Higher fresh fruit intake relates to larger grey matter volumes in areas involved in dementia and depression: A UK Biobank study

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**ABSTRACT**

The benefits of consuming fruits and vegetables are widely accepted. While previous studies suggest a protective role of fruits and vegetables against a variety of diseases such as dementia and depression, the biological mechanisms/effects remain unclear. Here we investigated the effect of fruit and vegetable consumption on brain structure. Particularly on grey matter (GM) and white matter (WM) volumes, regional GM volumes and subcortical volumes. Cross-sectional imaging data from UK Biobank cohort was used. A total of 9925 participants (Mean age 62.4 ± 7.5 years, 51.1 % men) were included in the present analysis. Measures included fruit and vegetable intake, other dietary patterns and a number of selected lifestyle factors and clinical data. Brain volumes were derived from structural brain magnetic resonance imaging. General linear model was used to study the associations between brain volumes and fruit/vegetable intakes. After adjusting for selected confounding factors, salad/raw vegetable intake showed a positive association with total white matter volume, fresh fruit intake showed a negative association with total grey matter (GM) volume. Regional GM analyses showed that higher fresh fruit intake was associated with larger GM volume in the left hippocampus, right temporal occipital fusiform cortex, left postcentral gyrus, right precentral gyrus, and right juxtapositional lobule cortex. We conclude that fruit and vegetable consumption seems to specifically modulate brain volumes. In particular, fresh fruit intake may have a protective role in specific cortical areas such as the hippocampus, areas robustly involved in the pathophysiology of dementia and depression.

1. Introduction

The health benefits of fruit and vegetable consumption are widely documented (Slavin and Lloyd, 2012; Dreher, 2018). In addition to being good sources of fibre and potassium, fruit and vegetable intake is promoted in dietary guidelines due to their enrichment in vitamins (e.g. vitamins C and A); phytochemicals (e.g. carotenoids and antioxidants); and minerals (e.g. electrolytes) (Slavin and Lloyd, 2012). The properties and nutritional components of fruits and vegetables obviously vary, and they can be categorized on this basis. Specifically, fruits are typically classified as fresh or dry, and vegetables as salad/raw or cooked. These distinctions are important for understanding nutritional content for dietary guidelines as the composition and concentration of their nutrients are affected (Slavin and Lloyd, 2012).

Fruits and vegetables also appear in dietary guidelines due to their role in reducing the risk of several diseases (Slavin and Lloyd, 2012; Dreher, 2018). Fruit and vegetable intake seems to help prevent cancer (specifically colorectal and lung cancer) (Kushi et al., 2012; Wang et al., 2019). Indeed, fruit and vegetable intake generally protects gastrointestinal health (Dreher, 2018) and seems to reduce the severity of chronic obstructive pulmonary disease and asthma. Furthermore, higher intake of fruits and vegetables has been associated with a reduced risk for developing hypertension (Wu et al., 2016), cardiovascular disease (Zhan et al., 2017), type 2 diabetes, and metabolic syndrome (Lee et al., 2019).

Among mental disorders, several studies have investigated possible associations between fruit and vegetable intake and risk of depression, anxiety or cognitive impairment/dementia. Recently, two meta-analyses showed evidence that high consumption of fruits and vegetables reduced the risk of depression (Liu et al., 2016; Saghafian et al., 2018). Similarly,
another meta-analysis concluded that increased consumption of fruits and vegetables was associated with a lower risk of cognitive impairment and dementia (Jiang et al., 2017). In spite of these promising associations, the possible mechanisms of fruit and vegetable intake in the prevention of these two diseases is limited. Even further, the relationship between fruit and vegetable intake and brain structure has never been specifically tested (to our knowledge).

A limited number of studies have shown that nutrition and dietary patterns may modulate structural changes in the brain, specifically in aging (Titova et al., 2013; Gu et al., 2013; Jackson et al., 2016; Zambroziewicz and Barbey, 2016; Luciano et al., 2017; Jensen et al., 2021). A few studies (in the elderly) have explored the relationship between total brain volume and adherence to the Mediterranean diet and showed that stricter adherence to the Mediterranean diet is associated with reduced brain atrophy while lax adherence was predictive of total brain atrophy (Gu et al., 2015; Luciano et al., 2017). Two other studies (in dementia-free participants with a wide range of age) explored the relationship between diet quality and brain structures (Croll et al., 2018; Prinelli et al., 2019). The first found that better adherence to a promoted diet (based on Dutch dietary guidelines) was directly related to total brain volume, grey (GM) volume, white matter (WM) volume and hippocampal volume (Croll et al., 2018). The second found that the highest intake of a specific group of nutrients (i.e. fiber and antioxidants) was related to a larger total brain volume and lower WM damage (Prinelli et al., 2019).

The aim of the present study was to investigate the relationship between fruit and vegetable consumption and brain structures in a large sample of healthy subjects with a wide age range. Specifically, we explored the relationship between fruit and vegetable intake and brain volumes including total grey matter (GM) and white matter (WM) volumes, total brain volume (GM + WM volume), regional GM volumes, and subcortical volumes.

2. Material and methods

2.1. Study sample and participants

UK Biobank (UKB) is a prospective cohort study and participants were recruited from twenty-two assessment centres across the UK between 2006 and 2010. The UKB study was approved by the North West Multi-centre Research ethics Committee and the current study was further approved by the regional Ethics Committee of Uppsala, Sweden (Sudlow et al., 2015). All participants provided written informed consent in accordance with the Declaration of Helsinki (Carlson et al., 2004). The detailed UKB protocol is available online (https://www.ukbiobank.ac.uk/wp-content/uploads/2011/11/UK-Biobank-Protocol.pdf). Similarly, the touch screen questionnaire and other resources are available on UKB website (http://www.ukbiobank.ac.uk/key-document/s/). Starting in 2014, after the initial recruitment, some of the participants were re-invited to participate in the brain, heart and body imaging. In the present study, we used brain Magnetic Resonance Imaging (MRI) data acquired between 2014 and 2019 that was made available to us under the UKB application: 30,172. At the time of acquisition, information regarding processed MRI data was available for 21,346 participants and a cross-sectional design was adopted. All the participants with BMI <18.5 (n = 141) were excluded as large weight loss may be a marker of certain underlying disease (Hamer and Batty, 2019). In addition, participants having any neurological or mental disorder (Shang et al., 2014; Zhang et al., 2016; Maurer et al., 2018) (based on ICD 10 codes from F00 to G99; n = 938) and/or having diabetes (Rosenberg, Lecheva et al. 2019) (self-reported, UKB Field ID: 2443; n = 976) and/or having reported major dietary changes in the past (UKB Field ID: 1538; n = 6515) were excluded from the study to avoid reverse causality (Hamer and Batty, 2019). Lastly, after removing all the participants with missing information for any the above-mentioned variables (n = 625) and for any covariates (education (n = 35), smoking (n = 28), alcohol use (n = 1), physical activity (n = 2156) and dietary variation (n = 6)) included in the study, the final study sample comprised of 9925 participants. Characteristics of the participants included and excluded from the analysis are provided in Supplementary Table 1a.

2.2. Imaging data

In UKB, Siemens Skyra 32-channel 3T scanner (Siemens Medical solutions, Germany) with 1 ×1 ×1 resolution and a view field of 208 ×256 ×256 was used for MRI scanning. Our study made use of pre-processed three-dimensional magnetization for rapid echo-gradient (3D MP-RAGE) T1-weighted image derived phenotypes generated by an image-processing pipeline developed and run on behalf of UK Biobank (Alfaro-Almagro et al., 2018). The full details of brain image processing is available online (https://biobank.ctsu.ox.ac.uk/crystal/crystal/docs /brain_mri.pdf). Several tools were used to derive structural numerical volume estimates for total GM volume, total WM volume and total brain volume (i.e. total GM volume + total WM volume) (all normalised for head size), as well as regional GM volumes (total 139 regions) and subcortical volumes (total 14 regions) used in the present study. UKB data codes for all imaging variables used are provided in Supplementary Table 1b. Briefly, the raw T1-weighted structural imaging data was processed using FAST (FMRIB’s Automated Segmentation Tool Zhang et al., 2001) and underwent SIENAX-style analysis (Structural Image Evaluation, using Normalisation, of Atrophy (Smith, 2002) to generate volumes of different tissue types and total brain volume, both normalised for head size, and not normalised, as imaging derived phenotypes (IDPs). The FAST GM segmentation was used to generate further 139 IDPs, by summing the GM partial volume estimates within 139 regions of interest. Subcortical structures (shapes and volumes) are modelled using FIRST (FMRIB’s Integrated Registration and Segmentation Tool (Patenaude et al., 2011) and volumes of these 14 subcortical structures were saved as IDPs. All these IDPs are accessible upon request from the UK Biobank database.

2.3. Diet data

A touchscreen questionnaire was presented to the participants at the assessment centre visit which also contained 29 questions about diet. In the present study, all the questions related to the reported frequency of intake of food and drink items (total 17 items), and the questions related to change and variation in diet (2 items) were included (Supplementary Table 1b) and the data corresponding to the imaging visit was used. For fruit intake, participants were asked to direct enter the number of pieces of dried/fresh fruit (with examples given as to what constitutes a piece eaten per day) and for vegetable intake, participants were asked to direct enter the number of heaped tablespoons of cooked vegetables and salad/raw vegetables eaten per day. For both intakes, participants can also select ‘less than one’, ‘do not know’ or ‘prefer not to answer’. Details of the questions related to other food and drink items, and dietary change and variation from touchscreen questionnaire and possible responses are provided in the supplementary material and corresponding UKB data codes are provided in Supplementary Table 1b.

2.4. Covariates

The covariates were selected based on previous knowledge (Akbaraly et al., 2018; Kokubun et al., 2020). The covariates considered in the present study include age, sex, body mass index (BMI), education, smoking status, alcohol intake frequency, physical activity, and dietary variation. Furthermore, sensitivity analyses were conducted after additionally adjusting the model for vascular diseases (hypertension, heart disease and cerebrovascular disease), ethnicity, and APOE genotypes. Since, dietary items can be intercorrelated, secondary sensitivity analyses were conducted in order to rule out the potential subthreshold
effects of the beforehand non-significant dietary items. In the secondary sensitivity analyses, the sensitivity analyses were further adjusted for all the available food and drink items. The detailed description of all the mentioned covariates is reported in the supplementary material.

2.5. Statistical analyses

All the statistical analyses were performed by using Statistical Package for Social Sciences, version 24 (IBM Corp, Armonk, NY, USA). From all the continuous variables (including both brain structure variables and dietary intakes) extreme outliers were removed (defined as having a z-score out of the range of ±3.29). For the dietary variables, intake of less than one was recoded as 0.5. Associations between fruit/vegetable intake and brain volumetric data was studied using general linear model with neuroimaging data as outcomes and fruit/vegetable intake as the determinant of main interest after adjusting for potential confounders. In the first model, we examined the association of all the dietary intakes available in the touchscreen questionnaire with the total GM volume, total WM volume and total brain volume (i.e. total GM volume + total WM volume) using general linear model after adjusting for age, sex, BMI, qualification, smoking status, alcohol intake frequency, physical activity, and dietary variation. In the second model, all the dietary variables (i.e., intakes of oily fish, poultry, cheese, cereal, coffee and water) that showed significant association with total brain volume, and/or total GM volume and/or total WM volume were additionally included as covariates along with the model 1. Model 2 was used in all the subsequent analyses between fruit/vegetable intakes and brain volumetric data (i.e., total GM volume, total WM volume, total brain volume, regional GM volumes and subcortical volumes). Moreover, a sensitivity analysis was performed to investigate associations between fruit/vegetable intakes and regional GM volumes and subcortical volumes by including the following additional covariates to Model 2: vascular diseases (hypertension, heart disease and cerebrovascular disease), and APO E genotypes. Furthermore, secondary sensitivity analyses were performed by additionally adding these sensitivity analyses with all the remaining dietary variables (intakes of non-oily fish, processed meat, beef, lamb/mutton, pork, bread and tea) that were initially not associated with either total brain, total GM or total WM volumes. A two-sided p-value of < 0.05 was considered significant in all the analyses concerning total GM volume, total WM volume and total brain volume. After correction for multiple testing (i.e. Bonferroni’s correction), a p-value of < 3.27×10⁻⁴ (0.05/153) was considered significant in analyses with regional GM volumes and subcortical brain volumes. Additionally, as exploratory analysis effect sizes (Cohen’s d) were calculated post-hoc on the grey matter areas that showed significant associations with fresh fruit consumption in the main and sensitivity analyses.

3. Results

The main characteristics of the study sample are shown in Table 1. After removing all the outliers and removal of individuals with missing data on the study covariates except diet variables (the number of participants corresponding to each diet variable vary considerably), the final study sample comprised of 9925 participants with a mean age of 62 (minimum 44 and maximum 80) years. Participants were slightly overweight (BMI (mean ± SD) = 26.12 (4.05) kg/m²) and 51.1 % of them were male. More participants had never smoked (64.4 %), had achieved a college/university degree (50.2 %) and experience week to week variation in their diet (62.0 %). Participants had a mean total brain volume of 1502550.49 ± 71688.93 mm³ and reported a mean intake of 2.10 ± 1.33 and 0.80 ± 1.16 pieces/day of fresh fruits and dry fruits, respectively. The mean reported intakes of cooked and raw vegetables were 2.62 ± 1.36 and 1.98 ± 1.53 tablespoons/day, respectively. A full list of other food and drink intake is reported in Supplementary Table 2.

Preliminary, we examined the association of each dietary intake available in the touchscreen questionnaire with the global brain volumes (i.e. total GM volume, total WM volume and total brain volume) after adjusting for model 1 in order to identify the potential dietary confounders. Poultry, cheese, cereal, coffee and water showed significant association with both total GM volume and total brain volume (P < 0.05 for all). Intake of oily fish was observed to be significantly associated with total WM volume (P = 0.036) and total brain volume (P = 0.020). Cereal intake also showed significant association with total WM volume (P = 0.030). Non-oily fish, processed meat, beef, lamb/mutton, pork, bread and tea were not at all associated with any of the total brain volume measures (Supplementary Table 3).

First, we examined the association between fruit and vegetable intakes, and global brain volumes (total GM volume, total WM volume and total brain volume) using model 2. A positive significant association was observed between salad/raw vegetable intake and total WM volume and

**Table 1**

<table>
<thead>
<tr>
<th>Study descriptives.</th>
<th>Data available (N)</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Continuous variables</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study sample</td>
<td>9925</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>9925</td>
<td>62.40 (7.53)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>9925</td>
<td>26.12 (4.05)</td>
</tr>
<tr>
<td>&quot;Total grey matter volume (mm³)&quot;</td>
<td>9925</td>
<td>795619.97 (47312.90)</td>
</tr>
<tr>
<td>&quot;Total white matter volume (mm³)&quot;</td>
<td>9925</td>
<td>706930.53 (40159.93)</td>
</tr>
<tr>
<td>&quot;Total Brain volume (grey + white) (mm³)&quot;</td>
<td>9925</td>
<td>1502550.49 (71688.93)</td>
</tr>
<tr>
<td>Dry fruit intake (pieces/day)</td>
<td>9802</td>
<td>0.80 (1.16)</td>
</tr>
<tr>
<td>Fresh fruit intake (pieces/day)</td>
<td>9865</td>
<td>2.10 (1.33)</td>
</tr>
<tr>
<td>Salad/raw vegetable intake (Tbsp spoons/day)</td>
<td>9797</td>
<td>1.98 (1.53)</td>
</tr>
<tr>
<td>Cooked vegetable intake (Tbsp spoons/day)</td>
<td>9799</td>
<td>2.62 (1.36)</td>
</tr>
<tr>
<td>Physical activity (MET minutes/week)</td>
<td>9925</td>
<td>2607.34 (2270.90)</td>
</tr>
<tr>
<td><strong>Categorical variables</strong></td>
<td>Frequency N (%)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
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<td></td>
</tr>
<tr>
<td>Men</td>
<td>5069</td>
<td>51.1 %</td>
</tr>
<tr>
<td>Women</td>
<td>4856</td>
<td>48.9 %</td>
</tr>
<tr>
<td>Qualification (university/college degree)</td>
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<td></td>
</tr>
<tr>
<td>No</td>
<td>4943</td>
<td>49.8 %</td>
</tr>
<tr>
<td>Yes</td>
<td>4982</td>
<td>50.2 %</td>
</tr>
<tr>
<td>Smoking status</td>
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<td></td>
</tr>
<tr>
<td>Never</td>
<td>6393</td>
<td>64.4 %</td>
</tr>
<tr>
<td>Previous</td>
<td>3145</td>
<td>31.7 %</td>
</tr>
<tr>
<td>Current</td>
<td>387</td>
<td>3.9 %</td>
</tr>
<tr>
<td>Alcohol intake frequency</td>
<td>9925</td>
<td></td>
</tr>
<tr>
<td>Daily</td>
<td>1868</td>
<td>(18.8 %)</td>
</tr>
<tr>
<td>3-4 times/week</td>
<td>3014</td>
<td>(30.4 %)</td>
</tr>
<tr>
<td>1-2 times/week</td>
<td>2629</td>
<td>(26.5 %)</td>
</tr>
<tr>
<td>1-3 times/month</td>
<td>1051</td>
<td>(10.6 %)</td>
</tr>
<tr>
<td>Special occasions</td>
<td>851</td>
<td>8.6 %</td>
</tr>
<tr>
<td>Never</td>
<td>512</td>
<td>5.2 %</td>
</tr>
<tr>
<td>Variation in diet</td>
<td>9925</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>3773</td>
<td>(38.0 %)</td>
</tr>
<tr>
<td>Yes</td>
<td>6152</td>
<td>(62.0 %)</td>
</tr>
</tbody>
</table>

BMI: body mass index; MET: metabolic equivalent of task; N: number of participants; SD: standard deviation. Values are Mean (SD) for continuous variables and N (%) for categorical variables. *Normalised for head size.
a negative significant association was observed between fresh fruit intake and total GM volume (Table 2). No associations were observed with total brain volume. Dry fruit intake and cooked vegetable intake did not show association with any of the global brain volume measures.

Second, we examined the association of fruit and vegetable intake with 139 regional GM volumes and volumes of the 14 subcortical regions of the brain (total = 153 areas) using model 2. After correction for multiple testing (using Bonferroni’s correction), significant positive associations were observed between fresh fruit intake and GM volume in left hippocampus, bilateral juxta-positional lobule cortex, left postcentral gyrus, and right temporal occipital fusiform cortex (Table 3). No other significant associations were observed (Supplementary Table 4). The sensitivity analysis confirmed the above mentioned results except for left juxta-positional lobule cortex. In addition, the sensitivity analysis showed a significant positive association between fresh fruit intake and GM volume in right precentral gyrus (Fig. 1 and Supplementary Table 5). The results of the secondary sensitivity analyses were consistent and in line with the main analyses and the sensitivity analyses (Supplementary Table 6).

Lastly, post-hoc analyses were conducted to investigate the impact of effect size for association of the fresh fruit intake with regional grey matter volumes that showed significant associations in the main and sensitivity analyses. The effect sizes as measured by Cohen’s d indicated very small effects (d < 0.1 for all) of higher fresh fruit intake (>2 servings per day) on regional grey matter volumes compared to those with low fresh fruit intake (<1 servings per day) (Supplementary Table 7).

4. Discussion

Our paper is the first attempt, to the best of our knowledge, to investigate the relationship between fruit and vegetable intake and structural brain changes. Using a large sample of men and women from the UK Biobank cohort, we explored relationships between fruit and vegetable intake and brain volumes (GM, WM, and total brain volume), as well as regional GM volumes and subcortical volumes.

Our main findings include: (1) a positive association between salad/raw vegetable intake and total WM volume, (2) a negative association between fresh fruit intake and total GM volume, (3) no associations between fruit or vegetable intake and total brain volume, and (4) a positive association between fresh fruit intake and the volume of the left hippocampus, the right temporal occipital fusiform cortex, the left postcentral, and the left and right juxta-positional lobule cortex (formerly supplementary motor cortex). Interestingly, the sensitivity analysis confirmed the above mentioned results except for the left juxta-positional lobule cortex (formerly supplementary motor cortex). The sensitivity analysis also showed a significant positive association between fresh fruit intake and GM volume in right precentral gyrus. The results of the secondary sensitivity analyses were consistent and in line with the main analyses and the sensitivity analyses. Our results were obtained after correction for lifestyle factors (e.g. physical activity, qualification, alcohol intake and smoking), dietary variation and other dietary variables (for details see methods and results sections). Moreover, effect size analysis performed on grey matter regions significantly associated with fresh fruit intake yielded a low Cohen’s d value, indicating a very small effect. However, the interpretation of these results is uncertain because firstly, the other studies in the field did not adopt this type of analysis (e.g. Gu et al., 2015; Jensen et al., 2021), and secondly, effect size in neuroimaging studies is still under debate and its cut-off and possible statistical approaches are not well defined (e.g. Emoto et al., 2020).

Our results on total GM and WM volumes generally suggest that consumption of fruits and vegetables can have an effect on global brain volumes. Our results also support previous studies associating dietary patterns with brain structures (Gu et al., 2015; Luciano et al., 2017; Croll et al., 2018; Prinelli et al., 2019). In particular, the positive association between salad/raw vegetable intake and total WM volume seem to be in line with two previous studies focusing on the Mediterranean diet in elderly samples (the two groups of research considered vegetable intake as a beneficial food component for scoring of the Mediterranean Diet) (Gu et al., 2015; Luciano et al., 2017). Another two recent studies, which used a similar approach as ours, found a similar result (Croll et al., 2018; Prinelli et al., 2019). The first study focusing on adherence to specific dietary guidelines (specifically Dutch dietary guidelines) and a number of food groups, found that better diet quality (including consumption of fruits and vegetables), was related to larger brain volumes and a higher WM volume in a large sample of dementia-free subjects (Croll et al., 2018; Prinelli et al., 2019). The second study, focusing on five nutrient patterns, found that a higher intake of the nutrient pattern comprised of fibre and antioxidants (both of which are abundant in fruits and vegetables) was directly correlated with total brain volume and a WM integrity in healthy people (Prinelli and Frastiglini, 2019). Conversely, our finding of a negative association between total GM volume and fresh fruit intake was unexpected and is not in line with the results of the two previously mentioned studies (Croll et al., 2018; Prinelli et al., 2019). Interestingly, Jensen and colleagues (2021), citing the study of Gu and colleagues (2015) that found an association between higher fresh fruit intake and lower GM volume, have suggested that this surprising result could be related to the high fruit sugar (fructose) consumption. Nevertheless, despite the negative relationship between total GM and fresh fruit intake, our regional GM analyses showed some direct relationships between fresh fruit intake and specific GM areas, as well as that fresh fruit intake does not affect total brain volume. Therefore, while we show that fresh fruit consumption had a surprising negative effect on total GM volume, there was a protective role for specific GM areas. Furthermore, our results of a direct relationship between salad/raw vegetable intake and total WM volume also suggest a protective role of salad/raw vegetable intake in WM integrity.

The impact of fresh fruit and salad/raw vegetable consumption on brain volumes may be related to several factors (Croll et al., 2018; Jensen et al., 2021). In particular, it can be speculated that the specific nutrients of fresh fruit and salad/raw vegetable throughout life may have an effect on neurodevelopment and brain health. In line with this hypothesis, it was demonstrated that breakfast staple types (i.e. rice group and bread group) seem to modulate GM volume in a sample of a healthy cohort (Gu et al., 2015; Luciano et al., 2017). In contrast, the results of two previous studies focusing on adherence to specific dietary guidelines, which used a similar approach as ours, found a similar result (Croll et al., 2018; Prinelli et al., 2019). The first study focusing on adherence to specific dietary guidelines (specifically Dutch dietary guidelines) and a number of food groups, found that better diet quality (including consumption of fruits and vegetables), was related to larger brain volumes and a higher WM volume in a large sample of dementia-free subjects (Croll et al., 2018; Prinelli et al., 2019). The second study, focusing on five nutrient patterns, found that a higher intake of the nutrient pattern comprised of fibre and antioxidants (both of which are abundant in fruits and vegetables) was directly correlated with total brain volume and a WM integrity in healthy people (Prinelli and Frastiglini, 2019). Conversely, our finding of a negative association between total GM volume and fresh fruit intake was unexpected and is not in line with the results of the two previously mentioned studies (Croll et al., 2018; Prinelli et al., 2019). Interestingly, Jensen and colleagues (2021), citing the study of Gu and colleagues (2015) that found an association between higher fresh fruit intake and lower GM volume, have suggested that this surprising result could be related to the high fruit sugar (fructose) consumption. Nevertheless, despite the negative relationship between total GM and fresh fruit intake, our regional GM analyses showed some direct relationships between fresh fruit intake and specific GM areas, as well as that fresh fruit intake does not affect total brain volume. Therefore, while we show that fresh fruit consumption had a surprising negative effect on total GM volume, there was a protective role for specific GM areas. Furthermore, our results of a direct relationship between salad/raw vegetable intake and total GM volume also suggest a protective role of salad/raw vegetable intake in WM integrity.

Table 2

Association of fruit and vegetable intakes with total grey matter, total white matter and total brain volume (grey–white).

<table>
<thead>
<tr>
<th>Dietary intakes</th>
<th>Total grey matter volume</th>
<th>Total white matter volume</th>
<th>Total brain volume</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>β</td>
<td>SE</td>
</tr>
<tr>
<td>Dry fruit intake (pieces/day)</td>
<td>9392</td>
<td>53.51</td>
<td>320.11</td>
</tr>
<tr>
<td>Fresh fruit intake (pieces/day)</td>
<td>9456</td>
<td>-613.51</td>
<td>283.46</td>
</tr>
<tr>
<td>Cooked vegetable intake (Tb spoons/day)</td>
<td>9393</td>
<td>-320.01</td>
<td>275.39</td>
</tr>
<tr>
<td>Salad/raw vegetable intake (Tb spoons/day)</td>
<td>9388</td>
<td>-178.86</td>
<td>245.74</td>
</tr>
</tbody>
</table>

Model 2 adjusted for age, sex, BMI, qualification, smoking status, alcohol intake frequency, physical activity, dietary variation and other dietary variables (intakes of oily fish, poultry, cheese, cereal, coffee and water). P values in bold represent statistically significant findings.
Moreover, it has been shown that adherence to Mediterranean diet seems to be related to higher plasma brain derived-neurotrophic factor (BDNF) levels (Sanchez-Villegas et al., 2011). Interestingly, BDNF is abundant in the hippocampus and it is associated with several actions such as neuronal survival and differentiation (Sanchez-Villegas et al., 2011). Secondly, it cannot be excluded that, although our results have been corrected for lifestyle factors, dietary variation and other dietary variables (intakes of oily fish, poultry, cheese, cereal, coffee and water). L: left; R: right; AD: anterior division. P values in bold represent statistically significant findings after Bonferroni correction.

Table 3
Regional grey matter volumes significantly associated with fruit and vegetable intakes.

<table>
<thead>
<tr>
<th>Brain volumes</th>
<th>Dry fruit</th>
<th>Fresh fruit</th>
<th>Raw vegetables</th>
<th>Cooked vegetables</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(\beta)</td>
<td>SE</td>
<td>(P)</td>
<td>(\beta)</td>
</tr>
<tr>
<td>Regional grey matter volume (mm(^3))</td>
<td>5.64</td>
<td>3.49</td>
<td>0.11</td>
<td>(1.16 \times 10^{-4})</td>
</tr>
<tr>
<td>Juxtopositional Lobule Cortex (formerly Supplementary Motor Cortex) (L)</td>
<td>6.36</td>
<td>5.14</td>
<td>0.22</td>
<td>(16.24 \times 10^{-4})</td>
</tr>
<tr>
<td>Juxtopositional Lobule Cortex (formerly Supplementary Motor Cortex) (R)</td>
<td>-0.39</td>
<td>5.13</td>
<td>0.94</td>
<td>(16.71 \times 10^{-4})</td>
</tr>
<tr>
<td>Postcentral Gyrus (L)</td>
<td>27.27</td>
<td>13.03</td>
<td>0.04</td>
<td>(53.47 \times 10^{-6})</td>
</tr>
<tr>
<td>Temporal Occipital Fusiform Cortex (R)</td>
<td>11.25</td>
<td>5.07</td>
<td>0.03</td>
<td>(18.82 \times 10^{-5})</td>
</tr>
</tbody>
</table>

Model 2 adjusted for age, sex, BMI, qualification, smoking status, alcohol intake frequency, physical activity, dietary variation and other dietary variables (intakes of oily fish, poultry, cheese, cereal, coffee and water). L: left; R: right; AD: anterior division. P values in bold represent statistically significant findings after Bonferroni correction.

Fig. 1. Statistically significant increases in grey matter volumes correlated with higher intake of fresh fruit, resulting from sensitivity analysis. (C) The two-color bar in the figure shows the \(p\) scores corresponding to the colors in sagittal (A), coronal (B) and axial (D) views.
patients with semantic dementia (Merck et al., 2017). Thus, our results both of these regions in major depression neurobiology, it can be preliminary hypothesized that fresh fruit consumption may play a protective role in the prevention of the abovementioned diseases and it can be confirmed as a key component in dietary guidelines.

Our second finding in the regional GM analysis was a direct relationship between fresh fruit intake and the volume of the right temporal occipital fusiform cortex. The fusiform cortex is involved in several functions (such as processing specific visual forms and related lexical/semantic understanding) (Simons et al., 2003). Specifically, it is considered a core brain region in processing and recognizing faces (Haxby et al., 2000). Although the debate on brain areas involved in semantic dementia is relatively open, bilateral loss of GM in the anterior fusiform region is considered a requirement in order to cause semantic dementia (Landin-Romero et al., 2016). Interestingly, an association was found between the volume of the left posterior fusiform cortex and the performance in a semantic sorting task for fruit and vegetable in patients with semantic dementia (Merck et al., 2017). Thus, our results for the temporal occipital fusiform cortex suggest a protective role of fresh fruit intake on this brain area. We can preliminarily suggest a possible role of fresh fruit intake in the prevention of semantic dementia.

Our third regional GM finding was a direct relationship between fresh fruit intake and the left postcentral gyrus and the right juxtapositional lobule cortex (formerly supplementary motor cortex). The postcentral gyrus is mainly involved in somatosensory function (Kropf et al., 2016) and it has shown GM loss in healthy aging (Minkova et al., 2017). Particularly, a larger GM loss was shown in the left postcentral gyrus compared to the right. Interestingly, a decrease in cortical thickness was also found in the postcentral gyrus in patients with early-onset, major depressive disorder (Truong et al., 2013). It is also of interest to note that the left postcentral gyrus is uniquely associated with one of the Alzheimer disease genetic risk variants (i.e. ABCA7) compared to other brain regions (Roshchupkin et al., 2016).

Regarding the juxtapositional lobule cortex, it is widely accepted that supplementary motor cortex is a key brain area for voluntary movement (Nachef et al., 2008). Moreover, it also seems to be involved in cognitive control, movement sequences and learning (Nachef et al., 2008). A recent meta-analysis showed a reduction in GM for the right supplementary motor area in first-episode depressive patients, suggesting a role of it in the neurobiology of the disease (Zhang et al., 2016). Additionally, several studies have shown alterations in the supplementary motor cortex in Parkinson’s disease. However, whether the juxtapositional lobule cortex is involved in the pathophysiology of Parkinson’s disease remains an open question (Nachef et al., 2008).

Again, our results suggest that fresh fruit intake may have a role in the protection of the GM volume of the left postcentral gyrus and the bilateral juxtapositional lobule cortex. Considering the involvement of both of these regions in major depression neurobiology, it can be preliminarily hypothesized that fresh fruit consumption may contribute to the prevention of major depressive disorder.

In addition, our sensitivity analysis showed a positive association between fresh fruit intake and GM volume in right precentral gyrus. The precentral gyrus is mainly involved in motor functions (Zhou et al., 2020) and physical training seems to be related with higher density of precentral gyrus grey matter (Wei et al., 2009). Interestingly, a grey matter loss of the precentral gyrus was found in patients with AD (van de Mortel et al., 2021) and patients with major depressive disorder (Klok et al., 2019). Moreover, a reduced functional connectivity in the precentral gyrus was found in patients with posterior cortical atrophy (Chen et al., 2022) and patients with major depressive disorder (Song et al., 2022; Guo et al., 2023).

4.1. Strengths and limitations

The present study has strengths and limitations that need to be acknowledged. The main strength is the vast UK Biobank imaging database (n > 10,000), combined with a great number of corresponding medical and lifestyle variables for each person scanned. This richness of data allow to take into account a wide range of possible confounding factors. On the other hand, as first limitation, although we tried to consider all medical and lifestyle factors that could be related to both brain volumes and diet, still there might be residual confounding from unmeasured confounders. A second limitation is that the present study is cross-sectional. Thus, while our results are indeed fascinating, longitudinal studies are required for greater support.

A third limitation is that dietary behaviour and lifestyle variables are collected by questionnaires that rely on recall. Thus, recall biases cannot be excluded. A final limitation is that the units of measurement for fruit and vegetable intake are pieces/day, without a classification among different types of fruits and vegetables. Considering that the concentration of nutrients may vary among different types of fruits and vegetables (Slavin and Lloyd, 2012), the lack of this classification may limit the possibility to explore the role of specific types of fruit and vegetable.

5. Conclusion

Our results show that fruit and vegetable consumption is associated with changes in brain volume, and suggest that their intake generally supports brain health. Higher salad/raw vegetable intake was associated with higher total WM volume. Moreover, although higher fresh fruit consumption was surprisingly associated with lower total GM volume, higher fruit consumption was associated with larger GM volumes in specific GM areas (e.g., the left hippocampus, the right temporal occipital fusiform cortex, the left postcentral gyrus, and the right juxtapositional lobule cortex). On the other hand, the estimated effect sizes for these regions were quite small. However, the interpretation of these last result is uncertain, because effect size is still under debate in neuroimaging studies (e.g. Emoto et al., 2020). Since majority of the above mentioned areas are also robustly involved in the pathophysiology of dementia and depression, our results highlight a possible protective role of fruit and vegetable consumption against developing both dementia and depression.

Thus, a simple prophylactic such as consuming more fruits and vegetables should perhaps be taken seriously by authorities. However, future research, also adopting longitudinal design, is needed to confirm our results and to better define the effects/mechanisms of fruit and vegetable consumption on brain health. Moreover, further studies are needed to clarify the different results between the type of analyses (i.e. correlation analysis vs effect size) that can be adopted in neuroimaging studies and in this field of research.

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CRediT authorship contribution statement

Santino Gaudio: Conceptualization, Methodology, Writing – original draft, Writing – review & editing. Gull Rukh: Formal analysis, Writing – original draft, Writing – review & editing. Vincenzo Di Ciammo: Writing – review & editing. Samuel Berkins: Formal analysis. Lyle Wiemerslage: Writing – review & editing. Helgi B. Schióth: Writing – review & editing, Supervision.

Declaration of Competing Interest

None.

Data availability

The data used in this study was made available to us by UK Biobank under the approved application 30172. UK Biobank is a publically available resource (https://www.ukbiobank.ac.uk/) and all variables used in this study are available upon request.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version at doi:10.1016/j.neuroimage.2023.120438.

References


