Hypoxic preconditioning induces neuroprotection against oxidative stress

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Abstract

Brain is an oxyregulator organ, however extremely vulnerable to oxygen. Both high and low oxygen concentrations generate free radicals and may cause oxidative stress and damage because of an insufficient response of the antioxidant system. Hypoxic preconditioning (HP) exerts neuroprotective effects and may be a protecting tool against oxygen fluctuations, thus preventing neuronal damage in events such as ischaemia, acute hypoxia, stroke, or traumatic brain injury, among others. This review aims to discuss the molecular mechanisms involved in the neuroprotective action of HP against oxidative stress and subsequently upon the brain under pro-oxidant conditions. Activation of the antioxidant defences represents the first line to neutralize oxidative stress and is characterized by low reactive oxygen species, reduced oxidative damage biomarkers, and increased level of reduced glutathione. These protective mechanisms decrease cell death activating anti-apoptotic signalling pathways and reducing neuroinflammation by the inactivation of microglia and astroglia cells. HP could be considered a new approach to reduce oxidative stress derived damage caused by a great variety of brain pathologies. Despite our intriguing findings, further experiments are needed for a better understanding of the molecular mechanisms involved in the neuroprotective actions of HP.

Keywords

- brain
- hypoxic preconditioning
- oxidative stress
- neuroprotection

Hypoxic preconditioning

Hypoxic preconditioning (HP) is defined as a phenomenon or response in which a mild and transient hypoxic exposure induces cellular protection, thus improving tissue tolerance to variable oxygen concentrations (Gidday 2006, Li et al. 2017). HP has been widely explored as a means of brain protection. Experimental studies suggest that the brain can be preconditioned to resist acute injuries, such as ischaemic stroke, neonatal hypoxia/ischaemia, trauma, and agents used in models of neurodegenerative diseases, such as Parkinson’s disease and Alzheimer’s disease (Stetler et al. 2014). This review aims to broaden the understanding of the neuroprotective role of HP against oxidative stress. Both terms, preconditioning and tolerance, were first introduced in the 1960s. Subsequent research has led to the understanding that HP is an adaptive response that interferes with cell death pathways following the activation of multiple genes (Janoff 1964, Feng & Bhatt 2015). But it was not until 20 years later that it was identified in the CNS. CNS is an oxyregulator tissue with a high oxygen consumption rate plus an inability to store energetic substrates. Consequently, the CNS requires a continuous supply of oxygen and is very sensitive to changes in...
the blood oxygen content (Luo et al. 2011). Therefore, maintaining brain homeostasis requires the presence of adaptive mechanisms that allow brain to survive during hypoxic episodes. Hypoxic tolerance stimulates brain plasticity fostering modifications in its function and organisation that improve the adaptability to the changing environment to which brain is exposed. A study in P6 rat offspring showed that HP protects myelin after a hypoxic–ischaemic insult either directly or by promoting the maturation of oligodendrocyte progenitors to regenerate lost or damaged myelin in the white matter (Suryana & Jones 2014). In another experiment performed in P3 mice, the effect of tracheal occlusion on blood pressure was compared to adult animals. Hence, while tracheal occlusion dropped arterial blood pressure to zero levels, newborn offspring responded with a significantly milder reduction and over a more prolonged time (Li et al. 2017). In another study, adult mice treated with an intraperitoneal brain homogenate from mice subjected to HP experienced a longer survival time in a hypobaric chamber. In addition, cells co-cultured under hypoxia with brain extract from preconditioned animals were substantially more viable than cells from the control group. When dissociated synaptosomes of the rat cortex were co-cultured under condition of hypoxia with this homogenate extract, an indicator of cell death such as lactate dehydrogenase was released to a lesser extent, indicating protection by the extract (Lu et al. 2005). These results indicate a neurochemical adaptation to hypoxic stress.

In vitro and in vivo studies have shown that HP induces protection against subsequent ischaemic brain injury in experimental adult and newborn models. Neuroprotection has been seen in different cell populations such as astrocytes (Liu & Alkayed 2005), hippocampal cells (Bickler & Fahlman 2009), and primary neuronal cultures (Arthur et al. 2004), as well as in adult murine models of cerebrovascular accident tolerance (Fan et al. 2011).

The different in vitro and in vivo models to study HP differ in the concentration of oxygen to induce hypoxia, as well as in the moments in which they are subjected to these conditions. Oxygen concentrations to which cell cultures are normally subjected in in vitro HP studies are around 5% O₂. In vivo studies often differ, but the most employed HP conditions target 8% O₂ for 3 h, 24 h before exposure to the injurious intervention. Rat pups at P6 are the most widely employed experimental model (Table 1).

Importantly, the duration of the tolerant state induced by HP may be age dependent. Thus, in adult mice, tolerance may be limited to 72 h (Zhan et al. 2010). However, in neonatal brains, the preconditioned period can be extended to 8 weeks and improve recovery after an ischaemic insult (Gustavsson et al. 2005). For adult brains, the repair capacity after injury is much lower, and if the animal is aged, HP has no protective effect upon brain deficit of oxygen and/or glucose (Bickler et al. 2010). In line with these studies, hypoxic–ischaemic injury in the neonatal brain is also less susceptible to oxidative injury and recovery is better than in the aged brain (Xu et al. 2007).

### Oxidative stress

Oxidative stress can be defined following Sies definition ‘as an imbalance between oxidants and antioxidants in favor of the oxidants, leading to a disruption of redox signalling and control and/or molecular damage’ (Sies 2015). Under normoxic conditions, the brain keeps a balance between pro- and antioxidants, but an excess of free radicals can lead to oxidative stress affecting cell signalling pathways (Sies 2017). The brain is particularly vulnerable to reactive oxygen species (ROS) due to its high content of unsaturated fatty acids which when oxidized produce peroxyl radicals. Moreover, the abundance of catalytic transition metals especially iron in some regions of the brain plus a low activity of antioxidant enzymes

### Table 1 Experimental models of HP in vivo/in vitro.

<table>
<thead>
<tr>
<th>In vitro/in vivo</th>
<th>Age</th>
<th>HP %O₂</th>
<th>Time of HP</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse cortical neurons</td>
<td>G16</td>
<td>5%</td>
<td>15 h</td>
<td>Liu et al. (2005)</td>
</tr>
<tr>
<td>Primary rat cortical neuronal cultures</td>
<td>G18-19</td>
<td>5%</td>
<td>25 min</td>
<td>Arthur et al. (2004)</td>
</tr>
<tr>
<td>Rat hippocampal slice cultures</td>
<td>P9</td>
<td>5%</td>
<td>1 h</td>
<td>Bickler &amp; Fahlman (2009)</td>
</tr>
<tr>
<td>Rat hippocampal slice cultures</td>
<td>2 year</td>
<td>5%</td>
<td>1–10 min</td>
<td>Bickler et al. (2010)</td>
</tr>
</tbody>
</table>

| Rats                      | P7   | 8%     | 2.5 h       |                                  |
| Rats                      | Adult| 7%     | 4 h/8 days  |                                  |

G, gestational day; P, postnatal day.
such as glutathione peroxidase (GPx) and catalase (CAT), and a high aerobic metabolic rate with high oxygen consumption undoubtedly cause an imbalance towards a pro-oxidant milieu (Coimbra-Costa et al. 2017).

Oxidative stress is linked to several neuropathological processes involving specific mitochondrial targets (Bhat et al. 2015). However, enzymatic complexes linked to other structures and functions not involved in mitochondrial respiration also generate ROS. Hence, cytochrome P450 mono-oxygenase system, xanthine oxidoreductase, NADPH oxidases, heme oxygenases, myeloperoxidases and nitric oxide synthase among others are also capable of producing significant amounts of ROS. Moreover, in the presence of ‘free’ metals such as iron, copper, and manganese, Fenton chemistry exacerbates the generation of highly toxic hydroxyl radicals (Sanderson et al. 2013).

ROS involved in neurodegeneration include hydrogen peroxide (H$_2$O$_2$), superoxide anion (O$_2^-$), and hydroxyl radical (HO). Reactive nitrogen species (RNS) such as nitric oxide (NO) and peroxynitrite (ONOO$^-$) also have a detrimental effect on neurons (Singh et al. 2019).

Increased ROS production results in increased lipid peroxidation, protein and DNA oxidation, and NO levels in brain tissue leading to oxidative injury, compromising mitochondrial integrity and energy production leading finally to cell death (Torres-Cuevas et al. 2017). Indeed, neurons rely almost exclusively on mitochondria producing the energy required for most of the cellular processes, including synaptic plasticity and neurotransmitter synthesis (Torres-Cuevas et al. 2019). Therefore, neurons and neuronal functions are highly susceptible to hypoxia, and a brief disruption of oxygen supply to the brain will lead to oxidative stress and cell damage (Wang & Michaelis 2010).

HP prior to severe acute hypoxia preserves at least partially the mitochondrial function. The preconditioning protocol of exposure to intermittent hypobaric hypoxia before an acute severe normobaric hypoxia insult leads to the preservation of a reducing milieu characterized by a lower level of ROS and the maintenance of intracellular glutathione (GSH) concentration and Mn superoxide dismutase (SOD) activity. This antioxidant response decreases the activity of pro-apoptotic cascades mediated by the downregulation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-$\kappa$B) and the upregulation of erythropoietin (EPO) highlighting the neuroprotective effect of HP. Furthermore, sublethal hypoxic conditions stimulate neurogenesis and angiogenesis similar to what occurs during embryonic brain development (Coimbra-Costa et al. 2021). Thus, the neuroprotective mechanisms triggered by HP include activation of antioxidant and anti-apoptotic pathways, suppression of excitotoxicity, promotion of cell proliferation, activation of anti-inflammatory responses, and enhancement of vascular regulation (Fan et al. 2020) (Fig. 1). HP could have, therefore, different therapeutic uses in the prevention of diseases where hypoxia is the basis of pathogenesis.

Biological response to HP may include two differentiated types of responses depending on the timing of the stimulus. First, a rapid onset response just a few minutes or hours after the exposure to hypoxia and results in post-translational responses such as alterations in ion channel permeability, protein phosphorylation, and a second with later onset period delayed by hours or days, which depends on gene expression and protein synthesis, involving survival and repair mechanisms. Both responses are transient but can be repeatedly induced (Gidday 2006).

Figure 1
Neuroprotective mechanisms resulting from HP. Preconditioning by hypoxia can produce a neuroprotective effect in the brain through the activation of several metabolic pathways that can be grouped into four main blocks: increased antioxidant defences, decreased neurotoxicity, decreased neuroinflammation, and improved cell survival. Hypoxia inducible factor (HIF-1), erythropoietin (EPO), glutathione (GSH), peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1a), B-cell lymphoma 2 (Bcl-2), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-$\kappa$B), and brain-derived neurotrophic factor (BDNF).
Mechanisms of neuroprotection

Activation of antioxidant defence

HP induces the activation of the transcription factor nuclear erythroid 2-related factor 2 (Nrf2). Nrf2 is a master regulator that upregulates an ample array of antioxidant enzymes such as heme oxygenase (HO-1), NAD(P)H quinone dehydrogenase 1, and GPx among others (Fig. 2). In adult mice, HP significantly increased Nrf2 and HO-1 protein levels 24 h after a traumatic brain injury causing a decrease in the level of oxidative stress by-products such as protein carbonyl, 4-hydroxy-2-nonenal, and 8-hydroxy-2-deoxyguanosine in the cerebral cortex (Shu et al. 2016). In vivo studies of cortical neurons first subjected to HP and then to oxygen and glucose deprivation (OGD) showed an increased activity of Nrf2 targets, specifically GPx, glutathione reductase (GR), and SOD with a concomitant reduction in the concentration of O$_2^-$ and H$_2$O$_2$ (Arthur et al. 2004). In another experimental study, mouse pups subjected to HP and subsequent ischaemia showed an increase in brain GPx and SOD activity (Alkan et al. 2008). These results are of especial relevance in neonatology where the immaturity of the antioxidant defence system generates a series of free radical-associated diseases and HP could be employed to prevent free radical-derived brain damage (Fan et al. 2020).

HP also increases the levels of GSH. GSH is the most relevant non-enzymatic cytoplasmic antioxidant. Under pro-oxidant conditions, two mols of GSH establish a di-sulphur bond to produce oxidized glutathione (GSGG) and provide ROS with reducing electrons. GPx and GR enzymes are responsible for the glutathione oxidation-reduction cycle, involved in the detoxification of H$_2$O$_2$ to water and oxygen. GPx oxidizes GSH to GSSG which is then further reduced to GSH by GR (Dwivedi et al. 2020). Adult mice subjected to HP compared to an acute hypoxia group showed increased GSH and decreased GSSG levels in the hippocampus which revealed enhanced GPx and GR activities (Liao et al. 2018). Increasing GSH levels in the brain could be a potential strategy against hypoxia-induced brain injury.

Astrocytes exposed to HP exhibited an increased expression of the peroxisome proliferator-activated receptor-γ coactivator (PGC-1α) gene. PGC-1α is a transcriptional coactivator that, in addition to being involved in mitochondrial biogenesis and function, participates in mitochondrial ROS detoxification by modulating the expression of mitochondrial antioxidant defence in cells (Rius-Pérez et al. 2020). Specifically, PGC-1α increases the levels of SOD, CAT, peroxiredoxins, UCP-2, and thioredoxin and, consequently, protects cells from mitochondrial dysfunction. In in vitro study, astrocytes

![Figure 2](https://rem.bioscientifica.com)
submitted to 24 h of intermittent HP produced an increase of PGC-1α mRNA levels and SOD, CAT, and GPx activity compared to the control group (Wu et al. 2021). These results could be indicative of the activation of PGC-1α by HP that could contribute to a decrease in oxidative stress beneficial for the recovery of the developing brain after ischaemic or hypoxic injuries (Jia et al. 2020). However, more studies will be necessary to further elucidate the induction of neuroprotective mechanisms of PGC-1α during HP.

**Decreasing neuro-excitotoxicity**

The increase in intracellular GSH constitutes an essential neuroprotective response to HP. However, GSH synthesis depends specifically on the availability of l-cysteine. The incorporation of l-cysteine to the astrocytes needs the concourse of the cystine/glutamate exchanger (Xc-). However, glutamate is one of the main excitatory neurotransmitters. Hence, during episodes of ischaemia or acute hypoxia, increased concentrations of glutamate inhibit the Xc- transporter system and subsequently the cystine uptake into cells leading to diminished GSH synthesis and subsequently to an increased oxidative stress. Thus, the Xc-system plays a key role promoting GSH synthesis and glutamatergic signalling (Sims et al. 2012, Lewerenz et al. 2013). Neuronal stem cells in a mouse model of HP exhibited decreased excitotoxicity due to an increment of the activity of the Xc- system resulting in less oxidative stress (Fan et al. 2020).

**Enhancing anti-inflammatory response**

HP decreases neuronal inflammation through the activation of different pathways. Inflammatory processes are of great pathophysiologic relevance in neurodegenerative conditions and in brain development both during gestation and postnatally. Inflammatory responses to injury occur through a variety of cellular and molecular mechanisms which may include free radicals. Recently, cellular and molecular mechanisms, such as transcriptional profiling that cause oxidative stress, were identified in cells of the innate immune system. In this study, a genetic signature was defined which produces oxidative injury and neurotoxicity that have been identified in neuroinflammatory diseases. This finding is very relevant as they can be used as therapeutic targets (Mendola et al. 2020). The immune system in the brain is mainly regulated by microglia (resident macrophages). Under stress conditions, the activation of microglia triggers a series of processes that culminate in a more cytotoxic phenotype. This response is the result of the secretion of proinflammatory cytokines such as IL-1β, IL-6, tumor necrosis factor alpha (TNFα), IFNγ, ROS, matrix metalloproteins, and excitatory amino acids such as glutamate (Kraft & Harry 2011). Thus, during sustained neuroinflammation, the neuroprotective microglial response switches from a protective to a neurotoxic response (Hickman et al. 2018). Thus, preventing the activation of microglial inflammatory signalling pathways may be a potential approach for neuroprotection (Muzio et al. 2021).

Another cell type essential for maintaining neuronal health are glial cells, especially astrocytes. In physiological conditions, astrocytes play a role as key homeostatic cells of the CNS by providing nutrients to neurons, maintaining the integrity of blood–brain barrier, controlling synaptic activity, and also in preventing oxidative stress. However, under pathological conditions, such as mitochondrial damage or calcium overload, astrocytes become activated. They produce harmful ROS and RNS which ultimately may induce microglial activation or even directly cause neural death since they express caspase-3 apoptotic markers leading to secondary cerebral damage (Chen et al. 2020, Goshi et al. 2020).

The activation of microglia by moderate hypoxia can be induced mainly by hypoxia-inducible factor (HIF) and its targets (vascular endothelial growth factor (VEGF), EPO), nitric oxide synthase, adenosine receptor 1, or glycogen synthase among others (Fan et al. 2020, Gao et al. 2021). P6 mice subjected to HP followed by hypoxia/ischaemia showed a significant decrease in the expression levels of iNOS, Cox-2, TNF-α, and IL-1β. Therefore, the results suggest that HP has anti-inflammatory effects at the brain level in neonates (Chen et al. 2015). In an *in vitro* assay, BV2 microglia cell line was exposed to OGD and reoxygenation and thereafter treated with mesenchymal stem cell culture medium that had been previously exposed to HP. Results showed an alleviation of the injury of microglia due to an inhibition of proinflammatory cytokines (TNF-α, IL-1β, and IL-6), CD86, and inducible nitric oxide synthase, with a significant decrease in ROS, while concomitantly increased levels of anti-inflammatory cytokine (IL-10), CD206, and arginase-1 were assessed. Mesenchymal stem cell cultures subjected to HP were more effective in alleviating cell injury and promoting anti-inflammatory microglia activation than those exposed to normoxia or acute hypoxia. These results...
demonstrate how HP exposure is able to induce the release of exosomes (bilayer lipid enclosed spheroids, actively transmitting CD9, CD63, and TSG101). Therefore, they have the capacity to exert anti-inflammatory functions by promoting the anti-inflammatory polarization of microglia (Yu et al. 2021).

Another signalling pathway that is activated following hypoxic–ischaemic brain injury leading to brain inflammation is the serine-threonine kinase, glycogen synthase kinase 3β (GSK-3β). This enzyme is involved in different cellular processes including proliferation, differentiation, apoptosis, adhesion, and migration. Moreover, GSK3 plays key roles in embryonic and tissue development, tumour suppression, and immune responses. Additionally, the protein is involved in the pathogenesis of numerous disorders affecting the CNS such as Alzheimer’s or Parkinson’s disease. GSK-3β inactivation, via the phosphoinositide 3-kinase (PI3K)/Akt signalling pathway, negatively modulates the NF-κB pathway. GSK-3β regulates the promoter-specific recruitment of NF-κB and consequently plays an essential role in gene transcription (i.e., transactivation activity and target gene expression). Therefore, the activation of the PI3K/Akt/GSK-3β signalling pathway also causes reduction in NF-κB nuclear translocation, and this pathway seems to be the main factor responsible for inflammatory protection. Furthermore, inhibition of GSK-3β can reduce the production of pro-inflammatory cytokines (such as IL-β, IL-6, and IFNγ) which, in turn, increases the release of anti-inflammatory cytokines (such as IL-10) (Hoffmeister et al. 2020). Studies with P7 rats showed increased phosphorylation of GSK-3β, through the PI3K/Akt pathway, and also decreased levels of inflammatory markers, such as NF-κB, Cox-2, CD68, myeloperoxidase, and microglia activation in the cerebral cortex, striatum, and hippocampus of mice subjected to HP followed by hypoxia/ischaemia (H/I) vs those subjected to H/I alone. These results show that HP-mediated increase in PI3K/Akt activity may contribute to protect the brain against hypoxic–ischaemic neonatal brain injury (Yin et al. 2007). Moreover, in further experiments, HP sustained the development of white matter and grey matter of the immature brain contributing to long-term neurological functional recovery after H/I brain injury. HP restored the differentiation and maturation capacities of oligodendrocyte progenitor cell and reduced microglia/macrophage activation and neuroinflammation (Xu et al. 2019).

HP could be relevant to neuroinflammatory conditions in which damage is caused by cerebral hypoxia or ischaemia.

Enhanced neuronal cell survival

Depending on the duration and severity of hypoxia, cells can adapt, become injured, or die. The transcription factor HIF-1 is a heterodimer composed of an O₂-regulated HIF-1α subunit and a constitutively expressed HIF-1β subunit. In response to hypoxia, HIF-1α is activated and upregulates a wide set of genes whose functions range from angiogenesis, glycolysis, and erythropoiesis to inflammation and remodelling. The degree of exposure to oxygen will have a determinant effect upon HIF signalling pathways (Schönenberger & Kovacs 2015). If hypoxia is significant and long-lasting, HIF-1α will activate apoptosis via p53, generating a zone of intense cell death (Merelli et al. 2021). However, HP prevents the degradation of HIF-1 and consequently enhances neuronal survival (Liu et al. 2005). HIF-1 upregulation following HP has been observed both in neonatal and adult brains (Jones et al. 2006). HIF-1 can induce genes with anti-apoptotic capacity in neurons such as EPO (Sirén et al. 2001). It has been proposed that the mechanism of action of EPO takes place through several signalling pathways that increase the expression of anti-apoptotic proteins of the Bcl-2 family, decreasing the expression and release of the main markers of the mitochondrial apoptotic pathway, such as cytochrome c and caspase-3 (Rabie & Marti 2008). In experimental studies, rat brains subjected to acute hypoxia exhibited increased cytochrome c and caspase 3. In contrast, when acute hypoxia was preceded by HP, no differences were found in these markers compared to normoxic rats (Coimbra-Costa et al. 2021) suggesting that HP may prevent mitochondrial dysfunction and apoptosis.

The mechanisms of hypoxic damage to brain neurons are closely related to oxidative stress. Sublethal ROS generated during HP can upregulate HIF-1α and EPO, stimulating neuroprotection through the Jak-Stat and NF-κB pathways, as seen in neurons preconditioned with hypoxia in vitro for 2 h (Liu et al. 2005). EPO binds to its receptor, phosphorylates, and activates Jak2 which, in turn, phosphorylates other kinases such as the transcription factor Stat family (Dawson 2002). Stat5 is able to induce the expression of Bcl-xl, a gene that regulates cytokine-induced survival signalling; thus, Jak-Stat signalling has an anti-apoptotic role (Liu et al. 2005, Ma et al. 2014). On the other hand, EPO may cause an interaction between the Jak2 and NF-κB signalling pathways, where activation of Jak2 phosphorylates the NF-κB inhibitor and allows its nuclear translocation and transcription of neuroprotective genes, such as Bcl-2 and Bcl-xl that prevent cellular apoptosis (Digicaylioglu & Lipton 2001).
NF-κB activation is also linked to another protective pathway involving the expression of brain-derived neurotrophic factor (BDNF), a neurotrophin belonging to a family of neurotrophic factors. The binding of BDNF to tropomyosin receptor kinase B triggers intracellular signalling cascades such as the PI3K/Akt pathways resulting in upregulation of pro-survival protein genes, in particular Bcl-2 (Reichardt 2006). In addition, BDNF positively controls the transcription of its own gene resulting in further upregulation of neuronal BDNF expression. BDNF upregulation has been demonstrated in cortical neurons of rat brains exposed to HP (Samoilov et al. 2014). In 2017, an additional example has been reported in which it has been demonstrated that HP improves the survival rate of rats subjected to cerebral ischaemia, reduce neurological deficits, and inhibits the inflammatory response. These effects are regulated by HIF-1α. Consequently, HP has a positive therapeutic effect on cerebral ischaemia in this model and may become a novel clinical treatment for cerebral ischaemia (Yang et al. 2017).

Conclusions

Finding strategies and/or mechanisms to reduce or minimize damage to such a complex and oxygen-sensitive organ as the brain is a challenge. Brain damage is linked to oxidative stress in different conditions and may be the cause or the consequence of cell death or neuroinflammation.

The effect of HP reducing cerebral oxidative stress is of paramount relevance and opens new lines of research that will contribute to unravel the intrinsic mechanisms of neuroprotection involved in neuronal cell protection in brain injury, such as stroke, hypoxic ischaemic encephalopathy, trauma, or neurodegenerative diseases. The next step will be to consolidate that HP represents an innovative therapeutic modality to induce neuroprotection, neuroplasticity, and brain recovery while remaining safe and harmless for the patients.

Declaration of interest

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Author contribution statement

I M, M C-D, and I T-C searched the literature, wrote the draft, and drew the figures of the manuscript. M V reviewed and approved the final version of the manuscript.

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