Better diet quality relates to larger brain tissue volumes: the Rotterdam Study

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ABSTRACT

Objective

To investigate the relation of diet quality with structural brain tissue volumes and focal vascular lesions in a dementia-free population.

Methods

From the population-based Rotterdam Study, 4,447 participants underwent dietary assessment and brain MRI scanning between 2005 and 2015. We excluded participants with an implausible energy intake, prevalent dementia or cortical infarcts, leaving 4,213 participants for the current analysis. A diet quality score (0-14) was calculated reflecting adherence to Dutch dietary guidelines. Brain MRI was performed to obtain information on brain tissue volumes, white matter lesion volume, lacunes and cerebral microbleeds. The associations of diet quality score and separate food groups with brain structures were assessed using multivariable linear and logistic regression.

Results

We found that better diet quality related to larger brain volume, grey matter volume, white matter volume, and hippocampal volume. Diet quality was not associated with white matter lesion volume, lacunes or microbleeds. High intake of vegetables, fruit, whole grains, nuts, dairy and fish and low intake of sugar-containing beverages were associated with larger brain volumes.

Conclusions

A better diet quality is associated with larger brain tissue volumes. These results suggest that the effect of nutrition on neurodegeneration may act via brain structure. More research, in particular longitudinal research, is needed to unravel direct versus indirect effects between diet quality and brain health.

INTRODUCTION

Diet is considered an important modifiable risk factor for dementia.[2-7] But the pathways underlying this association remain largely unknown. An important pathway may be through direct effects of diet on brain structures or focal vascular lesions,[8-15] as it is known that structural brain changes are an important risk factor for dementia.[8, 16] Moreover, a healthy diet is associated with better brain health and larger brain volumes.[9-15] However, studies performed on this research area were generally of limited sample size, considered only a limited age range, or used dietary adherence as a dichotomous variable rather than as a continuous variable.

Traditionally, epidemiological and animal studies on health effects of nutrition have focused on the effects of individual food nutrients and showed that specific nutrients such as B vitamins , vitamin E, and the *n*-3 fatty acid docosahexaenoic acid that can be found in for example vegetables, fruit and seafood, have neuroprotective effects.[10, 17] However, it is important to acknowledge that many complex interactions occur across different food components and nutrients, which has triggered the increasing interest to study effects of dietary patterns as a whole.[10] For example, adherence to a Mediterranean Diet showed protective effects against brain tissue loss,[13 18] including lower volumes of white matter hyperintensities.[19] Several other studies also linked other measures of diet quality to lower risk of dementia.[3, 6, 7]

Optimizing diet quality might be a suitable preventive strategy to maintain and augment cognition in healthy older adults.[2, 3] Hence, we investigated the association of dietary patterns and its components with structural brain volumes in a population-based sample of dementia-free middle aged and elderly individuals.

METHODS

Setting and study population

This cross-sectional study was embedded in the Rotterdam Study, a population-based community-dwelling cohort in the Netherlands since 1990 investigating determinants and consequences of ageing.[20] At study entry and subsequently every three to four years, all participants were invited to undergo extensive examinations in the dedicated research centre. By 2008, 14,926 individuals aged 45 years and older participated in the Rotterdam Study. For this study, 5,690 participants who visited the study centre between 2006-2012 for initial or re-examinations underwent extensive questionnaires on their dietary intake.[21] From 2005 onward, MRI scanning of the brain was included in the Rotterdam Study.[22] The MRI scans included in this study were performed between 2005 and 2015, and we excluded the participants without a brain MRI scan. This left

us with a total of 4,447 participants who had data on both dietary intake and a brain MRI scan. The median age interval between dietary assessment and MRI scanning was 0.13 months. From this group, we excluded participants with a reported daily energy intake of less <500 or >5,000 kcal/d (n = 162) and participants with prevalent dementia or cortical infarcts on MRI (n = 72), leaving a total of 4,213 participants for the current analyses.

The Rotterdam Study has been approved by the medical ethics committee of the Erasmus MC (registration number MEC 02.1015) and by the Dutch Ministry of Health, Welfare and Sport (Population Screening Act WBO, license number 1071272-159521-PG).

Dietary intake assessment

Dietary intake was assessed with a validated, self-administered, semi-quantitative food-frequency questionnaire (FFQ) consisting of 389 items. This FFQ was previously validated against the dietary history method and against nine-day food records in 2 other Dutch populations and was found to be an appropriate measurement tool for ranking people according to their food intake.[23, 24] For the different food items, questions about the number of servings per day and the frequency of consumption were included. Energy intake was calculated using the Dutch Food Composition Table (NEVO). Based on the information obtained from the FFQ, we evaluated adherence (yes/no) to 14 items of the Dutch dietary guidelines[25] (vegetables, fruit, whole grain products, legumes, nuts, dairy, fish, tea, whole grains of total grains, unsaturated fats and oils of total fats, red and processed meat, sugar-containing beverages, alcohol, and salt; Table 1). An overall diet score (0-14) reflecting adherence to the dietary guidelines was calculated by adding up the scores for the 14 above mentioned food groups, as described in more detail elsewhere.[21] For comparison with other studies, we additionally calculated a Mediterranean diet score based on sex and cohort specific median food intake of our study population, as previously described by Trichopoulou et al.[26]

Table 1. Population characteristics

Sample size	N =4,213
Women	56.8 %
Age, years	65.7 (10.8)
Age, years, range	45.5 – 97.5
Education, y	12.7 (3.9)
Lower	27.8 %
Middle	48.7 %

Table 1. Population characteristics (continued)

Sample size	N =4,213
Higher	23.5 %
Physical activity, MET-hours/week	59.9 (55.1)
Past or current smoking	14.5 %
Hypertension	22.2%
Hypercholesterolemia	52.0 %
Body mass index, kg/m^2	27.3 (4.1)
Type 2 diabetes	8.6 %
Dietary characteristics	
Energy intake, kcal/day	2,081 (1,684-2,542)[a]
Number of items adhered to (no.)	7 (6-8)[a]
Adherence to individual guideline components (%)	
Vegetables ≥200 g/day	44.2
Fruit 200 ≥ g/day	59.6
Whole grain products ≥ 90 g/day	63.6
Legumes ≥ 135 g/week	28.2
Nuts ≥ 15 g/day	21.8
Dairy ≥ 350 g/day	37.4
Fish ≥ 100 g/week	54.0
Tea ≥ 450 g/day	8.2
Whole grains ≥ 50% of total grains	79.3
Unsaturated fats and oils ≥ 50% of total fats	67.8
Red and processed meat ≤ 300 g/week	22.7
Sugar-containing beverages ≤ 150 g/day	80.6
Alcohol ≤ 10 g/day	57.7
Salt ≤ 6 g/day	63.5
Brain MRI tissue volumes	
Total brain volume, mL	932.01 (105.9)
Grey matter volume, mL	529.4 (62.4)
White matter volume, mL	402.7 (66.8)
Hippocampus volume, mL	7.7 (1.00)
Markers of cerebral small vessel disease	
Lacunes	4.6%
Microbleeds	20.6%
White matter lesion volume,[b] mL	8.2 (1.1)

Abbreviation: MET = metabolic equivalent of task. Values are based on imputed data. Numbers of missings per variable were 579 for amount of physical activity; 386 for total cholesterol; 316 for diastolic and systolic blood pressure; 302 for body mass index; 59 for years of education and 59 for highest obtained education level. [a] Values are mean (SD) for continuous variables or median (interquartile range) when indicated (*), percentages for dichotomous variables. [b] In-transformed.

Magnetic resonance imaging

Brain MRI was performed on a 1.5T MRI scanner with a dedicated eight-channel head coil (software version 11x; General Electric Healthcare, Milwaukee, WI).[22] The scan protocol included a T1-weighted sequence, a proton-density weighted sequence and a fluid-inversion-recovery sequence.[22, 27] To quantify brain volume, grey matter volume, white matter volume, white matter lesion volume, hippocampal volume and intracranial volume, automated brain tissue classification was used. This quantification strategy was based on a k-nearest neighbour classifier algorithm, extended with an in-house developed white matter lesion segmentation.[22, 27] Furthermore, T1-weighted MR images were processed using FreeSurfer (version 5.1) to obtain the hippocampus volume.[28] Visual evaluation of all scans was performed to assess the presence and amount of lacunes, cortical infarcts, and cerebral microbleeds, using a strategy that has been previously described in detail.[22]

Other measurements in the Rotterdam Study

Information on cardiovascular risk factors, medication use, physical activity, and educational level was obtained by interview, physical examinations and blood sampling. Smoking data were collected through self-report and categorized into never, former, and current smoking. Educational level was categorized as lower, middle or higher education. Total years of education was calculated. Height and weight, blood pressure, glucose levels and cholesterol levels were measured and body mass index was calculated (kg/m^2). Systolic and diastolic blood pressure was measured twice using a random zero-sphygmomanometer. Glucose was determined by the hexokinase method. Using an automatic enzymatic procedure, serum total cholesterol and high-density lipoprotein cholesterol were measured from fasting blood samples.[29] Hypertension was defined as systolic blood pressure ≥ 160 mmHg and/or diastolic blood pressure ≥ 90 mmHg and/or the use of blood pressure lowering medication.[27] Hypercholesterolemia was defined as total cholesterol concentration ≥ 6.2 mmol/L and/or the use of lipid-lowering medication.[27] Type 2 diabetes was defined as having fasting blood glucose concentrations >7.0 mmol/L, non-fasting blood glucose >11.1 mmol/L, or use of glucose-lowering medication. The LASA (Longitudinal Ageing Study Amsterdam) Physical Activity Questionnaire was used to assess the amount of physical activity. This is a validated questionnaire,[30, 31] that consists of questions about walking, cycling, gardening, sports, and housekeeping.[21] For each participant, data were recalculated into MET (metabolic equivalent of task) hours per week.[32]

Statistical analysis

Given the skewed distribution of white matter lesion volume, we natural log-transformed these values and used these in the analyses. The association of the diet quality score

with total brain volume, grey matter volume, white matter volume, white matter lesion volume and hippocampal volume was examined using multivariable linear regression models. In the first model we adjusted for age, sex, educational level, total energy intake, and intracranial volume (as proxy for head size). In the second model, we additionally adjusted for smoking, body mass index, and physical activity. A third model was constructed in which we adjusted model 2 with the addition of diabetes, hypertension, and hypercholesterolemia.

The association of diet quality scores with the presence of lacunes and cerebral microbleeds was assessed using logistic regression models, and adjustments were similar to the above-mentioned models. To further explore whether associations of the overall diet quality score were explained by certain items of the dietary guidelines, we investigated associations of adherence to guidelines for specific food groups with the global and focal brain structures using the same models. We checked for effect modification by sex, and we checked for interaction by age by using interaction terms. To check whether associations were not driven by one specific food component we repeated our main analysis by excluding each of the 14 individual guidelines from the total dietary guideline score one at a time, and examining the effect on the estimates. Finally, to analyse the robustness of our dietary guideline score and the comparability of it toward other populations, we also conducted analyses to investigate the associations between the Mediterranean diet score and brain volumetric and between the Mediterranean diet score and focal vascular brain lesions using the above-mentioned models. Missing variables (<1%) were imputed using the multiple imputation algorithm (5 imputations) of SPSS. For the analyses, IBM SPSS statistics version 23 (IBM Corp, Armonk, NY) was used.

RESULTS

Table 1 shows the characteristics of the study population. Mean age at time of dietary assessment was 65.7 years (SD 10.8, range 45.5 – 97.5), and 56.7% of the participants were women. Participants had a median energy intake of 2,081 kcal/d (interquartile range 1,684-2,542) and had a median dietary guideline adherence score of 7 (interquartile range 6-8) on a theoretical range of 0 to 14. Participants had a total brain volume of 932.0 mL (SD 105.9).

We found that, after adjustment for age, sex, intracranial volume, education, energy intake, smoking, physical activity and body mass index (model 2), a higher diet quality score related to larger total brain volume, grey matter volume, white matter volume, and hippocampal volume (Table 2). Additional adjustment for other cardiovascular risk factors (model 3) did not change these results (Table 2). A higher diet score was neither associated with the presence of lacunar infarcts and microbleeds nor the volume of

Table 2. Diet quality and brain volume

	Total brain volume	Grey matter volume	White matter volume	Hippocampus volume
	Difference in mL (95% CI)	Difference in mL (95% CI)	Difference in mL (95% CI)	Difference in mL (95% CI)
Model 1	2.04 (1.24, 2.85)	0.85 (0.15, 1.55)	1.19 (0.42, 1.97)	0.02 (0.01, 0.03)
Model 2	2.03 (1.24, 2.83)	0.88 (0.18, 1.59)	1.15 (0.37, 1.93)	0.02 (0.00, 0.03)
Model 3	2.01 (1.21, 2.80)	0.89 (0.19, 1.60)	1.11 (0.33, 1.89)	0.02 (0.00, 0.03)

Difference in volume in mL per one point better adherence to the dietary guidelines. CI: confidence interval *Model 1:* adjusted for age, sex, intracranial volume, education, energy intake. *Model 2:* adjusted for age, sex, intracranial volume, education, energy intake, smoking, physical activity and body mass index. *Model 3:* adjusted for age, sex, intracranial volume, education, energy intake, smoking, physical activity, body mass index, diabetes, hypertension and hypercholesterolemia. Statistically significant effect estimates ($p < 0.05$) apply to all data.

Table 3. Diet quality and focal brain lesions

	White matter lesions*	Lacunes	Microbleeds
	Difference (95% CI)	OR (95% CI)	OR (95% CI)
Model 1	-0.01 (-0.02, 0.01)	1.01 (0.93, 1.10)	0.99 (0.95, 1.04)
Model 2	-0.01 (-0.02, 0.01)	1.01 (0.93, 1.10)	0.99 (0.95, 1.04)
Model 3	-0.01 (-0.02, 0.01)	1.01 (0.93, 1.10)	0.99 (0.95, 1.04)

Difference in volume per 1-point better adherence to the dietary guidelines. OR: Odds Ratio. CI: confidence interval. * log-transformed. *Model 1:* adjusted for age, sex, intracranial volume, education, energy intake. *Model 2:* adjusted for age, sex, intracranial volume, education, energy intake, smoking, physical activity and body mass index. *Model 3:* adjusted for age, sex, intracranial volume, education, energy intake, smoking, physical activity, body mass index, diabetes, hypertension and hypercholesterolemia. No statistically significant effect estimates ($p < 0.05$).

white matter lesions (Table 3). We found no prominent differences between men and women (Supplementary tables 1 to 4 [links.lww.com/WNL/A531]), and there was no interaction by age (p for interaction > 0.05).

Regarding specific food components, we observed that associations of diet quality with brain volumes were not driven by one single component. Guideline adherence for multiple components, such as vegetables, fruit, whole grains, nuts, dairy and fish was associated with larger total brain and white matter volumes (Table 4). Moreover, adhering to the guidelines for whole grains and dairy was associated with larger grey matter volumes, and adhering to the guidelines of sufficient fruit and low sugar-containing beverage intake was related to larger hippocampus volumes (Table 4). In line with this, excluding each of the food groups one by one from the score resulted in similar associations with brain volumes as observed for the total dietary guideline score (Supplementary table 5 [links.lww.com/WNL/A531]). As demonstrated in Supplementary tables 6 and 7, the effect estimates of the association between Mediterranean diet score and

Table 4. Adherence to dietary guidelines for specific food groups and brain volume

	Total brain volume	Grey matter volume	White matter volume	Hippocampus volume
	Difference in mL (95% CI)	Difference in mL (95% CI)	Difference in mL (95% CI)	Difference in mL (95% CI)
Vegetables	3.35 (0.31, 6.39)[a]	-0.47 (-3.16, 2.22)	3.82 (0.85, 6.79)[a]	0.03 (-0.02, 0.08)
Fruit	4.17 (1.10, 7.24)[a]	0.67 (-2.05, 3.39)	3.50 (0.50, 6.50)[a]	0.06 (0.01, 0.11)[a]
Whole grains	3.45 (0.32, 6.58)[a]	3.11 (0.34, 5.88)[a]	0.34 (-2.72, 3.40)	0.03 (-0.02, 0.08)
Legumes	0.08 (-3.13, 3.29)	0.98 (-1.79, 3.76)	-0.91 (-3.73, 1.92)	-0.00 (-0.06, 0.05)
Nuts	5.91 (2.26, 9.55)[a]	1.41 (-1.82, 4.63)	4.50 (0.94, 8.07)[a]	-0.01 (-0.07, 0.06)
Dairy	2.45 (-0.59, 5.49)	2.76 (0.10, 5.42)[a]	-0.31 (-3.28, 2.67)	0.02 (-0.03, 0.07)
Fish	2.44 (-0.47, 5.35)	-1.60 (-4.17, 0.97)	4.04 (1.20, 6.87)[a]	0.05 (-0.00, 0.10)
Tea	-0.20 (-5.43, 5.02)	2.94 (-1.68, 7.56)	-3.15 (-8.25, 1.96)	-0.01 (-0.09, 0.08)
Grains	5.39 (1.84, 8.94)[a]	2.43 (-0.71, 5.57)	2.95 (-0.52, 6.42)	0.04 (-0.02, 0.10)
Fats	2.10 (-0.97, 5.16)	-0.31 (-3.03, 2.41)	2.40 (-0.60, 5.41)	0.01 (-0.04, 0.06)
Red meat	2.29 (-1.25, 5.83)	3.01 (-0.12, 6.13)	-0.72 (-4.17, 2.74)	0.01 (-0.05, 0.07)
Sugar containing beverages	-1.57 (-5.25, 2.12)	-1.00 (-4.23, 2.22)	-0.56 (-4.17, 3.04)	0.09 (0.02, 0.15)[a]
Alcohol	2.43 (-0.57, 5.43)	1.50 (-1.16, 4.15)	0.94 (-2.00, 3.87)	-0.01 (-0.06, 0.04)
Salt	0.69 (-3.15, 4.54)	2.04 (-1.36, 5.44)	-1.35 (-5.10, 2.41)	-0.03 (-0.10, 0.03)

Difference in volume in millilitres (95% confidence interval) for adherence (yes/no) to the guideline for the specific food group. CI: confidence interval. Adjusted for age, sex, intracranial volume, education, energy intake, smoking, physical activity and body mass index. Cut off values for guidelines: vegetables ≥200 g/day, fruit ≥200 g/day, whole grain products ≥90 g/day, legumes ≥135 g/week, nuts ≥15 g/d, dairy ≥350 g/day, fish ≥100 g/week, tea ≥450 g/day, whole grains ≥ 50% of total grains, fats (unsaturated) ≥50% of total fats, meat (red and processed) ≤300 g/week, sugar-containing beverages ≤150 g/day, alcohol ≤10 g/d, salt ≤6 g/day (Table 1).

[a] Statistically significant effect estimates ($p < 0.05$).

brain volume and between the Mediterranean diet score and focal brain lesions were similar to the results found for the Dutch dietary guidelines, as can be seen in Tables 3 and 4.

DISCUSSION

In this large sample of community-dwelling individuals free of dementia, we found that better overall diet quality is related to larger total brain volume, grey matter, white matter, and hippocampal volumes. These associations were not driven by one specific food group, though several food groups contributed differentially to the effect on brain changes. In particular, sufficient intake of vegetables, fruit, nuts, whole grains, dairy, and fish and limited intake of sugar-containing beverages were related to larger brain tissue volumes and thus together promote brain health together. We found no effects of diet

quality on focal vascular brain lesions, such as white matter lesions, or the presence of lacunes or microbleeds.

Strengths of our study included the population-based setting and (quantitative) assessment of structural brain changes using imaging. In addition, we used a novel, validated, food-based diet score that can be used to rate overall diet quality of adults.[21] Contrary to other dietary guidelines, this guideline is completely based on food groups instead of individual nutrients,[21] which represents a more accurate reflection of eating patterns. However, some limitations of the current study should also be acknowledged. First, the FFQ relies on an individual's capacity to recall their dietary behaviour over the past month. Recall bias in dietary behaviour could be a systematic bias. For example, alcohol consumption is known to be underreported, and thus an underestimation of the actual alcohol intake in our population might be expected, leading to an underestimation of the true effect on the brain.[33] Second, the dietary guideline score is constructed using a dichotomous variable per component (i.e., adherent or non-adherent) which may have resulted in loss of information leading to an underestimation of the true effect. Third, this is a cross-sectional study, hampering the possibility to infer causality between determinant and outcome. Fourth, this dietary guideline score is developed for and validated in a Dutch population, which might restrict generalizability to other countries and its populations. However, our results indicate that the Mediterranean diet score developed by Trichopoulou at al.[26] showed the same associations between diet quality and brain volume and between diet quality and focal vascular lesions. This supports the generalizability of the Dutch dietary guidelines and suggests that overall diet quality is important for brain structure irrespective of the exact index used to define diet quality. Nevertheless, it is also important to acknowledge that it is still necessary to use population-specific dietary guidelines and corresponding diet scores to accurately estimate diet quality of populations. The widely used Mediterranean Diet, for example, has been found to predict mortality risk in Mediterranean populations, but it predicts mortality less so in non-Mediterranean populaitons.[34] Finally, although we tried to adjust for lifestyle factors and other factors that may relate to both diet quality and brain health, there still might be residual confounding from unmeasured confounders.

We found that better diet quality related to larger total brain volume, grey matter volume, white matter volume and hippocampal volume, supporting our hypothesis that direct structural changes in the brain are influenced by variations in diet quality. There are few other studies that examined the association between diet quality and brain health. Those that did examine the association between diet quality and brain health mostly incorporated a Mediterranean Diet. Similar results have been found in those studies, with better adherence to a Mediterranean Diet associated with lower rates of brain atrophy and larger grey and white matter volumes.[14,11] Regarding the potential pathways through which diet can influence the brain, there are several pos-

sibilities. First, nutritional factors could have a direct effect on neuronal heath. In a randomized controlled trial, the effects of a Mediterranean Diet on plasma brain-derived neurotrophic factor levels,[35] a nerve growth factor promoting survival and growth effects on neurons, was investigated.[36] The authors found higher plasma brain-derived neurotrophic factor levels in the experimental group compared to the control group.[35] In animal studies, comparable results have been found.[37] Dietary interventions in mice improved cerebrovascular health and enhanced neuroprotective mechanisms, leading to an increase of the synthesis of synaptic proteins and phospholipids and an improvement of functional connectivity in the brain.[37] These results highlight the potential of direct neuroprotective effects of diet quality on the brain, but other potential pathways should also be considered.

Another pathway could be the influence of diet quality on vascular risk and cerebrovascular disease. Changes in nutrition are thought to be a promising way to lower the risk of cerebrovascular disease.[38] However, in our study, we found that diet quality was not associated with focal vascular brain lesions (white matter lesions, lacunes, or cerebral microbleeds), not supporting this hypothesis. It is of interest that a cross-sectional study with 1,091 participants found that adhering to a Mediterranean Diet does relate to a lower volume of white matter lesions,[39] and also more generally, a healthy dietary pattern has been related to a lower cardiovascular risk.[40-42] A randomized trial which was conducted in Spain in 2013 reported a lower incidence of major cardiovascular events (relative risk reduction of approximately 30%) among high-risk persons whom received a Mediterranean Diet supplemented with extra-virgin olive oil or nuts compared to the control group.[43] The absence of an association in our study might be attributable to information loss as we used the presence (yes/no) of infarcts and microbleeds, possibly leading to an underestimation of the true effect. Another plausible explanation lies in the fact that most research in nutrition and cerebrovascular disease is performed in clinical studies. Participants are thus assigned to a diet, which might be healthier than what they normally eat, whereas the participants in our study report what they eat in general, which might be less healthy than the diets assigned to in clinical trials. Thirdly, residual confounding may underlie the association between diet and brain structure. Although we corrected for lifestyle factors such as education, energy intake, smoking, physical activity and body mass index, there still might be residual confounding. For example, socio-economic status (SES) might be a confounder in the relationship between brain health and diet quality. However, we do not have enough data pertaining to income and occupation, for example, to construct a proper SES variable, and therefore we used education as a proxy for SES.

Finally, we might be looking at an effect of neurodevelopment where variations in diet quality throughout life have different effects on brain structure and brain health. In a study conducted in Japan, researchers compared 2 types of breakfast in children aged 5

to 18 years.[44] The breakfast types, rice or bread, influenced different regions in the brain. The rice group had larger grey matter volumes in several regions, such as the left superior temporal gyrus, whereas the bread group had significantly larger grey matter volumes in several other regions, including the bilateral orbitofrontal gyri. This suggests that optimal nutrition is important for brain maturation.[44] Moreover, research in infants showed that breastfeeding is associated with improved developmental growth in late maturing white matter association regions, and that extended breastfeeding was associated with improved white matter structure and higher cortical thickness.[45-47] Again, this underlines the importance of nutrition on brain development and maturation and thus brain health.

Regarding the specific food groups in the diet quality score we used, most of the components contributed to the associations observed for overall diet quality with brain volumes. We found that sufficient intake of each - vegetables, fruit, nuts and whole grains - significantly related to larger total brain volume and larger white matter volumes. Multiple studies have addressed specific nutrient patterns and brain health. One study found "Alzheimer's disease-protective" nutrient patterns where vitamin B_{12}, vitamin D, and zinc were positively associated with AD brain biomarkers.[17] In addition, grey matter volume was negatively associated with intake of cholesterol, sodium, and saturated and trans-saturated fats. These nutrient patterns were linked to a higher intake of fruit, vegetables, whole grains, fish, low-fat dairy, and nuts and with a lower intake of sweets, fried potatoes, processed meat, high-fat dairy, and butter.[17] Other studies also found associations between higher intake of fish, whole grain, dairy (low-fat), and lower intake of meat, alcohol, and sugar-containing beverages and larger brain volumes such as grey matter volume and hippocampal volume.[11, 48, 49] However, intake of these components are correlated and therefore should be interpreted as a dietary pattern rather than as individual components. People consume a diet that consists of multiple nutrients that have interactive effects. Therefore, considering individual components might be inadequate to taking the additive and interactive effects of nutrients into account.[10] Moreover, we found similar effect estimates when excluding one food component at a time from the overall diet quality score, suggesting that the associations of overall diet quality were not driven by one specific food component and highlighting the importance of the overall diet quality.

This study suggests that a better overall diet quality is associated with larger brain tissue volumes, in which the additive and interactive effects of certain food groups, such as high consumption of fruit, vegetables, whole grains, nuts, dairy and fish and low consumption of sugar-containing beverages, support brain health. These results highlight the potential of nutrition influencing cognition and the risk of developing dementia through brain health. More research, in particular longitudinal population-based research, is needed to unravel direct vs indirect effects between diet quality and brain health.

REFERENCES

1. Rijn Rv. Minerva. Den Haag, the Netherlands: Mauritshuis, 1630.
2. Raji CA, Eyre H, Wei SH, et al. Hot Topics in Research: Preventive Neuroradiology in Brain Aging and Cognitive Decline. AJNR Am J Neuroradiol 2015;36:1803-1809.
3. Cao L, Tan L, Wang HF, et al. Dietary Patterns and Risk of Dementia: a Systematic Review and Meta-Analysis of Cohort Studies. Mol Neurobiol 2016;53:6144-6154.
4. Morris MC, Tangney CC, Wang Y, et al. MIND diet slows cognitive decline with aging. Alzheimers Dement 2015;11:1015-1022.
5. Smith PJ, Blumenthal JA. Dietary Factors and Cognitive Decline. J Prev Alzheimers Dis 2016;3:53-64.
6. van de Rest O, Berendsen AA, Haveman-Nies A, de Groot LC. Dietary patterns, cognitive decline, and dementia: a systematic review. Adv Nutr 2015;6:154-168.
7. Lourida I, Soni M, Thompson-Coon J, et al. Mediterranean diet, cognitive function, and dementia: a systematic review. Epidemiology 2013;24:479-489.
8. Ikram MA, Vrooman HA, Vernooij MW, et al. Brain tissue volumes in relation to cognitive function and risk of dementia. Neurobiol Aging 2010;31:378-386.
9. Jackson PA, Pialoux V, Corbett D, et al. Promoting brain health through exercise and diet in older adults: a physiological perspective. J Physiol 2016;594:4485-4498.
10. Zamroziewicz MK, Barbey AK. Nutritional Cognitive Neuroscience: Innovations for Healthy Brain Aging. Front Neurosci 2016;10:240.
11. Gu Y, Brickman AM, Stern Y, et al. Mediterranean diet and brain structure in a multiethnic elderly cohort. Neurology 2015;85:1744-1751.
12. Titova OE, Ax E, Brooks SJ, et al. Mediterranean diet habits in older individuals: Associations with cognitive functioning and brain volumes. Experimental Gerontology 2013;48:1443-1448.
13. Mosconi L, Murray J, Tsui WH, et al. Mediterranean Diet and Magnetic Resonance Imaging-Assessed Brain Atrophy in Cognitively Normal Individuals at Risk for Alzheimer's Disease. J Prev Alzheimers Dis 2014;1:23-32.
14. Luciano M, Corley J, Cox SR, et al. Mediterranean-type diet and brain structural change from 73 to 76 years in a Scottish cohort. Neurology 2017;88:449-455.
15. Monti JM, Moulton CJ, Cohen NJ. The role of nutrition on cognition and brain health in ageing: a targeted approach. Nutr Res Rev 2015;28:167-180.
16. Verlinden VJA, van der Geest JN, Hofman A, et al. Brain MRI-markers Associate Differentially with Cognitive Versus Functional Decline Leading to Dementia. J Am Geriatr Soc 2017;65:1258-1266.
17. Berti V, Murray J, Davies M, et al. Nutrient patterns and brain biomarkers of Alzheimer's disease in cognitively normal individuals. J Nutr Health Aging 2015;19:413-423.
18. Morris MC. Nutrition and risk of dementia: overview and methodological issues. Ann N Y Acad Sci 2016;1367:31-37.
19. Wang M, Norman JE, Srinivasan VJ, Rutledge JC. Metabolic, inflammatory, and microvascular determinants of white matter disease and cognitive decline. Am J Neurodegener Dis 2016;5:171-177.
20. Hofman A, Brusselle GG, Darwish Murad S, et al. The Rotterdam Study: 2016 objectives and design update. Eur J Epidemiol 2015;30:661-708.
21. Voortman T, Kiefte-de Jong JC, Ikram MA, et al. Adherence to the 2015 Dutch dietary guidelines and risk of non-communicable diseases and mortality in the Rotterdam Study. European Journal of Epidemiology 2017.

22. Ikram MA, van der Lugt A, Niessen WJ, et al. The Rotterdam Scan Study: design update 2016 and main findings. Eur J Epidemiol 2015;30:1299-1315.
23. Goldbohm RA, van den Brandt PA, Brants HA, et al. Validation of a dietary questionnaire used in a large-scale prospective cohort study on diet and cancer. Eur J Clin Nutr 1994;48:253-265.
24. Feunekes GI, Van Staveren WA, De Vries JH, Burema J, Hautvast JG. Relative and biomarker-based validity of a food-frequency questionnaire estimating intake of fats and cholesterol. Am J Clin Nutr 1993;58:489-496.
25. Kromhout D, Spaaij CJ, de Goede J, Weggemans RM. The 2015 Dutch food-based dietary guidelines. Eur J Clin Nutr 2016;70:869-878.
26. Trichopoulou A, Costacou T, Bamia C, Trichopoulos D. Adherence to a Mediterranean diet and survival in a Greek population. N Engl J Med 2003;348:2599-2608.
27. Bos D, Vernooij MW, de Bruijn RF, et al. Atherosclerotic calcification is related to a higher risk of dementia and cognitive decline. Alzheimers Dement 2015;11:639-647 e631.
28. Fischl B, Salat DH, van der Kouwe AJ, et al. Sequence-independent segmentation of magnetic resonance images. Neuroimage 2004;23 Suppl 1:S69-84.
29. Bos D, van der Rijk MJ, Geeraedts TE, et al. Intracranial carotid artery atherosclerosis: prevalence and risk factors in the general population. Stroke 2012;43:1878-1884.
30. Stel VS, Smit JH, Pluijm SM, Visser M, Deeg DJ, Lips P. Comparison of the LASA Physical Activity Questionnaire with a 7-day diary and pedometer. J Clin Epidemiol 2004;57:252-258.
31. Caspersen CJ, Bloemberg BP, Saris WH, Merritt RK, Kromhout D. The prevalence of selected physical activities and their relation with coronary heart disease risk factors in elderly men: the Zutphen Study, 1985. Am J Epidemiol 1991;133:1078-1092.
32. Ainsworth BE, Haskell WL, Herrmann SD, et al. 2011 Compendium of Physical Activities: a second update of codes and MET values. Med Sci Sports Exerc 2011;43:1575-1581.
33. Livingston M, Callinan S. Underreporting in alcohol surveys: whose drinking is underestimated? J Stud Alcohol Drugs 2015;76:158-164.
34. Waijers PM, Feskens EJ, Ocke MC. A critical review of predefined diet quality scores. Br J Nutr 2007;97:219-231.
35. Sanchez-Villegas A, Galbete C, Martinez-Gonzalez MA, et al. The effect of the Mediterranean diet on plasma brain-derived neurotrophic factor (BDNF) levels: the PREDIMED-NAVARRA randomized trial. Nutr Neurosci 2011;14:195-201.
36. Binder DK, Scharfman HE. Brain-derived neurotrophic factor. Growth Factors 2004;22:123-131.
37. Wiesmann M, Zerbi V, Jansen D, et al. A Dietary Treatment Improves Cerebral Blood Flow and Brain Connectivity in Aging apoE4 Mice. Neural Plast 2016;2016:6846721.
38. Guzik A, Bushnell C. Stroke Epidemiology and Risk Factor Management. Continuum (Minneap Minn) 2017;23:15-39.
39. Gardener H, Scarmeas N, Gu Y, et al. Mediterranean diet and white matter hyperintensity volume in the Northern Manhattan Study. Arch Neurol 2012;69:251-256.
40. Gunge VB, Andersen I, Kyro C, et al. Adherence to a healthy Nordic food index and risk of myocardial infarction in middle-aged Danes: the diet, cancer and health cohort study. Eur J Clin Nutr 2017.
41. Wang DD, Toledo E, Hruby A, et al. Plasma Ceramides, Mediterranean Diet, and Incident Cardiovascular Disease in the PREDIMED Trial. Circulation 2017.
42. Fung TT, Pan A, Hou T, et al. Food quality score and the risk of coronary artery disease: a prospective analysis in 3 cohorts. Am J Clin Nutr 2016;104:65-72.

43. Estruch R, Ros E, Salas-Salvadó J, et al. Primary Prevention of Cardiovascular Disease with a Mediterranean Diet. New England Journal of Medicine 2013;368:1279-1290.
44. Taki Y, Hashizume H, Sassa Y, et al. Breakfast staple types affect brain gray matter volume and cognitive function in healthy children. PLoS One 2010;5:e15213.
45. Deoni SC, Dean DC, 3rd, Piryatinsky I, et al. Breastfeeding and early white matter development: A cross-sectional study. Neuroimage 2013;82:77-86.
46. Kafouri S, Kramer M, Leonard G, et al. Breastfeeding and brain structure in adolescence. Int J Epidemiol 2013;42:150-159.
47. Ou X, Andres A, Cleves MA, et al. Sex-specific association between infant diet and white matter integrity in 8-y-old children. Pediatr Res 2014;76:535-543.
48. Darnai G, Plozer E, Perlaki G, et al. Milk and dairy consumption correlates with cerebral cortical as well as cerebral white matter volume in healthy young adults. Int J Food Sci Nutr 2015;66:826-829.
49. Pase MP, Himali JJ, Jacques PF, et al. Sugary beverage intake and preclinical Alzheimer's disease in the community. Alzheimers Dement 2017.