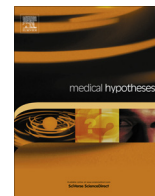


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A neurobiological model for cry-fuss problems in the first three to four months of life

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ABSTRACT

Although problem crying in the first three to four months of life is usually self-limiting, it is not a trivial condition. Early intervention is important, yet families receive conflicting advice from health professionals. The past decade has seen significant advances in neuroscience, lactation science, and developmental psychology, including new insights into the significance of developmentally sensitive windows. We propose a neurobiological model to explain the mechanisms of cry-fuss problems in the first months of life, and the mechanisms which underlie effective intervention, with a view to facilitating research collaboration and consistency of advice across health disciplines. We hypothesise that crying in the first three to four neurodevelopmentally sensitive months signals activation of the hypothalamic–pituitary–adrenal axis and adrenergic neuronal circuitry in response to perceptions of discomfort or threat. Susceptible infants may be conditioned by early stress, for example, by unidentified feeding difficulties, into a sensitised stress response, which usually settles at three to four months of age with neurodevelopmental maturity. Bouts of prolonged and unsoothable crying result from positive feedback loops in the hypothalamic–pituitary–adrenal and adrenergic systems. Importantly, epigenetic modulation of the infant's limbic neuronal circuitry may explain correlations between regulatory problems in the first months of life, and behavioural problems including feeding problems in later childhood.

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Background

One of the most common problems parents bring to paediatricians, general practitioners, child health nurses, midwives, psychologists and Emergency Departments in the first weeks and months of life is the baby who cries and fusses. One in five new parents report that their baby has problem crying [1]. Infant cry-fuss behaviour is a complex problem, emerging out of multiple dynamically interacting and co-evolving factors, including genetics, temperament, an individual baby's unique level of neurodevelopmental maturity, maternal prenatal stress and self-efficacy, birth complications, and parental psychosocial disadvantage [2–6]. Cry-fuss problems comprise a spectrum of neurobehaviour, from grizzling and fussing to bouts of prolonged and unsoothable crying. Crying is a late cue, usually preceded by pre-cry facial, other motor, and vocal signals along a gradient of intensity. Bouts of unsoothable crying are the most distressing form of crying behaviour for parents, with a frequency proportional to the overall amount of

crying and fussing [7]. Attempts to quantify unsettled infant behaviour have been confused, and 'colic', as defined by the Wessel's or modified Wessel's criteria, is an arbitrary upper end to the wide spectrum of infant crying in healthy infants. Clinically, problem crying is most usefully defined by parental perception, and this paper uses the terms excessive crying, cry-fuss problems, and unsettled infant behaviour interchangeably. Because crying, feeding and sleep problems interact and dynamically co-evolve in the first three to four months of life, they are often referred to collectively as regulatory problems.

Cry initiation rates remain relatively constant across all studied cultures, but mean total daily durations of infant crying vary markedly across cultures, even within the West [8]. Although most infant cry-fuss problems resolve without long-term effects, excessive crying is a marker of risk and is not a trivial condition. It is associated with an increased risk of postnatal depression, child abuse, premature breastfeeding cessation, and an increased risk of feeding and behavioural problems including Attention Deficit and Hyperactivity Disorder later in childhood, particularly if the crying persists beyond the first few months [9–12]. Intervention as early as possible is important, yet health professionals give parents conflicting advice. Parents with unsettled babies recourse to multiple health-care providers, including Emergency Departments, and are also admitted into expensive tertiary residential units [13]. In this review, we formulate a theoretical model, which aims to explain

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the neurobiological mechanisms underlying regulatory problems in the first few months of life, and the neurobiological rationale underlying clinical intervention, so that researchers and clinicians across multiple disciplines are better placed to re-examine their own explanatory frameworks and collaborate effectively in the management of this common but distressing presentation.

Cry-fuss problems emerge out of disrupted maternal–infant neurobehavioural synchrony

Biologically programmed, or innate, patterns of synchrony operate between the neuroendocrine systems of mother and infant, increasingly elucidated by functional MRI imaging of the brain and neurohormonal assay. These morphological and neurohormonal changes correlate with mother–infant neurobehaviours, for example, during birth, infant care, or feeds. Due to the highly social nature of our species, maternal–infant neuroendocrine and neurobehavioural synchrony may be either supported or impeded by various social behaviours. Intrapartum medical interventions and maternal postnatal depression also impact upon maternal–infant synchronies. Optimising the neurohormonal synchrony between mother and baby has mutually beneficial physical, behavioural and psychological effects for both, short and long-term [14].

The first three to four months of life are characterised by exquisite neuroplasticity and therefore neurodevelopmental sensitivity. When maternal–infant neurohormonal and neurobehavioural synchronies are disrupted, there is an unpredictable amplification of effects, and cry-fuss problems are more likely to emerge [4]. Disruption may prove more problematic in less neurodevelopmentally mature babies or in mother–baby pairs predisposed by prenatal stress, birth complications, and genetic or psychosocial or other factors [2,3,5,6]. Cry-fuss problems are more likely to emerge in the context of two social factors which disrupt maternal–infant neurobehavioural synchronies: First, a widespread failure to prevent, identify and manage feeding problems; and second, the popularity of behavioural interventions in the first months of life [15,16].

Unidentified feeding problems

Contemporary highly medicalised birthing practises may impair initiation and duration of breastfeeding, due to effects on both primitive neonatal reflexes and maternal neurohormone secretion [17–20]. But health professionals – even those with positive attitudes to breastfeeding – have significant knowledge gaps concerning the social behaviours and interventions that promote breastfeeding, and concerning identification and management of breastfeeding problems [21–23]. In Australia, which has higher breastfeeding rates than the US and the UK, 92% of mothers initiate breastfeeding, but by the end of the first week one in five mothers have introduced formula feeds. The two most common reasons mothers give for the premature introduction of formula and other weaning foods are unsettled behaviour and growth concerns. (Breast or nipple pain is the third common reason.) Mothers believe that cry-fuss behaviours, which in this age group frequently correlate with excessive feeding, feeding refusal, and excessive waking, signal poor infant satiety [24–27]. A randomised controlled trial of 77 infants at five weeks of age shows that those with cry-fuss problems have lower concentrations of plasma cholecystokinin, the hormone of satiety, suggesting that mothers may be competently reading their infant's cues, in the context of a lack of appropriate feeding advice and support [28].

The link between cry-fuss problems and feeding difficulties is clearly established, including by extensive paediatric gastroenterology research. Although the latter documents the link, it also inaccurately interprets the aversive feeding behaviours associated with

problem crying in the first weeks and months as signs of oesophagitis, extrapolating back from findings in older infants and children [16,29–31]. Almost all crying baby research is confounded by multiple unidentified and unmanaged feeding problems. For example, a cross-sectional study of 316 infants in the UK demonstrates that breastfeeding babies show more distress and are less soothable, but does not control for the effects of unidentified breastfeeding problems, including feed spacing [32].

Disrupted maternal–infant neurobehaviour during feeds quickly trenches in the first days and weeks, due to the neuroplasticity of both mother and baby in this sensitive period, and feeding problems, with associated disrupted and anxious maternal–infant relations, may then persist into later childhood [12,33–35].

Behavioural interventions

Societies which preference behavioural interventions in the first weeks and months have lower levels of physical contact with the baby, lower breastfeeding rates, and substantially longer durations of daily infant crying [5,8]. We define behavioural interventions as approaches to infantcare in the first few months of life which aim to entrain the biology of an infant's feeds and sleep, applied either as population strategies of prevention, or as interventions for unsettled infant behaviour.

Historical, sociological and midwifery studies detail the medicalisation of birth and infant care from the early 1900s in the west, which resulted in decreased maternal mortality ratios and infant mortality rates. However, traditional knowledge about the social behaviours that help optimise birth and breastfeeding outcomes also began to disappear, as did intergenerational role modelling and the extended family. Dr. Truby King developed “scientific mothering”, a regulatory approach to infant feeds and sleep, which emphasised measurement, routine, and expert supervision, and his methods were widely disseminated in the Anglosphere from the 1920s. In the second half of last century, the precepts of “scientific mothering” were reinforced by the rise of behavioural psychology. This historical belief that the interests of families are best served by behavioural interventions has been reinforced by the dominance of reductionist methodologies from the 1990s [36].

Today, as a result, public health messages often advocate behavioural interventions for infant feeds and sleep in the first weeks and months. However, studies cited as evidence that behavioural interventions in the first three to four months of life prevent or improve cry-fuss problems, improve maternal sleep duration, and improve behaviour and sleep in later childhood extrapolate data derived from older infants and their families back to the first few months of life [15,37]. These studies do not integrate the evidence that overly frequent or prolonged breastfeeding and excessive waking signal an underlying problem of poor milk transfer, caused by various feeding problems which require appropriate assessment and management, not feed spacing [38–40]. In addition, studies cited as evidence that behavioural interventions protect against postnatal depression are complex interventions with multiple covariates. The positive effects on maternal mood cannot be attributed to the behavioural intervention component, and are more likely relate to the positive effects of any caring therapeutic relationship [15]. A longitudinal cohort study of 10,419 mother–child pairs demonstrates that regulation of feeds from four weeks of age does not protect against postnatal depression [41]; a longitudinal cohort study of 1222 mother–child pairs demonstrates that increased maternal depressive symptoms cause increased duration of infant night waking over time, not the reverse [42]; and the evidence concerning strategies for the prevention of postnatal depression includes breastfeeding support but not behavioural interventions [43]. A number of well-conducted studies, including two prospective

cohort studies each of almost 200 mother–baby pairs, demonstrate that families who apply behavioural methods in the first weeks and months are at increased risk of cry-fuss problems [5,8].

Neurohormonal mechanisms of cry-fuss problems

The infant's nervous system

Neuroscience increasingly elucidates the neurocorrelates of mother–infant interaction and the neuronal circuitries of depression, anxiety and fear [14]. We hypothesise that when an infant's amygdala, which are mature at birth, are activated by a perceived need or threat either internally or in the environment, the hypothalamic–pituitary–adrenal (HPA) neurohormonal circuitry upregulates, triggering sympathetic nervous system (SNS) activity and adrenaline release, with associated cardiovascular, vocal, facial and other physiological changes along a gradient of crying. In a positive feedback loop evolved to ensure the infant's survival in threatening circumstances, SNS arousal causes further release of cortisol from the HPA axis; adrenaline and cortisol further upregulate SNS activity. We propose that this feedback loop explains bouts of unsoothable crying, so that an initial signal of discomfort or distress may become a temporarily stable behavioural state.

We hypothesise that high levels of SNS arousal and associated HPA activation sensitises a susceptible baby's limbic neural circuitry during this highly neuroplastic period, resulting in increased neural sensitisation to stress, also known as a conditioned fear response [44]. This sensitised stress response persists even after early triggers resolve, and continues to occur in response to triggers which may seem minimal or undetectable to the caregiver. A sensitised stress response usually settles around three to four months of age with increasing neurodevelopmental maturity. This model explains why some babies by-pass pre-cry cues and move directly into intense SNS activation and inconsolable crying. Certain infants may be susceptible to a sensitised stress response in the first three or four months of life due to unidentified and unmanaged problems including feeding problems; due to genetics, temperament, individual neuro developmental immaturity; maternal prenatal stress, or birth complications.

There is consensus across disciplines that early life stressors influence neuronal organisation and behavioural phenotypes long-term. Biological embedding of heightened stress sensitivity is thought to occur during developmentally sensitive periods, due to stable changes in the regulation of gene expression [45]. Human mother–infant pairs are remarkably resilient and adaptive, and most infants who cry excessively in the first three to four months sustain no long-term negative effects. However, we propose that the neuronal stress circuitry of a small but significant minority of crying babies sustains epigenetic modification, resulting in long-term adverse outcomes [45–47].

The infant's gut

Although infant crying is a non-specific neurobehavioural sign of distress correlating with HPA axis and SNS arousal, the term 'colic' reflects a widespread belief that infant crying is caused by abdominal pain. But gut dysfunction has a demonstrated, linear and causal relationship with cry-fuss problems only in the case of functional lactose overload, a correctable breastfeeding problem [48,49]. Other associated gut changes have a much more complex, not causative, relationship with infant crying.

Unnecessary medicalisation

Back-arching is a neurobehavioural cue of protest or discomfort. Back-arching at the breast or bottle is associated with feeding

refusal, and together, back-arching and feeding refusal signal feeding difficulty, for example, positional instability or oro-motor dysfunctions [19,50]. Over the past two decades, however, infant neurobehaviours commonly associated with crying and fussing, such as feeding refusal, back-arching, crying when put down, vomiting, and excessive night-waking, have been interpreted by medical researchers as signs of gut disease. This has resulted in widespread inappropriate diagnosis and treatment of gastro-oesophageal reflux disease (GORD), lactose intolerance, and food allergy in crying babies in the first three to four months of life [16,51,52]. Despite the ongoing popularity of these diagnoses, anti-secretory medications have been shown to be no more effective than placebo [53,54], and the mucosal inflammation of acid-peptic or allergic oesophagitis is very rarely demonstrated in crying babies in the first three or four months [55,56]. Complicated maternal elimination diets are popular amongst breastfeeding mothers. However, the results of the study most commonly cited as evidence that a maternal diet which eliminates cow's milk, eggs, peanuts, tree nuts, wheat, soy and fish decreases crying in exclusively breastfed infants are explained by cow's milk elimination alone [57].

Unnecessary medicalisation of infant crying in the first three to four months may result from failure to identify underlying treatable feeding problems, such as positional instability or oromotor dysfunctions [16]. Unnecessary medicalisation and failure to identify feeding problems risks the development of a conditioned fear response throughout the first neurosensitive few months by the previously described neurological mechanisms, and risks neurological entrenchment of maternal–infant feeding problems which may persist into later infancy and childhood [12,33–35]. Both maternal elimination diets and acid-suppressing medications paradoxically predispose to allergy in later childhood [58–60]. An early inappropriate diagnosis of GORD paradoxically predisposes to GORD in later infancy, by increasing the risks of breastmilk substitution, which in turn places the infant at increased risk of GORD (mediated by cow's milk allergy); by failing to identify and treat other factors that predispose to GORD, such as long interprandial periods; and by failing to identify and treat other factors that may underlie infant crying, since the crying itself increases frequency and noxiousness of refluxate [60,61]. That is, inappropriate diagnoses of allergy or GORD in the first months of life risk becoming self-fulfilling prophecies.

Unidentified feeding problems

Breastmilk is the newborn's gastro-intestinal environment of evolutionary adaptedness, uniquely protecting the immature and permeable gut epithelial barrier from the antigen loads of colonisation at birth and first nutrition. In addition to secretory IgA and live *Lactobacillus* and *Bifidobacterium longus*, human milk contains immune cells, cytokines, growth factors and multiple other bioactive anti-inflammatory factors. These exert beneficial effects by immune exclusion, which controls epithelial colonisation and inhibits epithelial penetration, and by hyporesponsiveness, the dampening down of local inflammatory responses to innocuous antigens.

Unidentified and unmanaged feeding difficulties disrupt gut permeability, motility, and microbiota in a number of ways. First, unidentified feeding difficulties commonly result in breastmilk substitution, which delays maturation of the intestinal epithelial barrier and increases permeability, alters intestinal motility, alters intestinal microbiota composition and diversity, and predisposes to allergy [9,62]. Second, unidentified feeding difficulties may result in functional lactose overload, which results in increased intestinal contractility, large volumes of gas, explosive, frothy, acidic stools, crying, and altered intestinal microbiota composition [49]. A randomised controlled trial of 302 breastfeeding mother–baby pairs demonstrates that functional lactose overload is a treatable cause

of infant crying [48], but signs of functional lactose overload are still commonly misdiagnosed as allergy or GORD [16,49]. Third, unidentified feeding difficulties, such as positional instability, anatomic abnormalities or oromotor dysfunctions, result in backarching and aversive feeding behaviours, also commonly misinterpreted as signs of acid-peptic or allergic GORD. These inappropriate diagnoses are treated with anti-secretory medications, which increase intestinal permeability and predispose to allergy, and maternal elimination diets, which may delay development of immune tolerance and predispose to allergy [58,60]. Fourth, unidentified feeding difficulties risk the development of a sensitised stress response in the first neurodevelopmentally sensitive three to four months, due to chronic HPA axis and SNS hyperarousal.

Neurohormonal effects of crying

A sensitised stress response not only results in excessive crying in susceptible infants in this age group, but also exerts neuroendocrine effects upon the gut. The gut is commonly referred to as “the second brain” because of the sophistication of the enteric nervous system, and the bi-directional nature of the gut-brain axis [63,64]. High levels of SNS arousal modulate gastrointestinal motility, including oesophageal motility, gastric emptying, frequency of gastro-oesophageal refluxate, and vomiting. High levels of SNS arousal also affect the composition of gut microbiota, and increase gut permeability, which predisposes to immune sensitisation [63,65]. It may be that cry-fuss behaviours predispose to allergy in later childhood not only as a result of the direct effects of anti-secretory medication and breastmilk substitution, but by the epigenetic effects of chronic HPA axis and SNS system hyperarousal during the highly plastic, neurodevelopmentally sensitive first three or four months of life [66,67].

Enteric microbiota signature

Multiple factors interact and co-evolve to affect intestinal microbiota, and the enteric microbiota signature of crying babies has a complex correlative, not causative, relationship with crying. A growing number of studies demonstrate that excessive infant crying is associated with less diverse infant gut microbiota; lower counts of protective anti-inflammatory bacteria, such as *Lactobacillus* and *Bifidobacterium longus*; higher counts of both pro-inflammatory bacteria such as *Bifidobacterium breve* and potentially pathogenic gram-negative and coliform bacteria; and higher levels of the inflammatory marker, faecal calprotectin [68–70]. Also, two randomised controlled trials, of 46 and 80 patients, demonstrate that crying in breastfed infants decreases with administration of the probiotic *Lactobacillus reuteri* DSM 17,938 [71,72]. These randomised controlled trials do not, however, control for feeding difficulties, and clinical intervention should first address the multiple primary factors, including unidentified feeding difficulties, which interact and co-evolve to create the intestinal microbiota signature of crying babies [73].

The mother's nervous system

Postpartum infant stimuli perpetuate a profound maternal morphological and functional neuroplasticity, which begins with pregnancy and birth [74,75]. A baby's cry triggers elevated maternal SNS activity. Chronically high levels of SNS arousal interfere with parental sleep efficiency; decrease neuronal activity in the hippocampus, where detailed positive memories are stored; and suppress serotonin. We propose that chronically high levels of SNS arousal throughout the first few months of an infant's life may result in potentiation of neural pathways in the maternal amygdala, so that the mother becomes sensitised to bouts of unsoothable crying. Whilst multiple factors predispose mothers to postnatal depression, the elevated serotonin of chronic SNS hyperarousal

may help explain why mothers of crying babies are at increased risk [10]. Oxytocin, triggered by visual and tactile contact regardless of feeding method, and by breastfeeding, downregulates neuronal anxiety circuits. Those mothers who feel most in control when their baby cries demonstrate increased activation of their pre-frontal cortex, which also downregulates neuronal anxiety circuits [14,46,76].

Neurohormonal mechanisms which underlie clinical intervention

The translation of a metanarrative review of the heterogeneous and interdisciplinary evidence concerning cry-fuss problems in the first months of life into a systematic, five-domain clinical intervention (“The Possums Approach”) is detailed elsewhere [31,73,77,78]. This intervention aims for early identification and management of problems that disrupt maternal–infant neurobehavioural synchronies. Regardless of feeding method, our intervention systematically addresses relevant factors in each of five domains, ‘baby's health and ‘mother's health,’ and the three neurobehavioural domains of ‘feeds,’ ‘sensation’ and ‘sleep.’ From the perspective of the underlying neurobiological mechanisms, clinical intervention aims to upregulate the anxiolytic dopaminergic, oxytocinergic and parasympathetic nervous systems, and to downregulate anxiety-inducing SNS and HPA axis activity, in both mother and baby. Intervention also aims to increase the baby's levels of plasma cholecystokinin, inducing satiety, relaxation and sleep. It aims to help the mother consolidate memories of pleasurable experiences with her baby in her hippocampus, and to strengthen the activity of her pre-frontal cortex, both of which dampen amygdala activity. To these ends, individualised plans are developed with the parents, which work systematically through the five domains, and which are aligned with their unique values and philosophies; flexibility and experimentation are supported as a key to resilience; and cross-professional communication and referral occur as necessary.

There is substantial literature exploring the relationship between infant crying and maternal–infant psychological attachment [79]. Clinical consideration of the five domains optimise the maternal–infant neurobiological synchronies, maternal prefrontal cortex activity, and family resilience which underpin healthy psychological attachment. Infantcare practises which promote a sensible alignment with innate maternal–infant neurobehaviour, in the context of appropriate identification and management of clinical problems, make life easier, not harder, for twenty-first century mothers with new babies as they manage complex and demanding roles and responsibilities.

Discussion

This neurobiological explanatory model for infant cry-fuss problems in the first few months of life (“The Possums Model”) has been developed from a synthesis of the evidence across multiple disciplines. The model proposes first, that crying in the first three to four neurodevelopmentally sensitive months signals activation of the HPA axis and adrenergic neuronal circuitry in response to perceptions of discomfort or threat. Second, this neurobiological model proposes that susceptible infants are conditioned by early stress, for example, by unidentified feeding difficulties, into a sensitised stress response which usually settles with neurodevelopmental maturity at three to four months of age. Third, a neurobiological model proposes that bouts of prolonged and unsoothable crying result from positive feedback loops in the HPA and adrenergic systems. Fourth, a neurobiological model proposes that epigenetic modulation of the infant's limbic neuronal

circuitry helps explain correlations between regulatory problems in the first months of life, and behavioural problems including feeding problems in later childhood.

The model explains why problem crying in the first few months of life, although usually self-limiting, is not a trivial complaint, but a marker of risk. Complex variables moderate infant and family susceptibility and resilience, including psychosocial, environmental, genetic, epigenetic, developmental, and neurochemical factors [80]. Due to the complexity of these moderating factors, retrospective or prospective reductive methodologies applied to establish causal links between infant crying in the first months of life and mental or physical health problems in later childhood or adulthood face significant limitations.

Nevertheless, unsettled behaviour in the first months of life has been linked in longitudinal birth cohort studies of over 4000 infants with long-term feeding problems, behavioural problems including Attention Deficit and Hyperactivity Disorder, and poorer cognitive performance in later childhood [81–83]. Another longitudinal birth cohort study of 1327 infants links regulatory problems between 2 and 10 months of age with a nearly threefold risk of functional somatic symptoms at school-age [84]. A retrospective study of 1467 children with sensory processing and autistic spectrum disorders found an increased rate of early regulatory problems [85]; a prospective study of 96 infants diagnosed with excessive crying in the first twelve weeks demonstrated an increased incidence of allergy and behavioural problems at ten years of age [86]; and a retrospective study of 208 children older than six years presenting with migraines showed they were more likely to have cried excessively in the first few months of life [87]. Widespread unnecessary medicalization of cry-fuss problems in the first three to four months predisposes to allergy and GORD in later infancy; allergy is associated with poorer neurodevelopmental outcomes [88], and GORD is associated with maternal psychological disturbance and persistent infant feeding problems [89]. A large multi-centre trial demonstrates that cry-fuss problems predispose mothers to postnatal depression [10]; another large-scale study demonstrates that crying babies are at risk of physically abusive behaviours from caregivers [11]. Breastmilk substitution, a common response to unsettled infant behaviour, is associated with health risks and substantial health system costs [9,23].

Given the significance of these correlations, existing attempts to quantify the cost of crying babies in the first few months of age, such as a 1998 estimate of £65 million annually in the UK for related consultations, may, from a health economics perspective, be only the tip of the ice-berg [90].

Conclusion

Despite the self-limiting nature of the condition for most, unsettled behaviour in the first few months of life requires early, integrated intervention. Our synthesis of the heterogenous evidence across multiple disciplines elucidates the underlying neurobiological mechanisms of infant crying, and the underlying neurobiological mechanisms of a five domain interdisciplinary clinical intervention. This shared explanatory framework aims to facilitate collaboration between researchers from different disciplines, and consistency of advice by health professionals when they are consulted by families whose babies have cry-fuss problems in the first few months of life, in order to optimise infant neurodevelopment and maternal and family resilience, from the very beginning.

Conflict of interest statement

Pamela Douglas and Peter Hill declare that they have no conflict of interest to report.

Competing interests

None declared.

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Author's contributions

PSD conceived of the study. PSH participated in conceptualization and critique of concept. PSD drafted the manuscript. PSH critically reviewed and edited the manuscript. Both authors approve the final version.

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