# Eat2beNICE

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

**H2020 - 728018**

# D 6.1: Manuscript: Effect of nutrition, lifestyle, impulsivity,compulsivity on the brain (UK Biobank)

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### Introduction

Behavioral disinhibition refers to the problematic and uncontrolled expression of impulsive speech and behavior (Sharma et al., 2014). Behavioral disinhibition is observed as an important symptomatic feature in a range of different neurodevelopmental and psychiatric disorders. Disorders like ADHD, OCD and Tourette's all are characterized by a disability to control speech or behavior (Chamberlain et al., 2005; Alderson et al., 2007; Kurtvis et al., 2020).

In addition to the link with psychiatric disorders, high behavioral disinhibition is also more generally linked to increased negative health outcomes (Amirian et al., 2010; Kubzansky et al., 2011), demonstrating the need to study the factors underlying behavioral disinhibition at the population level.

Several recent studies have indicated that lifestyle factors like dietary composition are associated with behavioral inhibition (Guerrieri et al., 2007; Terracciano et al., 2009; Nederkoorn et al., 2010; Lumley et al, 2016; Schweren et al., 2020). These observations may suggest that improvements in diet may reduce behavioral disinhibition in individuals, but this causal link between diet and disinhibition is difficult to confirm without the availability of large-scale direct intervention data.

However, another way to further our understanding of the influence of diet on disinhibition is to investigate the neurobiological mechanisms underlying the association between diet and behavioral disinhibition. An extensive body of literature shows that behavioral disinhibition is associated with both structural and functional changes in the brain (e.g. Luna et al., 2004; Fineberg et al., 2010; Bari et al., 2013; Cao et al., 2014; Zandbelt & Vink., 2010; Zeeuw & Durston, 2017; Zhang et al., 2017, van Rooij et al., 2015). In particular, structural alterations in subcortical volumes are a common underlying feature in many neurodevelopmental disorders featuring inhibition related symptoms, like ADHD (Hoogman et al., 2017) or OCD (Boedhoe et al., 2017; van Rooij et al., 2020). Given that recent literature also indicates that diet may influence brain development, we believe that variations in subcortical brain structure may potentially mediate the observed association between dietary composition and behavioral disinhibition.

The current study therefore aims to test whether the association between dietary composition and behavioral disinhibition is mediated by subcortical brain volumes. We hypothesize that 1) dietary composition is associated with subcortical brain volume. 2) Subcortical brain volumes and 3) dietary composition are each associated with behavioral disinhibition, and 4) part of the association between dietary composition and behavioral disinhibition is mediated by subcortical brain volumes.

## Abbreviations

**ADHD** Attention-Deficit/Hyperactivity Disorder
**OCD** Obsessive Compulsive Disorder
**DSM-IV** Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
**FFQ** Food frequency questionnaire
**MHQ** Mental Health Questionnaire
**MRI** Magnetic Resonance Imaging
**ICV** Intracranial Volume
**PCA** Principle Component Analysis

## 1. Deliverable report

Note: publishers' policies prevent sharing of detailed results prior to publication in a peer-reviewed journal. Detailed results, tables and uncompromised figures will be made available upon acceptance and/or as soon as the publisher's embargo has been lifted.

### Methods

*Sample*

Of the full UKBiobank sample, all subjects were included which had segmented T1 MRI data available, as well as the Mental Health Questionnaire (MHQ), the Food Frequency Questionnaire (FFQ) and self-reported fitness measures. Both MRI measurement and MHQ assessment were only obtained in a subsample of the full UKBiobank population. In total, the current sampled included 15,258 subjects (mean age=55, 7037 males).

*Behavioral disinhibition*

Behavioral disinhibition is not a standard measure available in the UKBiobank. Hence, we used a single aggregated measure for disinhibition that has been calculated on a much larger sample of the UKBiobank by Schweren et al., 2020. In that study, a principal component analysis (PCA) was performed on all available disinhibition-related items, to form a unitary inhibition construct. For each subject, a factor score was extracted with higher scores indicating a higher tendency for disinhibition. We opted not to re-run this analysis on our smaller subsample, but to directly use the factor scores from the original PCA.

*Dietary components*

Dietary composition data per subject was obtained from the Schweren et al., 2020 paper, where dietary composition was calculated based on the 29 items of the FFQ. These were used as input for a PCA, rendering four dietary components: Diet PC1, associated with healthy foods like vegetables, fruits and healthy oils; Diet PC2, associated with specific restrictions in bread and milk intake; Diet PC3, associated with meat and fish consumption, and Diet PC4, associated with specific intake of low-fat dairy products. For each subject, a factor score on these 4 components was calculated, indicating how strongly each subject matched with these four diet types. We chose not to re-calculate these data in our smaller subsample, but have taken the factor loading from Schweren et al. as input in our analyses.

*Structural brain volumes*

For all subjects with available MRI scans in UKBiobank, the T1 images are automatically segmented using Freesurfer ASEG. Volumes of the six subcortical segmentations were used (amygdala, caudate, hippocampus, pallidum, putamen and thalamus), as well as total intracranial volume (ICV). For the six nuclei, left and right hemisphere volumes were averaged to obtain one volume value per region. Outliers were removed at +/- 3xSD.

*Covariates*

Apart from age and sex, several other covariates were included in the model to correct for demographic features, which may influence the associations between diet and disinhibition. We included covariates potentially related to social-economic status (SES) as educational attainment, total household income, Indices of multiple deprivation (IMD) and ethnicity. To account for a generally healthier lifestyle outside of dietary composition, we also included BMI and Moderate-to-vigorous physical activity (MVPA) as covariates. MVPA was based on the self-reported number of days per week that subjects performed physical activity, as well as the number of minutes that they formed this activity on these days. Taken together, this gives us the total minutes of MVPA for the last week for each subject. To account for outliers, the highest 2.5% of MVPA values were removed from analysis.

*Statistical procedures*

First, a single regression model was run with all covariates as predictors and disinhibition as the outcome, to establish how the demographic and lifestyle factors that we incorporate in the further models are related to behavioral disinhibition scores.

Next, a correlation matrix was calculated to show the raw correlations between behavioral disinhibition, the four dietary components and the seven subcortical volume measures.

For the main analysis, four multiple regression models were run to attain the associations between dietary patterns, subcortical brain volume and disinhibition. The abovementioned covariates remained constant in every model.

A) This model was run with the dietary components as predictors and subcortical brain volumes as outcome variables.
B) This model included the subcortical brain volumes as predictors, and behavioral disinhibition as outcome variable.
C) This model included dietary components as predictors, and behavioral disinhibition as outcome variable (hence replicating the analysis of Schweren et al., 2020 in the current subsample)
D) This final model include both the dietary components and subcortical brain volumes as predictors, and behavioral disinhibition as outcome variable.

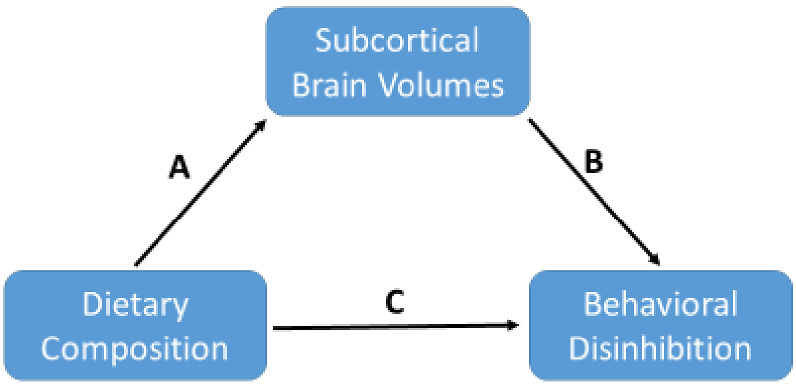
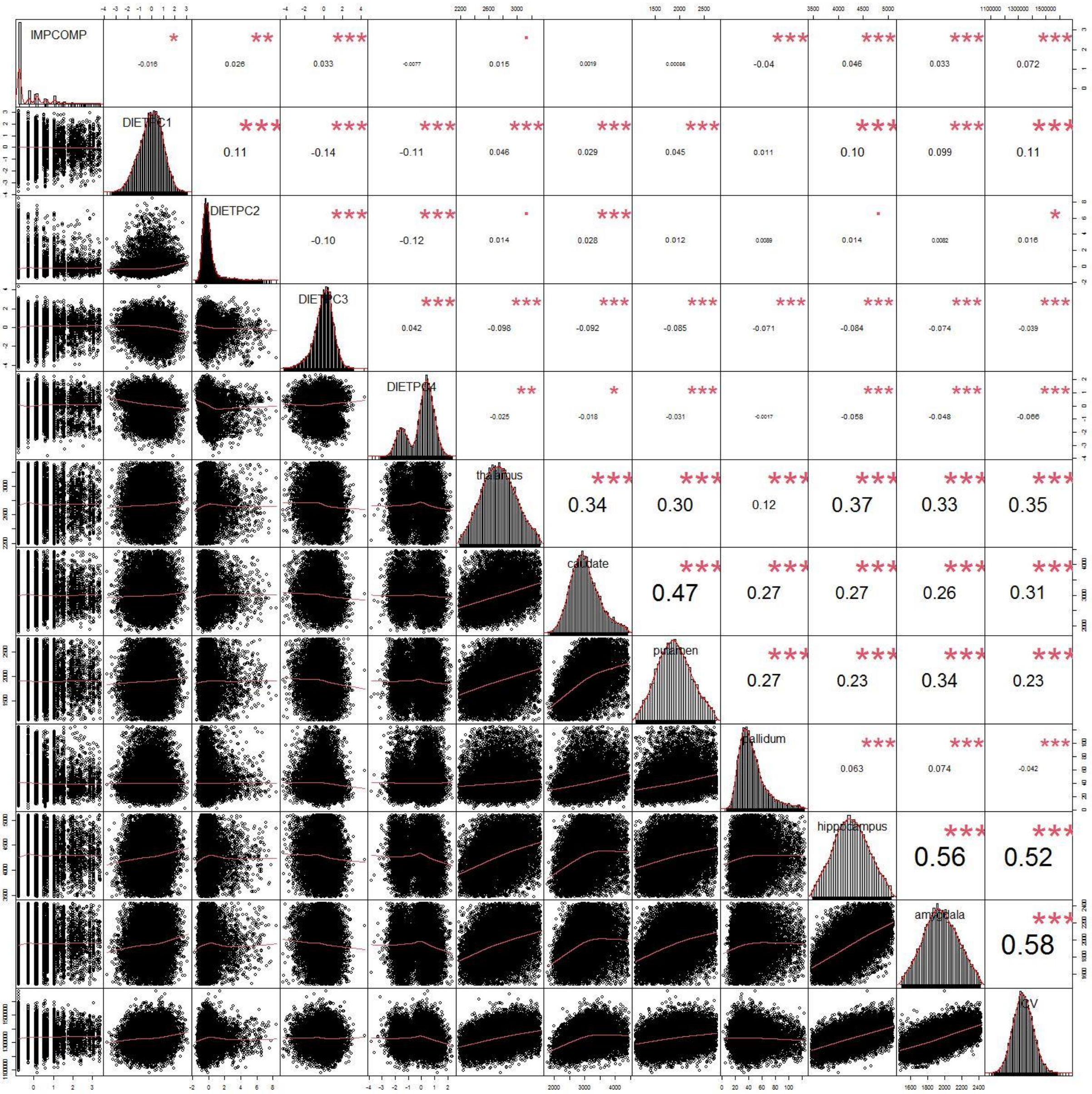



*Figure 1. Schematic illustration of the mediation model we hypothesize underlies the associations between diet, subcortical volumes and behavioral disinhibition. Arrows A-C correspond to the models run in the main analysis. Model D comprises of both model C and B taken together.*

**Results**

*Demographic and lifestyle factors*

Disinhibition was higher in men as compared to women (B=0.145, p<0.001). Disinhibition was significantly associated with younger age (B=-0204, p<0.001), unemployment (B=023, p=0.014), white ethnicity (B=0.12, p=0.035), and neighborhood deprivation (B=0.09, p<001). MVPA was associated with higher disinhibition (B= 0.029, p=0.003), as was BMI (B= 0.031, p=0.002). Disinhibition was not significantly associated with lower adjusted income and more years of education.




*Correlational analysis*

*Figure 1. Plot showing the correlations between behavioral disinhibition (IMPCOMP), the four diet PCs and the subcortical brain volumes. Correlation values and significance levels are plotted in the upper half, distributions of data on the median and scatter plots with a regression line fit on the lower half.*

*Multiple regression models*

*A) Diet composition predicting brain volume*

Individual regression models were calculated for each subcortical brain region. We found that Dietary component 1 (healthy diet) was positively associated with pallidum volume (B=0.481; p=0.032) and hippocampal volume (B=10.640; p=0.005). Dietary PC 2 (restricted diet) was not associated with any brain volume. Dietary PC 3 (meat/fish) was negatively associated with amygdala volume (B=-7.351; p<0.001) and putamen volume (B=-12.690; p<0.001). Dietary PC 4 (low-fat dairy) was positively associated with thalamus volume (B=6,499; p=0.009).

| | DIET PC1 | | DIET PC2 | | DIET PC3 | | DIET PC4 | |
|---|---|---|---|---|---|---|---|---|
| | Estimate | P-value | Estimate | P-value | Estimate | P-value | Estimate | P-value |
| Amygdala | | | | | -7.351 | 0.000 | | |
| Pallidum | 0.481 | 0.032 | | | | | | |
| Putamen | | | | | -12.690 | 0.001 | | |
| Caudate | | | | | | | | |
| Thalamus | | | | | | | 6.499 | 0.009 |
| Hippocampus | 10.640 | 0.005 | | | | | | |
| ICV | | | | | | | | |

*Table 1. Associations between Dietary components 1-4 and subcortical brain volume.*

*B) Brain volumes predicting behavioral disinhibition*

The second model indicated that volumes of the putamen (B=-0.030, p=0.018), amygdala (B=-0.038, p=0.011) and ICV (B=-0.051, p<0.001) are associated negatively associated with disinhibition scores, indicating that larger volumes are linked to less disinhibition symptoms. Caudate volume however was positively associated (B=0.049, p<0.001), indicating larger volumes are linked to higher disinhibition scores.

*C) Dietary composition predicting behavioral disinhibition*

The third model showed a negative association between Diet PC1 (healthy diet) and disinhibition (B=-0.021, p=0.04), and a positive association between Diet PC2 (restricted diet, B=0.029, p=0.003) and Diet PC 4 (low-fat dairy, B=0.021, p=0.04). No significant association between Diet PC3 and disinhibition was found.

*(D) Brain volumes and dietary composition predicting behavioral disinhibition*

The last model, predicting behavioral disinhibition from both subcortical volume and dietary composition, shows that the pattern of brain associations remains the same from model C, namely a negative association of putamen (B=-0.030, p=0.018), amygdala (B=-0.038, p=0.011) and ICV (B=-0.051, p<0.001) with disinhibition. A positive association was observed between caudate volume and disinhibition. In addition, this model also shows a positive association between Dietary PC2 (restricted diet) and disinhibition, but the previously found associations between Diet PC1 and PC4 from model B were no longer significant.

**Discussion**

In this study, we investigated the associations between dietary composition, subcortical brain volume and behavioral disinhibition. Our four models showed that: 1) There are significant associations between the dietary components and subcortical brain volumes. 2) Brain volumes are associated with behavioral disinhibition. 3) We replicate the effects of Schweren et al. (2020) in our sample, showing significant associations between the dietary components and behavioral disinhibition. 4) In the model including both subcortical volumes and dietary components, part of the variance in behavioral disinhibition explained by dietary components is captured by the subcortical brain volumes, while another part of the association between dietary components and disinhibition is unique, and remains significant in this model. All these results are in part confirming our hypotheses on the relation between dietary composition, subcortical brain volume and behavioral disinhibition. The results suggest that part of the association between dietary composition and behavioral disinhibition is mediated by subcortical brain volumes.

Model A confirms the link between dietary composition and subcortical brain volumes, and in particular shows that each dietary component has a unique link with subcortical volumes. Specifically, the health diet (PC1) was associated with higher volumes, but only of the pallidum and hippocampus. On the other hand, meat/fish consumption (PC3) was associated with lower volumes of amygdala and caudate, while low-fat dairy consumption (PC4) was associated with higher thalamic volume. These results suggest that different aspects of diet are associated with specific parts of the striatum. Interestingly, intracranial volume was not associated with dietary components, suggesting that dietary effects are rather local and region specific.

Model B shows that several of the subcortical brain volumes are associated with disinhibition, particularly caudate, putamen, amygdala and ICV. Of these, caudate and putamen are well known parts of cognitive control network, though our results indicate that these have opposite associations with behavioral disinhibition. It is somewhat surprising to find that higher caudate volumes are associated with more disinhibition behavior, as this is in contrast to previous literature showing reduced caudate volumes in ADHD (Castellanos et al., 2002; Greven et al., 2015). However, more recent studies containing large adult samples show much smaller volumetric alterations in adults with ADHD as compared to children (Hoogman et al., 2017; Boedhoe et al., 2020), indicating that some subcortical volumetric changes may diminish or even reverse with age. Given that the UKbiobank sample is an older adult sample, with a mean age of 55, this may explain why we observe higher caudate volumes associated with more disinhibition.

The findings of lower amygdala volume associated with higher inhibition also indicate a potential role for the limbic system in governing impulsive behaviors, and is in line with previous findings of reduced amygdala volumes in ADHD (Frodl et al., 2010; Tajima-Pozo et al., 2016; Hoogman et al., 2017). The negative association between ICV and disinhibition is also in line with previous observation of reduced brain volume in ADHD (Castellanos et al., 2002; Hoogman et al., 2012; Greven et al., 2015, Hoogman et al., 2017), and indicates that here is also an overall association with brain volume and inhibition, outside of the specific striatal cores, which will warrant further investigation.

Model C replicated the pattern of previous associations reported by Schweren et al (2020) between dietary components influence behavioral disinhibition. Here, we show that healthy diet (component 1) is associated with lower disinhibition scores, while 2 (restricted diet) and 4 (low-fat dairy) were associated with more behavioral disinhibition. This suggests that with respect to inhibition, a regular health diet including more fresh fruit, vegetables and healthy oils is related to better outcomes then more specific/restricted diets.

Model D subsequently tested whether the contributions of diet and brain volumes in explaining disinhibition were unique or whether the brain volumes were mediating the dietary effect. This was done by comparing the outcome of a single model encompassing both brain and dietary variables, and comparing these with the previous models. The outcome of this model shows that the influence of subcortical brain volumes on disinhibition remains the same irrespective of the dietary components in the model. Conversely however, the dietary association with disinhibition becomes weaker by adding the brain volumes to the model. This suggests that part of the effect between diet and disinhibition is mediated via subcortical brain volume, though another part of this association remains significant (particularly PC2), and is therefore not mediated. It is interesting to note that both dietary PC1 (healthy diet) and PC4 (low-fat dairy) were associated with brain volume in Model B, and are no longer significant in the final model, whereas PC2 (restricted diet), was not associated with brain volume in Model B, and remains significant in the final model. This is supporting evidence that those dietary components that show strongest associations with brain volume are also those which influence on disinhibition is mediated through the brain. Interestingly however, none of the dietary PC's was associated with caudate volume, which was uniquely associated with higher disinhibition. This indicates that some of the association between brain volume and disinhibition is unrelated to dietary composition or other lifestyle covariates included in the current study.

To conclude, this study shows that the previously shown association between dietary composition and behavioral disinhibition is partly mediated by subcortical brain volumes. We recommend that further research be aimed at investing a wider range of structural and functional brain measures, to further elucidate the mechanisms governing the influence of diet on disinhibition. We further postulate that large scale dietary intervention studies may be necessary to definitively prove the causal relations between diet, brain and behavioral disinhibition.

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## 2. Tables and other supporting documents where applicable and necessary

Not applicable.

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