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Resistance to developing brain pathology due to vascular risk factors: the role of educational attainment

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ABSTRACT

Brain pathology develops at different rates between individuals with similar burden of risk factors, possibly explained by brain resistance. We examined if education contributes to brain resistance by studying its influence on the association between vascular risk factors and brain pathology.

In 4111 stroke-free and dementia-free community-dwelling participants (62.9 ± 10.7 years), we explored the association between vascular risk factors (hypertension and the Framingham Stroke Risk Profile [FRSP]) and imaging markers of brain pathology (markers of cerebral small vessel disease and brain volumetry), stratified by educational attainment level.

Associations of hypertension and FSRP with markers of brain pathology were not significantly different between levels of educational attainment. Certain associations appeared weaker in those with higher compared to lower educational attainment, particularly for white matter hyperintensities (WMH). Supplementary residual analyses showed significant associations between higher educational attainment and stronger resistance to WMH among others.

Our results suggest a role for educational attainment in resistance to vascular brain pathology. Yet, further research is needed to better characterize determinants of brain resistance.

1. Introduction

Vascular brain pathology is one of the leading causes of cognitive decline, stroke and dementia in old age (Gorelick et al., 2011; Pantoni, 2010a). Cerebral small vessel disease (CSVD) and changes in brain volumes can indicate vascular brain pathology and can be measured by magnetic resonance imaging (MRI). Noninvasive imaging markers to measure CSVD are white matter hyperintensities (WMH), lacunes, cerebral microbleeds and perivascular spaces (PVS). Interestingly, the extent of vascular brain pathology does not directly correspond to the severity of cognitive decline across individuals (Jokinen et al., 2016; Pinter et al., 2015; Zieren et al., 2013). Some individuals seem less susceptible to the functional effects of brain damage than others with a similar extent of pathology. This better-than-expected cognitive performance despite vascular brain pathology is known as resilience. Similarly, people with the same amount of cardiovascular risk factors will not develop the same extent of vascular brain pathology. The difference in susceptibility to developing brain pathology is known as resistance (Fig. 1) (Arenaza-Urquijo and Vemuri, 2018).

This framework of resilience and resistance is built upon other existing concepts including cognitive reserve (Stern, 2009) and

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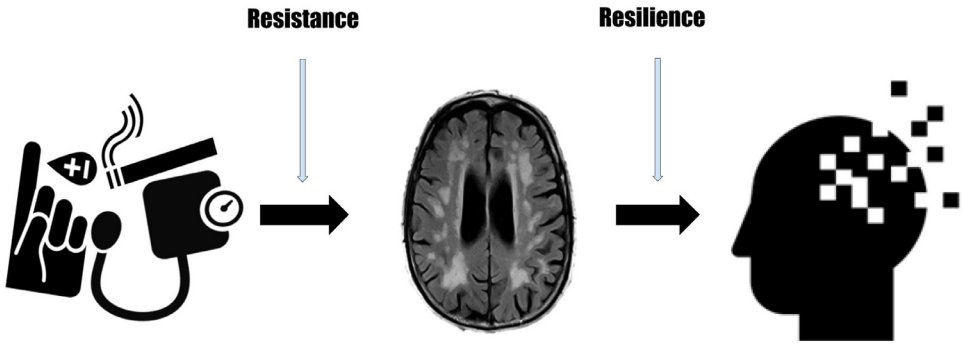

Fig. 1. Resistance and resilience Visual representation of resistance and resilience. Resistance modulates the relation between risk factors and brain pathology, whereas resilience modulates the relation between brain pathology and cognitive performance.

brain maintenance (Nyberg et al., 2012) among others. The aim is to unite different concepts and terminologies in a single framework. The nomenclature of resilience is used in the context of coping with brain pathology. Cognitive reserve is one mechanism of resilience which refers to the adaptability of cognitive processes that helps explain better-than-expected cognitive abilities despite brain aging or pathology. The nomenclature of resistance is used in the context of avoiding brain pathology. Brain maintenance is one mechanism of resistance which is defined as reduced accumulation of age-related brain changes and pathology over time. Educational attainment has been widely studied in the context of resilience and is often used as a proxy for cognitive reserve (Meng and D'Arcy, 2012; Stern, 2012). However, as educational attainment is mostly obtained in early adulthood, it could also be involved in the resistance to developing vascular brain disease. Little research has focused on resistance to vascular brain pathology, while more insight in this topic might lead to more possibilities for disease prevention. So far, recent studies solely investigated the direct effect of educational attainment on vascular brain pathology and did not explore the possible interaction of educational attainment with vascular risk factors on its association with vascular brain pathology (Brayne et al., 2010; Del Ser et al., 1999; Gianaros et al., 2013; Jung et al., 2018; Latimer et al., 2019; Noble et al., 2013; Pettigrew et al., 2020). Moreover, these studies did not include all well-known markers of vascular brain pathology, were limited in size, had under-represented healthy individuals or did not adjust for vascular risk factors which could contribute to vascular brain pathology. However, within a recent study in community-dwelling individuals with equal burden of cardiovascular risk factors, those with a higher level of education had a lower presence of moderate to severe CSVD compared to those without education (Field et al., 2016). Though a certain mechanism for resistance seems present in aforementioned study, this might not be captured by only studying the direct effect of different educational categories on vascular brain pathology markers.

Several factors like aging, hypertension, smoking, body mass index (BMI), diabetes, and dyslipidemia have been related to vascular brain pathology such as CSVD (Abraham et al., 2016; Jorgensen et al., 2018; Ostergaard et al., 2016; Pantoni, 2010b). Moreover, APOE -ε4 carriership, the strongest genetic risk factor for Alzheimer's Disease, also effects the risk of cardiovascular disease and vascular brain pathology (Belloy et al., 2019; Ingala et al., 2020). Of all cardiovascular risk factors, hypertension is consistently shown to have the strongest association with vascular brain pathology (Cannistraro et al., 2019). Furthermore, various vascular risk factors have previously been combined into a validated composite measure, namely the Framingham Stroke Risk Profile (FSRP) (Wolf et al., 1991). This measure has shown to be valuable in quantifying these factors for the risk of stroke and also to identify participants with poorer cognitive function and smaller brain volumes (Seshadri et al., 2004).

To further elucidate which factors influence resistance to brain pathology in a population-based study, we investigated the modifying effect of education on development of brain pathology due to vascular risk factors as measured by imaging markers of CSVD and brain volumes in the Rotterdam Study. We hypothesized that, compared to lower educational attainment, higher educational attainment attenuates the association between risk factors and brain pathology.

2. Methods

2.1. Study population

This study is embedded within the Rotterdam Study, an ongoing population-based cohort study aimed at investigating determinants of age-related diseases (Ikram et al., 2020). In brief, the original cohort started in 1990 (n = 7983) and was expanded in 2000 (n = 3011) and 2005 (n = 3932). Research visits take place every 3–4 years and consist of a home interview and multiple visits to the research center. The core Rotterdam Study protocol included structural brain magnetic resonance imaging (MRI) from 2005 onward (Ikram et al., 2015). The current study included 5079 eligible participants who underwent MRI between 2005 and 2014. Participants with incomplete or insufficient quality of MRI (n = 266), missing ratings for CSVD markers (n = 554) or MRI-defined cortical infarcts were excluded (n = 62). Moreover, participants with prevalent stroke, dementia or incomplete follow-up of these diseases (n = 86) were excluded. In total, 4111 participants were included in this study (Fig. 2).

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). All participants provided written informed consent to participate in the study and to have their information obtained from treating physicians.

2.2. Measurements

2.2.1. Educational attainment

Educational attainment was assessed on the baseline interview, asking participants about their highest level of completed education. These levels of education were further classified into three categories: lower education (primary, unfinished secondary and lower vocational), intermediate education (secondary or intermediate vocational education) and higher education (higher vocational education or university).

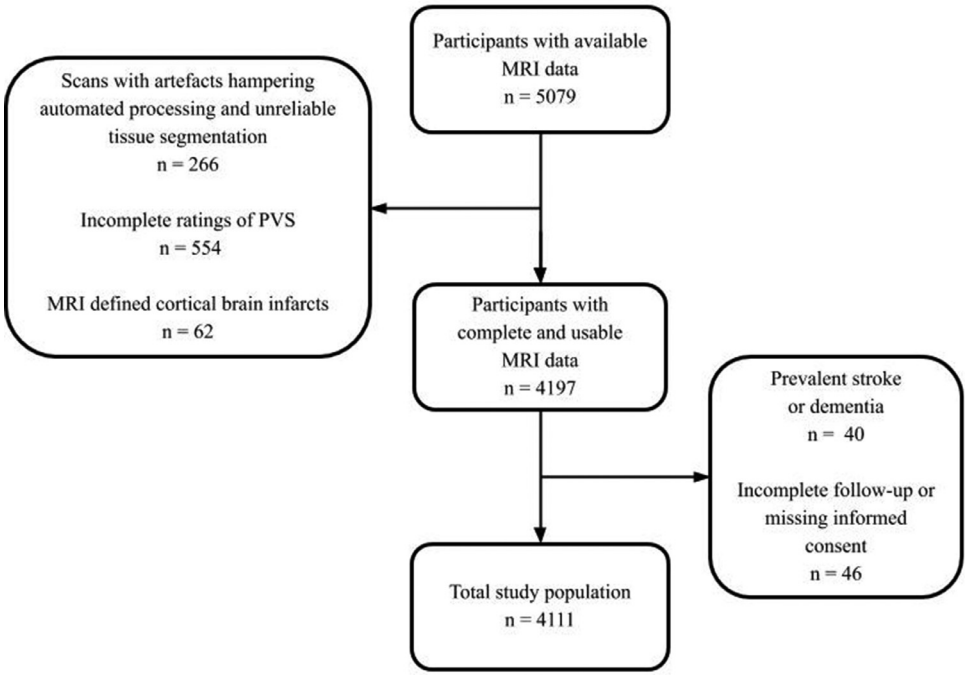

Fig. 2. Flowchart. A flowchart of the inclusion of participants with usable MRI scans. Abbreviations: MRI, magnetic resonance imaging; PVS, perivascular spaces.

2.2.2. Cardiovascular risk factors

Participants were interviewed and underwent laboratory and physical examinations during research center visits preceding brain MRI. Data regarding demographics, cardiovascular, and genetic risk factors were collected. Blood pressure was measured twice in sitting position at the right arm, and the average of these two measurements was used. Medication use, including blood pressure lowering medication, lipid lowering medication and antidiabetics, was assessed by interview. Hypertension was defined as a blood pressure >140/90 mm Hg or the use of blood pressure lowering medication (European Society of Hypertension-European Society of Cardiology Guidelines, 2003). The FSRP incorporated age, sex, history of cardiovascular disease, atrial fibrillation, left ventricular hypertrophy, diabetes mellitus, blood pressure-lowering medication, systolic blood pressure, and smoking status (Wolf et al., 1991). As previous literature showed no improvement of the revised FSRP over the original one, the latter was used in this study (Bos et al., 2017). According to standardized definitions, we assessed atrial fibrillation and prevalent coronary heart disease (defined as history of myocardial infarction or percutaneous or surgical revascularization procedure) (Leening et al., 2012). A Sokolow-Lyon voltage ≥3.5 mV for the amplitude of SV1and maximum of RV5 or RV6 defined left ventricular hypertrophy. Diabetes was defined as the use of antidiabetics, a fasting serum glucose level ≥7 mmol/L or a non-fasting glucose level ≥11.1 mmol/L. Total cholesterol was measured in serum in mmol/L (Gianaros et al., 2013). Smoking status (current, former, never) was assessed by interview. BMI was computed using the height (in cm) and weight (in kg) (kg/m^2). *APOE-ε4* carrier status was determined by polymerase chain reaction on coded DNA samples (Wenham et al., 1991).

2.2.3. MRI acquisition

Multisequence brain MRI was performed on a single 1.5T MRI scanner (GE Signa Excite, General Electric Healthcare, Milwaukee, USA). Imaging included T1-weighted, proton density-weighted, fluid-attenuated inversion recovery (FLAIR) and T2*-weighted gradient-recalled-echo sequences. The detailed imaging protocol can be found elsewhere (Ikram et al., 2015). Time between measurement of cardiovascular factors and brain markers was on average 3 months [interquartile range: 2–6 months].

2.2.4. Assessment of CSVD score

Trained research physicians rated all brain MRI scans for presence, number, and location of cortical infarcts, lacunes and microbleeds (Ikram et al., 2015). Subcortical lesions ≥3 mm and ≤15 mm in size with signal intensity similar to cerebrospinal fluid (CSF) on all sequences, and a hyperintense rim on FLAIR when located supratentorially were classified as lacunes. Focal round to ovoid areas <10 mm of very low signal intensity on T2*-weighted imaging were rated as microbleeds. Linear, ovoid-, or round-shaped hyperintensities of ≥1 mm and <3 mm were defined as PVS and counted in four regions on proton density-weighted images (Adams et al., 2015). These regions consisted of the centrum semiovale (predefined slice 1 cm above the uppermost part of the lateral ventricles), basal ganglia (predefined slice with the anterior commissure), and for hippocampi and midbrain all PVS were counted in the anatomical areas. PVS were categorized in a validated visual rating scale of 0 to 4, defined as 0 = no PVS; 1 ≤ 10 PVS; 2 = 11-20 PVS; 3 = 21-40 PVS and 4 ≥ 40 PVS (Doubal et al., 2010).

These CSVD markers were assessed individually and as a composite outcome (Yilmaz et al., 2018). The composite outcome, defined as the CSVD score, included the presence of (1) WMH burden in third or fourth quartiles, calculated by dividing WMH by intracranial volume and computing quartiles; (2) ≥1 lacune(s); (3) ≥1 microbleeds; and (4) ≥11 PVS in the basal ganglia. One point was awarded for the presence of each of these markers.

2.2.5. Assessment of volumetric brain markers

For tissue segmentation, images were segmented into CSF, gray matter, normal appearing white matter (Vrooman et al., 2007), and WMH (de Boer et al., 2009) using automatic processing algorithms. Total brain volume was computed by the sum of gray matter, normal appearing white matter, and WMH volumes. White matter was

the sum of normal appearing white matter and WMH volumes. Supratentorial intracranial volume, as a proxy for head size, was calculated by summing CSF volumes to the total brain volume. Hippocampal volume was obtained by processing T1-weighted MR images with FreeSurfer (version 6.0) and subsequently we summed the volumes of the left and right hippocampi (Fischl et al., 2004).

2.3. Statistical analysis

WMH and the FSRP score were natural log-transformed due to their skewed distribution. Volumetric brain measures and the FSRP score were standardized to Z-scores and modeled continuously. Additionally, FSRP score was dichotomized into low (below and including mean) and high (above mean) scores to facilitate comparison with hypertension. The presence of hypertension, lacunes, and microbleeds were modeled dichotomously. PVS and CSVD score were treated as count data, and analyzed with generalized linear models, with a negative binomial distribution for PVS and a Poisson distribution for CSVD score. Because of small numbers in categories 3 and 4 of the CSVD score, these were combined into one category. Missing variables ranged from 0.07% for BMI to 2.4% for left ventricular hypertrophy and were imputed 10 times with 20 iterations using chained equations (MICE) (van Buuren and Groothuis-Oudshoorn, 2011). The estimates from the models were pooled subsequently (Rubin, 1987).

Differences in baseline characteristics between groups of educational levels (low, intermediate, and high) were assessed using $\chi 2$ test for categorical variables with normal distributions. Continuous variables were tested with one-way analysis of variance (ANOVA), or with a Kruskal Wallis test for non-normally distributed data.

We investigated the modifying role of education on the association between hypertension or FSRP and brain pathology on MRI using multiple linear regression models for the continuous outcomes, and logistic regression models for the categorical outcomes, stratified by education level. To control for confounding we constructed 2 adjustment models. In the first model, we adjusted for age, sex, and additionally ICV for the volumetric outcomes. Further, in model 2 with hypertension as determinant of interest, we adjusted for other vascular risk factors (cholesterol, smoking, diabetes mellitus, BMI, *APOE*-ε4). For model 2 with FSRP as determinant of interest, we adjusted for vascular risk factors that were not already included in the FSRP score (cholesterol, BMI, *APOE*-ε4). Nonlinear effects of age were assessed by adding natural cubic splines with increasing degrees of freedom. As a result, splines of age with 2 knots were used in all models. Additionally, interaction effects between FSRP and educational attainment, and hypertension and educational attainment were modeled to test effect differences between educational levels.

Sensitivity analyses

As a sensitivity analysis all analyses were performed after excluding participants with a history of cardiovascular disease (n = 281). To test the robustness of our results, we applied an alternative supplementary analysis which has been established in the cognitive reserve literature (Reed et al., 2010). Resistance was defined as lower than expected brain pathology due to vascular risk factors according to the theoretical framework of Arenaza-Urquijo and Vemuri (2018, 2020). As a proxy for resistance, we extracted the residuals from model 2 which quantify the unexplained variance in brain pathology after cardiovascular risk factors and other covariates are accounted for. These residuals were multiplied by −1 for WMH, lacunar infarcts, CSVD and PVS so that higher residuals indicate lower than expected pathology. We then tested directly whether higher educational attainment is associated with a higher proxy measure of resistance. For these analyses, categorical outcomes were modeled with a linear regression to represent prevalence of the outcome instead of risks.

All analyses were conducted using R statistical software packages (version 3.5.1), we considered the significance threshold $p < 0.05$ (R Core Team, 2018)

3. Results

Population characteristics are shown in Table 1. The mean age of the 4111 participants was 62.7 years (SD: 10.5), and 55.7% were women. Nearly half of the participants had an intermediate education level, 28.0% had a lower education and 23.8% a higher education. Almost all characteristics were significantly different between the higher educated and the lower or intermediate educated, except for total cholesterol, number of smokers, and presence of lacunes. Compared to the lower education group, the higher education group was 5.8 years younger, had fewer females (42.4% vs. 67.9%), and a significantly lower FSRP (median 0.06 vs. 0.09). Moreover, the high educated had a lower burden of vascular brain pathology and larger brain volumes compared to those with a lower education.

3.1. Hypertension and CSVD markers

Overall, hypertension was significantly associated with WMH (β = 0.20, 95% CI 0.15; 0.25), lacunes (odds ratio [OR] = 1.55, 95% CI 1.08; 2.25) and CSVD score (rate ratio [RR] = 1.25, 95% CI 1.14; 1.36) as shown in Supplementary Table 1. The associations between hypertension and individual or combined CSVD markers did not differ for different levels of educational attainment (Table 2). However, the effect of hypertension on WMH was most pronounced in those with a lower education (β = 0.26, 95% CI 0.16; 0.37), compared to those with an intermediate education (β = 0.16, 95% CI 0.09; 0.23) or higher education (β = 0.19, 95% CI 0.10; 0.28), albeit not significantly different (Fig. 3A and Supplementary Table 1). Similar results were found for lacunes, with a slightly higher OR in persons with lower education (OR = 1.79, 95% CI 0.87; 3.71) compared to intermediate (OR = 1.73, 95% CI 0.98; 3.03) or higher education (OR = 1.14, 95% CI 0.58; 2.27) (Fig. 3C and Supplementary Table 1). Risk estimates of microbleeds were not significantly lower in individuals with hypertension and an intermediate education (OR = 0.97, 95% CI 0.73; 1.31) in comparison to individuals with hypertension and a lower education (OR = 1.31, 95%CI 0.90; 1.90). In contrast, risk estimates of the association between hypertension and microbleeds were higher in participants with a higher education level (OR = 1.57, 95%CI 1.02; 2.41) than in those with lower educational levels, albeit nonsignificant (Fig. 3C and Supplementary Table 1). Similarly, risk estimates for both perivascular spaces and the CSVD score were slightly lower in individuals with hypertension and an intermediate educational attainment and higher in those with a higher educational attainment, compared to those with a lower educational attainment (Fig. 3B and Supplementary Table 1).

3.2. FSRP and CSVD markers

Overall, FSRP score was significantly associated with all the individual and combined CSVD markers (Fig. 4 and Supplementary Table 2). The stratified effects of FSRP score on WMH, lacunes, and microbleeds were similar to those of hypertension (Supplementary Table 2). Interaction effects of education with FSRP score on CSVD markers were not significant, except for PVS count (p = 0.001 for intermediate vs. lower education and p = 0.022 for higher versus lower education, Table 2). Participants with a higher education had

Table 1
Characteristics of the study population grouped by education (N = 4111), average over 10 imputed datasets

Characteristics	Lower education(N = 1151)	Intermediate education(N = 1983)	Higher education(N = 977)	
Age, years	65.6 ± 10.8	62.5 ± 10.4	59.8 ± 9.4	<0.001[a,b]
Female sex, n	782 (67.9%)	1093 (55.1%)	414 (42.4%)	<0.001[a,b]
Hypertension, n	774 (67.2%)	1208 (60.9%)	499 (51.1%)	<0.001[a,b]
Total cholesterol, mmol/L	5.6 ± 1.1	5.6 ± 1.1	5.5 ± 1.0	0.93[a], 0.82[b]
Smoking				
Never	365 (31.7%)	603 (30.4%)	316 (32.3%)	0.01[a], 0.04[b]
Former	512 (44.5%)	981 (49.5%)	478 (48.9%)	
Current	274 (23.8%)	399 (20.1%)	183 (18.7%)	
Diabetes mellitus, n	127 (11.0%)	164 (8.3%)	73 (7.5%)	0.01[a,b]
BMI, kg/m^2	27.9 ± 4.3	27.5 ± 4.1	26.7 ± 3.7	0.02[a], <0.001[b]
APOE-ε4 carrier, n*	344 (29.9%)	580 (29.2%)	312 (31.9%)	0.69[a], 0.21[b]
FSRP (median, [IQR])	0.09 [0.04–0.20]	0.07 [0.04 - 0.16]	0.06 [0.03–0.12]	<0.001[a,b]
CSVD markers				
WMH, mL (median, [IQR])	3.3 [1.9–7.4]	2.7 [1.5–5.3]	2.4 [1.5–4.3]	<0.001[a,b]
Lacunes, n	73 (6.3%)	116 (5.8%)	54 (5.5%)	0.57[a], 0.43[b]
Microbleeds, n	266 (23.1%)	337 (17.0%)	147 (15%)	<0.001[a,b]
PVS count (median, [IQR])	3 [1–5]	3 [1–5]	3 [1–4]	0.24[a], 0.01[b]
CSVD score				
0	374 (32.5%)	889 (44.8%)	472 (48.3%)	<0.001[a,b]
1	539 (46.8%)	784 (39.5%)	385 (39.4%)	
2	200 (17.4%)	259 (13.1%)	103 (10.6%)	
3–4	38 (3.3%)	51 (2.6%)	17 (1.7%)	
Brain volumes				
Total brain volume, mL	911 ± 99	944 ± 97	979 ± 96	<0.001[a,b]
Intracranial volume, mL	1107 ± 112	1143 ± 114	1178 ± 114	<0.001[a,b]
Gray matter volume, mL	517 ± 53	532 ± 52	550 ± 55	<0.001[a,b]
Hippocampal volume, mL*	6.5 ± 0.7	6.7 ± 0.7	7.0 ± 0.7	<0.001[a,b]
NAWM volume, mL	387 ± 62	406 ± 59	425 ± 58	<0.001[a,b]

Key: BMI, body mass index; CSVD, cerebral small vessel disease; FSRP, Framingham Stroke Risk Profile; ; NAWM, normal appearing white matter; PVS, perivascular spaces; WMH, white matter hyperintensities.
*Imputed values are means (standard deviation) or numbers (valid percentages). FSRP, WMH and PVS count are shown in median and interquartile range with separate quartile ranges. Missing values; Hippocampal volume (41 for lower education, 72 for intermediate education, 28 in higher education), APOE carrier (29 for lower education, 50 for intermediate education, 19 in higher education).
[a] Intermediate compared to low education.
[b] High compared to low education.

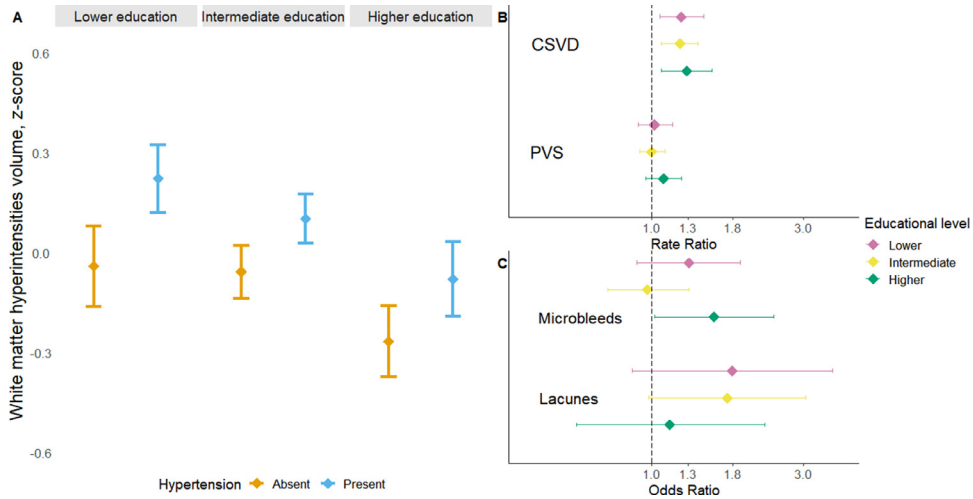

Fig. 3. The association between hypertension and vascular brain pathology stratified by educational attainment level. Continuous values are depicted as adjusted means. For the count values, rate ratios (RR) are depicted, and for the categorical variables, odds ratios (OR) are depicted. Values are adjusted for age, sex, intracranial volume (for white matter hyperintensities), presence of *APOE*-ε4, body mass index, diabetes mellitus, smoking and total cholesterol. Abbreviations: CSVD, cerebral small vessel disease; PVS, perivascular spaces.

a significantly stronger association between FSRP score and PVS count (RR = 1.15, 95%CI 1.03; 1.29), compared to participants with an intermediate education (RR = 1.06, 95% CI 0.98; 1.14) or lower education (RR = 1.02, 95% CI 0.92; 1.12). Furthermore, the association between FSRP score and CSVD score was slightly lower in those with a higher education (RR = 1.16, 95% CI 0.99; 1.35) than in those with a lower education (RR = 1.20, 95% CI 1.06; 1.36), while this association with hypertension was slightly higher in the higher education group.

Table 2
Interaction terms between education and vascular risk factor on brain pathology

Vascular brain pathology								
	White matter hyperintensities, z-score				**Lacunes**			
	Hypertension		**FSRP**		**Hypertension**		**FSRP**	
Interaction with education (vs low)	Adjusted mean difference (95%CI)	*p*-value	Adjusted mean difference (95%CI)	*p*-value	Odds ratio (95%CI)	*p*-value	Odds ratio (95%CI)	*p*-value
Intermediate	−0.03 (−0.14; 0.07)	0.53	0.02 (−0.04; 0.07)	0.59	1.16 (0.50; 2.71)	0.74	1.14 (0.80; 1.63)	0.48
High	0.00 (−0.13; 0.12)	0.18	0.03 (−0.03; 0.09)	0.36	0.69 (0.28; 1.69)	0.42	0.82 (0.54; 1.24)	0.35
	Microbleeds				**Perivascular spaces**			
	Hypertension		**FSRP**		**Hypertension**		**FSRP**	
Interaction with education (vs. low)	Odds ratio (95%CI)	*p*-value	Odds ratio (95%CI)	*p*-value	Relative risk (95%CI)	*p*-value	Relative risk (95%CI)	*p*-value
Intermediate	0.75 (0.49; 1.14)	0.18	0.89 (0.73; 1.08)	0.24	1.09 (0.95; 1.25)	0.22	1.11 (1.04; 1.18)	0.001
High	1.13 (0.68; 1.89)	0.63	1.05 (0.82; 1.35)	0.70	1.13 (0.96; 1.32)	0.14	1.10 (1.01; 1.18)	0.02
	CSVD score							
	Hypertension		**FSRP**					
Interaction with education (vs. low)	Relative risk (95%CI)	*p*-value	Relative risk (95%CI)	*p*-value				
Intermediate	1.08 (0.89; 1.30)	0.45	1.07 (0.98; 1.17)	0.11				
High	1.09 (0.87; 1.36)	0.44	1.05 (0.94; 1.16)	0.38				
Brain volumes								
	Total brain volume, z-score				**White matter volume, z-score**			
	Hypertension		**FSRP**		**Hypertension**		**FSRP**	
Interaction with education (vs. low)	Adjusted mean difference (95%CI)	*p*-value	Adjusted mean difference (95%CI)	*p*-value	Adjusted mean difference (95%CI)	*p*-value	Adjusted mean difference (95%CI)	*p*-value
Intermediate	−0.02 (−0.06; 0.03)	0.40	−0.01 (−0.03; 0.01)	0.30	0.01 (−0.07; 0.09)	0.81	0.01 (−0.03; 0.04)	0.68
High	0.00 (−0.05; 0.06)	0.88	−0.03 (−0.05; 0.00)	0.045	0.02 (−0.07; 0.11)	0.73	−0.03 (−0.08; 0.01)	0.17
	Gray matter volume, z-score				**Total hippocampal volume, z-score**			
	Hypertension		**FSRP**		**Hypertension**		**FSRP**	
Interaction with education (vs low)	Adjusted mean difference (95%CI)	*p*-value	Adjusted mean difference (95%CI)	*p*-value	Adjusted mean difference (95%CI)	*p*-value	Adjusted mean difference (95% CI)	*p*-value
Intermediate	−0.04 (−0.11; 0.03)	0.24	−0.03 (−0.06; 0.01)	0.11	0.01 (−0.09; 0.11)	0.87	−0.02 (−0.07; 0.03)	0.49
High	−0.01 (−0.09; 0.07)	0.81	−0.01 (−0.05; 0.03)	0.57	0.11 (−0.01; 0.22)	0.08	−0.01 (−0.07; 0.05)	0.76

Missing values; APOE carrier (29 for lower education, 50 for intermediate education, 19 in higher education).
Key: CI, confidence interval; CSVD, cerebral small vessel disease; FSRP, Framingham stroke risk profile.
Models: ~ hypertension/FSRP *education + age + sex + intracranial volume (for brain volumes) + smoking (for hypertension) + diabetes mellitus (for hypertension) + cholesterol + BMI + *APOE-ε4*.

3.3. Hypertension and volumetric brain measures

As shown in Fig. 5 and Supplementary Table 3, hypertension was significantly associated with total brain volume (β = −0.03, 95% CI −0.05; −0.01), white matter volume (β = −0.04, 95% CI −0.08; −0.01) and total hippocampal volume (β = −0.06, 95% CI −0.11; −0.02). This association did not differ for different levels of educational attainment (Table 2). Nonetheless, the association between hypertension and hippocampal volume was lower in the higher education group (β = 0.02, 95% CI −0.08; 0.11) compared to the lower education group (β = −0.11, 95% CI −0.20; −0.02) and intermediate education group (β = −0.08, 95% CI −0.15; −0.01), albeit insignificantly (Supplementary Table 3). Similar subtle differences were observed between education strata for total brain volume (β = −0.03, 95% CI −0.07; 0.01 for low education, β = 0.00, 95% CI −0.04; 0.05 for high education) and white matter volume (β = −0.06 for low education, 95% CI −0.13; 0.01, β = 0.00, 95% CI −0.08; 0.08 for high education), whereas limited difference was seen between education strata for gray matter volume (β = 0.01 for low education, 95% CI −0.01; 0.07, β = 0.00, 95% CI −0.07; 0.07 for high education).

3.4. FSRP and volumetric brain measures

FSRP score was significantly associated with total brain volume (β = −0.02, 95% CI −0.04; −0.01) and total hippocampal volume (β = −0.05, 95% CI −0.09; −0.01), as seen in Fig. 6 and Supplementary Table 3. The associations between FSRP and brain volumes did not differ significantly between levels of educational attainment, except for total brain volume (p = 0.01 for higher compared to lower educational level, Table 2). The association between FSRP and total brain volume was significantly lower in lower (β = −0.02, 95% CI −0.05; 0.01) compared to higher educational levels (β = 0.01, 95% CI −0.05; 0.03), as seen in Fig. 6A and Supplemen-

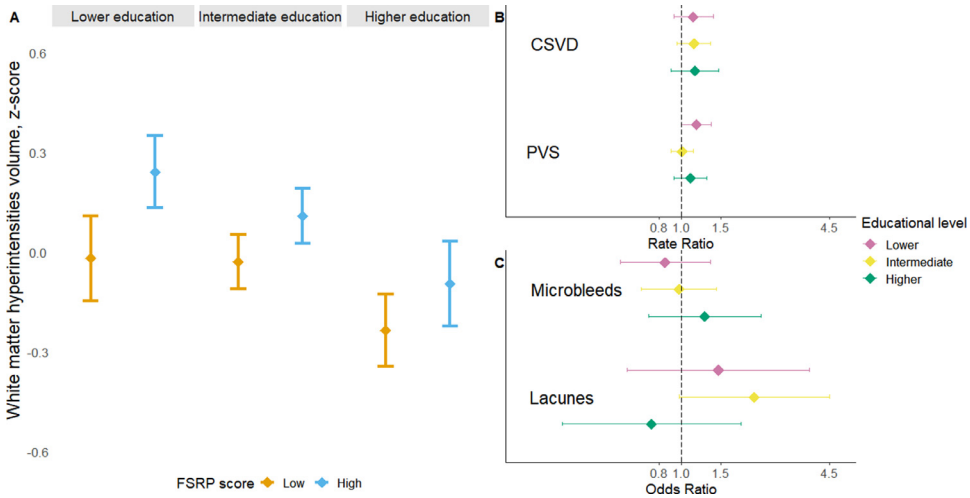

Fig. 4. The association between Framingham Stroke Risk Profile score and vascular brain pathology stratified by educational attainment level. Continuous values are depicted as adjusted means. For the count values, rate ratios (RR) are depicted, and for the categorical variables, odds ratios (OR) are depicted. Values are adjusted for age, sex, intracranial volume (for white matter hyperintensities), presence of *APOE*-ε4, body mass index and total cholesterol. Abbreviations: CSVD, cerebral small vessel disease; FSRP, Framingham Stroke Risk Profile; PVS, perivascular spaces.

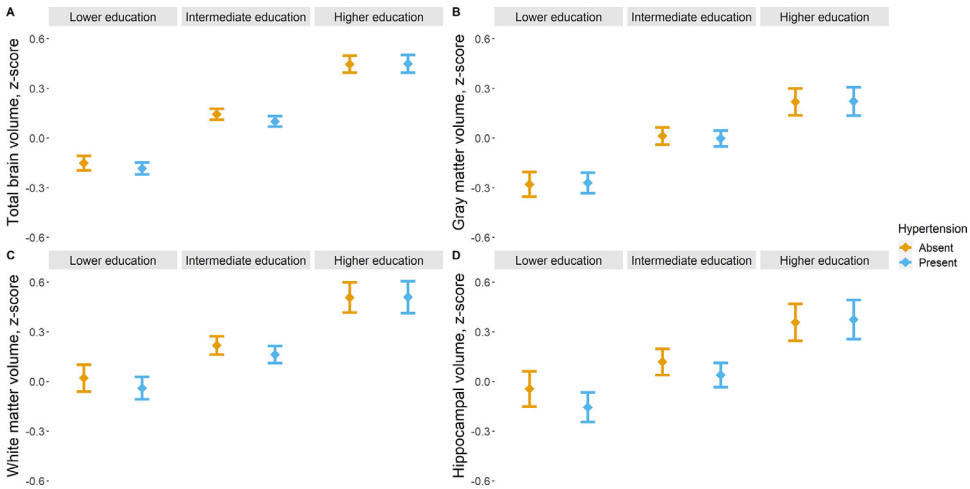

Fig. 5. The association between hypertension and vascular brain volumes by educational attainment level. Values are depicted as adjusted means. Values are adjusted for age, sex, intracranial volume, presence of *APOE*-ε4, body mass index, diabetes mellitus, smoking, and total cholesterol.

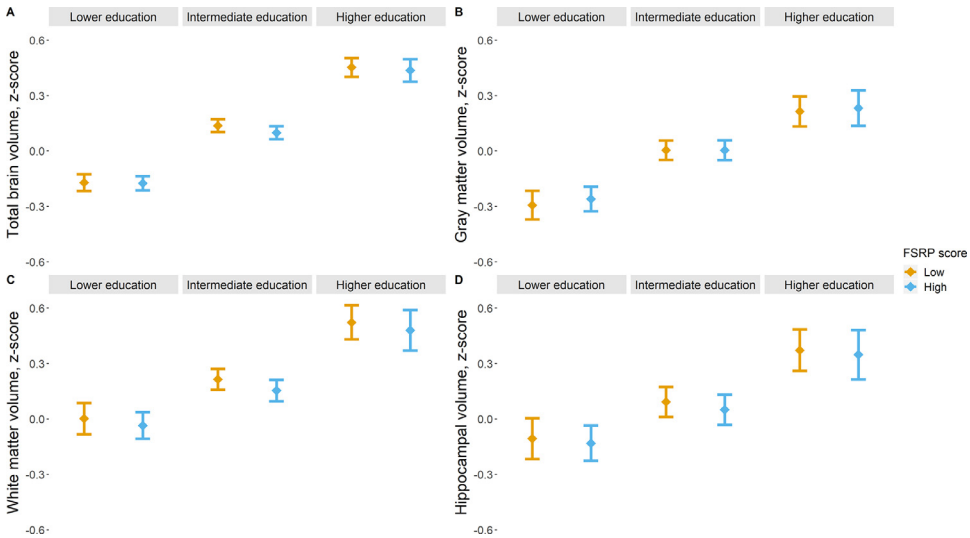

Fig. 6. The association between Framingham Stroke Risk Profile score and vascular brain volumes by educational attainment level. Values are depicted as adjusted means. Values are adjusted for age, sex, intracranial volume, presence of *APOE*-ε4, body mass index and total cholesterol. Abbreviations; FSRP, Framingham Stroke Risk Profile.

tary Table 4. Furthermore, the stratified effects of FSRP score on volumetric brain measures were similar to those of hypertension, except for hippocampal volume (Supplementary Table 4). The effect of FSRP on hippocampal volume did not differ between those with a lower education ($\beta = -0.03$, 95%CI −0.11;0.05) compared to higher education (Fig. 6D, $\beta = -0.03$, 95% CI −0.12; 0.07).

3.5. Sensitivity analyses

All associations did not alter after excluding participants with a history of cardiovascular disease. The results from the residual approach supported and enhanced our main findings, as educational attainment was significantly associated with higher proxy measures of resistance to WMH, microbleeds and CSVD sum score (Supplementary Table 5). Moreover, hippocampal volume resistance showed a trend to be greater in the high versus low education group (Supplementary Table 5). These results are in line with our main analyses, in which we saw the strongest modifying effect of education in the association between hypertension and WMH. Surprisingly, total brain volume resistance was significantly lower in those with an intermediate versus lower educational attainment (Supplementary Table 5).

4. Discussion

In this study we tested whether education is a determinant of resistance by investigating the modifying effect of educational attainment on the development of brain pathology due to vascular risk factors. Our main analyses suggest, although not statistically significant, that educational attainment contributes to resistance of the brain, as differences between levels of educational attainment on the association between vascular risk factors and brain pathology were in expected directions. The effect of education was mostly seen in the association between hypertension and WMH, in which the association was weaker in those with intermediate or higher educational levels, compared to those with lower educational levels. Similar patterns were seen when looking at FSRP, a combined score of vascular risk, and also for other brain markers, but not for all CSVD markers or for gray matter volume. These main findings were substantiated by results of a supplementary residual approach, in which we did find some significant evidence for a role of educational attainment in brain resistance. Higher educational attainment was significantly associated with higher proxy measures of resistance to WMH, as well as microbleeds and CSVD sum score. Taken together, these results do suggest a pattern in which those with a higher education level may be more resistant against the development of certain brain pathology than those with a lower educational level.

Limited previous research has focused on the framework of resistance and brain pathologies. Most studies on this framework did not include or correct for vascular risk factors and focused on the direct effect of educational attainment on brain pathology, except for Field et al. (2016). They investigated the role of early-life factors such as education on burden of CSVD, while adjusting for cardiovascular risk factors. They observed that in community-dwelling participants having a high level of education versus no education decreased the presence of moderate to severe CSVD, however this was not statistically significant. Similarly, we found a nonsignificant trend for weaker associations between vascular risk factors and individual markers of CSVD, including WMH and lacunes, in participants with a higher compared to a lower educational level. Yet, this trend was not present for the CSVD summary score. Discrepancies may be caused by differences in frameworks to study resistance in the brain. As the aim of aforementioned study differed from ours, it was not embedded within the resistance framework of Arenaza-Urquijo and Vemuri (2018) and did not examine the modifying effects of educational attainment on the development of brain pathology due to vascular risk factors. These methodological differences may explain the different findings. Our study is therefore a beginning for further exploration of different hypotheses within aforementioned conceptual framework.

There are 2 possible mechanisms that could explain the contribution of education to resistance: preventing brain pathology and engaging neural mechanisms of cellular repair. Limited human research is available investigating these mechanisms. Individuals with a better cognitive performance have increased neural efficiency and therefore need lesser neuronal activation to perform cognitive tasks (Stern et al., 2003). In Alzheimer's Disease patients and animal models, it has been shown that high levels of neural activity can predispose brain regions to amyloid deposition (Jagust and Mormino, 2011). Moreover, it is shown that a higher education is associated with lesser amyloid pathology (Pichet Binette et al., 2020). Furthermore, downregulation of neural excitation was associated with extended longevity, irrespective of amyloid deposits and neurofibrillary tangles (Zullo et al., 2019). Thus, better cognitive performance and higher levels of educational attainment may prevent AD-related and other brain pathology by increasing neural efficiency. So possibly, the increase of neural efficiency could also prevent development of other brain pathology. Some animal studies have investigated these proposed mechanisms. In dogs, cognitive enrichment modified the number of adult neurons in the hippocampus, but not that of newly formed neurons, suggesting cognitive enrichment is promoting neuroprotection (Siwak-Tapp et al., 2008). Moreover, environmental enrichment in mice has been shown to attenuate neuroinflammation, pointing to a neuroprotective effect of cognitive stimulation (Jurgens and Johnson, 2012). Furthermore, environmental enrichment in animals has been shown to induce a number of neuroplastic processes, including axon regeneration by promoting proregeneration genes (McDonald et al., 2018; Tang, 2020). Also, when translated to humans, stroke survivors engaged in an environmental enrichment had better outcomes in activity and function (McDonald et al., 2018).

In this study, we tested if educational attainment could be used as a proxy for resistance. Our results could imply that resistance may not be adequately captured by education, as the differences we found in the main analyses between educational levels were not significant. Therefore, we suggest looking into additional proxies for resistance besides educational attainment that could modulate the association between vascular risk factors and vascular brain pathology. Educational attainment is strongly influenced by sociodemographic and cultural factors. In the early years, women and men did not have equal access to education, which may affect the value of education as a proxy (van Hek et al., 2016). As a post-hoc analysis, we additionally stratified on sex to investigate whether the modifying role of education would be more pronounced in males compared to females due to this unequal access. Although we did observe differences in associational strengths between vascular risk factors and vascular brain pathology in males versus females (data not shown), we did not see an overall clearer pattern of effect modification by educational attainment in males compared to females. Moreover, although it was very rare in our study population for participants to receive extra education later in life, changes of education levels could influence resilience and resistance during lifetime and this static concept of highest attained education might not capture the dynamic process of resilience and resistance well enough. Therefore, other proxies or a combination of proxies to quantify resistance could be more com-

plete. These may include IQ, occupational complexity, socioeconomic status, and physical and social activity. The effect of environmental enrichment on neuroinflammation and neuronal repair in mice mentioned before is driven by cognitive enrichment, but also by physical exercise and social stimulation. Physical exercise has been associated with hippocampal neurogenesis in humans, (Firth et al., 2018) and better social health has been associated with a lower risk of dementia (Kuiper et al., 2015). In the field of cognitive reserve, which can be classified as either resilience or resistance, structural equation modeling has been introduced to combine multiple factors into one latent variable as a proxy for cognitive reserve (Reed et al., 2010). A similar approach for approximating resistance including above mentioned proxies could be explored in future research.

Strengths of our study are the large sample size, the correction for many potential confounders and the population-based setting, which increases understanding of underlying mechanisms which could be important for preventive strategies within a general population. Furthermore, participants had extensive data available on cardiovascular factors and brain markers. Interpretation of our results regarding causality is however limited because of the cross-sectional study-design. Moreover, our study population has an uneven distribution of educational attainment, with most participants in the intermediate educational attainment group. Although this is a good reflection of society, it might have disguised some effects as the power to detect effects would be optimal if groups were of equal size. Lastly, comparison with previous literature is challenging because the concepts of resilience and resistance can be defined, implemented and interpreted in different ways. Nevertheless, Arenaza-Urquijo and Vemuri (2018, 2020) provided clear definitions and we would advise consultation on their framework in future research on resistance and resilience in order to have more comparable studies. This will facilitate better understanding of the role of resistance and resilience and possibly their underlying mechanisms.

5. Conclusions

Our results suggest a partial role for educational attainment in resistance to brain pathology due to vascular risk factor. Although not significant in the main analyses, the impact of hypertension and FSRP on vascular brain pathology appeared less strong in participants with a higher educational level compared to persons with lower educational attainment for most markers of brain pathology. These main findings were substantiated by results of a supplementary residual approach, in which higher educational attainment was significantly associated with higher resistance to WMH, as well as microbleeds and CSVD sum score. Taken together, these results do suggest a pattern in which those with a higher education level may be more resistant against the development of certain brain pathology due to vascular risk factors than those with a lower educational level. To better characterize the concept of resistance within this framework, future research should study other proxies or a combination of proxies.

Author Statement

JVA, PY, MAI, MWV and RS contributed to the study design. Analyses were performed by JVA and PY. Interpretation of the results was done by JVA, PY, JN, SL, JZ, MAI, MWV and RS. The manuscript was written by JVA and PY and revised by all authors.

Disclosure statement

The authors have no actual or potential conflicts of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.neurobiolaging.2021.06.006.

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