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Neuroimaging

A priori collaboration in population imaging: The Uniform Neuro-Imaging of Virchow-Robin Spaces Enlargement consortium

Hieab H. H. Adams[a,b], Saima Hilal[c,d], Petra Schwingenschuh[e], Katharina Wittfeld[f], Sven J. van der Lee[g], Charles DeCarli[h], Meike W. Vernooij[a,b], Petra Katschnig-Winter[e], Mohamad Habes[i,j], Christopher Chen[d], Sudha Seshadri[k,l], Cornelia M. van Duijn[g], M. Kamran Ikram[c,d], Hans J. Grabe[f,m], Reinhold Schmidt[e], M. Arfan Ikram[a,b,n,*]

[a]*Department of Epidemiology, Erasmus MC, Rotterdam, The Netherlands*
[b]*Department of Radiology, Erasmus MC, Rotterdam, The Netherlands*
[c]*Department of Ophthalmology, National University of Singapore, Singapore*
[d]*Memory Aging and Cognition Center, National University Health System, Singapore*
[e]*Department of Neurology, Medical University of Graz, Graz, Austria*
[f]*German Center for Neurodegenerative Diseases (DZNE), Site Rostock/ Greifswald, Greifswald, Germany*
[g]*Genetic Epidemiology Unit, Department of Epidemiology, Erasmus MC, Rotterdam, The Netherlands*
[h]*Imaging of Dementia and Aging (IDeA) Laboratory, Department of Neurology and Center for Neuroscience, University of California at Davis, Davis, CA, USA*
[i]*Institute for Community Medicine, University Medicine Greifswald, Greifswald, Germany*
[j]*Section of Biomedical Image Analysis, Department of Radiology, University of Pennsylvania, Philadelphia, PA, USA*
[k]*Department of Neurology, Boston University School of Medicine, Boston, MA, USA*
[l]*Framingham Heart Study, Framingham, MA, USA*
[m]*Department of Psychiatry and Psychotherapy, University Medicine Greifswald, Greifswald, Germany*
[n]*Department of Neurology, Erasmus MC, Rotterdam, The Netherlands*

Abstract

Introduction: Virchow-Robin spaces (VRS), or perivascular spaces, are compartments of interstitial fluid enclosing cerebral blood vessels and are potential imaging markers of various underlying brain pathologies. Despite a growing interest in the study of enlarged VRS, the heterogeneity in rating and quantification methods combined with small sample sizes have so far hampered advancement in the field.

Methods: The Uniform Neuro-Imaging of Virchow-Robin Spaces Enlargement (UNIVRSE) consortium was established with primary aims to harmonize rating and analysis (www.uconsortium.org). The UNIVRSE consortium brings together 13 (sub)cohorts from five countries, totaling 16,000 subjects and over 25,000 scans. Eight different magnetic resonance imaging protocols were used in the consortium.

Results: VRS rating was harmonized using a validated protocol that was developed by the two founding members, with high reliability independent of scanner type, rater experience, or concomitant brain pathology. Initial analyses revealed risk factors for enlarged VRS including increased age, sex, high blood pressure, brain infarcts, and white matter lesions, but this varied by brain region.

Discussion: Early collaborative efforts between cohort studies with respect to data harmonization and joint analyses can advance the field of population (neuro)imaging. The UNIVRSE consortium will focus efforts on other potential correlates of enlarged VRS, including genetics, cognition, stroke, and dementia.

The authors of this article have nothing to declare.

*Corresponding author. Tel.: +31-10-70-43930; Fax: +31-10-70-43489.
E-mail address: m.a.ikram@erasmusmc.nl

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1. Introduction

Neuroimaging allows for the in vivo assessment of brain structure and function, thereby facilitating research on neurodegenerative, psychiatric, and cerebrovascular diseases. In the past decades, magnetic resonance imaging (MRI) has identified both early and late markers of brain pathology that have greatly contributed to our understanding of the pathophysiology of neurologic diseases. White matter lesions, for example, are now a well-established marker of cerebral small vessel disease, and hippocampal atrophy has even been translated into a diagnostic marker of Alzheimer's disease. For several neuroimaging markers, standardized definitions were recently proposed, but this was already after decades of research using considerably heterogeneous criteria [1]. Research on emerging neuroimaging markers would benefit from harmonization early on. This article focuses on enlarged Virchow-Robin spaces (VRS), which hold great potential as an MRI marker for various pathologies in the brain but remain poorly studied. VRS are fluid-filled spaces enveloping the brain vasculature only to become visible on MRI after a substantial increase in volume. Enlargement of these VRS was traditionally thought to be an inconsequential finding on MRI, but this view has repeatedly been questioned in recent years through established links with cerebral small vessel disease, Alzheimer's disease, and multiple sclerosis, among others. Several theories have been proposed for this enlargement, including brain atrophy, inflammation, hypertension, and microvascular obstruction (Fig. 1) [2–9]. Consequently, this resulted in the study of enlarged VRS in relation to a diverse range of diseases. However, the number of VRS studies almost equals the number of methods used for their assessment on MRI [2–4,10–13]. This has led to the current inability to compare or pool results from different studies, which are already limited in number and size. Now, cohorts worldwide have joined efforts in trying to harmonize VRS research early on, to overcome these problems; an initiative which may be exemplary for future population neuroimaging research.

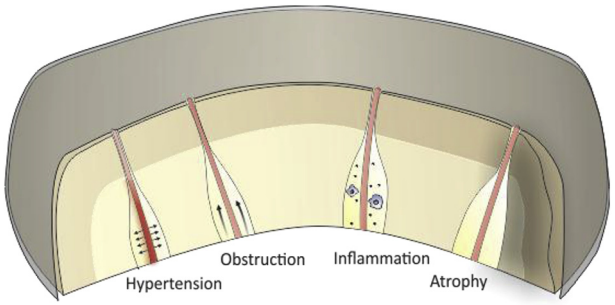

Fig. 1. Hypothesized etiologies for enlargement of Virchow-Robin spaces.

2. Methods

In 2010, the Rotterdam Scan Study (RSS) and Austrian Stroke Prevention Study (ASPS), two large population-based studies in aging populations, entered a collaboration with the goal to develop a robust VRS rating method that is reliable, incorporates relevant brain regions, and can be easily applied by other researchers [14]. Briefly, enlarged VRS are rated primarily on an axial T2-weighted sequence, which shows VRS as hyperintensities, but this has now been extended to allow T1-weighted images, where VRS are hypointense, as the primary sequence. VRS are tubular structures that, depending on their orientation within the image, can be linear, ovoid, or round in shape. VRS are considered enlarged when their diameter is $\geq$1 mm, to be able to distinguish "enlarged" VRS from "normal" VRS (Fig. 2). The diameter is determined visually by the rater and not manually measured for every VRS because the latter would be too time consuming. VRS are rated separately when these are $>$3 mm because these large lesions potentially represent different pathology. The shape of the lesion and its intensity on the fluid-attenuated inversion recovery (FLAIR) sequence are additionally used to differentiate between enlarged VRS, lacunar infarcts, and white matter hyperintensities.

During the development of our visual rating scale, we focused on its reliability and ease of use. The number of enlarged VRS is determined in four relevant brain regions: the centrum semiovale, basal ganglia, hippocampus, and mesencephalon. All unique enlarged VRS are counted in the hippocampus and mesencephalon, whereas only a single, predefined slice is used for the centrum semiovale and basal ganglia, which are large brain regions for which counting on all slices would be unfeasible. However, in a subset of 40 scans in which all VRS in the brain were counted, there was a high correlation (0.79) between the number from our single slice approach and the total number in that region, indicating that the VRS burden for the larger regions (centrum semiovale and basal ganglia) can be captured using only a single slice. We rate the actual counts for each region (either the whole region or a single slice), instead of categorizing this into a severity score, so that this information is not lost and can be analyzed continuously.

Furthermore, we are exploring the possibilities of an automated segmentation method for detecting enlarged VRS, similar to tools for white matter hyperintensities and hippocampal size. This would allow for the investigation of count and volume within the whole brain, as well as

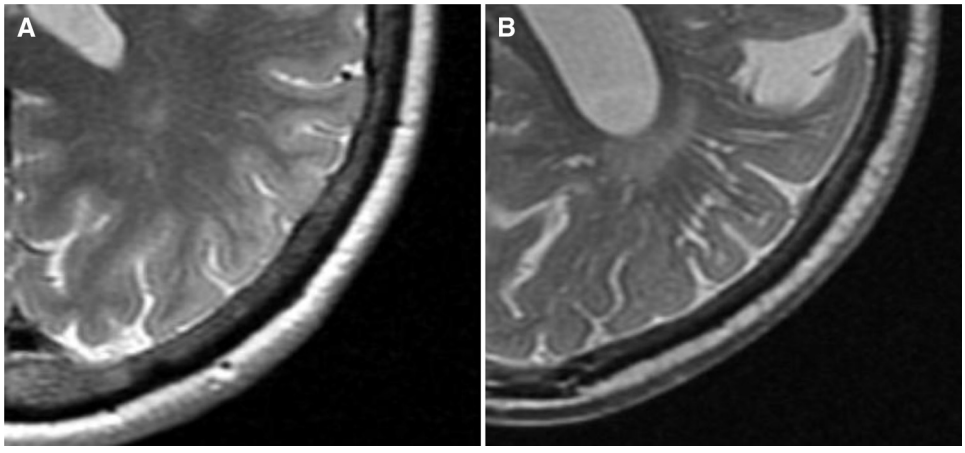

Fig. 2. Virchow-Robin spaces in the centrum semiovale of various sizes. Panel A shows a person with faint (< 1 mm) Virchow-Robin spaces whereas panel B shows a person with large (> 1 mm) spaces.

within regions of interest. Even though our visual rating method and those of others have been shown to be reasonably reliable, we expect this objective, quantitative approach to greatly reduce noise and increase analytical opportunities. We believe automated detection will replace the visual rating as the method of choice for determining enlarged VRS load once this is ready to be applied within our consortium. A recent study showed that high-resolution images obtained from 7-T scanners are better suited for automated segmentation [15], although other efforts suggested that this might be feasible with weaker field strengths [16].

Since the publication of this method, the founding members have been joined by other cohorts that share an interest in VRS research and acknowledge that questions regarding their etiology and clinical relevance are best answered through a combined effort. The Uniform Neuro-Imaging of Virchow-Robin Spaces Enlargement (UNIVRSE) consortium was formally established in 2013 and intends to study enlarged VRS using a harmonized approach.

The UNIVRSE consortium currently consists of 13 (sub) cohorts from five countries and encompasses >16,000 persons with over 25,000 MRI scans (Table 1). It includes prospective, population-based cohort and family studies from various ethnicities and which have all previously been described in detail. A brief overview is provided in the following. Other cohorts that want to join the consortium are referred to the consortium website (www.uconsortium.org) for further details.

2.1. Rotterdam Scan Study

The Rotterdam Study is a Dutch prospective, population-based cohort study that aims to investigate causes and determinants of diseases in the elderly [17]. A total of 14,926 subjects aged ≥45 years at baseline were recruited in three subcohorts (1990, 2000, and 2006) and they are still being followed up. MRI scanning is performed on all participants from 2005 onward as part of the RSS and is repeated every 3–4 years [18].

2.2. Austrian Stroke Prevention Study

The ASPS is a prospective cohort study on the effects of vascular risk factors on brain structure and function in cognitively normal middle-aged and elderly inhabitants of Graz, Austria [19]. In brief, 2007 subjects aged 50–75 years without neuropsychiatric disease were randomly selected from the official community register, of which a random subset of 1076 participants underwent MRI in two panels (1991–1994 and 1999–2003). Between 2006 and 2013, the Austrian Stroke Prevention Family (ASPS-Fam) study was recruited as an extension of ASPS using identical inclusion criteria and diagnostic work-up with updated MRI protocols; ASPS-Fam included 381 members of the original ASPS cohort and their relatives.

2.3. Study of Health in Pomerania

The Study of Health in Pomerania (SHIP) is a longitudinal general population study from Greifswald, Germany that enrolled 4308 middle-aged subjects in SHIP-0 (SHIP-0: 1997–2001; SHIP-1: 2003–2006; and SHIP-2: 2008–2012). In addition to SHIP, a new cohort was started in 2008 (SHIP-Trend) with 4420 subjects [20]. In SHIP-2 and SHIP-Trend, whole body MRI scanning was performed in 3317 subjects. The next follow-up starts in 2014/2015 and includes a follow-up MRI scan.

2.4. Framingham Heart Study

The Framingham Heart Study (FHS) is a single-site, community-based, prospective cohort study initiated in 1948 to investigate risk factors for cardiovascular disease and comprises three generations of participants. The original cohort of the FHS, generation 1, consisted of 5209 participants from Framingham MA who were enrolled into the study in

Table 1
Overview of the UNIVRSE consortium members and their MRI protocol for Virchow-Robin spaces rating

Cohort	Country	Sampling	Age range (y)	Baseline scans (n)	Follow-up scans (n)	Field strength (T)	Primary VRS rating sequence	Voxel size (mm)	Additional sequence(s)
ASPS									
ASPS original	Austria	Population based	44–82	810	377	1.5	T2 weighted	0.9 × 0.9 × 5.5	T1 weighted, FLAIR
ASPS family	Austria	Population based	38–83	320	120	1.5	T2 weighted	0.8 × 0.8 × 3.0	T1 weighted, FLAIR
EPOZ	Netherlands	Population based	60–94	514	687	1.5	T2 weighted	1.0 × 1.0 × 1.25	T1 and proton density weighted
ERF	Netherlands	Family study	55–75	129	—	1.5	T2 weighted	1.0 × 1.0 × 1.6	T1 weighted, FLAIR
FHS									
Generation 1	USA	Population based	79–103	353	224	1.5	T2 weighted	0.95 × 0.95 × 4.0	T1 weighted, FLAIR
Generation 2	USA	Offspring	33–90	2749	2257	1.5	T2 weighted	0.95 × 0.95 × 4.0	T1 weighted, FLAIR
Generation 3	USA	Offspring	19–63	2008	—	1.5	T2 weighted	0.95 × 0.95 × 4.0	T1 weighted, FLAIR
RS									
RS-I	Netherlands	Population based	68–100	1236	198	1.5	T2 weighted	1.0 × 1.0 × 1.6	T1 weighted, FLAIR
RS-II	Netherlands	Population based	60–98	1493	1377	1.5	T2 weighted	1.0 × 1.0 × 1.6	T1 weighted, FLAIR
RS-III	Netherlands	Population based	46–94	3075	3714	1.5	T2 weighted	1.0 × 1.0 × 1.6	T1 weighted, FLAIR
SHIP									
SHIP-2	Germany	Population based	30–90	1163	Planned	1.5	T1 weighted	1.0 × 1.0 × 1.0	FLAIR
SHIP-Trend	Germany	Population based	21–82	2154	Planned	1.5	T1 weighted	1.0 × 1.0 × 1.0	FLAIR
EDIS	Singapore	Population based	60–85	865	—	3.0	T2 weighted	1.0 × 1.0 × 3.0	T1 weighted, FLAIR

Abbreviations: UNIVRSE, Uniform Neuro-Imaging of Virchow-Robin Spaces Enlargement; MRI, magnetic resonance imaging; VRS, Virchow-Robin spaces; ASPS, Austrian Stroke Prevention Study; EPOZ, Epidemiological Prevention study Of Zoetermeer; ERF, Erasmus Rucphen Family; FHS, Framingham Heart Study; RS, Rotterdam Study; SHIP, Study of Health in Pomerania; EDIS, Epidemiology of Dementia in Singapore.

1948 (mean age, 44 years). Generation 2 included 5124 offspring of the original cohort and their spouses who were enrolled into the study in 1971 (mean age, 36 years). Individuals from generations 1 and 2 received an MRI of the brain between 1999 and 2004 and again between 2005 and 2011 [21,22]. The generation 3 cohort was initiated in 2000, and all subjects were scanned between 2009 and March, 2013 [23].

2.5. Epidemiology of Dementia in Singapore study

The Epidemiology of Dementia in Singapore (EDIS) study draws participants from the Singapore Epidemiology of Eye Disease Study, which is a population-based study among Chinese, Malays, and Indians [24]. EDIS aims to examine the prevalence of and investigate risk factors for cognitive impairment and dementia in these three major ethnicities of Singapore. A total of 865 subjects aged ≥60 years have been recruited between 2010 and 2013. Cranial MRI is performed in all the individuals.

2.6. Erasmus Rucphen Family study

The Erasmus Rucphen Family (ERF) study is a family-based cohort study in a genetically isolated population from a community in the south-west of the Netherlands (Rucphen municipality) including 3000 deeply phenotyped participants. Participants with brain MRI scanning in ERF aged 55–75 years and had hypertension to ensure a high prevalence of pathology [25]. Persons with a history of stroke or dementia or with MRI contraindications were excluded. Details about subject selection can be found elsewhere [26,27].

2.7. Epidemiological Prevention study Of Zoetermeer

The Epidemiological Prevention study Of Zoetermeer (EPOZ) is a population-based follow-up study that was initiated in 1975 [28]. It includes 10,361 subjects between 5 and 91 years old and originally focused on determinants of various chronic diseases. Participants underwent baseline MRI scanning in 1995–1996 and were rescanned in 1999–2000 and 2008 [29,30].

2.8. Statistical analyses

We will analyze enlarged VRS in a continuous manner when studying their potential determinants by using negative binomial regression models that take into account the continuous nature of our visual rating scale. Depending on the specific research question, we will use the appropriate statistical tools to analyze the data (e.g., Cox regression models for time-to-event data, linear regression for continuous cognitive scores).

3. Results

3.1. Study population

Table 1 summarizes basic demographics and MRI protocols for each study in the UNIVRSE consortium. The consortium includes participants from a wide age range (19–103 years), mainly sampled from a population-based

setting. The RSS and ASPS have performed multiple rounds of MRI scanning and most of the other cohorts are still ongoing or reserve the possibility to perform an additional round of follow-up. Furthermore, participants were often part of other rounds of non-MRI data collection because brain MRI was not always part of the core study protocol. For most cohorts, a wide range of measurements are available, of which the most relevant are summarized in Table 2.

3.2. Primary outcomes

We previously developed a rating method that evaluates four regions in the brain where enlarged VRS occur frequently: the centrum semiovale, the basal ganglia, the hippocampus, and the mesencephalon. The method was rigorously tested by six raters ranging from medical students to experienced specialists using MRI data from three different scanners, and showed excellent reliability [14]. To promote the use of our VRS rating protocol, it has been made freely accessible through our website (www.uconsortium.org). Additionally, we have now extended the rating protocol to MRI data from the SHIP study: enlarged VRS were rated on the T1-weighted instead of the T2-weighted sequence, which is the primary sequence for VRS rating but was of too low resolution in SHIP for identifying VRS. To evaluate how this affects reliability, 25 scans from the RS with both good quality T1- and T2-weighted sequences were twice rated using each sequence separately, with good reliability (mean intraclass correlation coefficient = 0.8).

The UNIVRSE consortium aims to elucidate the etiology and clinical relevance of enlarged VRS. Therefore, it will first investigate potential determinants of enlarged VRS, including markers of cerebral small vessel disease, amyloid pathology, and genetic factors. Results of a preliminary analysis from only the founding members showed region-specific risk factors including sex, APOE genotype, blood pressure, white matter hyperintensities, and lacunar infarcts [31]. Additionally, the consortium is determining how presence of enlarged VRS affects cognition [3,32,33] and whether it is a useful marker for predicting diseases such as stroke [2,34,35] and Alzheimer's disease [6].

4. Discussion

Here, we present our initial experiences with data harmonization and joint analyses in a large consortium of population neuroimaging studies. We used a robust visual rating method for measuring enlarged VRS, which was rigorously tested in three studies before implementation in the consortium, to decrease heterogeneity and promote interstudy comparisons and collaboration. Importantly, this collaboration was initiated already in a relatively early phase of VRS research, with all the

Table 2
Nonexhaustive list of measurements available across the UNIVRSE consortium member cohorts

Phenotype	ASPS	ASPS family	EDIS	EPOZ	ERF	FHS	RS-I	RS-II	RS-III	SHIP-2	SHIP-Trend
Demographics											
Age	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Gender	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Education	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Lifestyle factors											
Smoking	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Alcohol	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Physical activity	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Cognitive function	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Blood chemistry											
Cholesterol	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Glucose	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
C-reactive protein	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Cardiovascular											
Blood pressure	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Echocardiography	×	×	×	✓	✓	✓	✓	✓	✓	✓	✓
Brain MRI markers											
Intracranial volume	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Tissue-specific volumes	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Hippocampal volume	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Infarcts	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Microbleeds	×	✓	✓	✓	✓	✓	✓	✓	✓	×	×
Genetics											
Genome-wide SNP array	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Exome chip	×	✓	×	✓	×	✓	✓	×	×	✓	✓

Abbreviations: UNIVRSE, Uniform Neuro-Imaging of Virchow-Robin Spaces Enlargement; ASPS, Austrian Stroke Prevention Study; EDIS, Epidemiology of Dementia in Singapore; EPOZ, Epidemiological Prevention study Of Zoetermeer; ERF, Erasmus Rucphen Family; FHS, Framingham Heart Study; RS, Rotterdam Study; SHIP, Study of Health in Pomerania; MRI, magnetic resonance imaging; SNP, single nucleotide polymorphism.

participating studies not having published separately using their own methodology, but instead first harmonizing ratings across sites and then jointly analyzing the data. For other imaging markers of cerebrovascular disease, such collaborative efforts typically follow decades of research using heterogeneous methods [1]. Initial joint analyses prove the value of this collaboration compared with separate, underpowered efforts.

Although there is an abundance of VRS rating methods, they are usually restricted to studies using only a single MRI protocol and only rate the VRS in a limited number of regions. Additionally, rating reliability is not always reported and some methods require complex transformations of images to perform the actual rating. A crucial step in the development process was defining a lower limit for the diameter of VRS to be considered enlarged, which has not been done by any rating method before. We operationalized enlargement as VRS $\geq$1 mm, while realizing this is an arbitrary threshold. However, counting all enlarged VRS, regardless of size, would mean that with increasing spatial resolution of the used MRI scanner, persons would have more "enlarged" VRS. Every study uses an implicit lower bound because there is minimum size of enlarged VRS that can be detected, which is inherent to the field strength and protocol of the MRI scanner. Indeed, studies using a 3-T MRI have found a 100% prevalence of enlarged VRS, in contrast with much lower prevalences on 1.5-T images. Additionally, we found that using the T1-weighted images for the primary rating gave comparable results to T2-weighted images. This result further establishes our rating protocol as a method for reliably quantifying VRS burden, regardless of the sequence used for rating.

Furthermore, we focused on the ease of use and speed of the method and rated VRS only a single slice for the two larger regions (basal ganglia and centrum semiovale). However, we have counted all VRS in the brain for 40 scans and compared this with the single slice that we used in the rating. This showed a high correlation between our single slice approach and the total number in that region. Although counting all VRS would be ideal, it is extremely time consuming and given these results also seems unnecessary to capture the VRS burden. Still, we could have chosen the most severe slice instead of the predefined slice that we use now. We made this decision because of two reasons: (1) allowing the rater to choose the "most severe" slice adds an additional layer of subjectivity to the method and (2) it is currently unknown whether the spatial distribution of VRS is differentially related to pathology. If, for example, parietal VRS are related to amyloid depositions, it would introduce bias when only rating certain subjects with respect to that part of the brain.

Main strengths of the UNIVRSE consortium are (1) the increased statistical power to detect associations (Figure 3),

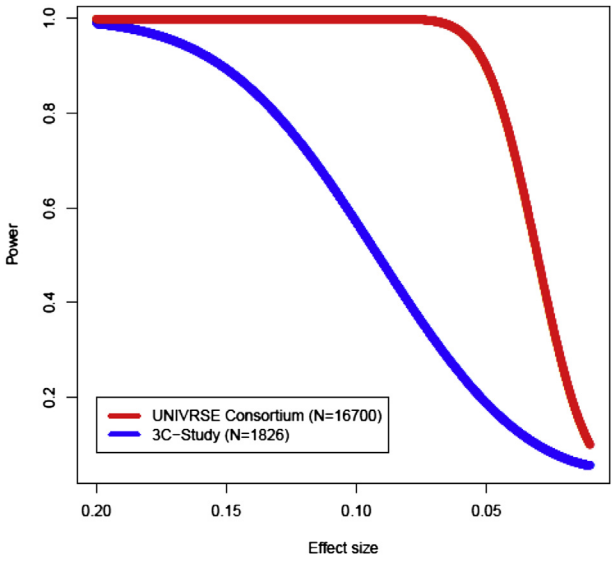

Fig. 3. Comparison of statistical power between the UNIVRSE consortium and the largest published study on Virchow-Robin spaces. Abbreviation: UNIVRSE, Uniform Neuro-Imaging of Virchow-Robin Spaces Enlargement.

achieved by combining data sets; (2) the harmonized approach of enlarged VRS rating, which facilitates the collaboration and allows for better comparisons; and (3) the inclusion of demographically diverse studies, with a broad range of phenotypic information available.

Although our rating protocol has several advantages in comparison with other scales, all methods still rely on the human assessment of VRS and are, therefore, subjective in nature and labor intensive. However, we are concurrently working on the development of an automated segmentation method, which is particularly difficult for VRS. In addition, the selection of the brain regions is based mostly on prevalence and current knowledge of VRS; therefore, new research could, for example, increase the interest in other regions and studying different pathology might also require changes in the protocol.

Our future research will include other determinants such as markers of cerebral small vessel disease, amyloid pathology, and genetic factors. In addition, we aim to determine how presence of enlarged VRS affects cognition and whether it is a useful marker for predicting diseases such as Alzheimer's disease and stroke.

5. Conclusions

The UNIVRSE consortium is a global initiative that was established in the young field of enlarged VRS research. It aims to implement at an early stage the hard-learned lessons on the value of data harmonization and joint analyses from decades of population imaging.

Acknowledgments

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RESEARCH IN CONTEXT

1. Systematic review: We searched for prospective, population-based cohort and family studies from various ethnicities. Particularly, we focused on studies which have performed extensive data collection to enable us to gain more insight into risk factors and consequences of enlarged Virchow-Robin spaces.
2. Interpretation: The UNIVRSE consortium was initiated to formally describe this collaboration between, as of yet, 13 (sub) cohorts from five countries. The consortium encompasses 16,000 research subjects with over 25,000 MRI scans
3. Future directions: Early collaborative efforts between cohort studies with respect to data harmonization and joint analyses can advance the field of population (neuro) imaging. The UNIVRSE consortium will focus efforts on other potential correlates of enlarged VRS, including genetics, cognition, stroke, and dementia.

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