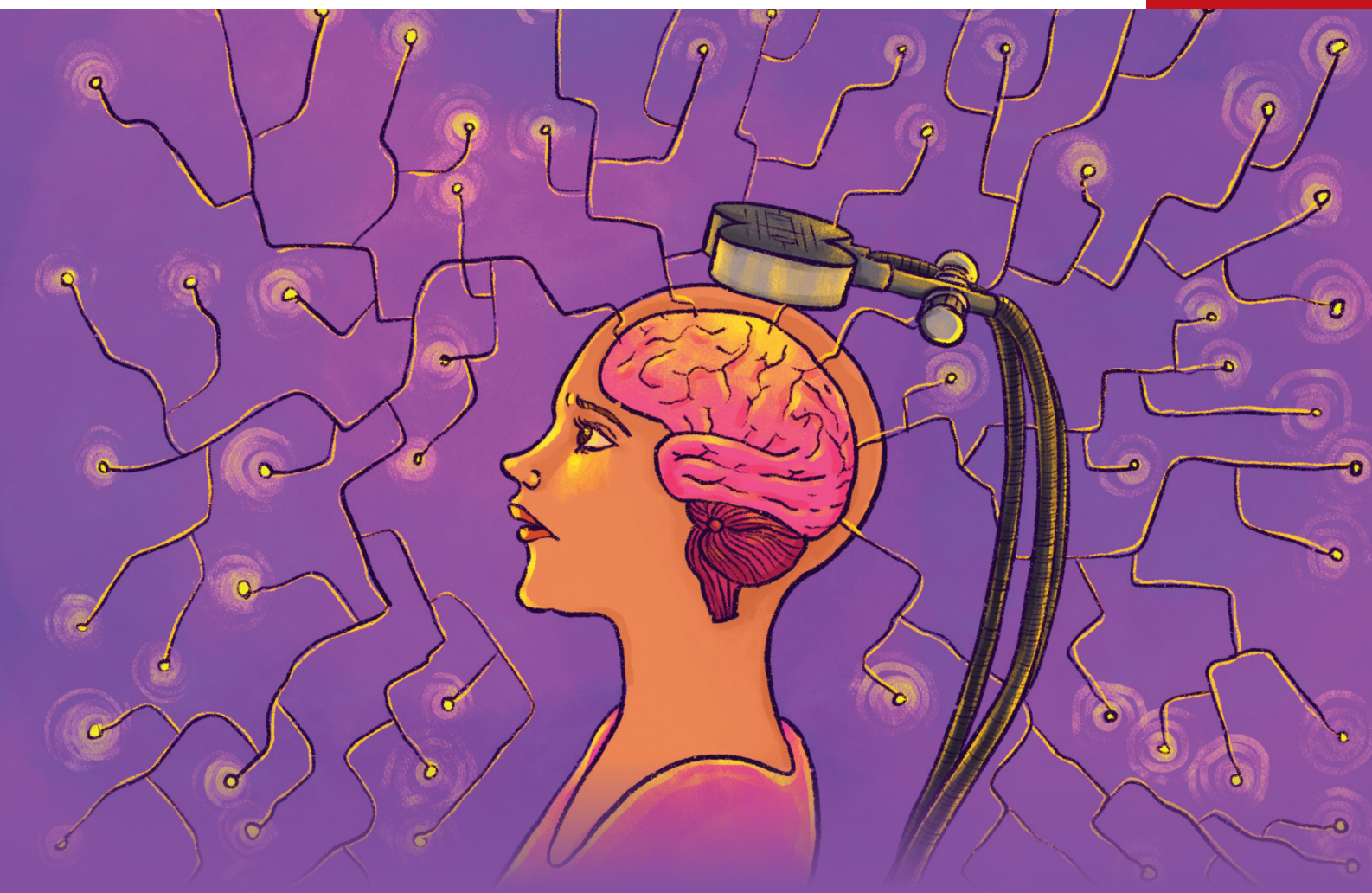
ANNALS

OFFICIAL JOURNAL OF THE ACADEMY OF MEDICINE, SINGAPORE

VOLUME 53
NUMBER 8
AUG 2024



Repetitive transcranial magnetic stimulation for major depression and obsessive-compulsive disorders in Singapore

Repetitive transcranial magnetic stimulation found to be effective in treatments, with higher response rates for major depressive disorder, while longer treatment durations may improve outcomes for obsessive-compulsive disorder. (See full article, p.471)

Illustration by Ladyfingers Co.

Also in this issue

ISSN 2972-4066

Annals, Academy of Medicine, Singapore
Volume 53 | Number 8 | AUGUST 2024

EDITORIALS

ORIGINAL ARTICLES

REVIEW ARTICLE

LETTERS TO THE EDITOR

Ann Acad Med Singap 2024;53:464-5
https://doi.org/10.47102/annals-acadmedsg.2024208

EDITORIAL

Transcranial magnetic stimulation in psychiatry: A Singapore perspective

Christopher Yi Wen Chan[1,2] *MMed (Psychiatry)*, Johnson Fam[3] *MMed (Psychiatry)*

The use of repetitive transcranial magnetic stimulation (rTMS) for major depressive disorder (MDD) and obsessive-compulsive disorder (OCD) has not been described in Singapore. Reports on the effectiveness of rTMS in populations outside of Western countries are also limited. Thus, Ye et al.'s study on the naturalistic outcomes of rTMS treatment is important in the Asian context.[1] The lifetime prevalence of depression in Singapore is 6.3%.[2] It has been estimated that 30%–60% of patients with MDD do not respond to a first-line antidepressant, whereas 40% do not respond to a second-line antidepressant. Treatment resistant depression (TRD) is a term often used when a patient has failed to respond to 2 different antidepressants, with adequate adherence for a duration of 4–8 weeks. Further trials of antidepressant medication result in diminishing response rates and prolonging illness duration.[3] Options for TRD include continued trials of different medications—utilising switching, augmentation or combination approaches and using psychotherapy and/or non-invasive neurostimulation techniques, such as rTMS and electroconvulsive therapy (ECT). While ECT is recognised as the most effective non-invasive neurostimulation treatment, studies have increasingly demonstrated that rTMS is more cost effective[4] and has demonstrated superiority to switching antidepressants.[5] In Singapore, the College of Psychiatrists endorsed the use of rTMS for MDD in 2015 and OCD in 2018. The Institute of Mental Health (IMH) has the largest psychiatric rTMS service in Singapore.

In Ye et al.'s observational study published in this issue of the Annals, 53 patients with MDD received rTMS treatment. Response (20.8%) and remission (17.0%) rates for depression based on MADRS mean scores were lower than expected. The largest (n=5010) naturalistic study to date reported higher response (57.7%) and remission (27.7%) rates based on self-report (PHQ-9).[6] Another naturalistic study (n=435) that focused only on TRD patients also reported higher response (31.0%) and remission (22.8%) rates based on clinician rating (MADRS).[7] The meta-analysis of randomised sham-controlled trials showed that active rTMS (n=840) had 39.7% response and 35.7% remission rates for TRD, while response and remission rates using sham rTMS were 13.7 and 8.4%, respectively.[8]

Higher levels of treatment resistance and greater depression severity in the current episode may result in lower treatment response. In Ye et al.'s cohort, not all MDD patients had TRD, and their average depression severity score (MADRS=28.1) pre-treatment was only in the moderate category (MADRS 20–34) and not severe category (MADRS 35–60). However, a large proportion of patients failed to respond to 3 or more antidepressants. Whether this cohort had psychotic features or other comorbidities that affected treatment outcome is unknown; hence, the authors could have described the clinical characteristics of patients in greater detail. Only 32/53 (60.4%) of MDD patients received rTMS over the left dorsolateral prefrontal cortex, which is currently the only rTMS target site for MDD that is approved by the US Food and Drug Administration (FDA). Other target sites for MDD are considered off-label. The treatment coil used in this study is a double-cone figure-8 (Fo8) coil with angled wings, which is a deviation from the flat Fo8 coil used in the MagPro system that is FDA-approved for MDD. Angled Fo8 coils have different depths of decay and focality compared to conventional flat Fo8 coils. These technical deviations should be examined closely by the authors in future to determine whether they have a bearing on treatment outcome.

Ye et al.'s study involved a small number (n=13) of OCD patients. The authors defined treatment response as achieving at least 20% reduction in clinician-rated OCD severity score (Yale–Brown Obsessive Compulsive Scale [Y-BOCS]). Clinical trials typically define response as a 30%–35% reduction in the Y-BOCS score. Had the authors used the conventional definition of response, the actual response rates would have been lower than reported. The low treatment efficacy was also observed in the mean change of severity scores. No statistically significant difference was detected between the pre and post-treatment scores. The study did not specify the exact stimulation site or stimulation frequency for OCD. The level of treatment resistance in OCD patients was also not clearly presented, which makes it difficult to understand why treatment efficacy was low in this

[1] Psychiatric Care Clinic, Mount Elizabeth Novena Hospital, Singapore
[2] Institute of Mental Health, Singapore
[3] Department of Psychiatry, Singapore General Hospital, Singapore
Correspondence: Dr Christopher Yi Wen Chan, Psychiatric Care Clinic, Mount Elizabeth Novena Hospital, 38 Irrawaddy Road Singapore 329563.
Email: drchristopherchan@psycareclinic.com

study. A larger cohort will be needed to determine whether this is a spurious observation.

This study reported that the subgroup of patients with less than 30 sessions of rTMS had a higher proportion of non-responders. Although the authors suggested that more than 30 sessions of rTMS may be helpful for better response, this was not substantiated by their subgroup analysis of mean difference in pre and post-treatment scores. This observation is limited by several factors. First, not all patients could afford to have an acute course of rTMS with more than 30 sessions, as the financial subsidy by the Ministry of Health in Singapore is only available for the first 24 treatment sessions. Second, the continuation of treatment beyond 30 sessions was only offered to patients who had >25% MADRS improvement at session 30. Some evidence suggests that patients can continue to benefit from more than 30 sessions of rTMS even if they did not experience significant improvement in the first 30 sessions.[9] Third is the hospital/clinic-based nature of rTMS treatment. Having to commute daily to and from a treatment centre over a longer course of treatment may be difficult for an individual who has MDD.

Despite the limitations, Ye et al.'s study highlighted an interesting therapeutic field that is rapidly progressing. rTMS treatment can be shortened using accelerated protocols where multiple treatment sessions are performed in 1 day instead of the standard 1 session per day.[10] This significantly reduces the total number of days required for a course of treatment that could improve both treatment uptake and adherence. Neuronavigation techniques based on structural and functional brain imaging are being utilised for more precise targeting and individualised treatment, resulting in enhanced treatment efficacy.[11] Access to rTMS in Singapore is no longer a barrier to treatment, as rTMS service is now provided by the public and private healthcare sectors. The financial burden of rTMS treatment has been alleviated by recent improvements to Medisave and insurance claim processes.

Given the known prevalence of MDD in Singapore and the estimates of TRD, Ye et al. investigated a relatively small number of patients who underwent rTMS in IMH over a 5-year period. rTMS likely remains underutilised in Singapore. There is room for improvement in raising public awareness towards this form of neurostimulation treatment. Psychiatrists should also gain more exposure to rTMS use. Training in rTMS is being proposed to be part of the psychiatry residency programme, and exploring the delineation of interventional psychiatry might increase visibility and enhance expertise. Further work could be done to strengthen collaboration in the areas of clinical service, research and education across healthcare clusters to position Singapore as a regional centre of excellence for rTMS.

Declaration

The authors declare there are no affiliations with or involvement in any organisation or entity with any financial interest in the subject matter or materials discussed in this manuscript.

Keywords: *depression, neurostimulation, obsessive-compulsive disorder, psychiatry, repetitive transcranial magnetic stimulation*

REFERENCES

1. Ye SJ, Lu LS, HH Phu et al. Repetitive transcranial magnetic stimulation for major depression and obsessive-compulsive disorders in Singapore. Ann Acad Med Singap 2024;53:471-80.
2. Subramaniam M, Abdin E, Vaingankar JA, et al. Tracking the mental health of a nation: Prevalence and correlates of mental disorders in the second Singapore mental health study. Epidemiol Psychiatr Sci 2019;29:e29.
3. Tor PC, Amir N, Fam J, et al. A Southeast Asia Consensus on the Definition and Management of Treatment-Resistant Depression. Neuropsychiatr Dis Treat 2022;18:2747-57.
4. Zhao YJ, Tor PC, Khoo AL, et al. Cost-Effectiveness Modeling of Repetitive Transcranial Magnetic Stimulation Compared to Electroconvulsive Therapy for Treatment-Resistant Depression in Singapore. Neuromodulation 2018;21:376-82.
5. Papakostas GI, Trivedi MH, Shelton RC, et al. Comparative effectiveness research trial for antidepressant incomplete and non-responders with treatment resistant depression (ASCERTAIN-TRD) a randomized clinical trial. Mol Psychiatry 2024.
6. Sackeim HA, Aaronson ST, Carpenter LL, et al. Clinical outcomes in a large registry of patients with major depressive disorder treated with Transcranial Magnetic Stimulation. J Affect Disord 2020;277:65-74.
7. Bouaziz N, Laidi C, Bulteau S, et al. Real world transcranial magnetic stimulation for major depression: A multisite, naturalistic, retrospective study. J Affect Disord 2023; 326:26-35.
8. Vida RG, Sághy E, Bella R, et al. Efficacy of repetitive transcranial magnetic stimulation (rTMS) adjunctive therapy for major depressive disorder (MDD) after two antidepressant treatment failures: meta-analysis of randomized sham-controlled trials. BMC Psychiatry 2023;23:545.
9. Avery DH, Isenberg KE, Sampson SM, et al. Transcranial Magnetic Stimulation in the Acute Treatment of Major Depressive Disorder: Clinical Response in an Open-Label Extension Trial. J Clin Psychiatry 2008;69:441-51.
10. Tan XW, Abdin E, Tor PC. Accelerated transcranial magnetic stimulation (aTMS) to treat depression with treatment switching: study protocol of a pilot, randomized, delayed-start trial. Pilot Feasibility Stud 2021;7:104.
11. Temasek Foundation. Singapore Pilots Personalised Transcranial Magnetic Stimulation for Treatment-Resistant Depression, 12 April 2024. https://temasekfoundation.org.sg/news/media-releases/singapore-pilots-personalised-transcranial-magnetic-stimulation-for-treatment-resistant-depression. Accessed 14 June 2024.

Ann Acad Med Singap 2024;53:466-7
https://doi.org/10.47102/annals-acadmedsg.2024188

EDITORIAL

Living longer and stronger: Are children and young adults with Down syndrome experiencing healthier and better lives?

Cristelle Chow[1] *MMED (Paeds)*

Down syndrome (DS) is the most common genetic cause of intellectual disability and is associated with multiple medical conditions affecting various organ systems, impacting the individual's health, development and function.[1] In Singapore, the live-birth prevalence of DS was 0.89 per 1000 births in the 1990s, a figure expected to decline further due to improved antenatal testing methods, despite the increasing trend in maternal age.[2] Advances in medical technology, including surgery for complex congenital heart disease, have extended the life expectancy of individuals with DS to around 60 years.[3] Although global life expectancy and disability-adjusted life years for individuals with DS have remained largely stable, the overall disease burden has increased due to longer years lived with disability. From 2010 to 2019, the estimated annual percentage increase in years lived with disability was 1.07 years.[4] Therefore, it is essential for service providers to shift their focus from merely prolonging life expectancy to improving the quality of life (QOL) for individuals with DS, which is the focus of the study by Chan et al. published in this issue of the *Annals*.[5]

The study highlights a significant gap in the literature regarding QOL in children and young adults with DS. This systematic review addresses this gap by providing a comprehensive analysis of QOL issues. The findings reveal that children with DS have significantly lower Pediatric Quality of Life Inventory (PedsQL) scores in social functioning compared to typically developing children. Social functioning is likely affected by intellectual disability and impaired social communication skills, which can impact the ability to form friendships with peers. Interestingly, older persons with DS report minimal difficulties in forming friendships, despite external perceptions of poorer peer relationships.[6] Additionally, this review found that children with DS tend to report higher QOL scores compared to their parents, indicating a discrepancy between self-reported and caregiver-reported QOL. This discrepancy highlights the challenge of QOL screening for individuals with intellectual disability and cognitive impairments, as assessments often rely on caregivers' perspectives. The studies in this review used several validated tools, including caregiver versions of PedsQL and KIDSCREEN. However, these tools are not specifically designed for children with intellectual disability and complex medical needs. One study utilised the newly developed KidsLife Down scale, tailored for caregivers of children with DS.[7] Another tool not used in the review but relevant is the Quality of Life Inventory-Disability measure, which is reliable across the spectrum of intellectual disability, including DS.[8]

PedsQL and KIDSCREEN are not interchangeable, as PedsQL focuses more on function, while KIDSCREEN emphasises well-being.[9] Customised QOL measures are essential to accurately assess specific patient populations, and clinicians need to be aware of the domains each instrument measures. Regular quantitative assessments for children and young adults with complex medical conditions are valuable, but in-depth conversations with caregivers are necessary to understand the specific unmet needs and challenges of the child and family. The review identified specific risk factors contributing to QOL outcomes in children and young adults with DS. Physical or functional comorbidities, such as low muscle tone, obesity, autism and epilepsy, as well as lower socio-economic status, were associated with poorer QOL scores. This highlights the importance of screening, early treatment and preventive measures to mitigate the impact of comorbidities and social discrepancies on physical health and QOL, especially in school functioning. DS, once considered a life-limiting condition, is now managed as a chronic disease. Numerous international guidelines provide evidence-based recommendations for the holistic and multidisciplinary care of individuals with DS.[1,3] The study recommends focusing on support in social and school functioning, suggesting evidence-based interventions such as standardised guidelines for health supervision, anticipatory guidance

[1] Department of Paediatrics, KK Women's and Children's Hospital, Singapore
Correspondence: Dr Cristelle Chow, Department of Paediatrics, KK Women's and Children's Hospital, Singapore, 100 Bukit Timah Rd, Singapore 229899.
Email: cristelle.chow.ct@singhealth.com.sg
This article was first published online on 14 August 2024 at annals.edu.sg.

for caregivers and educators on behavioural monitoring, and increased opportunities for inclusive schooling.[3,10] Adapted physical activity and sports programmes, as well as activities supported by adaptive technology have also shown benefits for autonomy and all aspects of QOL in individuals with DS.[11]

Despite longer lives, children and young adults with DS still do not experience a QOL on par with typically developing individuals. Healthcare professionals and educators should advocate for sustainable education systems that support skills development beyond typical schooling years. As society better understands the potential for development and socialisation of individuals with DS, there must be adaptations in social awareness, adaptive technologies and employment opportunities. This will enable them to contribute meaningfully to their community, reduce caregiving burden, and enhance the QOL of individuals with DS and their families.

REFERENCES

1. Bull MJ. Down syndrome. N Engl J Med 2020;382:2344-52.
2. Lai FM, Woo BH, Tan KH, et al. Birth prevalence of Down syndrome in Singapore from 1993 to 1998. Singapore Med J 2002;43:70-6.
3. Bull MJ, Trotter T, Santoro SL, et al. Health supervision for children and adolescents with Down syndrome. Pediatrics 2022;149:e2022057010.
4. Bu Q, Qiang R, Cheng H, et al. Analysis of the global disease burden of Down syndrome using YLDs, YLLs, and DALYs based on the global burden of disease 2019 data. Front Pediatr 2022;10:882722.
5. Chan YY, Wong BWZ, Cheok FE, et al. Quality of life of children and young adults with Down syndrome from caregivers' perspective: A systematic review and meta-analysis. Ann Acad Med Singap 2024;53:502-13.
6. Skotko BG, Levine SP, Goldstein R. Self-perceptions from people with Down syndrome. Am J Med Genet A 2011; 155A:2360-9.
7. Morán L, Gómez LE, Balboni G, et al. Predictors of individual quality of life in young people with Down syndrome. Rehabil Psychol 2022;67:205-14.
8. Downs J, Jacoby P, Leonard H, et al. Psychometric properties of the Quality of Life Inventory-Disability (QI-Disability) measure. Qual Life Res 2019;28:783-94.
9. Waters E, Davis E, Ronen GM, et al. Quality of life instruments for children and adolescents with neurodisabilities: How to choose the appropriate instrument. Dev Med Child Neurol 2009;51:660-9.
10. Dressler A, Perelli V, Bozza M, et al. The surplus effect in adaptive behaviour in Down syndrome: What can promote it? Brain Sci 2021;11:1188.
11. Muñoz-Llerena A, Ladrón-de-Guevara L, Medina-Rebollo D, et al. Impact of physical activity on autonomy and quality of life in individuals with Down syndrome: A systematic review. Healthcare (Basel) 2024;12:181.

Ann Acad Med Singap 2024;53:468-70
https://doi.org/10.47102/annals-acadmedsg.2024260

EDITORIAL

Deep brain stimulation in Parkinson's disease: Looking back, looking forward

Erle CH Lim[1,2] *FRCPS (Glasgow)*, Amy ML Quek[1,2] *MRCP (UK)*, Raymond CS Seet[1,2] *FRCP (Edin)*

Patients with Parkinson's disease (PD) may present with prodromal (e.g. hyposmia, sleep disorders, constipation), motor (e.g. tremors, rigidity, bradykinesia, postural dysfunction) and non-motor (e.g. cognitive dysfunction, depression) symptoms.[1] Treatment is symptomatic, targeting motor and non-motor manifestations, but there is presently no effective disease modifying treatment.[1] Although PD therapies have primarily been focused on supplementing dopamine, which has improved survival and quality of life of PD patients,[1-3] other neurotransmitter systems (e.g. serotonergic, cholinergic and noradrenergic) are also dysfunctional, especially for the non-motor symptoms.[1,4,5] By the time patients reach the later stages of PD, many of them would have developed significant gait and balance difficulties, dysarthria, dysphagia and motor fluctuations like wearing off and levodopa-induced dyskinesias (LID), as well as non-motor symptoms such as orthostasis, depression, dementia and psychosis.[1,2,6,7]

In addition to dopamine supplementation, other medical therapeutic options for the motor symptoms include anticholinergic agents, monoamine oxidase B inhibitors (e.g. selegiline and newer drugs such as rasagiline, safinamide and zonisamide), catechol-O-methyl transferase inhibitors, adenosine A2A inhibitors (such as istradefylline) and amantadine. Non-motor symptoms are treated with atypical antipsychotics, selective serotonin reuptake inhibitors, selective norepinephrine inhibitors, tricyclic antidepressants and anticholinesterase inhibitors.[1,2,8,9]

Patients in the later stages of PD often do not respond to (or respond less well to) therapeutic adjustments,[1] and other strategies may need to be considered, e.g. enteral levodopa and surgery.[1,10,11] Invasive (thalamotomy, subthalamotomy, pallidotomy) and noninvasive (MRI focused ultrasound) lesioning procedures may be useful to ameliorate the motor manifestations of PD.[1,12,13] Non-lesioning surgical therapy, i.e. deep brain stimulation (DBS), has been shown to decrease dopaminergic requirements, improve "ON" period motor function, activities of daily living and quality of life, and ameliorate LIDs.[7] DBS is typically considered when patients demonstrate the wearing-off phenomenon or LIDs.[1,2]

Neurosurgical interventions targeting the thalamus, globus pallidus and subthalamic nucleus (STN) to treat PD were based upon previous observations and interventions in animal models and PD patients, starting with James Parkinson's observation that the tremors of 1 of his 6 patients disappeared after a stroke.[14] Albe-Fessard, and later, Benabid, observed that high frequency stimulation (100-200 Hz) in the ventrointermediate nucleus of the thalamus (Vim) reduced tremors in PD patients.[15,16] Anatomical and physiological studies indicated overactivity of the globus pallidus pars interna (GPi) and STN in PD patients. Lesioning these structures in animal models ameliorated PD signs in animal models.[14,16,17]

Benabid's pioneering work on chronic stimulation of the Vim to treat tremors in PD, essential tremors and extrapyramidal dyskinesias[18] later led to DBS of the STN and GPi to treat motor manifestations and LIDs, respectively, in PD patients.[17,19,20] DBS of the STN and GPi have both been shown, in several highly powered randomised controlled trials to markedly reduce "OFF" medication motor severity (by 30–50% of the motor scale of the Unified Parkinson's Disease Rating Scale, or UPDRS); increase daily "ON" time (by 2–5 hours); and improve LIDs, activities of daily living and quality of life, compared to best medical treatment.[7,21] There is consistent evidence from observational follow-up studies showing sustained improvement of motor symptoms of up to 10–15 years and beyond, but what is unclear is whether there is long-term benefit on progression to disability or indeed, if early DBS improves the clinical progression or long-term outcome in PD patients.[7]

DBS to the STN and GPi both improve the motor symptoms of PD. STN stimulation allows a greater reduction in medications, whereas GPi stimulation

[1] Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore
[2] Division of Neurology, National University Hospital, Singapore
Correspondence: Associate Professor Erle CH Lim, Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, 1E Kent Ridge Road. Singapore 119228.
Email: mdcelch@nus.edu.sg

directly reduces LIDs.[21] Consisting of uni- or bilateral stimulating electrodes stereotactically implanted into the targets identified above (i.e. deep brain structures) and connected to an implantable pulse generator (IPG) emplaced subcutaneously on the chest wall,[22] the clinician adjusts the parameters of stimulation by means of a handheld device placed over the IPG. Adjustments are made to the number and configuration of anodal (positive) or cathodal (negative) electrode contacts turned on, the voltage or current of the stimulation pulse, the duration of each pulse width (charge-balanced pulse) and the frequency of the pulses.[22] DBS is believed to act via several different mechanisms. These include local and network-wide electrical and neurochemical effects of stimulation and modulation of oscillatory activity and synaptic plasticity. Some have postulated that DBS engenders neuroprotection and neurogenesis as well.[22]

The Vim is not considered a suitable DBS target in PD, as it does not sufficiently improve bradykinesia and rigidity, though it remains an eminently suitable target for the treatment of essential tremors.[22-24] DBS of the STN has the added advantage of reducing drug-refractory tremors.[7] The time course of response after DBS varies according to symptoms—of the order of seconds for relief of tremor, and minutes to hours for amelioration of rigidity and bradykinesia. It usually takes hours to days for a less profound relief of axial symptoms after DBS.[22] It is uncertain if, and to what extent, DBS alters either long-term outcomes or clinical progression of the disease.[7]

Cai et al. followed up 94 PD patients who received bilateral STN DBS over 10 years.[24] Their data were consistent with other long-term follow up studies, i.e. with reduction in dopaminergic medication requirements and motoric improvements (decreased "OFF" time), but did not appear to appreciably improve LIDs.[24] This is not surprising, as the GPi is thought to be a better target for the treatment of LIDs.[25] Movement Disorders Society(MDS)-UPDRS II and III scores increased from the fifth year after DBS, which is consistent with other studies, in which improvements in UPDRS motor scores became blunted, and "ON" medication motor scores declined below baseline levels by the fifth year.[7] Assessment of PD motor scores in the "OFF" condition are accepted as a surrogate marker of the underlying severity of the disease, i.e. progression of the disease.[7] It is thus unfortunate that Cai et al. only assessed the MDS-UPDRS II and III for their PD patients in the "ON" state.

DBS is now considered a mainstay of PD treatment, with promising new targets being investigated, such as the zona incerta, which ameliorates refractory tremor;[26] the substantia nigra pars reticulata and pedunculopontine nucleus to improve axial symptoms and the freezing of gait.[27] What remains to be definitively determined with conventional DBS is when to perform it in PD patients, and whether it confers any neuroprotective benefit.

Finally, conventional (open loop) DBS, which continuously delivers stimulation within fixed programmed parameters, is disadvantaged by requiring periodic adjustments, having limited motoric improvement, short battery life and manifesting side effects such as dyskinesia (from stimulation at a time when it is not needed).[28] Adaptive DBS, with real-time modification to stimulation parameters based on neural signals that co-vary with the severity of motor signs or to stimulation-induced adverse effects, may not only improve motor function and reduce side effects but prolong battery life.[28]

Declaration

The authors have no affiliations or financial involvement with any commercial organisation with a direct financial interest in the subject or materials discussed in the manuscript.

Keywords: *deep brain stimulation, DBS, Parkinson's disease, treatment, subthalamic nucleus*

REFERENCES

1. Armstrong MJ, Okun MS. Diagnosis and Treatment of Parkinson Disease: A Review. JAMA 2020;323:548-60.
2. Lim EC. A Walk Through the Management of Parkinson's Disease. Ann Acad Med Singap 2005;34:188-95.
3. Olanow CW, Watts RL, Koller WC. An algorithm (decision tree) for the management of Parkinson's disease (2001): treatment guidelines. Neurology 2001;56:S1-S88.
4. Factor SA, McDonald WM, Goldstein FC. The role of neurotransmitters in the development of Parkinson's disease-related psychosis. Eur J Neurol 2017;24:1244-54.
5. Schapira AHV, Chaudhuri KR, Jenner P. Non-motor features of Parkinson disease. Nat Rev Neurosci 2017;18:435-50.
6. Dong Y, Koay WI, Yeo LL, et al. Rapid Screening for Cognitive Impairment in Parkinson's Disease: A Pilot Study. Parkinsons Dis 2015;2015:348063.
7. Mahlknecht P, Foltynie T, Limousin P, et al. How Does Deep Brain Stimulation Change the Course of Parkinson's Disease? Mov Disord 2022;37:1581-92.
8. Fabbri M, Barbosa R, Rascol O. Off-time Treatment Options for Parkinson's Disease. Neurol Ther 2023;12:391-424.
9. Park A, Stacy M. Istradefylline for the treatment of Parkinson's disease. Expert Opin Pharmacother 2012;13:111-14.
10. Virhammar J, Nyholm D. Levodopa-carbidopa enteral suspension in advanced Parkinson's disease: clinical evidence and experience. Ther Adv Neurol Disord 2017;10:171-87.

11. Antonini A, Moro E, Godeiro C, et al. Medical and surgical management of advanced Parkinson's disease. Mov Disord 2018;33:900-8.
12. Sharma VD, Patel M, Miocinovic S. Surgical Treatment of Parkinson's Disease: Devices and Lesion Approaches. Neurotherapeutics 2020;17:1525-38.
13. Moosa S, Martínez-Fernández R, Elias WJ, et al. The role of high-intensity focused ultrasound as a symptomatic treatment for Parkinson's disease. Mov Disord 2019;34:1243-51.
14. Hariz M, Lees AJ, Blomstedt Y, et al. Serendipity and Observations in Functional Neurosurgery: From James Parkinson's Stroke to Hamani's & Lozano's Flashbacks. Stereotact Funct Neurosurg 2022;100:201-9.
15. Albe Fessard D, Arfel G, Guiot G, et al. Characteristic Electric Activities of Some Cerebral Structures in Man. Ann Chir 1963;17:1185–214.
16. Benabid AL, Torres N. New targets for DBS. Parkinsonism Relat Disord 2012;18:S21-3.
17. Aquino CH, Moscovich M, Marinho MM, et al. Fundamentals of deep brain stimulation for Parkinson's disease in clinical practice: part 1. Arq Neuropsiquiatr 2024;82:1-9.
18. Benabid AL, Pollak P, Seigneuret E, et al. Chronic VIM thalamic stimulation in Parkinson's disease, essential tremor and extra-pyramidal dyskinesias. Acta Neurochir (Wien) 1993; 58:39-44.
19. Limousin P, Pollak P, Benazzouz A, et al. Effect of parkinsonian signs and symptoms of bilateral subthalamic nucleus stimulation. Lancet 1995;345:91-5.
20. Siegfried J, Lippitz B. Bilateral chronic electrostimulation of ventroposterolateral pallidum: a new therapeutic approach for alleviating all parkinsonian symptoms. Neurosurgery 1994;35:1126–9.
21. Honey CR, Hamani C, Kalia SK, et al. Deep Brain Stimulation Target Selection for Parkinson's Disease. Can J Neurol Sci 2017;44:3-8.
22. Herrington TM, Cheng JJ, Eskandar EN. Mechanisms of deep brain stimulation. J Neurophysiol. 2016;115:19-38.
23. Guzzi G, Della Torre A, Chirchiglia D, et al. Critical reappraisal of DBS targeting for movement disorders. J Neurosurg Sci 2016;60:181-8.
24. Cai YZ, Zheng Y, Li W, et al. Long-term outcomes after subthalamic nucleus deep brain stimulation for Parkinson's disease in Singapore. Annals Acad Med Singap 2024;53:481-9.
25. Zhang J, Li J, Chen F, et al. STN versus GPi deep brain stimulation for dyskinesia improvement in advanced Parkinson's disease: A meta-analysis of randomized controlled trials. Clin Neurol Neurosurg 2021;201:106450.
26. Stenmark Persson R, Fytagoridis A, Ryzhkov M, et al. Long-Term Follow-Up of Unilateral Deep Brain Stimulation Targeting the Caudal Zona Incerta in 13 Patients with Parkinsonian Tremor. Stereotact Funct Neurosurg 2023;101:369-79.
27. Hvingelby VS, Pavese N. Surgical Advances in Parkinson's Disease. Curr Neuropharmacol 2024;22:1033-46.
28. Swann NC, de Hemptinne C, Thompson MC, et al. Adaptive deep brain stimulation for Parkinson's disease using motor cortex sensing. J Neural Eng. 2018;15:046006.

Ann Acad Med Singap 2024;53:471-80
https://doi.org/10.47102/annals-acadmedsg.202496

ORIGINAL ARTICLE

Repetitive transcranial magnetic stimulation for major depression and obsessive-compulsive disorders in Singapore

Ye Si Jia[1] *BSN*, Lu LinShan[1] *BSN*, Phu Hui Huang[1] *BSN*, Tan Xiao Wei[2] *PhD*, Tor Phern Chern[2] *MBBS*

ABSTRACT

Introduction: Repetitive transcranial magnetic stimulation (rTMS) is used for treatment-resistant major depressive disorder (MDD) and obsessive-compulsive disorder (OCD), but there are few studies on patient outcomes in Southeast Asia. In this study, we describe the clinical profile and outcome of patients with MDD and OCD treated with rTMS in Singapore.

Method: A naturalistic retrospective study of 71 patients (inpatient and outpatient) who received rTMS treatment between June 2018 and April 2023 was conducted. The depressive and obsessive outcome rating scales used were clinician-rated Montgomery–Åsberg Depression Rating Scale (MADRS), Yale–Brown Obsessive Compulsive Scale (Y-BOCS), Clinical Global Impressions-Severity (CGI-S) and self-rated Depression Anxiety and Stress Scale-21 (DASS-21).

Results: Clinician-rated and self-rated mood and general condition improved significantly. MADRS mean score improved from 28.1 (standard deviation [SD] 7.3) to 20.7 (SD 10.1) (P<0.0001) (20.8% response rate/17% remission rate). CGI-S mean 4.6 (SD 0.8) improved to 3.3 (SD 1.2) (P<0.0001). DASS-21 total mean improved from 67.3 (SD 24.6) to 49.6 (SD 28.0) (P<0.0001). Y-BOCS mean score displayed a trend towards improvement from 30.1 (SD 7.5) to 27.2 (SD 6.9) (P=0.799). However, 44.4% of patients with OCD responded with a minimal 20% reduction in baseline Y-BOCS. Moreover, the subgroup of 35.8% of patients with less than 30 rTMS sessions had contributed disproportionately to nonresponse (85.7%). Patients who received rTMS treatment (>30 sessions) had a trend of larger improvement of MADRS score when compared to patients with (≤30 sessions) (9.4 [SD 9.7] versus 3.8 [SD 12.3] [P=0.078]).

Conclusion: Response and remission rates for MDD and OCD suggest patients have a good response to rTMS treatment. Dosing longer rTMS sessions after an acute course helps to maximise effectiveness. Further research to determine predictors of outcome and characterise clinical features of late responders to target treatment more effectively is recommended.

Ann Acad Med Singap 2024;53:471-80

Keywords: major depressive disorder, naturalistic, obsessive-compulsive disorder, remission, repetitive transcranial magnetic stimulation, response

CLINICAL IMPACT

What is New

- This is one of the largest naturalistic study reporting outcomes of rTMS therapy in Southeast Asia for the treatment of major depression and obsessive-compulsive disorders.

Clinical Implications

- This study demonstrated that rTMS treatment was a rapid-acting, effective, safe and well-tolerated alternative treatment option for treatment-resistant depression and obsessive-compulsive disorders.
- This finding could affect the clinical practice of rTMS dosing. Dosing additional rTMS treatment with more than 30 sessions might help more patients with major depression to have a meaningful improvement.

INTRODUCTION

Repetitive transcranial magnetic stimulation (rTMS) is a novel and noninvasive neuromodulation therapy used for treatment-resistant major depressive disorder (MDD)[1] and obsessive-compulsive disorder (OCD).[2] OCD and depression are disabling psychiatric disorders, which have a detrimental impact on individuals, their families and society.[3,4] The lifetime prevalence of depression is high at 5.8% and OCD affects 1 in 28 Singaporeans.[5] Depression contributes substantially to the global burden of disease and disability.[6] However, despite effective pharmacological and psychological interventions, approximately 40% to 50% of patients have not responded satisfactorily to standard treatment.[7]

rTMS involves placing an electromagnetic coil against the scalp, which generates repetitive pulses to depolarise neurons in the outer cortex of the brain (via an alternating magnetic field).[8] Following the US Food and Drug Administration clearance

[1] Neurostimulation Department, Institute of Mental Health, Singapore
[2] Mood Disorder Department, Institute of Mental Health, Singapore
Correspondence: Ms Ye Si Jia, Neurostimulation Department, Institute of Mental Health, 10 Buangkok View, Buangkok Green Medical Park, Singapore 539747.
Email: yesijia@gmail.com

in 2008 for MDD[1] and in 2018 for OCD, rTMS has been adopted into routine clinical practice and established a favourable effectiveness and safety profile for psychiatric disorders. It has emerged as a mainstream treatment in many developed countries,[9,10] including Singapore, where the College of Psychiatrists endorsed the use of rTMS for depression in 2015 and OCD in 2018.[11] rTMS service is provided by the Institute of Mental Health, Singapore's only tertiary psychiatric hospital, with 1900 inpatient beds and about 40,000 outpatients.[12]

Most recent naturalistic and registry studies of the rTMS treatment of MDD reported that overall response and remission rates have ranged between 29% to 51% and 6% to 37%,[13-18] respectively. Although rTMS for treating OCD has been promising, Rostami et al. reported a response rate of 46.2%, based on a 30% reduction of Yale–Brown Obsessive Compulsive Scale (Y-BOCS) baseline scores.[19] The efficacy of rTMS treatment for naturalistic OCD patients remains under-explored. rTMS is well accepted by both patients and psychiatrists due to its cost-effectiveness[20] and the absence of serious side effects.

The optimal dosage of rTMS is unknown. rTMS outcomes were heterogeneous based on response trajectory.[21,22] Hence, there was no gold standard regarding rTMS dosing across clinics: Griffiths et al. averaging 26.6 sessions (standard deviation [SD] 9.45),[15] Dowling et al. reported 20 sessions[14] and Carpenter et al. reported an average of 28.1 sessions (SD 10.1)[17] for MDD. Studies examining the number of rTMS sessions on the clinical outcome are inconclusive. In an Australian study, 40% of patients who were nonresponsive to the previous course responded to second and third courses with the same rTMS modalities.[13] On the contrary, Dowling et al. underscored the possibility that briefer rTMS courses (20 courses over 4 weeks) contribute to a superior response rate of 54% and remission rate of 28%.[14] Additionally, Feffer et al. found that with early treatment response achieved at 10 sessions,[22] the effectiveness of rTMS might diminish or plateau despite continued treatment with more sessions of previous modalities. Therefore, consistent and robust dose-response effects had not yet emerged. Guidelines in Singapore suggested that rTMS requires at least 30 sessions for optimal therapeutic effects, with some individuals possibly benefiting from longer courses.[11] rTMS was often perceived to be inconvenient and costly. Patients' access to additional courses was limited due to cost and time commitment. The Ministry of Health (MOH), Singapore has approved a subsidy to cover the expense of rTMS treatment for an initial 24 sessions.[23] Patients had to self-pay for additional sessions in case of delayed response or not having achieved remission. Given the logistical burden of rTMS, there was a need to understand the average trajectory of symptom changes during the rTMS course, and the patient profile might benefit from the pronged treatment course.

To date, studies describing rTMS service in Southeast Asia remain limited. Clinical trials in Singapore with a similar multiethnic Asian population demonstrated the efficacy of rTMS.[24,25] However, participants were subject to restrictive selection criteria. In naturalistic studies, patients differ from those recruited in research and have a broader range of symptomatology and comorbidity.[26]

This study addressed the gap with 2 main objectives. First, we aimed to describe the clinical profile and outcome of rTMS (response and remission rates). We sought to compare symptomatic changes in subgroups (MDD and OCD) from pre- to post-rTMS treatment. Second, we aimed to examine whether dosing additional treatment (>30 sessions) resulted in further meaningful clinical improvement for MDD. Hutton et al. suggested that rTMS courses with less than 30 sessions are associated with inferior endpoint outcomes.[27] We hypothesised that the cohort where patients received longer treatment courses had a trend of a larger reduction in depressive symptoms.

METHOD

Study participants

We retrospectively analysed a dataset of patients who received rTMS between June 2018 and April 2023 at the Institute of Mental Health, Singapore. Patients were included if they: (1) received rTMS for a primary diagnosis of MDD and OCD; (2) are ≥18 years old; (3) had completed both baseline and post-treatment assessment measures. Exclusion criteria included the following: (1) drug or alcohol abuse or dependence (preceding 3 months); (2) unable to give informed consent; (3) acute suicidality; (4) significant neurological disorder, which may pose an increased risk to rTMS (epilepsy); (5) metal in the cranium, metallic implants, skull defects, pacemaker or other implantable electronic devices; (6) pregnancy. Patient's sociodemographic and clinical characteristics, including rTMS treatment and outcome, were extracted from the Clinical Alliance and Research in Electroconvulsive Therapy and Related Therapies (CARE) research database.[28] Ethical approval to conduct the study was obtained from the National Healthcare Group's Domain Specific Review Board (Reference no.: 2023/00415).

Patients were referred for rTMS assessment by attending psychiatrists who had made clinical diagnoses based on the Diagnostic and Statistical Manual of Mental Disorder, 5th Edition. The patients were typically referred for treatment-resistant MDD/OCD. The subgroup of patients treated for OCD with comorbid depressive symptoms was grouped under the "OCD" diagnosis.

rTMS procedure

Before receiving rTMS treatment, patients were assessed by a psychiatrist who confirmed the patient's suitability. The pre-rTMS assessment included thoroughly screening the patient's sociodemographic, medical and psychiatric history. The individualised treatment dose was determined via the resting motor threshold (RMT) from the respective first dorsal interosseous muscle for dorsolateral prefrontal cortex (DLPFC) targets or foot motor cortex for OCD and dorsomedial prefrontal cortex (DMPFC).[1] All patients gave written consent.

After the rTMS psychiatrist's assessment and determination of the treatment dosage, trained nurses conducted scalp measurement and pre-treatment screening for patients at the next visit. Patients experienced the feel of the stimulation on their hands before the actual treatment. During treatment, rTMS was conducted in a room with facilities to manage seizures. Patients were seated in a reclining chair with earplugs. The treatment dosage started low (80% of RMT), and intensity was slowly ramped up based on the patient's tolerability. On average, patients achieved the prescribed dosage by the 4th session. Nurses observed the patient and made minor adjustments if the coil is out of place. Nurses also ensured the patients are comfortable by asking how they are faring. Patients signalled to the nurse if they wish to request time out. Patients with OCD experience the treatment regimen differently, as nurses are required to provoke the patient using the provocation script. The tailored provocation scripts were prepared by psychologists and designed to activate patients' OCD traits and brain circuitry.

rTMS was delivered using TMS machine MagPro X100 and Coil Cool D-B80 (MagVenture Inc, GA, US). Scalp-based measurements of the distance between tragus to tragus, and nasion to the inion, accounting for head circumference and size, were used to ensure accurate coil placement. The scalp measurement procedure requires patients to wear treatment caps snugly. Nurses will verify the consistency of treatment cap placement prior to each treatment. Patients were treated using 1 of the 5 protocols: (1) in the high frequency (HF)-rTMS protocol, 10 Hz, 3000 pulses with 120% of motor threshold were delivered to the left DLPFC. The Beam F3 method was used to locate the DLPFC, following the location coordinates using the Beam F3 software (X and Y+1.5 cm). (2) In the low frequency (LF)-rTMS protocol, 1 Hz, 1500 pulses with 120% RMT were delivered to the right DLPFC. (3) In the dorsomedial (DM)-rTMS protocol, 20 Hz, 1200 pulses with 120% motor threshold were delivered to DMPFC, defined as 25% of the distance between the nasion to the inion along the midline of the head. The coil handle alternates from the right and left sides of the head.[29] (4) In the AF8-rTMS protocol, 1 Hz, 720 pulses with 120% RMT were delivered to the right orbitofrontal cortex, defined as 10% of the distance between the nasion to the inion anterior to the vertex in the sagittal plane, then 10% of head circumference to the right. The coil was orientated laterally with a handle perpendicular to the axial plane of the head.[30] (5) In the OCD-rTMS protocol, 2000 pulses with 100% RMT were delivered over 4 cm anterior to the optimal spot on the scalp, stimulating bilateral feet. The type of treatment and number of rTMS sessions were prescribed by the rTMS psychiatrist. Generally, 1 standard treatment course lasts about 20–30 minutes for 5 daily sessions per week, up to 24–30 sessions over 4–6 weeks, followed by maintenance treatment. Subsidies approved by MOH are currently only available for treatment-resistant major depressive disorder for the first 24 sessions in an acute course. Patients must self-pay a small amount of cash out of pocket. The cost of extended rTMS sessions was paid entirely by the patients. All patients received a standard course of 30 daily treatments. Those who achieved a >25% Montgomery–Åsberg Depression Rating Scale (MADRS) improvement at session 30 were offered additional treatment to optimise treatment response and durability. Clinically, the rTMS psychiatrist stopped at 30 sessions based on whether patients showed ≤25% improvement in MADRS score. Factors to consider in extending the acute course include a history of late response to anti-depressant treatment in prior episodes, having a lengthy duration of present episodes, being highly treatment-resistant, ability to pay, tolerability and convenience.[31]

Outcome measures

The MADRS,[32] Y-BOCS[33] and Clinical Global Impressions-Severity (CGI-S)[34] were assessed by the rTMS psychiatrist at baseline, and then fortnightly or after every 10 treatments until

completion of the acute course. Depression Anxiety and Stress Scale-21 (DASS-21)[35] was administered as a self-rated scale weekly.

MADRS was used to measure depression severity. The response was defined as a reduction ≥50% from baseline in MADRS score, and remission was defined as an MADRS score ≤10.[36] Y-BOCS were used to assess the clinical severity of obsessive symptoms, and the response rate is defined by a 20% or less reduction in baseline Y-BOCS score. The MADRS, Y-BOCS, CGI-S and DASS-21 were the primary outcome measures, and the other measures were treated as secondary measures.

Statistical analysis

A descriptive analysis was performed for sociodemographic, clinical rTMS characteristics and baseline assessment scores. Paired t-tests were used for continuous variables and chi-squared tests for categorical variables. Continuous variables were presented as mean (SD), whereas categorical variables were presented as percentages.

The number of rTMS treatment sessions was stratified into ≤30 sessions and >30 sessions. The trend difference in changes of MARDS scores from baseline to post-treatment in the 2 subgroups was analysed by Levene's test for equality of ariances and paired t-test. All statistical analyses were conducted using IBM SPSS Statistics version 22.0 (IBM Corp, Armonk, NY, US). Statistical significance was set at $P<0.05$.

RESULTS

Patient sociodemographic and clinical characteristics

A total of 71 patients (MDD 58 [81.7%]/OCD 13 [18.3%]) received a mean average of 47.8 (SD 40.5) rTMS sessions. The mean average age was 33.6 (SD 14.8), and there were more females (60%). Of the 71 patients, 33.8% were highly educated (defined by education level above university). The largest ethnic group was Chinese (73.2%), compared to Indian (14.1%), Malay (5.6%) and Others (7.0%).

This study population was mostly severely ill (based on baseline CGI-S score) and was typically referred for rTMS due to treatment resistance to pharmacological treatment (64.8%) with more than 24 months of illness duration (29.6%) and 3 or more previous episodes of their illness (28.2%). The majority of the rTMS treatment was left DLPFC (45%). Patients were receiving treatment with concomitant medications/therapy: antidepressants (73.2%), benzodiazepine (47%), clozapine (5.6%) and antipsychotics besides clozapine (40%); and 21.2% had tried electroconvulsive therapy (ECT) in the past.

Safety and tolerability

To ensure tolerability during stimulation, patients will undergo periodic mood assessments by rTMS psychiatrists after every 10th treatment. In addition, before and after each rTMS session, patients will be asked about any side effects and adverse events experienced. Spontaneous reports of side effects will be documented, and the rTMS psychiatrist will be notified. Most patients treated with rTMS reported no significant adverse events. There have been no seizures or mood switches to mania. The commonly reported adverse side effects were localised discomfort and mild headaches during the first week of treatment.

rTMS treatment outcome

For patients diagnosed with depression, rTMS induced an improvement in depressive symptoms. The response rate and remission rate were 20.8% and 17%, respectively. The MADRS total mean score improved from a baseline of 28.1 (SD 7.3) to 20.7 (SD 10.1) ($P<0.0001$). The patients were assessed as "markedly ill" based on CGI-S baseline mean score, which improved significantly ($P<0.0001$), from 4.6 (SD 0.8) to 3.3 (SD 1.2). For self-rated scales, DASS-21 total mean score improved from 67.3 (SD 24.6) to 49.6 (SD 28.0) ($P<0.0001$) (Table 2).

Y-BOCS displayed a trend towards improvement from 30.1 (SD 7.5) to 27.2 (SD 6.9) ($P=0.799$). However, 44.4% of patients with OCD responded with at least 20% reduction in baseline Y-BOCS (Table 3).

Clinical outcome is stratified by the number of rTMS treatment sessions

We further examined clinical outcomes in MDD patients based on the number of rTMS sessions. The subgroup of 35.8% of patients with less than 30 rTMS sessions had contributed disproportionately to nonresponse (85.7%). Patients who received rTMS treatment (>30 sessions) had a trend of larger improvement of MADRS score when compared to patients with (≤30 sessions) (9.4 [SD 9.7] vs 3.8 [SD 12.3] [$P=0.078$]) (Tables 4 and 5).

DISCUSSION

To our knowledge, this is the largest naturalistic study reporting outcomes in rTMS therapy in Southeast Asia for the treatment of MDD and OCD. This study demonstrated that rTMS treatment was a rapid-acting, effective, safe and well-tolerated

Table 1. Sociodemographic and clinical characteristics of the study sample.

Patient characteristics		Mean	SD
Age	71 patients	33.6	14.8
Average no. of rTMS sessions	70	47.89	40.5
		N	Percentage
Sex	Female	43	60.6
	Male	28	39.4
Ethnicity	Chinese	52	73.2
	Indian	10	14.1
	Malay	4	5.6
	Others	5	7.0
Education level	University and above	24	33.8
	College/Junior college	19	26.7
	The Institute of Technical Education/Diploma	9	0.1
	Secondary and below	13	18.3
MDD treatment sessions[a]	≤30 sessions	19	35.8
	>30 sessions	34	64.2
OCD treatment sessions	≤30 sessions	5	38.5
	>30 sessions	8	61.5
Diagnosis	OCD	13	18.3
	MDD	58	81.7
Treatment sites	F3	32	45.1
	F4	13	18.3
	OCD spot	13	18.3
	DMPFC	2	2.8
	AF8	11	15.5
Switching of rTMS modality	No	48	67.6
	Yes	22	31.0
Admission status	Inpatient (involuntary)	11	15.5
	Inpatient (voluntary)	18	25.4
	Outpatient	41	57.7
Duration of current episode[a]	Acute (≤12 months)	19	26.8
	Sub-acute (13–24 months)	11	15.5
	Chronic (>24 months)	21	29.6

Table 1. Sociodemographic and clinical characteristics of the study sample. (Cont'd)

Patient characteristics		N	Percentage
Previous depressive episode, range[a]	0	5	7.0
	1–3	17	23.9
	>3	20	28.2
Main reasons refer to TMS treatment	Difficult to treat with medications (poor tolerability/risks)	2	2.8
	Failure of medications	46	64.8
	Suicide	4	5.6
	Patient preference	6	8.5
	Previous good response to this treatment modality	1	1.4
	Others	1	1.4
Antidepressant[a]	No	5	7.0
	Yes	52	73.2
Clozapine[a]	No	52	73.2
	Yes	4	5.6
Antipsychotics other than clozapine[a]	No	27	38.0
	Yes	29	40.8
Lithium[a]	No	46	64.8
	Yes	10	14.1
Anticonvulsant[a]	No	39	54.9
	Yes	18	25.4
Stimulant[a]	No	51	71.8
	Yes	6	8.5
Benzodiazapine[a]	No	23	32.4
	Yes	34	47.9
No. of failed antidepressants	Failed ≥3 antidepressant	47	66.2
	Failed 1–2 antidepressant	15	21.1
	Failed 0 antidepressant	1	1.4
Past use of/Response to ECT[a]	No prior ECT	40	56.3
	Good response to prior ECT	2	2.8
	Partial response to prior ECT	6	8.5
	Poor response to prior ECT	7	9.9

[a]Data total not complete due to missing value
AF8: right orbitofrontal cortex; DMPFC: dorsomedial prefrontal cortex; ECT: electroconvulsive therapy; F3: left dorsolateral prefrontal cortex; F4: right dorsolateral prefrontal cortex; MDD: major depressive disorder; OCD: obsessive-compulsive disorder; rTMS: repetitive transcranial magnetic stimulation; SD: standard deviation

Table 2. rTMS-associated change of clinical MDD assessment outcome before and after treatment.

Assessment scales	Pre-rTMS			Post-rTMS			Paired t-test *P* value
	N	Mean	SD	N	Mean	SD	
MADRS	53	28.1	7.3	53	20.7	10.1	0.0001[a]
CGI-S	52	4.6	0.8	52	3.3	1.2	0.0001[a]
DASS-21 total scores	51	67.3	24.6	51	49.6	28.0	0.0001[a]

[a] Independent t-test: $P<0.001$
CGI-S: Clinical Global Impressions-Severity; DASS-21: Depression Anxiety and Stress Scale-21; MARDS: Montgomery–Åsberg Depression Rating Scale; MDD: major depressive disorder; rTMS: repetitive transcranial magnetic stimulation; SD: standard deviation

Table 3. rTMS-associated change of clinical OCD assessment outcome before and after treatment.

Assessment scale	Pre-rTMS			Post-rTMS			Paired t-test *P* value
	N	Mean	SD	N	Mean	SD	
Y-BOCS	12	30.1	7.5	11	27.2	6.9	0.799

OCD: obsessive-compulsive disorder; rTMS: repetitive transcranial magnetic simulation; SD: standard deviation; Y-BOCS: Yale–Brown Obsessive Compulsive Scale

Table 4. Change of MADR score stratified by 2 subgroups.

	Session	N	Mean	SD	Standard error mean
MADRSc	≤30	19	3.8	12.3	2.8
	>30	34	9.4	9.7	1.6

MADR: Montgomery–Åsberg Depression Rating Scale; MADRSc: change of MARDS score from baseline to post-rTMS treatment; SD: standard deviation

Table 5. Clinical outcome associated with change of MADR score.

		Levene's test for equality of variances		t-test for equality of means						
		F	Sig.	T	df	Sig. (2-tailed)	Mean difference	Standard error difference	95% confidence interval of the difference	
									Lower	Upper
MADRSc	Equal variances assumed	3.242	0.078[a]	-1.8	51	0.078	-5.517	3.067	-11.68	0.641
	Equal variances assumed			-1.7	30.69	0.103	-5.517	3.28	-12.21	1.176

[a] $P=0.078$
MADR: Montgomery–Åsberg Depression Rating Scale; MADRSc: change of MARDS score from baseline to post-rTMS treatment

alternative treatment option for treatment-resistant MDD and OCD. Patients who received more than 30 sessions of an rTMS course are more likely to have improvement in depressive symptom severity than those having less than 30 sessions.

This study showed the efficacy of rTMS, using novel neurostimulation techniques in treatment-resistant OCD and MDD. Results were consistent across naturalistic clinics using different outcome measurements, including Y-BOCS, Hamilton Depression Rating Scale (HAM-D), HAMD-17 and CGI-S. There were 44.4% of patients with OCD who responded to rTMS—this result was consistent with previous studies, which reported a response rate of 40% to 55% based on the minimal 30% to 35% reduction in Y-BOCS baseline score.[19,37] In comparing our depression clinician-reported outcome with similar naturalist studies, the remission rate of 17% was encouraging and comparable to 3 studies: 25.5% (HAM-D)[15] and 28% (HAMD-17),[14] lower than 37.1% (CGI-S).[17] However, the response rate of 20.8% was less robust than most studies that reported the response rates of 40.4% (HAM-D),[15] 54% (HAMD-17)[14] and 58.0% (CGI-S).[17]

The reasons for this difference remain unclear. Our treatment population displayed greater treatment resistance as evidenced by a higher proportion of failing at least 2 antidepressant trials when compared to Carpenter et al. (66.2% vs 54%). Higher baseline symptom severity and treatment resistance have been identified indicators of poor response to rTMS.[18] In our study, the proportion of patients receiving prior ECT was higher than in Carpenter et al.'s sample (18.6% vs 5.2%).[17] Galletly et al. found that prior ECT exposure was a significant nonresponse to rTMS.[13] The difference in outcome measurements and the varying definitions of treatment response used highlight the need to have a standardised definition of treatment response to facilitate fair comparisons of treatment outcomes across clinics.

Consistent with above hypothesis on the need for standardised definitions, the second finding suggested that dosing additional rTMS treatment with more than 30 sessions might help more MDD patients to have a meaningful improvement. This finding disagreed with the approach to exclude non-responders from further treatment with rTMS or predict poor response to rTMS at 10 sessions at 2 weeks.[22] Non-responders identified at session 10 could convert to responders with progressively longer rTMS courses administered beyond 30 sessions at a steady and slower rate.[27] Wilson et al. explained that daily conventional rTMS (i.e. 30 sessions over 6 weeks) would be insufficient for late-responders with highly treatment-resistant illnesses.[31] The average trajectory of depressive symptom changes for late responders corresponded to the rTMS course, which showed that the effectiveness of rTMS declined sharply after 10 sessions but peaked after 30 sessions.[27] Interestingly, this finding differs from ECT dosing (another form of neuromodulation therapy). Chan et al. suggested that the largest clinical improvement for most patients would be between the third and sixth ECT sessions with a plateau of treatment response after 6 sessions.[38] rTMS efficacy was dose-dependent. Robust dose and response effects were further supported by 2 studies: dosing an additional 6 sessions in non-responders after completing 20 treatment sessions resulted in a 61% response rate.[39] Preservation rTMS was used as a safe and effective strategy to sustain positive outcomes after completing an acute course of rTMS.[31] This study's results could help prevent the premature termination of rTMS treatment and potentially affect the clinical practice of rTMS dosing. However, not all patients had access to additional/preservation rTMS due to travel, cost, rTMS capacity or other constraints. These factors could confound the treatment outcome beyond 30 sessions. Future interventions, such as accelerated rTMS modalities, addressed this practical issue by adding more sessions and could theoretically expedite treatment response time.[24]

The strengths of this study include the use of clinician-rated and self-report scales to determine rTMS outcomes. The dual-source measurement outcomes offer a complimentary source of confidence in our findings, directly and indirectly reflecting the patient's mood and general condition pre- and post-RTMS treatment.

One of the limitations was missing data. The team could not ensure a complete assessment of secondary outcome measurement at the end of acute rTMS treatment. The sample size of 58 (MDD) and 13 (OCD) resulted in insufficient power to detect any significant demographic and clinical predictors of rTMS response. Another limitation was that patients continued their concurrent psychiatric medication unchanged during the rTMS course. Certain drugs (i.e. benzodiazepine, lithium) that could potentially undermine rTMS response had been screened by rTMS psychiatrists and withheld before pursuing rTMS treatment. However, similar to other observational studies, we did not control the factors that were known to attenuate rTMS efficacy, such as concomitant antipsychotic use in depression with psychotic features.

Further analysis of responders and non-responders to rTMS treatment should be conducted systematically by comparing their sociodemographic and clinical predictors. Doing so will facilitate the appropriate selection of rTMS patients as well as the optimisation of rTMS techniques (e.g. individual neuro-navigation) to have an optimal clinical outcome. Future studies need to characterise the clinical features of late responders.

CONCLUSION

In summary, at a group level, patients with MDD and OCD in Southeast Asia responded well to rTMS treatment. Patients who received longer rTMS (≥30 sessions) may be associated with better antidepressant outcomes. Additionally, the result of this study supports revising long-term rTMS subsidies for treatment-resistant depression to cover at least 30 sessions to better address clinical needs.

Declaration

The authors declare there are no affiliations with or involvement in any organisation or entity with any financial interest in the subject matter or materials discussed in this manuscript.

Ethics statement

The manuscript was approved by the National Healthcare Group's Domain Specific Review Board (Reference no.: 2023/00415).

Acknowledgement

The authors would like to acknowledge the staff of the neurostimulation unit for assistance with data collection.

REFERENCES

1. McClintock SM, Reti IM, Carpenter LL, et al. Consensus recommendations for the clinical application of repetitive transcranial magnetic stimulation (rTMS) in the treatment of depression. J Clin Psychiatry 2018;79:2-3.
2. Perera MPN, Mallawaarachchi S, Miljevic A, et al. Repetitive Transcranial Magnetic Stimulation for Obsessive-Compulsive Disorder: A Meta-analysis of Randomized, Sham-Controlled Trials. Biol Psychiatry Cogn Neurosci Neuroimaging 2021;6:947-60.
3. Albert U, Aguglia A. Treatment-Resistant Obsessive-Compulsive Disorder (OCD): Current Knowledge and Open Questions. Clin Neuropsychiatry 2013;10:19-30.
4. Ho RCM, Mak KK, Chua ANC, et al. The effect of severity of depressive disorder on economic burden in a university hospital in Singapore. Expert Rev Pharmacoecon Outcomes Res 2013;13:549-59.
5. Subramaniam M, Abdin E, Vaingankar JA, et al. Minding the treatment gap: results of the Singapore Mental Health Study. Soc Psychiatry Psychiatr Epidemiol 2020;55:1415-24.
6. World Health Organization. World health statistics 2019: Monitoring health for the SDGs, sustainable development goals. https://www.who.int/publications/i/item/9789241565707. Accessed 12 August 2023.
7. Rush JA, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry 2006;163:1905-17.
8. George MS, Post RM. Daily left prefrontal repetitive transcranial magnetic stimulation for acute treatment of medication-resistant depression. Am J Psychiatry 2011; 168:356-64.
9. Milev RV, Giacobbe P, Kennedy SH, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder: Section 4. Neurostimulation Treatments. Can J Psychiatry 2016;61:561-75.
10. Karasu B, Universities Y, Wang P, et al. Practice Guideline for the Treatment of Patients with Major Depressive Disorder (Revision). Am J Psychiatry 2000;157;1-45.
11. Academy of Medicine, Singapore. Practice Guidelines | Repetitive transcranial magnetic stimulation in the treatment of major depressive disorder, 2018. https://www.ams.edu.sg/view-pdf.aspx?file=media%5C4381_fi_752.pdf&ofile=Guidelines+for+rTMS+Treatment+of+Major+Depressive+Disorder+20180522+(fin....pdf. Accessed 13 August 2024.
12. Tan XW, Oon LK, Tsang YYT, et al. A Pilot Study of Switching Electroconvulsive Therapy for Patients with Treatment-Resistant Schizophrenia or Mood Disorder. J ECT 2021;37:202-6.
13. Galletly CA, Clarke P, Carnell BL, et al. A clinical repetitive transcranial magnetic stimulation service in Australia: 6 years on. Aus N Z J Psychiatry 2015;49:1040-7.
14. Dowling NL, Bonwick R, Dharwadkar NP, et al. Repetitive transcranial magnetic stimulation for major depression: A naturalistic observational study in an Australian private hospital. Psychiatry Res 2020;291:113275.
15. Griffiths C, O'Neill-Kerr A, Millward T, et al. Repetitive transcranial magnetic stimulation (rTMS) for depression: outcomes in a United Kingdom (UK) clinical practice. Int J Psychiatry Clin Pract 2019;23:122-7.
16. Sackeim HA, Aaronson ST, Carpenter LL, et al. Clinical outcomes in a large registry of patients with major depressive disorder treated with Transcranial Magnetic Stimulation. J Affect Disord 2020;277:65-74.
17. Carpenter LL, Janicak PG, Aaronson ST, et al. Transcranial magnetic stimulation (TMS) for major depression: A multisite, naturalistic, observational study of acute treatment outcomes in clinical practice. Depress Anxiety 2012;29:587-96.
18. Fitzgerald PB, Hoy KE, Anderson RJ, et al. A STUDY OF THE PATTERN OF RESPONSE TO rTMS TREATMENT IN DEPRESSION. Depress Anxiety 2016;33:746-53.
19. Rostami R, Kazemi R, Jabbari A, et al. Efficacy and clinical predictors of response to rTMS treatment in pharmacoresistant obsessive-compulsive disorder (OCD): a retrospective study. BMC Psychiatry 2020;20:372.
20. Zhao YJ, Tor PC, Khoo AL, et al. Cost-Effectiveness Modeling of Repetitive Transcranial Magnetic Stimulation Compared to Electroconvulsive Therapy for Treatment-Resistant Depression in Singapore. Neuromodulation 2018;21:376-82.
21. Kaster TS, Downar J, Vila-Rodriguez F, et al. Trajectories of Response to Dorsolateral Prefrontal rTMS in Major Depression: A THREE-D Study. Am J Psychiatry 2019;176:367-75.

22. Feffer K, Lee HH, Mansouri F, et al. Early symptom improvement at 10 sessions as a predictor of rTMS treatment outcome in major depression. Brain Stimul 2018;11:181-9.
23. Agency for Care Effectiveness. Repetitive transcranial magnetic stimulation for adults with treatment-resistant major depressive disorder. https://www.ace-hta.gov.sg/healthcare-professionals/ace-technology-guidances/details/repetitive-transcranial-magnetic-stimulation-for-adults-with-treatment-resistant-major-depressive-disorder. Accessed 13 August 2024.
24. Tan XW, Abdin E, Tor PC. Accelerated transcranial magnetic stimulation (aTMS) to treat depression with treatment switching: study protocol of a pilot, randomized, delayed-start trial. Pilot Feasibility Stud 2021;7:104.
25. Tor PC, Gálvez V, Goldstein J, et al. Pilot Study of Accelerated Low-Frequency Right-Sided Transcranial Magnetic Stimulation for Treatment-Resistant Depression. J ECT 2016;32:180-2.
26. Leon AC. Evaluation of psychiatric interventions in an observational study: issues in design and analysis. Dialogues Clin Neurosci 2011;13:191-8.
27. Hutton TM, Aaronson ST, Carpenter LL, et al. Dosing transcranial magnetic stimulation in major depressive disorder: Relations between number of treatment sessions and effectiveness in a large patient registry. Brain Stimul 2023;16:1510-21.
28. Martin DM, Gálvez V, Lauf S, et al. The Clinical Alliance and Research in Electroconvulsive Therapy Network: An Australian Initiative for Improving Service Delivery of Electroconvulsive Therapy. J ECT 2018;34:7-13.
29. Bakker N, Shahab S, Giacobbe P, et al. rTMS of the dorsomedial prefrontal cortex for major depression: safety, tolerability, effectiveness, and outcome predictors for 10 Hz versus intermittent theta-burst stimulation. Brain Stimul 2015;8:208-15.
30. Feffer K, Fettes P, Giacobbe P, et al. 1Hz rTMS of the right orbitofrontal cortex for major depression: Safety, tolerability and clinical outcomes. Eur Neuropsychopharmacol 2018;28:109-17.
31. Wilson S, Croarkin PE, Aaronson ST, et al. Systematic review of preservation TMS that includes continuation, maintenance, relapse-prevention, and rescue TMS. J Affect Disord 2022;296:79-88.
32. Quilty LC, Robinson JJ, Rolland JP, et al. The structure of the Montgomery-Åsberg depression rating scale over the course of treatment for depression. Int J Methods Psychiatr Res 2013;22:175-84.
33. Goodman WK, Price LH, Rasmussen SA, et al. The Yale-Brown Obsessive-Compulsive Scale. I. Development, use, and reliability. Arch Gen Psychiatry 1989;46:1006-11.
34. Busner J, Targum SD. The clinical global impressions scale: applying a research tool in clinical practice. Psychiatry (Edgmont) 2007;4:28-37.
35. Lovibond PF, Lovibond SH. The structure of negative emotional states: comparison of the Depression Anxiety Stress Scales (DASS) with the Beck Depression and Anxiety Inventories. Behav Res Ther 1995;33:335-43.
36. Rush AJ, Kraemer HC, Sackeim HA, et al. Report by the ACNP Task Force on response and remission in major depressive disorder. Neuropsychopharmacology 2006;31:1841-53.
37. Singh S, Kumar S, Gupta A, et al. Effectiveness and Predictors of Response to 1-Hz Repetitive Transcranial Magnetic Stimulation in Patients With Obsessive–Compulsive Disorder 2019;35:61-6.
38. Chan CYW, Abdin E, Seow E, et al. Clinical effectiveness and speed of response of electroconvulsive therapy in treatment-resistant schizophrenia. Psychiatry Clin Neurosci 2019;73:416-22.
39. Yip AG, George MS, Tendler A, et al. 61% of unmedicated treatment resistant depression patients who did not respond to acute TMS treatment responded after four weeks of twice weekly deep TMS in the Brainsway pivotal trial. Brain Stimul 2017;10:847-9.

Ann Acad Med Singap 2024;53:481-9
https://doi.org/10.47102/annals-acadmedsg.2023374

ORIGINAL ARTICLE

Long-term outcomes of subthalamic nucleus deep brain stimulation for Parkinson's disease in Singapore

Yi Zhan Cai[1], Yilong Zheng[2], Wei Li[3,4,5] *MN*, Saffari Seyed Ehsan[3,5] *PhD*, Hwee Lan Ng[3,4,5] *BSc (Nursing)*, Angela Zhan[3,4,5] *MN*, Zheyu Xu[3,4,5] *MB BChir*, Kay Yaw Tay[3,4,5] *MBBS*, Wing Lok Au[3,4,5] *MBBS*, Wai Hoe Ng[3] *MBBS*, Louis Chew Seng Tan[3,4,5] *MBBS*, Wan Kai Rui[3,4,5] *FRCS*, Shermyn Neo[3,4,5] *MBBS*

ABSTRACT

Introduction: Subthalamic nucleus deep brain stimulation (STN-DBS) is a proven treatment modality for Parkinson's disease (PD), reducing dyskinesia and time spent in the "OFF" state. This study evaluates the long-term outcomes of STN-DBS in PD patients up to 10 years post-surgery in Singapore.

Method: We conducted a retrospective review of Movement Disorders Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) scores, activities of daily living (ADLs), disease milestones, dopaminergic drug prescriptions, and adverse events in patients before and after STN-DBS surgery.

Results: A total of 94 PD patients who underwent bilateral STN-DBS were included. STN-DBS reduced time in the "OFF" state by 36.9% at 1 year (P=0.034) and 40.9% at 5 years (P=0.006). Time with dyskinesia did not significantly change. Levodopa equivalent daily dose was reduced by 35.1% by 5 years (P<0.001). MDS-UPDRS-II and III scores increased from 5 years post-DBS by 40.5% and 35.4%, respectively. Independence in ADLs decreased, though not significantly. The prevalence of frequent falls increased at 5 years. Surgery- and device-related adverse events were uncommon and generally mild.

Conclusion: STN-DBS provides sustained relief from motor complications and reduced medication requirements in PD patients in Singapore. This study highlights STN-DBS as an effective treatment option, significantly enhancing the quality of life for those with PD.

Ann Acad Med Singap 2024;53:481-9

Keywords: deep brain stimulation, neurology, neurosurgery, Parkinson's disease, subthalamic nucleus

CLINICAL IMPACT

What is New

- This is the first study examining both short-term and long-term outcomes of deep brain stimulation (DBS) in Parkinson's disease within Singapore.
- Subthalamic nucleus deep brain stimulation (STN-DBS) is shown to effectively reduce motor fluctuations and dyskinesia, even in an older cohort (mean age 60.6 years).
- The rate of adverse events related to STN-DBS in Singapore is low and comparable to global standards.

Clinical Implications

- STN-DBS is a highly effective treatment in improving clinical outcomes in patients in Singapore with Parkinson's disease, demonstrating a favourable risk profile.

INTRODUCTION

Parkinson's disease (PD) is a chronic and progressive neurodegenerative disorder characterised by motor symptoms such as limb bradykinesia, rigidity and resting tremor.[1] Non-motor symptoms, including mood disturbances, cognitive impairment, autonomic dysfunction and sleep disorders, are also common. Disease progression often leads to motor fluctuations and dyskinesias, along with worsening non-motor features. Deep brain stimulation (DBS) is a well-recognised surgical treatment for PD, especially for patients who respond to levodopa but experience refractory motor complications or intolerable medication side effects.[2] The 2 primary DBS targets in PD are the subthalamic nucleus (STN) and the internal segment of the globus pallidus (GPi).[3-5] Both targets are effective in improving motor symptoms,[5] but STN-DBS is particularly noted for significantly reducing levodopa dosage,[6] thus lowering drug burden and costs for patients.[7,8]

[1] Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore
[2] Yong Loo Lin School of Medicine, National University of Singapore, Singapore
[3] National Neuroscience Institute, Singapore
[4] Parkinson's Foundation Center of Excellence, United States of America
[5] Duke-NUS Medical School, Singapore
Correspondence: Dr Shermyn Neo, National Neuroscience Institute, 11 Jalan Tan Tock Seng, Singapore 308433.
Email: shermyn.neo.x.m@singhealth.com.sg
This article was first published online on 20 August 2024 at annals.edu.sg

In Singapore, STN-DBS is the most frequently utilised advanced surgical therapy for PD. STN-DBS has been shown to be more effective than medical therapy alone in alleviating motor complications,[9] with benefits potentially extending up to 10 years post-surgery.[10] However, there is a lack of data on the outcomes of STN-DBS of PD patients in Singapore. Given the invasive nature of the procedure, high implant cost and the need for periodic replacement of implantable generators, further data is essential to help clinicians and patients evaluate the risks and benefits of STN-DBS. This retrospective study aims to assess the short- and long-term outcomes (up to 10 years) of STN-DBS at the largest tertiary neurological centre in Singapore, with the primary focus on the efficacy of STN-DBS in reducing motor complications associated with levodopa therapy.

METHOD

Study population

This observational study utilises data from the National Neuroscience Institute's Parkinson's Disease and Movement Disorder (PDMD) database. Since 2002, the PDMD database has prospectively collected sociodemographic and medical information of all patients diagnosed with PD based on the National Institute of Neurological Disorders and Stroke (NINDS) criteria at the National Neuroscience Institute in Singapore. We extracted and analysed data for patients who underwent STN-DBS between 2008 to 2022 from electronic health records. For our surgical protocol, all patients were awake during the procedure, and multi-electrode recording was routinely employed. Bilateral STN leads were implanted simultaneously, as it was observed that patients rarely agreed to a second procedure later. Accurate placement of electrodes was confirmed through intra-operative macrostimulation and post-operative T2-weighted MRI.[11] Patients with electrodes implanted outside the subthalamic nucleus or those who underwent unilateral electrode implantation were excluded from the study. In our centre, rechargeable implantable pulse generators (IPGs) were only used in 4.6% of initial insertions, typically for younger patients. Older patients often preferred non-rechargeable models to avoid the hassle of regular battery charging, and earlier rechargeable IPG models offered only a marginal advantage in lifespan. For patients without written consent for data collection, only data up to March 2019 were used, in compliance with updated regulations requiring participant consent for inclusion in retrospective databases. The study was approved by the SingHealth Centralised Institutional Review Board (CIRB 2019/2039).

Data collection

Patient records, including Movement Disorders Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) sub-scores and total scores, PD clinic notes, operating theatre notes, drug prescriptions, and input from relevant specialities were reviewed for the study. The MDS-UPDRS, a revision of the original UPDRS, measures PD severity across 4 domains: non-motor aspects of daily living, motor aspects of daily living, motor examination and motor complications. Each item within these domains is graded on a scale of 0 to 4, with 4 being the most severe. Our centre switched from UPDRS to MDS-UPDRS in 2014, as the latter better captures non-motor symptoms and distinguishes between slight and mild manifestations of PD.[12] The primary outcome was the difference in time spent in the "OFF" state (MDS-UPDRS item 4.3 or UPDRS item 39), and time spent with dyskinesia (MDS-UPDRS item 4.1 or UPDRS item 32), measured at the 1-year ± 6 months (1Y), 5-year ± 6 months (5Y), and 10-year ± 6 months (10Y) periods post-operation, compared to the pre-operative baseline (POB). Secondary outcomes included the impact of DBS on MDS-UPDRS motor and non-motor scores, activities of daily living (ADLs), disease milestones (frequent falls, dementia and institutionalisation), changes in dopaminergic medication dosages, and adverse events associated with DBS. MDS-UPDRS Non-Motor Aspects of Experience of Daily Living (MDS-UPDRS-I), Motor Aspects of Experience of Daily Living (MDS-UPDRS-II), and Motor Examination (MDS-UPDRS-III) scores were evaluated at the same time points. All MDS-UPDRS-III scores were assessed with patients in the "ON" state. For consistency, all UPDRS scores were converted to their corresponding MDS-UPDRS scores. Data on ADLs were obtained from PD clinic notes, covering feeding, dressing, washing, toileting, transferring and walking. Patients requiring assistance with 3 or more ADLs were classified ADL-dependent, following practice guidelines in Singapore.[13] The percentage of ADL-dependent patients was compared pre- and post-operation. Significant disease milestones, such as frequent falls (as ≥2 falls within a 12-month period), dementia (identified by the prescription of cholinesterase inhibitors or memantine)[14] and institutionalisation, were recorded from clinic notes. Dopaminergic medication dosages were converted to levodopa equivalent daily doses (LEDD)[15] and compared from a pre-operative baseline to the 1-year, 5-year and 10-year time

points. Adverse events (AEs), defined as any undesirable outcome associated with the surgery or post-surgical DBS, were categorised into surgery-related, device-related and stimulation-related AEs. All AEs were recorded at intervals of 30 days, 6 months, 1 year, 5 years and 10 years post-operation. Stimulation-related AEs are excluded at the 30-day time point as DBS programming only began 1 month post-operatively.

For all pre-operative data, the most recent data within 18 months before the operation date were used. For post-operative follow-ups, the data entry closest to each time point was used, up to within 3 months.

Statistical analysis

For both primary and secondary outcomes, the Wilcoxon signed-rank test was used to compare follow-up with pre-operative data. All tests were two-tailed and done at the 0.05 level of significance. Continuous variables are presented as mean ± SD. Statistical analyses were performed using SPSS version 26 (IBM Corp, Armonk, US).

RESULTS

Between 2008 and 2022, our centre treated 2,490 PD patients, comprising 1,420 males (57.0%) and 1070 females (43.0%). The ethnic composition included 2038 Chinese (81.1%), 122 Malay (4.9%), 140 Indian (5.6%) and 190 from other racial backgrounds (7.6%). This demographic distribution is reflected in our study population (Table 1). Of 2,490 PD patients, 118 underwent STN-DBS. For this study, we included 94 patients with relevant primary or secondary outcome data. We excluded 23 patients due to lack of consent for data collection, and 1 patient due to missing data. The study cohort was primarily male (66%) and Chinese (76%), with a mean age at operation of 61 years, and a mean disease duration of 152 months (Table 1). The number of STN-DBS surgeries increased steadily from 2011 to 2018, peaking between 2016 and 2019. However, the number of surgeries declined from 2020 onwards due to the COVID-19 pandemic (Fig. 1). During the follow-up period, there were 13 mortalities. Pneumonia was the most common cause (8 cases), followed by cardiac arrest (1 case) and pulmonary embolism (1 case). No deaths were directly associated with the DBS surgery or implants. The cause of death was unavailable in 3 patients.

Primary outcomes

Out of the 94 patients included in the study, 79 had data relating to the primary outcomes. Compared to baseline (1.49 ± 0.87, n=77), time spent in the "OFF" state decreased significantly by 36.9% at 1 year (0.94 ± 1.00, n=52; *P*=0.034) and by 40.9% at 5 years (0.88 ± 1.03, n=41; *P*=0.006). However, this reduction was not maintained at 10 years (1.00 ± 1.28, n=12, *P*=0.44). Similarly, compared to baseline (0.73 ± 0.87, n=79), the time spent with dyskinesias decreased at 1 year (0.47 ± 0.70, n=51; *P*=0.10), 5 years (0.51 ± 0.84, n=41; *P*=0.15) and 10 years (0.25 ± 0.87, n=12, *P*=0.23), but these reductions were not statistically significant (Fig. 2).

Table 1. Breakdown of patient demographics.

Patient demographics (n=94)	
Sex (M/F)	62/32
Ethnicity (Chinese/Malay/Indian/Others)	71/13/5/5
Age at diagnosis (years)	50.33 ± 7.75
Age at DBS operation (years)	60.62 ± 6.83
Disease duration as of DBS operation (months)	152.39 ± 62.27
Pre-op MDS-UPDRS-III score (OFF)	55.62 ± 24.42
Pre-op MDS-UPDRS-III score (ON)	25.80 ± 12.42
Levodopa responsiveness (% improvement)	51.3%

DBS: deep brain stimulation; MDS-UPDRS-III score: Movement Disorder Society-Unified Parkinson's Disease Rating Scale Motor Examination score
Age, disease duration and MDS-UPDRS-III scores are reported as mean ± SD. Levodopa responsiveness is measured as the % decrease in MDS-UPDRS-III scores after the administration of dopaminergic medications.

Secondary outcomes

Effect of STN-DBS on MDS-UPDRS

Following STN-DBS, MDS-UPDRS-I, II and III scores showed a decrease at 1 year, but these changes were not statistically significant. However, MDS-UPDRS-II and III scores significantly worsened at the 5-year and 10-year time points. Up to 5 years, there was no significant change in MDS-UPDRS-I scores. At the 10-year point, there were insufficient data to determine the effect of STN-DBS on MDS-UPDRS-I scores (Table 2).

Effect of STN-DBS on ADLs

Independence in ADLs was compared among 45 patients. There was no significant difference between ADL independence from baseline (84.4% [38/45]) to 6 months (90.9% [40/44], *P*=0.727), 1 year (87.5% [35/40], *P*=1.000), and 5 years (63.2% [12/19], *P*=0.500) after STN-DBS.

Fig. 1. Overview of patient distribution.

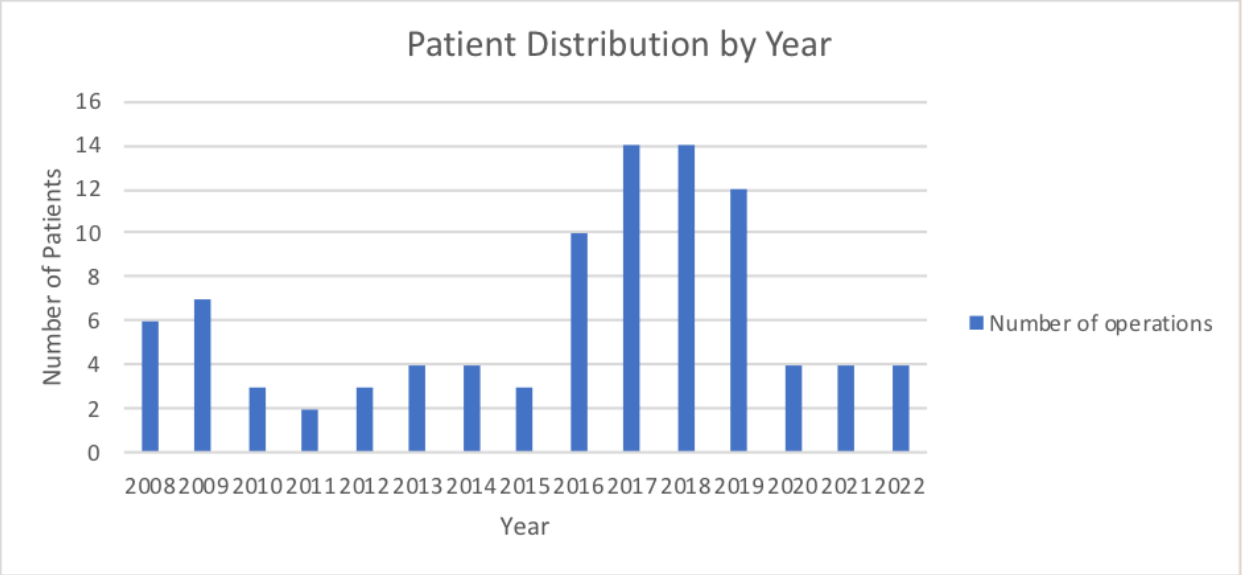
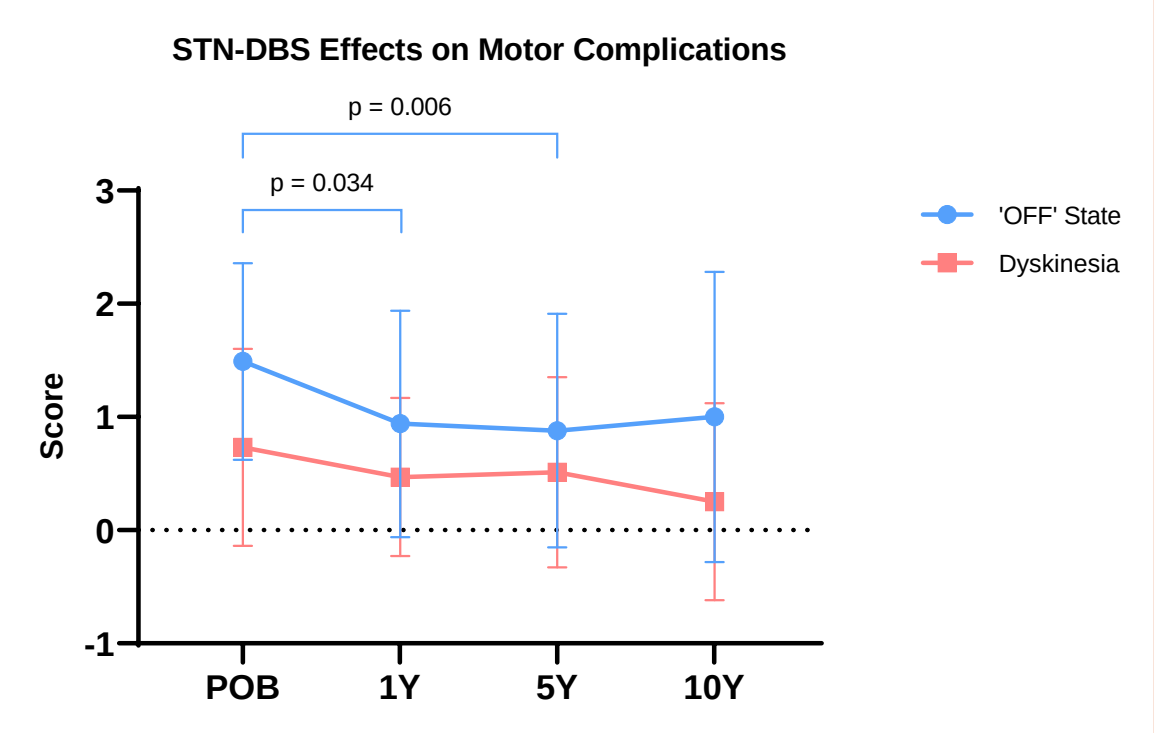


Fig. 2. Effects of subthalamic nucleus deep brain stimulation (STN-DBS) on motor complications of dopaminergic medication.



POB: pre-operative baseline
Data are presented as means with error bars for standard deviation. Statistically significant ($P<0.05$) changes are shown with significance bars. The y-axis represents the Movement Disorders Society-Unified Parkinson's Disease Rating Scale score as follows; 0: No dyskinesias/ time spent in the "OFF" state, 1: ≤5% of waking day, 2: 26–50% of waking day, 3: 51–75% of waking day, 4: >75% of waking day.

Table 2. Movement Disorders Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) scores at each time point.

	Time point	n	Mean	SD	*P* value	% change
MDS-UPDRS-I	POB	57	8.53	4.59		
	1Y	10	4.80	4.92	0.123	-43.7%
	5Y	36	8.19	4.70	0.506	-4.0%
	10Y	11	11.91	5.79	[a]	[a]
MDS-UPDRS-II	POB	69	15.99	8.91		
	1Y	15	8.90	4.47	0.051	-44.3%
	5Y	37	22.47	11.97	0.016	+40.5%
	10Y	11	23.36	11.62	0.028	+46.1%
MDS-UPDRS-III	POB	92	25.87	12.17		
	1Y	75	22.96	14.43	0.155	-11.2%
	5Y	43	35.03	17.94	<0.001	+35.4%
	10Y	13	46.38	20.23	0.002	+79.3%

MDS-UPDRS-I: Movement Disorder Society-Unified Parkinson's Disease Rating Scale Non-Motor Aspects of Experience of Daily Living; MDS-UPDRS-II: Movement Disorder Society-Unified Parkinson's Disease Rating Scale Motor Aspects of Experience of Daily Living; MDS-UPDRS-III: Movement Disorder Society-Unified Parkinson's Disease Rating Scale Motor Examination; POB: pre-operative baseline; SD: standard deviation
Statistically significant *P* values and % changes are in bold. All pre- and post-operative data shown were taken with patients in the "ON" state.
[a] Insufficient data for statistical analysis.

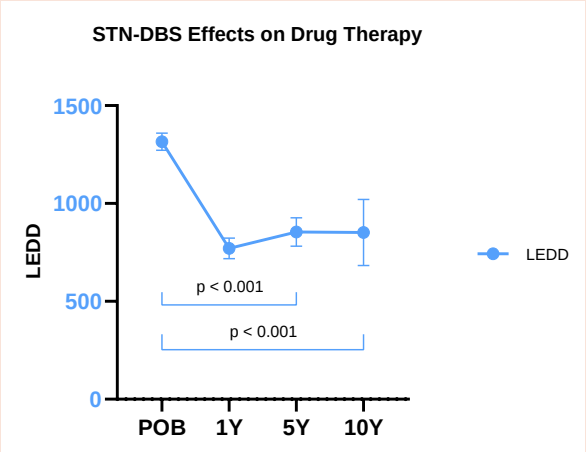
Effect of STN-DBS on PD milestones

Frequent falls were observed in 30.4% (17/56) of patients before surgery, decreasing non-significantly to 19.7% (13/66, *P*=0.332) at 1 year, but significantly increasing to 60.3% (35/58, *P*=0.027) at 5 years. Dementia was present in 1.7% (1/58) of patients pre-surgery, rising non-significantly to 2.8% (2/71, *P*=1.000) at 1 year and 10.7% (6/56, *P*=0.500) at 5 years. No patients were institutionalised at the time of operation and at 1 year post-operation. However, 3 patients were institutionalised between 1 and 5 years, and 1 patient between 5 and 10 years post-operation.

Effect of STN-DBS on drug therapy

Compared to the baseline (1315.40 ± 44.04, n=87), LEDD was significantly reduced by 41.4% at 1 year (771.09 ± 52.60 mg/day, n=80; *P*<0.001) and by 35.1% at 5 years (854.07 ± 72.65 mg/day, n=36; *P*<0.001). However, there was no significant reduction at the 10-year time point (852.20 ± 168.59 mg/day, n=10; *P*=0.139) (Fig. 3).

Fig. 3. Effects of subthalamic nucleus deep brain stimulation (STN-DBS) on drug therapy.



LEDD: levodopa equivalent daily dose; POB: pre-operative baseline
Data are presented as means with error bars for standard deviation. Statistically significant (*P*<0.05) changes are shown with significance bars.

Adverse events after STN-DBS

All reported adverse events (AE) are detailed in Table 3. Surgery-related AEs were observed only within the first 6 months post-operation. Device-related AEs, with infection being the most common (accounting for 50% of all device-related AEs), were observed at all time points but were most frequent between 30 days to 6 months and from 5 to 10 years post-operation. Infections led

Table 3. Adverse events associated with STN-DBS subthalamic nucleus deep brain stimulation (STN-DBS).

Adverse events		Post-op – 30 days	30 days – 6 months	6 months – 1 year	1 year – 5 years	5 years – 10 years	Total
Surgery	n	94	93	85	78	31	
	IVH	1 (1.1%)	0	0	0	0	1
	Peri- or post-operative confusion	6 (6.4%)	1 (1.1%)	0	0	0	7
	SDH	1 (1.1%)	1 (1.1%)	0	0	0	2
	Seizure	2 (2.1%)	0	0	0	0	2
	Transient neurological deficit	1 (1.1%)	0	0	0	0	1
	Total	11	2	0	0	0	
Device	n	94	93	85	78	31	
	Infection	1 (1.1%)	5 (5.3%)	0	2 (2.6%)	3 (9.7%)	11
	IPG battery failure	0	0	0	0	0	0
	Lead malfunction	1 (1.1%)	0	0	0	1 (3.2%)	2
	Lead reimplantation	1 (1.1%)	4 (4.3%)	0	1 (1.3%)	0	6
	Skin erosion	0	0	2 (2.4%)	0	0	2
	Total	3	9	3	4	4	
Stimulation	n		63	56	44	8	
	Anxiety		1 (1.6%)	0	3 (6.8%)	0	4
	Depression		0	2 (3.6%)	3 (6.8%)	0	5
	Dysarthria		0	3 (5.4%)	6 (13.6%)	2 (25.0%)	11
	Dysphagia		3 (4.8%)	7 (12.5%)	11 (25.0%)	1 (12.5%)	22
	Freezing of gait		3 (4.8%)	0	2 (4.5%)	0	5
	Hallucinations/psychosis		0	0	8 (18.1%)	1 (12.5%)	9
	Hypersalivation		7 (11.1%)	5 (8.9%)	4 (9.1%)	0	16
	ICD		2 (3.2%)	4 (7.1%)	4 (9.1%)	1 (12.5%)	11
	Incontinence		3 (4.8%)	1 (1.8%)	10 (22.7%)	0	14
	Total		19	22	51	5	

ICD: impulse control disorder; IPG: implantable pulse generator; IVH: intraventricular haemorrhage; SDH: subdural haemorrhage
Data are reported as number and percentage of patients affected by each complication. No data was collected for stimulation-related complications at the post-op to 30 days period as DBS programming was only performed 1 month after surgery.

to lead reimplantation in 4 patients. Additionally, 2 patients with lead malfunctions chose not to have their leads reimplanted, and 1 patient with lead infection had the leads explanted without replacement.

DISCUSSION

To our knowledge, this is the first study of short-term and long-term DBS outcomes in PD in Singapore. Among 2490 PD patients, 118 (4.7%) underwent DBS, a lower percentage than in other

similar high-income countries.[16] This discrepancy is likely multifactorial, including the high costs of surgery,[17] patient concerns about complications,[18] and governmental restrictions on elective operations during the pandemic. The ethnic and gender distribution of patients who underwent DBS was representative of our PD population, indicating equal access to care. In this retrospective study at a large referral centre, we found that STN-DBS significantly reduced time spent in the "OFF" state up to 5 years post-surgery, though this effect was not maintained at 10 years, likely due to disease progression.[2] Compared to studies showing sustained reduction in motor fluctuations beyond 10 years,[10,19] our cohort had poorer baseline MDS-UPDRS-III scores (in the "ON" state) and lower levodopa responsiveness. Additionally, our patients were significantly older at the time of DBS surgery, which likely contributed to their poorer motor function and levodopa responsiveness, despite similar disease durations.[10,19]

There was no significant change in the time spent with dyskinesia. However, our patients' baseline time spent with dyskinesia was significantly shorter than in other studies (0.73 versus [vs] 1.73–2.83) [10,20-23], which may be partially due to a lower prevalence of dyskinesias in Asian populations.[24] MDS-UPDRS-I, II and III scores remained stable in the short term, up to 1 year. MDS-UPDRS-II and III scores increased at 5 and 10 years, likely due to the natural progression of the disease. The pattern of initial improvement followed by gradual worsening of UPDRS scores has been reported in other studies as well, including a seminal review by Limousin et al.[2,20,22,23] Since all post-operative MDS-UPDRS scores were assessed with patients in the "ON" phase, significant improvement in motor symptoms beyond the effects of therapeutic drugs, even with stimulation, was not expected.[23] In this study, STN-DBS did not result in a significant change in patients' ability to perform activities of daily living, unlike previous studies that reported notable improvements in patient ADLs.[9,25,26] This discrepancy may be due to differences in the definition of ADL independence used in our study compared to others. Additionally, cultural factors play a role; in our setting, we tend to select patients with good social support for STN-DBS, given the intensive post-operative care required. As a result, patients may continue to receive assistance with ADLs post-surgery, even if they do not need it. The poorer motor baseline and older age profile of our patients may also contribute to the lack of improvement in ADL independence. Utilising more quantitative ADL assessment scales, such as the Katz ADL scale[27] and the Lawton Instrumental ADL[28] scale, could further clarify the effects of STN-DBS on patient ADLs.

In our study, STN-DBS did not significantly reduce the prevalence of frequent falls or prevent the long-term development of this disease milestone. This is likely due to the worsening of axial and motor symptoms, as indicated by the increase in MDS-UPDRS-III scores, a finding consistent with other studies.[29,30] The prevalence of dementia in our patients after STN-DBS (2.8% at 1 year, 10.7% at 5 years) is comparable to that reported in another study (2.3% at 1 year, 10.9% at 5 years),[31] despite our patients being older at the time of STN-DBS (60.6 vs 55.9 years). The same study also concluded that the prevalence and incidence are not higher than the general PD population, though this was not confirmed with a matched control group. Overall, our study did not show that STN-DBS delays late-stage milestones such as frequent falls and dementia.

STN-DBS also reduced the LEDD for at least 5 years, likely due to improvements in motor function.[32] By lowering drug dosage, STN-DBS can decrease medication costs for the patient[7,8] and alleviate the drug burden from polypharmacy, which may partially explain the improved quality of life observed with STN-DBS.[10] However, based on our data, it remains unclear whether the reduction of LEDD also reduces the prevalence of certain hyperdopaminergic side effects, such as psychosis.

Adverse events associated with STN-DBS are relatively uncommon, and our results indicate a risk profile comparable to existing literature.[10,22,33,34] No serious life-threatening complications were observed post-surgery. The most frequently observed device-related AE was infection, followed by lead reimplantation due to previous infection or unsatisfactory placement. A review of 6 randomised control trials with follow-up of 6 months to 2 years reported an infection rate of 4.49 events per 100 patients after probe implantation,[35] similar to our findings. The highest number of stimulation-related AEs were reported from 1 and 5 years post-surgery, likely due in part to disease progression and possibly influenced by other factors such as the development of unrelated comorbidities. It would be challenging to directly attribute stimulation-related AEs to STN-DBS because the progression of PD symptoms overlapped with some AEs associated with the treatment. All new stimulation-related AEs post-DBS surgery are thus only potentially related to STN-DBS and may be influenced by other

unconsidered factors. No suicide attempts were noted in our cohort.

The main limitation of this study is the high rate of loss to follow-up, particularly over the long term, which is typical of long-term retrospective studies. This issue is partly due to patient mortality, but also results from patients dropping out of the study and the lack of patient consent for data collection after the implementation of new regulations in March 2019. The small sample size may have led to some primary and secondary outcomes being statistically insignificant. Additionally, the study lacks a comparison with a matched control group receiving medical therapy, which would have helped to better delineate the effects of STN-DBS. Despite these limitations, our data strongly suggest that STN-DBS can sustain motor benefits over the long term while reducing the required dose of PD medications and associated side effects.

In conclusion, STN-DBS effectively reduces motor fluctuations and dyskinesia in PD patients over the long term, while also decreasing the need for dopaminergic medication. Although it does not halt disease progression, STN-DBS remains instrumental in improving outcomes with a favourable risk profile.

Declaration

No funding was received for this work. The authors declare they have no affiliations or financial involvement with any commercial organisation with a direct financial interest in the subject or materials discussed in the manuscript.

Acknowledgements

We would like to thank all our patients and their families for their support. We would like to thank Mr Aiden Wong for his logistical and data entry support.

REFERENCES

1. Jankovic J, Tan EK. Parkinson's disease: etiopathogenesis and treatment. J Neurol Neurosurg Psychiatry 2020;91:795-808.
2. Limousin P, Foltynie T. Long-term outcomes of deep brain stimulation in Parkinson disease. Nat Rev Neurol 2019; 15:234-42.
3. Okun MS. Deep-brain stimulation for Parkinson's disease. N Engl J Med 2012;367:1529-38.
4. Moum SJ, Price CC, Limotai N, et al. Effects of STN and GPi deep brain stimulation on impulse control disorders and dopamine dysregulation syndrome. PloS One 2012;7:e29768.
5. Lee PS, Crammond DJ, Richardson RM. Deep Brain Stimulation of the Subthalamic Nucleus and Globus Pallidus for Parkinson's Disease. Prog Neurol Surg 2018;33:207-21.
6. Mansouri A, Taslimi S, Badhiwala JH, et al. Deep brain stimulation for Parkinson's disease: meta-analysis of results of randomized trials at varying lengths of follow-up. J Neurosurg 2018;128:1199-213.
7. Hacker M, Cannard G, Turchan M, et al. Early subthalamic nucleus deep brain stimulation in Parkinson's disease reduces long-term medication costs. Clin Neurol Neurosurg 2021;210:106976.
8. Hacker ML, Currie AD, Molinari AL, et al. Subthalamic Nucleus Deep Brain Stimulation May Reduce Medication Costs in Early Stage Parkinson's Disease. J Park Dis 2016; 6:125-31.
9. Deuschl G, Schade-Brittinger C, Krack P, et al. A randomized trial of deep-brain stimulation for Parkinson's disease. N Engl J Med 2006;355:896-908.
10. Bove F, Mulas D, Cavallieri F, et al. Long-term Outcomes (15 Years) After Subthalamic Nucleus Deep Brain Stimulation in Patients With Parkinson Disease. Neurology 2021; 97:e254-62.
11. Karthick PA, Wan KR, An Qi AS, et al. Automated detection of subthalamic nucleus in deep brain stimulation surgery for Parkinson's disease using microelectrode recordings and wavelet packet features. J Neurosci Methods 2020;343:108826.
12. Skorvanek M, Martinez-Martin P, Kovacs N, et al. Differences in MDS-UPDRS Scores Based on Hoehn and Yahr Stage and Disease Duration. Mov Disord Clin Pract 2017;4:536-44.
13. Agency for Integrated Care, Interim Disability Assistance Programme for the Elderly (IDAPE). https://www.aic.sg:443/financial-assistance/interim-disability-assistance-programme-elderly. Accessed 30 October 2023.
14. Tisher A, Salardini A. A Comprehensive Update on Treatment of Dementia. Semin Neurol 2019;39:167-78.
15. Schade S, Mollenhauer B, Trenkwalder C. Levodopa Equivalent Dose Conversion Factors: An Updated Proposal Including Opicapone and Safinamide. Mov Disord Clin Pract 2020;7:343-5.
16. Fasano A, Fung VSC, Lopiano L, et al. Characterizing advanced Parkinson's disease: OBSERVE-PD observational study results of 2615 patients. BMC Neurol 2019;19:50.
17. Zhang C, Ramirez-Zamora A, Meng F, et al. An International Survey of Deep Brain Stimulation Utilization in Asia and Oceania: The DBS Think Tank East. Front Hum Neurosci 2020;14:162.
18. Kim MR, Yun JY, Jeon B, et al. Patients' reluctance to undergo deep brain stimulation for Parkinson's disease. Parkinsonism Relat Disord 2016;23:91-4.
19. Park HR, Im HJ, Park J, et al. Long-Term Outcomes of Bilateral Subthalamic Nucleus Deep Brain Stimulation for Patients With Parkinson's Disease: 10 Years and Beyond. Neurosurgery. 2022;91:726-33.
20. Rodriguez-Oroz MC, Obeso JA, Lang AE, et al. Bilateral deep brain stimulation in Parkinson's disease: a multicentre study with 4 years follow-up. Brain J Neurol 2005;128:2240-9.
21. Krack P, Batir A, Van Blercom N, et al. Five-Year Follow-up of Bilateral Stimulation of the Subthalamic Nucleus in Advanced Parkinson's Disease. N Engl J Med 2003; 349:1925-34.
22. Schüpbach WMM, Chastan N, Welter ML, et al. Stimulation of the subthalamic nucleus in Parkinson's disease: a 5 year follow up. J Neurol Neurosurg Psychiatry 2005;76:1640-4.
23. Moro E, Lozano AM, Pollak P, et al. Long-term results of a multicenter study on subthalamic and pallidal stimulation in Parkinson's disease. Mov Disord Off J Mov Disord Soc 2010;25:578-86.
24. Lim SY, Tan AH, Ahmad-Annuar A, et al. Parkinson's disease in the Western Pacific Region. Lancet Neurol 2019;18:865-79.
25. Gorecka-Mazur A, Furgala A, Krygowska-Wajs A, et al. Activities of Daily Living and Their Relationship to Health-Related Quality of Life in Patients with Parkinson Disease

After Subthalamic Nucleus Deep Brain Stimulation. World Neurosurg 2019;125:e552-62.

26. Zibetti M, Merola A, Rizzi L, et al. Beyond nine years of continuous subthalamic nucleus deep brain stimulation in Parkinson's disease. Mov Disord 2011;26:2327-34.
27. Katz S, Downs TD, Cash HR, Grotz RC. Progress in development of the index of ADL. Gerontologist 1970;10:20-30.
28. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. The Gerontologist 1969;9:179-86.
29. Zampogna A, Cavallieri F, Bove F, et al. Axial impairment and falls in Parkinson's disease: 15 years of subthalamic deep brain stimulation. NPJ Park Dis 2022;8:121.
30. Mahlknecht P, Foltynie T, Limousin P, et al. How Does Deep Brain Stimulation Change the Course of Parkinson's Disease? Mov Disord 2022;37:1581-92.
31. Bove F, Fraix V, Cavallieri F, et al. Dementia and subthalamic deep brain stimulation in Parkinson disease: A long-term overview. Neurology 2020;95:e384-92.
32. Nutt JG, Rufener SL, Carter JH, et al. Interactions between deep brain stimulation and levodopa in Parkinson's disease. Neurology 2001;57:1835-42.
33. Buhmann C, Huckhagel T, Engel K, et al. Adverse events in deep brain stimulation: A retrospective long-term analysis of neurological, psychiatric and other occurrences. PloS One 2017;12:e0178984.
34. Falowski S, Ooi YC, Smith A, et al. An evaluation of hardware and surgical complications with deep brain stimulation based on diagnosis and lead location. Stereotact Funct Neurosurg 2012;90:173-80.
35. Deuschl G, Paschen S, Witt K. Clinical outcome of deep brain stimulation for Parkinson's disease. Handb Clin Neurol 2013;116:107-28.

Ann Acad Med Singap 2024;53:490-501
https://doi.org/10.47102/annals-acadmedsg.202420

REVIEW ARTICLE

Quality of life of family caregivers of children and young adults with Down syndrome: A systematic review and meta-analysis

Fergus Edward Cheok[*1] *MBBS*, Natania Rae Tan Xiangqin[*2], Yu Yi Chan[2], Bryan Wong Wei Zhi[1] *MBBS*, Gwyneth Kong[1] *MBBS*, Zubair Amin[3,4] *MHPE*, Yvonne Ng Peng Mei[3,4] *MRCP*

ABSTRACT

Introduction: The aims of this systematic review and meta-analysis are to synthesise quality of life (QOL) of family caregivers of children and young adults with Down syndrome (DS) and determine factors affecting their QOL.

Method: This review was conducted as per Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline. Key search terms were "quality of life", "down syndrome" and "trisomy 21". Meta-analysis using random effect model was conducted where feasible. All studies underwent qualitative synthesis. The study protocol was registered with PROSPERO (CRD42023413532).

Results: Eighteen studies with 1956 caregivers were included. Of the 10 studies utilising the World Health Organization Quality of Life Instrument-Brief Version, 5 were included in the meta-analysis. Psychosocial domain had the highest score with mean (95% confidence interval [CI]) of 63.18 (39.10–87.25). Scores were poorer in physical, environmental and social domains: 59.36 (28.24–90.48), 59.82 (19.57–100.07) and 59.83 (44.24–75.41), respectively. Studies were heterogenous with I^2 values ranging from 99–100% (P<0.01). The remaining 8 studies used 6 other instruments. Qualitative synthesis revealed that caregivers' QOL was adversely affected by child-related factors, such as level of functional independence, developmental delay, presence of multiple comorbidities, impaired activities of daily living and poor sleep quality. Environmental factors that adversely affected caregivers' QOL included number of children, housing and support from the family. Personal factors that affected caregivers' QOL included age, being a single mother, low education and low income.

Conclusions: QOL of caregivers of children with DS was lower than population reference data. Understanding the factors that influence family caregivers' QOL is an essential step towards improving the QOL of caregivers and their children with DS.

Ann Acad Med Singap 2024;53:490-501

Keywords: FIM, parents, PedsQL, trisomy 21, WHOQOL-BREF

CLINICAL IMPACT

What is New

- Quality of life (QOL) of caregivers of children with Down syndrome (DS) was found to be lower than population reference data.
- QOL of caregivers were affected by personal factors (e.g. age, education and marital status), child-related factors (e.g. level of independence and presence of comorbidities) and environmental factors (e.g. housing, number of children and support from families).

Clinical Implications

- The measurement of family caregivers' QOL is an important element for high-quality care of children with DS and should be incorporated into clinical practice.

INTRODUCTION

The family caregiver is "any relative, partner, friend or neighbor who has a significant personal relationship with, and provides a broad range of assistance for a person with a chronic or disabling condition."[1] Family caregivers for children with chronic illnesses are commonly parents, who fulfil their children's physical and emotional needs while attending to their developmental progress, education and changing health status.[2] These responsibilities may result in caregivers suffering from physical, psychosocial, emotional, social, and financial stress and burden.[3]

The World Health Organization (WHO) defines quality of life (QOL) as "individuals' perceptions of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns."[4] QOL, often used interchangeably with health-related quality of life

[1] MOH Holdings, Singapore
[2] Yong Loo Lin School of Medicine, National University of Singapore, Singapore
[3] Department of Paediatrics, Yong Loo Lin School of Medicine, National University of Singapore, Singapore
[4] Department of Neonatology, Khoo Teck Puat-National University Children's Medical Institute, National University Hospital, Singapore
[*] Joint first authors
Correspondence: A/Prof Zubair Amin, Department of Neonatology, Khoo Teck Puat-National University Children's Medical Institute, National University Hospital, 5 Lower Kent Ridge Road, Singapore 119074.
Email: paeza@nus.edu.sg
This article was first published online on 19 August 2024 at annals.edu.sg.

or HRQOL,[5] allows holistic and longitudinal assessment of outcomes related to overall health and well-being.[6]

Down syndrome (DS) is the most common genetic cause of intellectual disability.[7] Due to associated comorbidities[8,9] individuals with DS are typically dependent on family caregivers. Adolescents and young adults with DS are at risk of deteriorating emotional and social well-being,[10,11] which in part contributes to continued care of individuals with DS by the family caregivers even in young adulthood.[12]

Qualitative studies reported family caregivers of children with DS to have emotional turmoil, high rates of depression, burnout and poorer overall mental health.[13,14] Caregivers of children with DS face variable level of burden and many experience higher burden of care when their child has disabilities.[13] Encouragingly, the majority of mothers adapt and gradually accept their child's condition,[14] and caregivers of children with DS have better psychological well-being and coping skills than mothers of children with autism or fragile X syndrome.[15]

We conducted a systematic review and meta-analysis to synthesise QOL of caregivers of children and young adults with DS. We included young adults below 30 years old as they may continue to live with and depend on their family caregivers. Our overarching goal is to provide practitioners and policymakers with evidence to improve the QOL of caregivers by identifying determinants of better and poorer QOL. Henceforth, the term children is used to denote both children and young adults.

METHOD

We performed the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[16] The protocol was registered on PROSPERO on 12 April 2023 (CRD42023413532).

Search strategy

We conducted the search under the guidance of a medical librarian. We searched 4 databases (PubMed, Embase, Web of Science and CINAHL) from the inception of respective databases until 24 April 2024, using Medical Subject Headings (National Library of Medicine's controlled vocabulary thesaurus used to index articles) or related terms such as "down syndrome", "trisomy 21" and "quality of life". The term "caregiver" or "parent" was not included, as inclusion of these terms restricted the number of articles retrieved. We also searched grey literature (e.g. Google Scholar and OpenGrey) and bibliography of relevant articles. Supplementary Appendix S1 illustrates the search strategy.

Eligibility and selection criteria

Table 1 summarises inclusion and exclusion criteria. Two authors independently sieved all titles and abstracts for articles meeting eligibility criteria for full-text reviews. Any discrepancies were resolved after discussion with senior authors.

Data extraction

Two authors independently extracted the following data: study characteristics (e.g. year of study, country, study design and aims); participant demographics (e.g. sample size, sex/gender, age, race, education, employment and family income); and outcomes (e.g. QOL instruments and results).

Data analysis

We analysed extracted data including subgroup analysis following the Cochrane Handbook.[17]

Table 1. Eligibility criteria of studies.

	Inclusion criteria	Exclusion criteria
Population	Studies involving family caregivers of children and young adults (0–30 years old) with Down syndrome (DS)	Studies with DS patients >30 years old; studies that combined different age groups where data could not be extracted for family caregivers of DS patients <30 years old
Exposure	DS or trisomy 21 including mosaic, translocation and partial trisomy	Studies with other trisomy disorders, or intellectual disabilities without DS
Outcomes	Studies on quality of life (QOL) of family caregivers of children with DS from their own perspectives	Studies on QOL of formal caregivers such as healthcare professionals
Study design	Quantitative studies; cohort, case control and case series studies; mixed method studies where quantitative data are available	Qualitative studies, interventional trials, validation studies of instruments
Others	Peer reviewed, full-text articles, data available in English	Consensus statement, reviews, opinions, commentaries, abstracts

We performed meta-analysis using R version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria) if data were available from 4 or more studies. We chose random effect model due to the heterogeneity of the studies.[17] For 1 study[18] that presented only the median and interquartile range (IQR), we estimated the mean and standard deviation (SD) using the method recommended by Hozo et al.[19] We performed qualitative synthesis of all studies according to the type of QOL instrument.

Quality assessment

Two authors independently assessed the quality of studies using the Newcastle-Ottawa Scale.[20] Any discrepancies were resolved through consensus.

RESULTS

We retrieved 2743 articles from literature search. After deduplication, and title and abstract screening, 18 studies with 1956 caregivers met inclusion criteria. We included 58 caregivers who participated in 2 different studies only once.[21,22] Out of all the caregivers, the majority were mothers, accounting for 78.6% (n=1468). In contrast, 21.4% (n=400) were fathers; while a small fraction consisted of grandmothers (n=2). The sex/gender of the remaining 86 caregivers was not specified. Fig. 1 presents the PRISMA flowchart and Supplementary Appendix S2 describes the instruments used. Ten studies used the World Health Organization Quality of Life Instrument-Brief Version (WHOQOL-BREF) while 8 studies used 6 other instruments. Table 2 and Table 3 summarise characteristics and key findings of the included studies using the WHOQOL-BREF and other instruments, respectively.

Quality of included studies

Supplementary Appendix S3 outlines the quality of included studies. The quality of all studies was satisfactory or better (≥5; maximum 10). Inter-rater agreement between 2 reviewers was 89% (16 out of 18 studies).

QOL measures using WHOQOL-BREF

The WHOQOL-BREF is an abbreviated version of the WHOQOL-100, which comprises 100 questions on the individual's perception of their health and well-being.[23]

The 10 studies involved 970 family caregivers of children with DS.[18,24-32] Two studies had parents/caregivers of typically developing (TD) children as the comparison group.[18,24] Three studies[24,25,27] used

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

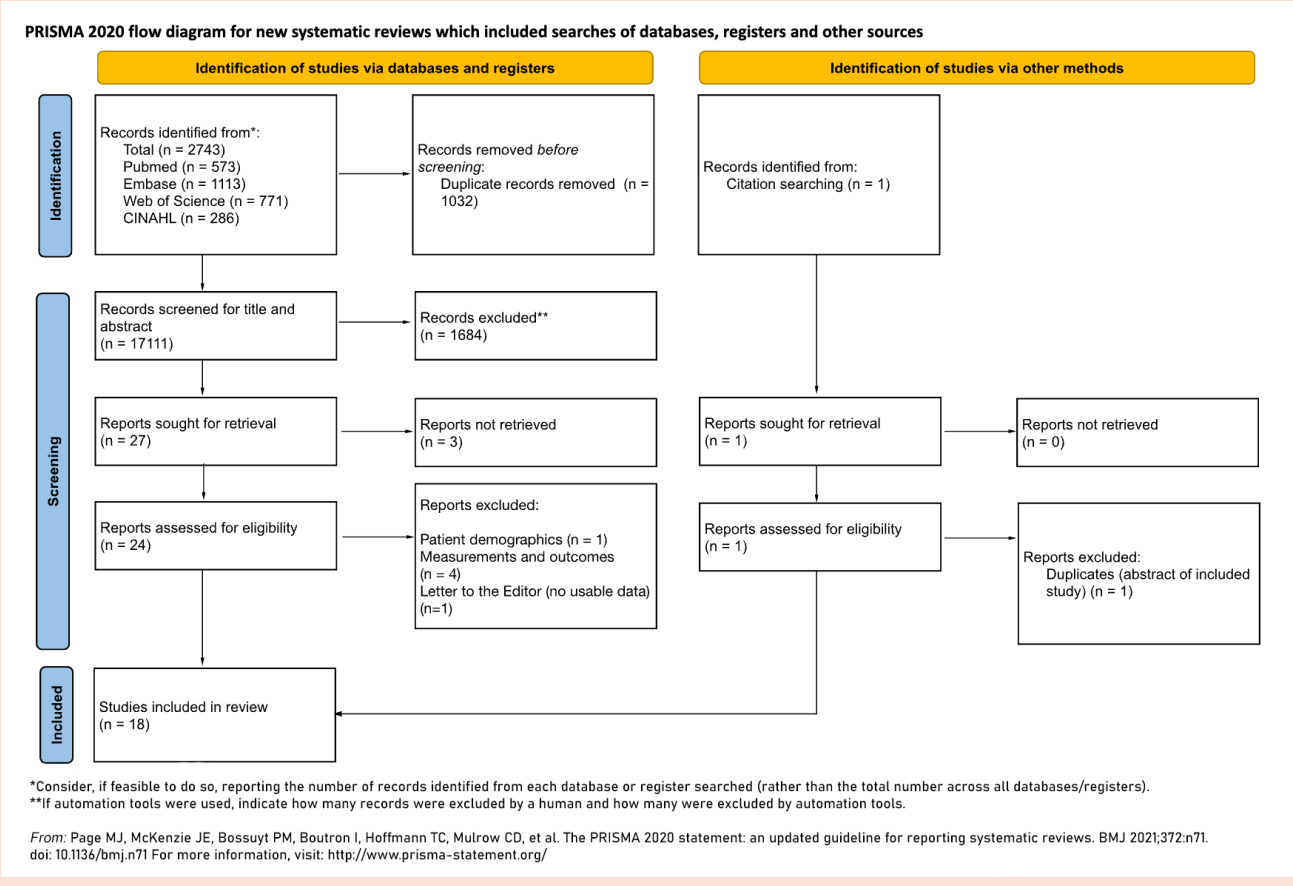


Table 2. Summary of included studies using the World Health Organization Quality of Life Instrument-Brief Version (WHOQOL-BREF).

Author and publication date, country, setting, study period	Sample size, study design, instrument	Age of children with DS, mean ± SD and/or range	Caregivers' age, mean ± SD or mode (no., %) median and/or range in years; sex (F/M), no. %	Comparison group	Highest scoring domain OR biggest difference[a] (score)	Lowest scoring domain OR lowest difference[a] (score)	Total score	Key factors adversely affecting QOL scores
Geok 2013,[25] Malaysia, 2009–2010	161, cross-sectional, WHOQOL-BREF	Mean ± SD: 9.3 ± 4.2 years	Mean: 43.67 SD: 8.49 F: 161, 100% M: 0, 0%	NA	Social (68.1)	Environment (58.1)	62.50	Rural household, low education, low income, being single and of older age
AlAhmari 2022,[26] Saudi Arabia, 2018–2019	261, cross-sectional, WHOQOL-BREF	Range: 0–14 years	Mode: above 40 (164, 62.8%) F: 137, 52.5% M: 124, 47.5%	NA	Environment (105)	Social (41)	NA	Education level, number of children and average monthly income
Abbassi 2016,[27] Iran, not specified	70, cross-sectional, WHOQOL-BREF	NA	Mean: 36.74 ± 7.5 F: 70, 100% M: 0, 0%	NA	Physical (61.88)	Environment (41.63)	46.30	Rental housing
Vadakedom 2017,[28] India, 2016	31, cross-sectional, WHOQOL-BREF	Mean ± SD: 1.48 ± 0.51 years	Mean: 30.6 F: 31, 100% M: 0, 0%	NA	Social (61.32)	Environment (50.29)	52.82	Urban families, income level, mothers with spouses with higher education level
Buzatto 2008,[29] Brazil, 2007	30, cross-sectional, WHOQOL-BREF	NA	Mean: 37 Range: 28–49 F: 24, 80% M: 6, 20%	NA	Social (80.72)	Psychological (60.28)	NA	
Oliveira 2011,[30] Brazil, not specified	31, cross-sectional, WHOQOL-BREF	Mean: 8 years 5 months Range: 1–16 years	Mode: 40–49 (17, 55%) F: 24, 77% M: 7, 23%	NA	Social (69.92)	Environment (53.33)	NA	Education, socio-economic factors

Table 2. Summary of included studies using the World Health Organization Quality of Life Instrument-Brief Version (WHOQOL-BREF). (Cont'd)

Author and publication date, country, setting, study period	Sample size, study design, instrument	Age of children with DS, mean ± SD and/or range	Caregivers' age, mean ± SD or mode (no., %) median and/or range in years; sex (F/M), no. %	Comparison group	Highest scoring domain OR biggest difference[a] (score)	Lowest scoring domain OR lowest difference[a] (score)	Total score	Key factors adversely affecting QOL scores
Senses Dinc 2019,[18] Turkey, 2010–2011	75, cross-sectional, WHOQOL-BREF	Range: 0–3 years	Median: 31 Range: 18–55 F: 75, 100% M: 0, 0%	Parents/ caregivers of healthy children	[a]Social (14.582)	Psychological (0.002)	NA	Comorbid disorders in the children, number of children in the household
Amaral 2020,[24] Brazil, 2017–2018	82, cross-sectional, WHOQOL-BREF	Range: DS: 4–30 years TD: 4–8 years	Mean: 58.2 SD: 10.8 Range 23–78 F: 67, 81.7% M: 15, 18.3%	Caregivers of typically developing children	[a]Environment (6.2)	Physical (0.6)	62.5	Family income, level of dependence on the child
Hussin 2022,[31] Malaysia, not specified–2020	151, cross-sectional, WHOQOL-BREF	Mean: 5 years Range: 1 month to 17 years	Mean: 43 Range: 28–61 F: 151, 100% M: 0, 0%	NA	Social (72.55) and environment (72.55)	Psychological (63.25)	NA	Older maternal age
Tekinarslan 2013,[32] Turkey, not specified	78, cross-sectional, WHOQOL-BREF	Range: 3–18 years	Median: 36–45 Range: <25 to >46 F: 78, 100%; M: 0, 0%	NA	Psychological (60.47)	Environment (57.01)	NA	

F: female; IQR: interquartile range; M: male; NA: Not applicable/not available; QOL: quality of life; SD: standard deviation
[a] The differences in individual QOL domain values between the control group and DS group of family caregivers (if applicable).

Table 3. Summary of included studies using instruments other than the World Health Organization Quality of Life Instrument-Brief Version.

Author and publication date, country, setting, study period	Sample size, study design, instrument	Age of children with DS, mean ± SD and/or range in years	Age of caregivers, mean ± SD or mode (no., %) or median ± SD and/or range in years; gender/sex (F/M), no. %	Comparison group	Highest domain OR biggest difference,[a] score (SD)	Lowest domain OR lowest difference,[a] score (SD)	Total score
Cetin 2017,[35] Turkey, not specified	37, cross-sectional study, SF-36	Mean ± SD: 7.9 ± 3.5	Mean ± SD: 40.1 ± 6.1 F: 37, 100% M: 0, 0%	NA	Physical: 15.2	Mental: 12.5	130.5
Bourke 2008,[36] Australia, 2004 to 2005	250, cross-sectional study, SF-12	Mean: 11.9	Mean: 44.4 F: 250, 100% M: 0, 0%	NA	Physical: 50.2	Mental: 45.2	NA
Darla 2020,[38] India, not specified	102, cross-sectional study, PedsQL FIM	Range: 1–15	Mode: 35–39 (38, 37.25%) F: 51, 50% M: 51, 50%	NA	Cognitive function: 71.67	Worry: 57.33	NA
Rozensztrauch 2023,[39] Poland, January 2022 to December 2022	53, cross-sectional study, PedsQL FIM	Mean ± SD: 6.48 ± 4.56 Range: 2–18	NA	NA	Cognitive function: 64.53 (24.42) Family relationship: 62.03 (24.49)	Worry: 41.98 (20.95) Daily activities: 44.97 (23.87)	57.51 (17.56)
Foley 2014,[41] Australia, 2009	289, cross-sectional study, BCFQOL	Range: 16–30	Range: 37–66 and older F: 150, 52% M: 139, 48%	NA	Physical/material well-being: 4.19	Emotional well-being: 3.49	NA
Brown 2006,[42] Canada, not specified	33, cross sectional study, FQOL	Range: 3–13	Mean (mothers): 38–40 Mean (fathers): 41–45	Typically developing children	[a]Leisure and enjoyment of life (0.821)	Support from disability related services (0.300)	NA
Marchal 2013,[21] Netherlands, 1999 to 2001	98, cross sectional study, TAAQOL	Mean ± SD: 7.1 ± 0.6	Median ± SD: 41.3 ± 4.4 Range 32.4–51.9 F: 84, 86% M: 14, 14%	NA	Cognitive function (F=11.57)	Vitality (F=6.60)	NA
Marchal 2016,[22] Netherlands, 2012 to 2013	124, cross sectional study, TAAQOL	Range: 11–13	Mothers, mean ± SD: 45.9 ± 4.2 Fathers, mean ± SD: 47.8 ± 5.4 F: 80, 65.5% M: 44, 35.5%	NA	Fine motor function Mother 96.3 (9.2) Father 98.6 (7.7)	Vitality (57.2)	NA

BCFQOL: Beach Center Family Quality of Life; FQOL: Family Quality of Life; NA: Not applicable/not available; IQR: interquartile range; PedsQL FIM: Pediatric Quality of Life Inventory Family Impact Module; SD: standard deviation; SF-12: 12-Item Short Form Survey; SF 36: 36-Item Short Form Survey; TAAQOL: TNO-AZL Questionnaire for Adult's Health Related Quality of Life; TNO-AZL: The Netherlands Organization for Applied Scientific Research Academical Medical Center

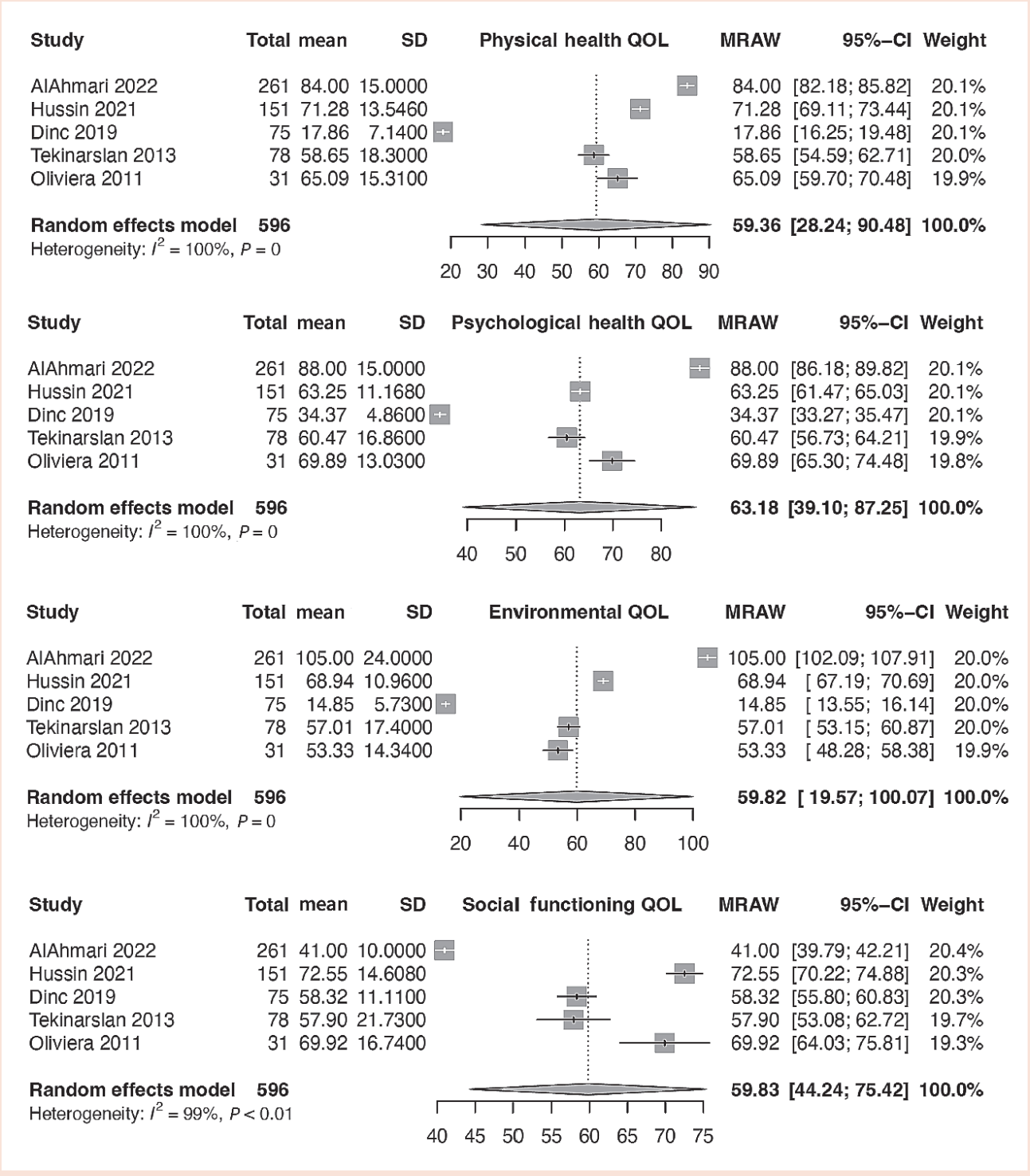
[a] The differences in individual QOL domain values between the control group and DS group of family caregivers (if applicable).

the 0–20 scale for the WHOQOL-BREF, which we transformed to 0–100 to enable comparison, using the formula stated in Supplementary Appendix S2. Supplementary Appendix S4 presents the qualitative analysis of these 10 studies.

Quantitative analysis

We conducted a meta-analysis of WHOQOL-BREF scores on 5 of 10 studies[18,26,30-32] with 596 participants. Five studies were excluded as standard deviation values were unavailable[28,29] or not

Fig. 2. Forest plot of combined data of 5 studies using the World Health Organization Quality of Life Instrument-Brief Version.



CI: confidence interval; MRAW: raw mean; QOL: quality of life; SD: standard deviation

calculable from transformed scores.[24,25,27] Fig. 2 shows the forest plot of compiled scores. Funnel plot was not constructed to measure publication bias due to the small number of studies.

Psychological health domain had the highest mean score (95% CI) of 63.18 (39.10–87.25). Scores were poorer in physical, environmental and social domains at 59.36 (28.24–90.48), 59.82 (19.57–100.07) and 59.83 (44.24–75.41), respectively. Studies were heterogenous with I^2 values ranging from 99–100% (all $P<0.01$). High heterogeneity stemmed from the relatively small number of included studies and diversity in the population studied. For example, Senses Dinc et al.'s[18] cohort stands out as an outlier with markedly poor physical, psychological and environmental health scores, which could be attributed to high prevalence (66%) of comorbidities, psychiatric symptoms and depressive disorders among mothers, high economic burden and caregiving for the youngest group of children with DS, aged 0 to 3 years. These factors may have exacerbated caregiving tasks for the caregivers and resulted in poorer QOL in multiple domains. AlAhmari et al.'s[26] study in Saudi Arabia reported much lower social functioning compared to other studies, where 64% of mothers had more than 4 children.

QOL measures using 36-Item Short Form Survey (SF-36) and 12-Item Short Form Survey (SF-12)

The SF-36 is a self-administered, standardised scale involving 8 domains of QOL studying limitations in various aspects in life.[33] The SF-12 is an abbreviated version of the SF-36.[34]

Cetin et al. investigated the effects of functional independence and age of children with DS on the QOL of 37 mothers in Turkey using SF-36.[35] The children were classified into "need observation" and "independent" using the Functional Independence Measure. Mothers of "independent" children had significantly higher QOL compared to children "needing observation", particularly in total QOL and mental subdomain ($P=0.036$ and $P=0.018$, respectively); but no difference was found in physical subdomain ($P=0.062$). The children's age did not have any effect on the mothers' QOL.

Bourke et al. explored the relationship of various characteristics of children with DS on their mothers' (n=250) physical, mental and overall health in Australia.[36] The mothers experienced lower QOL in physical health domain if their child had current heart problems or higher body mass index ($P=0.026$ and $P=0.006$, respectively). Mothers of children with DS fared worse in mental health (mean [SD] 45.2 [10.6], $P<0.0001$) than mothers of children without DS. Higher scores on the child's Developmental Behavior Checklist, which indicates poorer behaviour, were significantly associated with lower maternal physical and mental health. The child's age and sex, number of siblings, and maternal factors (education, family income and partner status) did not affect maternal QOL.

QOL measures using Pediatric Quality of Life Inventory Family Impact Module (PedsQL FIM)

PedsQL FIM 4.0 is a 36-item, self-reported QOL instrument for parents of children with chronic health conditions.[37]

Darla et al. studied 51 caregivers of children with DS in South India; majority were from upper-middle to upper class urban backgrounds.[38] Most of the caregivers experienced an average to good QOL (mean 68.98). They were most affected by worry (57.33%, z score = -1.91) and least affected in cognitive functioning (71.60%, z score = 1.22). Older caregivers (35–50 years) reported better QOL than younger caregivers (20–35 years). Upper-middle class caregivers reported better QOL compared to upper class caregivers (70.20 versus 59.92, respectively). Parents with children who had fewer comorbidities reported better QOL (73.78 for no comorbidities, 62.34 for 4 comorbidities). There was no correlation of QOL with the birth order and number of siblings.

Rozensztrauch et al. studied 53 Polish parents, and the relationship between child's QOL and parental QOL.[39] The total mean (SD) score was 57.51 (17.50), with worry and daily activities the worst affected domains. There was a positive association between the child's QOL and the QOL of their parents and family functioning, indicating that parental perception of better QOL in the child is positively correlated with parental QOL.

QOL measures using Beach Center Family Quality of Life Scale (BCFQOL)

BCFQOL is a self-report scale measuring quality of family life.[40]

Foley et al. studied 150 families of young adults with DS in Australia. Family QOL was correlated with activities of daily living (ADL) and day occupations of young adults with DS.[41] Families were most satisfied with their physical/material well-being (mean [SD] 4.19 [0.72]) and least satisfied in emotional well-being (mean [SD] 3.47 [1.00]). An open employment programme (mean [SD] 107.15 [13.63]), compared to sheltered employment (mean 94.91 [16.01]) or day recreation programmes (mean [SD] 93.24 [22.25]), improved family QOL moderately ($P<0.001$). Family QOL

was higher in children with DS with higher ADL abilities. Factors that elevated family QOL included higher levels of familial support (P<0.001) and access to services that enhance ADL functions.

QOL measures using Family Quality of Life (FQOL)

FQOL is a self-report instrument that measures family's QOL in nine domains.[42]

Brown et al. compared QOL of families in Canada who had children with DS (n=33), children with autism (n=18) and TD children (n=18, control group).[42] The control group had higher satisfaction than families of children with disability (DS and autism) in 8 of the 9 domains (the domain of disability-related services is not relevant to TD children). Families with children with DS had statistically higher satisfaction scores than families with children with autism except for support for disability-related services domain. In spiritual and cultural belief, parents of children with DS reported lower scores than parents of autistic children (P<0.001). QOL of families with children with DS compared to the control group were statistically lower in the domains of health (P<0.01), financial well-being (P<0.05) and support from others (P<0.001).

QOL measures using The Netherlands Organization for Applied Scientific Research Academical Medical Center Questionnaire for Adult's Health-Related Quality of Life (TAAQOL)

TAAQOL has 45 items in 12 domains.[21] Marchal et al. studied the effect of socio-demographic, child functioning and psychosocial factors on QOL of 98 parents of children with DS in Netherlands.[21] Psychosocial variables (social support, quality of partner relations and time pressure) affected QOL domains of cognitive functioning, social functioning, daily activities and vitality. Socio-demographic factors (gender of child and parent, and parental educational level) had less effect on parental QOL. Cognitive function was most dampened by night sleeping hours of child (P<0.01) and parents giving up a hobby since birth of child (P<0.01). Social functioning was most predicted by quality of inter-partner relations (P<0.001). Daily activities QOL domain was best predicted by whether parents had time to care for ill friends or family (P<0.01), and vitality was best predicted by whether parents had sufficient personal time (P<0.01).

In another study, Marchal et al. studied QOL of 124 parents of 88 adolescents (11–13 years old) with DS compared to a control group, and QOL fluctuations when the children were aged between 6 to 8 years old.[22] There were 58 parents with children with DS who had participated in the preceding study by the same authors.[21] Mothers of adolescents with DS compared to control group, reported lower score in the sexuality domain of QOL (P=0.001), while no QOL domain differed significantly in fathers. Fifty-eight parents of children with DS participated at 2 time points (children at age 6–8 years and 11–13 years).[21,22] Parents of 11–13 years old reported improved trend in cognitive functioning (mean [SD] 65.9 [31.1] versus 74.4 [26.8]; P=0.035) and aggressiveness (mean [SD] 85.6 [17.0] versus 90.4 [15.9]; P=0.041), where a higher score in aggressiveness indicates better functioning over time. The other QOL subdomains did not differ between the 2 time points.

DISCUSSION

To our knowledge, this is the first systematic review and meta-analysis of QOL of family caregivers of children and young adults with DS.

Our meta-analysis showed poorer scores among caregivers of children with DS compared to population norms of WHOQOL-BREF (who may or may not be involved in caregiving tasks) in high- and middle-income countries. Among caregivers of children with DS, the highest score was in psychological health with a mean of 63.18 (95% CI 39.18–87.28); all other domain scores were below 60. In comparison, population norms of Australian adults ages 20–79 years were: psychological health mean 70.6 (SD 14.0); physical health, mean 73.5 (SD 18.1); social relationship, mean 71.5 (SD 18.2) and environmental, mean 75.1 (SD 13.0).[43] Similarly, population norms in Brazilian adults aged 20–63 years were: psychological health, mean 65.9 (SD10.8); physical health, mean 58.9 (SD 10.5); social mean 76.2 (SD18.8) and environmental 59.9 (SD14.9).[44] All 5 studies in the meta-analysis were from non-Western countries; therefore, generalisability could be limited to countries with similar socio-economic background. As QOL depends on personal and socio-cultural factors as well as individual values and expectations, interpretation of QOL data needs to consider these factors. Furthermore, 4 individual case-control studies generally reported lower QOL in caregivers of children with DS compared to TD children.[18,22,24,42]

QOL of the caregivers is affected by various factors. Child-related factors included level of functional independence,[24,35] poor development,[36] presence of multiple comorbidities,[18,38] impaired ADL[41] and poor sleep quality.[21] Environmental factors included the number of children,[26] quality of housing[27] and support from family.[41] Personal factors included age of the caregivers,[31] being a single mother,[25] and having a low education and low

income among mothers.[25] Belief in organised religions had a positive impact of QOL.[28] Of note, the vast majority of individuals with DS, even in countries with good social support, continue to live with their family.[41]

Children and young adults with DS experience significant changes from infancy to young adulthood. During infancy, families grapple with the diagnosis (especially if it was not identified through antenatal screening) and cope with congenital conditions such as congenital heart diseases, feeding difficulties and gastrointestinal malformations.[9] These challenges may contribute to the reported poor QOL among parental caregivers of younger children.[18] As the child's congenital conditions are treated or improve, and the family adjusts to the diagnosis, coupled with the typical pleasant demeanour of children with DS,[10] caregivers' QOL tends to improve during early childhood. However, during adolescence and young adulthood, individuals with DS face new challenges, including social adjustments, peer relationships, and a higher prevalence of anxiety and depression. The phenomenon known as idiopathic regression in DS, further impacts the well-being of individuals with DS.[11] As the QOL of family caregivers is closely related to QOL of the children with DS,[39] it is prudent to screen caregivers' QOL with higher frequency during infancy, late childhood and adolescent years.

Twelve out of 18 studies were from non-Western countries. Some studies included rural population, thereby increasing the diversity of the study population.[25,28] As QOL is highly dependent on socio-cultural context, this global representation is a promising step towards broader understanding of QOL of family caregivers caring for children with DS from a diverse perspective.

We recommend using WHOQOL-BREF as a preferred tool to investigate QOL of caregivers caring for children with DS as this tool is more widely used, validated in many languages and free of cost. This would enable researchers to compare results across studies and aggregate data for future meta-analyses.

We would like to highlight several limitations. In the search strategy, we did not include intellectual disability, which could have broadened the search and plausibly retrieved more studies that included people with intellectual disabilities related to DS. We deviated slightly from the PROSPERO application where we specified an upper limit of age of 21 years, but we expanded the upper boundary of age to 30 years. Studies were heterogenous as reflected in the I^2 values. We posit that one of the primary reasons for this heterogeneity is the wide age range of children and young adults with DS (age range 1 month to 30 years) included in the studies. Across this wide age range, individuals with DS undergo significant changes in their developmental and medical needs, and emotional maturity resulting in varied caregiving tasks that can affect the QOL of caregivers. Most of participants in the studies were mothers, with underrepresentation of the fathers. In a few studies, a minority of the caregivers were not parents (e.g. maid, grandparents or sibling)[26] or not specified.[24] There was only 1 longitudinal follow-up study with a short follow-up duration (<5 years).[22] As the life expectancy of individuals with DS continues to improve, there is a need to investigate QOL of young adults and older individuals with DS living in diverse socio-cultural settings.

CONCLUSION

In this comprehensive review, we have identified several critical areas for future research. First, there remains a significant gap in longitudinal cohort studies conducted over an extended period. Such studies are essential to understand how caregivers' QOL evolves as their children with DS experience changes in their developmental, psychosocial and medical needs. Second, existing research predominantly focuses on female caregivers, typically mothers. However, to gain a more holistic perspective, it is crucial to explore the views of male caregivers as well and consider the input of other extended family members, such as grandparents and siblings. Last, there is a pressing need to determine the barriers and challenges at the practice level to implement QOL measures directed to the patients and their family caregivers.

Our systematic review fills a void in our contemporary understanding of QOL in caregivers of children with DS. Periodic assessment of QOL of family caregivers is needed to identify caregivers at risk of poorer QOL and institute appropriate measures.

Declaration

No funding was received for this work. All authors have no affiliations or financial involvement with any commercial organisation with a direct financial interest in the subject or materials discussed in the manuscript.

Supplementary materials

Supplementary Appendix S1. Search strategy.

Supplementary Appendix S2. Summary of instruments.

Supplementary Appendix S3. Quality of included studies using Newcastle-Ottawa Scale.

Supplementary Appendix S4. Qualitative analysis of studies using the World Health Organization Quality of Life instrument-Brief Version (WHOQOL-BREF).

REFERENCES

1. Family Caregivers Alliance. Definitions: What do we mean by. https://www.caregiver.org/resource/definitions-0/. Accessed 6 July 2024.
2. Liu F, Shen Q, Huang M, et al. Factors associated with caregiver burden among family caregivers of children with cerebral palsy: a systematic review. BMJ Open 2023; 13:e065215.
3. Kasuya RT, Polgar-Bailey P, Takeuchi R. Caregiver burden and burnout. A guide for primary care physicians. Postgrad Med 2000;108:119-23.
4. World Health Organization. The World Health Organization Quality of Life (WHOQOL). https://www.who.int/publications/i/item/WHO-HIS-HSI-Rev.2012.03. Accessed 6 July 2024.
5. Karimi M, Brazier J. Health, Health-Related Quality of Life, and Quality of Life: What is the Difference? Pharmacoeconomics 2016;34:645-9.
6. Chow MYK, Morrow AM, Cooper Robbins SC, et al. Condition-specific quality of life questionnaires for caregivers of children with pediatric conditions: a systematic review. Qual Life Res 2013;22:2183-200.
7. United Nations. World Down Syndrome Day 21 March. https://www.un.org/en/observances/down-syndrome-day#:~:text=The%20estimated%20incidence%20of%20Down. Accessed 6 July 2024.
8. Raut P, Sriram B, Yeoh A, et al. High Prevalence of Hearing Loss in Down Syndrome at First Year of Life. Ann Acad Med Singap 2011;40:493-8.
9. Bull MJ, Trotter T, Santoro SL, et al. Health Supervision for Children and Adolescents With Down Syndrome. Pediatrics 2022;149:e2022057010.
10. Grieco J, Pulsifer M, Seligsohn K, et al. Down syndrome: Cognitive and behavioral functioning across the lifespan. Am J Med Genet C Semin Med Genet 2015;169:135-49.
11. Walpert M, Zaman S, Holland A. A Systematic Review of Unexplained Early Regression in Adolescents and Adults with Down Syndrome. Brain Sci 2021;11:1197.
12. Parish SL, Pomeranz A, Hemp R, et al. Family Support for Families of Persons with Developmental Disabilities in the U.S.: Status and Trends. https://ici.umn.edu/products/prb/122/default.html. Accessed 6 July 2024.
13. Barros ALO, Barros AO, Barros GL de M, et al. Burden of caregivers of children and adolescents with Down Syndrome. Cien Saude Colet 2017;22:3625-34.
14. AlShatti A, AlKandari D, AlMutairi H, et al. Caregivers' perceptions and experience of caring for persons with Down syndrome in Kuwait: a qualitative study. Int J Dev Disabil 2021;67:381-90.
15. Abbeduto L, Seltzer MM, Shattuck P, et al. Psychological well-being and coping in mothers of youths with autism, Down syndrome, or fragile X syndrome. Am J Ment Retard 2004;109:237-54.
16. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021:n71.
17. Higgins J, Thomas J, Chandler J, et al. Cochrane Handbook for Systematic Reviews of Interventions Version 6.4 (Updated August 2023). Cochrane; 2023. www.training.cochrane.org/handbook. Accessed 6 July 2024.
18. Senses Dinc G, Cop E, Tos T, et al. Mothers of 0-3-year-old children with Down syndrome: Effects on quality of life. Pediatr Int 2019;61:865-71.
19. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol 2005;5:13.
20. Wells G, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed 6 July 2024.
21. Marchal JP, Maurice-Stam H, Hatzmann J, et al. Health related quality of life in parents of six to eight year old children with Down syndrome. Res Dev Disabil 2013;34:4239-47.
22. Marchal JP, Maurice-Stam H, Van Trotsenburg ASP, et al. Mothers and fathers of young Dutch adolescents with Down syndrome: Health related quality of life and family functioning. Res Dev Disabil 2016;59:359-69.
23. Vahedi S. World Health Organization Quality-of-Life Scale (WHOQOL-BREF): Analyses of Their Item Response Theory Properties Based on the Graded Responses Model. Iran J Psychiatry 2010;5:140-53.
24. Amaral MF, Carvalho KHTD, Aranega AM, et al. Evaluation of quality of life, depression, anxiety and stress among caregivers of people with or without Down Syndrome: a cross-sectional study. Research, Society and Development 2020;9:e813986193.
25. Geok CK, Abdullah KL, Kee LH. Quality of life among Malaysian mothers with a child with Down syndrome. Int J Nurs Pract 2013;19:381-9.
26. AlAhmari FS, Alageel AF, Aldosari MA, et al. The quality of life of parents of children with down syndrome in a tertiary care hospital: A qualitative research study at Saudi Arabia. Ann Med Surg (Lond) 2022;81:104428.
27. Abbasi S, Sajedi F, Hemmati S, et al. Evaluation of Quality of Life in Mothers of Children with Down Syndrome. PCP 2016;4:81-8.
28. Vadakedom SS, Mary Antony J, Krishnan Padma B, et al. Quality of Life of Mothers of Children with Down Syndrome. JEMDS 2017;6:2939-42.
29. Buzatto LL, Beresin R. Quality of life of parents with Down syndrome children. Einstein 2008;6:175-81.
30. Oliveira E de F, Limongi SCO. Quality of life of parents/caregivers of children and adolescents with Down syndrome. J Soc Bras Fonoaudiol 2011;23:321-7.
31. Hussin N, Ismail A, Ismail J, et al. The quality of life of mothers of down syndrome children with and without hearing impairment in Universiti Kebangsaan Malaysia medical center. Indian J Otol 2021;27:189.
32. Tekinarslan IC. A comparison study of depression and quality of life in Turkish mothers of children with Down syndrome, cerebral palsy, and autism spectrum disorder. Psychol Rep 2013;112:266-87.
33. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30:473-83.
34. Ware J, Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. Med Care 1996;34:220-33.
35. Cetin S, Calik B, Taspinar F, et al. The effect of functional independence level and age on the quality of life of mother's with down syndrome children. Curr Pediatr Res 2017; 21:652-7.

36. Bourke J, Ricciardo B, Bebbington A, et al. Physical and Mental Health in Mothers of Children with Down Syndrome. Journal Pediatr 2008;153:320-6.
37. Varni JW, Sherman SA, Burwinkle TM, et al. The PedsQL Family Impact Module: preliminary reliability and validity. Health Qual Life Outcomes 2004;2:55.
38. Darla S, Bhat D. Health-related quality of life and coping strategies among families with Down syndrome children in South India. Med J Armed Forces India 2021;77:187-93.
39. Rozensztrauch A, Wieczorek K, Twardak I, et al. Health-related quality of life and family functioning of primary caregivers of children with down syndrome. Front Psychiatry 2023; 14:1267583.
40. Hoffman L, Marquis J, Poston D, et al. Assessing Family Outcomes: Psychometric Evaluation of the Beach Center Family Quality of Life Scale. J Marriage Fam 2006; 68:1069-83.
41. Foley KR, Girdler S, Downs J, et al. Relationship between family quality of life and day occupations of young people with Down syndrome. Soc Psychiatry Psychiatr Epidemiol 2014;49:1455-65.
42. Brown RI, MacAdam–Crisp J, Wang M, et al. Family Quality of Life When There Is a Child With a Developmental Disability. Policy Practice Intel Disabi 2006;3:238-45.
43. Hawthorne G, Herrman H, Murphy B. Interpreting the WHOQOL-Brèf: Preliminary Population Norms and Effect Sizes. Soc Indic Res 2006;77:37-59.
44. Cruz LN, Polanczyk CA, Camey SA, et al. Quality of life in Brazil: normative values for the WHOQOL-bref in a southern general population sample. Qual Life Res 2011;20:1123-9.

Ann Acad Med Singap 2024;53:502-13
https://doi.org/10.47102/annals-acadmedsg.2023415

REVIEW ARTICLE

Quality of life of children and young adults with Down syndrome from caregivers' perspective: A systematic review and meta-analysis

Yu Yi Chan*[1], Bryan Wong Wei Zhi*[2] *MBBS*, Fergus Edward Cheok[2] *MBBS*, Natania Rae Tan Xiangqin[1], Gwyneth Kong[2] *MBBS*, Zubair Amin[3,4] *MHPE*, Yvonne Ng Peng Mei[3,4] *MRCP*

ABSTRACT

Introduction: Down syndrome (DS) negatively impacts the well-being of affected individuals. This study aimed to summarise the evidence on quality of life (QOL) of children and young adults with DS using quantitative measures from caregivers' perspective and identify factors that affected their QOL.

Method: Database search was conducted on PubMed, Embase, Web of Science and CINAHL on 24 April 2024. Meta-analysis using random effects model was conducted where feasible. All studies underwent qualitative synthesis. The study protocol was registered with PROSPERO (CRD42023413532).

Results: Seventeen studies involving 3038 children with DS using various QOL measures were included: Pediatric Quality of Life Inventory (PedsQL) (8 studies), KIDSCREEN (4 studies), KidsLife (2 studies), The Netherlands Organization for Applied Scientific Research Academic Medical Center Children's QOL (2 studies) and Personal Outcome Scale (1 study). Meta-analysis on PedsQL studies compared scores between children with DS and typically developing (TD) children. Total scale score was lower in children with DS (mean 70.28, 95% confidence interval [CI] 64.31–76.24) compared to TD children (mean 88.17, 95% CI 80.50–95.83). All subdomains of PedsQL were also lower in children with DS. Within the domain of psychosocial health, children with DS had statistically significant lower social functioning (standardised mean difference -1.40, 95% CI -2.27 to -0.53) and school functioning (standardised mean difference -1.09, 95% CI -1.55 to -0.62) scores, but similar emotional functioning scores. Qualitative synthesis revealed poorer subdomain QOL compared to TD children, especially in social functioning and cognitive functioning. QOL worsened during adolescent years. Family variables (parental education and occupation) did not affect parental perception of children's QOL. Children with DS who had higher intelligent quotient had better QOL.

Conclusion: Children with DS have lower caregiver-reported QOL than TD children, especially in social functioning and school functioning subdomains.

Ann Acad Med Singap 2024;53:502-13

Keywords: KidsLife-Down scale, KIDSCREEN, mental health, neonatology, paediatrics, parents, PedsQL, trisomy 21

CLINICAL IMPACT

What is New

- Children with Down syndrome (DS) have poorer overall caregiver-reported quality of life (QOL) compared to typically developing children, and experience poorer social and school functioning.
- Adolescents with Down syndrome are at risk of further deterioration of QOL.

Clinical Implications

- Clinical care of children with DS should include QOL assessment to identify gaps in service needs for targeted interventions.
- Targeted enhanced screening of QOL for adolescents with DS is recommended.

INTRODUCTION

Down syndrome (DS), with an incidence of about 1/1000 to 1/1100 live births[1] is the most common autosomal trisomy and genetic cause of intellectual disability. Individuals with DS may have multiple comorbidities including congenital cardiac and gastrointestinal anomalies, obesity, sleep disorders, and visual and hearing impairments.[2,3] Despite the comorbidities, with advancements in care, survival of individuals with DS has significantly improved over the years.[4] As the burden of disease at the population level has increased, service providers and researchers are paying more attention to quality of life (QOL) of individuals with DS.[5]

According to the World Health Organization, QOL measures one's position in life relating to culture, values, goals and standards.[6] QOL provides insight into treatment and prognosis,[7] and aids in holistic assessment of patients and

[1] Yong Loo Lin School of Medicine, National University of Singapore, Singapore
[2] MOH Holdings, Singapore
[3] Department of Paediatrics, Yong Loo Lin School of Medicine, National University of Singapore, Singapore
[4] Department of Neonatology, Khoo Teck Puat-National University Children's Medical Institute, National University Hospital, Singapore
* Joint first authors
Correspondence: A/Prof Zubair Amin, Department of Neonatology, Khoo Teck Puat-National University Children's Medical Institute, National University Hospital, 5 Lower Kent Ridge Road, Singapore 119074.
Email: paeza@nus.edu.sg
This article was first published online on 14 August 2024 at annals.edu.sg.

their disease outcomes.[8] Schalock et al. expanded the concept of QOL in persons with disability by proposing 8 core domains grouped into 3 higher order constructs: well-being (emotional well-being, physical well-being and material well-being), independence (personal development and self-determination), and social participation (interpersonal relations, social inclusion and rights).[9] This broader and more inclusive definition of QOL can improve evaluation of healthcare and social welfare processes, and outcomes relevant to people with disabilities, including individuals with DS.

Systematic reviews on QOL of children and adolescents with DS are surprisingly limited. We identified only 2 scoping reviews. Lee at al. studied the relationship between family variables and QOL of children with DS, identified gaps in existing knowledge and concluded that "conducting systematic reviews including analyses of statistical significance will be salient"[5] The second scoping review explored the self-reported QOL of adolescents with DS and included only 2 studies; the authors emphasised the need for more systematic investigations into the topic.[10] In addition, there are conflicting reports on QOL of patients with DS. For example, Lee et al. reported moderate or favourable overall QOL score, with emotional well-being subdomain having the lowest score.[11] Conversely, Xanthopoulos et al.'s study in the US showed significantly lower overall QOL score in children with DS compared to those without DS, but emotional functioning did not differ between the 2 groups.[12]

Therefore, we undertook a systematic review of quantitative studies on QOL of children and young adults with DS. We included young adults with DS since they remain dependent on their family and continue to live with them.[13] Our aims were to: (1) determine the QOL of children and young adults (≤21 years) from their caregivers' perspectives; and (2) identify factors that improve or worsen their QOL. Subsequently in this manuscript, reference to children with DS includes young adults with DS as well.

METHOD

We performed the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.[14] The protocol was registered on PROSPERO on 12 April 2023 (CRD42023413532).

Search strategies

We conducted the search under the guidance of a medical librarian with expertise in systematic reviews. We searched 4 databases (PubMed, Embase, Web of Science and CINAHL) from their inception until 24 April 2024, for articles on QOL of individuals with DS, using Medical Subject Headings (National Library of Medicine's controlled vocabulary thesaurus used to index articles) or related search terms such as "quality of life", "health related quality of life" and "trisomy 21". We also searched grey literature (e.g. Google Scholar and OpenGrey) and the bibliography of the relevant articles. The full search strategy is presented in Supplementary Appendix S1.

Study selection

Peer-reviewed studies (cohort, case series and case-control) reporting QOL of caregivers of children and young adults with DS that used quantitative methodology and were written or translated into English were screened for inclusion. Articles which met the eligibility criteria were selected for full-text review. Discrepancies were resolved by consensus between 2 authors. We contacted authors for studies with incomplete information.

Data extraction

Two authors independently screened the articles and extracted the following data:

(1) Study reference (author, year of publication, country, study design, aims and findings).
(2) Demographics and characteristics of subjects (number, sex, age, disease severity and comorbidities).
(3) Measurements and outcomes (QOL tools and variables).

Data synthesis and meta-analysis

We analysed extracted data, including subgroup analysis of the various QOL domains following the general principles set forth in the Cochrane Handbook.[15] We performed meta-analysis using R version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria) if data were available from 4 or more studies. In the meta-analysis, for 1 study[16] that presented only the median and interquartile range, we estimated the mean and standard deviation (SD) using the method recommended by Hozo et al.[17] In another study,[18] where QOL scores were stratified by age groups, we combined the scores as described in the Cochrane Handbook.[19]

We chose random effect model due to the heterogeneity of studies. We evaluated I^2 statistics according to the Cochrane Handbook.[15] The data from each study were pooled and used to calculate the mean scores with 95% confidence interval (CI). We calculated the standardised mean difference (SMD) using the means and SD of total QOL and subdomains scores for 4 studies which compared PedsQL 4.0 QOL scores between children with

DS and typically developing (TD) children. We performed qualitative synthesis of all studies according to the type of QOL instruments.

Quality assessment

Two authors independently evaluated the quality of included studies using the Newcastle-Ottawa Scale.[20] Any discrepancies were resolved through discussion with senior authors.

RESULTS

Literature search

We retrieved 2783 studies from our database search. After deduplication, and title and abstract screening, 21 studies met the inclusion criteria. After full-text review, 17 cross-sectional studies involving 3038 children with DS using the following QOL measures were included (Fig. 1): PedsQL (8 studies), KIDSCREEN (4 studies), KidsLife (2 studies), The Netherlands Organization for Applied Scientific Research Academical Medical Center (TNO-AZL) Children's QOL (2 studies), and Personal Outcome Scale (1 study). In our quantitative analysis, we excluded self-reported QOL data of 4 children from 1 study[18] and parent-proxy QOL data of 41 young adults (>21 years old) from another study.[21]

Table 1 summarises the characteristics of included studies, and Supplementary Appendix S2 presents the extracted key information from qualitative synthesis of each study. Supplementary Appendix S3 summarises the tools used.

Quality of the studies

Inter-rater agreement between 2 reviewers was 94.1% (16 out of 17 studies). The quality of all the studies was satisfactory or better (≥5; maximum 10) as shown in Supplementary Appendix S4.

QOL measures using PedsQL

The PedsQL 4.0 is a 23-item, self-administered, child or parent-proxy report, multidimensional questionnaire validated for QOL measurement in children and adolescents.[22] Eight studies involving 564 caregivers used PedsQL.[12,16,18,23-27] Four studies[12,16,23,27] included TD children as the control group. One study included children with autistic spectrum disorder (ASD),[23] and another included obese children without DS as the control group.[12]

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

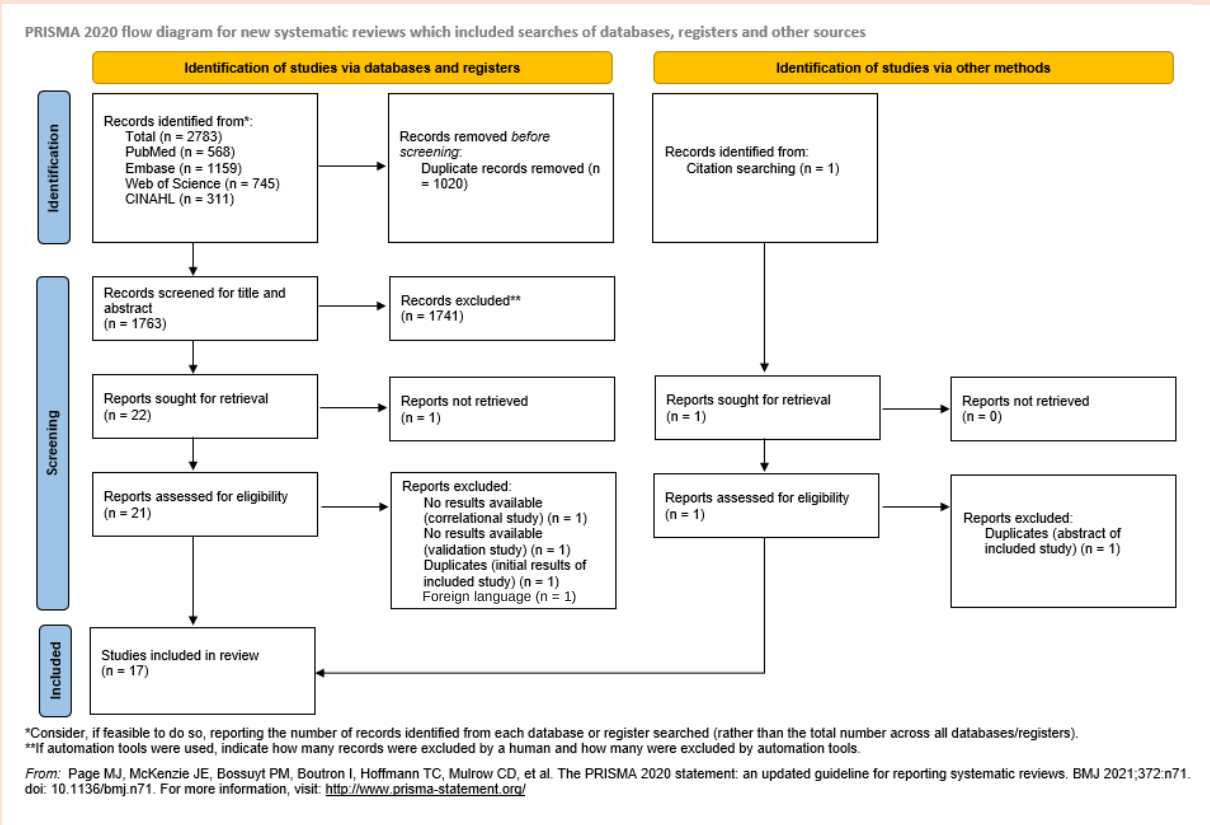


Table 1. Summary of included studies utilising the following quality of life measures: Pediatric Quality of Life Inventory (PedsQL) (8 studies), KIDSCREEN (4 studies), The Netherlands Organization for Applied Scientific Research Academic Medical Center (TNO-AZL) (2 studies), KidsLife (2 studies) and Personal Outcome Scale (1 study).

Author and publication date, study period, country, setting	Sample size, study design, instrument	Age of children with DS, mean ± SD/(SD) or median (IQR) or range in years	Age of caregivers, mean (SD) or median (IQR) and/or range in years; sex (F/M)	Comparison group	Main results		
					Better domain	Poorer domain	Unaffected domain
Studies utilising PedsQL							
Xanthopoulos 2017,[12] US, Children's Hospital of Philadelphia	209, secondary analysis from cross-sectional study, PedsQL	Mean ± SD: 14.6 ± 3.3	NA	Non-DS	NA	NA	NA
Katsiana 2020,[23] Greece	206, cross-sectional, PedsQL	Mean (SD): 7.3 (1.51)	NA	Typically developing children, autism spectrum disorder	NA	All domains	NA
Rojnueangnit 2020,[18] Thailand, June 2016 to May 2017, Thammasat University Hospital	50, descriptive research, PedsQL	Mean (SD): 3.03 (2.9)	Mean (SD): 38.8 (7.5) Range: 25–56; M:F 7:32	NA	NA	NA	NA
Fucà 2022,[24] Italy, December 2021 to April 2022, Child and Adolescent Neuropsychiatry Unit of the Bambino Gesù Children's Hospital in Rome	73, retrospective cross-sectional, PedsQL	Mean ± SD: 8.97 ± 2.24	NA	NA	NA	NA	NA
Fernández Scotto 2023,[16] Argentina, 2020 to 2021, tertiary care teaching hospital	102, cross-sectional, PedsQL	Median (IQR): 3.9 (2.8–4.2)	NA	Non-DS	NA	Physical health, psychosocial health, social functioning, school functioning	Emotional functioning
Rozensztrauch[25] 2023, Poland, January to December 2022	53, cross-sectional, PedsQL	Mean ± SD: 6.48 ± 4.56	NA	NA	NA	NA	NA

Table 1. Summary of included studies utilising the following quality of life measures: Pediatric Quality of Life Inventory (PedsQL) (8 studies), KIDSCREEN (4 studies), The Netherlands Organization for Applied Scientific Research Academic Medical Center (TNO-AZL) (2 studies), KidsLife (2 studies) and Personal Outcome Scale (1 study). (Cont'd)

Author and publication date, study period, country, setting	Sample size, study design, instrument	Age of children with DS, mean ± SD/(SD) or median (IQR) or range in years	Age of caregivers, mean (SD) or median (IQR) and/or range in years; sex (F/M)	Comparison group	Main results		
					Better domain	Poorer domain	Unaffected domain
Ciciora 2023,[26] US, October to December 2020	113, cross-sectional, PedsQL	Mean (SD): 10.3 (3.7)	NA	NA	NA	NA	NA
Alqahtani 2023,[27] Saudi Arabia, August to November 2021	67, cross-sectional, PedsQL	Median (IQR): 9.67 (8.58–11.17)	NA	TD	NA	All domains	NA
Rofail 2017,[21] multinational	90, longitudinal, non-intervention, KIDSCREEN-27	12–17 years old mean ± SD: 14.5 ± 1.6 18–30 years old mean ± SD: 22.7 ± 3.4	NA	KIDSCREEN-27 European normative group	Adolescents: School Environment	Adolescents: social support and peers	Physical well-being, psychological well-being, autonomy and parent relations
Shields 2018,[33] Australia, October 2013 to May 2014 (Victoria)/ 2011 (Western Australia), podiatry clinic of university campus (Victoria)/ questionnaire (Western Australia)	75, cross-sectional, KIDSCREEN-27	Mean: 13 years 2 months (SD: 7 years 8 months)	NA	Non-DS (norm referenced data)	NA	Physical well-being, social support and peers	Psychological well-being, autonomy and parent relation, school environment
Alrayes 2023,[34] Saudi Arabia	112, cross–sectional, KIDSCREEN-27	Female: 76.8%	NA	NA	NA	NA	NA
Jung 2017,[32] South Korea	36, KIDSCREEN-52	Mean: 6.8 ± 1.8	NA	Non-DS	NA	Overall QOL. Did not specify domains.	NA
Studies utilising TNO-AZL, TAPQOL and TACQOL-PF							
Van Gameren-Oosterom 2011,[37] Netherlands, June 2000 to February 2003, Leiden University Medical Centre,	337 total, 70 DS, TNO-AZL	Mean (SD): 8.1 (0.15)	NA	General population	nil	Gross motor skills, autonomy, social functioning, cognitive	Physical complaints, positive emotions, negative emotions

Table 1. Summary of included studies utilising the following quality of life measures: Pediatric Quality of Life Inventory (PedsQL) (8 studies), KIDSCREEN (4 studies), The Netherlands Organization for Applied Scientific Research Academic Medical Center (TNO-AZL) (2 studies), KidsLife (2 studies) and Personal Outcome Scale (1 study). (Cont'd)

Author and publication date, study period, country, setting	Sample size, study design, instrument	Age of children with DS, mean ± SD/(SD) or median (IQR) or range in years	Age of caregivers, mean (SD) or median (IQR) and/or range in years; sex (F/M)	Comparison group	Main results		
					Better domain	Poorer domain	Unaffected domain
Alhaddad 2023,[38] Saudi Arabia, June to August 2020, King Abdulaziz University Hospital	97, TNO-AZL, TAPQOL, TACQOL-PF	1–5 years old Mean ± SD: CHD: 2.7 ± 1.5 Non-CHD: 3 ± 1.2 6–15 years old Mean ± SD: CHD: 9.68 ± 2.6 Non-CHD: 9.67 ± 2.2	NA	NA	NA	NA	NA
Studies utilising KidsLife							
Lee 2021,[11] multinational	211, cross-sectional, KidsLife	Mean (SD): 10.9 (4.9)	Mean (SD): 38.5 (7.1) Range: 27–63	NA	NA	NA	NA
Moran 2022,[29] Spain	404, cross-sectional, KidsLife	Mean (SD): 12.1 (4.6)	Mean (SD): 45.3 (7) Female: 85%	NA	NA	NA	NA
Studies utilising Personal Outcome Scale							
Bermudez 2023,[39] Brazil	1187, cross-sectional, Personal Outcome Scale	Range: 4 to ≥31	NA	NA	NA	NA	NA

CHD: congenital heart diseases; DS: Down syndrome; F: female; IQR: interquartile range; M: male; NA: not available or not applicable; QOL: quality of life; SD: standard deviation; TAPQOL: TNO-AZL Preschool Quality of Life; TACQOL-PF: TNO-AZL Child Quality of Life Parent Form

Superscript numbers: refer to REFERENCES

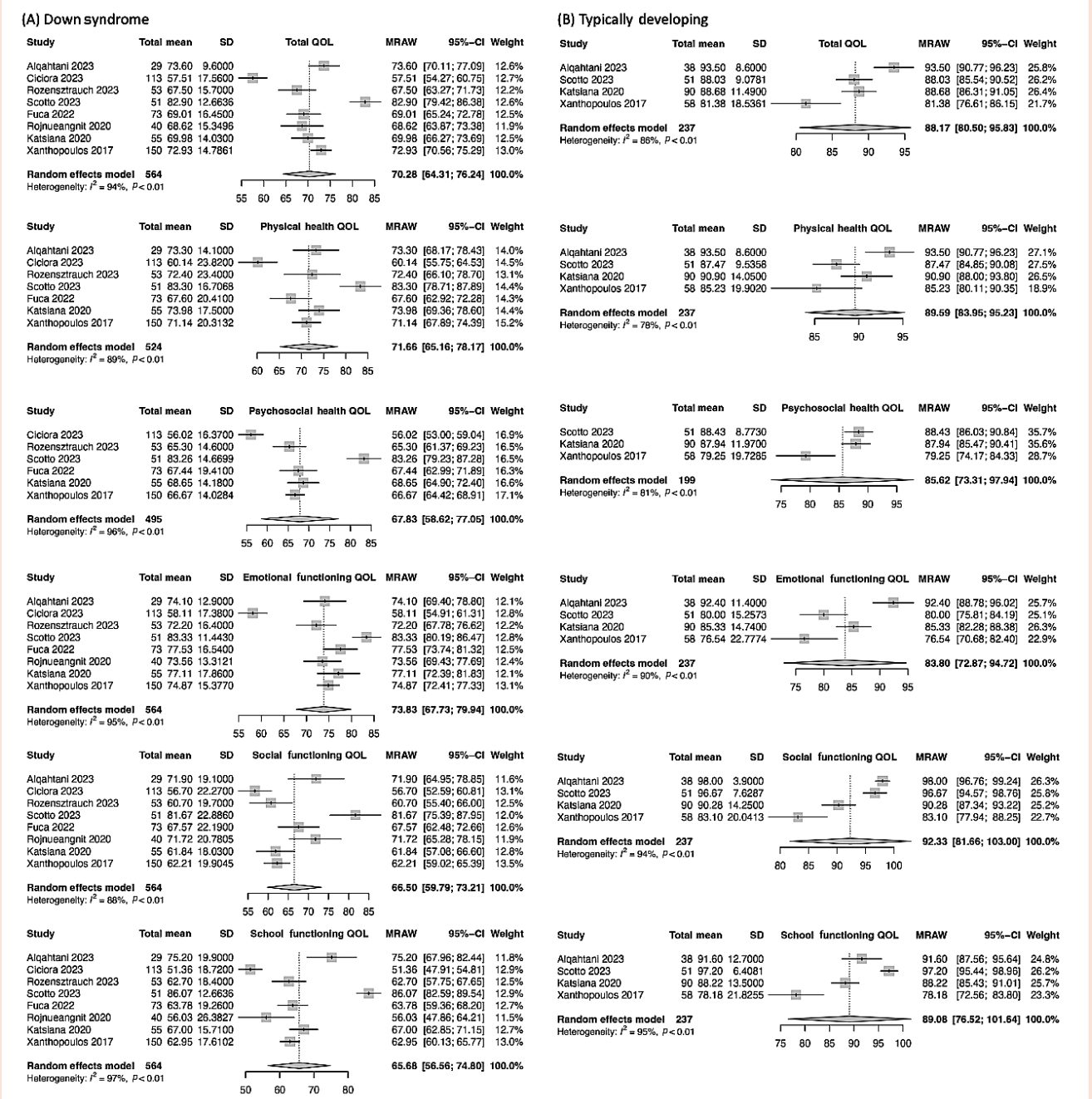
Quantitative analysis

We performed meta-analysis on studies using PedsQL. Fig. 2 displays the forest plot of the summary and subdomain scores for children with DS and TD children.[12,16,18,23-27]

Among children with DS, the pooled mean total scale score was 70.28 (95% CI 64.31–76.24; I^2=94%, P<0.01). Physical health summary score was 71.66 (95% CI 65.16–78.17; I^2=89%, P<0.01), and psychosocial health summary score (a composite score of emotional, social and school functioning) was 67.83 (95% CI 58.62–77.05; I^2=96%, P<0.01). For subdomain scores, emotional functioning scored the highest at 73.83 (95% CI 67.73–79.94; I^2=95%, P<0.01). Caregivers reported children with DS to have poor scores in social functioning and school functioning subdomains: 66.50 (95% CI 59.79–73.21; I^2=88%, P<0.01) and 65.68 (95% CI 56.56–74.80; I^2=97%, P<0.01), respectively.

Fig. 3 presents pooled data from 4 case control studies,[12,16,23,27] which compared children with DS

Fig. 2. Forest plot of the summary and subdomain PedsQL scores for (A) children with Down syndrome and (B) typically developing children.



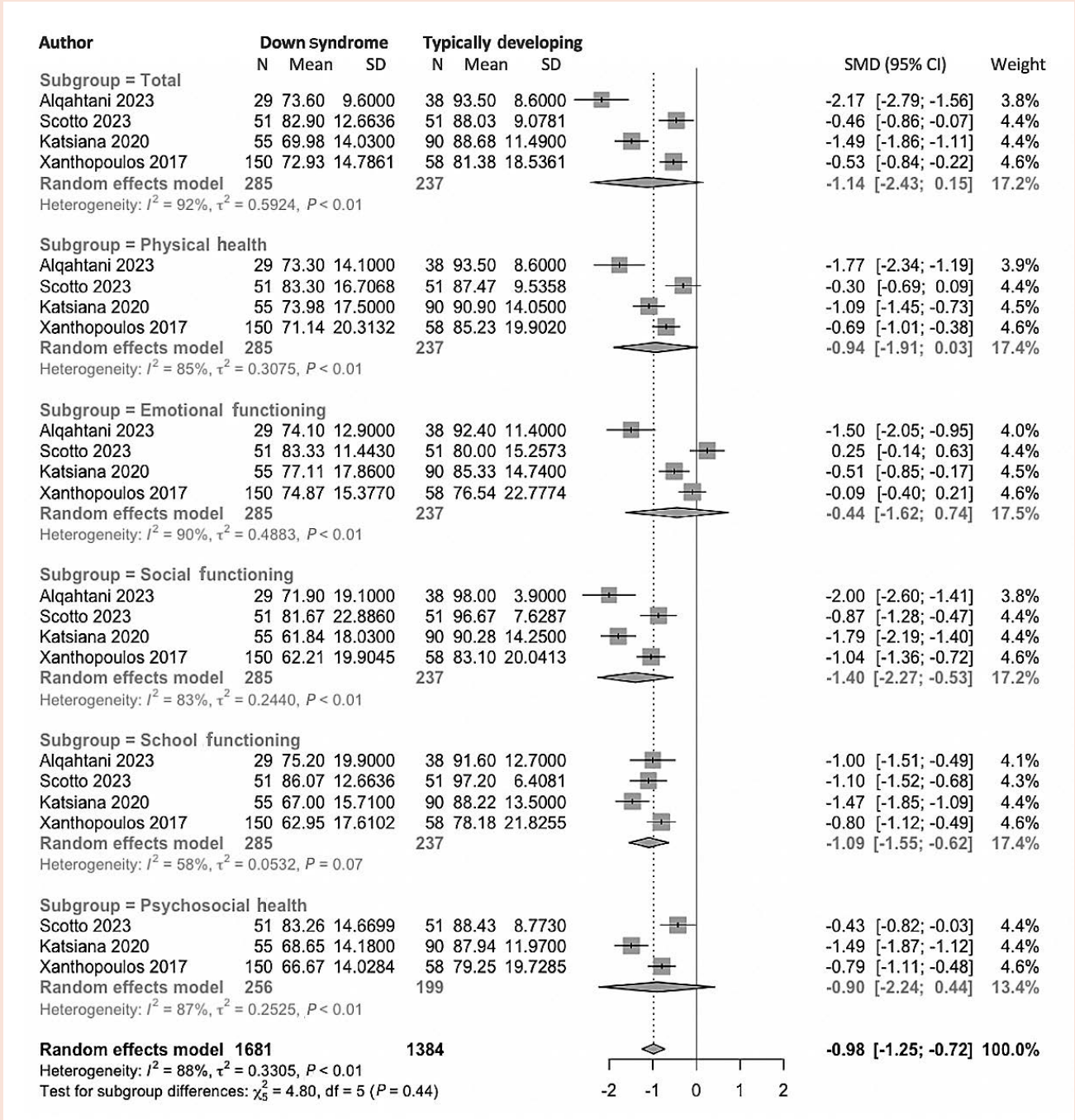
CI: confidence interval; PedsQL: Pediatric Quality of Life Inventory; MRAW: raw mean; QOL: quality of life; SD: standard deviation

against TD children. Total QOL scores, physical health and psychosocial health between children with DS and TD children did not show statistical difference. However, within the psychosocial health domain, children with DS had poorer scores in social functioning (SMD -1.40; 95% CI -2.27 to -0.53) and school functioning (SMD -1.09; 95% CI -1.55 to -0.62), but equivalent scores in emotional functioning as compared to TD children.

A comprehensive analysis of these studies revealed several significant themes. First and foremost, children with DS, when compared to their TD peers, have lower QOL scores as reported by caregivers. This is evident in all subdomains, where their scores are consistently lower. The subdomains of social and school functioning are the most adversely affected in children with DS. Children with DS with higher intelligent quotient have better QOL than those with lower intelligent quotient.[24]

Qualitative synthesis of the articles revealed further findings. Younger children (2–4 years old) have better emotional functioning scores than

Fig. 3. Standardised mean difference (SMD) of PedsQL scores comparing children with Down syndrome and typically developing children.



CI: confidence interval; PedsQL: Pediatric Quality of Life Inventory; MRAW: raw mean; QOL: quality of life; SD: standard deviation

older children.[16] Children with DS scored higher in emotional functioning than ASD children.[23] The presence of any comorbidity, whether physical (e.g. poor muscle tone)[25] or functional (e.g. irritable bowel syndrome)[26] triggers a domino effect on various subdomains of QOL in children with DS; whereas even a moderate level of physical activity has a positive effect on QOL.[27] Presence of obesity, a frequent comorbidity associated with DS, did not impact QOL among children with DS.[12] Self-reported scores from 4 children with DS were higher in emotional and school functioning, similar in physical health and lower in social functioning compared to parents' report, highlighting the importance of exploring self-reported QOL among suitable patients.[18]

QOL measures using KidsLife and KidsLife-Down

KidsLife was specifically developed to assess QOL of individuals with intellectual disabilities;[9] whereas KidsLife-Down specifically assesses QOL of children and young people with DS.[28] Two studies used these instruments.[11,29]

Lee et al. conducted a multinational study, with preponderance (77.7%) of children with DS from the US using KidsLife.[11] The authors reported moderate to favourable levels of QOL with the mean overall QOL score of 89.7 (SD 16.0; 70th to 71st percentile). Subdomains scores were at the following percentiles: social inclusion at 84th (highest), self-determination 75th, material well-being 63rd, physical well-being 50th, interpersonal relations 50th, personal development 50th, rights 50th and emotional well-being 37th. Morán et al. used KidsLife-Down in Spain and reported highest scores in the material well-being (43.35 ± 4.42), physical well-being (41.42 ± 5.25), and Rights (40.66 ± 5.33) subdomains.[29] Morán et al.[29] reported better scores in material well-being and physical well-being compared to Lee et al.,[11] which the authors attributed to wider availability of welfare programme for people with intellectual disability in Spain. On the other hand, self-determination and social inclusion were the 2 highest scoring subdomains reported by Lee et al., which is radically different from Moran et al.'s findings where these domains had the lowest scores. The plausible reasons include the use of KidsLife, rather than KidsLife-Down, by Lee et al. KidsLife was developed for people with significant intellectual disabilities who need extensive support. Thus, a ceiling effect may exist in some domains when high-functioning children with DS were surveyed.[29] Lee et al.'s cohort was also prone to self-selection bias as this was drawn from a support group with predominance of children with DS from US. The unexpected finding of poorer emotional well-being among older children could be due to higher prevalence of psychopathology and internalising symptoms,[30] underscoring the need for continuing vigilance among this group.

QOL measures using KIDSCREEN

KIDSCREEN includes a child or parent-proxy report questionnaire validated for QOL assessment in individuals aged between 8–18 years.[31] Four studies used KIDSCREEN.[21,32-34]

Jung et al. determined improvement in function and activities, and participation section of International Classification of Functioning, Disability and Health – Children and Youth Version was significantly correlated with QOL (R = -0.514, P<0.05), indicating importance of participation in physical activities among children with DS.[32] A significant finding from Shields et al. was that adolescents with DS (aged 13–18 years) had clinically significantly lower scores (>5 points) in all QOL domains compared to younger children with DS (aged 5–12 years).[33] Rofael et al. reported significantly higher scores in school environment and poor scores in the social support and peers domains among adolescents compared to normative European counterparts.[21] Alrayes et al. also reported higher scores in psychological well-being, autonomy, parental relation, and school and learning domains.[34] Plausible reasons for the unexpected high QOL results by Rofael et al. and Alrayes et al., as compared to Shields et al., include the use of KIDSCREEN-27,[21] which lacks the sensitivity and accuracy to effectively measure QOL of DS patients. Another reason could be due to face-to-face interviews adopted in Rofael's study, which may have influenced reporting of QOL by the parents. Shields et al.'s[33] study highlights the importance of continuing physical well-being and social support for children with DS even in high-resource countries, and extra vigilance in adolescent for possible deterioration of QOL.

QOL measures using TACQOL and TAPQOL

The TNO-AZL Child Quality of Life Parent Form (TACQOL-PF) is a 56-item (7 domains), child-self report or parent-proxy report questionnaire for children aged 6–15 years.[35] The TNO-AZL Preschool Quality of Life (TAPQOL) is a 43-item (4 domains) parent-proxy report questionnaire for preschool children aged 1–5 years.[36] Two studies used these tools.[37,38]

The study conducted by van Gameren-Oosterom stands as the earliest in this review and is unique in its national representation, encompassing nearly 50% of the Dutch population of children with

DS aged 8 years.[37] This study yielded significant findings, including a pronounced delay in development among children with DS, a higher prevalence of emotional and behavioral problems, and a less favourable QOL compared to TD children. A particularly noteworthy finding from Alhaddad's study, conducted in Saudi Arabia among children with DS with congenital heart disease, was the disparity in QOL between Saudi children who had ample social support and rehabilitation services, contrasted with non-Saudi children from lower-income families who lacked similar access.[38] This underscores the critical role of healthcare service accessibility for children with DS across all income groups.

QOL measures using Personal Outcome Scale

Bermudez et al.[39] studied 1187 patients with DS (including 151 patients >21 years old) from Brazil using Personal Outcome Scale, a specialised QOL tool for people with disability.[9,40] Good QOL was associated with being female, higher parental education level, mosaicism, adequate prenatal care, first medical consult at earlier age and employed mother.[39] Bad QOL was associated with family history of alcohol abuse, psychiatric condition, and presence of comorbidities such as autism and epilepsy.[39]

DISCUSSION

To our knowledge, this is the first systematic review and meta-analysis of the QOL of children, adolescents and young adults with DS from caregivers' perspectives.

Meta-analysis on included studies reporting PedsQL,[12,16,18,23-27] found that the total scale QOL scores of children with DS was 70.28 (95% CI 64.31–76.24), with subdomain scores ranging from 65.68 (95% CI 56.56–74.80) for school functioning to 73.83 (95% CI 67.73–79.94) for emotional functioning. Among these studies, Fernández-Scotto et al.'s study that had the youngest cohort of children at 2–4 years old, reported higher QOL scores in all subdomains, indicating that parents with young children with DS perceive their children to have better QOL.[16] Interestingly, parents of younger children with DS themselves self-reported poorer QOL.[41]

Using PedsQL, children with DS had significantly poorer scores in social functioning and school functioning compared to TD children.[12,16,23,27] In contrast, using KIDSCREEN, studies reported children with DS to have comparable scores to TD children in specific QOL subdomains. With better social support and educational systems, Shields et al.[33] reported 3 dimensions (psychological well-being, autonomy and parent relations, and school environment) in 13-year-old children with DS to be similar to normative data. In Rofail et al.'s study,[21] parents of adolescents with DS reported high school environment domain scores compared to the European normative group dataset. With their intellectual disabilities, children with DS are dependent on opportunities presented by society to improve their personal physical, emotional and psychosocial outcomes. This highlights the importance of ensuring that children with significant disabilities participate meaningfully in community activities.[42] Children with DS usually spend a lot more time than TD counterparts with their families, making familial support an integral part of social support, which can increase their QOL. Societal expectations about family responsibilities in caring for children with DS can vary greatly between Western and Eastern countries, depending on the support provided by each country.[5] As children with DS become teenagers and adults, integration into community via work or hobbies may become the primary source of social support.

A stereotypical view of children with DS is their vivacious personality and cheerfulness, which can be expected to predict good scores in emotional subdomain of QOL.[43] Our findings of high emotional/psychological domain scores in meta-analysis of PedsQL studies supported this premise,[18,24,33] and the scores were sometimes comparable to the TD population.[12] However, it is imperative to acknowledge that emotion is an inherently subjective experience of an individual. Therefore, caregivers' assessment of emotion is a surrogate of a child's emotional status, and self-reported QOL should be sought for whenever feasible.

QOL of children with DS deteriorate during adolescence. Adolescence and young adulthood are periods involving rapid change in biological and social factors. While a TD child may adjust to the changes by nurturing greater peer network, a child with DS may struggle to harness an adequate social and peer support network.[33] The decline in cognitive functioning and loss of previously achieved skills among adolescents is an area of emerging interest and concern.[44] Regression can happen unexpectedly, affecting cognitive and language functioning, ability to perform daily tasks, and cause alterations in personality and behaviour.[44] These abilities are closely linked to QOL measurements and may also explain the decline of QOL in an older child with DS. While there is a paucity of confirmed aetiologies, new evidence points towards immune dysfunction and stress from major life events and transitions as possible triggers

contributing to decline in QOL. Other causes may include psychiatric diseases like depression and anxiety, highlighting the importance of closer monitoring of adolescents with DS.[44,45]

Early interventions and educational therapy are proven to be beneficial for young children with DS. These can begin shortly after birth and continue through the toddler years. Later on, services can be provided through school or specialised centres taking care of children with DS or other disabilities.[2] Other interventions can be explored as well. For example, Fujino reported 2 cases of young adults with DS with psychiatric symptoms and marked disruption in their daily lives whose maladaptive behaviours improved after participation in a Dohsa-hou treatment programme (a psychological rehabilitation method in Japan).[46]

We would like to highlight several limitations of this review. The meta-analysis showed high heterogeneity with the lowest I^2 value of 89%. We postulate that the high heterogeneity is due to differences in age of the children with DS, study design, and country or regions of study. There are limited studies from non-Western countries. Caregivers were predominantly mothers, thus the views of other family caregivers were underrepresented. Finally, a minority of the informants were teachers and psychologists, and we could not separately analyse these data.

We identified several important research gaps. First, there were no longitudinal QOL studies as children with DS progress through developmental and biological stages. Second, only 1 study[29] used the DS specific KidsLife-Down that embraces the concept of individual QOL and includes a more comprehensive definition of QOL.

CONCLUSION

Based on our review, we recommend QOL measurements to be done every 6 months. During early childhood, this would allow healthcare providers to track caregivers' perception of their child's QOL as caregivers adapt to the child's diagnosis and medical conditions. We recommend the use of KidsLife-Down as it specifically assesses the QOL of children and young adults with DS. Due to the potential risk of QOL deterioration during adolescent and adult years, QOL during this period needs to be closely monitored. An unexpected change in QOL may suggest a change in clinical condition and therefore QOL may be used as a surrogate marker of the individual's health.

Declaration

No funding was received for this work. All authors have no affiliations or financial involvement with any commercial organisation with a direct financial interest in the subject or materials discussed in the manuscript.

Supplementary materials

Supplementary Appendix S1. Search strategy.

Supplementary Appendix S2. Extracted key information from qualitative synthesis of studies.

Supplementary Appendix S3. Summary of quality of life (QOL) tools.

Supplementary Appendix S4. Quality of included studies using Newcastle-Ottawa scale.

REFERENCES

1. United Nations. World Down Syndrome Day 21 March. Published 2023. https://www. un.org/en/observances/down-syndrome-day#:~:text=The%20 estimated%20incidence%20of%20Down. Accessed 18 May 2024.
2. Bull MJ, Trotter T, Santoro SL, et al. Health Supervision for Children and Adolescents With Down Syndrome. Pediatrics 2022;149:e2022057010.
3. Raut P, Sriram B, Yeoh A, et al. High Prevalence of Hearing Loss in Down Syndrome at First Year of Life. Ann Acad Med Singap 2011;40:493-8.
4. Kucik JE, Shin M, Siffel C, et al. Trends in Survival Among Children With Down Syndrome in 10 Regions of the United States. Pediatrics 2013;131:e27-36.
5. Lee A, Knafl K, Van Riper M. Family Variables and Quality of Life in Children with Down Syndrome: A Scoping Review. Int J Environ Res Public Health 2021;18:419.
6. World Health Organization. The World Health Organization Quality of Life (WHOQOL). Published 1 March 2012. https://www.who.int/publications/i/ item/WHO-HIS-HSI-Rev.2012.03. Accessed 18 May 2024.
7. Revicki DA, Osoba D, Fairclough D, et al. Recommendations on health-related quality of life research to support labeling and promotional claims in the United States. Qual Life Res 2000;9:887-900.
8. Chow MYK, Morrow AM, Cooper Robbins SC, et al. Condition-specific quality of life questionnaires for caregivers of children with pediatric conditions: a systematic review. Qual Life Res 2013;22:2183-200.
9. Schalock RL, Verdugo MA, Gomez LE, et al. Moving Us Toward a Theory of Individual Quality of Life. Am J Intellect Dev Disabil 2016;121:1-12.
10. Sheridan C, OMalley-Keighran M, Carroll C. What are the perspectives of adolescents with Down syndrome about their quality of life? A scoping review. Br J Learn Disabil 2020;48:98-105.
11. Lee A, Knafl G, Knafl K, et al. Quality of life in individuals with Down syndrome aged 4 to 21 years. Child Care Health Dev 2021;47:85-93.

12. Xanthopoulos MS, Walega R, Xiao R, et al. Caregiver-Reported Quality of Life in Youth with Down Syndrome. J Pediatr 2017;189:98-104.e1.
13. Parish SL, Pomeranz A, Hemp R, et al. Family Support for Families of Persons with Developmental Disabilities in the U.S.: Status and Trends. Policy Research Brief. https://ici.umn.edu/products/prb/122/default.html. Accessed 18 May 2024.
14. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021:372:n71.
15. Higgins J, Thomas J, Chandler J, et al. Cochrane Handbook for Systematic Reviews of Interventions Version 6.4 (Updated August 2023). www.training.cochrane.org/handbook. Accessed 18 May 2024.
16. Fernández Scotto E, Eymann A. Health-related quality of life in children with Down syndrome. Arch Argent Pediatr 2023;121:e202202756.
17. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol 2005;5:13.
18. Rojnueangnit K, Khaosamlee P, Chunsuwan I, et al. Quality of life and comprehensive health supervision for children with Down syndrome in Thailand. J Community Genet 2020;11:351-8.
19. Higgins JPT, Deeks JJ (Eds). Chapter 7: Selecting studies and collecting data. In: Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (Updated March 2011). https://handbook-5-1.cochrane.org/. Accessed 18 May 2024.
20. Wells G, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed 18 May 2024.
21. Rofail D, Froggatt D, de la Torre R, et al. Health-Related Quality of Life in Individuals with Down Syndrome: Results from a Non-Interventional Longitudinal Multi-National Study. Adv Ther 2017;34:2058-69.
22. Varni JW, Burwinkle TM, Seid M, et al. The PedsQL 4.0 as a pediatric population health measure: feasibility, reliability, and validity. Ambul Pediatr 2003;3:329-41.
23. Katsiana A, Strimpakos N, Ioannis V, et al. Health-related Quality of Life in Children with Autism Spectrum Disorder and Children with Down Syndrome. Mater Sociomed 2020;32:93-8.
24. Fucà E, Galassi P, Costanzo F, et al. Parental perspectives on the quality of life of children with Down syndrome. Front Psychiatry 2022;13:957876.
25. Rozensztrauch A, Wieczorek K, Twardak I, et al. Health-related quality of life and family functioning of primary caregivers of children with down syndrome. Front Psychiatry 2023;14:1267583.
26. Ciciora SL, Manickam K, Saps M. Quality of life measures in children with Down syndrome with disorders of gut–brain interaction. Am J Med Genet C Semin Med Genet 2023;193:e32071.
27. Alqahtani AS, Algabbani MF, Alhammad SA, et al. Physical activity status and its association with quality of life among children with down syndrome in Saudi Arabia: A comparative cross-sectional study. PLoS One 2024;19:e0297111.
28. Gómez LE, Verdugo MA, Rodríguez M, et al. Adapting a Measure of Quality of Life to Children with Down Syndrome for the Development of Evidence-based Interventions. Psychosoc Interv 2020;29:39-48.
29. Morán L, Gómez LE, Balboni G, et al. Predictors of individual quality of life in young people with Down syndrome. Rehabil Psychol 2022;67:205-14.
30. Vicari S, Pontillo M, Armando M. Neurodevelopmental and psychiatric issues in Down's syndrome: assessment and intervention. Psychiatr Genet 2013;23:95-107.
31. Ravens-Sieberer U, Auquier P, Erhart M, et al. The KIDSCREEN-27 quality of life measure for children and adolescents: psychometric results from a cross-cultural survey in 13 European countries. Qual Life Res 2007;16:1347-56.
32. Jung HK, Chung E, Lee BH. A comparison of the function, activity and participation and quality of life between down syndrome children and typically developing children. J Phys Ther Sci 2017;29:1377-80.
33. Shields N, Leonard H, Munteanu S, et al. Parent-reported health-related quality of life of children with Down syndrome: a descriptive study. Dev Med Child Neurol 2018;60:402-8.
34. Alrayes N, Issa NM, Alghubayshi OY, et al. Quality of life in children with Down syndrome and its association with parent and child demographic characteristics: Parent-reported measures. Mol Genet Genomic Med 2024;12:e2337.
35. Vogels T, Verrips GH, Verloove-Vanhorick SP, et al. Measuring health-related quality of life in children: the development of the TACQOL parent form. Qual Life Res 1998;7:457-65.
36. Fekkes M, Theunissen NCM, Brugman E, et al. Development and psychometric evaluation of the TAPQOL: A health-related quality of life instrument for 1–5-year-old children. Qual Life Res 2000;9:961-72.
37. van Gameren-Oosterom HBM, Fekkes M, Buitendijk SE, et al. Development, problem behavior, and quality of life in a population based sample of eight-year-old children with Down syndrome. PloS One 2011;6:e21879.
38. Alhaddad FA, Alkhushi NA, Alharbi AM, et al. Quality of Life Among Down Syndrome Patients With and Without Congenital Heart Disease at King Abdulaziz University Hospital, Jeddah, Saudi Arabia. Cureus 2023;15:e33553.
39. Bermudez BEBV, Franklin GL, Oliveira CMD, et al. Quality of life in Down syndrome in Brazil: a cross-sectional study. Arq Neuropsiquiatr 2023;81:943-8.
40. Claes C, Vandevelde S, Van Hove G, et al. Relationship between Self-Report and Proxy Ratings on Assessed Personal Quality of Life-Related Outcomes. J Policy Pract Intellect Disabil 2012;9:159-65.
41. Senses Dinc G, Cop E, Tos T, et al. Mothers of 0-3-year-old children with Down syndrome: Effects on quality of life. Pediatr Int Off J Jpn Pediatr Soc 2019;61:865-71.
42. Beadle-Brown J, Leigh J, Whelton B, et al. Quality of Life and Quality of Support for People with Severe Intellectual Disability and Complex Needs. J Appl Res Intellect Disabil 2016;29:409-21.
43. Grieco J, Pulsifer M, Seligsohn K, et al. Down syndrome: Cognitive and behavioral functioning across the lifespan. Am J Med Genet C Semin Med Genet 2015;169:135-49.
44. Walpert M, Zaman S, Holland A. A Systematic Review of Unexplained Early Regression in Adolescents and Adults with Down Syndrome. Brain Sci 2021;11:1197.
45. Sung M, Ooi YP, Law GC, et al. Features of autism in a Singaporean child with Down syndrome. Ann Acad Med Singap 2013;42:251-2.
46. Fujino H. Psychological Support for Young Adults with Down Syndrome: Dohsa-Hou Program for Maladaptive Behaviors and Internalizing Problems. Front Psychol 2017;8:1504.

Ann Acad Med Singap 2024;53:514-8
https://doi.org/10.47102/annals-acadmedsg.202449

LETTER TO THE EDITOR

Isolated remote site musculoskeletal *Mycobacterium bovis* infections after BCG immunisation in immunocompetent children

Jiawen Fong[1] *MBBS*, Dawn Sinn Yii Chia[1,2] *MBBS*, Darryl Ee Ming Chew[2,3] *MBBS*, Kenneth Pak Leung Wong[2] *MBBS*

Dear Editor,

The Bacillus Calmette–Guerin (BCG) vaccine, derived from wild-type *Mycobacterium bovis*, is administered in an attenuated form to prevent Mycobacterium tuberculosis (MTB) infections in children residing in endemic regions. Since the introduction of the Singapore Tuberculosis Elimination Programme in 1997—specifying mandatory BCG-immunisation at birth—the incidence fell drastically to 32.6 per 100,000 population in 2021,[1] with the paediatric population contributing 2.1% of infections.[2]

The vaccine is generally safe, but post-immunisation *M. bovis* infections (MBI) can occur, most commonly at the inoculation site forming localised MBI (L-MBI) such as cutaneous nodules, abscesses and lymphadenitis in immunocompetent children.[3] MBI resolves spontaneously without the need for treatment with oral anti-TB drugs or surgery.[4] Disseminated MBI (D-MBI) is rare and usually affects immunocompromised children in multiple sites including bones, joints, central nervous system, liver, spleen and lymph nodes. D-MBI also causes systemic complications of fever, weight loss, lymphadenopathy, hepatosplenomegaly and death.[5]

A third presentation variation described is the single site MBI (S-MBI), which affects a specific location remote from inoculation, without the presence of L-MBI or D-MBI, and has no correlation to the inoculation site. S-MBI involvement of the bone is estimated to occur in one per million vaccinations and affects the lower limbs, axial skeleton, upper limbs and multiple bones in decreasing frequency.[6,7] It is thought to occur through haematogenous dissemination and is seen as a lytic lesion in the metaphysis of the long bone, with low or the absence of inflammatory markers. Treatment regimens are highly varied, ranging from anti-TB drugs, chemotherapy and surgery, to undergoing no treatment at all. Musculoskeletal S-MBI in immunocompetent children is rare, and limited evidence-based literature is available describing its presentation and treatment. In this study, we aim to report the clinical characteristics of extremity bone and soft tissue S-MBI in immunocompetent children.

A retrospective review of children diagnosed with S-MBIs in a tertiary level paediatric hospital between 2017 and 2022 was performed with approval of the hospital ethics board. The inclusion criteria were children aged below 18, BCG vaccine administration following national immunisation guidelines, confirmed extremity musculoskeletal S-MBI, and absence of immunodeficiency conditions. L-MBIs were excluded. Data was collected on demographics; BCG vaccination details; S-MBI location and symptoms; and haematological, immunological and radiological investigations. Surgical details, anti-TB treatment regime, time to resolution, complications, readmissions and recurrence were recorded. Immunological tests for immunodeficiency included CD3, CD4, CD8 and CD20 levels; antibody testing for IgG, IgA, IgM and IgE levels; nitroblue tetrazolium levels; Mendelian susceptibility to mycobacterial diseases and immunological workup including interferon and gene sequence testing. MBI was confirmed through in-house laboratory mycobacterium culture or polymerase chain reaction (PCR) showing positive for *M. bovis*, and presence of acid-fast bacilli and necrotising granulomas on histology. PCR samples were sent for all patients. Mycobacterium cultures took on average 6 weeks for final results.

A total of 7 patients were included. Five were diagnosed with osteomyelitis, and 2 had deep soft tissue abscesses. The median age at presentation was 17.3 months (5.72–26.7). The median duration between symptom onset to seeking medical attention was 5 days (2–120). All reported pain, and the majority had localised swelling. Only 2 showed typical infective signs (redness and warmth), 1 had fever. All had normal immune workups. Two patients were subsequently diagnosed with thalassaemia and 1 with iron deficiency anaemia (Table 1).

[1] Department of Hand & Reconstructive Microsurgery, Sengkang General Hospital, Singapore
[2] Department of Orthopaedic Surgery, KK Women's and Children's Hospital, Singapore
[3] Department of Hand and Reconstructive Microsurgery, Singapore General Hospital, Singapore
Correspondence: Dr Dawn Chia, Department of Hand & Reconstructive Microsurgery, Sengkang General Hospital, 110 Sengkang East Way, Singapore 544886.
Email: drdawnchia@gmail.com

Table 1. Demographics, clinical signs, laboratory results, *Mycobacterium bovis infection* and surgery details in patient population.

Patient	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Gender	Male	Male	Female	Female	Female	Male	Male
Age at BCG vaccination, day	3	1	1	1	1	1	1
Age at presentation, day (month)	177 (5.8)	821 (26.0)	562 (17.9)	530 (17.3)	704 (23.0)	381 (8.6)	216 (7.0)
Duration of symptoms at presentation, day	2	30	5	5	4	120	3
BCG inoculation site	Left arm	Left arm	Left buttock	Left buttock	Left buttock	Left buttock	Left buttock
BCG infection site	Left humerus	Left humerus	Right arm	Left tibia	Left ankle	Right foot	Right knee
BCG strain given	Indian strain II	Indian strain II	Japan strain	Japan strain	Japan strain	Japan strain	Unknown
TB contact	No	No	No	No	No	No	No
Medical conditions	Nil	Transient tachypnoea of newborn	Nil	Small atrial septal defect	Nil	Nil	Dietary-related iron deficiency anaemia
Pain at infection site	+	+	+	+	+	+	+
Swelling	-	+	+	-	+	+	+
Redness and warmth	-	+	+	-	-	-	-
Fever	-	-	+	-	-	-	-
Lymphadenopathy	-	-	-	-	-	-	-
Hepatosplenomegaly	-	-	-	-	-	-	-
Haemoglobin, g/dL	11.50	11.00	10.99	11.90	11.40	11.30	12.81
Total white cell count, x10^9/L	19.75	16.74	10.15	16.91	11.49	9.83	12.81
Monocytes, x10^9/L	1.78	0.84	0.91	1.86	1.26	0.49	1.14
Platelets, x10^9/L	651	509	353	606	410	354	584
C-reactive protein, mg/L	3.4	1.5	12.6	17.0	10.9	0.40	31.6
CD4, g/L	Nil	25	36.7	37.9	43.6	41.3	35.0

Table 1. Demographics, clinical signs, laboratory results, *Mycobacterium bovis infection* and surgery details in patient population.

Patient	1	2	3	4	5	6	7
CD8, g/L	Nil	27.4	22.9	16.1	24.4	15.0	18.0
IgM, g/L	0.45	0.84	0.32	1.10	1.61	0.43	0.60
IgE, g/L	4.10	96.60	46.60	78.00	2.50	191.00	2.40
Immune workup	Normal	Normal	Normal	Normal	Normal	Normal	Normal
AFB stain	Negative	Negative	Negative	Negative	Negative	Negative	Negative
Mycobacterium PCR	Positive	Positive	Positive	Positive	Positive	Positive	Positive
Mycobacterium culture	M. bovis	M. bovis	M. bovis	M. bovis	M. bovis	M. bovis	*M. bovis*
Histology	AFB, necrotising granulomatous inflammation	Necrotising granulomas	Necrotising granulomatous inflammation	Necrotising granulomas	Necrotising granulomas	AFB, necrotising granulomatous inflammation	AFB, granulomatous inflammation
Type of infection	Bone	Bone	Soft tissue	Bone	Bone	Bone	Soft tissue
No. of surgeries	1	1	4	1	1	2	5
Mycobacterial drug treatment	RHEL 2 months, then RH 7 months	RHEL 4 months, RE 8 months	RHEL 12 months (recurrence after 1 month of treatment)	RHEZ 2 months, RE 7 months	RHEZL 3 months, then RH 7 months	RHEZ 2 months, RH 5 months (recurrence after 7 months of treatment) RHEL 2 months, RHE 5 months	RHEL 3 months REL 6 months (recurrence after 1 month of treatment)
Drug complications	Nil	Nil	Nil	Nil	Nil	Z-induced transaminitis	Isoniazid resistance
Re-infections	No	No	Yes	No	No	Yes	Yes
Time to recurrence, day	Nil	Nil	30	Nil	Nil	236	27
Follow-up complications	No	No	No	No	No	No	No

R: Rifampicin; E: Ethambutol; H: Isoniazid; L: Levofloxacin; Z: Pyrazinamide
+: present; -: absent; AFB: acid-fast bacilli; BCG: Bacillus Calmette–Guerin; CD4: cluster of differentiation 4; CD8: cluster of differentiation 8; IgM: immunoglobulin M; IgE: immunoglobulin E; MBI: *Mycobacterium bovis* infection; MSMD: Mendelian susceptibility to mycobacterial diseases; PCR: polymerase chain reaction; TB: tuberculosis
Immunological tests for immunodeficiency workup included CD4 and CD8 levels; antibody testing for IgM and IgE levels; nitroblue tetrazolium levels; Mendelian susceptibility to mycobacterial diseases workup and immunological workup, which involved interferon and gene sequence testing.

The median drug treatment duration was 10 months (9–20) with Rifampicin (R), Isoniazid (H), Ethambutol (E), Levofloxacin (L) and Pyrazinamide (P) in combinations of RHEL, RHEZ or RHEZL for the first 2 to 3 months, and RH for the next 7 to 10 months (Table 1). The number of surgeries ranged from once (4 patients) to 5 times (1 patient). The median number of surgeries were 4.5 and 1 for soft tissue and osteomyelitis, respectively; and all in the former had recurrence while 1 in the latter group recurred. MBI recurrences occurred at sites different from the original. Advanced imaging, such as MRI and ultrasound, was employed for soft tissue infections, showing extensive involvement crossing multiple anatomical planes. The median time to recurrence after the last operation was 30 days (27–236). All the children were followed up for at least 24 months after the completion of anti-mycobacterial treatment, and no recurrences occurred.

The pathophysiology of MBI in immunocompetent children is unclear and presents a diagnostic challenge, making it difficult to select relevant investigations for accurate early diagnosis. In our patients, the subclinical nature and long latency (median 17.3 months) meant that a high degree of suspicion was required for diagnosis and institution of treatment. Yet, early recognition is important due to the potentially serious outcome, extended treatment period and risk of recurrences and chronicity that is complex to treat.

More severe disease and increased mortality were reported with high levels of C-reactive protein and erythrocyte sedimentation rate; there were also blood count abnormalities, including anaemia, leukopaenia, thrombocytopaenia and neutropaenia.[8] Although we had 3 patients with anaemia, no correlation with infection severity was found. Our patients had no family history of autoimmune disease and had normal immune workups and hence deemed immunocompetent. Better characterisation of BCG-induced immune response can potentially help in understanding the variabilities in MBI occurrences. Controversy exists regarding the various hypotheses, and evidence points towards an unclassified inherited childhood immunodeficiency.[9,10]

Several notable differences between soft tissue abscesses and osteomyelitis were evident. The former demonstrated a shorter time to recurrence, higher number of surgeries and higher rate of recurrence. The sole osteomyelitis recurrence (patient 6) was postulated to be related to non-compliance to prescribed anti-mycobacterium medication regime. We also found that while soft tissue S-MBI was localised to a specific region, it was often poorly compartmentalised and spread to involve surrounding tissues. This was exemplified in patient 7 who had a recurrent extensive wrist abscess that crossed multiple tissue planes involving muscles, tendons and wrist joint. In such situations, treatment is largely dependent on multiple aggressive surgical debridement for clearance and source control, paired with extended medication.

Considering potential severity, we recommend mycobacterial cultures to be performed in atypical infection presentations. Early drug treatment could also be initiated in an attempt to obtain source control and limit spread. As the disease process remains poorly understood, more research on risk factors that might predict susceptibility to severe infection in immunocompetent children and treatment standardisation is needed to reduce MBI complications and improve quality of life for both children and their caregivers.

Declaration

The authors declare there are no affiliations with or involvement in any organisation or entity with any financial interest in the subject matter or materials discussed in this manuscript.

Ethics statement

The manuscript was approved by the SingHealth Centralised Institutional Review Board (CIRB 2023/2559). Waiver of consent was granted, as this was a retrospective deidentified review.

Keywords: *immunisation programme, infant growth, infectious diseases, osteomyelitis, tuberculosis*

REFERENCES

1. Ministry of Health, Singapore. Update on Tuberculosis Situation in Singapore, 24 March 2023. https://www.moh.gov.sg/news-highlights/details/update-on-tuberculosis-situation-in-singapore-2023. Accessed 11 February 2024.
2. Loh SW, Thoon KC, Tan NWH, et al. Paediatric tuberculosis in Singapore: a retrospective review. BMJ Paediatr Open 2018;2:e000308.
3. Tural-Kara T, Ozdemir H, Erat T, et al. Local Cutaneous Complications After Bacille Calmette-Guerin Vaccine: Experience of a Single Center. Int J Clin Pediatr 2017;6:37-41.
4. Villanueva P, Pittet LF, Curtis N. Management of Bacille Calmette-Guérin Lymphadenitis and Abscess in Immunocompetent Children: A Systematic Review. Pediatr Infect Dis J 2021;40:1037-45.
5. Amanati A, Pouladfar G, Kadivar MR, et al. A 25-year surveillance of disseminated Bacillus Calmette–Guérin disease treatment in children in Southern Iran. Medicine (Baltimore) 2017;96:e9035.
6. Lin WL, Chiu NC, Lee PH, et al. Management of Bacillus Calmette-Guérin osteomyelitis/osteitis in immunocompetent children—A systematic review. Vaccine 2015;33:4391-7.

7. Mortensson W, Eklöf O, Jorulf H. Radiologic aspects of BCG-osteomyelitis in infants and children. Acta Radiol Diagn (Stockh) 1976;17:845-55.
8. Sharifi Asadi P, Aghamohammadi A, Mahmoudi S, et al. Clinical, laboratory and imaging findings of the patients with disseminated bacilli Calmette–Guerin disease. Allergol Immunopathol 2015;43:254-8.
9. Denis M, Forget A, Pelletier M, et al. Control of the Bcg gene of early resistance in mice to infections with BCG substrains and atypical mycobacteria. Clin Exp Immunol 1986;63:517-25.
10. Al Busaidi N, Kp P, Al-Jardani A, et al. The Spectrum of Bacille Calmette–Guérin Diseases in Children—A Decade of Data from Neonatal Vaccination Settings. Vaccines (Basel) 2021;9:150.

Ann Acad Med Singap 2024;53:519-22
https://doi.org/10.47102/annals-acadmedsg.202455

LETTER TO THE EDITOR

Impact of risk stratification on cardiovascular outcomes in patients with stable chest pain

Yi Yi Chua*[1] *MRCP*, Jonathan Yap*[1,2] *MRCP*, Yi Ling Eileen Koh[3] *BSc*, Khung Keong Yeo[1,2] *MD*, Siang Jin Terrance Chua[1,2] *FRCP*, Ngiap Chuan Tan[2,3] *FCFP*, Zhen Sinead Wang[2,4] *FCFP*

Dear Editor,

Chest pain is a common presenting complaint among patients visiting primary care[1] and is a frequent reason for referral to the outpatient cardiology clinic. The European Society of Cardiology (ESC) and American College of Cardiology/American Heart Association (ACC/AHA) guidelines advocate estimating pre-test probability (PTP) of obstructive coronary artery disease (CAD) in the evaluation of stable chest pain in order to guide the need for and type of downstream investigations.[2,3] The PTP of obstructive CAD depends on the clinical characteristics of the patient and disease prevalence. Since the introduction of the Diamond-Forrester model in 1979,[4] contemporary risk scores, such as the CAD consortium score[5] (CCS) and the ESC 2019 PTP risk score,[2] have been developed.

These risk scores predict the risk of having obstructive CAD and not clinical outcomes like mortality, myocardial infarction and stroke. Subsequent studies have shown that having a low PTP of obstructive CAD confers a good prognosis with low adverse clinical outcomes and in this group of patients, additional cardiac testing such as stress testing and coronary imaging may be safely deferred.[2,3,6] This could potentially translate to time and cost savings to the patient and healthcare system.

The majority of these risk scores were designed for Western cohorts, with subsequent clinical outcomes also validated in similar populations. In Singapore, the Predictive Risk scorE for CAD In Southeast Asians with chEst pain (PRECISE) was recently developed as a risk prediction tool for obstructive CAD in Southeast Asians presenting with stable chest pain.[7] We aim to report on the incidence of cardiac testing, as well as objective cardiovascular outcomes, across the different strata of PTP of obstructive CAD.

The detailed methodology has previously been described.[7] In summary, the PRECISE cohort comprises patients who attended primary care for stable chest pain and were referred to the National Heart Centre Singapore, Cardiology clinic for further assessment between July 2013 and December 2016. Patients with prior CAD, acute coronary syndrome and under the age of 30 years were excluded. Ethical approval was obtained. All participants provided written informed consent.

Patients were classified according to their PTP of obstructive CAD, using both the PRECISE simple risk and CCS clinical risk scores. These risk scores use variables including age, sex, cardiovascular risk factors (e.g. hypertension, diabetes mellitus, dyslipidaemia and smoking status), type of chest pain and whether the pain radiated to the neck, and have been previously published.[5,7] Additional cardiac stress or anatomical testing (decided by the managing cardiologist) was performed on some patients, and these included treadmill electrocardiogram, stress echocardiogram, myocardial perfusion imaging, computed tomography coronary angiogram, and invasive coronary angiography. Outcomes that were studied include mortality and major adverse cardiovascular events (MACE) defined as a composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke and revascularisation (percutaneous coronary intervention [PCI] and/or coronary artery bypass graft surgery). All patients were followed-up for 1 year.

A total of 1658 patients were included with 1469 patients (88.6%) undergoing cardiac testing (stress testing or anatomical evaluation). Using the PRECISE risk score, 793 patients (47.8% of the whole cohort) had a PTP of <5%; within this group, the 1-year mortality and MACE rates were 0.0% and 1.4% respectively, and 86.0% had tests performed. A total of 512 patients (30.9% of the whole cohort) had a PTP of 5%–14.99%; in this group, the 1-year mortality and MACE rates were 0.2% and 6.4% respectively, and 88.9% had tests

[1] Department of Cardiology, National Heart Centre Singapore, Singapore
[2] Duke-NUS Medical School, Singapore
[3] Department of Research, SingHealth Polyclinics, Singapore
[4] Outram Polyclinic, SingHealth Polyclinics, Singapore
* Joint first authors
Correspondence: Dr Zhen Sinead Wang, SingHealth Polyclinics (Outram branch), 3 Second Hospital Avenue, #02-00 Health Promotion Board Building, Singapore 168937.
Email: sinead.wang.zhen@singhealth.com.sg

Table 1. Incidence of cardiac testing and cardiovascular outcomes at 1 year in the PRECISE population across the strata of PTP of obstruction CAD using both the PRECISE simple risk and CCS risk clinical scores.

	PTP	Total n (%)	No test n (%)	1 test n (%)	>1 test n (%)	All-cause mortality n (%)	MACE n (%)	CV mortality n (%)	MI n (%)	Stroke n (%)	Revascularisation n (%)
PRECISE simple risk score	<5%	793 (100)	111 (14)	628 (79.2)	54 (6.8)	0 (0)	11 (1.4)	0 (0)	0 (0)	1 (0.1)	10 (1.3)
	5%–9.99%	351 (100)	42 (12)	289 (82.3)	20 (5.7)	0 (0)	19 (5.4)	0 (0)	4 (1.1)	3 (0.9)	15 (4.3)
	10%–14.99%	161 (100)	15 (9.3)	132 (82)	14 (8.7)	1 (0.6)	14 (8.7)	1 (0.6)	1 (0.6)	1 (0.6)	12 (7.5)
	15%–24.99%	190 (100)	10 (5.3)	145 (76.3)	35 (18.4)	0 (0)	20 (10.5)	0 (0)	1 (0.5)	0 (0)	20 (10.5)
	25%–49.99%	144 (100)	10 (6.9)	108 (75)	26 (18.1)	1 (0.7)	24 (16.7)	1 (0.7)	2 (1.4)	1 (0.7)	21 (14.6)
	≥50%	19 (100)	1 (5.3)	15 (78.9)	3 (15.8)	0 (0)	9 (47.4)	0 (0)	1 (5.3)	0 (0)	9 (47.4)
CCS clinical score risk	<5%	326 (100)	47 (14.4)	260 (79.8)	19 (5.8)	0 (0)	2 (0.6)	(0)	(0)	(0)	2 (0.6)
	5%–9.99%	313 (100)	38 (12.1)	255 (81.5)	20 (6.4)	0 (0)	6 (1.9)	(0)	(0)	1 (0.3)	5 (1.6)
	10%–14.99%	191 (100)	21 (11)	149 (78)	21 (11)	0 (0)	10 (5.2)	(0)	1 (0.5)	1 (0.5)	9 (4.7)
	15%–24.99%	241 (100)	24 (10)	193 (80.1)	24 (10)	1 (0.4)	18 (7.5)	1 (0.4)	3 (1.2)	2 (0.8)	14 (5.8)
	25%–49.99%	247 (100)	21 (8.5)	197 (79.8)	29 (11.7)	0 (0)	28 (11.3)	(0)	(0)	1 (0.4)	27 (10.9)
	≥50%	106 (100)	7 (6.6)	76 (71.7)	23 (21.7)	1 (0.9)	26 (24.5)	1 (0.9)	3 (2.8)	1 (0.9)	23 (21.7)

Tests include treadmill electrocardiogram, stress echocardiogram, myocardial perfusion imaging, computed tomography (CT) coronary angiogram, and invasive coronary angiography (excludes CT calcium score). "No test" includes patients who were not offered and those who declined testing. Revascularisation refers to percutaneous coronary intervention and/or coronary artery bypass graft surgery. CAD: coronary artery disease; CCS: coronary artery disease consortium score; CT: computed tomography; CV: cardiovascular; MACE: major adverse cardiovascular event; MI: myocardial infarction; PRECISE: Predictive Risk scorE for CAD In Southeast Asians with chEst pain; PTP: pre-test probability

The total number of patients classified by the CCS clinical risk score is smaller than the total number of patients classified by the PRECISE simple risk score, due to missing data for the CCS risk clinical score in the original cohort.

performed. Additionally, 190 patients (11.5% of the whole cohort) had a PTP of 15%–24.99%; in this group, the 1-year mortality and MACE rates were 0.0% and 10.5% respectively, and 94.7% had tests performed. Moreover, 163 patients (9.8% of the whole cohort) had a PTP of ≥25%; in this group, the 1-year mortality and MACE rates were 0.6% and 20.2% respectively, and 82.8% had tests performed. The majority of MACE rates were driven by revascularisation. Table 1 shows the breakdown of the individual outcomes by risk strata. In a previous publication,[7] the PRECISE risk score was found to be more accurate with the CCS clinical risk score overclassifying risk in our Singapore cohort. The results from the CCS clinical risk score are shown in Table 1 for reference.

According to the ESC guidelines, while it may be overall safe to defer testing in patients classified to have a PTP <15%,[2] further testing may be considered in a patient with a PTP of 5%–15% depending on patient preference, local resources, availability of tests, clinical judgement and appropriate patient information.[2] The ACC/AHA guidelines also advocate deferring testing in patients classified to be low risk. In our Singapore cohort, the 1-year MACE rate in those at very low risk (<5%) was low at 1.4% driven predominantly by revascularisation. However, testing was performed in the vast majority (>80%). In those at low risk (5%–14.99%), the 1-year MACE rate was slightly higher at 6.4%, once again driven predominantly by revascularisation, but the vast majority (about 90%) underwent testing. Additional cardiac testing may be over-utilised, especially in the very low-risk group (PTP<5%). The reasons for these tests are unclear but could be due to multiple reasons, such as patient request, physician preference and perceived malpractice risk. The benefits of cardiac testing in the very low-risk population remain unclear, and reduction of such testing may alleviate the burden on the patient and healthcare system. Unnecessary testing may increase the financial burden on patients, create anxiety and lead to unintended consequences with false positive tests. With regard to the healthcare system, the avoidance of unnecessary testing would free up available limited resources to patients who truly require them, alleviating manpower and resource constraints. This very low-risk patient group accounts for a large majority of referrals, and savings may be substantial. Similar findings have been noted. In a Brazilian study, while lower than in the private sector, there was still a significant amount of inappropriate treadmills (about 57%) ordered in the public sector with the majority of patients having low or very low PTP of CAD.[8] Another study in the US estimated that about a third of cardiac stress tests were inappropriate, resulting in increased annual costs and harm.[9]

Some limitations exist. Whether cardiac testing could have potentially improved cardiovascular outcomes by facilitating the initiation of medical therapy is unknown, as medication data were not readily available. In addition, whether testing led to subsequent revascularisation and consequently reduced mortality or myocardial infarction is unclear. Moreover, many studies have not shown improvement of survival with revascularisation (especially PCI) in stable chest pain.[10] Also, in the very low-risk group (PTP <5%), the number of revascularisations is low. Finally, selection bias may exist as not all subjects agreed to take part in the study.

In conclusion, while the incidence of adverse cardiovascular outcomes increased with higher PTP risks, absolute numbers remain low. In the very low-risk strata (PTP <5%), incidence of adverse cardiovascular outcomes is low, and efforts could potentially be made towards reduction in unnecessary testing in this group.

Disclosure

Dr Jonathan Yap received speaker's honorarium from Abbott, Biosensors, Biotronik, Boston Scientific, Edwards, GE healthcare, J&J, Kaneka, Medtronic and Terumo.

Ethics statement

The manuscript was approved by the SingHealth Centralised Institutional Review Board (CIRB2018/2851).

Acknowledgements

The authors would like to express their heartfelt thanks to the doctors and nurses from SingHealth polyclinics (Dr Andrew Ang, Dr Paul Goh, Dr Lee Cia Sin and Nurse Clinician Joanna Tan), SingHealth Polyclinics Department of Research, and support staff from the National Heart Centre Singapore Specialist Outpatient Clinics for their invaluable help in this project.

Keywords: *cardiology, chest pain, coronary artery disease, family medicine, myocardial infarction*

REFERENCES

1. Frese T, Mahlmeister J, Heitzer M, et al. Chest pain in general practice: Frequency, management, and results of encounter. J Family Med Prim Care 2016;5:61-6.
2. Knuuti J, Wijns W, Saraste A, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J 2020;41:407-77.

3. Gulati M, Levy PD, Mukherjee D, et al. 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR Guideline for the Evaluation and Diagnosis of Chest Pain: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation 2021;144:e368-e454.
4. Diamond GA, Forrester JS. Analysis of probability as an aid in the clinical diagnosis of coronary-artery disease. N Engl J Med 1979;300:1350-8.
5. Genders TSS, Steyerberg EW, Hunink MGM, et al. Prediction model to estimate presence of coronary artery disease: retrospective pooled analysis of existing cohorts. BMJ 2012;344:e3485.
6. Reeh J, Therming CB, Heitmann M, et al. Prediction of obstructive coronary artery disease and prognosis in patients with suspected stable angina. Eur Heart J 2019;40:1426-35.
7. Wang ZS, Yap J, Koh YLE, et al. Predicting Coronary Artery Disease in Primary Care: Development and Validation of a Diagnostic Risk Score for Major Ethnic Groups in Southeast Asia. J Gen Intern Med 2021;36:1514-24.
8. Silva AML, Armstrong AC, Silveira FJC, et al. Prevalence and factors associated with inappropriate use of treadmill exercise stress test for coronary artery disease: a cross-sectional study. BMC Cardiovasc Disord 2015;15:54.
9. Ladapo JA, Blecker S, Douglas PS. Physician decision making and trends in the use of cardiac stress testing in the United States: an analysis of repeated cross-sectional data. Ann Intern Med 2014;161:482-90.
10. Sedlis SP, Hartigan PM, Teo KK, et al. Effect of PCI on Long-Term Survival in Patients with Stable Ischemic Heart Disease. N Engl J Med 2015;373:1937-46.

Ann Acad Med Singap 2024;53:523-4
https://doi.org/10.47102/annals-acadmedsg.2024205

LETTER TO THE EDITOR

"Leveraging ChatGPT to aid patient education on coronary angiogram": Correspondence

Hinpetch Daungsupawong[1] *PhD*, *Viroj* Wiwanitkit[2] *MD*

Dear Editor,

"Leveraging ChatGPT to aid patient education on coronary angiogram"[1] is an interesting article. The study assessed ChatGPT's ability to conversely provide information regarding the coronary angiography process, pointing out its advantages and disadvantages. Although ChatGPT provided information in an exhaustive and methodical manner, it also had flaws, including factual errors, omissions and recommendations that lacked flexibility. The results imply that although ChatGPT and other natural-language artificial intelligence (AI) models can be useful resources for patient education, they should not take the place of the individualised guidance and treatment given by medical experts.

The study's dependence on ChatGPT, a single AI model, may not adequately capture the breadth of natural-language AI options for healthcare applications, which is one of its weak points. It would be useful to assess how well ChatGPT performs in comparison to other AI models when it comes to giving people medical information. Furthermore, the study's concentration on coronary angiography, a particular cardiology technique, raises concerns about the findings' generalisability to other medical specialties or themes. Subsequent investigations may examine ChatGPT's efficacy in disseminating knowledge on a more extensive array of healthcare subjects.

Concerns regarding the possible effects of natural language AI on patient education and healthcare delivery are brought up by the study. How can medical practitioners ensure information integrity and dependability while integrating AI technologies, such as ChatGPT, into patient education campaigns? More importantly, how can AI models be enhanced to overcome the shortcomings this study found, such as factual errors and rigid recommendations? Future research and development in the area of natural-language AI in healthcare can be guided by these questions.

The study concludes by highlighting the potential benefits and difficulties of utilising ChatGPT and other natural language AI models for patient education in the healthcare industry. Although ChatGPT showed promise in terms of offering thorough information, it also had shortcomings that should be fixed. Healthcare practitioners should be aware of these advantages and disadvantages of AI in patient education and work with AI developers to enhance the quality and dependability of the information given to patients in order to optimise the technology's benefits. Prospective avenues for investigation may encompass investigating the utilisation of AI models across an expanded array of healthcare domains and specialisations, in addition to formulating tactics to augment the efficacy of AI in providing tailored healthcare recommendations.

Declaration

The authors have no affiliations or financial involvement with any commercial organisation with a direct financial interest in the subject or materials discussed in the manuscript.

Keywords: *cardiology, ChatGPT, clinical, diagnosis*

REFERENCES

1. Koh SJQ, Yeo KK, Yap JJ. Leveraging ChatGPT to aid patient education on coronary angiogram. Ann Acad Med Singap 2023;52:374-7.

Authors' reply:

Dear Editor,

We appreciate the insightful comments regarding our article, "'Leveraging ChatGPT to aid patient education on coronary angiogram': Correspondence".[1]

We agree that ChatGPT represents a single large language model (LLM) and may not fully encompass the diversity of artificial intelligence models available. However, given ChatGPT's widespread

[1] Private Academic Consultant, Phonhong, Lao People's Democratic Republic
[2] Saveetha Medical College and Hospital, Saveetha Institute of Medical and Technical Sciences Saveetha University India, India
Correspondence: Dr Hinpetch Daungsupawong, Private Academic Consultant, Lak52, Phonhong, Vientiane 10000 Lao People's Democratic Republic.
Email: hinpetchdaung@gmail.com

accessibility and popularity, as evidenced by its rapid growth in monthly users and significant market share,[2] it is highly relevant as the primary LLM tool for evaluation in this study. Moreover, numerous studies have used ChatGPT as a benchmark, including one that demonstrated its potential medical accuracy through its performance on the United States Medical Licensing Examination (USMLE).[3]

Coronary angiography, while relatively common, is an invasive procedure that often prompts questions from patients and public, forming the basis of our article's assessment. Given ChatGPT's conversational nature, we have also explored its utility in addressing queries related to end-stage heart failure,[4] with similar findings, suggesting that this evaluation can be extended to other medical fields.

We concur that while ChatGPT shows promise, there are potential pitfalls that healthcare practitioners should be aware of. As more patients turn to these platforms for health information, it is essential for healthcare providers to understand the limitations of these models and to anticipate and address potential misinformation.

Samuel Ji Quan Koh[1] *MRCP*, Jonathan Yap[1,2] *MRCP*

[1] Department of Cardiology, National Heart Centre Singapore
[2] Duke-NUS Medical School, Singapore

Correspondence:
Dr Samuel Ji Quan Koh and Dr Jonathan Jiunn-Liang Yap, Department of Cardiology, National Heart Centre Singapore, 5 Hospital Dr, Singapore 169609.
Email: Koh sk_jiquan@yahoo.com.sg
Email: yap.j.l@singhealth.com.sg

REFERENCES

1. Koh SJQ, Yeo KK, JJL Y. Leveraging ChatGPT to aid patient education on coronary angiogram. Ann Acad Med Singap 2023;52:374-7.
2. Reuters. ChatGPT sets record for fastest-growing user base - analyst note, 2 February 2023. https://www.reuters.com/technology/chatgpt-sets-record-fastest-growing-user-base-analyst-note-2023-02-01/. Accessed 9 July 2024.
3. Kung TH, Cheatham M, Medenilla A, et al. Performance of ChatGPT on USMLE: Potential for AI-assisted medical education using large language models. PLOS Digit Health 2023;2:e0000198.
4. Koh SJQ, Sim DKL, SH N. Letter to the Editor: Educating Patients With Advanced Heart Failure Through Chat Generative Pretrained Transformer and Natural-Language Artificial Intelligence: Is Now the Time for It? J Palliat Med 2023; 26:893-5.

ANNALS, ACADEMY OF MEDICINE, SINGAPORE
81 Kim Keat Road, #11-00 & #12-00 NKF Centre, Singapore 328836
Email: annals@ams.edu.sg | Website: https://www.annals.edu.sg