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Research priorities to improve stroke outcomes

See **Online** for appendix

The James Lind Alliance (JLA) Stroke Priority Setting Partnership involved stroke survivors, carers, and healthcare and other professionals in setting the research agenda by identifying and prioritising evidence uncertainties.[1] Investment in research to address these uncertainties can ensure that more lives are saved and rebuilt after stroke. Research has identified several interventions that improve outcomes for patients after ischaemic stroke (eg, stroke unit care, thrombolysis, or thrombectomy). However, stroke remains a leading cause of death and disability worldwide.[2] Although age-standardised stroke mortality has decreased,[2] specific interventions for people with haemorrhagic stroke are needed.

By 2035, in the UK, the incidence of stroke is expected to double compared with 2015.[3] Even in people with mild disability or who make a complete physical recovery, fatigue and psychological issues can hugely affect quality of life. Further action is needed to improve interventions for primary and secondary stroke prevention, and rehabilitation to reduce the burden of stroke. However, only about 1·2% of research funding in the UK is spent on stroke,[4] and the COVID-19 pandemic further reduced funding to this sector. Given the need for innovation in stroke care and restricted funds for research, the Stroke Priority Setting Partnership established a consensus on the priority areas to allocate resources that can have the greatest impact. In 2011, a JLA Partnership established research priorities on rehabilitation and long-term care,[5] but priorities across the whole stroke pathway were still needed.

We followed the well established JLA priority setting processes to ensure useful outcomes.[1] In July, 2019, a steering group was set up that could represent people affected, healthcare and other professionals, and third sector organisations in stroke. From February to August, 2020, more than 1400 stroke survivors, carers, and professionals participated in an online survey to collect unanswered questions for research. The submitted questions were checked against the partnership scope, existing evidence, and collated to form uncertainties. From February to March, 2021, stroke survivors, carers, and professionals participated in online surveys to prioritise uncertainties. In April, 2021, online workshops with stroke survivors, carers, and professionals reached a consensus on the top ten uncertainties.

The Stroke Priority Setting Partnership generated two lists with ten uncertainties, ranked in order of importance, one for prevention and acute care and the other for rehabilitation and long-term care (table; appendix pp 2–3). Six of the priority areas address stroke-related impairments. Three areas address stroke prevention, three focus on stroke treatment, and eight relate to delivery and experience of care. Psychological and cognitive effects remain top priorities since the previous JLA Partnership.

We provide a clear roadmap for research investment that can make the greatest impact to improve stroke outcomes. These priorities should inform the activities of funding

	Prevention, diagnosis, and treatment	Rehabilitation and long-term care
1	Best interventions for primary stroke prevention	Assessment of the impact of psychological effects and interventions to reduce them
2	Recognition and early diagnosis of stroke and transient ischaemic attack	Evaluation of cognitive disfunction and interventions to reduce it
3	Evaluation of risks and benefits of intracerebral haemorrhage treatments	Assessment of communication problems and interventions to reduce them
4	New therapies for neuroprotection	Understanding fatigue and how to reduce it
5	Risk of secondary stroke and secondary prevention	Organisation of community stroke services to meet all survivor needs
6	Availability of thrombectomy to more patients with ischaemic stroke	Evaluation of long-term effects on activities of daily living and interventions to tackle these effects
7	Interventions to delay changes in brain function after subarachnoid haemorrhage	Evaluation of the duration, intensity, location, and frequency of therapeutical interventions to achieve long-term outcomes
8	Strategies to reduce complications of stroke	Improvement of carers support
9	Evaluation of risks and benefits, and personalised anticoagulation treatment	Strength and exercise interventions for recovery and secondary stroke prevention
10	Effect of comorbidities and health characteristics on stroke	Improving stroke survivor and carer experience of the stroke pathway

Table: **Top priorities for stroke research**

bodies, researchers, and decision makers investing in stroke research.

We declare no competing interests. Members of the Stroke Priority Setting Partnership Steering group are listed in the appendix (p 1).

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Exercise training in multiple sclerosis

Exercise training has been identified as a neuroprotection-inducing approach in patients with multiple sclerosis.[1] However, recently published reviews involving small numbers of randomised controlled trials (RCTs) concluded that exercise training is not associated with neuroprotection.[2,3] We argue that the absence of evidence does not constitute evidence of absence.

These RCTs typically involve 1–6 months of general exercise training with exploratory, whole-brain structural neuroimaging metrics in patients with mild-to-moderate multiple sclerosis without pre-existing deficits. Short exercise training durations are insufficient for yielding measurable increases in whole-brain volume, as even powerful disease modifying therapies do not exert such effects in 1–6 months.[4] The exercise programmes are not designed for inducing brain adaptations based on neurophysiological hypotheses (which would be analogous to conducting a regulatory disease modifying therapy trial without incorporating preclinical research). The RCTs do not involve a-priori hypothesised regions of interest for studying exercise neuroprotection and disproportionately rely on whole-brain or exploratory structural neuroimaging for generating conclusions on neuroprotection.[5] That approach embodies a generalised search for a possible signal within the CNS and is inconsistent with research demonstrating focal, exercise-induced neuroprotection in patients with spinal cord injury using non-volumetric neuroimaging. The RCTs include patients without measurable, pre-existing CNS damage. This precludes inferences of neuroprotection, which involves stopping or reversing existing and measurable neural damage or decline. The RCTs did not include follow-up assessments beyond 6 months. Longer-term follow-up assessments are crucial for evaluating protection against future CNS decline, consistent with measurement intervals of disease modifying therapy trials.[4]

The absence of evidence for exercise training and neuroprotection in multiple sclerosis is disappointing, and we are not engaging in turf protection. We argue that the few, poorly designed studies render the generation of any strong conclusions moot. Researchers should carefully evaluate the evidence when making sweeping inferences that can stall a field of inquiry; this field will not advance with studies that collectively include short-term and generalised exercise, poorly defined multiple sclerosis cohorts, and exploratory, whole-brain neuroimaging endpoints over short time periods. We acknowledge that a shift in scientific paradigm is slow and arduous, yet we encourage the design of stronger RCTs that methodically address the possibility of neuroprotection through exercise training in patients with multiple sclerosis.

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