Fluoxetine for motor recovery after acute ischaemic stroke (FLAME): a randomised placebo-controlled trial

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Summary

Background Hemiplegia and hemiparesis are the most common deficits caused by stroke. A few small clinical trials suggest that fluoxetine enhances motor recovery but its clinical efficacy is unknown. We therefore aimed to investigate whether fluoxetine would enhance motor recovery if given soon after an ischaemic stroke to patients who have motor deficits.

Methods In this double-blind, placebo-controlled trial, patients from nine stroke centres in France who had ischaemic stroke and hemiplegia or hemiparesis, had Fugl-Meyer motor scale (FMMS) scores of 55 or less, and were aged between 18 years and 85 years were eligible for inclusion. Patients were randomly assigned, using a computer random-number generator, in a 1:1 ratio to fluoxetine (20 mg once per day, orally) or placebo for 3 months starting 5–10 days after the onset of stroke. All patients had physiotherapy. The primary outcome measure was the change on the FMMS between day 0 and day 90 after the start of the study drug. Participants, carers, and physicians assessing the outcome were masked to group assignment. Analysis was of all patients for whom data were available (full analysis set). This trial is registered with ClinicalTrials.gov, number NCT00657163.

Findings 118 patients were randomly assigned to fluoxetine (n=59) or placebo (n=59), and 113 were included in the analysis (57 in the fluoxetine group and 56 in the placebo group). Two patients died before day 90 and three withdrew from the study. FMMS improvement at day 90 was significantly greater in the fluoxetine group (adjusted mean 34.0 points [95% CI 29.7–38.4]) than in the placebo group (24.3 points [19.9–28.7]; p=0.003). The main adverse events in the fluoxetine and placebo groups were hyponatraemia (two [4%] vs two [4%]), transient digestive disorders including nausea, diarrhoea, and abdominal pain (14 [25%] vs six [11%]), hepatic enzyme disorders (five [9%] vs ten [18%]), psychiatric disorders (three [5%] vs four [7%]), insomnia (19 [33%] vs 20 [36%]), and partial seizure (one [<1%] vs 0).

Interpretation In patients with ischaemic stroke and moderate to severe motor deficit, the early prescription of fluoxetine with physiotherapy enhanced motor recovery after 3 months. Modulation of spontaneous brain plasticity by drugs is a promising pathway for treatment of patients with ischaemic stroke and moderate to severe motor deficit.

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Introduction Thrombolysis with alteplase given within the first few hours of an ischaemic stroke has long been the only treatment recognised to improve the spontaneous recovery of neurological functions. However, we have learnt over the past decade, by use of neuroimaging and electrophysiological techniques, that spontaneous recovery of neurological functions is associated with a large intracerebral reorganisation of the damaged human brain.

Various interventions, such as monoaminergic drugs, have been shown to modulate brain plasticity after a stroke and to reduce the residual neurological deficit and subsequent disability. Amphetamines have enhanced recovery in animal models of acute brain lesions, whereas neuroleptic drugs or benzodiazepines have reduced it. Little evidence exists for the efficacy of serotonin-reuptake inhibitors in studies of animals, but these inhibitors have an acute neuroprotective action on the ischaemic brain and promote hippocampal neurogenesis. In clinical trials of amphetamine in patients with stroke, either no positive effect was noted on the recovery of motor function or the results were contradictory.

The few small clinical trials of serotonin-reuptake inhibitors that have been reported (table I) all suggest that drugs of this type might have a positive effect. Use of functional MRI in other trials showed that single doses of fluoxetine and paroxetine overactivated motor cortices compared with placebo in both healthy individuals and patients with stroke, and use of transcranial magnetic stimulation showed that cortex overactivation was associated with drug-induced cortex hyperexcitability.

In the fluoxetine in motor recovery of patients with acute ischaemic stroke (FLAME) trial, we aimed to test whether a 3-month treatment with fluoxetine would enhance motor recovery when given early after an ischaemic stroke to patients with moderate to severe motor deficits.
Table 1: Reported prospective randomised placebo-controlled clinical trials of selective serotonin-reuptake inhibitors in motor recovery after ischaemic stroke

<table>
<thead>
<tr>
<th>Drug(s)</th>
<th>Dose, regimen, and treatment duration</th>
<th>Number of patients</th>
<th>Trial design</th>
<th>Time of inclusion after stroke</th>
<th>Clinical outcome criteria</th>
<th>Other outcome criteria</th>
<th>Patients in rehabilitation programme</th>
<th>Main results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dam et al12</td>
<td>Fluoxetine and maprotiline</td>
<td>48</td>
<td>Parallel groups (three groups)</td>
<td>1–6 months</td>
<td>Graded neurological scale (HSS)</td>
<td>None</td>
<td>Yes</td>
<td>10.7% improvement in HSS score</td>
</tr>
<tr>
<td>Pariente et al13</td>
<td>Fluoxetine</td>
<td>8</td>
<td>Crossover</td>
<td>15–30 days</td>
<td>Finger tapping and dynamometer</td>
<td>Functional MRI; hyperactivation of motor cortices</td>
<td>Yes</td>
<td>20–30% finger tapping and dynamometer improvement</td>
</tr>
<tr>
<td>Zintel et al14</td>
<td>Citalopram</td>
<td>8</td>
<td>Crossover</td>
<td>More than 6 months</td>
<td>Motor dexterity with nine-hole-peg test</td>
<td>None</td>
<td>Yes</td>
<td>11.4% improvement in nine-hole-peg test</td>
</tr>
<tr>
<td>Acler et al15</td>
<td>Citalopram</td>
<td>20</td>
<td>Parallel groups (two groups)</td>
<td>Not reported</td>
<td>NIHSS score</td>
<td>TMS: modulation of cortical excitability</td>
<td>Yes</td>
<td>38% improvement of NIHSS score</td>
</tr>
</tbody>
</table>

Results of all trials showed positive effects on motor performance. Results of a randomised placebo-controlled trial by Gerdelat-Mas and colleagues16 in healthy individuals also confirmed the modulation of transcranial magnetic stimulation (TMS) with a single and chronic doses of paroxetine. HSS=hemispheric stroke scale. NIHSS=National Institutes of Health stroke scale.

Table 2: Demographic and baseline characteristics

<table>
<thead>
<tr>
<th>Fluoxetine (n=59)</th>
<th>Placebo (n=59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>66.4 (13.1)</td>
</tr>
<tr>
<td>Men</td>
<td>37 (63%)</td>
</tr>
<tr>
<td>Body-mass index (kg/m²)</td>
<td>26.2 (4.4)</td>
</tr>
</tbody>
</table>

Vascular risk factors

- Diabetes: 14 (24%) vs 11 (19%)
- Hypertension: 39 (66%) vs 40 (68%)
- Dyslipidaemia: 36 (61%) vs 33 (56%)
- Current smoker: 30 (51%) vs 26 (44%)
- Previous cardiac disease: 34 (58%) vs 28 (47%)
- Atrial fibrillation: 6 (10%) vs 7 (12%)
- Previous stroke: 10 (17%) vs 4 (7%)

Stroke characteristics

Location

- Carotid territory: 51 (86%) vs 49 (83%)
- Vertebrobasilar territory: 6 (10%) vs 4 (7%)
- Lacunar: 2 (3%) vs 6 (10%)

Baseline stroke severity

- Total FMMS score: 171 (117) vs 134 (88)
- Upper limbs FMMS score: 55 (55) vs 47 (42)
- Lower limbs FMMS score: 116 (79) vs 87 (69)
- NIHSS score: 12 (8.2) vs 13 (4.3)
- NIHSS motor component score: 9 (9.2) vs 10 (3.9)
- Modified Rankin scale score: 0–2

Data are number (%) or mean (SD). FMMS=Fugl-Meyer motor scale. NIHSS=National Institutes of Health stroke scale. MADRS=Montgomery Åsberg depression rating scale.

Methods

Participants

Patients who had an acute ischaemic stroke within the past 5–10 days that caused hemiparesis or hemiplegia were prospectively enrolled from nine stroke units in France. Those who were aged between 18 years and 85 years and who had Fugl-Meyer motor scale (FMMS) scores of 55 or less at baseline were eligible for inclusion. Patients were excluded if they had severe post-stroke disability (National Institutes of Health stroke scale [NIHSS] score >20), substantial premorbid disability, or a pre-existing deficit that could interfere with assessments—i.e., residual motor deficit from a previous stroke, comprehension deficits severe enough to prevent understanding of motor testing, or severe aphasia masking detection and assessment of depression. Patients were excluded if they were clinically diagnosed with depression or Montgomery Åsberg depression rating scale (MADRS) score of more than 19;7 taking antidepressant drugs, monoamine oxidase inhibitors, neuroleptic drugs, or benzodiazepines during the month before inclusion; or due to underwent carotid endarterectomy. Other exclusion criteria included pregnancy and other major diseases that would prevent follow-up. Enrolment, follow-up, and clinical assessments were done in each centre by the investigators.

The study was approved for all centres, according to the French law, by the Toulouse Ethics Committee. All patients provided written informed consent.

Randomisation and masking

Randomisation was balanced by centre, with an allocation sequence based on a block size of four, generated with a computer random-number generator by the pharmacist at the coordinating centre (Hôpital Purpan, Toulouse). The pharmacist assigned the participants to the trial groups in accordance with the randomisation list. Allocation was concealed by use of sequentially numbered...
Opaque envelopes. Fluoxetine and placebo capsules were both prepared by the pharmacist for the study. The capsules were distributed to each centre by the Toulouse Hospital Pharmacy. The placebo was identical to the active drug in appearance and packaging.

An independent organisation (Centre d’Investigation Clinique, Toulouse, France) was in charge of the logistic coordination of the study. Patients, carers, all site study staff, and investigators were masked to treatment assignment.

Procedures
Patients were randomly allocated to fluoxetine (20 mg once per day, orally) or placebo for 90 days. All patients, irrespective of the treatment group, also received physiotherapy during the treatment period. Physiotherapists were instructed not to design a specific rehabilitation programme but to use the normal protocol for their centre. All participants received standard care, delivered by an organised inpatient stroke care team.

The primary outcome was the mean change in FMMS score between inclusion (day 0) and day 90. FMMS is an index that is widely used for assessment of motor recovery after stroke and has excellent intra-rater and inter-rater reliability and validity. The motor domain ranges from a score of 0 (flaccid hemiplegia) to 100 (normal movement), with 66 points for the upper limb and 34 points for the lower limb; each item is rated as not, partly, or fully performed. All motor assessments were made by a physiotherapist at day 0 (baseline) and then 30 days and 90 days after enrolment. Secondary endpoints were NIHSS, modified Rankin scale (mRS), and MADRS, with all scores measured at baseline, day 30, and day 90.

Data were gathered for adverse events and deaths within 3 months after randomisation. Reports were periodically examined by the FLAME executive committee, which tried to assess whether the side-effects could be related or not to the drug intake, but the committee remained masked during the study. When depression occurred (according to clinical assessment) during the 3 months of treatment, clinicians were instructed to continue the study treatment (fluoxetine or placebo), to avoid use of any other antidepressant drugs and, if necessary, to give open-label fluoxetine (20 mg once a day) so that the patient received either 20 mg (placebo group) or 40 mg per day (fluoxetine group). If a patient was given another antidepressant drug, the study treatment was stopped. The blinding code was not broken. All patients were followed up until day 90.

Statistical analysis
The trial was designed to have greater than 90% power to detect a 40% difference in the change in the FMMS score (ie, 12 points, which corresponds to a full recovery of six functions or incomplete recovery of 12 functions, and is judged to be clinically relevant) 3 months after the stroke if 100 patients were enrolled, assuming a spontaneous 30-point (SD 18) mean increase at day 90. Because we expected frequency of patients lost to follow-up to be high, related to depression and complications after stroke, we planned to enrol up to 168 patients. However, the loss to follow-up was lower than expected, leading us to stop the enrolment after 118 patients.

Baseline characteristics, including disease description, were reported by use of descriptive statistics (eg, mean and SD for continuous variables, or frequency...
limb score, and lower limb score) over 90 days. We did a multiple linear regression analysis to control for centre and baseline factors that showed treatment group imbalance. The same approach was used to assess changes from day 0 to day 90 in MADRS scores (secondary endpoint). We also undertook post-hoc binomial regression analyses to test whether the treatment had an effect at day 90 on the mRS scores (probability of being an independent patient—ie, with a score of 0–2) and on NIHSS scores (probability of having a less severe outcome—ie, with scores of 0–5) compared with placebo. The analyses were adjusted for centre, age of patient, history of stroke, and mRS or NIHSS scores, accordingly, at baseline. All reported p values are two-sided. The statistical analyses were done by use of STATA (version 11.0).

This study is registered with ClinicalTrials.gov, number NCT00657163.

Role of the funding source

The sponsor had no involvement in study design, data collection, data analysis, data interpretation, or writing of the report. The principal investigator (FC) had full access to all the data in the study and had final responsibility for the decision to submit the report for publication.

Results

Between March 14, 2005, and June 9, 2009, 118 patients were prospectively enrolled. The two groups were well balanced in terms of baseline and demographic characteristics and stroke severity (table 2). However, mean age was slightly higher and previous history of stroke was more frequent in the fluoxetine group than in the control group. FMMS score at inclusion was higher in the fluoxetine group than in the placebo group (table 2). NIHSS, mRS, and MADRS mean scores did not differ in the two groups (table 2).

Treatment compliance was similar in the two groups. The mean cumulative dose at day 90 (defined as the sum of all doses taken during the treatment period) was 88·3 tablets (SD 11·6) in the fluoxetine group and 87·4 tablets (12·3) in the placebo group (p=0·722). The mean dose intensity at day 90 (calculated as the overall cumulative dose divided by the number of days that the patient was receiving a dose) was 0·9 tablets (0·1) per day in both groups (p=0·854). The mean relative dose intensity (dose intensity divided by the planned dose intensity) was 94·8% (12·6) in the fluoxetine group and 94·0% (13·0) in the placebo group (p=0·854).

Study treatment began a similar number of days after the stroke in the fluoxetine and placebo groups. 113 patients were included in the full-set analysis (figure I). Two patients died before day 90, and three withdrew from follow-up (figure I). Mean progression in FMMS total score from baseline to day 90 was significantly higher in the fluoxetine group than in the placebo group after controlling for centre, age, history of stroke, and FMMS
score at inclusion (table 3). The gain was significant for both the upper and the lower limb scores. The adjusted mean FMMS total score was significantly higher at day 90 in the fluoxetine group than in the placebo group (figure 2).

3 months after the stroke, NIHSS total score did not significantly differ in the fluoxetine and control groups, whereas the motor component score was significantly higher in the fluoxetine group (table 4). However, after controlling for age, history of stroke, and FMMS score at baseline, the probability of having a NIHSS score of 0–5 did not significantly differ between groups. Independence in activities of daily life, measured by use of mRS, improved during treatment in both groups, but at day 90 the proportion of independent patients (mRS scores 0, 1, or 2) adjusted for centre, age, history of stroke, and mRS score at baseline was significantly higher in the fluoxetine group than in the control group (table 4; figure 3).

The distribution of the MADRS scores did not differ significantly between the fluoxetine and control groups at inclusion or at day 90, whereas the adjusted mean change in MADRS scores between day 0 and day 90 was significantly lower in the fluoxetine group (24·2 [19·6–28·7]; p=0·004). In a sensitivity analysis of the subgroup of patients who were not given thrombolysis (n=36 in fluoxetine group, n=40 in placebo), improvement in FMMS was still significantly higher in the fluoxetine group (37·7 [32·0–43·3]) than in the placebo group (24·4 [19·1–29·7]; p=0·002).

Two patients died (one in each group; figure 1). The cause of death was related to their neurological disorder (septic shock, respiratory distress; figure 1). The main adverse events were hyponatraemia, transient digestive disorders including nausea, diarrhoea, and abdominal pain, hepatic enzyme disorders, psychiatric disorders, insomnia, and partial seizure (table 5). Two of the adverse events in the fluoxetine group were serious (one hyponatraemia and one partial seizure). Transient digestive disorders were more frequent in the fluoxetine group (p=0·19). Treatment was not interrupted in patients with adverse events.

**Discussion**

We noted a positive effect on motor recovery in patients with acute ischaemic stroke who were treated with fluoxetine for 3 months. This effect, assessed as a change in FMMS score between day 0 and day 90, was noticeable in the FMMS subscores for both the upper and the lower limb at day 90. By contrast, no effect was noted with NIHSS at day 90. However, NIHSS motor component score at day 90 was lower in the fluoxetine group than in the placebo group, in agreement with the data for FMMS scores. The mRS scores showed more independent patients (scores 0–2) in the fluoxetine group than in the placebo group at day 90, which, when combined with the efficacy of fluoxetine, confirms the major role of motor function recovery in global recovery and return to independent activities of everyday life.

Results from some early and more recent studies suggested that a tight coupling between physiotherapy and drug therapy was necessary for beneficial motor changes. In our study, all patients were admitted to a dedicated stroke unit and were all included in the local daily inpatient management. Some were given acute
thrombolysis with intravenous alteplase within the first 4–5 h after the stroke, in accordance with the recommendations of the French health authorities. The number of patients given thrombolysis was not significantly different in the fluoxetine and the placebo groups, and we did not note any confounding effect of thrombolysis in this study. Physiotherapy and rehabilitation was delivered to each patient during the 3-month treatment. Because intercentre variability in the rehabilitation interventions was high, we decided that each centre would propose rehabilitation interventions according to the current onsite procedures rather than according to a unified procedure. A possible centre effect was taken into account in the linear regression analysis.

Patients were enrolled, allocated to treatment, and first given treatment between days 5 and 10 after the stroke to exclude those who had early complications that would have compromised follow-up. Depressed patients and those with comprehension disturbances related to profound aphasia or cognitive impairment were also excluded. Patients had an initial severe motor deficit as assessed with the FMMS score (table 1), probably more severe than in patients in other trials: for example, in a trial of dexamfetamine that included 71 patients, mean FMMS score at inclusion was 26·9 in the dexamfetamine group and 30·0 in the placebo group.9

The treatment was well tolerated. Occurrence of depression during the 3 months was significantly lower in the fluoxetine group than in the placebo group, suggesting that fluoxetine when given early after the stroke can prevent depression. These results are in accord with those reported in other studies, showing the beneficial effect of serotonin-reuptake inhibitors on the occurrence of depression after stroke.26–28 An effect of fluoxetine on mood is likely, as shown by the significant difference in the change in MADRS score between the two groups. However, we do not think that fluoxetine acted only through antidepressant mechanisms in this study. In a previous study,35 a single dose of fluoxetine improved hand motor function and increased activity in the motor cortex compared with placebo in patients recovering from stroke, showing a specific motor effect, whereas a mood effect is unlikely after a single dose. However, a fluoxetine-mediated attention effect cannot be excluded in our patients.

Studies in animals show that the rate and extent of functional recovery after brain injury can be modulated by the effects of drugs on neurotransmitters in the CNS.29–31 For example, infusion of norepinephrine hastens recovery in rats with brain lesions, whereas antagonists delay the recovery process.7 Further evidence for modulation of recovery has come from studies showing drug-induced physiological or structural changes in the brain that might be relevant to recovery. By contrast, little evidence exists to suggest that serotonin-reuptake inhibitors induce motor recovery after focal ischaemia in rats.9 However, fluoxetine was recognised to have a neuroprotective effect in the post-ischaemic brain through its anti-inflammatory effects, and it has improved ischaemia-induced spatial cognitive deficits by increasing hippocampal neurogenesis after stroke in rats.3 One hypothesis is that a primary function of the brain serotoninergic system is to facilitate motor output, which emphasises that the drug intake would be more efficient when paired with training. In *Aplysia*, serotonin enhances short-term facilitation, storage of long-term memory in sensorimotor synapses, long-term facilitation, and growth factor gene expression.36 As a monoamine, serotonin might promote long-term potentiation, optimise activity-dependent learning, and possibly facilitate relearning after stroke in human beings.7

Few clinical trials with serotonin-reuptake inhibitors have been reported (table 1; panel). They have all included small numbers of patients; all have results that suggest a positive effect on recovery after stroke. In an early trial, fluoxetine and maprotiline were tested against placebo for 3 months in patients with hemiplegic stroke enrolled 1–6 months after the stroke.21 The patients in the fluoxetine group (n=16) had a better outcome than did those in the maprotiline or placebo groups.12 Acler and colleagues37 confirmed this finding in ten patients in the active-treatment group versus ten in the placebo group. In a double-blind placebo-controlled study, Pariente and colleagues,38 by combining clinical motor testing and functional MRI motor recovery in context

**Systematic review**

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) on the Cochrane Library (issue 1, 2010), Medline (1985–2010), and Embase (1985–2010). We included placebo-controlled, randomised clinical trials in which the effects of selective serotonin-reuptake inhibitors on motor recovery after stroke were assessed. We also selected key articles and illustrative reviews of studies in animals, selective serotonin-reuptake inhibitors, and depression after stroke, and found a large number of references for clinical trials of amphetamines and dopamine in motor recovery after stroke.

**Interpretation**

The few previous clinical trials of selective serotonin-reuptake inhibitors after stroke were small and their results have suggested a positive effect on motor recovery. The results of the FLAME trial extend these findings by showing in a larger group of patients with moderate to severe hemiplegia after ischaemic stroke that early treatment with fluoxetine enhances motor recovery and reduces the number of dependent patients. The positive effect of the drug on motor function of recovering patients suggests that the neuronal, non-vascular-targeted action of selective serotonin-reuptake inhibitors provides a new pathway that should be explored further in the treatment of acute ischaemic stroke.
assessment in patients recovering from post-stroke hemiplegia (n=8), showed that a single dose (20 mg) of fluoxetine improved hand motor function and was correlated with an overactivation of motor cortices on functional MRI. In a subsequent double-blind, placebo-controlled trial in healthy individuals, transcranial magnetic stimulation has shown that the intake of a single dose of the serotonin-reuptake inhibitor paroxetine was associated with a hyperexcitability of the primary motor cortex, whereas chronic intake was associated with hypoexcitability of brain motor cortices. Serotonin-reuptake inhibitors increase interneuron-facilitating activity in the primary motor cortex. In a double-blind, placebo-controlled crossover trial, Zittel and colleagues investigated the effects of a single dose (40 mg) of citalopram in eight patients with chronic stroke; dexterity was significantly improved. Our trial is the largest in which the effects of serotonin-reuptake inhibitors and stroke recovery were investigated, and the largest in the specialty of monoamines and stroke recovery. Several trials with amphetamine or amphetamine-like drugs have been reported. The results of a few studies suggested amphetamine and norepinephrine were efficacious, but this positive effect was not confirmed in further larger trials. Notably, most of the trials included only a few patients (from eight to 71) and the dose (amphetamine 10 mg once per day) and regimen (1–17 days) remain questionable because no rationale was proposed for dose and duration of treatment. Results of other small trials of drugs including levodopa were contradictory and no definite conclusions could be drawn from them.

Although the results of the FLAME trial show the efficacy of fluoxetine in motor recovery of patients with ischaemic stroke, we must draw attention to some limitations of the study. First, the number of patients included was small. Those who were included were selected for motor deficit and did not represent the general population of stroke patients, as shown by the inclusion and exclusion criteria and the clinical characteristics at inclusion (table 2). Second, treatment was stopped after 90 days and we have no idea of the long-term development of patients’ motor function and whether the treatment effect persisted in the months after treatment was stopped. Third, a potential random error cannot be eliminated completely and our results remain to be confirmed, even though error is unlikely because of the low p value associated with the change in the FMMS score at day 90 (p=0·003). However, the effect of fluoxetine seems to be strong and clinically relevant, and the data show a global coherence (ie, motor improvement in FMMS and motor items of NIHSS). Future studies should include a larger number of patients whose characteristics are more similar to those of the general population of patients with stroke; the primary outcome criteria should be more functional (mRS, which scores the capacity of patients to return to home daily life, rather than FMMS, which is a pure neurological analytical scale of motor function), and the duration of treatment and permanence of the effects will have to be addressed. Selective serotonin-reuptake inhibitors are not a uniform category of drugs, and further basic science and pharmacology studies will also be needed to increase understanding of their mechanisms of action.

Fluoxetine is a well tolerated drug that no longer has a patent, and therefore its cost is reasonable. Acute deocclusion of brain arteries is already a successfully validated approach to treatment, and modulation of spontaneous brain plasticity by external agents is undoubtedly another promising pathway for patients with stroke.

Contributors
FC was the principal investigator, participated in the study design and data analysis, and wrote the report. JFA and JT participated in data collection, data analysis, and correction of the report. CA and EB participated in the statistical analysis and data analysis. CT contributed to the study design and data analysis, and liaised with the funding source. CL, YB, SD, AJ, BG, TM, and PN participated in data collection, reading the report, and giving scientific advice, and contributed to discussions. PM and JP contributed to the design of the study and correction of the report. IL gave scientific advice, and participated in reading and correction of the report.

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Conflicts of interest
We declare that we have no conflicts of interest.

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References


