Supplementary Material

Associations of Pulmonary Function with MRI Brain Volumes: A Coordinated Multi-Study Analysis

Age, Gene/Environment Susceptibility Study (AGES)

General information

    The AGES-Reykjavik Study is a continuation of the Reykjavik Study. The Reykjavik Study was initiated in 1967 by the Icelandic Heart Association and included men and women born in 1907–1935 and living in the Reykjavik area. From September 2002 to February 2006, new data were collected for the AGES-Reykjavik Study, aimed to investigate the genetic and environmental factors contributing to clinical and subclinical disease at older age. The study design and initial assessments of the cohort have been described previously [1,2]. As part of the assessments at the research center, a questionnaire was administered, a clinical examination was performed, and images were acquired of the brain, musculoskeletal system, body composition, vasculature and heart. From June 2006 to March 2007 a sub-sample of the cohort was re-imaged. The AGES-Reykjavik Study has been approved by the Icelandic National Bioethics Committee, which acts as the Institutional Review Board for the Icelandic Heart Association, and by the Institutional Review Board for the Intramural Research Program of the National Institute on Aging, National Institutes of Health, USA. Informed consent was obtained from all participants. All MR images were screened by a neuroradiologist for evidence of brain pathology that warranted medical follow-up.

Data collection

    Spirometry. Spirometry was performed with a Vitalograph Gold StandardPlus (Vitalograph Ltd., Buckingham, UK). The procedure was explained in details before starting and was done in a sitting position in a standardised manner. Three attempts were made for each individual. Inclusion criteria for acceptable spirometry was completion of at least two spirometry attempts, no more than 300 ml difference between the attempts and ability to exhale for at least 6s. No bronchodilator was given, so airflow limitation was defined as FEV1/FVC ratio less than 0.7. For further details we refer to Gudmundsson et al. [3].

Magnetic resonance imaging. MR images were acquired on a single research-dedicated 1.5T Signa Twinspeed EXCITE system (General Electric Medical Systems, Waukesha, WI) using a multi-channel phased array head cap coil. The structural image protocol included a T1-weighted three dimensional spoiled gradient echo (3D-SPGR) sequence (TE (time to echo), 8 ms; TR (time repetition), 21 ms; FA (flip angle), 30°; FOV (field of view), 240 mm; matrix, 256 × 256). Each volume consisted of 110 slices with 1.5 mm slice thickness and in-plane pixel size of 0.94 mm × 0.94 mm. A proton density (PD)/T2 - weighted fast spin echo (FSE) sequence (TE1, 22 ms; TE2, 90 ms; TR, 3220 ms; echo train length, 8; FA, 90°; FOV, 220 mm; matrix, 256 × 256), and a fluid attenuated inversion recovery (FLAIR) sequence (TE, 100 ms; TR, 8000 ms, inversion time, 2000 ms, FA, 90°; FOV, 220 mm; matrix, 256 × 256). These latter two sequences were acquired with 3-mm thick slices and in-plane pixel size of 0.86 mm × 0.86 mm. All images were acquired to give full brain coverage and were localised at the AC/PC commissure line. Details on the quantification of brain volumes and white matter hyperintensities can be found elsewhere [4,5].

Analytic sample

Spirometric measurements and brain MRI variables were available for 1,655 participants (1,655 for white matter lesions). 123 participants were excluded because of structural abnormalities of the brain (e.g., large cysts, brain tumors) or history of stroke. The final analytic sample comprised data of 1,655 participants (1,655 for white matter lesions).

Funding

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The Atherosclerosis Risk in Communities (ARIC) Study

General information

The Atherosclerosis Risk in Communities (ARIC) study is a prospective epidemiologic investigation of the causes of atherosclerosis, its clinical consequences, and differences in cardiovascular risk factors, disease, and medical care by geography, race, sex, and time [1]. Initiated in 1987 with financial support from the National Heart, Lung, and Blood Institute (NHLBI), the study recruited 15,792 middle-aged (45-64 years) participants from four U.S. communities: Forsyth County, North Carolina; Jackson, Mississippi; suburban Minneapolis, Minnesota; and Washington County, Maryland [1]. The suburban Minneapolis, Washington County, and Forsyth participants represented the racial/ethnic mix of their community, with the former two comprised of White participants and the latter comprised of both Black and White participants. The Jackson field center recruited Black participants only.

This investigation used a subset of participants from the fifth examination (2011-2013) who underwent brain magnetic resonance imaging as part of the ARIC Neurocognitive study [2]. Participants considered for MRI scans included 1) all participants with a previous brain MRI from an ancillary study conducted in 2004-2006; 2) all individuals with cognitive impairment as evidenced by low Mini-Mental State Examination scores (<19 for Blacks and <21 for Whites) at the fifth clinic visit or low age-, race-, and education-adjusted z scores on at least 1 of 5 cognitive domains (failure on the clock reading test for visuospatial domain or z scores below −1.5 for memory, language, executive function, or attention domains) at the fifth visit accompanied by cognitive decline from prior visits (below the 10th percentile for change in the digit symbol substitution, delayed word recall, or word fluency test or below the 20th percentile for change on ≥2 of these tests); and 3) an age- and field center-stratified random sample of cognitively normal individuals. 1,977 participants had non-missing values of at least one brain MRI measure of interest at the fifth examination.

Data collection

Demographic variables (sex, race, and date of birth) were self-reported at the baseline visit (1987-1989). Standing height was measured at the fifth examination, while smoking status was obtained via self-report combining responses from interviews at the fifth visit and previous visits. Diabetes was determined from blood drawn or medication use reported at the fifth clinic visit;

participants were classified as diabetic if they had eight-hour fasting blood glucose values ≥ 126 mg/dL, non-fasting glucose values ≥200 mg/dL, or used oral medication or insulin for diabetes in the past two weeks. Spirometry was conducted during the fifth clinic visit, while brain imaging in a subset of fifth visit participants was scheduled for a subsequent visit.

Spirometry. Lung function measures were obtained from 4,673 participants during the fifth ARIC examination. The instruments and methods conformed to the combined spirometry guidelines published by the American Thoracic Society (ATS) and the European Thoracic Society (ERS) [3] and surpassed their accuracy and repeatability recommendations. Forced vital capacity (FVC) and forced expiration volume in one second (FEV1) were measured using the SensorMedics model 1022 dry-rolling seal volume spirometers (OMI, Houston, TX) and OMI software (version 5.05.11). The best FVC and FEV1 values from three acceptable maneuvers were chosen for each participant. The FEV1/FVC ratio was calculated from these measured values. The spirometry testing protocols were standardised across the four ARIC field centers, including daily calibration checks. Data collection and management were coordinated by a single pulmonary function reading center. For more details see [4].

Magnetic resonance imaging. The MRI scans were performed using 3T scanners at each study site (Maryland: Siemens Verio; North Carolina: Siemens Skyra; Minnesota: Siemens Trio; Mississippi: Siemens Skyra) using a standardised protocol [5]. All MRI images were analysed at a centralised location, namely the Mayo Clinic in Minnesota. The FreeSurfer imaging analysis software (version 5.1) was used to derive the regional grey matter volumes (including hippocampal volumes) and the estimated total intracranial volumes from the sagittal T1-weighted 3-D volumetric magnetisation-prepared rapid gradient-echo (MPRAGE; 1.2 mm slices) sequences. For this project, the total grey volume was derived as the sum of the four lobar volumes (frontal, parietal, temporal, and occipital) and the deep grey subcortical structure volumes (e.g., thalamus, caudate, putamen, globus pallidum) [6]. The total brain volume was estimated from the MPRAGE sequences using in-house methods [7,8]. The white matter hyperintensities volume was quantified from the axial T2 fluid-attenuated inversion recovery (FLAIR; 5mm slices) images using a semi-automated algorithm developed by the Mayo Aging and Dementia Imaging Research Laboratory [9].

Analytic sample

1,977 participants had non-missing values of at least one brain MRI measure of interest at the fifth examination. We excluded participants with race classified as neither black or white (N=6), MRI images acquired at the wrong field center (N=9), restrictions on data use (N=1), missing values of all spirometry measures (N=461), a history of stroke (N=37), multiple sclerosis (N=1), a brain tumor or cyst (N=1), missing values of covariates (N=83), or pulmonary function z-scores lying more than five standard deviations from the sample mean (N=13). The final analytic sample included 1,365 participants.

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Cardiovascular Health Study (CHS)

General information

The Cardiovascular Health Study is a population-based cohort study of risk factors for coronary heart disease and stroke in adults ≥65 years conducted across four field centers [1]. The original predominantly European ancestry cohort of 5,201 persons was recruited in 1989-1990 from random samples of the Medicare eligibility lists; subsequently, an additional predominantly African-American cohort of 687 persons was enrolled for a total sample of 5,888. The baseline examinations consisted of a home interview and a clinic examination that assessed not only traditional risk factors but also measures of subclinical disease, including carotid ultrasound, echocardiography, electrocardiography, and pulmonary function. The study conducted extensive annual clinical exams between 1989-1999 along with semi-annual phone calls and events adjudication.

Data collection

The spirometry and participant characteristic data used in these analyses were derived from the 1997 exams; cranial MRIs data is from scans conducted from 1997-1999. Diabetes was defined based on self-report. The study was approved by local institutional review boards and all participants provided informed consent.

Spirometry. Lung function examinations were conducted with 2,841 participants using a water-sealed spirometer (Survey I; Warren E. Collins, Braintree, MA). It was connected to an IBM PS2 model 30/286 personal computer using an eight-channel, 12-bit analog-to-digital converter. The software (S&M instruments, Doylestown, PA) assisted the technician with quality control of maneuvers, calculated the Pulmonary Function variables, suggested interpretations, printed reports, and compressed graphics data for transmission and archival storage [2]. The performance of this spirometry system was validated by third-party testing and found to meet American Thoracic Society standards [3].

The FVC maneuver was repeated up to eight times or until at least three acceptable and two reproducible FVC maneuvers were obtained, in accordance with ATS recommendations. Technicians were trained and certified prior to start of the study. Each week all test sessions were reviewed at the Pulmonary Function Reading Center by a single QC supervisor. Time zero of each maneuver was determined using the back extrapolation technique. The FEV1, FVC, peak

flow (FEFmax), back extrapolated volume, and forced expiratory time (FET) were all computed by standardised techniques, with resolutions of 10 mL volume, 10 mL/s flow, and 1 ms FET. The three acceptable FVC maneuvers variables with the highest sum of FVC plus FEV1 were stored by the spirometry system. The largest FEV1 and the largest FVC from the three stored acceptable FVC maneuvers were reported. For more details, see Enright et al. [4].

Magnetic resonance imaging. MRI scanning was completed at each of the four sites using 1.5 Tesla scanners. The scanning protocol included a 3-D volumetric T1 weighted Spoiled Gradient Recall (SPGR) sequence covering the whole brain (TE/TR = 5/25, flip angle = 40°, NEX = 1, slice thickness = 1.5 mm/0 mm interslice gap), with an in-plane acquisition matrix of $256 \times 256 \times 124$ image elements, 250×250 mm field of view and an in-plane voxel size of 0.98 mm3 [5–7]. T1-weighted MRI scans for 938 participants were processed with the image-processing pipeline FreeSurfer version 5.3.0, which is documented and freely available for download online (http://surfer.nmr.mgh.harvard.edu) [8]. The processing includes segmentation of the cerebral cortex and subcortical regions and calculation of total brain volume, gray matter volume, hippocampal volume (sum of left and right). FreeSurfer also gives an estimate of the total intracranial volume, which can be used to account for some of the variability between the study participants.

Analytic sample

Spirometric measurements and brain MRI variables were available for 821 participants. Analyses were limited to 776 participants without a history of stroke at the time of MRI; 2 others were subsequently excluded for outlier values for multiple MRI parameters. The final analytic sample comprised data of 774 participants.

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The Framingham Heart Study (FHS)

General information

The FHS is a three-generation, single-site, community-based, ongoing cohort study that was initiated in 1948 to investigate the risk factors for cardiovascular disease. It now comprises 3 generations of participants: the Original cohort followed since 1948 [1]; their Offspring and spouses of the Offspring (Gen 2), followed since 1971 [2]; and children from the largest Offspring families enrolled in 2000 (Gen 3) [3]; only the first 2 generations are being studied in this grant. The Original cohort enrolled 5,209 men and women who comprised two-thirds of the adult population then residing in Framingham, MA. Survivors continue to receive biennial examinations. The Offspring cohort comprises 5,124 persons (including 3,514 biological offspring) who have been examined approximately once every 4 years. The population of Framingham was largely of European descent in 1948 when the Original cohort was recruited. Two additional multiethnic samples, the older Omni and younger Omni2 were enrolled in 1990 and 2001 respectively and are followed in tandem with the Offspring and Gen 3 cohorts respectively [4]. All participants gave written informed consent. The study was approved by an ethics committee and complies with the declaration of Helsinki. Data used in our analysis come from the Exam 7, which that took place between 1998 and 2001.

Data collection

FHS participants undergo medical history, lifestyle, dietary, and physical activity questionnaires, phlebotomy, physical exam, ECG, blood biomarkers, urinalysis, and surveillance for CVD events and death. Spirometry measures were carried out during subsequent medical examinations. Participants were invited to undergo brain MRI starting in 1999. MRI images were initially obtained on a 1T (1999-2001), then a 1.5T Siemens Magnetom (2001-2013) and more recently on a 3T Siemens or Phillips MRI (2014 onwards). 3 rounds of MRI scans have been obtained, ~6 years apart, and include T1, T2, FLAIR, GRE sequences (5 mm, no gaps) and since 2009 also DTI. Since 2014 resting state fcMRI was added in a large subsample (900 of total ~4500 persons with multiple MRIs) [5–11].

Spirometry. For the pulmonary examinations, the variables FEV1 and FVC were assessed using spirometry based on a standardised protocol devised by the American Thoracic Society committee described previously by Culver et al. [12]. For FEV1 and FVC, spirometry was

performed three times with training of participants to exhale as hard and fast as possible. The highest FEV1 and FVC values from the three trials were used.

Magnetic resonance imaging. Participants underwent brain MRI examination on a 1.5T Siemens Magnetom Avanto scanner. We used 3D T1-weighted coronal spoiled gradient-recalled echo images and fluid-attenuated inversion recovery (FLAIR) sequences. The segmentation and quantification of white matter hyperintensities (WMH) were performed on a combination of FLAIR and 3D T1 images using a modified Bayesian probability structure based on a previously published method of histogram fitting [13]. The segmentation of gray matter volumes was based on an Expectation-Maximisation algorithm that iteratively refines its segmentation estimates to produce outputs that are most consistent with the input intensities from the native-space T1 images along with a model of image smoothness [14,15]. The segmentation was refined using a Markov Random Field model and an adaptive priors model [15]. Hippocampal volume was computed using a segmentation method that employs a standard atlas-based diffeomorphic approach [16], with the minor modification of label refinement. We further modified this methodology to include the EADC-ADNI harmonised hippocampal masks as previously described [17]. Total intracranial volume was derived from 3D T1 after removal of non-brain tissues. The skull is removed using an atlas-based method [18] followed by human quality control to provide generally minor cleanup when needed.

Analytic sample

Spirometric measurements and brain MRI variables were available for 1,758 participants (1,707 for white matter lesions). 38 participants were excluded because of structural abnormalities of the brain (e.g., large cysts, brain tumors) or history of stroke. The final analytic sample comprised data of 1,720 participants (1,669 for white matter lesions).

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The Rotterdam Study (RS)

General information

The Rotterdam Study (RS) is a prospective population-based cohort study comprising of 14,926 subjects aged 45 years or older. Details of this study have previously been published [1]. In brief, the study was initiated in 1990 with a study population of 7,983 participants aged ≥55 years, who were living in the Ommoord suburb of Rotterdam. The cohort was subsequently expanded twice, first in 1999 including an additional 3,011 individuals who had reached the eligible age or had moved into the study area, and again in 2005 with 3,932 individuals from the same area aged 45 or over. Participants partake in extensive interviews and examinations at a dedicated research facility approximately every 4 years. In addition, the entire cohort is continuously under surveillance for disease outcomes through linkage of electronic medical records with the study database. All participants gave written informed consent. The study was approved by the ethics committee of the Erasmus University Medical Center of Rotterdam and complies with the declaration of Helsinki. Data used in our analyses derive from baseline examinations, which took place between 2009 and 2013.

Data collection

Medical history and socio-demographic variables were assessed by standardized questionnaires during home interview. Spirometry measures, blood samples, and measurement of body height were carried out during routine examinations at the research center. Type 2 diabetes was defined as a fasting serum glucose level ≥7.0 mmol/L (126 mg/dL), or a nonfasting serum glucose level ≥11.1 mmol/L (200 mg/dL), and/or the use of blood glucose-lowering medication. MRI of the brain is part of the routine examination since 2005.

Spirometry. Pre-bronchodilator spirometry was performed by trained paramedical personnel using a Master Screen PFT Pro (Care Fusion, Houten, the Netherlands), which meets the American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines [2]. Forced spirometric manoeuvres were performed to assess forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV1). For more details on spirometry assessments, we refer to Loth et al. [3].

Magnetic resonance imaging. MRI of the brain was performed on a 1.5T scanner (General Electric Healthcare, Milwaukee, WI) using an 8-channel head coil. Imaging acquisition included

a high-resolution axial T1-weighted sequence, a fluid-attenuated inversion recovery sequence, a proton density–weighted sequence, and a T2*-weighted gradient echo sequence. Details about the sequences, preprocessing, and the classification algorithm have been described previously [4]. Total intracranial and tissue volumes and volume of white matter hyperintensities (WMHs) were quantified via automated tissue segmentation [5]. These segmentations were visually inspected and manually corrected if needed. Segmentation of the hippocampus was performed using FreeSurfer 6.1 [6].

Analytic sample

The current study includes all participants who underwent spirometric measurements and brain MRI between 2009 and 2014, during the 5th examination round of the first cohort, the 3rd examination of the second cohort, and the 2nd examination of the third cohort. Participants with structural abnormalities of the brain (e.g., large cysts, brain tumors, infarcts) were excluded if these interfered with the automated tissue segmentation. The final analytic sample comprised data of 3,857 participants (3,558 for hippocampal volume).

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The Study of Health in Pomerania (SHIP)

General information

The Study of Health in Pomerania (SHIP) is a prospective population-based cohort of adults from West Pomerania, a north-eastern region in Germany of approximately 220,000 inhabitants [1]. The data used in our analyses were derived from SHIP-Trend, a cohort initiated ten years after SHIP in the same region. In brief, from the total population of West Pomerania a two-stage stratified cluster sample of 8,016 adults between the ages of 20–79 years was drawn. A total of 4,420 individuals agreed to participate in the study. All participants gave written informed consent. The study was approved by the ethics committee of the University Medicine Greifswald and complies with the declaration of Helsinki. Data used in our analyses come from the baseline examinations, which took place between 2008 and 2011.

Data collection

Medical history and socio-demographic variables were assessed by standardised questionnaires during a computer-assisted face-to-face interview. Spirometry, taking of blood samples, and measurement of body height were carried out during subsequent medical examinations. Diabetes was defined either based on self-report, intake of anti-diabetic medication (ATC code A10), glycated hemoglobin $\geq 6.5\%$ (International Expert Committee 2009), or blood glucose ≥ 11.1 mmol/l (IDF-WHO 2006). MRI of the head was performed during a second visit.

Spirometry. Lung function examinations were conducted using a body plethysmograph equipped with a pneumotachograph (MasterScreen Body/Diff.; VIASYS Healthcare, JAEGER, Hoechberg, Germany), which meets American Thoracic Society (ATS) criteria [2]. All calibrations and tests were carried out in accordance with European Respiratory Society (ERS) and ATS recommendations [3]. The procedures were conducted with the subject in a sitting position and wearing a nose-clip. Forced spirometric manoeuvres were obtained to measure forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV1). At least three acceptable attempts at fulfilling reproducibility criteria for all variables according to the ATS/ERS guidelines were required (variability < 150 ml) [3,4]. For more details we refer to Gläser et al. [5].

Magnetic resonance imaging. T1-weighted and fluid-attenuated inversion recovery (FLAIR) scans of the head were obtained from 2,150 and 2,146 participants, respectively, with a 1.5 T Siemens Magnetom Avanto scanner (Siemens, Erlangen, Germany) [6]. The following parameters were used: T1: orientation=axial plane, TR=1,900 ms, TE=3.37 ms, flip angle 15 °, slice thickness=1 mm, and resolution 1 mm x 1 mm, FLAIR: orientation=axial plane, TR=5,000 ms, TE=325 ms, slice thickness=3 mm, and resolution 0.9 mm × 0.9 mm.

T1-weighted scans were processed with the image-processing pipeline FreeSurfer version 7.1, which is documented and freely available for download online (http://surfer.nmr.mgh.harvard.edu) [7]. The processing includes segmentation of the cerebral cortex and subcortical regions as well as calculation of total brain volume, gray matter volume, and hippocampal volume (sum of left and right hippocampal volume). FreeSurfer also gives an estimate of the total intracranial volume, which can be used to account for some of the variability between the study participants. After preprocessing and coregistration of T1-weighted and FLAIR scans, white matter lesions were segmented using the Brain Intensity AbNormality Classification Algorithm (BIANCA) [8].

Analytic sample

Spirometric measurements and brain MRI were available for 1,777 participants. 55 participants were excluded because of structural abnormalities of the brain (e.g., large cysts, brain tumors) or history of stroke. Clinical variables were incomplete for 2 participants. The final analytic sample comprised data of 1,720 participants.

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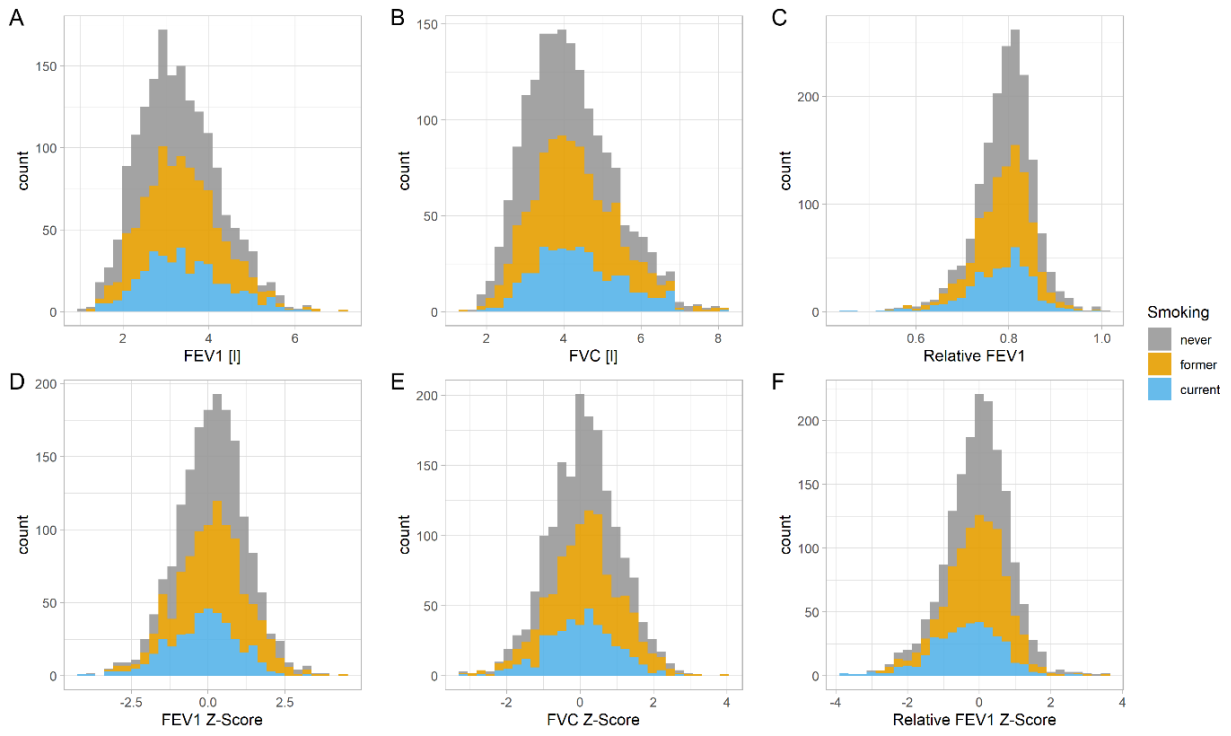
Supplementary Figure 1. Histograms of raw (A-C) and standardised (D-F) spirometry measurements in the SHIP sample (n=1,720).

Supplementary Table 1. Associations of spirometry measurements with hippocampal volume (in ml, HV) and brain volume (in ml, BV) in each study. Analyses were adjusted for age, sex, intracranial volume, body height, smoking status, and diabetes mellitus.

Outcome	Exposure	Study	N	Effect (95% CI)	Weight	p	
HV	FEV1	AGES	1644	0.027 (0.0047, 0.0499)	0.21	0.018	*
		ARIC	1365	0.023 (-0.0171, 0.0638)	0.07	0.257	
		CHS	772	0.046 (-0.0093, 0.1019)	0.03	0.103	
		FS	1675	0.010 (-0.0142, 0.0350)	0.18	0.407	
		RS	3850	0.032 (0.0143, 0.0496)	0.34	4.0E-4	***
		SHIP	1718	0.039 (0.0133, 0.0637)	0.17	0.003	**
	FVC	AGES	1644	0.024 (-0.0030, 0.0506)	0.20	0.082	.
		ARIC	1365	0.010 (-0.0334, 0.0531)	0.08	0.655	
		CHS	772	0.041 (-0.0215, 0.1042)	0.04	0.197	
		FS	1675	0.019 (-0.0088, 0.0467)	0.18	0.181	
		RS	3850	0.030 (0.0098, 0.0500)	0.35	0.004	**
		SHIP	1713	0.034 (0.0052, 0.0636)	0.16	0.021	*
	relative FEV1	AGES	1644	0.026 (-0.0004, 0.0515)	0.22	0.054	.
		ARIC	1365	0.022 (-0.0205, 0.0646)	0.10	0.310	
		CHS	772	0.052 (-0.0156, 0.1196)	0.05	0.132	
		FS	1675	-0.011 (-0.0394, 0.0173)	0.19	0.446	
		RS	3850	0.020 (-0.0012, 0.0413)	0.27	0.064	.
		SHIP	1715	0.037 (0.0058, 0.0687)	0.17	0.021	*
BV	FEV1	AGES	1644	5.329 (3.2895, 7.3691)	0.17	3.4E-7	***
		ARIC	1365	2.535 (0.1007, 4.9698)	0.14	0.041	*
		CHS	772	2.524 (-0.6603, 5.7073)	0.11	0.121	
		FS	1674	2.228 (1.1118, 3.3436)	0.24	9.5E-5	***
		RS	3850	5.615 (3.4090, 7.8219)	0.16	6.4E-7	***
		SHIP	1717	2.389 (0.6396, 4.1384)	0.19	0.008	**
	FVC	AGES	1644	5.600 (3.1778, 8.0222)	0.16	6.3E-6	***
		ARIC	1365	3.339 (0.7419, 5.9363)	0.15	0.012	*
		CHS	772	2.532 (-1.0675, 6.1307)	0.10	0.168	
		FS	1674	2.689 (1.4333, 3.9452)	0.25	2.9E-5	***
		RS	3850	5.742 (3.2195, 8.2654)	0.15	8.4E-6	***
		SHIP	1712	1.766 (-0.2636, 3.7953)	0.19	0.088	.
	relative FEV1	AGES	1644	3.757 (1.3983, 6.1156)	0.17	0.002	**
		ARIC	1365	-0.645 (-3.2081, 1.9186)	0.15	0.622	
		CHS	772	3.348 (-0.5229, 7.2182)	0.08	0.090	.
		FS	1674	0.880 (-0.4131, 2.1723)	0.28	0.183	
		RS	3850	2.469 (-0.1678, 5.1051)	0.14	0.067	.
		SHIP	1714	2.257 (0.0719, 4.4430)	0.18	0.043	*

FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity. Significance levels: *p<0.05, **p<0.01, ***p<0.001

Supplementary Table 2. Associations of spirometry measurements with gray matter volume (in ml, GMV) and white matter hyperintensities volume (in mm3, natural log-transformed, WMHV). Analyses were adjusted for age, sex, intracranial volume, body height, smoking status, and diabetes mellitus.

Outcome	Exposure	Study	N	Effect (95% CI)	Weight	p	
GMV	FEV1	AGES	1646	4.339 (2.6728, 6.0060)	0.14	3.7E-7	***
		ARIC	1365	1.562 (0.3500, 2.7735)	0.18	0.012	*
		CHS	772	1.855 (-0.0900, 3.8009)	0.12	0.062	.
		FS	1675	0.869 (-0.0366, 1.7749)	0.21	0.060	.
		RS	3850	2.194 (0.8896, 3.4983)	0.17	9.9E-4	***
		SHIP	1717	2.561 (1.4860, 3.6351)	0.19	3.2E-6	***
	FVC	AGES	1646	3.573 (1.5918, 5.5543)	0.09	4.2E-4	***
		ARIC	1365	1.617 (0.3218, 2.9116)	0.19	0.015	*
		CHS	772	1.222 (-0.9803, 3.4234)	0.07	0.277	
		FS	1675	1.193 (0.1732, 2.2124)	0.29	0.022	*
		RS	3850	2.108 (0.6169, 3.5993)	0.15	0.006	**
		SHIP	1712	2.339 (1.0915, 3.5871)	0.21	2.5E-4	***
	relative FEV1	AGES	1646	4.577 (2.6588, 6.4953)	0.15	3.2E-6	***
		ARIC	1365	0.282 (-0.9950, 1.5599)	0.18	0.665	
		CHS	772	3.941 (1.5863, 6.2954)	0.13	0.001	**
		FS	1675	0.214 (-0.8307, 1.2590)	0.19	0.688	
		RS	3850	0.976 (-0.5803, 2.5321)	0.17	0.219	
		SHIP	1714	1.547 (0.1984, 2.8964)	0.18	0.025	*
WMHV	FEV1	AGES	1642	-0.069 (-0.1029, -0.0355)	0.18	6.0E-5	***
		ARIC	1365	-0.035 (-0.0753, 0.0047)	0.17	0.084	.
		CHS	772	-0.094 (-0.1414, -0.0463)	0.15	1.2E-4	***
		FS	1675	0.019 (-0.0219, 0.0589)	0.17	0.369	
		RS	3850	-0.030 (-0.0551, -0.0057)	0.21	0.016	*
		SHIP	1718	-0.040 (-0.0976, 0.0175)	0.13	0.173	
	FVC	AGES	1642	-0.085 (-0.1247, -0.0448)	0.19	3.4E-5	***
		ARIC	1365	-0.060 (-0.1025, -0.0172)	0.17	0.006	**
		CHS	772	-0.084 (-0.1375, -0.0296)	0.14	0.002	**
		FS	1675	0.005 (-0.0404, 0.0509)	0.16	0.821	
		RS	3850	-0.055 (-0.0836, -0.0273)	0.24	1.2E-4	***
		SHIP	1713	-0.064 (-0.1304, 0.0028)	0.10	0.061	.
	relative FEV1	AGES	1642	-0.042 (-0.0809, -0.0032)	0.18	0.034	*
		ARIC	1365	0.031 (-0.0112, 0.0731)	0.17	0.150	
		CHS	772	-0.114 (-0.1718, -0.0560)	0.16	1.2E-4	***
		FS	1675	0.030 (-0.0161, 0.0769)	0.17	0.201	
		RS	3850	0.022 (-0.0078, 0.0510)	0.19	0.150	
		SHIP	1715	0.052 (-0.0197, 0.1241)	0.14	0.155	

FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity. Significance levels: *p<0.05, **p<0.01, ***p<0.001