**eMethods: Assessment of brain structure**

* 1. **MRI acquisition**

MRI examination was performed on a 3-T Achieva scanner (Philips Medical System, the Netherlands) equipped with a SENSE 8-channel head coil. Anatomical high resolution MRI volumes were acquired in transverse plane using a three-dimensional magnetization prepared rapid gradient echo (MPRAGE) T1-weighted sequence with the following parameters: TR/TE=8.2/3.5 ms, 7-degree flip angle, FOV 256×256 mm2 to cover the whole brain, yielding 180 contiguous slices, voxel size 1×1×1 mm3. Diffusion-weighted images were performed using a single-shot echo-planar sequence with the following parameters: TR/TE=9188/60 ms, 90-degree flip angle, FOV 224×224 mm2, yielding 60 contiguous slices, voxel size 1.5 ×1.5 ×2 mm3. One image with b=0 was acquired and diffusion gradients were applied in 21 non-collinear directions (b-value=1000 s/mm2). To increase signal-to-noise ratio, the sequence was repeated in four successive runs. All acquisitions were aligned on the anterior commissure/posterior commissure plane.

* 1. **MRI processing**
     1. *Assessment of grey matter and white matter volumes*

Brain volumes were assessed using Voxel-Based Morphometry (VBM) (1,2) procedure implemented in SPM12 software (Statistical Parametric Mapping release 12) (3). Anatomical T1 images were first spatially normalized and segmented into grey matter (GM), white matter (WM) and cerebrospinal fluid (CSF) according to their intensity distribution and spatial information derived from the ICBM default tissue probability maps. Then, a so-called modulation was applied to the resulting individual GM, WM and CSF probability maps using the Jacobian determinants derived from the spatial normalization parameters, so the voxel intensity of segmented normalized images was adjusted for the strength of deformation in order to preserve the subject’s original tissue quantity after its transfer to the reference space. Finally, GM and WM probability maps were smoothed using an 8-mm full width at half-maximum Gaussian Kernel. For each subject, GM, WM and CSF volumes were computed by multiplying the voxel value by the voxel volume and summing the results for all of the voxels in the corresponding modulated tissue image; and total intracranial volume (TIV) was defined as their sum.

* + 1. *Assessment of white matter microstructure*

WM microstructure integrity was assessed through Diffusion Tensor Imaging (DTI) parameters, evaluating both the directionality and the magnitude of the diffusion of water molecules in brain tissue. DTI parameters include: Fractional Anisotropy (FA), that represents the degree of directionality of water diffusivity along WM fibers; Axonal Diffusivity (AD) and Radial Diffusivity (RD), which quantify the diffusion of water molecules along the principal (i.e., parallel) and perpendicular direction of WM fibers, respectively; and Mean Diffusivity (MD), a global measure of water diffusion. Within WM tissue, the diffusion of water molecules in restricted along axonal bundles; thus higher directionality (i.e., higher FA value) and lower magnitude of diffusion (i.e., lower AD, RD and MD) generally indicate preserved architecture of WM fiber tracts.

Diffusion-weighted images were processed using FMRIB Software Library (FSL). For each subject, images were corrected for motion and eddy distortions by co-registration to the reference volume b0 with an affine transformation. FMRIB’s Diffusion Toolbox was used to average data from the four successive runs performed during the DTI sequence, and to compute FA, MD, AD and RD maps by fitting a tensor model to the raw diffusion data. Tract-Based Spatial Statistics (TBSS) pipeline (4) within FSL was used to optimize DTI maps. Each individual FA images were registered on the FMRIB58-FA template (i.e., the default template in FSL) using nonlinear transformations. A mean FA WM mask was generated using all registered individual FA maps, and then thinned to create a mean FA skeleton corresponding to the center of all tracts common to all subjects to limit the effects of miswarping across subjects. A threshold FA value of 0.2 was applied to reduce inclusion of voxels that are likely to be composed of multiple tissue types (non-white matter tissue). Finally, each subject’s FA map was projected onto the FA skeleton by searching for maximum FA values perpendicular to the skeleton. The resulting individual skeletonized FA images for each participant were used in statistical analysis. The same transformations were applied to the AD, RD and MD maps.

**References**

1. Ashburner J, Friston KJ. Voxel-based morphometry--the methods. Neuroimage. 2000;11:805–21.

2. Good CD, Johnsrude IS, Ashburner J, Henson RN, Friston KJ, Frackowiak RS. A voxel-based morphometric study of ageing in 465 normal adult human brains. Neuroimage. 2001;14:21–36.

3. The FIL Methods Group. SPM12 Manual [online]. London, UK. Available from: https://www.fil.ion.ucl.ac.uk/spm/doc/manual.pdf. Accessed February 2, 2021.

4. Smith SM, Jenkinson M, Johansen-Berg H, et al. Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. Neuroimage. 2006;31(4):1487–505.

**eFigure 1. Flow chart of participants included in the study, the Three-City Bordeaux study, 2001-2018**

**171** Excluded

**96** without dietary survey

**75** with missing data for at least 1 dietary component

**349** Excluded: without follow-up

**172** Excluded

**70** with dementia at time of dietary assessment

**102** without follow-up data

**1412** Individuals included in the analytic sample

**1584** Individuals with complete dietary survey at first visit

**1755** Individuals at first visit (2001-2002)

**2104** Participants included in Three-City Study – Bordeaux at baseline (1999-2000)

**eTable 1. Correlations between intakes estimated by the Food Frequency Questionnaire and the 24-hour recall for food components available in both surveys, the 3C Bordeaux study, 2001 (N = 1,412)**

|  |  |  |
| --- | --- | --- |
| **Food components** | **Spearman correlation coefficient** | ***P-value*** |
| Other vegetables | 0.36 | <0.001 |
| Beans | 0.19 | <0.001 |
| Fish | 0.22 | <0.001 |
| Poultry | 0.19 | <0.001 |
| Red meats/products | 0.28 | <0.001 |
| Cheese | 0.51 | <0.001 |
| Pastries and sweets | 0.36 | <0.001 |
| Fried/fast food | 0.09 | 0.001 |
| Butter/margarine | 0.66 | <0.001 |
| Wine | 0.81 | <0.001 |

Intakes from the Food Frequency Questionnaire were estimated as number of eating occasions per week (or number of glasses per week for wine), and intakes from the 24-hour recall were estimated in grams per day.

**eTable 2. MIND diet components\* and distribution of scoring categories, the Three-City Bordeaux study, 2001 (N = 1,412)**

| **Components** | **Intake category for scoring** | | |
| --- | --- | --- | --- |
| Score: 0 | Score: 0.5 | Score: 1 |
| Whole grains† |  |  |  |
| Cut-offs by *Morris et al*. (servings/day) | <1 | 1 – 2 | ≥3 |
| French-adapted cut-offs (g/day) | 0 | - | >0 |
| No. (%) | 1295 (91.7) |  | 117 (8.3) |
| Average intake (SD) | 0.0 (0.0) |  | 82.3 (69.2) |
| Nuts† |  |  |  |
| Cut-offs by *Morris et al*. (servings/week) | <1 /month | 1 /month – 5 | ≥5 |
| French-adapted cut-offs (g/day) | 0 | - | >0 |
| No. (%) | 1332 (94.3) |  | 80 (5.7) |
| Average intake (SD) | 0.0 (0.0) |  | 47.3 (38.1) |
| Total polyphenols† |  |  |  |
| Cut-offs by *Morris et al*. (berries, serving/week) | <1 | 1 | ≥2 |
| French-adapted cut-offs (g/day) | ≤0.77 | 0.77 – 1.21 | >1.21 |
| No. (%) | 471 (33.4) | 470 (33.3) | 471 (33.4) |
| Average intake (SD) | 522.1 (175.6) | 990.9 (127.5) | 1682.0 (477.9) |
| Green leafy vegetables† |  |  |  |
| Cut-offs by *Morris et al*. (servings/week) | ≤2 | 2 – 6 | ≥6 |
| French-adapted cut-offs (g/day) | 0 | 0 – 60 | >60 |
| No. (%) | 627 (44.4) | 377 (26.7) | 408 (28.9) |
| Average intake (SD) | 0.0 (0.0) | 38.2 (15.5) | 189.4 (123.8) |
| Other vegetables |  |  |  |
| Cut-offs by *Morris et al*. (servings/week) | <5 | 5 – 7 | ≥7 |
| French-adapted cut-offs (eating occasions/week) | <7 | 7 – 14 | >14 |
| No. (%) | 86 (6.1) | 638 (45.2) | 688 (48.7) |
| Average intake (SD) | 4.1 (1.6) | 11.4 (2.0) | 19.3 (3.8) |
| Beans |  |  |  |
| Cut-offs by *Morris et al*. (servings/week) | <1 | 1 – 3 | >3 |
| French-adapted cut-offs (eating occasions/week) | <1 /month | 1 /month – 1 | ≥2 |
| No. (%) | 306 (21.7) | 1003 (71.0) | 103 (7.3) |
| Average intake (SD) | 0.0 (0.0) | 0.64 (0.35) | 2.33 (0.96) |
| Fish |  |  |  |
| Cut-offs by *Morris et al*. (servings/week) | Rarely | 1 – 3 /month | ≥1 |
| French-adapted cut-offs (eating occasions/week) | <1 | 1 | ≥2 |
| No. (%) | 89 (6.3) | 292 (20.7) | 1031 (73.0) |
| Average intake (SD) | 0.3 (0.3) | 1.2 (0.2) | 3.6 (1.5) |
| Poultry |  |  |  |
| Unchanged cut-offs (eating occasions/week) | <1 | 1 | ≥2 |
| No. (%) | 230 (16.3) | 481 (34.1) | 701 (49.6) |
| Average intake (SD) | 0.4 (0.2) | 1.1 (0.2) | 2.8 (1.1) |
| Red meats/products |  |  |  |
| Cut-offs by *Morris et al*. (servings/week) | ≥7 | 4 – 6 | <4 |
| French-adapted cut-offs (eating occasions/week) | ≥7 | 4 – 6 | ≤4 |
| No. (%) | 591 (41.9) | 393 (27.8) | 428 (30.3) |
| Average intake (SD) | 9.7 (2.8) | 5.5 (0.6) | 2.8 (1.2) |
| Cheese |  |  |  |
| Cut-offs by *Morris et al*. (servings/week) | ≥7 | 1 – 6 | <1 |
| French-adapted cut-offs (eating occasions/week) | >7 | 1 – 7 | <1 |
| No. (%) | 546 (38.7) | 759 (53.8) | 107 (7.6) |
| Average intake (SD) | 12.4 (2.8) | 5.4 (2.0) | 0.1 (0.2) |
| Pastries and sweets |  |  |  |
| Unchanged cut-offs (eating occasions/week) | ≥7 | 5 – 6 | <5 |
| No. (%) | 448 (31.7) | 55 (3.9) | 909 (64.4) |
| Average intake (SD) | 10.3 (5.0) | 5.5 (0.5) | 0.8 (1.2) |
| Fried/fast food |  |  |  |
| Cut-offs by *Morris et al*. (servings/week) | ≥4 | 1 – 3 | <1 |
| French-adapted cut-offs (eating occasions/week) | >2 | 1 – 2 | <1 |
| No. (%) | 39 (2.8) | 225 (15.9) | 1148 (81.3) |
| Average intake (SD) | 3.8 (1.4) | 1.3 (0.4) | 0.2 (0.2) |
| Butter and margarine |  |  |  |
| Cut-offs by *Morris et al*. (servings/day) | >2 | 1 – 2 | <1 |
| French-adapted cut-offs (eating occasions/week) | >14 | 7 – 14 | <7 |
| No. (%) | 43 (3.0) | 771 (54.6) | 598 (42.4) |
| Average intake (SD) | 18.8 (2.5) | 8.1 (1.9) | 1.2 (1.8) |
| Olive oil |  |  |  |
| Unchanged definition (primary added fat) | No | - | Yes |
| No. (%) | 1121 (79.4) |  | 291 (20.6) |
| Wine |  |  |  |
| Cut-offs by *Morris et al*. (number of glasses/day) | Never or >1 | 1 /month – 6 | 1 |
| French-adapted cut-offs (number of glasses/week) | Never or >10 | 1 /month – 7 | [7 –10] |
| No. (%) | 969 (68.6) | 241 (17.1) | 202 (14.3) |
| Average intake (SD) | 8.9 (6.8) | 1.9 (1.6) | 7.3 (0.8) |

\* French-adapted MIND diet components were selected according to *Morris et al*. *Alzheimers Dement*. 2015, and thresholds were adapted to French dietary habits and guidelines.

†Data derived from the 24-hour recall, with a binary threshold for components not frequently consumed among study participants (whole grains, nuts) or thresholds set according to tertiles of daily intake (green leafy vegetables, polyphenols).

**eTable 3. Associations between individual components of the MIND diet and risks of all-cause dementia estimated by multivariable Cox models\*, the 3C Bordeaux study, 2001-2018 (N = 1,412)**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Exposure** | **Fully-adjusted models** | | |  | **Fully and mutually-adjusted model** | | |
| **HR** | **95% CI** | ***Pcor-rected***  ***\*\**** |  | **HR** | **95% CI** | ***P*** |
| Whole grains (g/day, for 1 SD) | 1.06 | (0.94; 1.19) | 1.00 |  | 1.08 | (0.96; 1.22) | 0.18 |
| Nuts (g/day, for 1 SD) | 0.87 | (0.75; 1.02) | 1.00 |  | 0.86 | (0.73; 1.01) | 0.07 |
| Total polyphenols (g/day, for 1 SD) | 0.93 | (0.83; 1.05) | 1.00 |  | 0.94 | (0.83; 1.08) | 0.39 |
| Green leafy vegetables (g/day, for 1 SD) | 0.93 | (0.84; 1.04) | 1.00 |  | 0.95 | (0.85; 1.06) | 0.36 |
| Other vegetables (for 1 eating occasion/w) | 0.99 | (0.97; 1.01) | 1.00 |  | 0.99 | (0.97; 1.01) | 0.41 |
| Beans (for 1 eating occasion/w) | 0.92 | (0.76; 1.10) | 1.00 |  | 0.89 | (0.74; 1.08) | 0.24 |
| Fish (for 1 eating occasion/w) | 0.96 | (0.91; 1.03) | 1.00 |  | 0.99 | (0.92; 1.05) | 0.68 |
| Poultry (for 1 eating occasion/w) | 0.92 | (0.84; 1.00) | 0.90 |  | 0.94 | (0.85; 1.03) | 0.16 |
| Red meats/products (for 1 eating occasion/w) | 1.02 | (0.99; 1.05) | 1.00 |  | 1.02 | (0.98; 1.05) | 0.32 |
| Cheese (for 1 eating occasion/w) | **1.03** | **(1.00; 1.05)** | 0.45 |  | 1.02 | (1.00; 1.05) | 0.06 |
| Pastries and sweets (for 1 eating occasion/w) | 1.00 | (0.98; 1.03) | 1.00 |  | 1.00 | (0.98; 1.02) | 0.93 |
| Fried/fast food (for 1 eating occasion/w) | 1.03 | (0.91; 1.16) | 1.00 |  | 1.02 | (0.90; 1.15) | 0.75 |
| Butter/margarine (for 1 eating occasion/w) | 0.98 | (0.96; 1.00) | 1.00 |  | **0.98** | **(0.95; 1.00)** | **0.04** |
| Olive oil (primary added fat vs no use) | 0.83 | (0.63; 1.09) | 1.00 |  | 0.82 | (0.62; 1.09) | 0.18 |
| Wine (for 1 additional glass/w) | 1.01 | (0.99; 1.03) | 1.00 |  | 1.02 | (1.00; 1.04) | 0.09 |

Abbreviations: 3C = Three-City; CI = Confidence Interval; HR = Hazard Ratio; MIND = Mediterranean-DASH Diet Intervention for Neurodegenerative Delay; SD = Standard Deviation.

\* Cox proportional hazard models with delayed entry and age as time scale, adjusted for sex, status for ɛ4 allele of the apolipoprotein E gene, educational level, total energy intake, body mass index, tobacco consumption, practice of regular physical activity, diabetes, history of cerebral and cardiovascular diseases, hypertension, hypercholesterolemia and high depressive symptoms. HR given for each additional eating occasion per week, except for wine (for 1 glass per week) and for whole grains, nuts, total polyphenols, and green leafy vegetables (for 1 SD). The proportional hazards assumption was investigated and verified for each individual component using Schoenfeld residuals, and no deviation from the linearity hypothesis was observed using restricted cubic splines.

\*\*P-value corrected for multiple testing using Bonferroni correction (15 comparisons, one for each of the 15 food components).

**eTable 4. Sensitivity analyses of associations between the French-adapted MIND diet score and risks of dementia and Alzheimer disease estimated by multivariable Cox models\*, the 3C Bordeaux study, 2001-2018**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **No. of cases/total No.** | **HR** | **95% CI** | ***P*-value** |
| MMSE<26 excluded |  |  |  |  |
| Incident dementia | 273/1169 | 0.86 | (0.79; 0.93) | <.001 |
| Incident Alzheimer disease | 184/1169 | 0.86 | (0.78; 0.95) | .004 |
| Complete case analysis |  |  |  |  |
| Incident dementia | 238/1033 | 0.88 | (0.80; 0.96) | .003 |
| Incident Alzheimer disease | 165/1033 | 0.88 | (0.79; 0.98) | .02 |

Abbreviations: 3C = Three-City; CI = Confidence Interval; HR = Hazard Ratio; MIND = Mediterranean-DASH Diet Intervention for Neurodegenerative Delay; MMSE = Mini-Mental State Examination.

\* Cox proportional hazard models with delayed entry and age as time scale, adjusted for sex, status for ɛ4 allele of the apolipoprotein E gene, educational level, total energy intake, body mass index, tobacco consumption, practice of regular physical activity, diabetes, history of cerebral and cardiovascular diseases, hypertension, hypercholesterolemia and high depressive symptoms.

**eTable 5. Comparison of baseline characteristics between included participants with and without missing data and the MRI sub-study sample, the 3C Bordeaux study, 2001-2018**.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Sample without missing data for primary analysis**  **(n = 1,033)** | **Sample with missing data imputed for primary analysis**  **(n = 379)** | **MRI sub-study sample**  **(n = 175)** | |
| Age, mean (SD), y | 75.5 (4.6) | 76.6 (5.2)\* | 73.2 (3.7)† | |
| Female, n (%) | 639 (61.9) | 251 (66.2) | 106 (60.6) | |
| Educational level, n (%) |  |  |  | |
| None or primary | 317 (30.7) | 138 (37.1) | 41 (23.4)† | |
| Secondary | 294 (28.5) | 93 (25.0) | 47 (26.9)† | |
| High school | 239 (23.1) | 70 (18.8) | 48 (27.4)† | |
| University | 183 (17.7) | 71 (19.1) | 39 (22.3)† | |
| *APOE*ɛ4 status, n (%) | 187 (18.1) | 44 (18.1) | 29 (17.5) | |
| Regular physical activity, n (%) | 357 (34.6) | 54 (37.2) | 62 (38.8) | |
| Tobacco consumption, mean (SD), packs/y | 9.1 (18.1) | 6.7 (15.7)\* | 9.5 (19.4) | |
| BMI, mean (SD), kg/m² | 26.6 (4.1) | 26.1 (4.4) | 26.5 (3.9) | |
| Diabetes, n (%) | 101 (9.8) | 54 (21.3)\* | 9 (5.4)† | |
| Hypertension, n (%) | 773 (74.8) | 298 (78.8) | 109 (62.6)† | |
| Hypercholesterolemia, n (%) | 629 (60.9) | 214 (69.7)\* | 99 (57.9) | |
| History of cardiovascular diseases, n (%) | 285 (27.6) | 133 (35.1)\* | 38 (21.7)† | |
| High depressive symptoms, n (%) | 73 (7.1) | 30 (7.9) | 7 (4.0) | |
| MMSE score (range, 0-30), mean (SD) | 27.8 (1.8) | 27.5 (2.1)\* | 27.9 (1.7) | |
| Total energy intake, mean (SD), kcal/day | 1618.4 (512.1) | 1633.7 (477.4) | 1662.0 (541.1) | |
| French MIND diet score (range 0-15), mean (SD) | 7.2 (1.5) | 7.0 (1.5)\* | 7.2 (1.5) | |
| French MIND diet components intake from FFQ, mean (SD), times/week | | | |
| Other vegetables | 14.8 (5.5) | 14.9 (5.7) | 14.6 (5.5) | |
| Beans | 0.6 (0.6) | 0.7 (0.8) | 0.6 (0.6) | |
| Fish | 2.9 (1.7) | 2.8 (1.8) | 2.8 (1.7) | |
| Poultry | 1.8 (1.2) | 1.9 (1.4) | 1.8 (1.2) | |
| Red meats and products | 6.4 (3.5) | 6.4 (3.7) | 6.3 (3.6) | |
| Cheese | 7.5 (4.5) | 8.1 (4.7)\* | 7.4 (4.3) | |
| Pastries and sweets | 3.9 (5.4) | 4.1 (5.2) | 3.5 (4.4) | |
| Fried and fast food | 0.4 (0.7) | 0.5 (1.0) | 0.5 (0.8) | |
| Butter and margarine | 5.6 (4.5) | 5.2 (4.6) | 5.4 (4.5) | |
| French MIND diet components intake from 24h recall, mean (SD), g/day | | | |
| Green leafy vegetables | 65.1 (103.0) | 64.3 (110.4) | 52.9 (76.3) | |
| Whole grains | 7.3 (31.7) | 5.5 (25.3) | 6.5 (35.4) | |
| Nuts | 2.9 (14.9) | 2.0 (12.1) | 2.7 (12.7) | |
| Total polyphenols | 1.1 (0.6) | 1.0 (0.5)\* | 1.1 (0.6) | |
| Wine intake (glasses/day), mean (SD) | 7.6 (6.2) | 6.9 (6.2) | 7.0 (6.4) | |
| Olive oil (preferred source of added fat), n (%) | 221 (21.4) | 70 (18.5) | 28 (16.0) | |
| Incident cases of dementia, n (%) | 238 (23.0) | 118 (31.1)\* | 46 (26.3) | |
| Incident cases of Alzheimer disease, n (%) | 165 (16.0) | 75 (19.8) | 36 (20.6) | |

Abbreviations: 3C = Three-City; *APOE*ɛ4 = ɛ4 allele of the apolipoprotein E gene; BMI = Body Mass Index; FFQ = Food Frequency Questionnaire; MIND = Mediterranean-DASH Diet Intervention for Neurodegenerative Delay; MMSE = Mini-Mental State Examination; SD = standard deviation.

Differences between samples with (n = 379) or without (n = 1033) missing data (\*) and samples included (n = 175) or not (n = 1237) in the MRI sub-study (†) were tested by Chi-square test for categorical variables and Student test for continuous variables, with a significance threshold of *P* < 0.05.