A Review of Functional Neuroimaging in People with Down Syndrome with and without Dementia

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\textbf{Abstract}

\textbf{Background:} Individuals with Down syndrome (DS) are at high risk of dementia which is difficult to diagnose in DS. Neuroimaging has been identified as a potential tool to aid diagnosis by detecting changes in brain function. We carried out a review comparing functional neuroimaging in DS individuals with and without dementia. \textbf{Summary:} A literature search was conducted using PubMed to identify relevant studies. In DS subjects with dementia, fluorodeoxyglucose-positron emission tomography (PET) studies showed glucose hypometabolism particularly in the parietal and/or temporal regions whilst magnetic resonance spectroscopy studies showed increased myoinositol and decreased N-acetylaspartate. Ligand-based PET studies revealed significant Pittsburgh compound B binding in DS subjects over the age of 40, particularly if they had dementia. \textbf{Key Messages:} Neuroimaging may aid the early detection of dementia in DS; however, further longitudinal studies are required.

\section*{Introduction}

Individuals with Down syndrome (DS) are at an increased risk of cognitive decline and dementia compared to the general population [1]. In particular, those who are aged 40 years and over show an age-related cognitive decline with early memory involvement as well as the presence of amyloid plaques and neurofibrillary tangles deposited throughout the brain [2–4]. These neuropathologic changes are typically pathognomonic for Alzheimer’s disease (AD).

The prevalence rates of AD in DS are reported to be of less percentage in 30–39 year olds, 10 and 25% in 40–49 year olds, between 20 and 50% in 50–59 year olds, and between 30 and 75% in those aged 60 years and over [5]. This increased risk of AD in DS is thought to be due to the extra copy of chromosome 21. It is this trisomy 21 which leads to an overexpression of the amyloid precursor protein gene which is located on chromosome 21. This in turn leads to the early onset and rapid accumulation of β-amyloid plaques in the brain [6–8].

Dementia can be difficult to diagnose in DS for various reasons. For example, the accuracy of DS-specific cognitive tests has been debated as it has been difficult to
### Table 1. FDG-PET studies on DS with and without dementia

| Study          | Study design           | Region of interest                                                                 | Cohort                                                                 | Clinical data                                                                 | Main findings                                                                                                                                                                                                 |
|---------------|------------------------|-----------------------------------------------------------------------------------|----------------------------------------------------------------------|--------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Cutler [18]   | Case control           | Right cerebral hemisphere, frontal lobe, parietal lobe, temporal lobe, occipital lobe | \( n = 10 \) nondemented DS (aged 19–23), \( n = 2 \) nondemented DS (aged 41–64), \( n = 2 \) demented DS (aged 41–64), \( n = 14 \) controls (aged 20–35) and \( n = 19 \) controls (aged 40–60) | Not stated                                                                    | Age-related declines in brain metabolism were found in the middle-aged (nondemented) DS subjects and further reductions observed in the demented DS subjects                                                                 |
| Schapiro et al. [19] | Case report           | Right and left hemispheres, orbital frontal, superior frontal, precentral, postcentral, inferior parietal, occipital cortex, temporal, basal ganglia, cerebellum, cingulate, parietal association/sensorimotor, lateral temporal association/occipital | \( n = 1 \) DS (aged 47 with autopsy confirmed AD), \( n = 13 \) nondemented DS (aged 19–33) | PPVT -revised, the block patterns subtest from the Hiskey Nebraska tests of learning aptitude, WISC-R block design subtest, extended block design test, digit span, block tapping, object span, visual recognition memory | The demented DS subject’s mean hemispheric CMRglc was 28% less than the group of 13 nondemented younger DS subjects. Marked glucose hypometabolism evident in parietal and temporal lobes |
| Schapiro et al. [4] | Case control           | Parietal, lateral temporal, sensorimotor, occipital                                | \( n = 20 \) DS (aged 19–34), \( n = 5 \) nondemented DS (aged 45–63), \( n = 4 \) demented DS (aged 45–63) and \( n = 13 \) controls (aged 22–38) | DSMSE, WISC-R block design subtest, Extended block design Test, Hiskey Nebraska block pattern subtest, design span, PPVT (revised), Stanford-Binet, digit span, Block tapping, Object span | Demented DS showed glucose hypometabolism with relatively greater involvement of parietal-temporal association neocortices and relative sparing of primary sensorimotor neocortex, cerebellum, thalamus, and caudate and lenticular nuclei |
| Azari et al. [20] | Case control           | Prefrontal, premotor, parietal                                                   | \( n = 15 \) young DS, \( n = 10 \) older nondemented DS, \( n = 4 \) demented DS and \( n = 15 \) young controls | PPVT, MMSE and NINCDS-ADRDA criteria                                                                 | Compared with young DS and old nondemented DS, old demented DS showed reduced absolute metabolic rates in all ROIs as well as the whole-brain. This reduction was particularly evident in the left premotor and parietal lobe |
| Dani et al. [21]  | Longitudinal cohort study | Parietal, temporal and sensorimotor primary cortex                                | \( n = 12 \) nondemented DS (aged 31–59) on longitudinal evaluation \( n = 2 \) (aged 49 and 50 years) became demented | DSMSE                                                                 | The 2 subjects who became demented, exhibited a rapid decline in glucose metabolism in the parietal and temporal regions, whilst the nondemented DS subjects did not show changes in glucose metabolism over the 7 years |
| Sabbagh et al. [24] | Case control           | Frontal, temporal, parietal, anterior cingulate, posterior cingulate and precuneus | \( n = 5 \) demented DS, \( n = 12 \) nondemented DS and \( n = 9 \) normal controls | DLD, MMSE, BPT, SIB, the VABS–second edition | DS demented subject showed hypometabolism in posterior cingulate, lateral parietal, temporal and frontal regions. Furthermore, demented DS had lower glucose metabolic rates in additional frontal regions than controls |
establish reliable cutoff scores in these tests in the first place, given the heterogeneity of intellectual functioning amongst the DS population [9, 10]. Additionally, individuals with DS are likely to struggle with communication leading the assessor to rely on information provided by family and/or carers to make a diagnosis of dementia which will be subjective and therefore not always reliable. Given this, neuroimaging may present as an objective way in which important information can be obtained to potentially support a diagnosis of dementia in individuals with DS [9].

There are relatively few DS and dementia neuroimaging studies available [11, 12]. This is thought to be due to the challenges in scanning people with DS and its time-consuming and costly nature [9]. Additionally, recruitment of adequate numbers of age-matched DS subjects with and without AD, who are also able to tolerate MRI has proved difficult [13]. Furthermore, neuroimaging of DS subjects is associated with high levels of motion artifact which can affect the quality of the images and though sedatives can be used in the general population with regard to scanning, the use of these in the DS population raises an ethical dilemma [5, 14, 15].

Despite this, neuroimaging may help researchers identify early structural, functional, neurochemical, and metabolic changes which occur with AD in DS, potentially allowing for a better understanding of AD pathogenesis. This will hopefully lead to a clearer and more effective diagnostic protocol for this population. Furthermore, given the age-dependent neuropathology of AD in DS, it may also be possible to monitor the progression of AD in DS longitudinally with neuroimaging focused on particular biomarkers, thereby providing researchers with vital information regarding potential targets for therapeutic intervention even in the preclinical phase [9, 11]. The aim of this review is to provide an overview of functional neuroimaging studies within this field over the past 80 years or so.

## Review

In order to identify relevant articles on neuroimaging in DS, with and without dementia, we searched the PubMed database until 31 December 2020. All reference lists from any systematic reviews identified in the initial search were hand searched to find any additional studies of interest. We included studies that were in the English language, peer reviewed, and included brain functional neuroimaging conducted in people with DS with any dementia, of any age and from both genders.

### Table 1 (continued)

| Study          | Study design | Region of interest                                                                 | Cohort                                                                 | Clinical data | Main findings                                                                                                                                 |
|----------------|--------------|-------------------------------------------------------------------------------------|----------------------------------------------------------------------|---------------|---------------------------------------------------------------------------------------------------------------------------------------------|
| Lao et al.     | Cross-sectional | Anterior cingulate, frontal cortex, parietal cortex, precuneus, striatum, temporal cortex, hippocampus | $n = 16$ nondemented DS (average age 35 years – PiB-negative), $n = 5$ nondemented DS (average age 47 years – PiB-positive), $n = 3$ demented DS (average age 49 years) | PPVT          | Given small sample of demented DS ($n = 3$), study did not have power to identify differences between demented and nondemented DS. Instead used nested models to demonstrate influence of nondemented PiB(+) and demented individuals on the associations between Aβ burden, metabolism, and GM volume. Overall demented DS subjects appear to have negative association with PiB SUVR, FDG SUVR, and GM volume. |
We identified 7 studies that investigated brain metabolism using fluorodeoxyglucose-positron emission tomography (FDG-PET) (Table 1), 4 which investigated brain neurochemistry using magnetic resonance spectroscopy (MRS) (Table 2) and 4 which investigated amyloid accumulation within the brain using ligand-based PET (Table 3). All studies sought to compare DS patients with dementia to those without dementia.

**FDG-PET Studies**

FDG-PET studies have been vital in the assessment of brain metabolism in AD and DS. Research indicates that reductions in regional brain metabolism are evident in AD and that these reductions are roughly proportional to the severity of the dementia. In DS subjects with dementia, these reductions appear to be greater in the association sensory and motor neocortical regions (as opposed to the primary regions) and correlate with cognitive decline, neuropathology, and neuronal loss [9, 16, 17].

Regarding the 7 studies which investigated brain metabolism, DS subjects with dementia demonstrated glucose hypometabolism relative to nondemented DS subjects or controls within the same brain regions (see Table 1). In a study from the 1980s, age-related declines in brain metabolism were found in the middle-aged nondemented DS subjects whilst further reductions were observed in the demented DS subjects [18]. A 1988 case report revealed the cerebral metabolic rate of glucose (CMRglc) to be 28% less in an older DS subject with dementia than young nondemented DS subjects and significant glucose hypometabolism was noted in the parietal and temporal lobe association cortices in particular [19]. Older DS subjects with dementia have demonstrated the same pattern of abnormal glucose metabolism as seen in subjects with AD, where newer association areas of parietal and temporal neocortices are mainly affected but there is relative sparing of the primary sensorimotor neocortex, cerebellum, thalamus, and caudate and lentilcular nuclei [4]. Compared with young nondemented DS subjects and old nondemented DS subjects, old DS subjects with dementia showed reduced absolute metabolic rates in the association prefrontal, premotor, and parietal regions well as in the whole-brain, again supporting the findings of earlier studies [20].

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**Table 2. MRS studies on DS with and without dementia**

| Study          | Study design     | Region of interest                          | Cohort                                                                 | Clinical data                                                                 | Main findings                                                                                     |
|----------------|------------------|---------------------------------------------|------------------------------------------------------------------------|--------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|
| Shonk and Ross [33] | Case control     | Occipital cortex, parietal white matter      | n = 23 nondemented DS (age unknown), n = 1 demented DS                 | Not stated                                                                    | MI was elevated in nondemented DS subjects when compared with controls. MI was further elevated in demented DS while NAA was found to be decreased |
| Lamar et al. [8]       | Case control     | Hippocampus                                 | n = 35 demented DS (average age = 52.8 years), n = 18 nondemented DS (average age 47.2 years), n = 13 controls (average age 50.6 years), n = 39 sporadic AD (average age 76.8 years) | CAMCOG                                                                         | MI was significantly higher in demented DS than nondemented DS, controls and sporadic AD. NAA was significantly reduced in demented DS compared to nondemented DS but was similar to controls |
| Tan et al. [35]        | Case control     | Hippocampus                                 | n = 35 nondemented DS (average age 35 years), n = 11 demented DS (average age 52 years) and n = 39 controls (average age 35 years) | CAMCOG                                                                         | There was no significant difference in the hippocampal Glx concentration between demented DS and nondemented DS, or between either of the DS groups and the healthy controls |
| Lin et al. [34]        | Case control     | Posterior cingulate cortex                  | n = 22 nondemented DS (average age 46.7 years), n = 5 demented DS (average age 53.7 years), n = 15 control (average age 47.8 years) | BPT, SIB, Dementia Questionnaire for Persons with Mental Retardation (DMR) and NINCDS-ADRDA criteria | NAA and Glx were significantly lower in demented DS subjects than nondemented DS and healthy controls. MI increased in DS when compared with controls but not further increased in demented DS |

DS, Down syndrome; MI, myoinositol; NAA, N-acetylaspartate; CAMCOG, Cambridge Cognition Examination; AD, Alzheimer’s dementia; Glx, glutamate-glutamine complex; BPT, Brief Praxis Test; SIB, Severe Impairment Battery; DMR, Dementia Questionnaire for Persons with Mental Retardation; NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association; MRS, magnetic resonance spectroscopy.
In a longitudinal study of 12 DS subjects, 2 of the DS subjects had relatively stable brain function prior to developing dementia, after which both glucose metabolism and cognitive function demonstrated rapid decline, whilst the DS subjects who did not develop dementia showed no such decline [21]. Interestingly, with regard to the 2 DS subjects (who eventually developed dementia), nonmemory cognitive function showed a stable phase lasting at least 7 years preceding dementia, followed by a linear decline following its onset. Additionally, data indicated that changes in glucose metabolism followed a similar bilinear decline; with the onset of dementia characterized by non-memory cognitive functions in the first phase. This suggests that a subtle neocortical metabolic decline may precede neocortical (nonmemory) cognitive abnormalities, thus medical intervention at this stage may slow disease progression and therefore may delay the clinical manifestations of dementia [21].

Significantly lower CMRglc bilaterally in DS subjects with dementia has been previously shown to be preferentially affected in the clinical and preclinical stages of late-onset AD [22, 23]. Overall, the DS subjects showed lower CMRglc than the healthy controls in additional frontal regions, whether they had dementia or not, although this was thought to reflect differences in brain development [24]. A more recent study was unable to identify statistically significant differences between the nondemented DS subjects and the DS subjects with dementia due to lack of power; however, with the use of nested models, it showed that the DS subjects with dementia demonstrated glucose hypometabolism within the anterior cingulate, frontal cortex, parietal cortex, precuneus, striatum, temporal cortex, and hippocampus regions which cannot be explained solely by reduction in gray matter volume [25]. Interestingly, other studies have reported increased inferior and medial temporal region CMRglc in middle-aged nondemented DS subjects, raising the possibility that compensatory mechanisms are initiated and local neuronal activity is therefore increased in the early stages of AD [17, 24, 26]. It is clear that further research is required on this.

| Study  | Study design | Region of interest | Cohort | Clinical data | Main findings |
|--------|--------------|--------------------|--------|---------------|---------------|
| Landt et al. [5] | Case control | Anterior cingulate, calcarine, hippocampus, posterior cingulate, prefrontal, superior parietal | $n = 9$ DS (aged 25–64 and of whom $n = 5$ had a diagnosis of AD), $n = 14$ non-demented healthy controls (aged 33–69) | CAMDEX-R, Gregory and Hodges criteria | When compared with the healthy controls, only participants with DS older than 45 years showed significant PiB binding usually associated with AD, regardless of a dementia diagnosis or not |
| Anns et al. [39] | Cross-sectional | Striatum (caudate nucleus and putamen), amygdala, thalamus and hippocampus | $n = 9$ nondemented DS, $n = 10$ demented DS (all participants aged 25–65) | CAMDEX-DS, CAMCOG | Nondemented DS exhibited PiB binding in significantly fewer regions than demented DS |
| Mak et al. [44] | Case report | Precuneus, striatum, frontoparietal cortices, temporal lobes | $n = 1$. Age = 40 on recruitment (nondemented DS with MCI who later developed dementia during the 7-year follow-up) | CAMDEX-DS, CAMCOG | Baseline scan showed elevated PiB binding (amyloid-beta plaque). 2 years prior to onset of dementia sharp increase in PiB binding seen in frontoparietal cortices. At onset of dementia PiB binding plateaued. $[18F]$-AV1451 (tacau binder) binding elevated in bilateral precuneus and temporoparietal cortices after dementia onset but striatum was relatively spared |
| Wilson et al. [45] | Cross-sectional | – | $n = 34$ total (19 PiB-negative and 15 PiB-positive) | CAMDEX-DS, CAMCOG-DS | No significant difference in IQ between PiB +ve and PiB −ve DS participants. 3 PiB −ve had dementia and 5 PiB +ve had dementia |

DS, Down syndrome; CAMDEX-R, Cambridge Mental Disorders of the Elderly Examination – Revised; PiB, Pittsburgh compound B; AD, Alzheimer’s dementia; CAMCOG, Cambridge Cognition Examination; MCI, mild cognitive impairment; PET, positron emission tomography.
All studies consistently showed glucose hypometabolism specifically within the parietal and/or temporal regions (with 4 of them demonstrating marked glucose hypometabolism within these regions) indicating that these regions are likely affected first in the preclinical stages of AD. It is therefore reasonable to suggest that FDG-PET imaging may prove useful in detecting preclinical dementia in the DS population but further studies are required.

**MRS Studies**

Proton MRS ($^1$H-MRS) can be used to measure in vivo brain concentrations of glutamate-glutamine complex (Glx), myoinositol (MI), N-acetylaspartate (NAA) (a marker of neuronal density and/or mitochondrial function), choline-containing compounds (a measure of membrane synthesis/turnover), and creatine and phosphocreatine (a measure of cellular energy metabolism) [27–29]. Specifically, NAA and Glx decrease and MI increase correlate with both aging and AD, thus $^1$H-MRS is widely used to characterize the neurochemistry of brain health and disease [30, 31]. Additionally, the ratio of NAA to MI can also be used to distinguish nondemented from demented people [32].

DS subjects with dementia showed significantly higher MI levels with lower levels of NAA in the hippocampus, than nondemented DS subjects and healthy controls [8]. A 1995 case report showed that a DS subject with dementia had elevated MI levels and reduced NAA levels when compared with 23 nondemented DS subjects [33]. These results have again been demonstrated by a more recent study, where DS subjects with dementia showed reduced levels of NAA and Glx within the posterior cingulate cortex, when compared with nondemented DS subjects and healthy controls, but increased levels of MI [34]. Interestingly there was no significant difference in the levels of Cr + PCr or Cho between DS subjects with dementia, nondemented DS subjects and healthy controls nor was there any significant difference in hippocampal Glx concentration between DS subjects with dementia and nondemented DS subjects [8]. Furthermore, there was no correlation between hippocampal Glx concentration, cognitive ability and memory as measured by the Cambridge Cognition Examination (CAMCOG) scores in either of the DS groups [35].

It appears that $^1$H-MRS provides useful information with regard to changes in neuronal biomarkers implicated in AD in DS. In 3 out of the 4 studies, increased MI and decreased NAA were consistently observed in DS subjects with dementia when compared with nondemented DS subjects notably within the hippocampus, posterior cingulate cortex, occipital cortex and parietal white matter. Given this, further studies investigating the link between these biomarkers, cognition, and different regions of the brain may provide researchers with targets for early therapeutic interventions.

**Ligand-Based PET Studies**

Post-mortem studies have shown that by the age of 40 years, DS subjects show neuropathologic changes (i.e., neurofibrillary tangles and amyloid plaques) consistent with a diagnosis of AD [3]. Pittsburgh compound B (PiB) is used to assess amyloid accumulation in AD. PiB specifically binds to amyloid arranged in beta sheets in classic plaques, cerebrovascular amyloid angiopathy, and to a lesser extent, diffuse plaques [9, 36–38].

In a case control study of 9 subjects with DS and 14 healthy controls, it was shown that when compared with healthy controls, only DS subjects older than 45 years showed significant PiB binding usually associated with AD, regardless of a dementia diagnosis or not [5]. The study unfortunately did not comment specifically on any differences (or lack of) between the PiB binding observed in the DS subjects with dementia and the nondemented DS subjects. The researchers also expressed caution over generalizing their results due to the small sample size.

Nondemented DS subjects exhibited PiB binding in significantly fewer regions in comparison with DS subjects with dementia [39]. Studies have demonstrated that amyloid accumulation first occurs, in DS subjects, in the striatum at around age 40 years followed by the rostral prefrontal-cinguloparietal regions, then caudal frontal, rostral temporal, primary sensorimotor and occipital regions, and lastly the mediotemporal regions and remainder of the basal ganglia [9, 39–43]. It has been suggested that initial amyloid deposition triggers a process whereby amyloid accumulates, reaches a steady state and subsequently elicits a chain of events leading to synaptic dysfunction, neuronal loss, and dementia [8].

A more recent case report suggests a sharp increase in PiB binding is detectable prior to the clinical onset of dementia in DS, particularly in the precuneus and striatum, and there is also a sharp rise in PiB binding in the frontoparietal cortices during this time, but this eventually plateaus on follow-up imaging [44]. Another study categorized DS participants as either PiB-positive or PiB-negative and found that clinical correlation for dementia identified 3 PiB-negative participants were demented and 5 PiB-positive participants were demented highlighting that amyloid deposition alone may not to blame for dementia in DS [45]. Interestingly, one study revealed PiB
Neuroimaging is a potential tool for monitoring biomarkers and changes in brain morphology associated with progression from preclinical to symptomatic dementia in DS but it does present with limitations. It is important to note that brain changes noted on ligand-based PET may occur too late for effective intervention, so other neuroimaging modalities such as FDG-PET may actually prove to be more useful with regard to revealing early brain changes [9].

The DS brain differs from the non-DS brain even in the absence of dementia so this must be kept in mind when collating and interpreting any data obtained from neuroimaging [9, 43]. Longitudinal studies may be helpful in distinguishing changes in the brain due to dementia alone from other causes, such as age-associated changes. Another limitation is that some changes occurring to the brain may not be detectable by neuroimaging until the disease has progressed significantly, therefore potentially limiting its use in the preclinical phase where the individual’s level of functioning and cognition still permits a good quality of life.

In studies involving people with DS, the sample sizes tend to be smaller. This can make it difficult to determine whether certain results are statistically significant or not. Sample sizes can be small for a number of reasons. First, recruitment is generally difficult with regard to neuroimaging studies due to people’s fear of being scanned [47]. Second, people with DS tend to have a higher prevalence of obesity which in itself can lead to discomfort in the scanner, potentially precluding them from participating in neuroimaging studies [11, 48]. Third, it may be more difficult for people with DS (especially those with dementia and older in age) to understand and comply with instructions and remain motionless during the scanning process leading to artifact [9]. Additionally, the unique structure of the neck and face in DS individuals means it can be quite uncomfortable for them to remain in the prone position for considerable lengths of time [11].

Sedative medication can be administered to help relax the participants, but this carries its own ethical implications and the sedatives themselves can directly affect the functional measures that are being investigated, leading to skewed results [5, 11]. It would be prudent, in the first instance, to allow the DS participants the opportunity to visit the scanning site and become familiar with the scanning process. This would hopefully cause a strong trust relationship to develop between the researchers and participants, causing the latter to feel more relaxed and more likely to comply adequately with the entire process, thus avoiding the need for sedation. Utilizing mock scanners
and reducing scan waiting times may also prove helpful in putting participants at ease.

It is important to note that neuroimaging is costlier and more time-consuming than other clinical tests such as psychiatric assessments, thus limiting its feasibility as a widespread diagnostic tool [9]. Neuroimaging may be more beneficial when used in conjunction with cognitive and clinical assessments.

Though not covered in this review, structural neuroimaging studies investigating DS subjects with and without dementia may yield further useful information. It will allow researchers to identify which specific brain regions undergo atrophy and other physical changes and how these relate to cognitive decline, abnormal PiB binding as well as metabolic and biochemical changes. This will hopefully lead to better diagnostic protocols and therapeutic interventions.

In conclusion, neuroimaging is a powerful tool which may aid researchers in the detection of early structural, functional, biochemical, and metabolic changes which occur with AD in DS, allowing clinicians to intervene in high-risk patients prior to disease progression thereby preserving cognition function and a good quality of life. There are no preventative treatments for AD and current treatments are mainly aimed at managing symptoms. Data obtained from neuroimaging in this population may aid in the development of novel treatments and allow for the efficacy of the same to be monitored. More longitudinal studies with large sample sizes will be vital in increasing our understanding of the pathogenesis of AD in DS and tracking the disease’s course, improving outcomes within this specific population.

Statement of Ethics

Ethical approval was not required.

Conflict of Interest Statement

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Author Contributions

F.D. contributed to literature search, data extraction, and writing the initial manuscript. J.K. contributed to literature search, data extraction, and writing the manuscript. L.S.L.L. contributed to literature search, data extraction, and writing the manuscript. L.V. contributed to conceptualization, supervision of data extraction, and provided critical comments on the manuscript. S.B. contributed to conceptualization, supervision of data extraction, and provided critical comments on the manuscript and finalized the manuscript.

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