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NARRATIVE REVIEW

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Association of Parkinson's disease to Parkinson's plus syndromes, Lewy body dementia, and Alzheimer's dementia

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Abstract

Background: Parkinson's disease (PD) is a condition that affects movement and is usually seen in those over the age of 50. It is caused by the death of dopaminergic neurons, particularly in the substantia nigra. PD has shifted from being perceived as an uncommon condition to a significant neurological illness, mostly due to the increasing number of elderly individuals and the impact of environmental factors. Parkinson's plus syndromes, such as progressive supranuclear palsy (PSP), multiple system atrophy (MSA), corticobasal degeneration (CBD), and vascular Parkinsonism (VaP), provide difficulties in distinguishing them clinically from PD since they have similar characteristics.

Methodology: A thorough examination was performed utilizing the PubMed, Medline, Scopus, and Web of Science databases. The search utilized specific keywords like "Parkinson's disease," "Parkinson's plus syndrome," "Lewy body dementia," "Alzheimer's dementia," "progressive supranuclear palsy," and "multiple system atrophy." The selection criteria were aimed at English-language literature, with a particular focus on examining the connection between PD and associated disorders or dementias.

Results and Discussion: Parkinson's plus syndromes, such as PSP, MSA, CBD, and VaP, exhibit unique clinical characteristics, imaging results, and diverse reactions to levodopa. This makes it difficult to distinguish them from PD. LBD is characterized by Lewy bodies containing α-synuclein, which leads to both motor and cognitive deficits. PD and Alzheimer's disease (AD) exhibit a complex interaction, including common pathogenic processes, genetic predispositions, and clinical characteristics of dementia.

Conclusion: The interrelatedness of PD, Parkinson's plus syndromes, LBD, and AD highlights the significance of comprehending shared disease-causing processes. Aberrant protein clumping, impaired functioning of mitochondria, increased oxidative stress, and inflammation in the brain are common factors

which can be addressed for specific treatments. More research is essential for understanding complicated connections and developing effective therapies for these sophisticated neurological illnesses.

KEYWORDS

Alzheimer's dementia, Lewy body dementia, multiple system atrophy, Parkinson's disease, Parkinson's plus syndrome, progressive supranuclear palsy

1 | INTRODUCTION

A primarily motor disorder that usually begins after 50 years old age and is caused by the loss of dopaminergic neurons, especially in the substania nigra is the common description of Parkinson's disease. The disease is progressive and was first clearly described by James Parkinson[1] after whom it's named. PD also occurs with the accumulation of α-synuclein (intracellular eosinophilic inclusions) containing Lewy bodies. Rapid eye movement sleep behavior disorder (RBD) is more likely in men >50 years old and has a strong association with the future development of α-synuclein-induced PD. Resting tremors (Pill-rolling), rigidity (cogwheel), akinesia/bradykinesia, and postural instability are some of the main symptoms of PD. Even though it is mostly present after 50 years, it is also seen in patients before 50 years of age.[2] There is a 30%–70% loss of neurons seen in the substantia nigra on examination after the motor symptoms start showing.[3] For a long time, PD is considered a rare disease but the increase in the aging population and the side effects of environmental changes and industrialization has now made it the major cause of neurological disorders.[4] Steele mentioned that different clinical variants of the disease occur as different parts of the brain are affected at different times and degrees.[5] These are called Parkinson's plus syndromes. Shy drager syndrome (multisystem atrophy-Parkinsonian type) (MSA-P), multisystem atrophy-cerebellar type (MSA-C), progressive supranuclear palsy (PSP), corticobasal degeneration are the major types of Parkinson-plus syndromes. Multisystem atrophy is also a progressive neurodegenerative disorder that is often more damaging than PD.[6] It was found that the accumulation of α-synuclein in oligodendrocytes begins the loss of cells in the brain and causes MSA.[7] MSA-P causes dysautonomia (especially orthostasis). MSA-C is the cerebellar type. PSP causes oculomotor deficits with no tremors. Corticobasal degeneration causes impaired cognition, sensory deficits, dystonia, and myoclonus. PSP was described by Steele as a syndrome that causes vertical gaze palsy, progressive rigidity, mild dementia, and pseudobulbar palsy.[8]

Highlights

- We discusses the association between Parkinson's disease (PD) and related syndromes like Parkinson's plus syndrome, Lewy body dementia (LBD), and Alzheimer's dementia (AD).
- Parkinson's plus syndrome includes disorders like PSP, MSA, and CBD, sharing similar symptoms with PD but exhibiting additional features due to progressive neurodegeneration beyond the dopaminergic system.
- Shared pathogenic mechanisms among these disorders include abnormal protein aggregation, mitochondrial dysfunction, oxidative stress, and inflammation.
- We also emphasized the potential for developing targeted therapies and diagnostic approaches by understanding these shared mechanisms, impacting treatment strategies, prognosis, and quality of life for patients.

2 | METHODOLOGY

A thorough search was conducted in the PubMed, Medline, Scopus, and Web of Science databases to gather relevant information for this review article.

The search strategy involved using a combination of keywords and phrases such as “Parkinson's disease,” “Parkinson's plus syndrome,” “Lewy body dementia,” “Alzheimer's dementia,” “progressive supranuclear palsy,” and “multiple system atrophy” using a combination of AND/OR phrases. A detailed search strategy for each database is available in Supporting Information File 1.

We limited the search to articles published in English to ensure accessibility and comprehension of the literature. The inclusion criteria were predefined to identify studies that provided relevant insights into the association between PD and the mentioned syndromes or dementias. After the initial search, the titles and abstracts of the identified articles were screened to exclude irrelevant studies. The included studies were critically analyzed and evaluated to extract key information pertaining to the shared pathophysiology, clinical implications, and diagnostic challenges associated with the relationship between PD, Parkinson's plus syndromes, LBD, and AD.

3 | RESULTS AND DISCUSSION

3.1 | Parkinson-plus syndromes

Several entities are described to be associated with PD but differ from this condition depending on the response to levodopa (present or absent) (Table 1). There are other Parkinson-associated syndromes, which are challenging to differentiate from PD itself clinically.

TABLE 1 An overview of clinical features, imaging, treatment, and prognosis of Parkinson-plus syndromes.

Parkinson-plus syndromes	Clinical features	Imaging findings	Response to levodopa and prognosis
Progressive supranuclear palsy	Early balance difficulties, personality changes, visual disturbances, abnormal eye movements, vertical gaze palsy that progresses to fixed gaze, and autonomic dysfunction	MRI reveals midbrain atrophy, "hummingbird sign"	Poor response to levodopa, faster and more severe disability progression compared to Parkinson's disease
Multiple system atrophy	Early autonomic dysfunction	MRI shows hot-cross-bun sign in the pons	Poor response to dopaminergic therapies, drug-induced dyskinesias, and death occurs within 7–9 years
Corticobasal degeneration	Asymmetric progressive parkinsonism, alien limb phenomena, supranuclear palsy, Alzheimer's, and frontotemporal degeneration	MRI shows asymmetric focal cortical atrophy, superior parietal lobe involvement	
Vascular Parkinsonism	Gait instability progressing to incontinence and cognitive impairment	MRI shows extensive subcortical white matter lesions, and involvement of basal ganglia	Reduced response to levodopa, associated with vascular lesions with an overlap with Binswanger's illness

Parkinson's plus-syndromes include PSP,[9] multiple system atrophy (MSA), corticobasal degeneration (CBD), and vascular Parkinsonism (VaP).

Due to the presence of most of the clinical features described in PD, the term *Parkinsonism* is given to all these pathologies. Bradykinesia as stated before needs to be present, however, certain other characteristics which may be subtle but present make the differential diagnosis possible. In the physical examination aimed to assess bradykinesia, it is described that we must allow the patient to repeat the various tests (repetitive finger tapping, sequential finger tapping, and repetitive hand opening) for 15 s minimum. While postural instability is not an early indication or hallmark of Parkinson's disease, its presence should alert the doctor to the possibility of an atypical Parkinsonian condition. The age of onset is particularly crucial since atypical Parkinsonian illnesses appear sooner than Parkinson's disease. Although clinical evaluation is essential, diagnosis is based on a thorough medical history, timeline of symptoms, thorough physical examination, and early detection of crucial clinical indicators, as well as being aware of the differential diagnosis and expertise.[9]

3.2 | Progressive supranuclear palsy

It is also referred to as Steele–Richardson–Olszewski[10] (Richardson syndrome). Patients present with early difficulties in balance, changes in personality (apathy), visual disturbances, and abnormal eye movements, which over time become reduced, first in a vertical plane to becoming fixed eventually. Severe autonomic dysfunction is not developed in patients with this condition. On imaging, the magnetic resonance imaging (MRI) images show midbrain atrophy, creating the so-called "hummingbird sign." The progression of PSP disability is faster and more severe than in PD.

However, other clinical forms of this entity have been identified in the literature, including PSP-Parkinsonism, the most common PSP variant. PSP-Parkinsonism frequently manifested clinically with an asymmetrical incidence and a moderate first response to levodopa, particularly in the first year of illness initiation, and tremor, thus giving the impression that it may be Parkinson's disease.

PSP-Parkinsonism usually has a better prognosis; however, the illness can progress to PSP-Richardson syndrome over time. As a result, it is possible that it is clinically equivalent to Parkinson's disease and PSP. The clinical and phenomenology of PSP-Richardson illness and PSP-Parkinsonism may become comparable after a few years.[9,10]

3.3 | Multiple system atrophy

This neurodegenerative disease is rare. The substantia nigra here suffers neuronal degeneration (subtypes: MSA-P; MSA-C).

In this pathology, autonomic dysfunction is characteristic and often dominates the early clinical picture, making motor symptoms appear later in the disease. This diagnosis is considered in patients presenting increased urinary urgency, constipation, and orthostatic hypotension. In males, erectile dysfunction is common.[11]

MSA-P presents predominantly with parkinsonian features and was previously known as striatonigral degeneration.

MSA-C predominantly presents cerebellar features (ataxia, imbalance, dysmetria, dysarthria, and nystagmus) and was referred to as olivopontocerebellar atrophy.

It is also characterized by a slow evolution of symptoms which often leads to a mistake in diagnosis. Its epidemiology describes a prevalence of 4–5 cases per 100,000 individuals and has an incidence of 0.6 cases per 100,000 individuals/year.

It responds poorly to dopaminergic therapies and drug-induced dyskinesias may also appear, and usually exhibits features similar to somewhat symmetrical Parkinsonism. As mentioned earlier, besides clinical observations, it is recommended to measure blood pressure while the patient is lying down and standing up, to identify orthostatic hypotension. On the MRI, the *hot-cross-bun* sign may be seen as a cross-shaped signal enhancement in the pons, typical of MSA but not pathognomonic.

Both PD and MSA must be clinically differentiated, Because the conditions are linked with the production of filamentous α-synuclein inclusion bodies as the distinguishing neuropathological feature. Parkinson's disease is identified as a movement disorder that can be treated with levodopa medication, whereas MSA presents a combination of extrapyramidal, cerebellar, and autonomic features that do not respond to therapy and typically lead to death within 7–9 years.[11]

The presence of intraneuronal cytoplasmic and neuritic inclusions is the distinguishing feature of PD, MSA is distinguished by the cytoplasmic inclusions located in the glial cells or intranuclear neuronal inclusions and neuropil threads.[9]

Furthermore, because both conditions share a main pathogenic feature of the substantia nigra dopaminergic neurodegeneration, α-synuclein in patients' brains suffering from MSA were not uniformly detected in dopaminergic neurons as was the case for PD patients. This suggests that the rate of neuronal death containing MSA α-synuclein complexes may be higher than the death rate of neurons in PD.[11]

3.4 | Corticobasal degeneration

This syndrome describes an asymmetric progressive Parkinsonism with motor abnormalities, often affecting one limb only. The alien limb phenomena, defined by involuntary gripping, motions that are purposeless, or elevation of a limb that is apraxic,[12] refers to the sense that the diseased limb does not belong to the patient. It can also be present with supranuclear palsy, Alzheimer's disease, and frontotemporal degeneration.

It usually appears in the 5th–7th decades of a person's life, with an incidence of 1 case per 100,000 individuals/year. MRI shows asymmetric focal cortical atrophy, usually in the superior parietal lobule as the most constant feature, basal ganglia atrophy bilaterally along with corpus callosum atrophy. CBD has a distinct pattern of atrophy from PSP due to atrophy in the posterolateral and medial frontal cortical areas and relatively maintained brainstem structure.

3.5 | Vascular Parkinsonism

As the name suggests, it arises due to vascular lesions and was initially described by Critchley in 1929. VaP is suspected in the clinical picture of lower-body Parkinsonism shown as gait instability,[13] which progresses to incontinence and finally cognitive impairment. Comparable to the atypical Parkinson-plus syndromes, responsiveness to Levodopa is missing or significantly reduced,[14] and extrapyramidal symptoms are present. Brain MRI demonstrates extensive lesions in the subcortical white matter, predominantly affecting the basal ganglia, in lacunar form, and/or "Binswanger" type subcortical white matter vasculopathy (small vascular dementia). Although uncommon, a single striatal infarct, striatal cribriform cavities, or ischemic changes in the substantia nigra have all been reported.[13] Because of the widespread overlap, it's debatable if VaP and Binswagner illness are part of the same disease.

4 | RELATIONSHIP TO LEWY BODY DEMENTIA

Lewy bodies are neuronal intracytoplasmic inclusion bodies of misfolded proteins always found predominantly in the substantia nigra with α-synuclein being the primary structural component that displaces other cell components. In PD, the Lewy bodies are always spotted in substantia nigra, locus coeruleus, dorsal vagal nucleus, nucleus basalis of Meynert and hypothalamus, and sometimes in other sites such as the cerebral cortex, thalamus, and autonomic ganglia.[14] The presence of Lewy bodies marks the loss of nigral neurons and increased neuronal destruction.[14] Lewy bodies increase progressively by the 6th to 9th decade, indicating the disease's progression. The prevalent symptoms of Lewy body dementia are motor and cognitive impairment along with behavioral and sleep disturbances.

Parkinson's disease patients may exhibit both dementia with Lewy bodies (DLB) and Parkinson's disease with dementia (PDD), which are two separate manifestations of the same underlying disease process that results in the deposition of α-synuclein. The varied temporal presentations of extrapyramidal motor symptoms help clinically identify PDD from LDB alone.[15]

Parkinson's disease dementia begins as a movement disorder with symptoms congruent to PD advancing towards cognitive and behavioral symptoms later on. However, it is challenging to determine who may acquire dementia if an individual has PD. Neurotransmitter dysregulation has been linked to cognitive symptoms but reduced cholinergic transmission is presently believed to be the key mechanism in the emergence of cognitive impairment.[14]

Although LBD is incurable, to treat dementia and its concomitant behavioral symptoms in PDD and DLB, cholinesterase inhibitors are utilized to temporarily alleviate the symptoms.

5 | RELATIONSHIP TO ALZHEIMER'S DEMENTIA

In many individuals, Parkinson's and Alzheimer's disease can co-occur. PD involves progressive loss of dopaminergic neurons in the substantia nigra and intracellular accumulation of α-synuclein-containing

Lewy bodies, leading to characteristic motor symptoms including bradykinesia, rigidity, tremor, and postural instability (Figure 1).[16,17] In contrast, AD is characterized by extracellular deposition of amyloid beta plaques and intraneuronal neurofibrillary tangles composed of hyperphosphorylated tau protein. This results in insidious cognitive decline, specifically impacting memory, visuospatial skills, and executive functions.[18]

Although PD and AD have distinct clinical profiles and pathological hallmarks, considerable scientific evidence demonstrates an overlap between the two diseases. Population-based autopsy studies reveal a high burden of AD pathology, including neocortical amyloid plaques and neurofibrillary tangles, in post-mortem brains of PD patients.[19] Large epidemiological studies and meta-analyses consistently show PD patients have a significantly increased risk and frequency of developing AD dementia compared to age-matched controls without PD.[20,21] After 20 years, up to 80% of PD patients develop dementia (PDD), with AD changes contributing substantially to their cognitive decline in most cases.[22]

The pathological mechanisms linking PD and AD are not fully elucidated but likely involve direct interactions between α-synuclein and AD pathology. Neuronal Lewy bodies immunoreactive for α-synuclein are found in 40%–60% of autopsy-confirmed AD brains, particularly in the amygdala, a region critical for memory.[23] Accumulation of misfolded α-synuclein may promote hyperphosphorylation of tau, neuritic plaque deposition, and amyloid aggregation in AD.[24] Conversely, amyloid beta oligomers can trigger α-synuclein fibrillization and transmission between neurons.[25] These synergistic interactions between α-synuclein and AD pathology likely contribute to more rapid cognitive decline in patients with both PD and AD.

Chronic neuroinflammation is another shared mechanism linking PD and AD pathogenesis. Prolonged microglial activation and elevated pro-inflammatory cytokines such as tumour necrosis factor-α, interleukin--1β (IL-1β), and IL-6 are found in the CNS of both PD and AD patients.[26] Sustained inflammation creates a neurotoxic environment, propagating protein aggregation, synaptic dysfunction, and neuronal death. Post-mortem studies reveal greater microglial activation in PD patients with PDD compared to those without dementia, supporting an inflammatory basis for cognitive decline.[27]

The dysfunction occurring in the mitochondrial along with the oxidative damage also play key roles in both PD and AD. Positron emission tomography imaging demonstrates reduced metabolism of

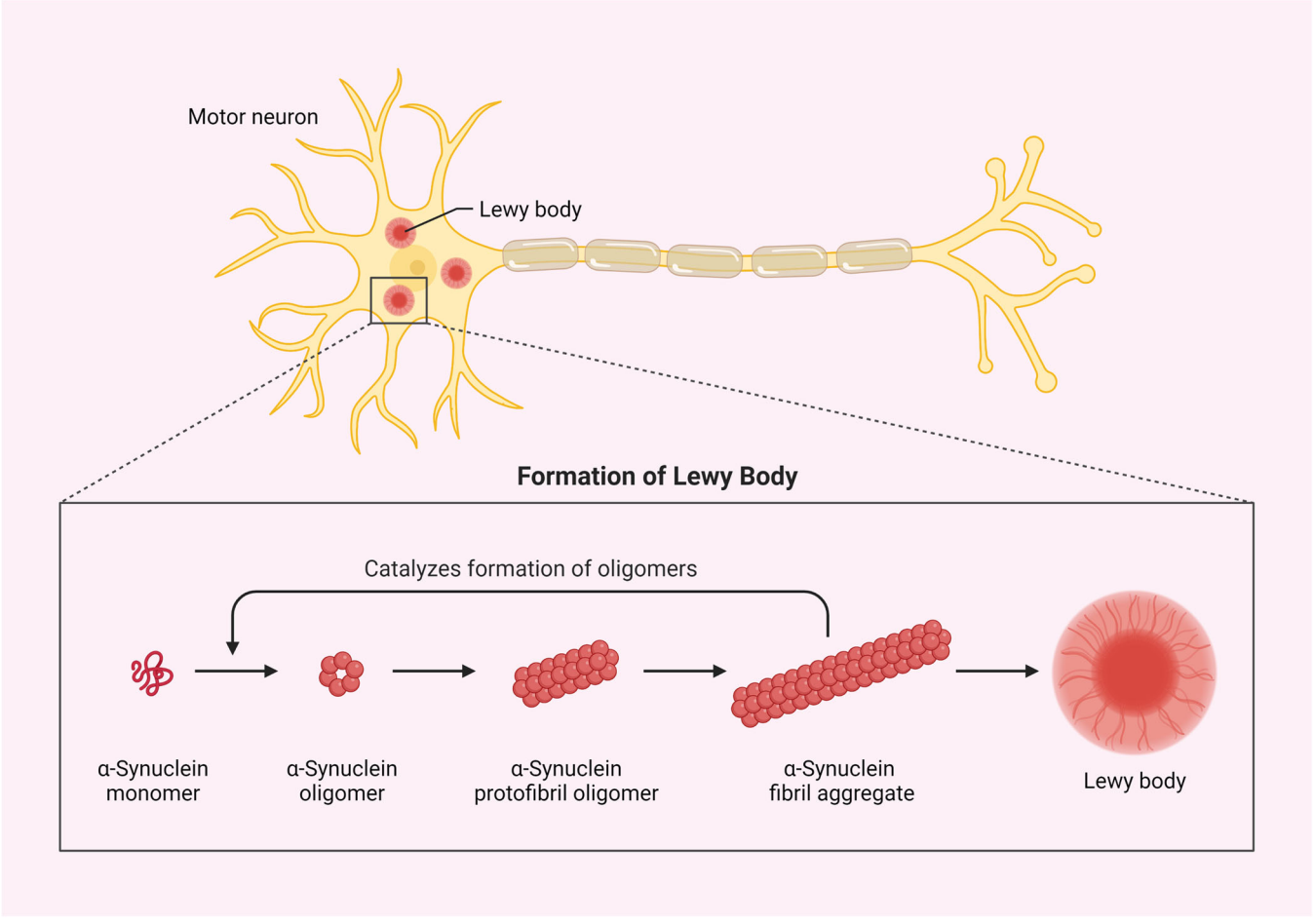

FIGURE 1 Formation of Lewy body from α-synuclein. α-Synuclein fibril aggregate from the monomeric form.

glucose in the temporoparietal and posterior cingulate cortices of PD patients with mild cognitive impairment, resembling metabolic patterns in early AD.[28] Impaired mitochondrial dynamics and increased reactive oxygen species likely contribute to cellular dysfunction in both diseases.[29]

Genetic studies also reveal an overlap between PD and AD. Carriers of the apolipoprotein E-epsilon 4 allele have a heightened risk for the development of both PD dementia and AD.[30] Polymorphisms in microtubule-associated protein-tau similarly increase susceptibility to cognitive decline and dementia in PD populations.[31] Understanding the genetic risks shared between PD and AD may lead to earlier identification of at-risk patients and targeted preventative therapies.

In summary, a growing body of research demonstrates important links between PD and AD in terms of pathological mechanisms, genetic risks, and clinical features of dementia. Further investigation into the molecular intersections between the two diseases will hopefully enable development of promising disease-modifying therapies that target shared pathogenic processes.

6 | CONCLUSION

Parkinson's disease is closely associated with other neurological conditions, including Parkinson's plus syndromeplus syndrome, Lewy body dementia, and Alzheimer's dementia. These syndromes share common pathogenic mechanisms such as abnormal aggregation of proteins, dysfunction in mitochondria, oxidative stress, and inflammatory processes. Understanding these shared mechanisms holds promise for developing targeted therapies and diagnostic approaches, which can have a significant impact on treatment strategies, prognosis, and quality of life for patients. However, accurate diagnosis and differentiation among these syndromes remain challenging, requiring advanced imaging techniques, biomarkers, and multidisciplinary collaboration. Further research is needed to elucidate the complex relationships and develop effective interventions for these interconnected disorders.

7 | LIMITATIONS

Despite the valuable insights provided by this review, there are certain limitations to consider. First, the literature search was restricted to English-language publications, potentially excluding relevant studies in other languages. Second, while efforts were made to include comprehensive databases, there is a possibility of missing some studies that may have contributed to the topic. Additionally, the review primarily focused on the shared pathophysiology and clinical implications, and further investigation into specific treatment modalities and long-term outcomes is warranted. Further, the possibility of the presence of information bias cannot be ruled out.

AUTHOR CONTRIBUTIONS

Priyadarshi Prajjwal: Conceptualization; methodology; validation; writing—original draft. **Nikhil Deep Kolanu**: Methodology; resources; validation; writing—original draft. **Yeruva Bheemeswara Reddy**: Conceptualization; validation; writing—original draft. **Aneeqa Ahmed**: Validation; visualization; writing—original draft. **Mohammed Dheyaa Marsool Marsool**: Validation; visualization; writing—original draft; writing—review and editing. **Krupanagram Santoshi**: Validation; writing—original draft; writing—review and editing. **Himani Harshad Pattani**: Visualization; writing—original draft; writing—review and editing. **Jobby John**: Visualization; writing—original draft. **Kiran Kishor Chandrasekar**: Validation; visualization; writing—original draft. **Omniat Amir Hussin**: Visualization; writing—original draft.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

All the data used in this study are present within the study itself. No new data were created or analyzed in this study.

TRANSPARENCY STATEMENT

The lead author Omniat Amir Hussin affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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