Brain white matter damage in aging and cognitive ability in youth and older age

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ABSTRACT

Cerebral white matter hyperintensities (WMH) reflect accumulating white matter damage with aging and impair cognition. The role of childhood intelligence is rarely considered in associations between cognitive impairment and WMH. We studied community-dwelling older people all born in 1936, in whom IQ had been assessed at age 11 years. We assessed medical histories, current cognitive ability and quantified WMH on MR imaging. Among 634 participants, mean age 72.7 (SD 0.7), age 11 IQ was the strongest predictor of late life cognitive ability. After accounting for age 11 IQ, greater WMH load was significantly associated with lower late life general cognitive ability ($\beta = -0.14$, $p < 0.01$) and processing speed ($\beta = -0.19$, $p < 0.001$). WMH were also associated independently with lower age 11 IQ ($\beta = -0.08$, $p < 0.05$) and hypertension. In conclusion, having more WMH is significantly associated with lower cognitive ability, after accounting for prior ability, age 11 IQ. Early-life IQ also influenced WMH in later life. Determining how lower IQ in youth leads to increasing brain damage with aging is important for future successful cognitive aging.

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1. Introduction

White matter hyperintensities (WMH) are a common sign of cerebrovascular disease visible on brain imaging in older people (O'Sullivan, 2008). WMH contribute substantially to loss of independence at older ages through a 3-fold increased risk of stroke and a 2-fold increased risk of dementia (Debette and Markus, 2010); in addition, WMH accelerate aging-related cognitive decline (Debette and Markus, 2010; O'Sullivan, 2008; Schmidt et al., 2007). Although previously regarded as clinically "silent," WMH are now recognized to be associated with subtle neurological symptoms (Haley et al., 2009) and subjective awareness of cognitive decline (Silbert et al., 2009). It is generally considered that the cognitive impairment

seen with WMH (Almkvist et al., 1992) is caused by the WMH and not related to premorbid cognitive ability.

Childhood intelligence is the strongest predictor of late-life cognitive ability (Deary et al., 2003) and may protect against the effects of cognitive aging (Stern, 2009). Higher childhood intelligence is also associated with many health outcomes across the life course, including a lower risk of vascular dementia (Deary et al., 2009, 2010b). Similarly, higher educational attainment is also associated with decreased incidence of dementia (Dufouil et al., 2003), an association that is as yet unexplained. Early-life cognitive ability might therefore influence the risk of developing cerebrovascular disease including WMH.

Many longitudinal studies show that WMH progression is associated with worsening cognition at older ages and that WMH progression is worst in those with more WMH at inception (Bartres-Faz et al., 2001; Debette and Markus, 2010; Schmidt et al., 2007) (we summarize other longitudinal studies not included in those reviews in Supplementary Table 1). Most studies adjusted for educational level and other confounds (Bartres-Faz et al., 2001; Schmidt et al., 2007) (Supplementary Table 1), but most did not examine whether prior cognitive ability or educational level modified the longitudinal WMH–cognition association or was associated with cross-sectional WMH burden. In 1 study of 800

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individuals, the association between WMH and impaired cognition in older age was strongest in those with lower educational level (Dufouil et al., 2003). In another study, increased duration of education was associated with less executive dysfunction, but not with WMH severity, in 475 patients with stroke (Ojala-Oksala et al., 2012); however, this study may have been underpowered to detect any education–WMH burden association.

A few studies of WMH and cognition were able to control for prior cognitive ability using a validated mental test obtained in youth (Deary et al., 2003), but these were modestly powered, given the expected effect sizes (e.g., about 100 individuals of nearly 80 years of age (Deary et al., 2003; Murray et al., 2012), or 233 to 249 participants nearly 70 years of age (Murray et al., 2011, 2012) and did not consider the effect of stroke. Although these showed an important association between IQ at age 11 years and late-life cognitive ability, along with the well-documented association between WMH and late-life cognitive decline, they did not find (and were probably underpowered to do so) an association between age 11 IQ and WMH or other factors that might explain why lower childhood intelligence may increase the risk of vascular dementia (Deary et al., 2010b).

We hypothesized that childhood IQ would account not just for much of cognitive ability in older age, but would explain some of the apparent cross-sectional WMH–cognitive ability association in later life, and that lower childhood IQ would be associated with increased WMH. We used both qualitative (visual scores) and quantitative (WMH volume) indicators of white matter damage, examined 3 key cognitive domains, and used a large, narrow-age cohort to minimise the powerful effect of age on progressing vascular disease.

2. Methods

2.1. Participants

The LBC1936 are community-dwelling surviving members of the Scottish Mental Survey of 1947, who were all born in 1936 and sat the Moray House Test No. 12 (MHT) of general intelligence at age 11 years. Most were resident in Edinburgh and the surrounding Lothians when initially recruited at a mean age of 70 years (Deary et al., 2007). Here, we use data from the second wave of testing (mean age = 72.7 years, SD = 0.7 years), at which time 700 participants underwent brain structural magnetic resonance imaging (MRI). Of the 700, 672 had all relevant sequences to assess WMH volumes (detailed below) (Wardlaw et al., 2011). Participants with Mini Mental State Examination scores <24 were excluded as scores below this level are commonly taken to be indicative of possible pathological cognitive impairment. The current analyses (see below) required complete data for all covariates, resulting in a final sample of 634 adults (men, n = 337, 53.2%).

Written informed consent was obtained from all participants under protocols approved by the Lothian (REC 07/MRE00/58) and Scottish Multicentre (MREC/01/0/56) Research Ethics Committees. The study was conducted according to the STROBE criteria (www.equator-network.org).

The participants provided their history of hypertension, diabetes, hypercholesterolemia (in each case, a medical diagnosis or current medication for these conditions), smoking status (which we classified as current/former smoker or never smoked) and of vascular disease including medically confirmed myocardial infarction and of stroke. Details were checked with the study medical advisor and family doctor or hospital records where necessary. Details of the full LBC 1936 assessment protocol have been published (Deary et al., 2007).

2.2. MRI brain image acquisition and processing

All MRI data were acquired using a 1.5T GE Signa Horizon HDxt clinical scanner (General Electric, Milwaukee, WI) operating in research mode and using a self-shielding gradient set with maximum gradient of 33 mT/m, and an 8-channel phased-array head coil. We acquired T1-weighted, T2-weighted, fluid-attenuated inversion recovery (FLAIR) and T2* axial structural sequences, the full details of which have been published previously (Wardlaw et al., 2011) but are provided in Supplementary Table 2.

All analyses were performed with the analysts blinded to cognitive and all clinical data, and, along with the validation, are described in detail in Supplementary Table 2. We defined "WMH" as the collective term for punctate or diffuse areas in the white matter and deep gray matter of the cerebral hemispheres or in the brainstem that were 3 mm or larger in diameter and hyperintense with respect to normal-appearing white and gray matter on T2-weighted and FLAIR images; some hypointensity on T1-weighted MRI was allowed, as long as this was not as hypointense as cerebrospinal fluid (CSF). We appreciate that not all would agree with including deep gray and white matter hyperintensities in the term WMH, but we are simply using it as an operational term in this instance. We defined infarcts as cortical or large subcortical areas of hyperintensity on T2-weighted or FLAIR, consistent with cerebromalacea and in a vascular distribution. Areas of tissue loss and replacement by CSF due to infarcts (including lacunes) were also included in the stroke lesion volume. Where stroke lesions were occasionally contiguous with WML, the boundary between the 2 was determined by evaluation of the WML and underlying anatomy in the contralateral hemisphere and neuroradiological knowledge.

We co-registered each subject's structural MRI scans using FLIRT (http://www.fmrib.ox.ac.uk/fsl) and measured intracranial volume (ICV), total brain tissue volume, cerebrospinal fluid (CSF) volume, and WMH volume using a validated semi-automated image processing tool, MCMxxxVI (available for download at http://sourceforge.net/projects/bric1936/), which implements multispectral color fusion and minimum variance quantization (Valdes Hernandez et al., 2010) and performs at least as well as other multispectral methods (Valdes Hernandez et al., 2012a). MCMxxxVI maps 2 or more different MRI sequences (e.g., FLAIR and T2*) that display the tissues/lesions at different signal intensity levels to the red/green/blue (RGB) color space. It then reduces the color levels of the fused image to 32 clusters using minimum variance quantisation. To segment the WMH, the T2*-weighted sequence was mapped to the red and FLAIR was mapped to the green color space. The subarachnoid space and ventricles appear in red and WMH and any cortical or other discrete hyperintense infarcts appear in yellow. Further details of the tissue segmentation are given in Supplementary data.

We visually inspected all segmented images and manually edited any incorrectly classified tissues. We also identified and masked separately any visible cortical, cerebellar, or subcortical infarcts or lacunes to exclude them from erroneously influencing the WMH or CSF volumes. Neuroradiological experts identified these infarcts according to established diagnostic criteria as wedge-shaped or rounded lesions, conforming to a vascular territory, with tissue atrophy and signal characteristics consistent with malacic change. Infarcts, defined as above, were separated from WMH manually by thresholding the FLAIR sequences using a region-growing algorithm from Analyze 10.0 (http://www.analyzedirect.com/Analyze/).

Three different WMH volume measures ("WMH volume," "percentage of WMH volume in ICV," and "percentage of WMH volume in brain tissue volume") all correlated very highly (0.99 to 1.00), so we used only the "percentage of WMH in ICV" in the statistical analysis. Separately, and blinded to all other data, an expert neuroradiologist provided a WMH visual Fazekas score in periventricular and subcortical areas (Fazekas et al., 2003) using FLAIR- and T2-weighted sequences.

2.3. Cognitive testing

Full descriptions of the cognitive testing have been published (Deary et al., 2007). We used 14 subtest scores from 12 cognitive ability tests covering domains of cognitive ability that display differential patterns of age-related decline.

General cognitive ability (abbreviated as g) was measured using 6 subtests of the Wechsler Adult Intelligence Scale—III^{UK} (Wechsler, 1997a) (WAIS-III^{UK}), namely Digit Symbol, Symbol Search, Digit Span Backwards, Letter–Number Sequencing, Block Design, and Matrix Reasoning. Here we explicitly define g based on non-verbal cognitive test scores because tests of more fluid reasoning abilities have been shown to show greater declines in aging (Salthouse, 2009). We acknowledge that some fluid reasoning tests may contain verbal content; however, knowledge and verbal abilities, such as vocabulary, are largely sustained in healthy aging (Salthouse, 2009). As our primary aim was to produce cognitive scores sensitive to age-related decline, and for consistency, we elected to exclude verbal tests from our definition of g. General memory ability (g-memory), was measured using 5 subtest scores from the Wechsler Memory Scale—III^{UK} (Wechsler, 1997b) (WMS-III^{UK}), namely Logical Memory Immediate and Delayed Recall, Verbal Paired Associates Immediate and Delayed Recall, and Spatial Span. WAIS-III^{UK} Letter–Number Sequencing and Digit Span Backward were also indicators of g-memory. We note that this measure of g-memory does not include subscales that primarily test episodic memory. Finally, general processing speed (g-speed), was measured using Simple and Choice Reaction Time means, a visual processing speed task called Inspection Time (Deary et al., 2007), and 2 WAIS-III^{UK} subtests (Digit Symbol and Symbol Search).

A number of the cognitive subtests are used to identify more than 1 cognitive latent variable. In estimating latent constructs of cognitive ability, the use of a greater number of indicators in generally preferred; hence our decision to use subtests with substantive overlap as indicators in multiple models. For example, Digit Symbol Coding is a test of information processing speed, and thus contains elements of both reasoning (here our g factor) and processing speed (g-speed). Thus our cognitive latent variables both conceptually and operationally overlap. g correlated at 0.81 ($p < 0.001$) with g-memory and 0.49 ($p < 0.001$) with g-speed when subtests were loaded on more than 1 factor. These correlations were 0.81 ($p < 0.001$) and 0.89 ($p < 0.001$) respectively, when the model was re-estimated with non-overlapping tests. Thus, there are substantial correlations among the 3 latent constructs.

For childhood intelligence, we used the IQ-type score computed from the raw age 11 MHT scores. This paper-and-pencil test was administered in 1947 as part of the Scottish Mental Survey when participants were a mean age of 11 years. It contains a variety of items with an emphasis on verbal reasoning, and also some items that involve non-verbal reasoning and arithmetic (Deary et al., 2007).

2.4. Statistical analysis

All models were estimated using structural equation modeling (SEM) in MPlus 6.0 (Muthén and Muthén, 2010). A full description of basic SEM is given in Supplementary Table 3 (see also Penke and Deary, 2010). Briefly, SEM combines factor analysis and regression to model latent variables and the correlations and directed or regression paths between latent variables.

In the current study, we estimated a latent WMH factor with 3 indicators, volume of WMH as a percentage of ICV and Fazekas ratings in the periventricular and subcortical areas. Cognitive ability factors were indicated by the sets of subtests noted above. In each model, latent factors were identified by fixing the latent factor

variance to 1.0. We included direct paths between WMH and each cognitive ability factor to assess the extent to which WMH predicts later life ability. These regression paths may be thought of as partial β coefficients and interpreted accordingly. In addition, we included direct paths from age 11 IQ and the model covariates to both WMH and cognitive ability latent factors. As such, any associations between WMH and cognitive ability are present after controlling for variance associated with prior ability and the other model covariates.

All models were estimated based on the whole sample and also as multi-group models, split by participants' stroke status. Participants who had any prior history of stroke or radiologically identified cortical or subcortical infarct or lacune, or both, were categorized as "stroke" and those who did not have any of these as "no stroke." The use of multi-group SEM models allows for formal tests for any differences in the strength of associations between variables across groups (see Supplementary Table 3).

We first established measurement invariance in our latent constructs. If measurement invariance is established across groups, then the latent constructs can be considered identical, and meaningful comparisons across groups can be made (French and Finch, 2006; Widaman, 1993). Measurement invariance of latent constructs can be assessed at multiple levels, each providing a sequentially stricter test of invariant measurement (Widaman and Reise, 1997) Configual invariance requires the pattern of factor loadings to be the same across groups. Metric invariance requires the degree of the loadings to be equivalent across groups. Scalar invariance requires the intercepts of the indicators to be the same across groups. Here our interest was in metric invariance, because when metric invariance is established, correlation and direct paths between latent constructs can be investigated across groups.

Here we considered whether the cognitive ability–WMH associations differed by stroke status, and also whether the effects of age 11 IQ and model covariates differed across these groups. Differences in parameters were tested by constraining the parameter to be equal across groups and considering the change if χ^2 statistic based on a single degree of freedom.

All models were estimated using maximum likelihood estimation. Model fit was evaluated based on commonly adopted cut-off points of 0.05 for the standardized root mean residual, 0.06 for the root mean square error of approximation, and ≥0.95 for the Tucker–Lewis Index, and the Comparative Fit Index (Schermelleh-Engel et al., 2003).

3. Results

3.1. Participant characteristics

The participants were a median age of 72.7 years (range, 71.0–74.2 years) at MR imaging (cognitive testing was performed no more than a few weeks before MR imaging) (Table 1). Approximately half of the participants had hypertension (49%) or hypercholesterolemia (42%). Lower proportions of individuals had diabetes (10%) or any cardiovascular disease (170, 27%) including 135 (21%) with ischemic heart disease alone; 43 participants reported having had a stroke (of whom 19 also had a focal cortical, cerebellar, or distinct subcortical stroke lesion on imaging), and an additional 70 had imaging-only evidence of a focal cortical, cerebellar, or discrete subcortical stroke lesion, giving a total with any stroke of 113 (18%). Some WMH were detectable in 97.3% of participants. Median WMH volume for the whole group was 7.7 mL (range 0–98.4 mL) or median of 0.53% of ICV. WMH volume in the 113 participants with history and/or radiological evidence of stroke was larger than that in the 521 participants without stroke (median 15.3 mL vs. 7.2 mL, respectively, $p < 0.001$, Mann–Whitney U test.).

Table 1
Characteristics of study sample

Demographics		
Sex male, n (%)	337 (53.2%)	297 (46.8%)
Self-report stroke, n (%)	43 (6.8%)[a]	
Imaging evidence stroke, n (%)	70 (11.0%)[a]	
Total stroke, n (%)	113 (17.8%)[a]	
	Mean	**SD**
Age (y) at MRI	72.66	0.73
Cognitive ability		
Age 11 IQ (Moray House Test, No.12)	100.86	15.31
Logical Memory Total Immediate Recall WMS-III	45.68	10.43
Logical Memory Delayed Recall WMS-III	28.81	8.20
Verbal Paired Associates Immediate Recall WMS-III	2.81	2.34
Verbal Paired Associates Delayed Recall WMS-III	6.37	2.10
Spatial Span Total Score WMS-III	14.76	2.71
Simple Reaction Time Mean Score	0.27	0.05
Choice Reaction Time Mean Score	0.65	0.09
Inspection Time Total Correct Responses	111.51	11.36
Digit Symbol WAIS-III[UK]	56.42	12.16
Digit Span Backward WAIS-III[UK]	7.88	2.29
Block Design WAIS-III[UK]	34.28	10.01
Letter-Number Sequencing WAIS-III[UK]	10.98	3.00
Matrix Reasoning WAIS-III[UK]	13.45	4.88
Symbol Search WAIS-III[UK]	24.72	6.18
	Median	**IQR (25%–75%)**
Qualitative white matter lesion ratings		
Fazekas: periventricular total	1.00	1.00–2.00
Fazekas: deep total	1.00	1.00–2.00
Quantitative white matter lesion variables		
ICV (mL)	1448.49	1346.50–1552.72
Total WMH volume (mL)	7.74	3.64–17.20
WMH volume in ICV (%)	0.53	0.24–1.16
WMH volume in brain tissue (%)	0.68	0.31–1.47
	No	**Yes**
Health covariates: history		
Diabetes, n (%)	571 (90.1%)	63 (9.9%)
Hypercholesterolemia, n (%)	365 (57.6%)	269 (42.4%)
Cardiovascular disease history (ischemic heart disease and/or stroke) self-reported, n (%)	464 (73.2%)	170 (26.8%)[b]
Ischemic heart disease and also stroke self-reported, n (%)		13/170 (7.6%)
Ischemic heart disease self-reported and imaging evidence of stroke, n (%)		22/170 (12.9%)
Hypertension, n (%)	323 (50.9%)	311 (49.1%)
History of smoking		
Never smoked, n (%)	292 (46.1%)	
Ex-smoker, n (%)	292 (46.1%)	
Current smoker, (%).	50 (7.9%)	

Key: ICV, intracranial volume; IQR, interquartile range; MRI, magnetic resonance imaging; SD, standard deviation; WAIS, Wechsler Adult Intelligence Scale; WMH, white matter hyperintensities.

[a] Of the participants, 19 had both history of stroke and an infarct or hemorrhage on imaging.

[b] In all, 135 of 634 participants (21.3%) had ischemic heart disease alone.

All non-categorical variables were approximately normally distributed, with skew ranging from −1.27 to 1.70. All imaging variables that involved WMH showed a small degree of positive skew.

For fullness of reporting, the bivariate correlations between the three measures of WMH and the 14 cognitive ability subtest scores are presented in Supplementary Table 4. Correlations among the vascular risk factors (hypercholesterolemia, diabetes, hypertension, and smoking history) and cardiovascular disease or stroke, WMH variables, and cognitive ability test results are shown in Supplementary Table 5.

3.2. Structural equation modeling

All SEMs showed excellent fit to the data (Figs. 1–3). In all models, the factor loadings for the latent variables were moderate to large (the g cognitive tests' loadings range from 0.49 to 0.67,

mean = 0.61; the g-memory tests' range was 0.45 to 0.69, mean = 0.56; the g-speed tests' range was −0.32 to 0.84, mean = 0.62; the WMH volume indicators' range was 0.70 to 0.94, mean 0.79). These values show that the latent variables, g, g-memory, and g-speed, account for between 20% and 84% of variance in the individual cognitive ability subtests (Figs. 1–3). This supports the appropriateness of estimating latent constructs. Figs. 1–3 show the final results for g, g-memory, and g-speed, respectively. Age 11 IQ explained the greatest proportion of variance in late-life cognitive ability in all models, ranging from approximately 24.0% to 45.1%. Over and above the effect of age 11 IQ, WMHs were associated significantly in older age with g ($\beta = -0.14$, $p < 0.01$) and g-speed ($\beta = -0.19$, $p < 0.001$) which accounted for approximately 2.6 and 4.4% of additional variance respectively. There was no significant association between WMH and g-memory ($\beta = -0.05$, $p = 0.23$).

Given the similarity in the effect sizes for the g and g-speed models, as well as the magnitude of the correlations between the
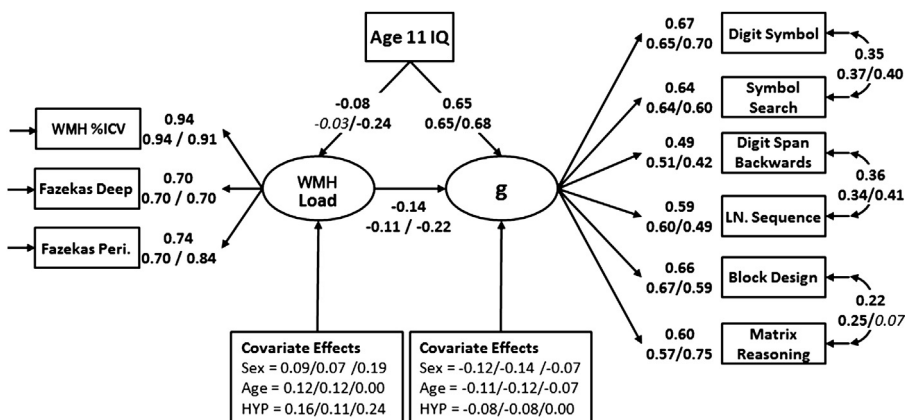
Fig. 1. Structural equation model diagram for white matter hyperintensities (WMH) predicting general cognitive ability (whole sample/no stroke/stroke). Abbreviations: g, general cognitive ability; HYP, hypertension; ICV, intracranial volume; L.N. sequence, letter–number sequencing; Peri., periventricular. Model fit: $\chi^2 = 112.51$ (50), $p < 0.001$; Comparative Fit Index = 0.97; Tucker–Lewis Index = 0.96; root mean square error of approximation = 0.044 (95% confidence interval = 0.033–0.055); standardized root mean residual = 0.034. Values next to arrows are the standardized parameter estimates. An additional covariate path was included between Sex and Digit Symbol ($\beta = 0.19$, $p < 0.001$). Rectangles represent measured variables; ellipses, latent variables; single-headed arrows, directed paths or partial β coefficients; and double-headed arrows, correlations.

latent factors, we tested the whether each of the latent constructs acted as a mediator for the other with respect to the association with WMH. As may be expected, the inclusion of g-speed as a mediator of the WMH to g association, and of g in the WMH to g-speed association, resulted in the WMH direct effects falling to ±0.01 ($p > 0.05$).

3.3. Structural parameter equivalence across stroke vs. no stroke

Multi-group SEM testing examined the associations across those with and without evidence of stroke (see Supplementary data S2 for procedure and S4 for invariance results). We found evidence based on model fit indices for measurement invariance across the stroke and no stroke groups for each of the latent constructs in our models. As such, the latent constructs can be considered to be equivalent across groups, and any differences in structural parameter estimates are not a result of measurement bias. No significant differences were found across the stroke and no stroke groups in the associations between WMH and later life cognitive abilities. However, in 2 of the 3 models (Fig. 1 [g] and Fig. 2 [g-memory]), the association between age 11 IQ and WMH

was significantly different between the stroke and no stroke groups (χ^2 difference test, stroke = −0.24; no stroke = −0.03; $\Delta\chi^2 = 4.18$, df = 1, $p < 0.05$), indicating that the association between lower age 11 IQ and more WMH at age 73 years was stronger in those with stroke.

3.4. Covariate attenuations

The pattern of covariate associations with WMH suggested that those with a history of hypertension, with lower age 11 IQ, who were older (even within this narrow age range), and female, had more WMH. Furthermore, hypertension, age, and sex all had significant effects on g; sex and age both had significant effects on g-memory; and only age was a significant covariate for g-speed. These covariate effects accounted for approximately 1% to 2% of the variance in later life cognitive ability scores.

Re-estimating all models by including cardiovascular disease and stroke, diabetes, smoking history, and cholesterol as additional covariates did not attenuate the associations between WMH and cognition, with any changes being at the second decimal place. The
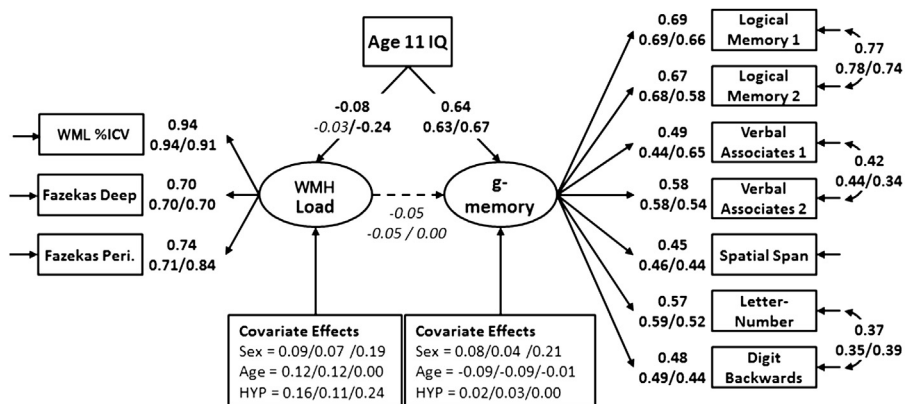

Fig. 2. Structural equation model diagram for white matter hyperintensities (WMH) predicting general memory ability (whole sample/no stroke/stroke). Abbreviations: g-memory, general memory ability; HYP, hypertension; ICV, intracranial volume; L.N. sequence, letter–number sequencing; Peri., periventricular. Model fit: $\chi^2 = 175.50$ (62), $p < 0.001$; Comparative Fit Index = 0.96; Tucker–Lewis Index = 0.95; root mean square error of approximation = 0.054 (95% confidence interval = 0.044–0.063); standardized root mean residual = 0.040. Values next to arrows are the standardized parameter estimates. Dashed lines signify non-significant parameters. An additional covariate path was included between Sex and Spatial Span ($\beta = -0.19$, $p < 0.001$). Rectangles represent measured variables; ellipses, latent variables; single-headed arrows, directed paths or partial β coefficients; and double-headed arrows, correlations.
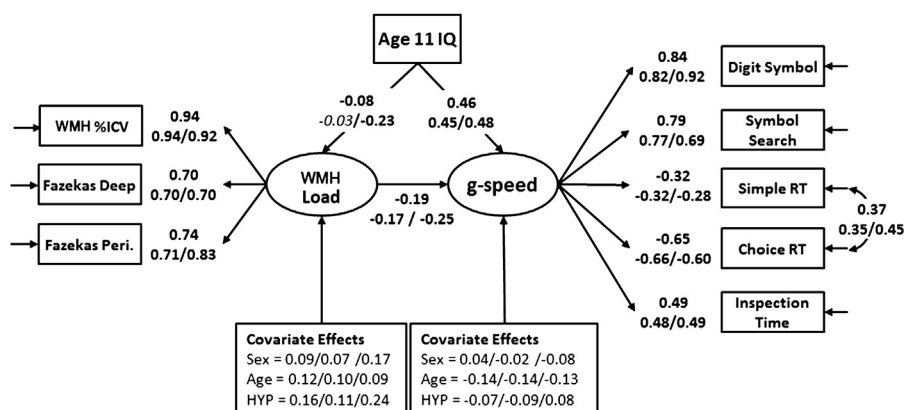
Fig. 3. Structural equation model diagram for white matter hyperintensities (WMH) predicting processing speed (whole sample/no stroke/stroke). Abbreviations: g-speed, general processing speed; HYP, hypertension; ICV, intracranial volume; RT, reaction time; Peri., periventricular. Model fit: $\chi^2 = 86.21$ (40), $p < 0.001$; Comparative Fit Index = 0.98; Tucker–Lewis Index = 0.97; root mean square error of approximation = 0.043 (95% confidence interval = 0.030–0.055); standardized root mean residual = 0.029. Values next to arrows are the standardized parameter estimates. An additional covariate path was included between Sex and Digit Symbol ($\beta = 0.15$, $p < 0.001$) and sex and inspection time ($\beta = -0.13$, $p < 0.001$). Rectangles represent measured variables; ellipses, latent variables; single-headed arrows, directed paths or partial β coefficients; and double-headed arrows, correlations.

only significant difference was a small additional negative effect of smoking on all 3 cognitive traits.

3.5. MMSE cut-off sensitivity analysis

To investigate the effect of using a higher cut-off value for the MMSE, we re-ran all models using a cut-off of ≥ 26. This resulted in the removal of 20 participants and a remaining sample of 614. Of the 20 participants removed, 3 (2.6%) were in the stroke group and 17 (3.3%) in the no stroke group. Changes in the direct effects of WMH on g (-0.13), g-speed (-0.18), and g-memory (-0.04) were at the second decimal place. Furthermore, the differences in these associations across the stroke and no stroke groups remained non-significant, as did the significant differences in the association between age 11 IQ and WMH in the g and g-memory models.

4. Discussion

To our knowledge, the current study is the first that uses longitudinal measures of intelligence from childhood and older age within the same large sample of non-demented individuals, with qualitative and quantitative assessment of WMHs and key health covariates, to identify associations between early-life IQ and WMH in later life, particularly among those participants with clinical or imaging evidence of stroke, and to quantify the incremental effect of WMH on reducing cognition in later life. Early-life cognitive ability was the strongest single predictor of cognitive ability at about age 73 years. The incremental effect of WMH on reducing both general cognitive ability and processing speed but not memory in later life, after controlling for early-life cognitive ability and health covariates, was modest but relatively robust. WMH had a similarly negative effect on later life cognition in participants with and without stroke.

WMH in later life were associated with lower age 11 IQ. This association was stronger in participants with any evidence of stroke who had almost double the volume of WMH compared with those without stroke, independent of vascular risk factors. The general pattern remained when the participants with MMSE <26 (n = 20) were excluded. Our finding warns against assuming that cognitive status in older age is due only to being older or having an aging-associated disease that may affect cognition, such as cerebrovascular disease or incipient dementia. The findings suggest that

later-life cognitive decline, the accumulation of WMH and also of stroke may have some of their origins in youth, perhaps through factors that overlap with determinants of lifelong-stable differences in general cognitive ability (Deary et al., 2010a). Speculative reasons might include that lower intelligence might be associated with lifestyle choices that predispose to WMH and stroke (Deary et al., 2010b), or because higher IQ might be associated with greater resilience to brain insults, for example, through the intelligence–white matter integrity association (Penke et al., 2012), or socio-economic effects that are not simply acting through greater vascular risk factor exposure (Deans et al., 2009), or other, completely unknown factors. These interpretations are speculative. However, the finding is highly consistent with, and may provide an explanation for, the evidence from cognitive epidemiology research that finds childhood IQ is associated with a range of adverse vascular disorders later in life, including vascular dementia (Deary et al., 2010b; Stern, 2009). This might also explain the association observed in other studies between educational level and late-life cognitive ability and dementia (Dufouil et al., 2003), in which educational level could be acting as a proxy for childhood IQ. Although the association between age 11 IQ and WMH was modest, the fact that a significant association can be detected at all, across approximately 6 decades, suggests that it is important and worthy of further evaluation in other large population studies. It would also explain why other, smaller studies that did examine for educational level and WMH did not find this association. These results should not be construed as suggesting that studies on aging, cognition, vascular disease, and brain structure should require cognition measured in early life, but rather as suggesting that proxy measures of premorbid cognitive ability should be considered. This might include the National Adult Reading Test, which provides a good estimate of childhood as well as of premorbid IQ when measured in older age (Deary et al., 2004, 2007); or possibly the highest educational attainment or years of education (collected in many previous studies of WMH; Supplementary Table 1) could be used cautiously. Future studies should consider the role of early-life cognitive ability in development of aging-related diseases, particularly cerebrovascular disease.

Childhood intelligence is a potential confounder of any examination of cognitive and brain aging (Deary et al., 2010b). Consistent with previous findings, the strongest contemporaneous associations were between WMH and g-speed (Gunning-Dixon and Raz, 2000;

Rabbitt et al., 2007). These associations did not differ significantly between those with or without stroke. Furthermore, in accordance with past research, hypertension (de Leeuw et al., 2002) and smoking history (Benowitz, 2003; Longstreth et al., 2005) had the largest covariate effects on both WMH and g, but these were modest.

Across studies investigating the associations between WMH and cognitive ability in later life, varied findings may result from the method of WMH assessment (qualitatively or quantitatively), the wide age range of participants (where increasing WMH may reflect advancing age; it should be noted that the effect of advancing age was significant even within this very narrow age range cohort), prior cognitive ability, the domains of cognition investigated across studies, and health status such as prior stroke; not only do ischemic stroke lesions have signal properties that confound measurement of WMH volume (Wang et al., 2012), but stroke itself causes cognitive impairment (Pendlebury and Rothwell, 2009).

The strengths of the current study included a large, age-homogenous sample (about 3 times larger than those in other studies that have examined early and late-life cognition) (Deary et al., 2003; Murray et al., 2011, 2012); use of validated cognitive assessment methods (Deary et al., 2007; Wardlaw et al., 2011); use of both qualitative and quantitative WMH measures (Valdes Hernandez et al., 2012b); and imaging methods that carefully exclude infarcts reducing contamination of WMH volume estimates. We demonstrated highly consistent associations using either type of WMH assessment (Supplementary data) consistent with their known strong correlation (Valdes Hernandez et al., 2012b). Methodologically, the large sample and large number of cognitive tests allowed us to apply structural equation modeling, allowing the creation of error-free latent variables for cognitive functions and WMH. As well as providing a framework within which measurement error is accounted for, and in which both substantive and covariate effects can be modeling simultaneously, we were able to apply a multi-group model and to explicitly test for differences in associations in participants with and without evidence of stroke.

This study also has limitations. First, WMH are only 1 component of cerebral small vessel disease. Additional research should consider other markers of small vessel disease and other markers of all types of stroke. Second, we were reliant on participants' self-reported medical histories for some study covariates, although these were checked with the medical advisor to the study. Third, the substantial correlations between the latent factors and the results of the mediation models suggests that the effects seen in the g and g-speed models may not be entirely independent effects. Nonetheless, the results still show a clear and robust effect of WMH on later-life cognitive function, but not on memory ability.

Finally, although the current sample has many strengths, it represents a somewhat select group in that, at entry into the study at age 70 years, participants were largely healthy and free of any major age-related disorders. For the current analyses, this can be seen in the comparatively low proportion of individuals who were hypertensive. As such, a question may be asked as to the degree our findings will generalize to other populations. However, given the selectiveness of the current sample in the upper portions of the health distribution, the estimates provided here are likely underestimates of the true association between WMH and aspects of cognitive function in the population, due to the impact of truncation on parameter estimates (Muthen, 1990).

In summary, here we show a novel association between early-life IQ and WMH, a known important adverse risk factor for stroke and dementia (Debette and Markus, 2010). Many studies of WMH, cognition and aging have collected information on duration of education or of educational attainment (Supplementary Table 1), which could be used cautiously as a proxy measure of cognitive ability in youth to explore for evidence of an association with occurrence of WMH and/or stroke in later life. The reason for this early-life cognition–WMH association and its contribution to impaired cognition and cerebrovascular disease in older age is an important focus for further research.

Disclosure statement

None of the authors have any actual or potential conflicts of interest to disclose.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neurobiolaging.2013.05.032.

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