



## Associations of subclinical cerebral small vessel disease and processing speed in non-demented subjects: A 7-year study

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### ABSTRACT

Markers of cerebral small vessel disease (CSVD) have previously been associated with age-related cognitive decline. Using longitudinal data of cognitively healthy, older adults ( $N = 216$ , mean age at baseline = 70.9 years), we investigated baseline status and change in white matter hyperintensities (WMH) (total, periventricular, deep), normal appearing white matter (NAWM), brain parenchyma volume (BPV) and processing speed over seven years as well as the impact of different covariates by applying latent growth curve (LGC) models. Generally, we revealed a complex pattern of associations between the different CSVD markers. More specifically, we observed that changes of deep WMH (dWMH), as compared to periventricular WMH (pWMH), were more strongly related to the changes of other CSVD markers and also to baseline processing speed performance. Further, the number of lacunes rather than their volume reflected the severity of CSVD. With respect to the studied covariates, we revealed that higher education had a protective effect on subsequent total WMH, pWMH, lacunar number, NAWM volume, and processing speed performance. The indication of antihypertensive drugs was associated with lower lacunar number and volume at baseline and the indication of anti-hypercholesterolemic drugs came along with higher processing speed performance at baseline. In summary, our results confirm previous findings, and extend them by providing information on true within-person changes, relationships between the different CSVD markers and brain-behavior associations. The moderate to strong associations between changes of the different CSVD markers indicate a common pathological relationship and, thus, support multidimensional treatment strategies.

### 1. Introduction

The medical term «cerebral small vessel disease» (CSVD) refers to clinical and imaging findings that result from abnormalities in perforating cerebral arterioles, capillaries, and venules (Shi and Wardlaw, 2016). In accordance to the STandards for ReportIng Vascular changes on nEuroimaging (STRIVE), signs of CSVD include recent small subcortical infarcts, white matter hyperintensities (WMH) of presumed vascular origin, lacunes of presumed vascular origin, perivascular spaces (PVS), cerebral microbleeds, and brain atrophy (Wardlaw et al., 2013). Singly, these lesions may be clinically silent, and many affected individuals are asymptomatic, but in combination and in increasing number, single CSVD markers are associated with cognitive impairment,

dementia, depression, gait problems, and increased risk of stroke (Debette et al., 2019). According to Pantoni (2010), 45% of dementia cases, 25% of ischemic (or lacunar) strokes, and 20% of all strokes around the globe are caused by CSVD. In turn, with the rapidly aging population, cognitive impairment due to CSVD is becoming more common (Baker et al., 2012), and burdens societies worldwide. Advanced age is strongly associated with WMH (Brickman et al., 2008b; Chowdhury et al., 2011), reflected by the fact that up to 90% of the adult population older than 65 years present WMH on magnetic resonance images (MRI) (Schmidt et al., 2016). Higher age is also an important risk factor for lacunes (Ghaznawi et al., 2019), whose prevalence ranges from 11% to 31% in healthy older (Bernick et al., 2001; Han et al., 2018; Howard et al., 1998; Longstreth et al., 1998; Price et al., 1997; Schmidt

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et al., 2005; Vermeer et al., 2002). Another major risk factor for WMH and lacunes is hypertension (Dufouil et al., 2001) – specifically a high systolic blood pressure (Maillard et al., 2012). Other risk factors previously identified are smoking (Gons et al., 2011; Jeerakathil et al., 2004; Moroni et al., 2018), type-2 diabetes (Ling and Chabriat, 2020; van Harten et al., 2007), late-life depression (Firbank et al., 2012; Herrmann et al., 2008), and recently also visceral obesity (Kim et al., 2017; Lampe et al., 2019b). On the positive side, it has been shown that lifestyle adjustments, like physical activities, for which robust evidence exists in the secondary prevention of cardiovascular events (Williams et al., 2018), can slow the progression of CSVD (Franchetti et al., 2020; Landman et al., 2021; Torres et al., 2015). In addition, reserve and compensatory mechanisms slow down the progression of CSVD, at least until these mechanisms are exhausted and functional performance declines after all (Ter Telgte et al., 2018).

Frequently reported pathophysiology of WMH are demyelination, loss of oligodendrocytes, and axonal damage (Fazekas et al., 1993; Fazekas et al., 1998; Gouw et al., 2011; Grueter and Schulz, 2012; Shi and Wardlaw, 2016). Other studies also suggest fluid leakage due to a disrupted blood–brain barrier (BBB) (Black et al., 2009; Muñoz Maniega et al., 2017), as well as ischemia, infarction, inflammation, increased vascular permeability, and venous insufficiency as causes (E. Smith et al., 2017). Importantly, different appearances of WMH indicate different degrees of severity of the underlying pathological changes. For example, Alber et al. (2019) described that mild tissue changes, presented as punctate WMH, are associated with myelin damage, gliosis, and PVS, whereas severe pathological changes, described as confluent WMH, include some degree of myelin loss, axonal disruption, and astrogliosis.

WMH appear hyperintense on T2-weighted MR-images such as fluid-attenuated inversion recovery (FLAIR) images (Schmidt et al., 2011; Wardlaw et al., 2013). WMH can be divided into periventricular (pWMH) and deep WMH (dWMH) (De Groot et al., 2002), which appear to represent functionally, histopathologically, and etiologically distinct entities (Kim et al., 2008).

Cross-sectional studies with data from non-demented older adults demonstrated that higher WMH load is related to poorer cognition (Godin et al., 2010; Timothy, 2015), particularly in executive functioning (Lampe et al., 2019a) and in processing speed (Nebes et al., 2006; van den Heuvel et al., 2006). Also, longitudinal studies confirmed associations of WMH load increases and cognitive function losses, especially in processing speed, as summarized in a recent meta-analysis by Caunca et al. (2019).

When looking more specifically at the two subtypes of WMH, pWMH and dWMH, the associations with cognitive ability are more heterogeneous. For example, van den Heuvel et al. (2006) showed negative associations between pWMH load and processing speed performance, while two recent studies conclude that dWMH are functionally more relevant than pWMH (Brugulat-Serrat et al., 2020; Wen et al., 2006). In line with the latter, C. D. Smith et al. (2016) reported that elevated dWMH compared to pWMH were more likely to be associated with a diagnosis of vascular dementia (VAD) than Alzheimer's disease (AD) – concluding that dWMH go along with more pervasive impairment than pWMH.

Lacunes are fluid-filled cavities with a signal intensity similar to the cerebrospinal fluid (CSF), round or ovoid, subcortical, of between 3 and 15 mm in diameter (Wardlaw et al., 2013), and represent areas of infarction (Vermeer et al., 2003a). Lacunes are not only detected in stroke patients or in patients with dementia, but also in healthy older individuals. Because of the latter, lacunes have been found to be a major cause of so-called «silent infarcts» in the elderly (Vermeer et al., 2003b). Previous research has concluded that these «silent infarcts» were not clinically silent but could be a factor inducing cognitive dysfunction, especially executive functioning and processing speed (Azeem et al., 2020; Lei et al., 2019). Moreover, it was shown that elderly subjects with lacunes exhibit a greater cognitive decline than people without lacunes

and an increased risk of developing dementia than people without lacunes (Vermeer et al., 2003b). Although lacunes have been associated with decreased cognitive performance in population-based cohort studies of the elderly, very few longitudinal studies examined non-demented samples (Azeem et al., 2020; Caunca et al., 2019).

Brain atrophy occurs with the normal aging process, although the extent varies interindividually. In healthy older adults above 65 years, age-related brain atrophy amounts to ~1% per year (Longstreth et al., 1998; Price et al., 1997; Vermeer et al., 2003a). Higher rates are observed in pathological diseases, such as Alzheimer's disease (Fox and Freeborough, 1997; Karas et al., 2004). The importance of brain atrophy as a marker of CSVD has long been underestimated (Jouvent et al., 2010). Associations between brain atrophy and other CSVD markers, namely WMH load and number of lacunes, have been reported in previous studies (Appelman et al., 2009; Jouvent et al., 2007; Kloppenborg et al., 2012).

Because of the frequent coexistence of the different CSVD markers, even in healthy older individuals, we consider it relevant to include the different CSVD markers in one study to learn more about potentially cumulative effects. To our knowledge, there is no single-center study to date that has examined a comprehensive set of CSVD markers with multiple measurement occasions in the context of healthy aging over such a long period of time.

Based on the gaps in previous literature, we used longitudinal data from healthy older adults that cover a time period of seven years to analyze WMH (total, periventricular, deep), lacunes (number, volume), brain parenchyma volume (BPV) and normal appearing white matter (NAWM) volume and changes in those CSVD markers over time. We further explored associations between the CSVD markers and tested the influence of demographic characteristics (age, sex, education), medication use (antihypertensives, antihypercholesterolemics) and risk factors previously associated with CSVD (obesity and depressive symptoms). Finally, we were interested in the associations between CSVD markers and processing speed – a fluid cognitive ability that is markedly affected also in the process of healthy aging (Oschwald et al., 2019). We analyzed the data using the approach of latent growth curve (LGC) modeling (Bollen, 2005; McArdle and Epstein, 1987; Meredith and Tisak, 1990).

## 2. Material and methods

### 2.1. Study sample

Longitudinal magnetic resonance imaging (MRI) and cognition data were taken from the Longitudinal Healthy Aging Brain (LHAB) database (Zöllig et al., 2011). We used data from five measurement occasions (baseline, 1-year follow-up, 2-year follow-up, 4-year follow-up, 7-year follow-up). The baseline dataset included 232 participants (mean age baseline:  $M = 70.8$ ; range: 64–87; F:M = 114:118). At each measurement occasion, participants completed an extensive battery of neuropsychological and psychometric cognitive and motor assessments and underwent brain imaging. The brain imaging session was conducted in close temporal proximity to the behavioral assessments (difference between behavioral and MRI assessments in days ( $M \pm SD$ ): baseline:  $2.2 \pm 5.2$ , 1-year follow-up:  $2.6 \pm 5.2$ , 2-year follow-up:  $4.3 \pm 13.0$ , 4-year follow-up:  $4.6 \pm 9.3$ , 7-year follow-up:  $6.7 \pm 8.0$ ). Inclusion criteria for study participation at baseline were age  $\geq 64$ , right-handedness, fluent German language proficiency, a score of  $\geq 26$  on the Mini Mental State Examination (MMSE; Folstein et al., 1975), no self-reported neurological disease of the central nervous system and no contraindications to MRI. The study was approved by the ethical committee of the canton of Zurich. Participation was voluntary and all participants gave written informed consent in accordance with the declaration of Helsinki.

For the present analysis, participants were excluded if either structural MRI or cognition data were missing for all measurement occasions. With this criterion we were able to include 231 participants from the

LHAB baseline sample (mean age at baseline:  $M = 70.8$ , F:M = 113:118). The MR images were reviewed by a neuroradiologist with over 30 years of experience to assure that they are free of intracranial hemorrhages, intracranial space occupying lesions, multiple sclerosis lesions or large chronic, subacute or acute infarcts. Five T1w images had to be excluded due to insufficient MRI data quality. Further, 38 data points were excluded from analysis due to the use of drugs affecting the central nervous system (hypnotics, sedatives and anxiolytics, opioids, antipsychotics, antidepressants, anticonvulsants), three data points due to a drop of the MMSE score below 23 points during the follow-up measurements and another eight data points due to either process errors during segmentation or massive WMH segmentation errors. Outlier values in CSVD load and processing speed performance were removed using a moderately conservative cut-off of 2.5 median absolute deviations (MADs) above or below the sample's distribution, respectively (Leys et al., 2013). This resulted in a baseline sample size of  $N = 216$  (mean age at baseline:  $M = 70.9$ , range = 64–87, F:M = 105:111), with 51.4 % holding a bachelor's, master's, or doctoral degree and achieving a median IQ of 124 [range = 93–145]. At the 7-year follow-up, the dataset comprised 51.9 % of our baseline sample ( $N = 112$ , mean age:  $M = 76.7$ , range = 71.5–89.3, F:M = 44:68). As reported in other publications with this sample (Malagurski et al., 2020; Oschwald et al., 2019), selectivity analyses showed that the participants remaining in the study did not substantially differ from the baseline sample in terms of age, education or physical and mental health.

## 2.2. MRI data acquisition

Longitudinally structural MRI data were acquired at the University Hospital of Zurich on a Philips Ingenia 3 T scanner (Philips Medical Systems, Best, The Netherlands) using the dsHead 15-channel head coil. T1w images were recorded with a 3D T1w turbo field echo (TFE) sequence, repetition time (TR): 8.18 ms, echo time (TE): 3.799 ms, flip angle (FA): 8°, 160 × 240 × 240 mm<sup>3</sup> field of view (FOV), 160 sagittal slices, in-plane resolution: 256 × 256, voxel size: 1.0 × 0.94 × 0.94 mm<sup>3</sup>, scan time: ~7:30 min. The 2D FLAIR image parameters were: TR: 11000 ms, TE: 125 ms, inversion time (TI): 2800 ms, 180 × 240 × 159 mm<sup>3</sup> FOV, 32 transverse slices, in-plane resolution: 560 × 560, voxel size: 0.43 × 0.43 × 5.00 mm<sup>3</sup>, interslice gap: 1 mm, scan time: ~5:08 min. The 3D FLAIR image parameters were: TR: 4800 ms, TE: 281 ms, TI: 1650 ms, 250 × 250 mm FOV, 256 transverse slices, in-plane resolution: 326 × 256, voxel size: 0.56 × 0.98 × 0.98 mm<sup>3</sup>, scan time: ~4:33 min.

The T1w and FLAIR images were used for the automated segmentation of the WMH. 3D FLAIR images were only considered (sporadically) for the differentiation between PVS and lacunes.

## 2.3. Definition and terminology of the cerebral small vessel diseases measures

The terminology and definitions of the subclinical CSVD used in this study are in line with the STRIVE (Wardlaw et al., 2013).

**White matter hyperintensities of presumed vascular origin** have a variable diameter, appear hyperintense on T2w MRI sequences, like FLAIR sequences, and isointense or hypointense on T1w sequences but not as hypointense as CSF – without cavitation (Wardlaw et al., 2013). We categorized the WMH volumes into total WMH (tWMH), pWMH and dWMH. In this work, we used the term white matter hyperintensities (WMH) for those of presumed vascular origin and found in white matter without those found in deep gray matter (GM) and brainstem (Wardlaw et al., 2013).

**Lacunes of presumed vascular origin** are small round or ovoid, CSF-filled cavities (Wardlaw, 2008), have a size of between 3 mm and 15 mm in diameter. A hyperintense rim can be seen on FLAIR images but it is non-specific since a hyperintense rim can also surround PVS when they pass through a WMH. Sometimes the lacunes may appear totally hyperintense due to not suppressed central cavity fluid on FLAIR images

(Wardlaw et al., 2013). Therefore, it is important to examine the same lesion in successive slices of a given MR image and in different MR modalities (i.e., T1w in addition to FLAIR images, and exclude the lacunes in WMH segmentation. We carefully distinguished lacunes from PVS according to the STRIVE, and calculated an interrater reliability of two operators. The measures of interest were number of lacunes and lacunar volume. In this work, we referred to lacune(s) as those of presumed vascular origin.

**Brain parenchyma volume.** Parenchyma is the term for organ-specific tissue that determines the function of an organ. In the brain, the functional neurons form the brain parenchyma (Psyhyrembel, 2020). Since lacunes are filled with CSF (Wardlaw, 2008) we subtracted the lacunar volumes from the BPV as they contain no functional neurons.

**Normal-appearing white matter volume** is referred to the normal, non-diseased cerebral white matter (WM) tissue. For this reason, we subtracted the WMH and lacunar volume from the cerebral white matter volume.

## 2.4. Demographic factors, medication use and risk factors

The demographic factors we controlled were *age*, *sex*, and *education*. *Antihypertensives* and *antihypercholesterolemics* were defined by self-reported physician prescription for the respective drug used to treat the condition. Height and weight were used to calculate the body mass index (BMI) (weight-height-ratio in kg/m<sup>2</sup>) to define *obesity* by a mean BMI across all time points of  $\geq 30$  kg/m<sup>2</sup> according to WHO (World Health Organisation Obesity, 2000). *Depressive symptoms* were assessed using the German version of the Hospital Anxiety and Depression Scale (HADS-D) using the cut-off of  $\geq 8$  points (Herrmann-Lingen et al., 2011). Age was the only metric variable, sex, medication use and the risk factors were dichotomous variables.

## 2.5. Assessment of cognition

The *global cognitive status* was estimated with the MMSE (Folstein et al., 1975), and the *global intelligence* with a German multiple-choice vocabulary intelligence spot-the-word test, the so-called Mehrfachwahl-Wortschatz-Intelligenztest, version B (MWT-B) (Lehrl, 2005). It is well known that crystalline abilities that capture, for example, vocabulary do not decline with increasing age and the MWT-B can thus be seen as an economic estimator of global intelligence. The cognitive ability measures of the subjects are listed in Supplementary Table 1.

*Processing speed* was measured using the number of correct responses from (a) the Digit Symbol (DS) – subtest of the German version of the Wechsler Adult Intelligence Scale (WAIS-III) (WIE; von Aster et al., 2006), (b) the Identical Pictures Test (IPT) (KIT; Ekstrom et al., 1976), (c) the subtest 14 of the Leistungsprüfungssystem 50+ (LPS 50+) (Sturm et al., 1993), a German intelligence test developed to measure Thurstone's (Thurstone, 1938) primary mental abilities, and (d) from the completion time of the Trail-Making-Test, part A (TMT-A) (Reitan and Wolfson, 2004) (the scores were reversed so that the higher scores equaled better performance and vice-versa). The individual scores of processing speed were standardized to  $T$  scores ( $M = 50$ ,  $SD = 10$ ) with respect to baseline and averaged across subtests to calculate the domain-average composite scores. For a description of the measured skill(s) by test on processing speed, see Supplementary Table 2.

## 2.6. Assessment of cerebral small vessel disease measurements

### 2.6.1. White matter hyperintensities

For automatically quantifying the WMH subtypes we used the WMH volumes outputted by unidentified bright objects (UBO) Detector (Jiang et al., 2018) – a  $k$ -nearest neighbor ( $k$ -NN) algorithm. In our previous paper we comprehensively validated and compared these UBO Detector WMH volumes of tWMH, pWMH, and dWMH with other automatic or semi-automatic WMH extraction methods (Hotz et al., 2020).

We applied a Diffeomorphic Anatomical Registration through Exponentiated Lie template (Ashburner, 2007) of 70–80 years to best approximate the age of our cohort and a GM mask to reduce the possibility of false positive voxels. To define the borders of pWMH we choose the 12 mm threshold as recommended by Jiang and colleagues (2018). The customization of the WMH probability maps was done in our previous study (Hotz et al., 2020) evaluating different thresholds and nearest neighbors ( $k$ ) between manually segmented WMH and the WMH outputted by UBO Detector using different accuracy measures. The best performance was achieved with a threshold of 0.9 and a NN of  $k = 3$ . In this preceding study, the tWMH, pWMH, and dWMH volumes, estimated by UBO Detector (2D FLAIR + T1w input), were strongly correlated with the Fazekas scores ( $N = 756$ ; tWMH =  $r_s = 0.80$ , pWMH =  $r_s = 0.74$ , dWMH =  $r_s = 0.60$ ). The Dice Similarity Index (DSC) between manually segmented WMH and automated segmented WMH by UBO Detector was also good to very good ( $n = 16$ ; DSC = 0.531,  $SD = \pm 0.113$ ) according to Dadar et al. (2017).

Consistent with the STRIVE, we excluded the WMH volume lesions in the brainstem from the tWMH volume (tWMH volume = pWMH volume + dWMH volume + WMH volume in cerebellum), since UBO Detector includes them in the «whole brain WMH volume». WMH volumes outputted by UBO Detector are in DARTEL space, and are therefore not necessary to adjust for intracranial volume (ICV). For additional quality assurance, every WMH map was visually checked using FSLeves (McCarthy, 2018) for false positives and to ensure that all lacunes were correctly removed from the WMH segmentation. For one subject with lacunes, UBO Detector did not omit the WMH in which lacunes were located. For this subject, the incorrectly segmented voxels were added to the correct segmentation volumes, a procedure that has been reported in previous studies (e.g., Ghaznawi et al., 2018).

### 2.6.2. Lacunes

Lacunes were segmented manually, their volume in  $\text{mm}^3$  and the lacunar number were extracted and outputted with Python (Rossum et al., 2009) (version 3.7.4) using pandas (The pandas development team, 2020). The estimation of the lacunar volume was extracted within each parcel of FreeSurfer's white matter parcellation (wmparc.mgz) so that the volumes within the brainstem could be estimated for later subtraction from NAWM volume. To distinguish lacunes from PVS we used a combination of FLAIR (2D and 3D) and T1w images following the STRIVE criteria including size (3–15 mm), signal intensity on MR images (similar to that of CSF on all sequences, and usually a hyperintense rim), and orientation (follow the typical course of a vessel as it goes through gray or white matter). The inter-rater reliability was determined on 13 randomly selected scans with lacunes and PVS as follows: Operator 1 marked 100 lesions in the 13 scans that could be either a lacune or a PVS with a voxel on the axial T1w scan. Operator 2 and 3 divided the lacunes and PVS independently into the two categories (0 = PVS; 1 = lacune) (Cohen's kappa = 0.94). The lacunar volume was adjusted for brain size using FreeSurfer's estimated Total Intracranial Volume (eTIV).

### 2.6.3. Brain parenchyma volume and normal appearing white matter volume

We used FreeSurfer v6.0.1 (Fischl, 2012) as implemented in the FreeSurfer BIDS-App (Gorgolewski et al., 2017) to obtain volumetric measurements. Global volume measurements were also extracted from FreeSurfer's aseg segmentation. FreeSurfer's longitudinal analysis stream was applied to ensure an unbiased registration between time points. We estimated BPV and NAWM as follows (both metrics do not include the brainstem): (1) BPV = total GM volume (lhCortex + rhCortex + SubCortGray + CerebellumGM) + total WM volume (lhCerebralWhiteMatter + rhCerebralWhiteMatter + WM hypointensities + Cerebellar White Matter Volume) - lacunar volume, (2) NAWM volume = total WM volume (lhCerebralWhiteMatter + rhCerebralWhiteMatter + WM hypointensities + Cerebellar WM Volume) - tWMH volume UBO Detector (without WMH in brainstem) - lacunar

volume (without lacunes in brainstem). BPV and NAWM volume was adjusted for brain size using FreeSurfer's eTIV.

### 2.7. Computer equipment

All CSVD measurements were undertaken on a Supermicro X8QB6 workstation with 4 × Intel Xeon E57-4860 CPU (4 x10 cores, 2.27 GHz) and 256 GB RAM. The computing host was a KVM virtualized guest instance with Ubuntu 18.04.4 LTS with 32 × Intel Xeon E7-4860 CPU (2.27 GHz) and 92 GB RAM.

### 2.8. Statistical analysis

All statistical analyses were done in R version 4.0.3 (R Core Team, 2020). WMH volumes and lacunar volumes were natural log-transformed ( $\log_e(x)$ ) to obtain a normal distribution since the original data followed a log-normal distribution. The defined  $p$  value threshold was set to  $p \leq 0.05$ . The results of the univariate LGC model with the covariates, and the effect size estimates for the covariances (univariate and bivariate LGC models) were reported as standardized effect estimates ( $\beta$ ) to provide comparable, unit-independent measures of effects for different determinants and outcomes. These correlation coefficients were interpreted according to Cohen (1992): 0.10 = weak effect, 0.30 = moderate effect, 0.50 = strong effect size.

#### 2.8.1. Inference statistics of demographic characteristics of the lacunes versus the non-lacunes group

To compare the age in the population with lacunes to those without lacunes a Welch two-sample  $t$ -test was performed. For the variable sex and medication use ( $n > 50$ ), differences were determined using the Pearson's Chi-squared test ( $\chi^2$ -test) with Yates' continuity correction, for the variable education, no correction was applied because the degrees of freedom (df) were 2. For the risk factors obesity and depressive symptoms (expected cell frequency  $n < 5$ ) a Fisher's exact test was applied (Table 2).

#### 2.8.2. Latent growth curve modeling

Since the LGC modeling framework is more flexible than traditional approaches such as ANOVA or multiple regressions, and also allows for the inclusion of covariates in the same model (Duncan and Duncan, 2009), we chose this statistical procedure to answer our longitudinal research questions:

- 1) How do the trajectories of CSVD and processing speed measures evolve over the 7-year period, and is there interindividual variance in intercept and slope?
- 2) Are CSVD and processing speed measures and their trajectories over time influenced by demographic factors, medication use, and risk factors?
- 3) Are there baseline-change associations for the different CSVD and processing speed measures (i.e., does baseline lacunar volume predict lacunar volume changes?)
- 4) Are there cross-domain associations of CSVD and processing speed measures at baseline? Do baseline levels in one domain predict the amplitude of change in the other, and can we find evidence for coupled changes?

For questions 1), 2) and 3) we estimated univariate LGC models, and for question 4) bivariate LGC models in the structural equation modeling (SEM) framework using the lavaan package version 0.6–7 (Rosseel, 2012) in R. Missing values were treated as Missing at Random (MAR) (R. J. A. Little, 1995). Thus, these values could be preserved in the model using Full Information Maximum Likelihood Estimation (FIML) (Finkelbeiner, 1979; Schafer and Graham, 2002) to handle incomplete data, which is clearly an advantage of LGC modeling techniques over other techniques. Furthermore, we included the following covariates into the

univariate models: age at baseline (0 = 70 years – median of the sample), sex (0 = female, 1 = male), education (set to level 2 – medium level), antihypertensives (0 = no, 1 = yes), antihypercholesterolemics (0 = no, 1 = yes), obesity (0 = no, 1 = yes), and depressive symptoms (0 = no, 1 = yes). For subjects with lacunes ( $n = 58$ ) the distribution of the covariate depressive symptoms was too small ( $n = 1$ ), and it was therefore excluded as covariate from the univariate model. Consequently, the intercept parameter corresponded to the estimate for a 70-year-old woman with a medium level of education (high schools, secondary technical schools), and no evidence of the aforementioned intake of medication or risk factors.

2.8.3. Univariate latent growth curve

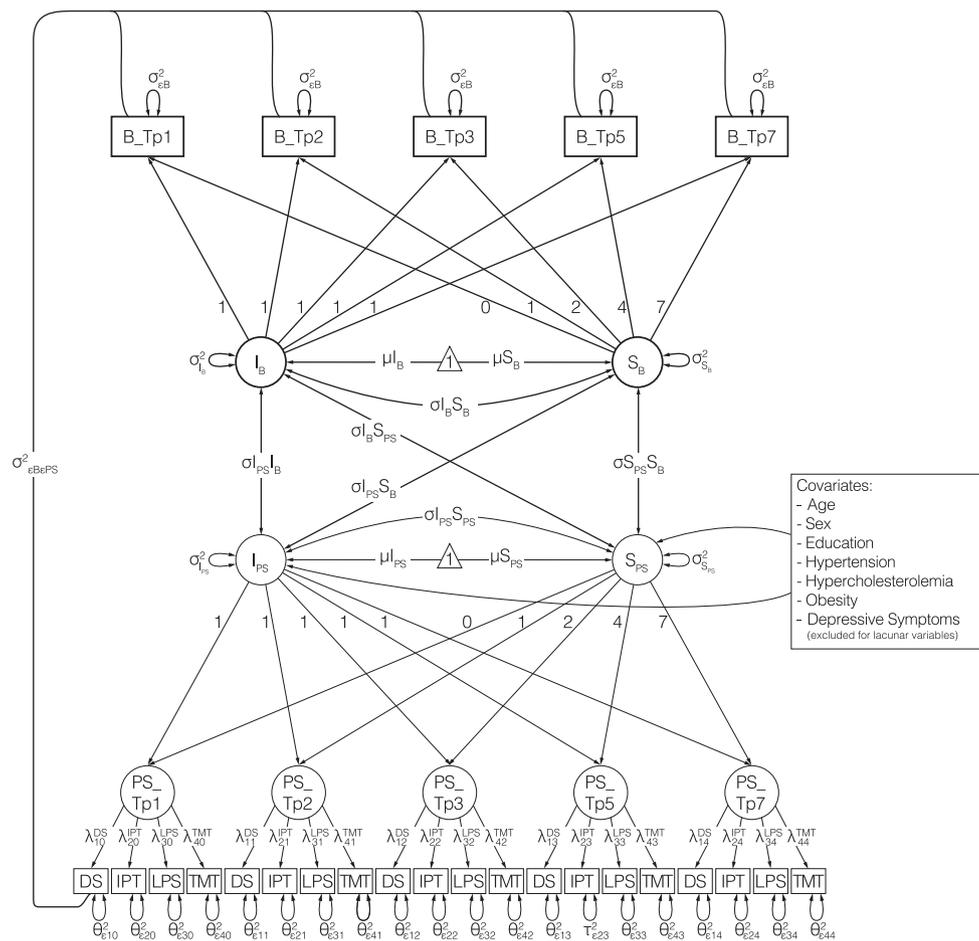
To model the trajectories of CSVD we built a 1st-order Latent Growth Curve (1LGC) model to estimate latent intercepts and slopes, as well as their variances. The variances of the manifest variables were held constant (theta), assuming strict measurement invariance. To maintain uniform intervals between measurement occasions, we included a latent placeholder variable for the follow-up years 3, 5, and 6 (T. D. Little, 2013). We estimated a latent intercept (I) and slope factor (S) to capture baseline levels and overall change across time. The means of these factors reflected the mean baseline value (Intercept) and the annual change (Slope) in the specific variable across the entire sample (i. e., fixed effects). In addition, the variances of these latent factors reflected the

variability between persons (i. e., random effects). For processing speed, we calculated a 2nd-order Latent Growth Curve (2LGC) model on the basis of four manifest indicators (four test scores). The exact procedure for this is described under **Factorial invariance – processing speed**, and a simplified path diagram is depicted in Fig. 1.

The overall model fit was evaluated by the ratio of the  $\chi^2$ -test to the respective degrees of freedom ( $\chi^2 / df$ ) (Jöreskog and Sörbom, 1993; Marsh and Hocevar, 1985), the Comparative Fit Index (CFI) (Bentler, 1990), and the root mean square error of approximation (RMSEA) (Browne and Cudeck, 1992; Steiger and Lind, 1984). Good model fit was defined as:  $\chi^2 / df \leq 2$ , CFI > 0.97, RMSEA  $\leq 0.05$  while adequate fit was defined as  $\chi^2 / df \leq 3$ , CFI > 0.95, RMSEA 0.05 – 0.08 (Hu and Bentler, 1998; Jöreskog and Sörbom, 1993; Schermelleh-Engel et al., 2003).

2.8.4. Factorial invariance – processing speed

For each time point, we modeled a processing speed factor that captured the shared variance of the four manifest test values (1st-order factors). From these latent processing speed factors, in turn, the 2nd-order factors were calculated, consisting of a latent intercept ( $I_{PS}$ ) and slope ( $S_{PS}$ ). To ensure that the same construct is assessed on the same metric across every measurement (Meredith and Teresi, 2006; Meredith, 1993) we tested the factorial invariance (FI) across time by comparing four models (configural, weak, strong, and strict invariance constraints) according to Widaman et al. (2010). We assumed that the model with



**Fig. 1.** Simplified path diagram of linear growth curve (LGC) models associating the trajectories of the cerebral small vessel disease (CSVD) measure (brain variables B) to the trajectories of the processing speed (PS) measure over five-time points (Tp1, Tp2, Tp3, Tp5, Tp7). The diagram shows the univariate models (thin lines), the bivariate models (bold lines), and the covariates (box). Circles represent latent variables; squares represent observed variables. One-headed arrows stand for regression paths, two-headed arrows represent variances and covariances of latent variables (sigma;  $\sigma$ ). Parameters with the same label are fixed to be equal. Intercept and slope of CSVD ( $I_B$ ,  $S_B$ ) and PS ( $I_{PS}$ ,  $S_{PS}$ ) are controlled for the covariates. CSVD is measured as 1st-order Latent Growth Curve (1LGC) model, and PS estimated as 2nd-order Latent Growth Curve (2LGC) model with a latent construct (at each measurement occasion, with four manifest indicators). Strong factorial invariance (FI) is applied to the PS model by setting the factor loadings and intercepts of the manifest indicators equal over time. Correlated residuals of the same manifest indicator over time were estimated, but are also not shown for visual clarity. As in all fitted models, the residuals were assumed to be the same over the time points and the residual-residual associations were also assumed to be the same for each time point. An exception is the model for PS. The strong model had a better fit than the strict model, so that the error variance (theta;  $\theta$ ) was not kept constant here. For simplicity, the latent placeholder variables (Tp4, Tp6), and the training effect slope for the PS measures are not shown. For visual clarity the manifest indicator intercepts ( $\tau$ ) are not shown. DS = Digit Symbol task; IPT = Identical Picture Test; LPS = Leistungsprüfungssystem 50+, subtest 14; TMT

= Trail Making Test, part A.

strong FI would achieve an adequate fit for the latent processing speed variables. In this model, both the loadings of the observed indicators ( $\lambda$ ) on the latent factor, and the indicator intercepts ( $\tau$ ) were constrained to be equal across measurement occasions (Widaman et al., 2010) (see also Fig. 1). To compare the four models, the  $\chi^2$ -test (for nested models), and the sample size adjusted Bayesian Information Criterion (BIC) (Raftery, 1995) were used. With the BIC, smaller values meant a better model fit (Raftery, 1995). The threshold for the  $\chi^2$ -test was set down to  $p < .01$  to reduce the probability of type I errors, although, as noted before, these could not be explicitly controlled for and thus not entirely ruled out.

### 2.8.5. Training effect in processing speed tests

Repeated testing of the same person over time may result in a training effect (TE) and thus lead to better results over time. Training effect and true performance of the person mix inseparably and result in a complex trajectory. Nevertheless, to obtain an estimate for the TE we modeled a 2nd-order latent variable (loading baseline = 0, loading follow-up 1 to follow-up 7 = 1). The variance of this factor was set to 0, corresponding to a main effect that is the identical for all individuals.

### 2.8.6. Bivariate latent growth curve models (intercept-intercept/intercept-slope/slope-intercept/slope-slope)

To estimate cross-domain relations between CSVD indicators and processing speed, we combined the univariate LGC models into bivariate LGC models, see also Fig. 1. In these models, we set the covariance of the manifest cross-domain variable to equal (covariance of, e. g., tWMH and NAWM is the same at time point 1 as at the remaining time points). Further, we modeled covariances between the intercepts and between the slopes as well as between the intercept and slopes of the respective variables, to examine the temporal dynamics in more detail, and thus to

answer our research question 4).

We simplified the bivariate model for the variables *lacunar volume* and *lacunar number* due to the small sample size ( $n = 58$ ) for subjects with lacunes. We therefore calculated a 1LGC with the factor loadings for processing speed from the 2LGC model to ensure the comparability of the results of question 4) (see the processing speed-loadings below Supplementary Table 6).

## 3. Results

In the first section, an overview of the characteristics of the study cohort is shown in Table 1. Plots of individual trajectories of CSVD and processing speed measures across chronological age, separately for men and women, are shown in Supplementary Fig. 1. In the following, the study questions are answered: Table 3 lists the annual changes in percentage for the CSVD and processing speed measures, and Table 4 summarizes the inner-domain results of the univariate LGC models with the influences of the covariates on the CSVD and processing speed variables. The results of the last two study questions regarding the univariate inner-domain covariances and the cross-domain bivariate correlations of the CSVD and processing speed measures are combined in Table 5.

Model estimates and fit parameters are listed in Supplementary Table 3, Supplementary Table 3, and Supplementary Table 6.

### 3.1. Changes of CSVD markers and processing speed over time

#### 3.1.1. White matter hyperintensities

Total WMH showed an average overall volume of 11.52 cm<sup>3</sup> ( $\pm$ SD 9.18 cm<sup>3</sup>). The majority of the WMH were in the periventricular region

**Table 1**  
Characteristics of the study cohort.

Demographic characteristics	All data points	Tp1	Tp2	Tp3	Tp5	Tp7
<b>Number of subjects, n</b>	828	216	189	164	147	112
Age, mean (SD) (years) <sup>a</sup>	72.8 (5.1)	70.9 (5.1)	71.9 (5.1)	72.6 (4.8)	73.8 (4.0)	76.7 (4.0)
Sex, female, n (%)	382 (46.1)	105 (48.6)	90 (47.6)	78 (47.6)	65 (44.2)	44 (39.3)
<b>Education category, n (%)<sup>b</sup></b>						
Secondary with/without apprenticeship		60 (28.6)				
High schools, secondary technical schools		42 (20.0)				
Bachelor, Master, Doctorate		108 (51.4)				
<b>Medication use n (%)<sup>c</sup></b>						
Antihypertensives	366 (49.1)	84 (41.2)	83 (47.7)	76 (51.4)	59 (50.9)	64 (61.5)
Antihypercholesterolemics	144 (19.3)	32 (15.7)	28 (16.1)	32 (21.6)	30 (25.9)	22 (21.2)
<b>Risk factors n (%)<sup>b</sup></b>						
Obesity, BMI $\geq 30$	59 (8.4)	10 (6.0)	17 (9.9)	15 (10.1)	9 (7.9)	8 (8.0)
Depressive symptoms (HADS-D $\geq 8$ )	54 (7.3)	8 (3.9)	15 (8.7)	11 (7.6)	10 (8.5)	10 (9.6)
<b>WMH, mean volume (SD)<sup>d</sup></b>						
Total WMH volume cm <sup>3</sup>	11.52 (9.18)	10.37 (8.54)	10.90 (8.58)	11.45 (9.10)	12.14 (9.60)	14.07 (10.43)
Total pWMH volume cm <sup>3</sup>	8.69 (7.29)	7.68 (6.61)	8.27 (7.10)	8.76 (7.58)	9.25 (7.89)	10.47 (7.34)
Total dWMH volume cm <sup>3</sup>	3.58 (6.36)	3.29 (6.08)	3.40 (5.83)	3.71 (7.18)	4.10 (7.85)	3.53 (3.88)
<b>Lacunes</b>						
Number of Subjects, n (% of the entire dataset)	242 (29.23)	58 (26.85)	57 (30.16)	48 (29.27)	44 (29.93)	35 (31.25)
Mean volume mm <sup>3</sup> (SD) <sup>e</sup>	63.4 (63.2)	57.5 (57.3)	62.8 (63.7)	65.7 (65.3)	64.4 (66.4)	69.9 (67.3)
Mean lacunar number [range]	4.35 [1–18]	4.35 [1–14]	4.17 [1–14]	4.42 [1–16]	4.68 [1–18]	4.37 [1–13]
<b>Brain volumes, mean % (SD)<sup>e</sup></b>						
BPV in cm <sup>3</sup>	1029.3 (76.0)	1037.6 (77.7)	1031.2 (77.7)	1030.0 (78.5)	1026.1 (74.7)	1012.5 (71.0)
<b>Number of subjects, n</b>	<b>821</b>	<b>213</b>	<b>188</b>	<b>163</b>	<b>145</b>	<b>112</b>
NAWM in cm <sup>3</sup>	444.41 (47.8)	450.17 (46.2)	445.70 (49.9)	444.67 (48.8)	443.41 (45.8)	430.00 (46.3)

Notes: Education according to International Standard Classification for Education (ISCED): 1 = Secondary with/without apprenticeship, 2 = High schools, secondary technical schools, 3 (ISCED 6, 7, 8) = academic career: Bachelor, Master, Doctorate. Obesity = BMI  $\geq 30$  kg/m<sup>2</sup> according to WHO (World Health Organisation Obesity, 2000). HADS-D = Depression variables from the German version of the Hospital Anxiety and Depression Scale (HADS-D) (Herrmann-Lingen et al., 2011).

WMH = white matter hyperintensities; pWMH = periventricular white matter hyperintensities; dWMH = deep white matter hyperintensities; BPV = brain parenchyma volume; NAWM = normal appearing white matter volume.

<sup>a</sup> at the time of the MRI acquisition.

<sup>b</sup> via questionnaire.

<sup>c</sup> via medication.

<sup>d</sup> WMH volumes are in DARTEL space, and therefore not necessary to adjust for intracranial volume (ICV).

<sup>e</sup> Adjustment for brain size was done by using the residuals of least square derived linear regressu in between brain volumes and estimated total intracranial volume (eTIV) to calculate normalized brain volumes (Voevodskaya et al., 2014).

**Table 2**  
Comparison of subjects with lacunes ( $n = 58$ ) with subjects without lacunes ( $n = 158$ ).

Demographic characteristics	Subjects with lacunes at baseline	Subjects without lacunes at baseline	<i>p</i> -value
<b>Number of subjects, <i>n</i></b>	58	158	
Age, mean (SD) (years) <sup>a</sup>	72.6 (5.5)	70.24 (4.8)	<b>0.005</b>
Sex, female, <i>n</i> (%)	24 (41.4)	81 (51.27)	0.256
<b>Education category, <i>n</i> (%) <sup>b</sup></b>			0.480
Secondary with/without apprenticeship	15 (26.3)	45 (29.4)	
High schools, secondary technical schools	9 (15.8)	33 (21.6)	
Bachelor, Master, Doctorate	33 (57.9)	75 (49.0)	
<b>Medication use, <i>n</i> (%) <sup>c</sup></b>			
Antihypertensives	25 (44.6)	59 (39.9)	0.646
Antihypercholesterolemics	8 (14.3)	24 (16.2)	0.902
<b>Risk factors, <i>n</i> (%) <sup>b</sup></b>			
Obesity, BMI $\geq 30$	4 (8.16)	6 (5.0)	0.480
Depressive symptoms (HADS-D $\geq 8$ ) <sup>d</sup>	1 (1.75)	7 (4.7)	0.449

Notes: Age was compared using a Welch two-sample *t*-test. For Sex, Education and Medication use ( $n > 50$ ) the Pearson's Chi-square was used, for the risk factors (expected cell frequency  $n < 5$ ) a Fisher's exact test was applied. Education according to International Standard Classification for Education (ISCED): 1 = Secondary with/without apprenticeship, 2 = High schools, secondary technical schools, 3 (ISCED 6, 7, 8) = academic career: Bachelor, Master, Doctorate. Obesity = BMI  $\geq 30$  kg/m<sup>2</sup> according to WHO (World Health Organisation Obesity, 2000). HADS-D = Depression variables from the German version of the Hospital Anxiety and Depression Scale (HADS-D) (Herrmann-Lingen et al., 2011).

WMH = white matter hyperintensities; pWMH = periventricular white matter hyperintensities; dWMH = deep white matter hyperintensities; BPV = brain parenchyma volume; NAWM = normal appearing white matter volume.

<sup>a</sup> at the time of the MRI acquisition.

<sup>b</sup> via questionnaire.

<sup>c</sup> via medication.

<sup>d</sup> excluded as covariate from the univariate model.

(75.4%). On average, all WMH variables increased significantly ( $p < .0001$ ) over the 7-year period. The mean tWMH volume showed a yearly increase of 7.9%. Women showed on average a non-significantly faster acceleration per year in dWMH compared to men (7.5 % versus 5.8 %) (see Table 3). Further, all WMH variables showed interindividual variance in intercept (tWMH:  $\beta = 0.800$ , pWMH:  $\beta = 0.846$ , dWMH:  $\beta = 0.747$ ) and slope (tWMH:  $\beta = 0.858$ , pWMH:  $\beta = 0.916$ , dWMH:  $\beta = 0.862$ ).

### 3.1.2. Subjects with lacunes

At baseline, 26.9 % ( $n = 58$ ) of all subjects showed at least one lacune, whereas of these, 26.3% ( $n = 15$ ) showed a single lacune, and 74.1 % ( $n = 43$ ) showed multiple lacunes. Over the 7 years 38 subjects (65.5%) showed no incident lacunes, whereas 25 (43.1%) developed new lacunes. The mean lacunar number was 4.35 (median = 3) with a range of 1 to 18 lacunes, and the mean lacunar volume was 63.4 mm<sup>3</sup> (median = 44.6 mm<sup>3</sup>) and showed a range between 5.0 mm<sup>3</sup> and 347.5 mm<sup>3</sup>. Both variables increased significantly from baseline to 7-year follow-up ( $p < .0001$ ), and significant interindividual variance was demonstrated in intercept (lacunar volume:  $\beta = 0.753$ , lacunar number:  $\beta = 0.660$ ), and slope (lacunar volume:  $\beta = 0.786$ , lacunar number:  $\beta = 0.572$ ). The lacunar volume increased on average about 6.8% per year, and with each year of aging, the lacunar number increased on average around 4.6% – with no sex differences (see Table 3). 20.8 % (5/24) of the subjects in the lacune subgroup taking antihypertensives were also taking antihypercholesterolemics, and 62.5% (5/8) of subjects using antihypercholesterolemics were also taking antihypertensives. To investigate whether there were different characteristics between subjects with lacunes and those without lacunes, we compared these two

groups. According to the descriptive inferential statistics, the group with lacunes was significantly older on average at baseline ( $n = 58$ ; 72.6 years) and thus does not represent the same population as the group without lacunes ( $n = 158$ ; 70.2 years) (95%-CI[0.74, 3.99]),  $t(90.28) = 2.89$ ,  $p = .005$ ,  $d = 0.467$ . All other associations were not significantly different (see Table 2).

### 3.1.3. Brain parenchyma volume and normal appearing white matter volume

The BPV showed a mean volume of 1029.3 cm<sup>3</sup> at baseline, and it decreased significantly ( $p < .0001$ ) over the 7 years with a yearly mean decrease of 0.6%. Further, interindividual mean variance was evident in intercept ( $\beta = 0.561$ ), and slope ( $\beta = 0.896$ ). The mean volume of the NAWM was 444.4 cm<sup>3</sup>, and it showed a significantly average decline over the 7-year period ( $p < .0001$ ) with a yearly mean decline of 0.95%. Men showed a significantly ( $p < .006$ ) greater mean annual decline compared with women. BPV and NAWM volume showed interindividual variance in intercept (BPV:  $\beta = 0.561$ , NAWM:  $\beta = 0.656$ ) and slope (BPV:  $\beta = 0.896$ , NAWM:  $\beta = 0.841$ ). See Table 3 for more details.

### 3.1.4. Processing speed

For the description of the cognitive profile of the subjects at baseline see Supplementary Table 1. Processing speed declined significantly ( $p < .0001$ ) over the 7-year period with a yearly mean decline of 0.9% (see Table 3). There were interindividual differences in performance at baseline ( $\beta = 0.751$ ), and also the slope did significantly vary across the sample ( $\beta = 0.624$ ).

### 3.2. Associations of CSVD and processing speed measures with the covariates at baseline level (intercept–intercept), and with subsequent changes (intercept–slope)

Table 4 provides an overview of the results of the univariate models with the focus on the influencing factors on CSVD and processing speed measures. A summary of the univariate LGC model fits for linear trends for the CSVD and processing speed measures is listed in Supplementary Table 3.

#### 3.2.1. White matter hyperintensities and covariates

The older the subjects were at baseline the higher the WMH volume was at baseline: tWMH ( $p < .0001$ ), pWMH ( $p < .0001$ ), and dWMH ( $p < .0001$ ). Women showed higher tWMH ( $p = .021$ ), and higher pWMH ( $p = .002$ ) volumes than men at baseline. An academic education was associated with higher initial tWMH ( $p = .018$ ) and pWMH ( $p = .018$ ). However, a reverse effect was seen over time; an academic education was associated with less steep slopes of tWMH ( $p = .012$ ) and pWMH ( $p = .035$ ). Subjects with depressive symptoms showed less dWMH volume increases ( $p = .010$ ).

#### 3.2.2. Lacunes and covariates

Older age at baseline was associated with a higher initial lacunar volume ( $p < .0001$ ), more lacunes ( $p < .0001$ ) at baseline, and also with a progression of lacunar number over time ( $p = .001$ ). Subjects with a higher education had fewer lacunes at baseline ( $p = .006$ ) and also showed less progression in lacunar number ( $p = .009$ ). Subjects taking antihypertensives showed initially smaller lacunar volumes ( $p = .023$ ) and also less lacunes ( $p = .011$ ).

#### 3.2.3. Brain parenchyma volume/normal appearing white matter volume and covariates

Older baseline age and female sex were initially associated with lower BPV and lower NAWM volume (all:  $p < .0001$ ). Women ( $p = .006$ ) and academics ( $p = .029$ ) showed less subsequent decline in NAWM volume. Obesity was related to more initial BPV ( $p = .030$ ), and depressive symptoms to a lower BPV at baseline ( $p = .035$ ).

**Table 3**

Estimates for mean changes per year in percent (%) with 95% confidence intervals [CI] for the CSVD and processing speed measures – separate for females, males and total.

	Female mean	Male mean	Total mean	Slope mean <i>p</i> -value	Slope sex <i>p</i> -value	Slope variance <i>p</i> -value
<b>Total WMH</b>						
Change per year in % [CI]	+8.44 [7.38;9.50]	+7.36 [6.31;8.42]	+7.90 [6.84;8.96]	< 0.0001	0.194	< 0.0001
<b>Total pWMH</b>						
Change per year in % [CI]	+8.97 [7.60;10.16]	+8.44 [7.17;9.20]	+8.65 [7.38;9.94]	< 0.0001	0.739	< 0.0001
<b>Total dWMH</b>						
Change per year in % [CI]	+7.47 [5.79;9.16]	+5.76 [4.11;7.43]	+6.61 [4.95;8.29]	< 0.0001	0.110	0.002
<b>Lacunar volume</b>						
Change per year in % [CI]	+7.25 [5.17;9.37]	+6.40 [4.33;8.50]	+6.82 [4.75;8.94]	< 0.0001	0.346	0.006
<b>Lacunar number</b>						
Change per year in % [CI]	+5.28 [4.65;5.65]	+3.89 [2.92;4.50]	+4.56 [3.74;5.06]	< 0.0001	0.480	< 0.0001
<b>BPV</b>						
Change per year in % [CI]	-0.62 [-0.68;-0.57]	-0.66 [-0.71;-0.61]	-0.64 [-0.69;-0.59]	< 0.0001	0.088	< 0.0001
<b>NAWM</b>						
Change per year in % [CI]	-0.90 [-0.99;-0.82]	-1.00 [-1.075;-0.918]	-0.95 [-1.03;-0.87]	< 0.0001	0.006	0.001
<b>Processing Speed</b>						
Change per year in % [CI]	-0.76 [-1.19;-0.36]	-1.02 [-1.46;-0.61]	-0.89 [-1.33;-0.49]	< 0.0001	0.328	< 0.0001

Notes: «Slope mean *p*-value» describes the significance of the mean increase or decrease of the different variables over the 7 years. «Slope sex *p*-value» shows whether the slope of a particular variable differed significantly between the two sexes over the 7 years. «Slope variance *p*-value» lists the significance of the slope of the variance over the 7 years.

WMH = white matter hyperintensities; pWMH = periventricular white matter hyperintensities; dWMH = deep white matter hyperintensities; BPV = brain parenchyma volume; NAWM = normal appearing white matter volume.

The log<sub>e</sub>(*x*) transformed variables (tWMH, pWMH, dWMH, lacunar volume) were transformed back for calculation (formula: e<sup>slope</sup>).

**Table 4**

Representation of the results of the univariate LGC models with the covariates. Listed are the standardized effect estimates (β) for intercept (I) and slope (S) in the original measurement units. For the WMH subtypes and lacunar volume these are given in log<sub>e</sub>(*x*), for lacunar number in number, for BPV and NAWM volume in cm<sup>3</sup>, for processing speed in a latent score.

Variables	Cerebral Small Vessel Disease and Processing Speed Measures ~ Covariates													
	~Age		~Sex		~Education		~Antihypertens <sup>a</sup>		~Antihyperchol <sup>b</sup>		~Obesity		~Depr. Symptoms <sup>c</sup>	
	I	S	I	S	I	S	I	S	I	S	I	S	I	S
tWMH (log)	0.410***	—	-0.148*	—	0.157*	-0.276*	—	—	—	—	—	—	—	—
pWMH (log)	0.326***	—	-0.193**	—	0.156*	-0.217*	—	—	—	—	—	—	—	—
dWMH (log)	0.494***	—	—	—	—	—	—	—	—	—	—	—	—	—
LAC <sub>VOL</sub> (log)	0.446***	—	—	—	—	—	-0.262*	—	—	—	—	—	—	—
LAC <sub>NR</sub>	0.467***	0.559**	—	—	-0.356**	-0.343**	-0.269*	—	—	—	—	—	—	—
BPV (cm <sup>3</sup> )	-0.568***	—	0.271***	—	—	—	—	—	—	0.108*	—	-0.086*	—	—
NAWM (cm <sup>3</sup> )	-0.529***	—	0.231***	-0.319**	—	0.250*	—	—	—	—	—	—	—	—
PS	-0.393***	-0.581***	—	—	0.137*	0.238*	—	—	0.189**	—	—	—	—	—

Notes: The intercept corresponds to a female subject with a median age of 70 years, with a medium level of education (level 2). Antihypertensives (0 = no, 1 = yes), antihypercholesterolemics (0 = no, 1 = yes), obesity (=BMI ≥ 30) (0 = no, 1 = yes), and depressive symptoms (0 = no, 1 = yes).

tWMH = total white matter hyperintensities; pWMH = periventricular white matter hyperintensities; dWMH = deep white matter hyperintensities; LAC<sub>VOL</sub> = lacunar volume; LAC<sub>NR</sub> = lacunar number; BPV = brain parenchyma volume; NAWM = normal appearing white matter volume; PS = processing speed.

Standardized beta (β), 0.10 = weak effect, 0.30 = moderate effect, 0.50 = strong effect size (Cohen, 1992).

\**p* < 0.05; \*\**p* < 0.01; \*\*\**p* < 0.001.

<sup>a</sup> Subjects taking antihypertensives (antihypertens).

<sup>b</sup> Subjects taking antihypercholesterolemics (antihyperchol).

<sup>c</sup> via questionnaire; depressive symptoms (Depr. Symptoms) via German version of the Hospital Anxiety and Depression Scale (HADS-D) (Herrmann-Lingen et al., 2011).

### 3.2.4. Processing speed and covariates

The older the subjects were at baseline, the worse their performance on processing speed at the beginning of the study (*p* < .0001) and the steeper also the decrease (*p* < .0001). Academic education was associated with better initial performance in processing speed (*p* = .049) and also with an increase in performance over time (*p* = .024) compared to the other two education groups. An intake of antihypercholesterolemics was related to a better performance on processing speed at baseline (*p* =

.006).

**Model fit for processing speed:** The model fit for FI for the strong model had an acceptable to good fit for all fit measures, and the model fit for training effect even improved, achieving a good fit for two of three criteria and one acceptable model fit (see **Supplementary Methods: Factorial Invariance Model Fit Testing – Processing Speed**).

Inner-Domain Correlations of CSVD and Processing Speed Measures in Baseline and Subsequent Changes (intercept–slope), and Cross-

**Table 5**

Combined summary of covariances between CSVD and processing speed measures controlled for all covariates (age, sex, education, antihypertensives, anti-hypercholesterolemics, obesity, depressive symptoms (except for lacunar variables)); All bivariate cross-domain correlations (intercept–intercept, intercept–slope, slope–slope), and the univariate inner-domain correlations between baseline and progression (intercept–slope). The first column lists the variables that turned out to be significant, and the first row lists all variables. Values describe standardized effect estimates ( $\beta$ ); long dashes indicate non-significant results.

Variables	tWMH	pWMH	dWMH	BPV	NAWM	LACVOL	LACNR	PS
Intercept ~	~ Intercept	$\beta$						
tWMH		+0.946***	+0.816***	-0.197**	-0.288***	—	+0.505**	-0.155*
pWMH			+0.636***	-0.168**	-0.282***	—	+0.444**	—
dWMH				—	-0.194**	+0.358*	+0.584***	-0.196**
BPV					—	—	—	+0.243**
NAWM						—	—	+0.251**
LACNR						+0.663***	—	—
Intercept ~	~ Slope		$\beta$					
tWMH	-0.269 <sup>a</sup>	-0.481***	—	—	-0.386**	—	+0.420*	—
pWMH	-0.251*	-0.554*** <sup>a</sup>	+0.233*	—	-0.348**	—	+0.397*	—
dWMH	-0.362**	-0.403**	— <sup>a</sup>	—	-0.314*	—	+0.439*	—
BPV	—	—	-0.272*	+0.216 <sup>a</sup>	— <sup>b</sup>	—	—	—
NAWM	—	—	-0.306**	— <sup>b</sup>	— <sup>a</sup>	—	—	—
LACVOL	—	—	-0.390*	—	—	— <sup>a</sup>	+0.303*	—
LACNR	—	-0.692**	—	—	—	—	+0.470*** <sup>a</sup>	—
PS	—	—	—	+0.318**	—	—	—	— <sup>a</sup>
Slope ~	~ Slope	$\beta$						
tWMH		+0.862***	+0.662***	-0.380*	-0.577**	—	—	—
pWMH	—	—	—	—	-0.388*	—	-0.572*	—
dWMH	—	—	—	-0.429*	-0.506*	—	—	—
LACVOL	—	—	—	—	—	—	+0.376*	—

Notes: Standardized beta ( $\beta$ ), 0.10 = weak effect, 0.30 = moderate effect, 0.50 = strong effect size (Cohen, 1992).

tWMH = total white matter hyperintensities; pWMH = periventricular white matter hyperintensities; dWMH = deep white matter hyperintensities; LACVOL = lacunar volume; LACNR = lacunar number; BPV = brain parenchyma volume; NAWM = normal appearing white matter volume; PS = processing speed.

\* $p < 0.05$ ; \*\* $p < 0.01$ ; \*\*\* $p < 0.001$ .

<sup>a</sup> results of the univariate inner-domain covariances between baseline and progression (Intercept – Slope).

<sup>b</sup> no calculated combination.

Domain Correlations of the CSVD and Processing Speed Measures at Baseline Level (intercept-intercept), Subsequent Changes (intercept-slope), and Coupled Changes (slope-slope)

Table 5 lists the results of all bivariate cross-domain covariances and the univariate inner-domain covariances between baseline and progression of the CSVD and processing speed measurements.

For detailed results of the covariances see **Supplementary Table 4**, for the results and model fits of the bivariate LGC models see **Supplementary Table 5 and 6**.

#### 4. Discussion

In this 7-year, five-wave, longitudinal study with cognitively healthy subjects, we used latent growth curve models to examine the influence of age, sex, education, antihypertensives, antihypercholesterolemics, obesity, and depressive symptoms on a multitude of CSVD markers (tWMH, pWMH, dWMH, lacunar volume, lacunar number, BPV, NAWM volume) and processing speed measures. In addition, we investigated baseline-baseline, baseline-change and change-change associations within and between the CSVD and processing speed measurements.

##### 4.1. Influence of age on CSVD and processing speed

Age affected all included CSVD and processing speed measures at baseline with moderate to strong effect sizes: The older the subjects, the higher the initial CSVD disease and the worse the initial processing speed performance, which is consistent with previous research (Brickman et al., 2008a; Caunca et al., 2019; Chowdhury et al., 2011; Longstreth et al., 1998; Price et al., 1997; Schmidt et al., 2016; Vermeer et al., 2003a). Further, the older the subjects were at baseline the greater the increase in lacunar number and the greater the decrease in processing speed over the 7 years, indicating non-linear trajectories. All other CSVD markers showed no associations with age in terms of their change over time, suggesting a constant linear trend for these variables in our

sample.

##### 4.2. Influence of sex on CSVD and processing speed

Women showed higher initial pWMH (and tWMH), lower BPV and NAWM volume than men. The findings are consistent with other studies in which women also showed a higher tWMH load (Alqarni et al., 2021; de Leeuw et al., 2001; Longstreth et al., 1996; Sachdev et al., 2009), a lower BPV (Ritchie et al., 2018), and a lower WM volume (for review see: Cosgrove et al., 2007; Lenroot and Giedd, 2010). Compared with men, women might be influenced by other risk factors such as genetic and/or hormonal factors (Miller et al., 2013; Sachdev et al., 2016; Seo et al., 2013; ten Kate et al., 2018). With regards to the subsequent change, there were no sex differences in WMH but in NAWM volume women showed a smaller decline over the seven years than men. In our study, however, these initial structural «disadvantages» of women had no adverse effects on their processing speed, and they performed equally well as men at baseline and over time. Also Roivainen (2011) showed no general sex differences, but indicated that there are different speed abilities in which sex differences occur – as opposed to a general processing speed ability.

##### 4.3. Influence of education on CSVD and processing speed

It is of interest that subjects with an academic education (Bachelor, Master, Doctorate) showed a higher initial pWMH (and tWMH), while they showed less progression over time in these markers. This combination of effects could occur if subjects with an academic education developed WMH earlier in life but with a less steep progression than subjects with a lower education. While the former may be related to factors such as stress (Yu et al., 2020), the reduced increase of WMH load over time may reflect a «reserve-effect» of education. In line with the latter, we were able to show that higher levels of education had a positive impact on lacunar number and processing speed at baseline as well

as on trajectories of lacunar number, NAWM volume and processing speed over time (Brickman et al., 2011; Jokinen et al., 2016; Nebes et al., 2006; Pinter et al., 2015; Serra et al., 2015).

#### 4.4. Influence of medication and risk factors on CSVD and processing speed

Our results show that the use of antihypertensive drugs had a weak to moderate protective effect on both initial lacunar number and lacunar volume, and that the use of antihypercholesterolemic drugs was associated with better performance on processing speed at baseline, showing a weak effect size. Both results seem counter-intuitive if the variables were understood as risk factors and not as protective factors. However, both, antihypertensive drugs (Williams et al., 2018) and antihypercholesterolemic drugs, such as statins (Cholesterol Treatment Trialists' (CTT) Collaboration, 2010), have robust evidence in reducing of cardiovascular events and mortality. Furthermore, a reinforcing productive factor in those participants taking the respective medication could be lifestyle changes recommended by the physician according to the 2016 European guidelines (Piepoli et al., 2016) during regular check-ups. A meta-analysis involving >330000 people showed the quantitative dose-response relation of physical activity and hypertension (Liu et al., 2017), and two further meta-analyses (Sundström et al., 2015; Thomopoulos et al., 2014) have revealed significant treatment-induced reductions in cardiovascular events and mortality. Moreover, van Middelaar et al. (2018) performed a systematic review and meta-analysis on the effect of antihypertensives on CSVD. They showed that antihypertensives were effective in slowing down the progression of WMH but had no effect on brain atrophy. Although not significant, our data point in a similar direction by showing less steep increases in tWMH in people taking antihypertensives and/or antihypercholesterolemic. The non-significant results could be due to the relatively low tWMH volumes in our subjects, as Dufouil et al. (2005) found a stronger effect of antihypertensives in subjects with severe WMH at baseline. For lacunar number and volume, the effect of taking antihypertensives was significant. This may be explained by the fact that subjects with lacunes were older than the subjects without lacunes. Based in this one could hypothesize that older people have been taking antihypertensive drugs for a longer period of time and that, therefore, the effect on lacunes was already evident at the beginning of the study. Previous research is in line with our result and indicates that antihypertensives reduce the incidence of both hemorrhagic and ischemic (including lacunar) strokes (Perry et al., 2000). Also, in the 3-year Leukoaraiosis and Disability Study (LADIS) Gouw et al. (2008), were able to show in the multivariate analyses – with a sample including subjects with history of stroke, myocardial infarction, and arterial fibrillation – that a high diastolic blood pressure and high low-density lipoprotein (LDL) were a protective factor for incident lacunes. It should be noted that older adults frequently take both, antihypertensives and antihypercholesterolemic, which may lead to effect enhancement. In general, however, much more research is needed to gain a better understanding of the effect that a particular pharmaceutical exerts on CSVD markers. Also, our result of antihypercholesterolemic being associated with better processing speed at baseline can be aligned with previous work. Although case reports suggest a risk with statin use for impaired cognitive function such as memory loss, forgetfulness, amnesia, memory impairment, confusion, large meta-analyses show no increase in risk (Gauthier and Massicotte, 2015). Swiger et al. (2013) conducted a meta-analysis by examining the effects of statins on short-term cognition within one year of drug initiation. They found a non-significant trend toward improvement in digit symbol substitution test scores in patients taking statins compared with the placebo group. Again, the above-mentioned lifestyle change mechanisms could act to improve processing speed performance, e.g., indirectly via physical activity.

The effects of obesity and depressive symptoms onto CSVD markers have to be interpreted with caution due to the small group size and weak

effect sizes. Further, it should be noted that the depressive symptoms used in this study are not a clinical diagnosis, but a self-reported symptom in a questionnaire. In our analyses, subjects with depressive symptoms showed less BPV at baseline (very weak effect size), which is consistent with previous studies (Espinoza Oyarce et al., 2020; Kumar et al., 1998; Lebedeva et al., 2018; Nunes et al., 2018). On the other hand, our subjects with depressive symptoms showed a decrease in dWMH over time (weak effect size), while several other previous studies have, in a clinical context, associated depression with higher WMH load (Krishnan et al., 2006; Nebes et al., 2002; Teodorczuk et al., 2007). In obese subjects we demonstrated a higher initial BPV but no significant differences in progression compared with non-obese subjects. This result also seems counterintuitive as studies with more obese subjects suggest that these adults have smaller total brain volumes than normal weight or overweight individuals (Dekkers et al., 2019; Gunstad et al., 2008; Hamer and Batty, 2019; Ward et al., 2005). Hence, future studies are needed to learn more about the associations between CSVD markers and depressive symptoms/obesity in healthy older populations.

#### 4.5. Baseline-change associations within CSVD markers

In contrast to previous studies including subjects with substantial tWMH lesion load (Gouw et al., 2008; Longstreth et al., 2005; Sachdev et al., 2007; Schmidt et al., 2003; Taylor et al., 2003; Whitman et al., 2001), we did not find evidence for steeper slopes following on higher initial tWMH load. Instead, we revealed the opposite pattern for the WMH subtype pWMH (and tWMH) but not for dWMH. Only among the WMH subtypes we could find that higher pWMH at baseline was associated with steeper increases of dWMH. In case of the lacunes, the initial lacunar number but not the initial volume was related to a subsequent increase. Further, the greater the initial BPV, the steeper the slope over time. No baseline-change associations were observed for NAWM volume, which is in line with the work of Ritchie et al. (2015), who used two-wave longitudinal data.

#### 4.6. Associations of WMH subtypes and brain volumes

Expectedly, all associations between WMH subtypes and NAWM were negative. In addition, tWMH and pWMH were negatively associated with BPV at baseline. Further, we found coupled changes with moderate to strong effect sizes for WMH subtypes and brain volumes: Changes in tWMH and dWMH were moderately to strongly negatively correlated with changes in BPV, and changes in all WMH subtypes were also negatively correlated with changes in NAWM, with the dWMH subtype showing the strongest correlation. The findings of our study largely replicate those of Ritchie et al. (2015), who reported that initial tWMH volume was predictive of the subsequent NAWM volume decrease and that the increase in tWMH volume was accompanied by a decrease in NAWM volume. Also, Schmidt et al. (2005) showed that the increase in tWMH at 3- and 6-year follow-up was correlated with a decrease in BPV. In general, these results highlight the relevance of including global atrophy measurements such as BPV as they could be predictive of WMH burden.

#### 4.7. Associations of WMH subtypes and lacunes

The relation between the volume and the number of lacunes at baseline showed an expected strong but not nearly perfect correlation ( $\beta = 0.663$ ) indicating that there are also subjects with few large lacunes or with many small lacunes. The baseline lacunar volume was predictive of the subsequent increase in the number of lacunes – but not vice versa, although moderate positive coupled changes between lacunar volume and lacunar number were revealed.

We found no associations between NAWM or BPV and lacunes. A higher load in all initial WMH subtypes were accompanied by higher initial number of lacunes and also by a progression in number of lacunes,

showing moderate to strong effect sizes. On the other hand, lacunar volume at baseline was associated only with the dWMH subtype at baseline. In a 7-year study in the general population in China with baseline and follow-up measure, Xia et al. (2020) demonstrated that higher baseline tWMH was associated with a higher risk of incident lacunes and vice versa. Lacunar volume was not assessed. However, in our study the higher the volume and number of lacunes at baseline, the smaller the increase of pWMH and dWMH volume, respectively, developed over time. In line with this, there was a negative correlation between the changes in lacunar number and pWMH. These results may indicate that WMH might transition into lacunes over time, which is consistent with the study by Gouw et al. (2008) in which it was hypothesized that WMH might develop into lacunes via an intermediate stage of a subtype of lacunes that are not yet cavitated. Also a recent study concluded that CSVD should be considered as a dynamic «whole-brain» disease, possibly based on some common intrinsic microvascular pathologies (Shi and Wardlaw, 2016). However, the results reflect the complex nesting and interactions of these two CSVD markers, and highlights that moderate to strong associations between initial WMH subtypes and future progression of lacunar number, even in healthy, non-demented individuals exists. Additionally, WMH seem to be predictive for lacunar number and less for lacunar volume, whereas only dWMH and lacunar volume seem to be related at baseline. These complex associations need to be further investigated in future studies.

#### 4.8. Associations of CSVD and processing speed

Higher initial tWMH, dWMH, smaller BPV, NAWM volume, were linked to worse performance in processing speed at baseline. For pWMH no correlation was found. Further, our results show that dWMH rather than pWMH are initially related to processing speed. This fits with the study of Wen et al. (2006) where dWMH were reported to be more functionally relevant. Also, the results of Brugulat-Serrat et al. (2020) showed that the behavior of the composite executive function was mainly driven by the indirect effects of dWMH, especially for processing speed. We found that the initial performance of processing speed could predict BPV with a moderate effect size: the better the initial performance the steeper the slope of BPV. We did not show any association between changes in CSVD markers and changes in processing speed in our sample, which is in line with the study by Ritchie et al. (2015), who showed that brain volumes and WMH were not predictive for decline in processing speed, but in contrast to Schmidt et al. (2005), who revealed a decrease in BPV as a strong predictor of decline in processing speed.

#### 4.9. Strength and limitations

This study has several strength and limitations. The main advantages of this study are: it is a single-center study with a 3 Tesla MRI, the long observation time of seven years, the five measurement time points, and the therefore possible statistical procedure by using LGC models, which makes the error variance highly predictable. Further, we carefully performed the outlier analysis, and additionally excluded people with CNS active drugs due to the possible influence on, among others, processing speed as reported by Rollin et al., 2009. Another benefit is the automated quantification of the WMH volumes using UBO Detector, an algorithm validated and customized on the same sample in our previous paper (Hotz et al., 2020).

Nevertheless, a larger sample size for subjects with lacunes would have been desirable to generate more robust results, especially with the covariates. This applies in general to the risk factors depressive symptoms and obesity, where the results can only be interpreted with caution. Another desirable addition would have been the measurement of serum low-density lipoprotein (LDL) to have objective data for harmful lipids in blood serum. But in this case, as in the measurement of blood pressure, the distinction between protective factor and risk factor would remain difficult, especially at this sample size. Finally – in addition to

BMI – a waist-to-hip ratio or even more sophisticated abdominal fat tissue measurement with a computed tomography or MRI would have provided valuable and more coherent results, as some studies have associated visceral fat with increased CSVD burden (Kim et al., 2017; Lampe et al., 2019b).

## 5. Conclusion

The presented longitudinal analysis of CSVD markers in relation to processing speed and different covariates on cognitively healthy older adults demonstrates the importance of including multiple CSVD markers to better understand the complex underpinnings of CSVD.

From the multiple analyses reported in this work, we can conclude that older age is associated with higher initial CSVD loads and poorer processing speed performance. Within-individuals, an increase of CSVD load over time was observed, and changes in lacunar number and processing speed were accelerated in older age. Further, we discovered sex-specific differences in CSVD loads at baseline and over time, and showed that higher education, blood pressure and/or lipid-lowering drugs had protective effects on brain and behavior. Importantly, our results indicate that changes of dWMH, as compared to pWMH, are more strongly related to the changes of the other CSVD markers but also to initial processing speed performance. With respect to the lacunes, our data indicate that their number rather than their volume reflect the severity of CSVD.

The effects sizes for baseline-change and change-change associations were moderate to strong (range: absolute  $\beta = 0.272$ – $0.692$ ) pointing to a common pathological mechanism and, thus, support multidimensional treatment strategies.

## Ethics statement

This study involving human participants was reviewed and approved by the Ethics Committee of the Canton of Zurich. The participants provided their written informed consent to participate in this study.

## Data and code availability statement

The data supporting this manuscript are not publicly available because the used consent does not allow for the public sharing of the data.

## Software availability statement

The following openly available software were used:  
FreeSurfer (<https://cheba.unsw.edu.au/research-groups/neuroimaging/pipeline>)  
UBO Detector (<https://cheba.unsw.edu.au/research-groups/neuroimaging/pipeline>)

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## CRediT authorship contribution statement

**Isabel Hotz:** Conceptualization, Software, Methodology, Validation, Formal analysis, Data curation, Writing – original draft, Writing – review & editing, Visualization. **Pascal Frédéric Deschwanden:** Methodology, Validation, Formal analysis, Data curation, Writing – review & editing. **Susan Mérillat:** Conceptualization, Investigation, Resources, Data curation, Writing – review & editing, Supervision, Project administration, Funding acquisition. **Franziskus Liem:** Software, Data curation. **Spyridon Kollias:** Validation, Supervision. **Lutz Jäncke:**

Conceptualization, Investigation, Resources, Writing – review & editing, Supervision, Project administration, Funding acquisition.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.nicl.2021.102884>.

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