

# BMJ Open Radiologically isolated syndrome: an uncommon finding at a university clinic in a high-prevalence region for multiple sclerosis

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## ABSTRACT

**Objective:** The improved availability of MRI in medicine has led to an increase in incidental findings. Unexpected brain MRI findings suggestive of multiple sclerosis (MS) without typical symptoms of MS were recently defined as radiologically isolated syndrome (RIS). The prevalence of RIS is uncertain. The aim of this study was to determine the prevalence of RIS at a university hospital in a region with a high prevalence for MS and describe the long-term prognosis of the identified patients.

**Design:** Retrospective cohort study conducted in 2012.

**Setting:** All brain MRI examinations performed at Karolinska University Hospital in Huddinge, Stockholm, Sweden during 2001 were retrospectively screened by a single rater for findings fulfilling the Okuda criteria. The sample year was chosen in order to establish the long-term prognosis of the patients identified. The examinations of interest were re-evaluated according to the Barkhof criteria by a neuroradiologist with long experience in MS.

**Participants:** In total 2105 individuals were included in the study. Ages ranged from 0 to 90 years with a median age of 48 years. Only one patient with RIS was identified, equivalent to a prevalence of 0.05% in the studied population, or 0.15% among patients aged 15–40 years. The patient with RIS developed symptoms consistent with MS within 3 months accompanied with radiological progression and was diagnosed with MS.

**Conclusions:** RIS, according to present criteria, is an uncommon finding in a tertiary hospital setting in a high-prevalence region for MS where awareness and clinical suspicion of MS is common. In order to study the prognosis of RIS, multicentre studies, or case–control studies are recommended.

## INTRODUCTION

MRI has revolutionised our ability to image the central nervous system and it has become readily accessible in clinical practice. With the

## Strengths and limitations of this study

- This is the first study reporting on the frequency of radiologically isolated syndrome in a high-prevalence region for multiple sclerosis.
- The study was a systematic re-evaluation of a yearly sample at a large university clinic.
- The retrospective nature of the study gives the possibility to report on the long-term prognosis for the patients, but also gives rise to losses to follow-up.
- The generalisability of the results to non-tertiary hospital settings and to regions with a lower prevalence of multiple sclerosis is limited.

improved availability and sensitivity of MRI there is an increase in incidental findings.<sup>1</sup> In 2009, Okuda *et al*<sup>2</sup> defined incidental MRI findings suggestive of multiple sclerosis (MS) without typical MS symptoms as radiologically isolated syndrome (RIS). This has led to an increased awareness of this condition and a convergence in terminology.<sup>3</sup>

Since the definition of RIS, studies by several groups have shown that there is a close association between RIS and MS. Patients with RIS often have a subclinical cognitive impairment with a similar test profile of deficits compared with patients with MS.<sup>4–6</sup> The association of RIS and MS is also strengthened in that both patient groups show similarities in both qualitative and quantitative MRI measurements.<sup>6–8</sup> There are case reports with follow-ups of up to 10 years,<sup>4 9 10</sup> and the range of mean follow-up times in the published cohorts are 2.4–7 years.<sup>2 11–17</sup> These studies show that roughly two-thirds progress radiologically and one-third develop clinical symptoms, and thereby convert to clinically isolated syndrome or MS, during their follow-up times.<sup>3</sup> This suggests that RIS in some cases may be considered to be

preclinical MS. The patients with RIS are therefore of particular interest to study in a pathophysiological aspect since it may shed light on early changes that precedes the onset of classical MS symptoms.

Headache is the most common reason for performing the initial MRI unveiling RIS, but it is unclear if there is a causative relationship between the incidental MRI findings and the headaches.<sup>3</sup> Recently a study by Liu *et al* showed that among patients undergoing MRI of the brain due to headaches, MRI findings fulfilling the Barkhof criteria are common. Depending on the definition of juxtacortical and periventricular, 2.4–7.1% of the patients fulfilled the Barkhof criteria.<sup>18</sup>

Incidental MS findings are previously known from autopsy studies from the late 20th century indicating a frequency of unexpected postmortem MS findings in the range 0.08–0.2%.<sup>19–22</sup> The incidence and prevalence of the newly defined RIS is, however, currently unknown.<sup>3</sup> In 2009 Morris *et al*<sup>1</sup> published a meta-analysis of 16 studies including 15 559 healthy control participants that reported nine cases of ‘definite demyelination’ and four cases of ‘possible demyelination’ corresponding to a frequency of 0.06% and 0.03%, respectively. There is unfortunately no report on the clinical history or neurological examination of these cases as to why the results cannot be assumed to reflect RIS. Instead the results of five original articles, identified as the most relevant, are described below.

An American study published in 1996, described 23 patients with MRI findings highly suggestive of MS (according to Paty’s classification) in a population of 2783 psychiatric patients. However, 13 patients had neurological symptoms that were not further specified, which gives a possible asymptomatic frequency of roughly 0.4%. It is unknown if these patients had any neurological findings that would exclude them from an RIS diagnosis.<sup>23</sup> The results are nonetheless interesting since psychiatric symptoms have frequently been reported as the original indication for performing the MRI examination that unveiled the RIS.<sup>3</sup> A second American study published in 1999 showed that among 1000 asymptomatic participants, there were 3 persons (0.3%) with findings classified as possible demyelinating disease.<sup>24</sup> A German study published in 2006 described a cohort of 2536 young male military recruits in which 1 person (0.04%) had findings suggestive of demyelinating disease, but it is not specified if this person had any neurological symptoms or findings.<sup>25</sup> A second German study was published in 2010, which showed that of 206 healthy young volunteers 2 (1%) had multiple white matter lesions, but it is unclear whether the findings fulfilled the Barkhof criteria.<sup>26</sup>

The first study reporting on the frequency of RIS since its definition was a hospital-based study from Pakistan published in 2011. It revealed that of 864 persons in the ages 15–40 years there were six cases (0.7%) of incidental MRI findings suggestive of MS in patients without relapsing neurological symptoms or pathological neurological

findings.<sup>27</sup> This study reported a surprisingly high frequency of such findings in a region with a low prevalence of MS (<5/100 000 population).<sup>28</sup> In comparison the estimated prevalence of MS in Sweden, where the present study was conducted, is 189/100 000 population.<sup>29</sup> Recently a second study using the RIS criteria was published in 2013 that demonstrated the frequency of RIS findings in asymptomatic relatives to MS patients and healthy controls. It showed that 2 of 68 (2.9%) healthy relatives of MS patients and 2 of 82 (2.4%) of the healthy controls fulfilled the Okuda criteria.<sup>30</sup>

In conclusion there has not been any study reporting on the hospital-based prevalence of RIS in a high-prevalence region for MS since the definition of RIS. This study aims to clarify in what frequency RIS findings can be expected in a tertiary hospital setting in a high-prevalence region for MS and depict the long-term prognosis of RIS in the patients identified.

## METHODS

### Study population and ethical approval

The study sample in this retrospective study conducted in 2012 is based on the digital radiological information system and digital patient charts at Karolinska University Hospital, Huddinge (formerly Huddinge University Hospital), Stockholm, Sweden. The hospital is a tertiary referral hospital for the greater southern Stockholm area with a population of 800 000 inhabitants. Although the study was conducted in 2012, the sample year was chosen to be 2001, when both the patient charts and the radiological data were fully digitalised, in order to be able to show the natural long-term prognosis over the past 11 years for any RIS cases identified. All persons undergoing a brain MRI at the hospital during the sample year were included in the study. The written informed consent was obtained according to the approval in those cases where more information was necessary through access of the clinical patient charts.

### Screening method

The screening of the study population was made systematically by one physician at the radiology department with previous experience of radiological research (TG). All documentation from the MRI examinations from 2001 was available to the screener and read to full extent. The material included both the query, the clinical information in the referral (clinical history, symptoms and findings) as well as the radiological findings according to the regular clinical radiological assessment.

### MRI examinations

All MRI examinations were performed in the regular clinical setting in one of two 1.5 T MRI machines, Siemens Magnetom Vision and Symphony (Siemens Medical Systems GmbH, Erlangen, Germany). The MRI examinations were performed according to standard clinical protocols depending on the original clinical

query and white matter anomalies were in most cases further characterised with the standardised MS MRI protocol used at the clinic described in [table 1](#).

### Radiological assessment

All examinations had been reviewed, signed and contra-signed as part of the regular clinical radiological routine. At least one of the clinical reviewers was a specialist in neuroradiology. The examinations identified with possible RIS findings in the screening process were re-evaluated according to the Barkhof criteria by another neuroradiologist (JM) with long experience of classifying MS-like findings.

### Clinical assessment

The referring doctor conducted the initial clinical assessments. All patients that were identified as possible RIS cases in the screening had been examined by a neurologist as part of the following clinical investigation. All patients diagnosed with MS received their diagnosis according to contemporaneous diagnostic criteria after careful investigation lead by a neurologist with experience of MS.

## RESULTS

### Prevalence of RIS

During the year of 2001 a total of 2105 individuals had at least one MRI examination of the brain at Karolinska University Hospital in Huddinge, Stockholm, Sweden. Among the patients there were 903 men (43%) and 1202 women (57%) with an age span of 0–90 years with 669 persons being between 15 and 40 years of age. The mean age was 46.2 years and median age was 48 years. The following results are also schematically described in [figure 1](#). Of all patients 542 had normal findings. The spectrum of findings is presented in [table 2](#). Common findings besides white matter changes were tumours, atrophy, infarctions and sinusitis.

In total 789 patients had white matter anomalies (not involving those caused by other diseases). Of these patients, 433 had unspecific white matter changes that did not fulfil the Barkhof criteria (solitary findings) or had a more likely explanation; such as an ischaemic-

degenerative pattern in elderly and/or patients with known severe cardiovascular disease. Of the 356 patients with white matter changes possibly reflecting demyelinating disease, 158 patients were known to have MS and 6 received their MS diagnosis as part of the investigation in question. Of the 192 remaining patients 139 were reported to have apparent neurological symptoms in the referral that would exclude the findings from being classified as RIS according to the B criteria in the Okuda classification, but where it was unclear if they had already gotten a diagnosis of clinically isolated syndrome or MS. After this screening only 53 patients remained with findings that were plausible RIS but where more clinical information was needed. In compliance with the ethical approval these patients were asked for written informed consent in order for us to evaluate their clinical patient charts.

Of these 53 patients where further information was needed, 3 patients were deceased, 7 did not respond and 4 declined participation. The patient charts of the remaining 39 persons that gave their informed consent were then examined in order to better understand the patients' clinical history, symptoms and neurological findings. This additional information revealed that 21 had been diagnosed with MS. Another 12 had intermittent clinical symptoms dismissing an RIS classification, presented in [table 3](#), but where the patients had not yet received a diagnosis of MS. In three cases there were insufficient clinical data to draw a conclusion. In the end, three patients with plausible RIS remained and after neuroradiological assessment one patient was classified as having RIS. This is equivalent to a prevalence of 0.05% in the studied population and 0.15% among the patients in the ages of 15–40 years.

### Case description

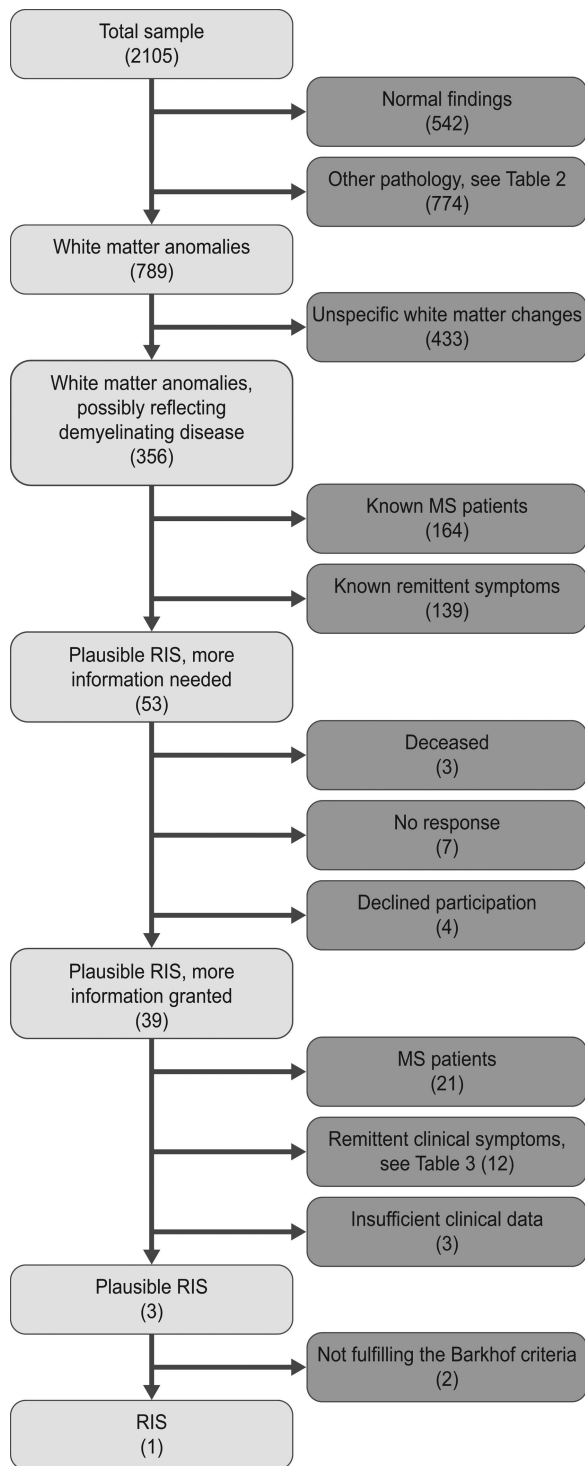
The patient with RIS was a 43-year-old woman without any neurological symptoms or any history of neurological disorders except for migraine since more than 10 years. A neurological examination did not reveal any pathological findings. She had good effect of triptanes. Owing to her long history of migraine and still frequent attacks she was referred for MRI of the brain in February 2001. The scan showed 15 supratentorial T2

**Table 1** MRI parameters of the standardised MS protocol

Sequence	Plane	SLT (mm)	TR (ms)	TE (ms)	TI (ms)	FA (°)
T1 MPRAGE	Axial	1.5	13.5	7	300	15
PD TSE	Axial	3.0	4761	22	–	180
T2 TSE	Axial	3.0	4761	90	–	180
T2 TSE*	Sagittal	4.0	3500	96	–	180
FLAIR*	Axial	5.0	9000	110	2500	180
T1 SE*	Axial	5.0	570	14	–	90

\*Acquired postgadolinium-DTPA contrast media.

FA, flip angle; FLAIR, fluid attenuated inversion recovery; MPRAGE, three-dimensional magnetisation prepared rapid acquisition gradient echo; MS, multiple sclerosis; PD, proton density; SE, spin echo; SLT, slice thickness; TE, echo time; TI, inversion time; TR, repetition time; TSE, turbo spin echo.



**Figure 1** Flow chart of the screening process to identify patients with possible radiologically isolated syndrome.

lesions, of which 12 were periventricular and 2 were juxtacortical. Gadolinium-enhanced sequences showed enhancement in one of the lesions. Thus three of the four of the Barkhof criteria were fulfilled.<sup>31</sup> Images obtained from this patient can be seen in figure 2. Owing to the MRI findings, she was referred to a neurologist in March where a second neurological examination was normal. Cerebrospinal fluid analysis revealed

**Table 2** Overview of MRI findings (n)

Within normal limits	542
<b>Cerebrovascular disorders</b>	326
Aneurysm	8
Carotid dissection or occlusion	12
Cavernous malformation	19
Cerebral contusions	4
Cortical infarction	89
Developmental venous anomaly	29
Lacunar infarction	133
Intracerebral haemorrhage	15
Cerebral venous sinus thrombosis	5
Subarachnoid haemorrhage	3
Subdural haematoma or hygroma	6
Other	3
<b>White matter and neurodegenerative disorders</b>	1143
Atrophy	285
Basal ganglia disorders	12
Hydrocephalus	20
Marked perivascular spaces	37
Possibly inflammatory white matter changes	356
Unspecific or degenerative white matter changes	433
<b>Infectious, inflammatory and metabolic disorders</b>	88
Cerebral abscess	7
Congenital metabolic disorders	4
Encephalitis	10
Meningitis	15
Optical neuritis	37
Vasculitis	4
Other	11
<b>Neoplasms</b>	311
Acoustic neuroma	19
Glioma	21
Meningioma	44
Metastasis	18
Pituitary adenoma	31
Unspecified or other type of neoplasm	46
<b>Cysts and malformations</b>	74
Arachnoid cyst	24
Empty sella	9
Malformation or dysplasia	16
Parenchymal cyst	5
Pineal cyst	13
Pituitary cyst	7
<b>Sinonasal and orbital disorders</b>	191
Sinusitis	164
Mastoiditis	23
Other	4

oligoclonal bands and an elevated IgG index. In May she returned to the neurological clinic due to a sudden onset of intermittent bilateral symptoms in arms and hands. A new neurological examination revealed bilateral tremor and dysmetria. A new MRI in June showed three new non-enhancing supratentorial lesions. She was diagnosed with MS and at a follow-up in September the

**Table 3** Presenting symptoms in the 12 patients not classified as RIS

Sex	Age (years)	Symptoms
F	25	Optical neuritis, Lhermitte's sign
F	26	Diplopia, hemiparesis
F	39	Optical neuritis, facial hemidysesthesia
F	43	Optical neuritis
F	47	Recurrent hemidysesthesia
F	58	Trigeminal neuralgia
F	62	Hemidysesthesia, facial paralysis
F	62	Hemidysesthesia
M	18	Severe vertigo, ataxia
M	18	Lhermitte's sign
M	27	Diplopia, vertigo, dysesthesia
M	44	Hypesthesia

F, female; M, male; RIS, radiologically isolated syndrome.

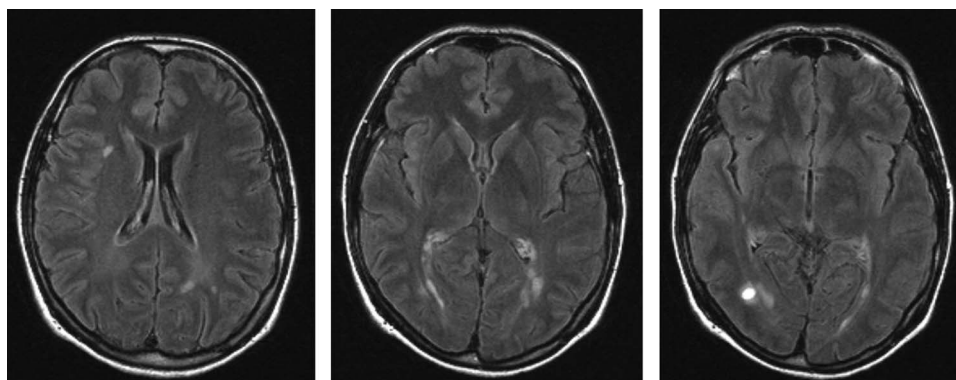
symptoms in the upper extremities had worsened. She received prednisolone treatment and was started on interferon  $\beta$  therapy. In November she had Lhermitte's sign and MRI showed a cervical spine lesion. Except for one occurrence of lower extremity symptoms in 2005, she has remained relapse free as of the latest neurological follow-up in March 2013.

## DISCUSSION

This study showed that RIS, according to present stringent criteria, is an uncommon finding, in a tertiary radiological clinic in a region with a high prevalence of MS, where awareness and clinical suspicion of MS is common.<sup>29</sup> The RIS frequency of 0.05% is in alignment with previous anatomopathological studies and earlier MRI studies have shown that 'incidental' or 'asymptomatic' MS is relatively uncommon.<sup>19–26</sup> The only hospital-based reported frequency of RIS since its definition, 0.7%, comes from a report from the Karachi region of Pakistan.<sup>27</sup> In contrast, the current study reports a frequency of RIS of 0.15% in the same age group. Although the studies are not directly comparable due to

dissimilarities in methodology, it is of interest to consider the difference in results further. A possible explanation may be the high awareness of MS in Sweden and frequent clinical suspicion when referring patients for MRI. The results could possibly also be affected by the fact that a majority of the referrals to the radiological clinic participating in this study comes from the in-hospital clinics, while patients initially seeking their family practitioner might have been referred to a non-tertiary radiological clinic for MRI. How the fact that the study site is a tertiary setting has affected the reported prevalence is therefore hard to appreciate. Another explanation for the difference might be that the study from Pakistan was a semiretrospective and semiprospective study, which might have been more effective in identifying patients with these findings and suffering from less losses to follow-up. In the study from Pakistan there were also fewer patients examined in a more densely populated area, likely mirroring a lower availability of MRI in the Karachi region than in the Stockholm region, perhaps making the patients who were examined with MRI of the brain in Karachi more likely to have findings. The published RIS cohorts are samples from Brazil, France, Italy, Spain, Turkey and the USA,<sup>2 7 11–17</sup> regions that vary from low to high prevalence.<sup>32</sup> It would be of interest to further evaluate the RIS prevalence in relation to the global MS prevalence.

Interestingly, the study published by Gabelic *et al*<sup>30</sup> shows that 2.9% of the healthy relatives of MS patients and 2.4% of the healthy controls in their study fulfilled Okuda's RIS criteria. This might indicate that the frequency of RIS findings would paradoxically be higher in the general population than found in the current study. However, differences in methodologies and demography of the research participants limit the comparability of the current study to Gabelic's work. The studies were not performed in the same region and with different aims. While this study aimed to describe the hospital-based frequency of RIS without limitations in terms of age groups, Gabelic's study was performed in a different country and studied the frequency of RIS in healthy hospital personnel and volunteers recruited through



**Figure 2** Axial fluid attenuated inversion recovery images of the identified radiologically isolated syndrome patient illustrating the multiple T2 hyperintensities and the contrast-enhancing lesion in the far right image.

newspaper advertisement within a homogenous age group with a mean age of 40 years.

A limitation of this study is the retrospective design with a single rater that may have led to patients being missed in the screening although a systematic approach was taken. By relying on the clinical evaluations in the screening process it is possible that patients with findings fulfilling the Barkhof criteria were missed. We believe that such gross errors are unlikely since at least one neuroradiologist and in total usually two radiologists evaluated all examinations as part of the clinical diagnostics. This being said, any patient missed would affect the reported frequency significantly due to the low prevalence of RIS. In terms of losses to follow-up, assuming that the frequency of RIS was the same in the 17 plausible RIS patients lost to follow-up as in those with all data available (1 case of RIS in 36 patients with plausible RIS), this would be equivalent to  $1/36 \times 17 = 0.47$ . This would increase the RIS frequency to 0.07%, or double the reported frequency to 0.1%, if rounded up to one patient. It is also unexpected that no elderly patients were classified as RIS since the presence of asymptomatic white matter lesions increase with age.<sup>33</sup> This might be due to the clinical information being available in the screening process, making it more likely to classify these white matter changes as ischaemic-degenerative. The study period was chosen to be the year 2001 in order to be able to show the natural long-term prognosis for the RIS cases identified with a potential follow-up period of 11 years. The reasoning for this was that regarding the published RIS cohorts, especially the retrospective cohorts, it is often unclear how the patients were initially identified. The hypothesis was therefore that patients with RIS that do not progress clinically are less likely to be noticed in the clinical setting, decreasing the chance of being included in a cohort, giving the observed cohort a worse prognosis. The study design did unfortunately not prove very helpful since only one case was identified, which limits the possibility of studying the prognosis. Although the study was conducted in 2001, it was conducted on modern 1.5 T MRI machines why the low frequency of RIS findings is hardly explained by technical reasons.

In conclusion this study suggests that RIS, according to present stringent criteria, is an uncommon finding in a tertiary hospital setting in a region with a high prevalence of MS. In order to more accurately determine the frequency of RIS in relation to MS prevalence, non-selected populations in large prospective studies actively involving both radiologists and neurologists are needed. In order to be able to study the prognosis of these patients large multicentre studies or case-control studies are recommended.

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**Contributors** TG initiated the study, designed data collection tools, performed the screening of all MRI examinations, monitored data collection, and drafted the paper. He is guarantor. JM performed neuroradiological image analysis.

TG, JM, MKW, PA and SF all conceived and designed the study, analysed the data and revised the paper.

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**Competing interests** SF has received honoraria for lectures or educational activities from Allergan, Bayer, Biogen Idec, Merck Serono, Novartis, Sanofi and Teva.

**Patient consent** Obtained.

**Ethics approval** This study was conducted with the approval of the regional ethical review board in Stockholm at Karolinska Institutet.

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**Data sharing statement** No additional data are available.

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