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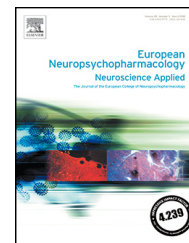
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SHORT COMMUNICATION

Serotonin transporter occupancy by the SSRI citalopram predicts default-mode network connectivity



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Abstract

The default mode network (DMN) is an important connectivity hub, and alterations may play a role in the pathophysiology of several neuropsychiatric disorders. Despite the growing body of research on DMN (dys)function, the underlying neurochemical substrate remains to be elucidated. The serotonergic neurotransmitter system has been suggested to play a substantial role in modulating the DMN. Therefore, we investigated the association between serotonin transporter (SERT) occupancy by the selective serotonin reuptake inhibitor citalopram and DMN functional connectivity. Forty-five healthy female volunteers (mean age = 21.6y) participated in a double-dose study. The subjects were randomized to pre-treatment with placebo, a low (4mg; ‘low group’) or clinically standard (16mg; ‘high group’) oral citalopram dose (corresponding to 0%, ~40% and ~80% SERT occupancy, respectively). They underwent [¹²³I]FP-CIT single-photon emission computed tomography (SPECT) imaging to assess SERT occupancy. In addition, resting-state functional magnetic resonance imaging was used to measure DMN connectivity. With non-parametric permutation testing we assessed the association between SERT occupancy and DMN connectivity. We found that SERT occupancy by citalopram was negatively associated with DMN connectivity with a number of cortical regions, including the anterior cingulate cortex (ACC), paracingulate gyrus, postcentral gyrus, superior parietal gyrus and

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temporal pole. These findings provide further neurochemical evidence that the serotonin system dose-dependently modulates DMN function.

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1. Introduction

The default-mode network (DMN) is a brain network that is most active when a subject is not performing a particular task. It consists of several functionally connected regions encompassing the medial prefrontal cortex (mPFC), posterior cingulate cortex (PCC) and inferior parietal cortex (iPC) (Buckner et al., 2008), and is typically assessed using resting-state functional magnetic resonance imaging (rs-fMRI). Aberrant rs-fMRI connectivity within the DMN has been associated with neuropsychiatric disorders, e.g. major depressive disorder (MDD) (Greicius et al., 2007; Sheline et al., 2010).

Although the neurochemical mechanisms underlying modulation of the DMN remain unknown, studies have suggested a substantial role for the serotonin (5HT) neurotransmitter system, as its receptor expression has considerable spatial overlap with the main DMN regions, and 5HT neurons in the raphe nuclei prominently innervate the DMN regions (van de Ven et al., 2013). For example, a positron-emission tomography (PET) study has shown that individual variations in dorsal raphe 5HT_{1A} receptor binding predict DMN connectivity (Hahn et al., 2012). In addition, depletion of the 5HT precursor tryptophan resulted in changes in DMN connectivity (Biskup et al., 2016; Helmbold et al., 2016; Kunisato et al., 2011). Also, selective 5HT reuptake inhibitors (SSRIs), a widely used class of antidepressant drugs that block reuptake of 5HT by the 5HT transporter (SERT), may decrease DMN connectivity (Klaassens et al., 2015; van de Ven et al., 2013). This is interesting, given that higher DMN connectivity has been reported in MDD patients, which has been associated with depressive rumination. Indeed, Delaveau et al. (2011) concluded that antidepressants could restore normal DMN suppression during emotional processing tasks.

Altogether, this suggests that 5HT plays a modulatory role in the regulation of DMN connectivity with other brain regions. Although PET and single-photon emission computed tomography (SPECT) studies have suggested that at least 80% SERT occupancy is necessary to obtain sufficient therapeutic effects of SSRIs (Meyer et al., 2004), it remains unclear whether SSRIs also affect DMN connectivity in a dose-dependent manner. Therefore, we set out to investigate the association between SERT occupancy (assessed with SPECT) and functional connectivity with the DMN (assessed with rs-fMRI) in a dose-dependent manner. We hypothesized that a higher SERT occupancy would be associated with a decreased connectivity with the DMN.

2. Experimental procedures

2.1. Participants

Forty-five healthy female volunteers (mean age = 21.6 years, age range 18–28) were included. Exclusion criteria

were a history of a chronic neurological or psychiatric disorder (assessed with Mini-International Neuropsychiatric Interview (M.I.N.I.) Plus (Van Vliet and De Beurs, 2007)), family history of sudden heart failure, current use of psychostimulant medication, abnormal electrocardiogram (ECG), excessive consumption of alcohol (> 21 units/week), caffeine (more than eight cups of coffee per day) or nicotine (more than 15 cigarettes per day), and standard contra-indications for the MRI or SPECT exam. All participants were on hormonal contraceptives and an ECG precluded cardiac abnormalities (Maljuric et al., 2015). The study was approved by the local Institutional Review Board and all participants provided written informed consent.

2.2. Study design and procedures

To study the dose-dependent effects of citalopram on resting-state functional connectivity and SERT occupancy, a double-blind, dose-response design was used. Participants received potassium iodide tablets prior to [¹²³I]N- ω -fluoropropyl-2 β -carbomethoxy-3 β -(4iodophenyl)nortropine ([¹²³I]FP-CIT) administration (approximately 110 MBq; specific activity > 750 MBq/nmol; radiochemical purity > 98%, produced according to GMP criteria at GE Healthcare) to block thyroid uptake of free radioactive iodide. The first SPECT scan was conducted 2 hours post-injection to assess baseline SERT availability (data not shown). After that, participants were randomized into one of the three groups: those receiving placebo ('placebo' $N=15$), those receiving a low dose (4 mg; 'low group' $N=15$) and those receiving a clinical dose (16 mg; 'high group' $N=15$) of oral citalopram (solution dissolved in lemonade, 16 mg equivalent to 20 mg in tablet form, Lundbeck). These doses have been shown before to correspond to 0%, ~40% and ~80% SERT occupancy, respectively (Klein et al., 2006). After three hours, participants underwent a second SPECT scan, followed by a resting state MRI scan. Blood samples were obtained 3 h after citalopram administration.

2.3. Subjective effects

Subjective effects of citalopram were assessed prior to and 3 h after administration. To assess these effects we used Visual Analogue Scales (VAS) measuring subjective well-being and mood, including the following variables: 1) nausea and dizziness for side effects of citalopram 2) anxious, content, nervous for mood effects. Subjects were asked to mark a cross on the line that represented their feeling at that moment in time.

2.4. SPECT acquisition and analysis

SPECT scans were acquired using a brain-dedicated InSpira-HD SPECT camera (Neurologica, Boston, USA) with the following parameters: matrix = 121×121 ; slice thickness = 4 mm; acquisition time per slice = 180 s; energy window = 159 keV (with 20% lower and upper boundaries). 3D images were reconstructed (using an iterative expectation maximization algorithm, correction using a CT template and spatial smoothing (3 mm)). SPECT images were co-registered with the individual 3DT₁-weighted (T1w) MR image using SPM12 (Wellcome Trust Centre for Neuroimaging, London, UK). A region of interest (ROI) analysis was performed to determine SERT binding in the thalamus. We used the thalamus as a proxy of citalopram-induced changes in brain SERT here, because it shows the most reliable binding potential measurements for this ligand (Booij et al., 2007). Thalamic masks were extracted from individual T1w scans using Freesurfer. The cerebellum was used as a reference region to assess non-specific binding. Specific to non-specific binding ratios (binding potential; BP) were calculated as follows: (mean thalamic binding – mean cerebellum binding) / mean cerebellum binding. The BP assessed after the administration of placebo or citalopram represents SERT occupancy, in that a lower BP reflects a higher occupancy of the SERT.

2.5. MRI acquisition and processing

MRI data were acquired using a 3.0T Ingenia (Philips, Best, the Netherlands) equipped with a 32-channel receive-only head coil. A 3D anatomical MRI was obtained using a T1-weighted sequence. Rs-fMRI data were acquired for approximately 9 min using a T2*-weighted gradient-echo EPI sequence using the following parameters: TR/TE = 2150/27 ms; FOV = $240 \times 240 \times 131$ mm, voxel size = $3 \times 3 \times 3$ mm; gap = 0.3 mm; flip angle = 76.2°; dynamics = 240. Subjects were instructed to keep their eyes open and let their mind wander.

Rs-fMRI data were preprocessed using tools from the FM-RIB Software Library (Smith et al., 2004). All fMRI time series were visually inspected, brain-extracted, motion-corrected and spatially-smoothed with a 5 mm kernel and normalized to MNI space using the T1-weighted image. Automatic Removal Of Motion Artifacts based on Independent Component Analysis (ICA-AROMA vs0.3-beta) was used to detect and remove motion-related artifacts (Pruim et al., 2015). Subsequently, dual-regression with variance normalization was applied using a predefined default-mode network mask (Smith et al., 2009), with additional masks for white matter and CSF to regress out residual physiological noise components (Beckmann et al., 2009).

2.6. Statistical analysis

To assess correlations between SERT binding after citalopram administration and DMN connectivity, correlational analyses were carried out using Randomise (5000 permutations, (Winkler et al., 2014)) across all participants. All

analyses were initially thresholded at p -value < 0.05 with a family wise error (FWE) correction using threshold free cluster enhancement (TFCE) (Smith and Nichols, 2009). To assess changes within the DMN only, analyses were repeated using a DMN mask. In addition, DMN connectivity differences between the three pre-treatment groups were assessed using a one-way analysis of variance (ANOVA), with follow-up post-hoc tests between the groups. Furthermore, blood plasma levels were log-transformed and correlated with DMN connectivity. For significant clusters, mean Z-values from subject-specific spatial maps (output of the dual-regression stage) were extracted for visualization purposes.

3. Results

3.1. Subjective effects

We did not find an interaction effect between time and citalopram dose for mood (all $p > 0.45$) or side-effects (all $p > 0.25$); nor did we find a main effect of time for side-effects (all $p > 0.5$). For mood, there were trends for an increase in anxiety ($p = 0.07$) and nervousness ($p = 0.06$) for all groups, but not for being content ($p = 0.2$).

3.2. SERT occupancy and DMN connectivity

In total, rs-fMRI scans from 43 subjects could be analyzed. As expected, SERT occupancy was significantly associated with citalopram dose (one-way ANOVA of group: $F = 7.98$ $p < 0.01$), although quite some inter-individual variation was present. The higher thalamic SERT occupancy (reflected by a lower BP) was further associated with a decreased DMN connectivity with a number of cortical regions, including the anterior cingulate cortex (ACC), paracingulate gyrus, postcentral gyrus, superior parietal gyrus and temporal pole (Table 1, Fig. 1A). Interestingly, we observed that these brain regions also show a negative correlation between blood-plasma levels (at 3 h post-citalopram) and DMN connectivity (Fig. 1B). In contrast, we found no SERT-related changes with connectivity within DMN regions when the analysis was restricted to a DMN mask.

3.3. Group differences in DMN connectivity

In Fig. 2, the mean connectivity with the DMN is displayed for the placebo, low and high group. showing a significant difference between the 3 groups in a small cluster in the precentral gyrus/ACC (Fig. 3A). A linear contrast of placebo $>$ low $>$ high showed a similar pattern of differences in DMN connectivity as for the correlation with the SPECT (Fig. 3B). Post-hoc tests showed a significant difference between the placebo and the high group (Fig. 3C), but the difference between the placebo and low group and low and high group failed to reach significance.

Table 1 Association SPECT and DMN connectivity.

Correlation with DMN connectivity	# of voxels	t-value	MNI coordinates			Brain area
			x	y	z	
<i>SERT occupancy (positive correlation)</i>	327	5.05	4	20	24	Anterior cingulate cortex
	214	6.01	-10	10	44	Paracingulate gyrus
	178	4.65	-14	-36	66	Left postcentral gyrus
	155	4.32	-52	18	-10	Temporal pole
	133	4.13	-22	-32	60	Right postcentral gyrus
	103	4.5	-16	-50	62	Left superior parietal lobule
	349	5.08	-58	-44	26	Left posterior supramarginal gyrus
<i>Blood plasma levels (negative correlation)</i>	312	4.85	-12	20	54	Precentral gyrus

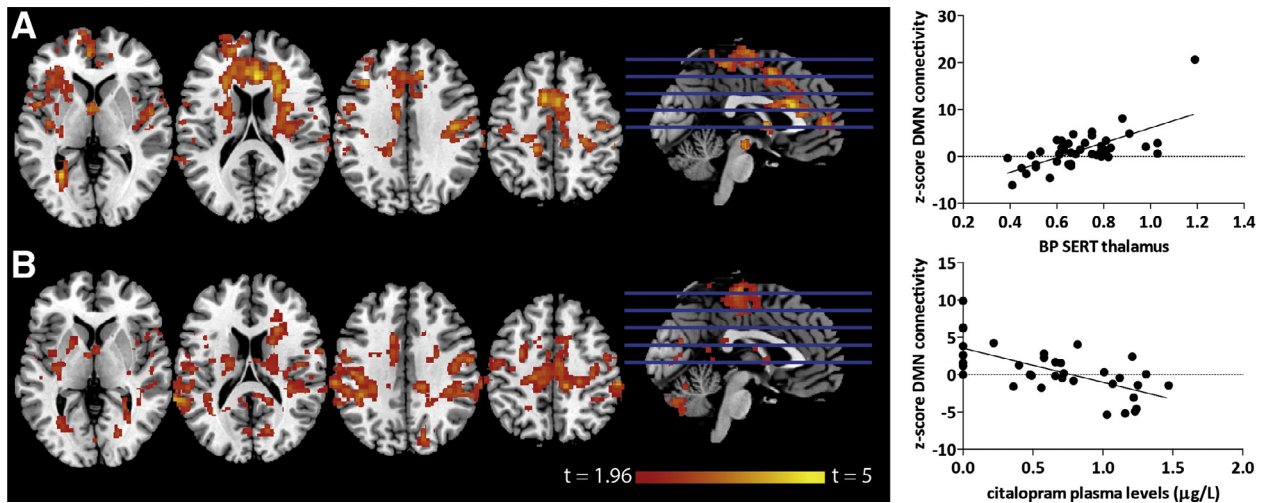


Fig. 1 Correlation SERT occupancy and citalopram blood plasma levels with DMN connectivity. Left: Maps displaying significant voxels ($P < 0.05$, FWE corrected) of the association between DMN connectivity and A) SERT occupancy B) log-transformed citalopram plasma levels. Right: For visualization purposes, mean Z-values from subject-specific spatial maps (output of dual-regression) were extracted from the voxels showing a significant correlation between DMN connectivity and A) SERT binding potential (BP; a lower BP represents a higher SERT occupancy) B) citalopram blood plasma levels.

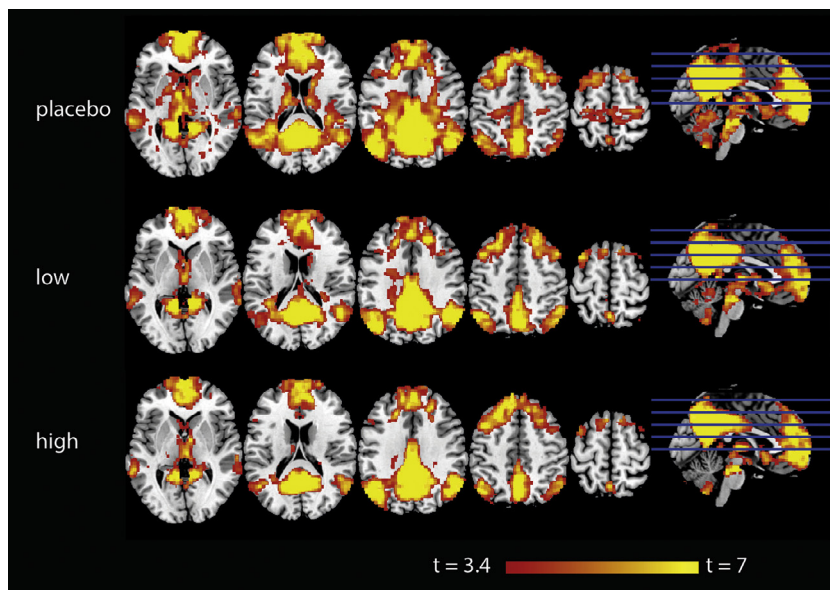


Fig. 2 Mean group connectivity. The maps display the mean DMN connectivity for the three experimental groups ($P < 0.05$, FWE corrected).

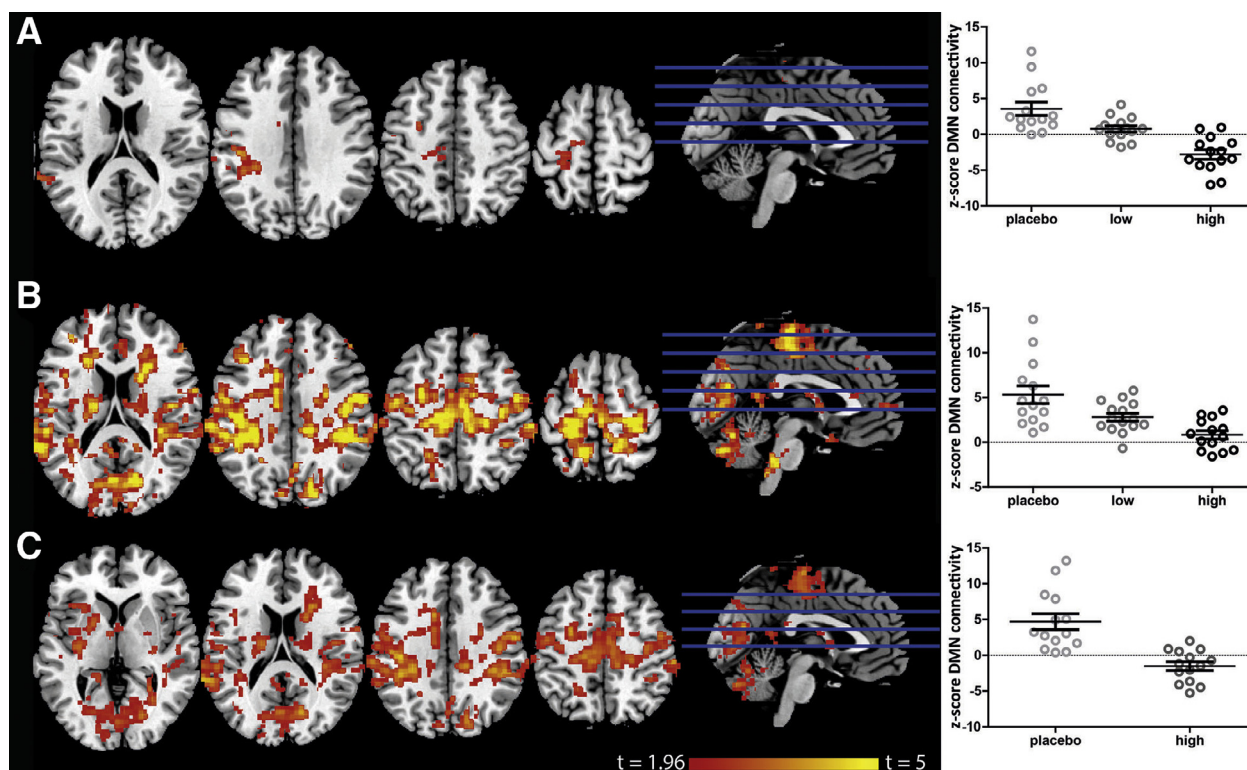


Fig. 3 Group differences in DMN connectivity. A) Results of the one-way ANOVA for the three experimental groups. B) Regions showing a significant linear relation between citalopram group and connectivity with the DMN. C) Post-hoc tests revealed a cluster showing significantly lower connectivity with the DMN for the high compared to the placebo group ($P < 0.05$, FWE corrected).

4. Discussion

This study examined the effects of manipulation of SERT occupancy using different doses of oral citalopram on resting-state connectivity with and within the DMN. Consistent with existing literature, citalopram decreased resting-state connectivity with the DMN. Interestingly, we further show for the first time that a higher SERT occupancy by citalopram was associated with a reduced connectivity of the DMN with the anterior (para)cingulate cortex and precentral gyrus. No connectivity changes were found within DMN regions.

These results corroborate previous studies that have so far investigated the effect of a single-dose SSRI on DMN connectivity. For example, [Klaassens et al. \(2015\)](#) administered the SSRI sertraline orally, and found reduced DMN connectivity in the ACC and precentral gyrus as well. Although another study did not find significant effects of escitalopram on DMN in voxel-based analyses, probably due to low power, ROI analysis did show that escitalopram reduced pairwise connectivity between ACC and DMN ROIs ([van de Ven et al., 2013](#)). Our results are also in line with acute tryptophan depletion (ATD) studies; ATD decreases 5HT synthesis and thereby reduces serotonergic firing and extracellular serotonin, resulting in the opposite effect of SSRIs. Indeed, two studies reported that ATD, compared to sham, increased DMN connectivity with the parietal and frontal areas, including the precentral gyrus ([Helmbold et al., 2016](#); [Kunisato et al., 2011](#)). Interestingly, both studies report that ATD decreased DMN connectivity with the precuneus. In sum, the current study reproduced

previous studies, thereby providing further evidence for robust effects of SSRIs on DMN connectivity with ACC and precentral gyrus, despite some differences in study design, SSRI type or analysis method.

This is the first study that investigated the relationship between SERT occupancy, blood plasma levels and DMN connectivity. It was previously shown that approximately 80% occupancy of the SERT was necessary to obtain treatment effects ([Meyer et al., 2004](#)). Further dose escalation does not result in much higher SERT occupancy or further improvements in treatment efficacy in MDD ([Ruhé et al., 2008](#)). Consistent with literature ([Meyer et al., 2004](#)), we found a log-linear relationship between blood plasma and SERT occupancy (not shown). In line with this, a log-linear and linear relation was present between DMN connectivity and blood plasma and SERT occupancy, respectively. This suggests that DMN activation depends on activation of the 5HT system in a linear fashion and that DMN can be modulated in a dose-dependent manner. Our data suggest that in MDD patients, connectivity with the DMN may already be normalized to that of healthy controls even with low SSRI doses. This is relevant, since overactivation of the DMN has been associated with excessive rumination in depressed patients ([Sheline et al., 2010](#)). Treatment with duloxetine has indeed shown a reduction in rumination before, which was associated with reductions of functional connectivity with the DMN ([van Wingen et al., 2013](#)). It would therefore be interesting to investigate to what extent DMN connectivity is associated with the treatment response in MDD, as this could suggest that in some patients, depending on baseline

SERT levels or baseline DMN connectivity, very low doses could already have therapeutic effects. Should such a relation indeed be found, rs-fMRI could then become informative as a biomarker for early treatment prediction and monitoring.

4.1. Methodological considerations

We have further explored how our results would be affected when analyzing our results in a different way. The dose-dependency effects are stronger when analyzing the data using correlation analyses, rather than binning the subjects in groups. This likely reflects inter-individual variation in metabolism and therefore in blood plasma levels and SERT occupancy and, and different doses could therefore have different effects across individuals, further highlighting the importance of precision medicine when treating MDD. We here focused on thalamic SERT, as the thalamus provides the most reliable estimate of SERT occupancy using [¹²³I]FP-CIT SPECT (Booij et al., 2007), but we acknowledge interregional variation in SERT and citalopram-induced changes in SERT occupancy, which could potentially be investigated using specific SERT ligands (Baldinger et al., 2014).

Moreover, the current study was conducted in females on contraceptive medication only, and therefore studies in males, or females not on contraceptives, might reveal different effects. So far, this seems unlikely as Helmbold et al. (2016) investigated females who were not on contraceptives and, although some effects were found of sex hormones interacting with serotonin function, their results are overall comparable to our study. Additionally, this study was conducted in healthy controls, and it would be important to investigate also the dose-dependent effects of SSRIs in depressed patients, and particularly try to assess at which dose of citalopram DMN connectivity would normalize. Finally, our study investigated the effect of a single dose SSRI, and it is known that therapeutic effects of SSRIs are associated with its prolonged effects on 5HT_{1A} autoreceptors. Therefore, future studies should consider conducting rs-fMRI studies at different time points.

5. Conclusion

The current results strengthen the evidence that SSRIs affect DMN connectivity. In addition, we show that DMN connectivity is linearly associated with SERT occupancy, and log-linearly with blood plasma concentrations. Thus, together, our findings underpin the important role serotonin plays in maintaining proper function of the DMN.

Role of the funding source

The funding agencies had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Contributors

AS, LR and JB designed the study and AS wrote the protocol. AS collected the data, conducted the analyses and wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflicts of interest statement

All authors declare that they have no conflicts of interest.

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