heavy drinking contributed to disinhibition scores. Binary contrasts were created for each food type (e.g. 'brown bread' vs. 'any other bread type') and elimination item (e.g. 'I never eat eggs' vs. 'no restrictions'). The resulting 58 food items/contrasts, regressed on age and sex, were entered in a PCA with promax rotation on the residuals, starting with a single component and adding components one-by-one. Components were retained as long as they remained unique, interpretable and stable. The optimal outcome contained four dietary components (Table 1). DC1 reflects a prudent diet, with positive loadings for fruits, vegetables, wholegrain bread and fish, and negative loadings for refined carbohydrate products, processed meat and instant coffee. DC2 reflects elimination of wheat, dairy and/or eggs. DC3 reflects meat and to a lesser extent fish consumption, and DC4 reflects consumption of full-cream milk and butter/spreads. Correlations between components were modest ($r \leq 0.124$)

Next, we performed latent profile analysis (R-package 'mclust' [26]) based on the four diet scores to derive relatively homogenous participant groups. Based on model fit, parsimony, stability, group size and plausibility, the optimal model comprised five mutually exclusive latent groups (SDC Section 3, Table 2). The largest group (n=49,463, 31.4%) had relatively high prudent diet scores and moderate scores across the other three DCs and was set as the reference group ('prudent-moderate'). The second group was characterised by a generally unhealthy (i.e. non-prudent) diet and high consumption of full-cream dairy products ('unhealthy', n=42,663, 27.1%). The third group comprised individuals who avoided meat and adhered to a prudent diet ('avoid meat', n=21,797, 13.9%). The remaining two groups were each driven by a single DC: one group comprised participants who avoided full-cream dairy products ('low-fat dairy': n=32,555, 20.7%), and one group comprised participants who eliminated wheat/dairy/eggs but not sugar from their diet ('restricted'; n=10,876, 6.9%).

Physical activity

Participants self-reported their frequency (days/week) and duration (minutes/day) of engaging in moderate and vigorous physical activity. MVPA was calculated as the sum of moderate and vigorous physical activity in minutes/week. MVPA was strongly skewed, ranging from 0 to 8,640 minutes/week with a median of 180 minutes/week and 80% of participants being active for ≤480 minutes/week.

MVPA was thus converted to pseudo-continuous quintile scores: 1: 0-43 minutes/week; 2: 43-120 minutes/week; 3: 120-240 minutes/week; 4: 240-480 minutes/week; 5: >480 minutes/week.

In sensitivity analyses, we also evaluated moderate and vigorous physical activity (MPA *resp.* VPA) separately. For MPA, quintile scores were created as before (1: 0-30 minutes/week, 2: 30-80 minutes/week, 3: 80-151 minutes/week, 4: 151-360 minutes/week, 5: >360 minutes/week). A large proportion of the sample never performed VPA, thus VPA was split in three groups (1: never; 2: 0-median i.e. 0-80 minutes/week; 3: >80 minutes/week).

Statistical procedures

The following covariates were included in each model: ethnicity (white/other), body mass index (BMI) in kg/m^2, self-reported habitual sleep duration (short: <7 hours/night; normal: 7-9 hours/night or 7-8 hours/night for adults age ≥65; long: >9 *resp.* >8 hours/night), neighbourhood-based index of multiple deprivation (IMD) by region (England, Scotland, Wales), self-reported annual household income adjusted for household size, self-reported unemployment status (unemployed/other), and years of education [27] (no qualifications: 7y; CSEs: 10y; O-levels/GCSEs: 10y; A levels/AS levels: 13y; other professional qualification: 15y; NVQ or HNC: 19y; college or university degree: 20y). Missing values for all variables were imputed with multivariate imputation using chained equations (R-package 'MICE' [28]).

Subsequent steps were performed in men and women separately. First, all variables were standardised. For descriptive purposes, we next predicted disinhibition from all covariates. Next, in six single-predictor models, we predicted disinhibition from DC1-4, the dietary grouping variable (reference group='prudent-moderate') and MVPA. Initially, an age-by-predictor interaction term was included in each model as well; however, no relevant interactions were detected (SDC Section 4), hence age-interaction terms were discarded. To assess unique associations between disinhibition and each predictor, we ran two multiple-predictor models: one predicting disinhibition from the DC1-4 and MVPA, and one predicting disinhibition from the dietary grouping variable and MVPA. Again, age-interactions were discarded upon finding no relevant interaction effects.

Alpha was conservatively adjusted for testing four DCs, one dietary grouping variable with five levels, and MVPA, in men and women separately: $\alpha=0.05/((4+(5-1)+1)*2)=0.0028$. Provided power=0.8, $\alpha=0.0028$ and n≥66,419, we were able to detect associations of $\beta\geq0.02$. Differentiation between statistically and clinically significant findings is not achieved by further lowering of α, but by investigating β. Absolute βs of 0.2 are generally referred to as 'weak'; however, in models predicting complex behaviours, large βs are not expected and small βs can be informative [29]. Consensus regarding denotation is lacking. Here, for interpretational purposes, we qualify absolute βs of

significant associations (p<0.0028) between 0.02-0.19 as very weak, 0.2-0.39 as weak, 0.4-0.59 as moderate, 0.6-0.79 as strong and ≥0.8 as very strong. Absolute β<0.02 is qualified as not associated.

Results

Disinhibition

Disinhibition scores were higher in men (M=0.01, SD=1.09) compared to in women (M=-0.11, SD=1.05; β_{FEMALE}=-0.118, se=0.005, p<0.0001). In the covariate-only model, disinhibition was associated with younger age (men: β=-0.226, se=0.004; women: β=-0.212, se=0.003), unemployment (men: β=0.215, se=0.027; women: β=0.275, se=0.035), white ethnicity (men: $\beta_{NON\text{-}WHITE}$=-0.189, se=0.022; women: $\beta_{NON\text{-}WHITE}$=-0.123, se=0.019), long sleep duration (men: β=0.201, se=0.024; women: β=0.215, se=0.023), short sleep duration (men: β=0.129, se=0.009; women: β=0.122 se=0.008), neighbourhood deprivation (men: β=0.112, se=0.004; women: β=0.111, se=0.004), and BMI (men: β=0.040, se=0.004; women: β=0.036, se=0.003). In women, disinhibition was also associated with lower adjusted income (β=-0.036, se=0.003) and more years of education (β=0.022, se=0.003).

Dietary components

In the single-predictor models including all covariates, prudent diet (DC1) was associated with lower disinhibition scores in men (β=-0.036) and women (β=-0.043; Table 3). By contrast, elimination of wheat, dairy and/or eggs (DC2) was associated with higher disinhibition scores in both groups (β_{MEN}=0.030, β_{WOMEN}=0.038). Meat consumption (DC3) and full-cream dairy consumption (DC4) were associated with more disinhibition in men (β_{DC3}=0.041; β_{DC4}=0.023) but not in women. Note that no association exceeded β=0.2 indicating very weak effects. Associations between disinhibition and each DC remained virtually unchanged in the multiple-predictor model that included all dietary components simultaneously as well as MVPA (Table 3), suggesting a) minimal overlap between the four dietary components, and b) that associations between disinhibition and diet were not accounted for by physical activity.

Dietary groups

Demographic/socioeconomic differences between the five dietary groups are shown in Table 2. Taking into account all covariates, disinhibition was significantly lower in the prudent-moderate diet group compared to all other diet groups (Table 3). In men, the difference in disinhibition compared to the prudent-moderate diet group was strongest in the restricted group (β=0.125), weaker in the unhealthy (β=0.087) and meat-avoiding (β=0.075) groups, and least pronounced in the low-fat dairy group (β=0.042). In women, relatively strong effects were found in the restricted diet group

(β=0.156) and the meat-avoiding group (β=0.154), followed by the unhealthy group (β=0.097) and the low-fat dairy group (β=0.054). Again, however, all effects were qualified as very weak (β<0.2). Model estimates were minimally affected by adding MVPA to the model (Table 3).

Moderate-to-vigorous physical activity

MVPA was not associated with disinhibition in men (β=-0.007) or women (β=-0.009; Table 3). Estimates were further attenuated after adding DC1-4 or the dietary grouping variable to the model. In sensitivity analyses, the models were rerun for moderate (MPA) and vigorous (VPA) physical activity separately. In the single-predictor models, MPA was not associated with disinhibition in men (β=<-0.001; SE=0.004, p=0.9186) or women (β=-0.004; SE=0.003, p=0.1647), while VPA was very weakly associated with lower disinhibition in both groups (men: β=-0.023; SE=0.004, p<0.0001; women: β=-0.023; SE=0.003, p<0.0001). Adding the dietary grouping variable to the model, the association between VPA and disinhibition remained significant (men: β=-0.021; SE=0.004, p<0.0001; women: β=-0.021; SE=0.003, p<0.0001), while the association fell short of significance after adding DC1-4 (men: β=-0.018; SE=0.004, p<0.0001; women: β=-0.016; SE=0.003, p<0.0001).

Discussion

We investigated dietary habits, physical activity and behavioural disinhibition in individuals age 40 and older. Among men and women and across the age range, adherence to a prudent diet was associated with lower disinhibition scores, while elimination of wheat, dairy and/or eggs was associated with higher disinhibition scores. In men, disinhibition was also associated with higher habitual consumption of meat and high-fat dairy products. Classifying participants based on their multivariate diet patterns, disinhibition scores were higher in the unhealthy diet, restricted diet, meat-avoiding and low-fat dairy groups compared to the prudent-moderate diet reference group. All associations between diet and disinhibition were very weak (β<0.2). MVPA was not associated with disinhibition.

Observed associations are weak in strength

Our finding of a negative association between prudent diet and disinhibition among middle-aged and older men and women corroborates and extends the existing disinhibition literature that tends to focus on the young, especially young males. We also add to the available knowledge by qualifying the association between prudent diet and disinhibition as 'very weak'. Short sleep duration, for instance, was >2.5 times more strongly associated with disinhibition, and age and unemployment

were >5 times more strongly associated. The weak association strength of this and all other associations detected in our study should be kept in mind when reading the below discussion.

Early-life malnutrition, food intolerances and dietary restraint

Unexpectedly, the strongest lifestyle predictor of disinhibition was a diet restricted in wheat, dairy and/or eggs. Within the restricted diet group, most individuals eliminated a single food group and each food group was equally often eliminated (wheat: 30.5%; dairy: 27.4%; eggs: 27.6%), suggesting that disinhibition is likely not associated with a lack of nutrients specifically provided by either product. Note that the restricted diet group was also characterised by lower overall diet quality compared to the prudent-moderate diet group, potentially suggesting a more general lack of nutrients or residual confounding. Participants in the restricted diet group were more often born outside the UK and of lower socioeconomic status, potentially pointing towards early life exposure to malnutrition. In animals, malnutrition early in life is known to cause impulsiveness in adulthood [30]. Alternatively, elimination of specific foods may suggest a higher prevalence of (allergic) food intolerances among impulsive individuals. Common genetic variants have been identified between allergic diseases and psychiatric disorders including ADHD, OCD and addiction [31]. Studies of dieting/weight control provide another alternative explanation: highly-impulsive individuals tend to score higher on dietary restraint, a cognitive concept characterised by the intention to limit food intake, among others [32]. However, participants were instructed to report dietary habits, not intentions. Finally, higher endorsement of elimination items ("Which of the following do you *never* eat?") may reflect a higher tendency among high-impulsive individuals compared to low-impulsive individuals to endorse these items, even if they do not fully meet the never-criterion.

Our findings regarding meat consumption were contradictory. In prior studies, meat consumption has been associated with emotional instability and impulsive/thrill-seeking traits [33], [34], but the opposite [6], [35] and null findings [36], [37] have also been reported. Here, in men only, meat consumption was associated with higher disinhibition scores. By contrast, both men and women in the meat-avoiding group had higher disinhibition scores compared to those in the prudent-moderate diet group. Higher disinhibition in the meat-avoiding group cannot be not explained by lower intake of omega-3 fatty acids (essential fish oil nutrients with potential limited efficacy in treating symptoms of ADHD [38]): oily fish consumption in the prudent-moderate and the meat-avoiding groups were similar (data not shown). Compared to the prudent-moderate diet group, the meat-avoiding group had higher levels of wheat/dairy/eggs restrictions, and, similar to the dietary restrictions group, a relatively large proportion of individuals of non-white ethnicity and born outside the UK. The early-malnutrition and food-intolerance hypotheses may thus apply to the meat-avoiding

group as well. Alternatively, the decision to (partially) eliminate meat from one's diet might be influenced by fluctuating societal trends, to which impulsive individuals may be more sensitive.

No unique association between disinhibition and physical activity

Finally, the absence of an association between MVPA and disinhibition is of note. In line with cardiovascular health benefits being greater for vigorous compared to moderate intensity activities [39], we found a very weak association between disinhibition and VPA but not MPA; however this association was partially accounted for by dietary factors. Similarly, leisure time MVPA may be associated with better outcomes compared to occupational MVPA ([40]), but our data did not allow stratification by MVPA-type. Thorough investigation of specific physical activity characteristics is beyond the scope of the current paper, and is recommended for future studies.

Strengths and limitations

Strengths of the current study include the application of state-of-the-art data-reduction techniques across modalities to capture complex latent variables. The so-created disinhibition scale robustly showed the expected associations with sociodemographic variables. Associations between diet and disinhibition were assessed both at the food-group level and at the level of multivariate dietary patterns, ensuring ecological validity, and were adjusted for other lifestyle parameters. Finally, socioeconomic status was modelled at the societal-, household- and individual level, lowering the risk of residual confounding. The current study has limitations as well. The cross-sectional and observational nature of our study precludes causal inferences. Observed associations might reflect an effect of disinhibition on dietary choices, an effect of dietary intake on disinhibited behaviours, or both. Another inherent vulnerability of observational studies is the possibility of unmeasured confounding, i.e. both disinhibition and dietary behaviours might be driven by an unmeasured third variable (e.g. genetic confounding). Finally, dietary habits and physical activity levels were self-reported and might be subject to systematic bias (e.g. less accurate reporting in high-impulsive participants).

To conclude, we found significant and age-independent associations between dietary habits and behavioural disinhibition among middle-aged and older men and women. Although all associations were of very weak strength, our findings generate specific hypotheses that might be tested in alternative study designs.

Table 1. Factor loadings (≤-0.20 or ≥0.20) per dietary component (DC1-4).

	DC1	DC2	DC3	DC4
Wholegrain bread vs. any other bread	0.58			
Dried fruit frequency	0.48			
Oily fish frequency	0.47		0.27	
Raw vegetables / salad frequency	0.45			
Fresh fruit frequency	0.45			
Cooked vegetables frequency	0.38			
Water frequency	0.34			
Non-oily fish frequency	0.33		0.33	
Cereal frequency	0.31	-0.20		
Ground coffee vs. any other coffee	0.32			0.20
Cereal vs. 'I never eat cereal'	0.28	-0.23		
Muesli vs. any other cereal	0.26			
Processed meat frequency	-0.24		0.48	
Instant coffee vs. any other coffee	-0.31			
Refined sugar-sweetened cereal products	-0.33			
White bread vs. any other bread	-0.55			
'I never eat dairy' vs. no restrictions		0.64		
'I never eat wheat' vs. no restrictions		0.64		
I never eat eggs, sugar, wheat or dairy' vs. no restrictions		0.51		
'I never eat eggs' vs. no restrictions		0.50		
'I never eat dairy' vs. no dairy restrictions		0.34		
'I never eat wheat' vs. no wheat restrictions		0.34		
Soy milk vs. any other milk		0.28		
'I never eat eggs' vs. no eggs restrictions		0.24		
Other bread vs. any other bread		0.22		
Other milk vs. any other milk		0.20		
Coffee vs. 'I never drink coffee'		-0.20		
Milk vs. 'I never drink milk'		-0.24		0.26
Bread frequency		-0.26		
'I never eat sugar' vs. no restrictions		-0.31		
Bread vs. 'I never eat bread'		-0.38		
Lamb frequency			0.75	
Beef frequency			0.73	
Pork frequency			0.73	
Poultry frequency			0.40	
Added salt frequency			0.31	
Fat content of milk				0.83
Semi-skimmed milk vs. any other milk				0.55
Full cream milk vs. any other milk				0.31

	DC1	DC2	DC3	DC4
Butter vs. any other spread				0.29
Cheese frequency				0.25
Skimmed milk vs. any other milk				-0.84

Table 2. Descriptive statistics per dietary group

	Prudent-moderate M(SD) / N(%)	Unhealthy M(SD) / N(%)	Low-fat dairy M(SD) / N(%)	Avoid meat M(SD) / N(%)	Restricted M(SD) / N(%)
N	49,463 (31.4)	42,663 (27.1)	32,555 (20.7)	21,797 (13.9)	10,876 (6.9)
Male	20,315 (41.1)	20,143 (47.2) [a]	12,054 (37.0) [a]	11,287 (51.8) [a]	4,461 (41.0) [a]
Age	55.5 (7.7)	55.9 (7.8) [bc]	56.3 (7.6) [bc]	56.2 (7.9) [ab]	56.4(7.7) [bc]
BMI	26.2 (4.3)	27.4 (4.7) [bc]	27.3 (4.7) [bc]	26.1 (4.3) [c]	26.7 (4.8) [bc]
IMD	13.4 (10.7)	15.7 (12.6) [bc]	14.5 (11.7) [bc]	15.5 (12.1) [bc]	16.6 (13.2) [bc]
Years in education	17.1 (4.1)	15.6 (4.7) [bc]	16.3 (4.5) [bc]	17.0 (4.3) [bc]	16.0 (4.7) [bc]
Annual income [d]	32.9 (16.0)	29.1 (14.9) [bc]	31.8 (16.0) [bc]	32.2 (16.7) [b]	30.6 (16.4) [bc]
Unemployment	524 (1.1)	672 (1.6) [b]	394 (1.2)	289 (1.3)	177 (1.6) [b]
Non-white ethnicity	956 (1.9)	1,136 (2.7) [bc]	697 (2.1) [b]	1,209 (5.6) [bc]	561 (5.2) [bc]
Sleep duration					
Short	9,592 (19.4)	9,762 (22.9) [bc]	7,271 (22.3) [bc]	4,862 (22.3) [bc]	2,831 (26.0) [bc]
Long	782 (1.6)	1,111 (2.6) [bc]	721 (2.2) [bc]	527 (2.4) [bc]	326 (3.0) [bc]
DC1 (prudent diet)	0.55 (0.62)	-0.92 (0.72)	0.10 (0.95)	0.42 (0.92)	-0.04 (1.12)
DC2 (no wheat/dairy/eggs)	-0.46 (0.37)	-0.25 (0.38)	-0.15 (0.49)	0.36 (0.56)	2.84 (1.54)
DC3 (meat)	0.14 (0.78)	0.34 (0.77)	0.05 (0.94)	-0.90 (1.21)	-0.29 (1.26)
DC4 (full-cream dairy)	0.53 (0.51)	0.45 (0.47)	-1.55 (0.39)	0.44 (0.69)	-0.38 (1.10)
MVPA quintiles	3.06 (1.36)	2.82 (1.43) [bc]	2.96 (1.39) [bc]	3.11 (1.40) [bc]	3.03 (1.43)

a. significantly different from the prudent-moderate diet group in unadjusted analyses; b. significantly different from the prudent-moderate diet group in unadjusted analyses for men; c. significantly different from the prudent-moderate diet group in unadjusted analyses for women. d. *1,000 euros, adjusted for household size. Abbreviations: BMI = body mass index; IMD = index of multiple deprivation; DC = dietary component; MVPA = moderate-to-vigorous physical activity.

Table 3. Regression model outcomes

		Single-predictor models				Multiple-predictor model [a]			
		β	SE	P		β	SE	P	
Men	DC1 (prudent diet)	-0.036	0.004	<0.0001	*	-0.031	0.004	<0.0001	*
	DC2 (no wheat/dairy/eggs)	0.030	0.004	<0.0001	*	0.039	0.004	<0.0001	*
	DC3 (meat)	0.041	0.004	<0.0001	*	0.039	0.004	<0.0001	*
	DC4 (full-cream dairy)	0.023	0.004	0.0001	*	0.022	0.004	<0.0001	*
	Unhealthy vs. prudent-moderate	0.087	0.010	<0.0001	*	0.086	0.010	<0.0001	*
	Restricted vs. prudent-moderate	0.125	0.016	<0.0001	*	0.124	0.016	<0.0001	*
					*				*
	Avoid meat vs. prudent-moderate	0.075	0.011	<0.0001	*	0.075	0.011	<0.0001	*
	Low-fat dairy vs. prudent-moderate	0.042	0.011	0.0002	*	0.042	0.011	0.0002	*
	MVPA quintiles	-0.007	0.004	0.0508		-0.004	0.004	0.2432	
Women	DC1 (prudent diet)	-0.043	0.003	<0.0001	*	-0.049	0.003	<0.0001	*
	DC2 (no wheat/dairy/eggs)	0.038	0.003	<0.0001	*	0.043	0.003	<0.0001	*
	DC3 (meat)	-0.017	0.003	0.0036		-0.018	0.003	0.0001	
	DC4 (full-cream dairy)	0.010	0.003	0.0023		0.011	0.003	0.0014	
	Unhealthy vs. prudent-moderate	0.097	0.009	<0.0001	*	0.095	0.009	<0.0001	*
	Restricted vs. prudent-moderate	0.156	0.013	<0.0001	*	0.156	0.013	<0.0001	*
					*				*
	Avoid meat vs. prudent-moderate	0.154	0.011	<0.0001	*	0.154	0.011	<0.0001	*
					*				*
	Low-fat dairy vs. prudent-moderate	0.054	0.009	<0.0001	*	0.054	0.009	<0.0001	*
	MVPA quintiles	-0.009	0.003	0.0054		-0.003	0.003	0.3343	

a. For DC1-4: adding the other dietary components and MVPA to the model; for dietary groups: adding MVPA to the model; for MVPA: adding DC1-4 to the model. ** p<0.0028 & β=0.1-0.2; * p<0.0028 & β=0.02-0.1. Abbreviations: DC = dietary component; MVPA = moderate-to-vigorous physical activity.

References

[1] L. Sharma, K. E. Markon, and L. A. Clark, "Toward a theory of distinct types of 'impulsive behaviors': a meta-analysis of self-report and behavioral measures," *Psychol. Bull.*, vol. 140, no. 2, pp. 374–408, 2014.

[2] S. Cortese, C. R. Moreira-Maia, D. St Fleur, C. Morcillo-Peñalver, L. A. Rohde, and S. V. Faraone, "Association between ADHD and obesity: A systematic review and meta-analysis," *Am. J. Psychiatry*, vol. 173, no. 1, pp. 34–43, 2016.

[3] L. D. Kubzansky, N. Park, C. Peterson, P. Vokonas, and D. Sparrow, "Healthy Psychological Functioning and Incident Coronary Heart Disease," *Arch. Gen. Psychiatry*, vol. 68, no. 4, p. 400, 2011.

[4] S. Van Blyderveen, A. Lafrance, M. Emond, S. Kosmerly, M. O'Connor, and F. Chang, "Personality differences in the susceptibility to stress-eating: The influence of emotional control and impulsivity," *Eat. Behav.*, vol. 23, pp. 76–81, 2016.

[5] R. Guerrieri, C. Nederkoorn, and A. Jansen, "How impulsiveness and variety influence food intake in a sample of healthy women," *Appetite*, vol. 48, no. 1, pp. 119–122, 2007.

[6] M. Bénard *et al.*, "Impulsivity is associated with food intake, snacking, and eating disorders in a general population," *Am. J. Clin. Nutr.*, vol. 109, no. 1, pp. 117–126, 2019.

[7] O. K. Loewen, K. Maximova, J. P. Ekwaru, M. Asbridge, A. Ohinmaa, and P. J. Veugelers, "Adherence to life-style recommendations and Attention-Deficit/Hyperactivity Disorder: a population-based study of children aged 10 to 11 years," *Psychosom. Med.*, vol. 82, no. 3, pp. 305–315, 2020.

[8] D. Łojko, M. Stelmach-Mardas, and A. Suwalska, "Diet quality and eating patterns in euthymic bipolar patients," *Eur. Rev. Med. Pharmacol. Sci.*, vol. 23, no. 3, pp. 1221–1238, 2019.

[9] A. Alkerwi *et al.*, "Smoking status is inversely associated with overall diet quality: Findings from the ORISCAV-LUX study," *Clin. Nutr.*, vol. 36, no. 5, pp. 1275–1282, 2017.

[10] C. C. Steele, J. R. A. Pirkle, and K. Kirkpatrick, "Diet-induced impulsivity: Effects of a high-fat and a high-sugar diet on impulsive choice in rats," *PLoS One*, vol. 12, no. 6, pp. 1–16, 2017.

[11] S. Krishna *et al.*, "Neurochemical and electrophysiological deficits in the ventral hippocampus and selective behavioral alterations caused by high-fat diet in female C57BL/6 mice," *Neuroscience*, vol. 297, pp. 170–181, 2015.

[12] S. Sharma, M. F. Fernandes, and S. Fulton, "Adaptations in brain reward circuitry underlie

palatable food cravings and anxiety induced by high-fat diet withdrawal," *Int. J. Obes.*, vol. 37, no. 9, pp. 1183–1191, 2013.

[13] A. A. J. Verlaet, D. B. Noriega, N. Hermans, and H. F. J. Savelkoul, "Nutrition, immunological mechanisms and dietary immunomodulation in ADHD," *Eur. Child Adolesc. Psychiatry*, vol. 23, no. 7, pp. 519–529, 2014.

[14] L. M. J. Pelsser, J. K. Buitelaar, and H. F. J. Savelkoul, "ADHD as a (non) allergic hypersensitivity disorder: A hypothesis," *Pediatr. Allergy Immunol.*, vol. 20, no. 2, pp. 107–112, 2009.

[15] P. Wakimoto and G. Block, "Dietary Intake, Dietary Patterns, and Changes With Age: An Epidemiological Perspective," *Journals Gerontol. Ser. A Biol. Sci. Med. Sci.*, vol. 56, no. Supplement 2, pp. 65–80, 2001.

[16] J. Westenhoefer, "Age and gender dependent profile of food choice," *Forum Nutr.*, vol. 57, pp. 44–51, 2005.

[17] A. J. Schuit, A. J. M. Van Loon, M. Tijhuis, and M. C. Ocké, "Clustering of lifestyle risk factors in a general adult population," *Prev. Med. (Baltim).*, vol. 35, no. 3, pp. 219–224, 2002.

[18] M. I. Kinnunen, J. Suihko, N. Hankonen, P. Absetz, and P. Jallinoja, "Self-control is associated with physical activity and fitness among young males," *Behav. Med.*, vol. 38, no. 3, pp. 83–89, 2012.

[19] C. K. Cardol, C. I. Escamilla, W. A. Gebhardt, and J. C. Perales, "Exploring the direct or inverse association of physical activity with behavioral addictions and other self-regulation problems," *Adicciones*, vol. 31, no. 1, pp. 18–32, 2019.

[20] P. Pokhrel, S. Schmid, and I. Pagano, "Physical Activity and Use of Cigarettes and E-Cigarettes Among Young Adults," *Am. J. Prev. Med.*, vol. 58, no. 4, pp. 580–583, 2020.

[21] J. I. Gapin, J. D. Labban, and J. L. Etnier, "The effects of physical activity on attention deficit hyperactivity disorder symptoms: The evidence," *Prev. Med. (Baltim).*, vol. 52, no. SUPPL., pp. S70–S74, 2011.

[22] M. T. Bardo and W. M. Compton, "Does physical activity protect against drug abuse vulnerability?," *Drug Alcohol Depend.*, vol. 153, pp. 3–13, 2015.

[23] C. Sudlow *et al.*, "UK Biobank: An Open Access Resource for Identifying the Causes of a Wide Range of Complex Diseases of Middle and Old Age," *PLoS Med.*, vol. 12, no. 3, pp. 1–10, 2015.

[24] K. A. S. Davis *et al.*, "Mental health in UK Biobank Revised," *MedRxiv*, 2019.

[25] J. B. Cole, J. C. Florez, and J. N. Hirschhorn, "Comprehensive genomic analysis of dietary habits

in UK Biobank identifies hundreds of genetic associations," *Nat. Commun.*, vol. 11, no. 1, pp. 1–11, 2020.

[26] C. Fraley, A. E. Raftery, L. Scrucca, T. B. Murphy, and T. Fop, "Package ' mclust .'" pp. 1–169, 2020.

[27] W. D. Hill *et al.*, "Genome-wide analysis identifies molecular systems and 149 genetic loci associated with income," *Nat. Commun.*, vol. 10, no. 1, pp. 1–16, 2019.

[28] S. van Buuren and K. Groothuis-Oudshoorn, "mice: Multivariate imputation by chained equations in R," *J. Stat. Softw.*, vol. 45, no. 3, pp. 1–67, 2011.

[29] P. Nieminen, H. Lehtiniemi, K. Vähäkangas, A. Huusko, and A. Rautio, "Standardised regression coefficient as an effect size index in summarising findings in epidemiological studies," *Epidemiol. Biostat. Public Heal.*, vol. 10, no. 4, pp. 1–15, 2013.

[30] M. Alamy and W. A. Bengelloun, "Malnutrition and brain development: An analysis of the effects of inadequate diet during different stages of life in rat," *Neurosci. Biobehav. Rev.*, vol. 36, no. 6, pp. 1463–1480, 2012.

[31] D. S. Tylee *et al.*, "Genetic correlations among psychiatric and immune-related phenotypes based on genome-wide association data," *Am. J. Med. Genet. Part B Neuropsychiatr. Genet.*, vol. 177, no. 7, pp. 641–657, 2018.

[32] J. S. Mills, L. Weinheimer, J. Polivy, and C. P. Herman, "Are there different types of dieters? A review of personality and dietary restraint," *Appetite*, vol. 125, pp. 380–400, 2018.

[33] R. Sariyska, S. Markett, B. Lachmann, and C. Montag, "What Does Our Personality Say About Our Dietary Choices? Insights on the Associations Between Dietary Habits, Primary Emotional Systems and the Dark Triad of Personality," *Front. Psychol.*, vol. 10, no. November, pp. 1–11, 2019.

[34] T. M. Pfeiler and B. Egloff, "Personality and eating habits revisited: Associations between the big five, food choices, and Body Mass Index in a representative Australian sample," *Appetite*, vol. 149, no. May 2019, 2020.

[35] C. A. Forestell and J. B. Nezlek, "Vegetarianism, depression, and the five factor model of personality," *Ecol. Food Nutr.*, vol. 57, no. 3, pp. 246–259, 2018.

[36] C. Keller and M. Siegrist, "Does personality influence eating styles and food choices? Direct and indirect effects," *Appetite*, vol. 84, pp. 128–138, 2015.

[37] T. M. Pfeiler and B. Egloff, "Examining the 'Veggie' personality: Results from a representative

German sample," *Appetite*, vol. 120, pp. 246–255, 2018.

[38] R. E. Cooper, C. Tye, J. Kuntsi, E. Vassos, and P. Asherson, "The effect of omega-3 polyunsaturated fatty acid supplementation on emotional dysregulation, oppositional behaviour and conduct problems in ADHD: A systematic review and meta-analysis," *J. Affect. Disord.*, vol. 190, pp. 474–482, 2016.

[39] D. P. Swain and B. A. Franklin, "Comparison of cardioprotective benefits of vigorous versus moderate intensity aerobic exercise," *Am. J. Cardiol.*, vol. 97, no. 1, pp. 141–147, 2006.

[40] O. Byambasukh, H. Snieder, and E. Corpeleijn, "Relation Between Leisure Time, Commuting, and Occupational Physical Activity With Blood Pressure in 125 402 Adults: The Lifelines Cohort," *J. Am. Heart Assoc.*, vol. 9, no. 4, 2020.

Supplemental Digital Content

belonging to publication:

LJS Schweren, D van Rooij, H Shi, A Arias-Vasquez, L Li, H Larsson, L Grimstvedt Kvalvik, J Haavik, J Buitelaar & CA Hartman (2020). Diet, physical activity and disinhibition: capturing complex behaviours in middle-aged and older adults.

Table of contents:

Section 1: PCA to derive behavioural disinhibition scores

We performed a principal component analysis (PCA) on all disinhibition-related items. First, all datafields related to disinhibition, impulsivity, compulsivity and/or emotional instability were selected by two independent authors (Supplementary tables ST1.1-1.2). Non-binary items were binarized. Next, to ascertain a balanced representation of disinhibited behaviour types, cases were defined for nine groups of disinhibited behaviours (i.e. externalising, obsessive-compulsive, addiction, self-harm, personality, mania, risk-taking, cannabis use, smoking). Case-ness was defined such that it captured relatively extreme behaviours, aiming at a 5-10% endorsement rate. For instance, participants were considered a case for addiction when they either self-reported being or having been addicted, or had at any time received a diagnosis of substance dependence syndrome in hospital, resulting in 6.1% of the sample being a case.

Next, we performed a PCA based on tetrachoric correlations between behavioural groups (ST1.3). The theoretical framework underlying our approach is that impulsive, compulsive and emotionally unstable behaviours reflect a unitary disinhibited phenotype and share a common origin. Therefore, the single-component model was preferred a priori, and more complex models were only considered if the simpler model presented with statistical or interpretational shortcomings. All behaviours loaded positively on the first principal component, with factor loadings ranging from 0.335 to 0.708 (Table 2). Models with two and three principal components are shown in ST1.4. The two-PC model differentiates between behaviours related to substance abuse (PC2) and other disinhibited behaviours (PC1), but contains double loadings for self-harm and addiction. The three-PC model adds a component reflecting unstable personality/mania, but also has double loadings (addiction, personality) and triple loadings (self-harm). Hence, the single-component model was adopted. For each subject, a factor score was extracted with higher scores indicating a higher tendency for disinhibition. Finally, after trimming at 97.5% to replace extreme values by the cut-off value (i.e. 3.4), disinhibition scores ranged from -0.78 to 3.40 (M=-0.14, SD=0.93).

Table S1.1. Selected UK Biobank items related to disinhibition, impulsivity, compulsivity and/or emotional instability and their binarised response categories.

Data-field	Source	Description	Response categories (original)	Response categories (binary)
1239	IAV	Do you smoke tobacco now?	- No - Yes, on all/most days - Only occasionally	- No / only occasionally - Yes, on all/most days
1920	IAV	Does your mood often go up and down?	- No - Yes	- No - Yes

Data-field	Source	Description	Response categories (original)	Response categories (binary)
1940	IAV	Are you an irritable person?	- No - Yes	- No - Yes
1960	IAV	Do you often feel fed-up?	- No - Yes	- No - Yes
20544	MHQ	Have you been diagnosed with one or more of the following mental health problems by a professional, even if you don't have it currently? (tick box)	- OCD - Mania - ADHD	- No - Yes (per diagnosis)
20548	MHQ	Try to remember a period when you were in a "high" or "irritable" state (tick box) (conditional to: ever had period of extreme irritability/excitability)	- More restless than usual - Thoughts were racing - Easily distracted - More active than usual	- No - Yes, ever had period of mania/irritability with at least one of these symptoms
20401	MHQ	Have you been addicted to or dependent on one or more things, including substances (not cigarettes/coffee) or behaviours (such as gambling)?	- No - Yes	- No - Yes
20416	MHQ	How often do you have six or more drinks on one occasion? (conditional to: frequency of drinking alcohol)	- Never - Less than monthly - Monthly - Weekly - (Almost) daily	- Never / less than weekly - Weekly / (almost) daily
20453	MHQ	Have you taken cannabis (marijuana, grass etc.), even if it was a long time ago?	- No - Yes, 1-2 times - Yes, 3-10 times - Yes, 11-100 times - Yes, more than 100 times	- No / less than 11 times - Yes, 11 times / more
20480	MHQ	Have you deliberately harmed yourself, whether or not you meant to end your life?	- No - Yes	- No - Yes
41202 and 41204	LHR	Main or secondary ICD-10 diagnoses from hospital inpatient records	See supplementary table ST1.2	- No - Yes (per diagnostic group)

Abbreviations: IAV= initial assessment visit, MHQ= mental health questionnaire, LHR= linked health records, ICD-10= international classification of diagnoses, 10th edition.

Table ST1.2. ICD-10 diagnoses related to impulsivity, compulsivity and/or emotional instability per diagnostic group.

Addiction	F102	Dependence syndrome of alcohol
	F112	Dependence syndrome of opioids
	F122	Dependence syndrome of cannabinoids
	F132	Dependence syndrome of sedatives or hypnotics
	F142	Dependence syndrome of cocaine
	F152	Dependence syndrome of other stimulants
	F162	Dependence syndrome of hallucinogens
	F192	Dependence syndrome of multiple drug use and use of other psychoactive substances
Externalising	F900	Disturbance of activity and attention
	F901	Hyperkinetic conduct disorder
	F908	Other hyperkinetic disorders
	F909	Hyperkinetic disorder unspecified
	F910	Conduct disorder confined to the family context
	F911	Unsocialised conduct disorder
	F912	Socialised conduct disorder
	F913	Oppositional defiant disorder
	F918	Other conduct disorders
	F919	Conduct disorder unspecified
	F920	Depressive conduct disorder
	F928	Other mixed disorders of conduct and emotions
	F929	Mixed disorder of conduct and emotions unspecified
Mania	F300	Hypomania
	F301	Mania without psychotic symptoms
	F302	Mania with psychotic symptoms
	F308	Other manic episodes
	F309	Manic episode unspecified
	F310	Bipolar affective disorder current episode hypomanic
	F311	Bipolar affective disorder current episode manic without psychotic symptoms
	F312	Bipolar affective disorder current episode manic with psychotic symptoms
	F313	Bipolar affective disorder current episode mild or moderate depression
	F314	Bipolar affective disorder current episode severe depression w/o psychotic symptoms
	F315	Bipolar affective disorder current episode severe depression with psychotic symptoms
	F316	Bipolar affective disorder current episode mixed
	F317	Bipolar affective disorder currently in remission
	F318	Other bipolar affective disorders
	F319	Bipolar affective disorder unspecified
OCD	F420	Predominantly obsessional thoughts or ruminations
	F421	Predominantly compulsive acts [obsessional rituals]
	F422	Mixed obsessional thoughts and acts
	F428	Other obsessive-compulsive disorders
	F429	Obsessive-compulsive disorder unspecified

	F633	Trichotillomania
	F950	Transient tic disorder
	F951	Chronic motor or vocal tic disorder
	F952	Combined vocal and multiple motor tic disorder [de la Tourette]
	F958	Other tic disorders
	F959	Tic disorder unspecified
	F605	Anankastic personality disorder
Personality	F603	Emotionally unstable personality disorder
Risk-taking	F100	Acute intoxication with alcohol
	F101	Harmful use of acohol
	F110	Acute intoxication of opioids
	F111	Harmful use of opioids
	F120	Acute intoxication cannabinoids
	F121	Harmful use cannabinoids
	F130	Acute intoxication of sedatives or hypnotics
	F131	Harmful use of sedatives or hypnotics
	F140	Acute intoxication of cocaine
	F141	Harmful use of cocaine
	F150	Acute intoxicationof other stimulants
	F151	Harmful use of other stimulants
	F160	Acute intoxication of hallucinogens
	F161	Harmful use of hallucinogens
	F190	Acute intoxication due to multiple drug use and use of other psychoactive substances
	F191	Harmful use due to multiple drug use and use of other psychoactive substances
	F630	Pathological gambling
	F631	Pathological fire-setting [pyromania]
	F632	Pathological stealing [kleptomania]
	F638	Other habit and impulse disorders
	F639	Habit and impulse disorder unspecified

Table S1.3: Number of cases per disinhibited behaviour group, their sensitivity and factor loadings.

Group	N (%)	Loading	Definition
Addiction	9,534 (6.1)	0.708	a) participant self-reports past or current addiction – OR –
			b) hospital diagnosis of substance dependence syndrome
Self-harm	6,871 (4.4)	0.637	a) participant self-reports past or current self-harm
Mania	25,763 (16.4)	0.613	a) participant self-reports diagnosis of mania by professional – OR –
			b) hospital diagnosis of mania/bipolar disorder – OR –
			c) participant has experienced period with at least one symptom of mania
OCD	996 (0.6)	0.591	a) participant self-reports diagnosis of OCD by professional – OR –
			b) hospital diagnosis of OCD/tic disorder/trichotillomania/anankastic PD
Externalising	134 (0.1)	0.589	a) participant self-reports diagnosis of ADHD by professional – OR –
			b) hospital diagnosis of any externalising disorder
Cannabis use	11,205 (7.1)	0.552	a) participant self-reports having used cannabis >10 times in life
Personality	23,892 (15.2)	0.536	a_1) participant self-reports moods going up and down – AND –
			a_2) participant self-reports being easily fed-up – AND –
			a_3) participant self-reports being irritable – OR –
			b) hospital diagnosis of emotionally unstable PD
Smoking	7,615 (4.8)	0.475	a) participant self-reports current daily smoking
Risk-taking	23,994 (15.3)	0.335	a) participant self-reports weekly binge-drinking – OR –
			b) hospital diagnosis of acute intoxication with alcohol/drugs

Abbreviations: ADHD = attention-deficit/hyperactivity disorder; OCD = obsessive-compulsive disorder; PD = personality disorder

Table S1.4. Tetrachoric correlations between the nine disinhibited behaviour groups.

	OCD	Mania	Externalising	Personality	Risk-taking	Smoking	Addiction	Self-harm
Mania	0.285							
Externalising	0.527	0.298						
Personality	0.276	0.413	0.214					
Risk-taking	0.000	0.090	0.048	0.098				
Smoking	0.096	0.156	0.065	0.119	0.196			
Addiction	0.278	0.295	0.287	0.221	0.298	0.357		
Self-harm	0.318	0.322	0.239	0.265	0.075	0.217	0.366	
Cannabis	0.090	0.156	0.205	0.118	0.273	0.354	0.392	0.288

Table S1.5. PCA results extracting one, two and three principal components. The two-PC model differentiates between behaviours related to substance abuse (PC2) and other disinhibited behaviours (PC1), but contains double loadings for self-harm and addiction. The three-PC model adds a component reflecting unstable personality/mania, but also has double loadings (addiction, personality) and triple loadings (self-harm).

	Model: 1 PC	Model: 2 PCs		Model: 3 PCs		
	PC1	PC1	PC2	PC1	PC2	PC3
OCD	0.591	0.816	-0.153	0.847		
Mania	0.613	0.634				0.788
Externalising	0.589	0.739		0.883		-0.113
Personality	0.536	0.692		-0.108	-0.103	0.925
Risk-taking	0.335	-0.223	0.686	-0.287	0.658	
Smoking	0.475		0.715	-0.107	0.712	
Addiction	0.708	0.259	0.627	0.218	0.650	
Self-harm	0.637	0.482	0.283	0.272	0.278	0.295
Cannabis	0.552		0.749		0.788	-0.167

Section 2: PCA to derive dietary components (DC1-4) and dietary groups (DC1-5)

After removal of items related to alcohol intake, raw food frequency questionnaire (FFQ) data included nine continuous variables (e.g. tablespoons of vegetables), nine ordinal variables (e.g. oily fish intake frequency), five food type descriptions (e.g. bread type: brown/white/wholemeal/other), and one tick-box item assessing elimination of specific food groups (eggs, dairy, wheat, sugar; ST2.1). Ordinal intake frequency items were mapped to a continuous scale in days per month. Added salt (never, sometimes, often, always) was mapped to 0/0.333/0.667/1. Binary contrasts were created for each food type variable, such that each response category contrasted with all other categories (e.g. 'brown bread vs. any other type of bread') and that the never category contrasted with all other categories (e.g. 'I never eat bread vs. any type of bread'). One additional ordinal variable was created for fat content of milk ('no milk', 'skimmed milk', 'semi-skimmed milk', 'full-cream milk'). For the elimination item, we contrasted each restriction to having no restrictions (e.g. 'I never eat eggs vs. I do eat eggs, dairy, wheat and sugar') and to having no restrictions or other restrictions (e.g. 'I never eat eggs vs. no eggs restrictions'). Contrasts 'I never eat sugar vs. no restrictions' and 'I never eat sugar vs no sugar restrictions' were collinear ($r>0.85$), hence the latter was removed. The remaining 58 dietary items and contrasts are listed in ST2.2. All dietary items and contrasts were conditioned to age and sex, and continuous items were normalised applying rank-based inverted normal transformation.

Next, we performed a PCA with promax rotations, starting with one principal component and adding components one by one. Added components were retained when they contributed unique information, were interpretable and plausible, and remained stable upon including additional components to the model. The optimal model contained four dietary components (DC1-4) that were modestly correlated among each other (ST2.3).

Table S2.1. UK Biobank items related to diet. Note that items related to alcohol intake are not included, since heavy drinking contributed to our outcome of interest.

Type	UKB ID	Item	Unit
Continuous	1289	Cooked vegetables	Tablespoons / day
	1299	Raw vegetables	Tablespoons / day
	1309	Fresh fruit	Pieces / day
	1319	Dried fruit	Pieces / day
	1438	Bread	Slices / week
	1458	Cereal	Bowls / week
	1488	Tea	Cups / day
	1498	Coffee	Cups / day
	1528	Water	Glasses / day
Frequency	1329	Oily fish	Times / week
	1339	Non-oily fish	Times / week
	1349	Processed meat	Times / week
	1359	Poultry	Times / week
	1369	Beef	Times / week
	1379	Lamb	Times / week
	1389	Pork	Times / week
	1408	Cheese	Times / week
	1478	Added salt	Never or rarely / sometimes / usually / always
Type	1418	Milk	Full-cream / semi-skimmed / skimmed / soy / other non-dairy / never
	1428, 2654	Spreads	Butter / block margarine / tub margarine / benecol / olive-oil based / sunflower-based / low-fat / other / never
	1468	Cereal	Bran / biscuit / oat / muesli / refined sugar-sweetened / never
	1508	Coffee	Decaffeinated / instant / ground / other / never
	1448	Bread	Brown / white / wholegrain / other / never
Elimination	6144	I never eat (tick box)	Eggs / dairy / wheat / sugar

Table S2.2. Restructured items included in the PCA, and their factor loadings in the final model with four principal components (DC1-4)

	% endorsed	DC1	DC2	DC3	DC4
Cooked vegetables	NA	0.38	0.11	0.16	-0.05
Raw vegetables / salad	NA	0.45	0.09	0.07	-0.04
Fresh fruit	NA	0.45	0.04	-0.04	-0.09
Dried fruit	NA	0.48	0.00	-0.05	0.07
Bread	NA	-0.12	-0.26	-0.03	0.05
Cereal	NA	0.31	-0.20	-0.09	0.07
Tea	NA	0.03	-0.05	0.01	0.04
Coffee	NA	0.00	-0.17	0.19	-0.09
Water	NA	0.34	0.15	0.02	-0.01
Oily fish	NA	0.47	0.07	0.27	-0.09
Non-oily fish	NA	0.33	0.02	0.33	-0.11
Processed meat	NA	-0.24	-0.07	0.48	0.05
Poultry	NA	-0.07	0.01	0.40	-0.11
Beef	NA	-0.05	0.00	0.73	0.02
Lamb	NA	0.09	0.04	0.75	0.05
Pork	NA	0.01	0.00	0.73	0.01
Cheese	NA	0.02	-0.05	0.01	0.25
Added salt	NA	-0.09	0.04	0.31	0.12
Fat content of milk	NA	-0.06	-0.01	0.05	0.83
Full cream milk vs. any other milk	6.0	-0.12	0.08	0.03	0.31
Semi-skimmed milk vs. any other milk	66.2	0.01	-0.11	0.06	0.55
Skimmed milk vs. any other milk	21.9	0.00	-0.11	0.01	-0.84
Soy milk vs. any other milk	4.7	0.11	0.28	-0.18	0.07
Other non-dairy milk vs. any other milk	1.2	0.00	0.20	-0.03	0.02
Milk vs. 'I never drink milk'	96.2	0.08	-0.24	-0.02	0.26
Spread vs. 'I never use spreads'	88.3	-0.16	-0.17	0.02	0.18
Butter vs. any other spread	41.8	0.05	0.09	0.15	0.29
Block margarine vs. any other spread	<0.1	-0.02	0.02	0.02	0.02
Tub margarine vs. any other spread	5.1	-0.17	0.01	-0.02	-0.01
Benecol vs. any other spread	10.1	0.06	-0.01	-0.01	-0.16
Olive-oil based spread vs. any other spread	16.2	0.11	-0.06	-0.05	-0.05
Sunflower-based spread vs. any other spread	19.3	-0.07	-0.09	-0.06	-0.14
Low-fat spread vs. any other spread	5.0	-0.05	-0.03	-0.03	-0.12
Other spread vs. any other spread	2.4	-0.04	0.15	-0.07	0.04
White bread vs. any other bread	20.6	-0.55	0.09	0.05	0.01
Brown bread vs. any other bread	10.1	-0.13	0.03	0.02	0.01
Wholegrain bread vs. any other bread	64.8	0.58	-0.19	-0.06	-0.02
Other bread vs. any other bread	4.5	-0.07	0.22	0.01	0.02
Bread vs. 'I never eat bread'	96.4	-0.04	-0.38	-0.02	0.05

	% endorsed	DC1	DC2	DC3	DC4
Bran vs. any other cereal	16.8	0.02	-0.08	0.01	-0.09
Biscuit vs. any other cereal	15.4	-0.12	-0.07	0.01	-0.03
Oat vs. any other cereal	26.2	0.10	0.07	0.03	-0.08
Muesli vs. any other cereal	25.5	0.26	-0.02	-0.06	0.17
Refined sugar-sweetened cereal products	16.0	-0.33	0.09	0.02	0.02
Cereal vs. 'I never eat cereal'	84.2	0.28	-0.23	-0.09	0.10
Decaffeinated coffee vs. any other coffee	18.5	0.03	-0.01	-0.03	-0.12
Instant coffee vs. any other coffee	51.2	-0.31	-0.08	0.02	-0.09
Ground coffee vs. any other coffee	28.9	0.32	0.10	0.00	0.20
Other coffee vs. any other coffee	1.3	-0.02	0.02	-0.03	-0.01
Coffee vs. 'I never drink coffee'	80.6	0.10	-0.20	0.14	-0.04
'I never eat eggs' vs. no restrictions	2.5	-0.07	0.50	-0.06	0.04
'I never eat eggs' vs. no eggs restrictions	10.1	-0.07	0.24	-0.05	0.05
'I never eat dairy' vs. no restrictions	2.3	-0.03	0.64	-0.03	0.04
'I never eat dairy' vs. no dairy restrictions	9.4	-0.04	0.34	-0.02	0.06
'I never eat wheat' vs. no restrictions	2.6	-0.06	0.64	0.07	0.05
'I never eat wheat' vs. no wheat restrictions	10.6	-0.06	0.34	0.05	0.07
'I never eat sugar' vs. no restrictions	16.5	0.08	-0.31	0.01	-0.07
I never eat eggs, sugar, wheat or dairy' vs. no restrictions	19.9	0.06	0.51	0.03	-0.09

Table S2.3. Correlations between DC1-4

	DC1	DC2	DC3	DC4
DC1: Prudent diet	1.000			
DC2: Wheat/dairy/egg elimination	0.112	1.000		
DC3: Meat	-0.121	-0.097	1.000	
DC4: Full-cream dairy	-0.107	-0.124	0.045	1.000

Section 3: Latent profile analysis to derive multivariate dietary groups (DC1-5)

R-package 'mclust' [26] performs model-based clustering of participants based on parameterized finite Gaussian mixture models. Input to the clustering algorithm were dietary components DC1-4. We defined no a priori model constraints, and allowed a maximum of 16 clusters or subject groupings. Clustering is an iterative process, hence we performed 100 permutations and calculated Light's generalisation of Cohen's kappa's as an indicator of model stability, setting kappa>0.8 as our threshold for acceptable stability. Model fit was assessed using Bayesian information criterion (BIC), striving for maximal parsimony without compromising model fit. In addition, each cluster should represent no less than 1% of the full sample, and the model solution should be both interpretable and plausible. Figures S3.1 and S3.2 show that only the five-cluster solution has both stable model fit and acceptable model stability. Once the optimal model had been identified, group membership of each participant was set to the mode of classifications across 1,000 permuted model fittings.

Figure S3.1. Light's generalisation of Cohen's kappa's across one hundred permutations for models containing two to sixteen principal components. Kappa illustrates reproducibility of the model among permuted datasets and should ideally by 0.8 or higher.

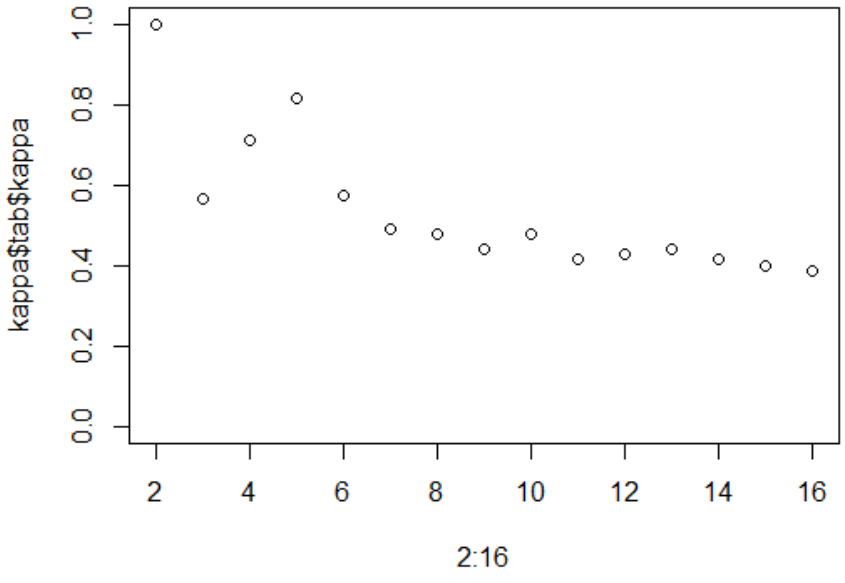
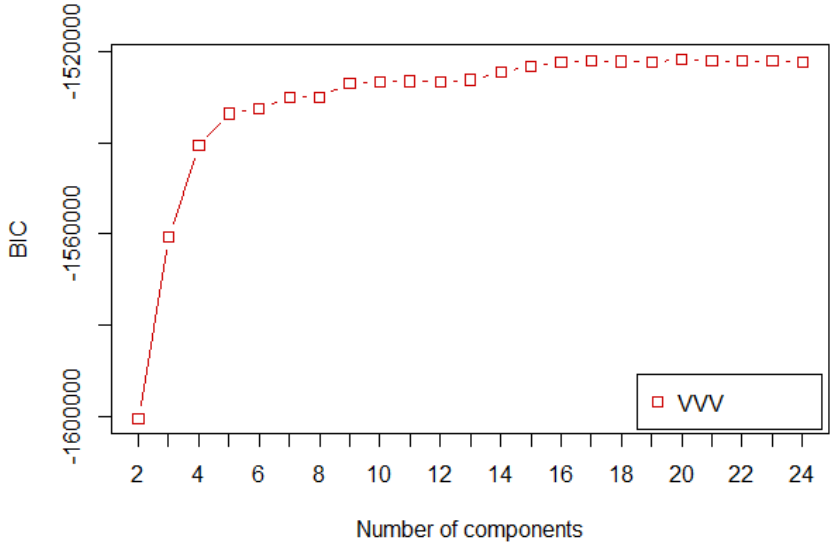


Figure S3.2. Increase in BIC upon adding latent participant clusters. Note that stabilisation starts after adding the fourth cluster, and is completed after adding the sixteenth cluster. VVV indicates a model with no *a priori* constraints.



Section 4: Outcomes when including age-by-predictor interaction terms

None of the associations reported in the main paper changed upon adding age-interaction effects (ST4.1). Moreover, most age-interaction effects were non-significant (ST4.2). In women, age-interactions with the unhealthy-vs-moderate-and-prudent, restricted-vs-moderate-and-prudent and low-fat dairy-vs-moderate-and-prudent group contrasts reached significance. In men, the age-by-DC2 interaction reached significance. For these interactions, we calculated the simple slopes of the dietary predictor for ten age-deciles (ST4.3). Note that a) the direction of effect remains the same across the age range, and b) the effect remains significant across the age range except at very late age. We conclude that some associations between diet and disinhibition may be stronger at younger age, especially in women, but that overall associations between diet and behavioural disinhibition are not moderated by age.

Table S4.1. Associations as reported in the main paper, after including an age-by-predictor interaction term

		Men			Women		
		β	**SE**	**P-value**	**β**	**SE**	**P-value**
Single-predictor	DC1	-0.036	0.004	<0.0001	-0.043	0.003	<0.0001
	DC2	0.031	0.004	<0.0001	0.038	0.003	<0.0001
	DC3	0.041	0.004	<0.0001	-0.016	0.003	<0.0001
	DC4	0.023	0.004	<0.0001	0.010	0.003	0.0036
	Unhealthy-vs-moderate-and-prudent	0.086	0.010	<0.0001	0.096	0.009	<0.0001
	Restricted-vs-moderate-and-prudent	0.125	0.016	<0.0001	0.158	0.013	<0.0001
	Avoid meat-vs-moderate-and-prudent	0.075	0.011	<0.0001	0.153	0.011	<0.0001
	Low-fat dairy-vs-moderate-and-prudent	0.041	0.011	0.0002	0.054	0.009	<0.0001
	MVPA	-0.007	0.004	0.0523	-0.009	0.003	0.0053
Multiple predictor	DC1	-0.031	0.004	<0.0001	-0.049	0.003	<0.0001
	DC2	0.040	0.004	<0.0001	0.044	0.003	<0.0001
	DC3	0.039	0.004	<0.0001	-0.018	0.003	<0.0001
	DC4	0.022	0.004	<0.0001	0.010	0.003	0.0017
	Unhealthy-vs-moderate-and-prudent	0.085	0.010	<0.0001	0.094	0.009	<0.0001
	Restricted-vs-moderate-and-prudent	0.125	0.016	<0.0001	0.157	0.013	<0.0001
	Avoid meat-vs-moderate-and-prudent	0.075	0.011	<0.0001	0.153	0.011	<0.0001
	Low-fat dairy-vs-moderate-and-prudent	0.041	0.011	0.0002	0.053	0.009	<0.0001
	MVPA	-0.004	0.004	0.2522	-0.003	0.003	0.3733

* β>0.02 & p<0.0028.

Table S4.2. Age-by-predictor interaction terms, added to the models as described in the main paper.

		Men			Women		
		β	**SE**	**P-value**	**β**	**SE**	**P-value**
Single-predictor	DC1-by-age	-0.002	0.004	0.5530	0.011	0.003	0.0007
	DC2-by-age	-0.019	0.004	<0.0001	-0.014	0.003	<0.0001
	DC3-by-age	<0.001	0.004	0.9122	0.003	0.003	0.3356
	DC4-by-age	-0.004	0.004	0.2709	0.004	0.003	0.2653
	Unhealthy-vs-moderate-and-prudent-by-age	-0.014	0.010	0.1521	-0.031	0.009	0.0003*
	Restricted-vs-moderate-and-prudent-by-age	-0.044	0.016	0.0045	-0.065	0.013	<0.0001*
	Avoid meat-vs-moderate-and-prudent-by-age	-0.032	0.011	0.0061	-0.027	0.011	0.0135
	Low-fat dairy-vs-moderate-and-prudent-by-age	-0.022	0.011	0.0466	-0.031	0.009	0.0005*
	MVPA-by-age	-0.005	0.004	0.1422	0.001	0.003	0.6528
Multiple predictor	DC1-by-age	0.004	0.004	0.2564	0.013	0.003	0.0001
	DC2-by-age	-0.021	0.004	<0.0001*	-0.015	0.003	<0.0001
	DC3-by-age	-0.002	0.004	0.6387	0.002	0.003	0.4604
	DC4-by-age	-0.007	0.004	0.0486	0.003	0.003	0.3806
	Unhealthy-vs-moderate-and-prudent-by-age	-0.014	0.010	0.1364	-0.030	0.009	0.0004*
	Restricted-vs-moderate-and-prudent-by-age	-0.045	0.016	0.0044	-0.065	0.013	<0.0001*
	Avoid meat-vs-moderate-and-prudent-by-age	-0.030	0.011	0.0061	-0.027	0.011	0.0130
	Low-fat dairy-vs-moderate-and-prudent-by-age	-0.023	0.011	0.0451	-0.031	0.009	0.0006*
	MVPA-by-age	-0.007	0.004	0.0821	-0.001	0.003	0.8340

* β>0.02 & p<0.0028.

ST4.3 Simple slopes at ten age-deciles for the association between disinhibition and the dietary predictor, in those instances where the age-by-dietary predictor interaction term reached significance.

			Single-predictor model			Multiple-predictor model		
		Age	**β**	**SE**	**P-value**	**β**	**SE**	**P-value**
Women	Unhealthy-vs-moderate-and-prudent	-2.0	0.151	0.019	<0.0001	0.149	0.019	<0.0001
		-1.6	0.138	0.016	<0.0001	0.136	0.016	<0.0001
		-1.1	0.124	0.013	<0.0001	0.123	0.013	<0.0001
		-0.7	0.111	0.010	<0.0001	0.110	0.010	<0.0001
		-0.3	0.098	0.009	<0.0001	0.097	0.009	<0.0001
		0.2	0.085	0.009	<0.0001	0.084	0.009	<0.0001
		0.6	0.072	0.010	<0.0001	0.071	0.010	<0.0001
		1.0	0.059	0.012	<0.0001	0.058	0.012	<0.0001
		1.5	0.046	0.015	0.0026	0.045	0.015	0.0031
		1.9	0.032	0.018	0.0754	0.032	0.018	0.0823
	Restricted-vs-moderate-and-prudent	-2.0	0.288	0.030	<0.0001	0.288	0.030	<0.0001
		-1.6	0.260	0.025	<0.0001	0.260	0.025	<0.0001
		-1.1	0.232	0.020	<0.0001	0.232	0.020	<0.0001
		-0.7	0.204	0.016	<0.0001	0.204	0.016	<0.0001
		-0.3	0.176	0.014	<0.0001	0.175	0.014	<0.0001
		0.2	0.147	0.013	<0.0001	0.147	0.013	<0.0001
		0.6	0.119	0.015	<0.0001	0.119	0.015	<0.0001
		1.0	0.091	0.018	<0.0001	0.091	0.018	<0.0001
		1.5	0.063	0.022	0.0049	0.063	0.022	0.0051
		1.9	0.035	0.027	0.1996	0.035	0.027	0.2026
	Low-fat dairy-vs-moderate-and-prudent	-2.0	0.111	0.019	<0.0001	0.110	0.019	<0.0001
		-1.6	0.098	0.016	<0.0001	0.097	0.016	<0.0001
		-1.1	0.085	0.013	<0.0001	0.085	0.013	<0.0001
		-0.7	0.072	0.011	<0.0001	0.072	0.011	<0.0001
		-0.3	0.059	0.009	<0.0001	0.059	0.009	<0.0001
		0.2	0.047	0.009	<0.0001	0.046	0.009	<0.0001
		0.6	0.034	0.010	0.0006	0.033	0.010	0.0007
		1.0	0.021	0.012	0.0830	0.021	0.012	0.0898
		1.5	0.008	0.015	0.5816	0.008	0.015	0.6027
		1.9	-0.005	0.018	0.8032	-0.005	0.018	0.7833
Men	DC2	-2.4				0.090	0.010	<0.0001
		-1.9				0.080	0.008	<0.0001
		-1.4				0.070	0.007	<0.0001
		-0.9				0.059	0.005	<0.0001
		-0.4				0.049	0.004	<0.0001
		0.0				0.039	0.004	<0.0001
		0.5				0.029	0.004	0.0006
		1.0				0.019	0.005	0.0003

	Single-predictor model	Multiple-predictor model		
1.5		0.009	0.007	0.1965
2.0		-0.002	0.008	0.8416

2. Tables and other supporting documents where applicable and necessary

All tables and supplementary information have been incorporated in the aforementioned manuscripts 3a and 3b, respectively.

3. Acknowledgement and Disclaimer

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 728018.