Supplementary data

Supplementary Appendix 1. Details of PubMed search terms

We performed a structured search of PubMed to identify trials which randomly assigned patients to mechanical thrombectomy or control on a background of medical therapy which could include thrombolysis where eligible. We applied limits on the available dates from 1 January 2010 to 2 July 2020. No language restriction was applied.

The search string was as follows: randomised controlled trial [pt] OR controlled clinical trial [pt] OR randomised [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab] NOT (animals [mh] NOT humans [mh]) AND ((thrombectomy [tiab]) OR (clot retrieval [tiab]) OR intraarterial[tiab]) AND (stroke[tiab]).

Supplementary Appendix 2. Supplementary results

With the addition of these three trials, there were a total of 3,694 patients, of whom 1,955 were randomised to thrombectomy and 1,739 to control.

Including these data, thrombectomy reduced disability at 90 days assessed using the mRS (OR 0.64, 95% CrI 0.57 to 0.72, pr <0.0001) **(Supplementary Figure 2A)**. The reduction in all-cause mortality with thrombectomy was less certain (OR 0.88, 95% CrI 0.73 to 1.04, pr=0.070) **(Supplementary Figure 2B)**. Finally, the odds of SIH were similar between the two groups (OR 1.11, 95% CrI 0.81 to 1.51, pr=0.74) **(Supplementary Figure 2C)**.

Supplementary Table 1. Impact of setting increasingly flat priors for the β coefficients for the primary outcome (mRS score at 90 days).

SD of prior (normal distribution)	Odds of a higher mRS score with thrombectomy
0.25	OR 0.99 (95% CrI 0.97 to 1.01)
1	OR 0.86 (95% CrI 0.80 to 0.92)
10	OR 0.54 (95% CrI 0.47 to 0.61)
100	OR 0.52 (95% CrI 0.45 to 0.60)
10000	OR 0.52 (95% CrI 0.46 to 0.60)

mRS: modified Rankin Scale; OR: odds ratio; SD: standard deviation

Supplementary Table 2. Impact of setting increasingly flat priors for the random effect on primary outcome (mRS score at 90 days).

Mean of prior (exponential distribution)	Odds of a higher mRS score with thrombectomy
10	OR 0.53 (95% CrI 0.45 to 0.60)
1	OR 0.53 (95% CrI 0.46 to 0.60)
0.25	OR 0.52 (95% CrI 0.46 to 0.60)
0.1	OR 0.53 (95% CrI 0.46 to 0.61)

mRS: modified Rankin Scale; OR: odds ratio;. SD: standard deviation

Supplementary Table 3.
Impact of setting increasingly flat priors for the β coefficients for the endpoint of mortality.

SD of prior (normal distribution)	Odds of a higher risk of mortality with thrombectomy
0.25	OR 1.00 (95% CrI 0.98 to 1.02)
1	OR 0.97 (95% CrI 0.90 to 1.04)
10	OR 0.82 (95% CrI 0.67 to 1.00)
100	OR 0.81 (95% CrI 0.65 to 0.99)
10000	OR 0.81 (95% CrI 0.66 to 0.99)

OR: odds ratio; SD: standard deviation

Supplementary Table 4. Impact of setting increasingly flat priors for the random effect on the endpoint of mortality.

Mean of prior (exponential distribution)	Odds of a higher risk of mortality with thrombectomy
10	OR 0.81 (95% CrI 0.66 to 0.99)
1	OR 0.81 (95% CrI 0.66 to 0.99)
0.25	OR 0.81 (95% CrI 0.66 to 1.00)
0.1	OR 0.81 (95% CrI 0.66 to 1.00)

OR: odds ratio; SD: standard deviation

Supplementary Table 5. Cochrane risk of bias assessment tool for included studies.

Trial	Random sequence allocation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Overall quality
ESCAPE [20]	Low risk "A real-time, dynamic, internet-based, randomised minimisation procedure (minimal sufficient balance method)"	Unclear	High risk Open label trial	Low risk "The primary outcome was assessed by trained personnel who were unaware of the treatment-group assignments"	Low risk One patient removed due to improper consent just after randomisation. One patient was lost to follow-up in the intervention arm and three patients were lost to follow-up in the control arm.	Low risk Most endpoints on CT.gov reported.	High Well conducted open-label trial with outcomes assessed by personnel unaware of treatment assignment.
EXTEND-1A [21]	Low risk "Patients were randomised - by means of a centralised website and stratified according to the site of arterial occlusion"	Unclear	High risk Open label trial	Low risk "Neurological impairment and functional scores were measured by a clinician trained in their administration and blinded to treatment assignment"	Low risk Eight patients in the intervention arm did not receive intervention (2 patients did not have angiogram performed due to change in their clinical status, 4 had no retrievable thrombus remaining on first angiographic run, 1 had mTICI 2b flow after stenting of extracranial ICA, 1 patient had vessel perforation and extravasation with microcatheter manipulation)	Low risk All endpoints on CT.gov reported.	High Well conducted open-label trial with outcomes assessed by personnel unaware of treatment assignment.
MR CLEAN [22]	Low risk "The randomisation procedure was Web-based, with the use of permuted blocks"	Unclear	High risk Open label trial	Low risk "A single experienced trial investigator, who was unaware of the treatment-group assignments, conducted the follow-up interviews at 90 days by telephone with the patient, proxy, or healthcare provider. This interview provided reports for the	Low risk 2 patients declined participation after randomisation to control arm. 17 patients in the intervention arm did not undergo catheter angiogram (8 had clinical improvement before intervention, 6 protocol violations by local investigators, 1 had no femoral access, 1 withdrew consent for intervention, 1 was	Low risk All pre-specified endpoints reported	High Well conducted open-label trial with outcomes assessed by personnel unaware of treatment assignment

				assessment of the modified Rankin score by reviewers who remained unaware of the treatment-group assignments."	haemodynamically unstable. 20 patients in the intervention arm did not have intervention (10 had ICA disease, 8 had no clot visible, 2 technical problems)		
PISTE [7]	Low risk "Randomisation was conducted using an interactive voice-response system managed by the Robertson Centre for Biostatistics, University of Glasgow"	Unclear	High risk Open label trial	Low risk "Day 90 outcomes were assessed by site staff blinded to treatment allocation"	Low risk 3 patients in the intervention arm did not receive intervention (2 had more than 33% disease in MCA territory, 1 patient had treatment crossover). 4 patients in the control arm did receive IVT alone (1 patient had an ineligible CTA occlusion, 1 had more than 33% disease in MCA territory, 1 patient had mRS >2 on review, 1 patient had treatment crossover). In the control arm, two patients were lost to follow-up at 90 days.	Low risk All endpoints on CT.gov reported.	High Well conducted open-label trial with outcomes assessed by personnel unaware of treatment assignment
REVASCAT [23]	Low risk "a real-time computerised randomisation procedure" with stratification.	Unclear	High risk Open label trial	Low risk "Local and external certified assessors who were unaware of study-group assignments separately evaluated the primary outcome variable in each patient by means of a structured interview"	Low risk One patient withdrew consent just after randomisation. 33 patients in the intervention arm and 23 patients in the control arm did not receive tPA. Five patients in the intervention arm did not undergo intervention (3 had TICI 3 and 2 had TICI 2b perfusion score)	Low risk All endpoints on CT.gov reported in primary analysis.	High Well conducted open-label trial with outcomes assessed by local and external assessors unaware of treatment assignment
SWIFT PRIME [24]	Low risk "Subject allocation to treatment will be accomplished by using	Unclear	High risk Open label trial	Low risk "The 90-day mRS was assessed by study personnel certified in the scoring of the mRS using the RFA-A, and	Low risk 11 patients in the intervention arm did not receive intervention (7 had complete or partial resolution of	Low risk All endpoints on CT.gov reported	High Well conducted open-label trial with outcomes

	an interactive web response or interactive voice response system.			blinded to treatment assignment"	target occlusion, 2 had no target occlusion at the time of enrolment and 2 had inaccessible target occlusions). Final assessment data were unavailable in 5 patients in the control arm (2 were withdrawn by the investigator after entry criteria deviation and 3 patients withdrew their consent)	in primary analysis.	assessed by staff blinded to treatment assignment
THRACE [18]	Low risk "Randomisation was done at the coordination centre by a computer analyst who was masked to the investigation centres and to the patients. Randomisation was done with a computer-generated sequence and was stratified by centre, and sequential minimisation with a factor of 85% was used to avoid imbalance in treatment."	Unclear	High risk Open label trial	High risk "Clinical assessments were done by vascular neurologists who were not masked to the treatment to which the patients had been allocated."	Low risk 2 patients withdrew consent after randomisation. 59 patients in the intervention arm did not have thrombectomy and 4 patients in the intervention group discontinued intervention because of catheterisation problems. 8 patients in the control arm eventually received intervention because of poor clinical evolution. 2 patients in the intervention arm and 2 patients in the control arm were lost to follow-up. 2 patients in the intervention arm and 4 patients in the control arm had missing data for efficacity analysis	Low risk All endpoints on CT.gov reported in primary analysis.	Intermediate Well conducted open-label trial but absence of blinded adjudication of clinical assessments reduces quality of trial
THERAPY [6]	Low risk "Randomisation was performed through a centralised interactive voice response system"	Unclear	High risk Open label trial	Low risk "The primary outcome measure (90-day mRS) was assessed by independent blinded adjudicators. Adjudicators reviewed videotapes of assessments performed by blinded, trained,	Low risk 3 patients in the intervention arm and 5 patients in the control arm were lost to follow-up. Two patients in the intervention arm and two patients in the control arm withdrew consent.	Low risk All endpoints on CT.gov reported in primary analysis.	High Well conducted open-label trial with outcomes assessed by staff blinded to treatment assignment

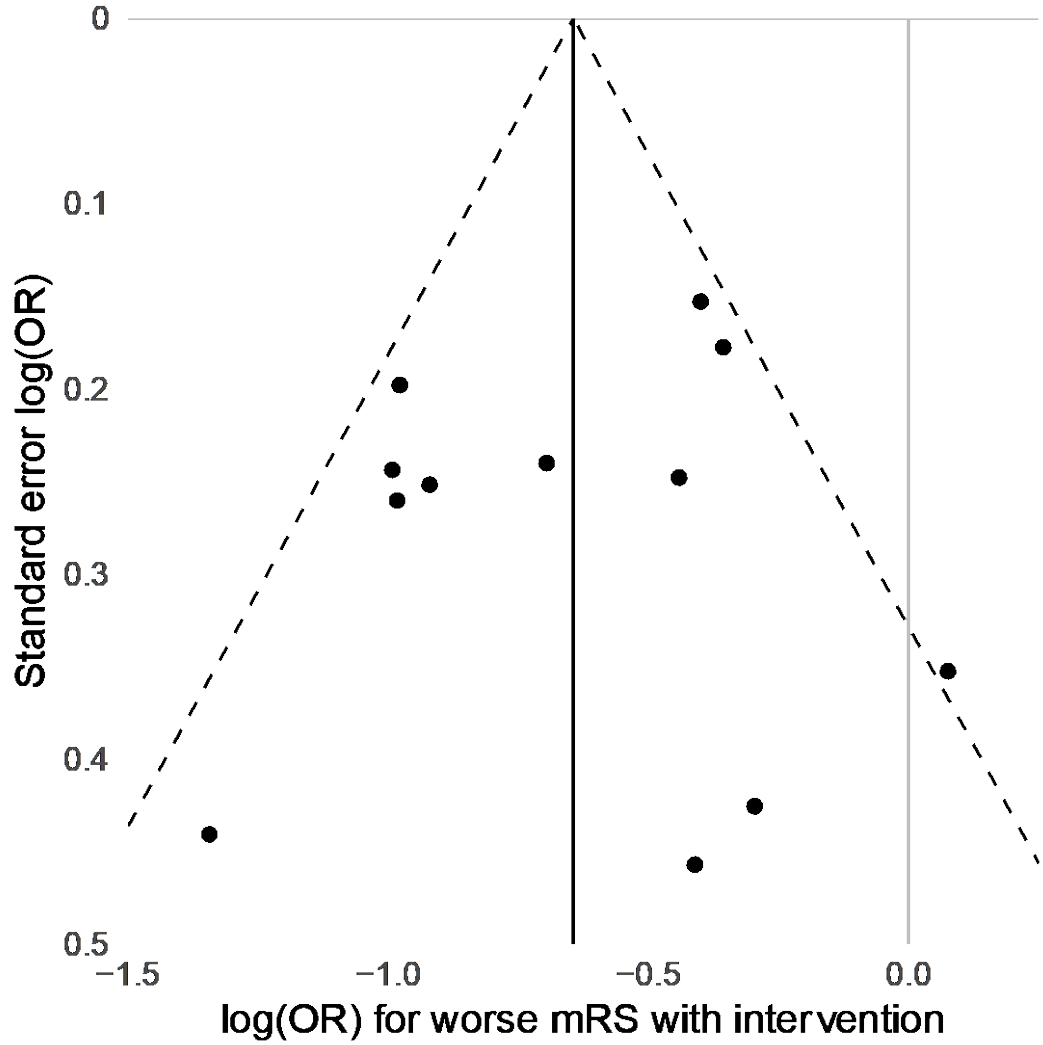
				and certified local investigators. “ “SiCH was defined as any new haemorrhage identified by the core laboratory with a concomitant ≥4-point worsening in NIHSS as recorded by a blinded, NIHSS-certified assessor.”			
DAWN [9]	Low risk “Randomisation was performed with the use of a central, Web-based procedure, with block minimisation processes to balance the two treatment groups, and was stratified according to mismatch criteria”	Unclear	High risk Open label trial	Low risk “For the coprimary endpoints, scores on the modified Rankin scale were obtained through in-person, formal, structured interviews with patients and caregivers that were performed by local certified assessors who were unaware of the treatment assignments.” Safety endpoints, procedure-related complications, and serious adverse events were adjudicated by an independent clinical events committee.	Low risk Two patients in the intervention arm did not receive intervention due to spontaneous recanalisation of target vessel on conventional angiogram	Low risk All endpoints on CT.gov reported in primary analysis.	Intermediate Well conducted open-label trial. Although safety endpoints were adjudicated by independent assessors, it is unclear if they were blinded to treatment allocation. This reduces the quality of the trial.
DEFUSE 3 [10]	Low risk “Randomisation - with the use of a Web-based dynamic randomisation system. Randomisation was stratified”	Low risk	High risk Open label trial	Low risk “The score (referring to mRS) was assessed in person, or by telephone if an in-person visit was not feasible, by a certified rater who was not aware of the trial-group assignments”	Low risk Two patients in the intervention group did not receive intervention due to intervention deemed unsafe/not feasible by the operator.	Low risk All endpoints on CT.gov reported in primary analysis.	High Well conducted open-label trial with outcomes assessed by independent staff, blinded to treatment assignment
RESILIENT [8]	Low risk	Unclear	High risk	Low risk	Low risk	Low risk	High

	"Randomisation was performed through a real-time, dynamic, internet-based, randomised minimisation procedure to balance the numbers of patients across the two groups"		Open label trial	"Assessment was based on central adjudication by consensus of two certified neurologists, who were unaware of the treatment assignments and who viewed video recordings of structured patient or family interviews."	In the intervention arm, 35 did not receive intravenous tPA and 31 patients in the control group did not receive intravenous alteplase. One person in the control group did not receive intervention. One patient in the control group was lost to follow-up	All endpoints on CT.gov reported in primary analysis.	Well conducted open-label trial with outcomes assessed by independent staff, blinded to treatment assignment
EASI [19]	Low risk "Randomisation through a web-based application package. Minimisation was used as a method of adaptive stratified sampling"	Unclear Low risk	High risk Open label trial	High risk "All data and outcome measures were collected by routine care personnel in this care trial design and thus no blinding was involved"	Low risk 10 patients in the intervention arm did not receive intervention (1 patient had no angiography due to aortic dissection, 4 patients had distal thrombus, 3 patients had no thrombus found and 2 patients had inaccessible basilar artery). Three patients in the control arm received intervention due to request from the neurologist or family	Low risk All endpoints on CT.gov reported in primary analysis.	Intermediate Well conducted open label trial but lack of blinding for outcome evaluation reduces the quality of the trial.

Supplementary Table 6. Summary characteristics for trials added to the sensitivity analysis.

TRIAL n MT/CON	Journal	Year	Sites	Median NIHSS MT/CON	Max delay EVT from symptom onset (hrs)	Imaging modality for inclusion	Proportion received IV thrombolytic therapy MT/CON	Protocol-mandated thrombectomy technique	Symptom onset to groin puncture (mins)	Attempt with any MT device¶	Proportion of MT with stent retriever	Proportion of MT with aspiration catheter	TICI 2b-3 at procedure end (%)
MR RESCUE [25] 64/54	NEJM	2013	22 sites, N. America	16/19//16/20	≤8	MRA or CTA	43.8 / 29.6	Any FDA approved device. Merci retriever (77%)	381±74	95.3 61/64	0.0% 0/61	39.3% 24/61	25.0% 16/64
IMS III [26] 434/222	NEJM	2013	58 sites, N. America, AUS, Europe	17/16	<5	NCCT	100 / 100	IA tPA‡ and/or Merci (22%), Penumbra (12%), Solitaire (1%)	208±47	39.2% 170/434	8.2% 14/170	38.8% 66/170	39.6% 126/318
SYNTHESIS Expansion [27] 181/181	NEJM	2013	24 sites, Italy	13/13	<6	NCCT	0.0* / 98.3	IA tPA‡ +/- device utilisation (31%)	225 (194-250)	30.9% 56/181	41%‡‡ 23/56	16.1% 9/56	Not specified

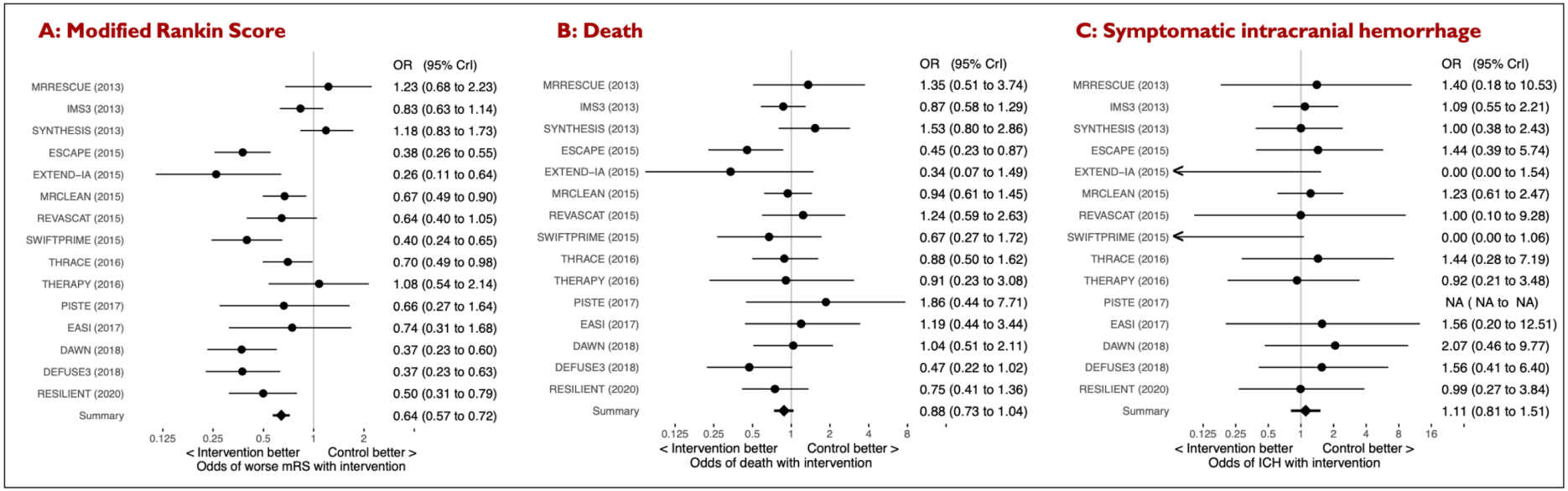
¶ Figure for proportion of patients in the intervention group who received an attempt at EVT with a dedicated EVT device.
‡ Intra-arterial tPA administered through a microcatheter +/- mechanical clot disruption typically using a guidewire.
‡‡ Only Solitaire and Trevo devices reported.
* Patients in the thrombectomy arm were eligible for intra-arterial thrombolysis at the discretion of the interventionalist.
CON: control arm; CTA: CT angiogram; DSA: digital subtraction angiography; dwMR: diffusion weighted magnetic resonance; INT: intervention arm; MRA: magnetic resonance angiography; MT: mechanical thrombectomy; NCCT: non-contrast computed tomography; NIHSS: National Institutes of Health Stroke Scale; TICI: Thrombolysis In Cerebral Infarction score



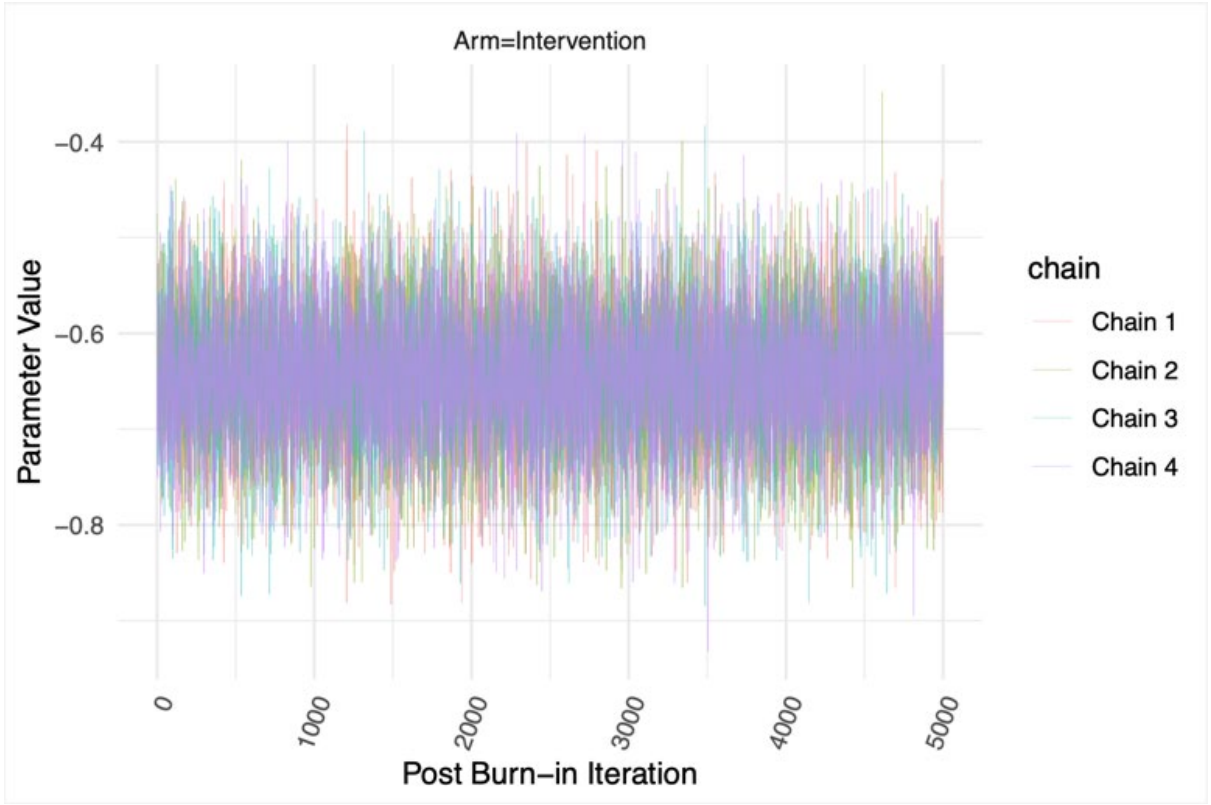
Supplementary Figure 1. Funnel plot.

Funnel plot demonstrating a low risk of publication bias for the primary endpoint across studies included in this meta-analysis (Egger's test, p=0.2).

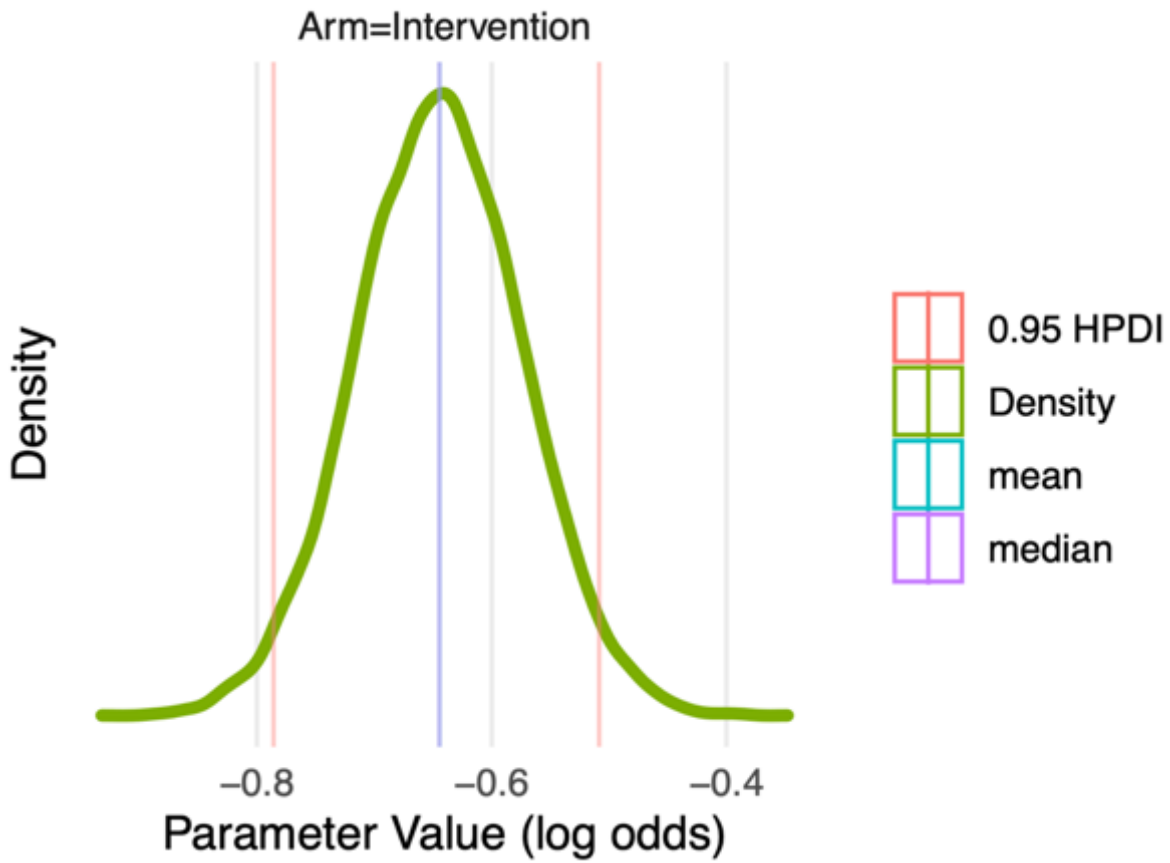
mRS: modified Rankin Scale score; OR: odds ratio



Supplementary Figure 2. Sensitivity analysis forest plots indicating the effect of mechanical thrombectomy versus control for the treatment of acute ischaemic stroke on 90-day outcomes of (A) modified Rankin Scale score, (B) all-cause mortality, and (C) symptomatic intracranial haemorrhage.
CrI: credible interval; mRS: modified Rankin Scale score; OR: odds ratio; ICH: intracranial haemorrhage

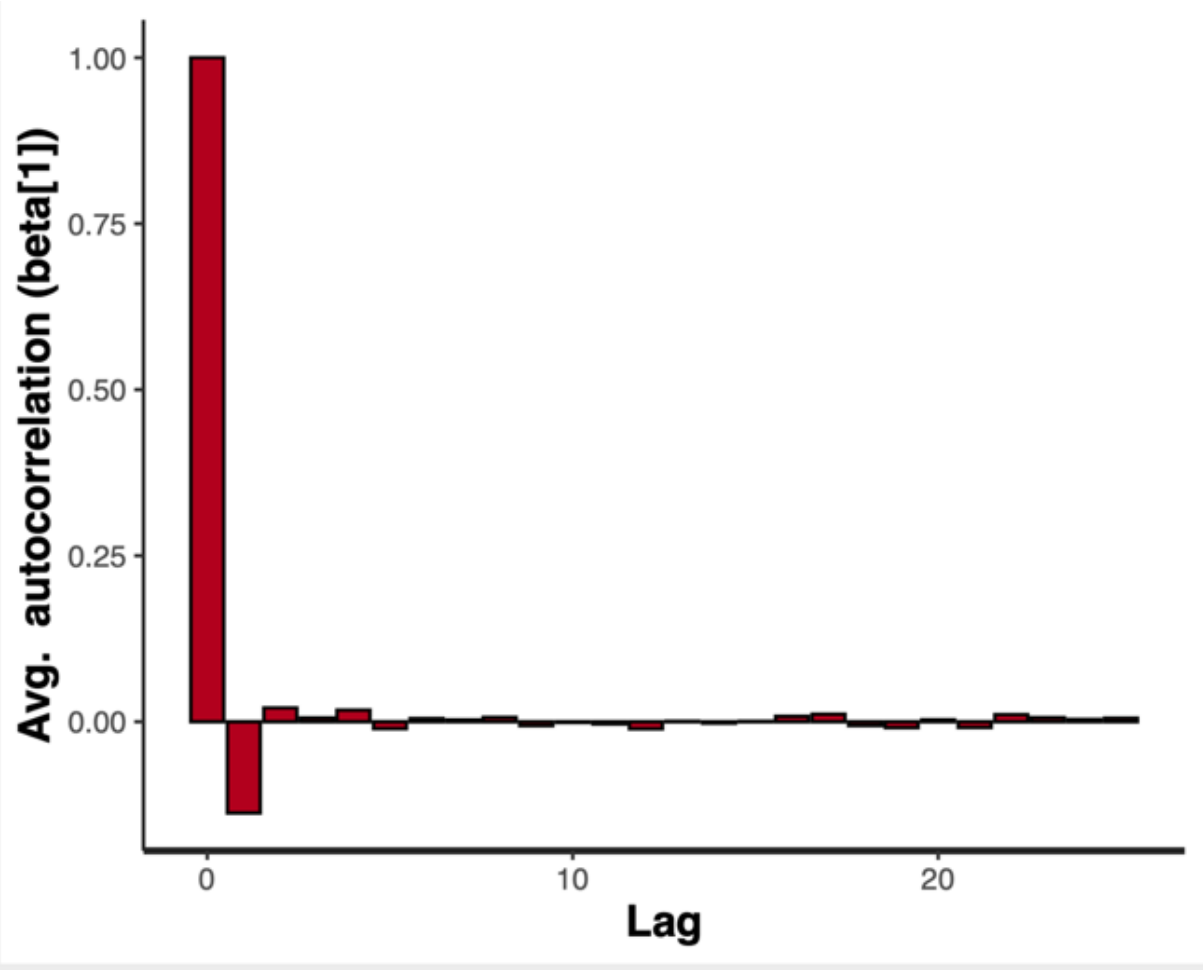


Supplementary Figure 3A. Sample diagnostic plot (mRS): trace.

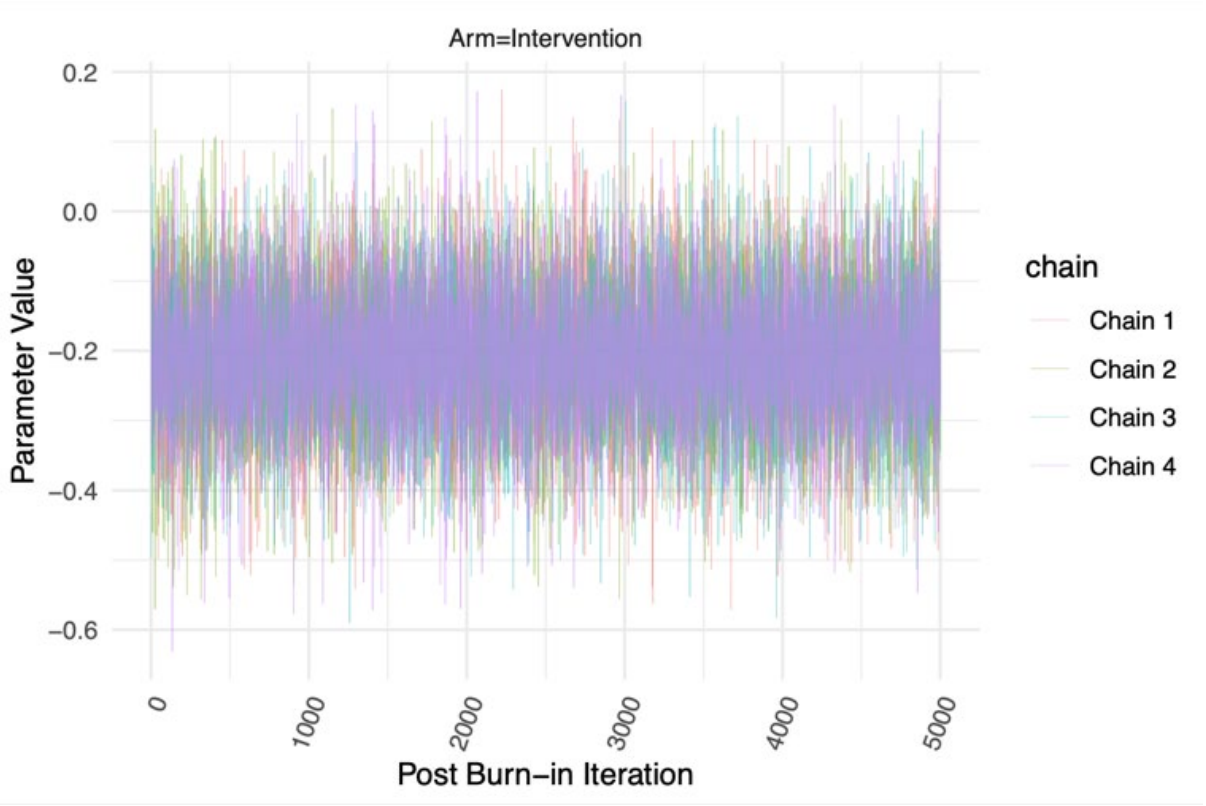


Supplementary Figure 3B. Sample diagnostic plot (mRS): density.

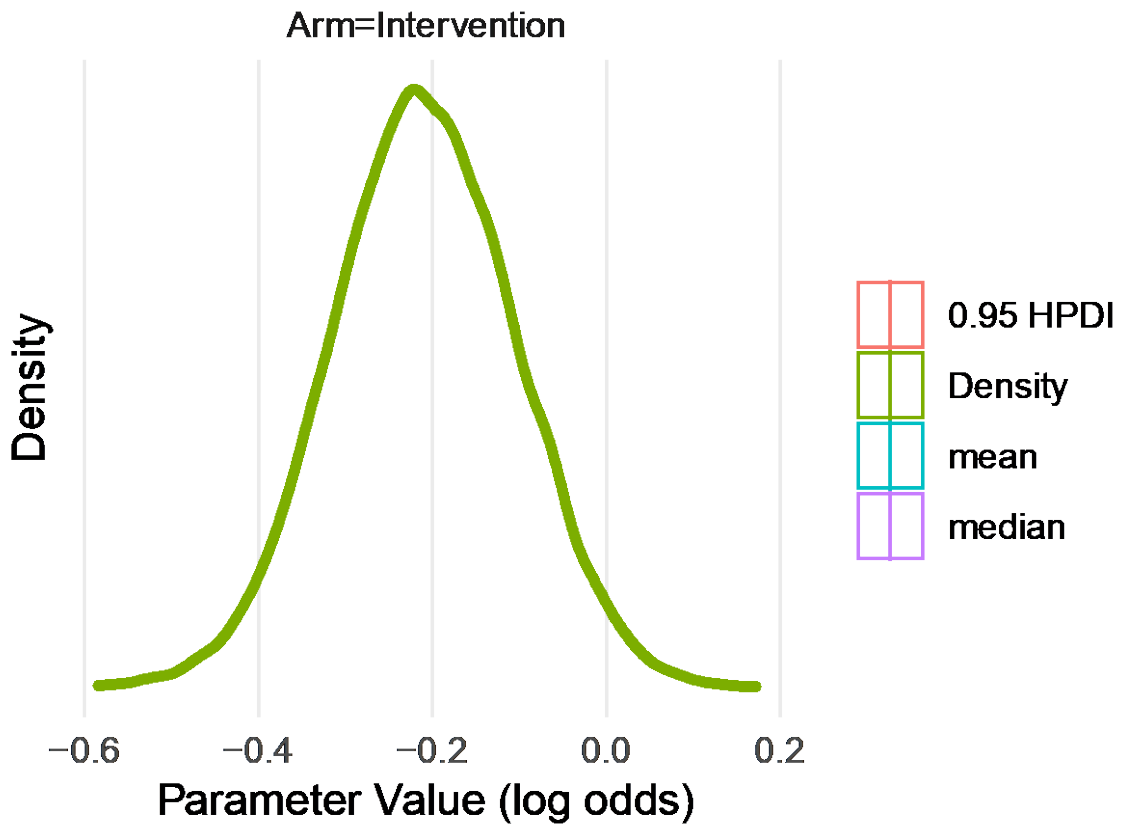
HPDI: highest posterior density interval



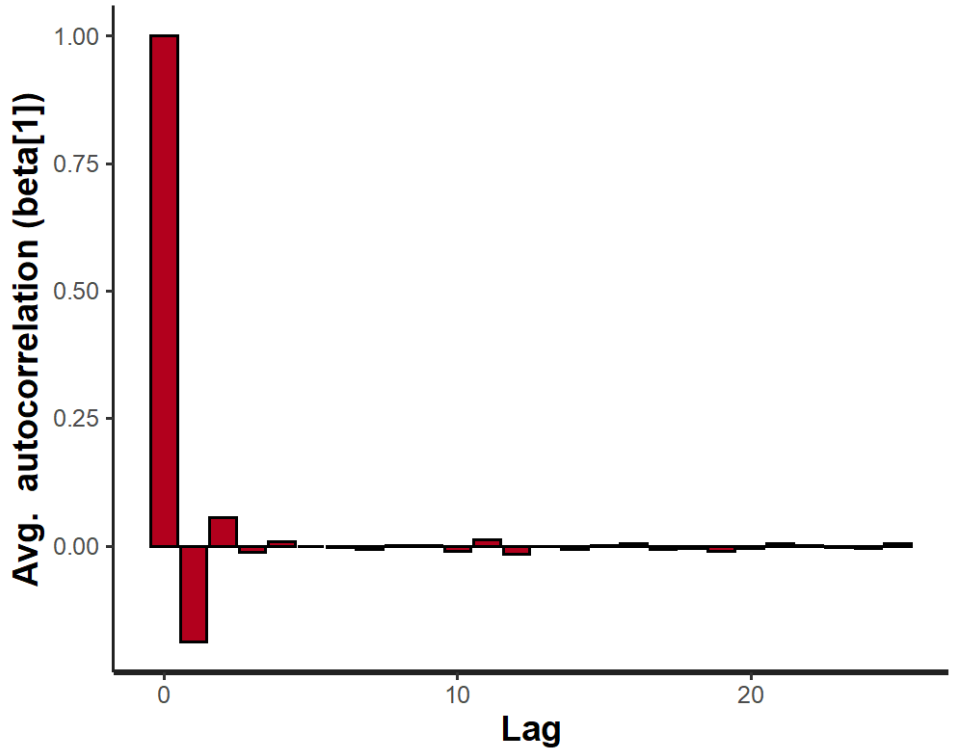
Supplementary Figure 3C. Sample diagnostic plot (mRS): autocorrelation.



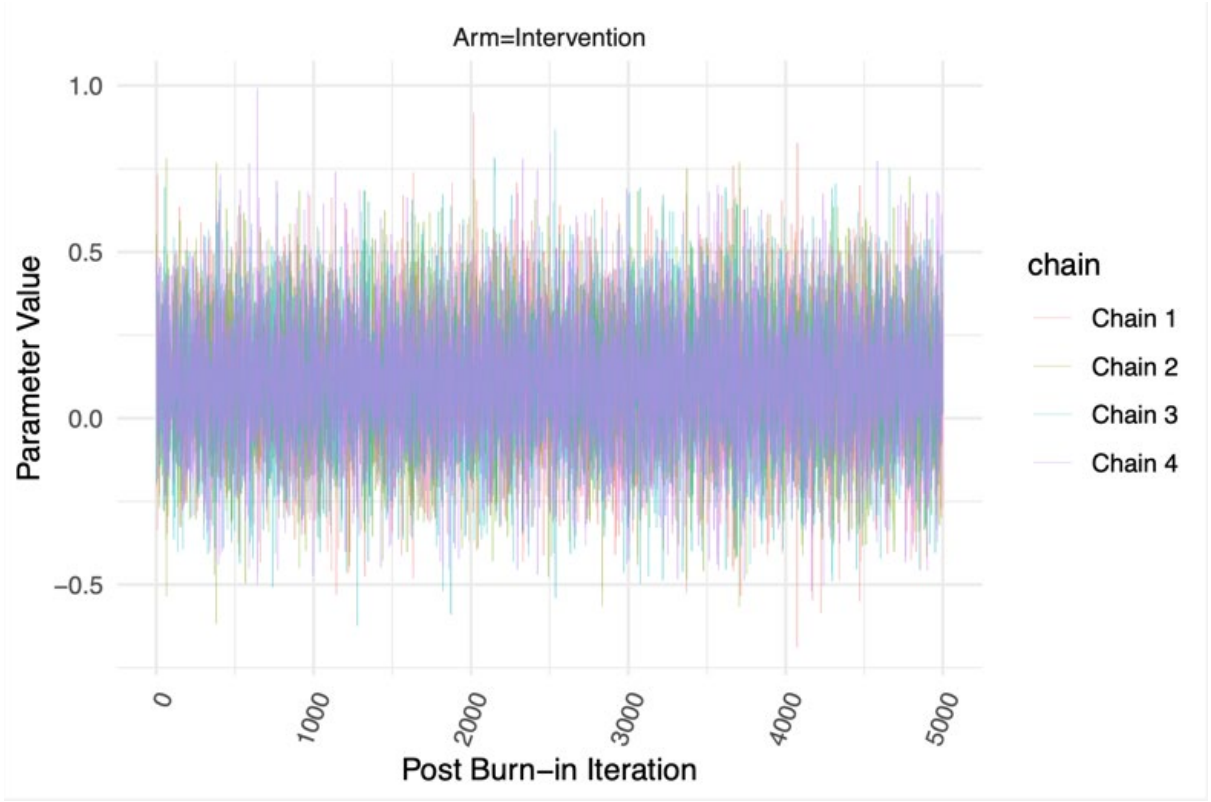
Supplementary Figure 4A. Sample diagnostic plot (death): trace.



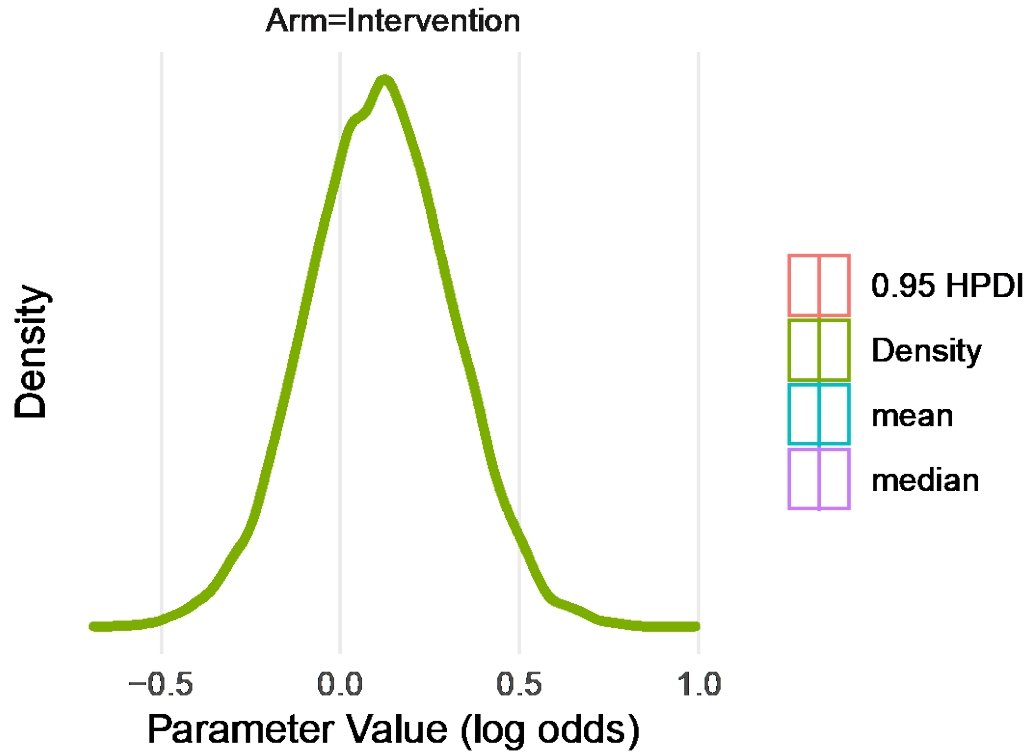
Supplementary Figure 4B. Sample diagnostic plot (death): density.
HPDI: highest posterior density interval



Supplementary Figure 4C. Sample diagnostic plot (death): autocorrelation.

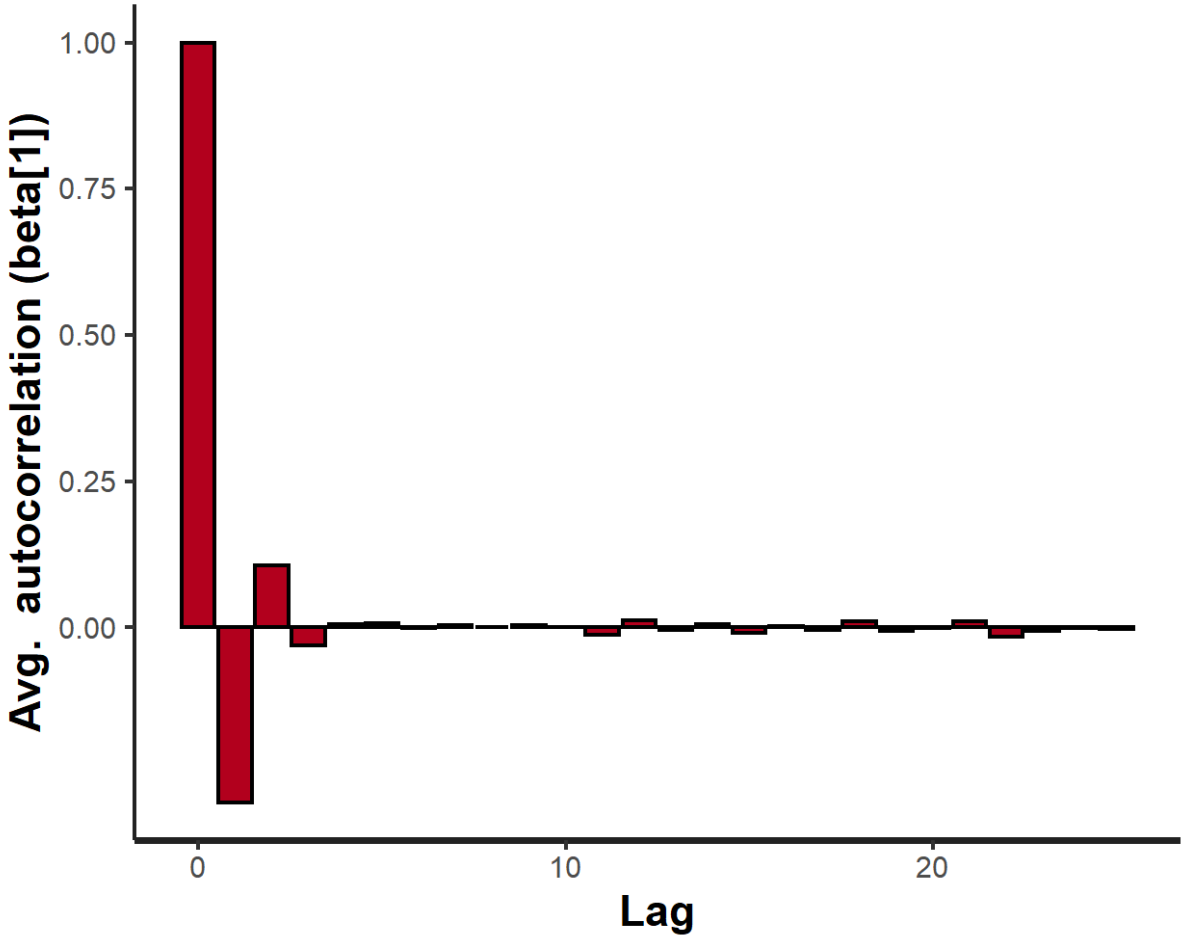


Supplementary Figure 5A. Sample diagnostic plot (symptomatic intracranial haemorrhage): trace.



Supplementary Figure 5B. Sample diagnostic plot (symptomatic intracranial haemorrhage): density.

HPDI: highest posterior density interval



Supplementary Figure 5C. Sample diagnostic plot (symptomatic intracranial haemorrhage): autocorrelation.