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Supplementary Appendix S1. Search strategy.

Database	Records Identified	Search
PubMed	568	1. "Down Syndrome"[Mesh] 2. Down Syndrome[Title/Abstract] OR Downs Syndrome[Title/Abstract] OR Down's Syndrome[Title/Abstract] OR Trisomy 21[Title/Abstract] OR Mongolism[Title/Abstract] 3. 1 OR 2 4. "Quality of Life"[Mesh] 5. Quality of life[Title/Abstract] OR Life Quality[Title/Abstract] OR HRQOL[Title/Abstract] OR QOL[Title/Abstract] 6. 4 OR 5 7. 3 AND 6
Embase	1159	1. 'down syndrome'/exp 2. 'down syndrome':ab,ti OR 'downs syndrome':ab,ti OR 'trisomy 21':ab,ti OR mongolism:ab,ti 3. 1 OR 2 4. 'quality of life'/exp 5. 'quality of life':ab,ti OR 'life quality':ab,ti OR hrqol:ab,ti OR qol:ab,ti 6. 4 OR 5

		7. 3 AND 6
Web of Science	745	TS=((“Down Syndrome” OR “Downs Syndrome” OR “Down's Syndrome” OR “Trisomy 21” OR Mongolism) AND (“Quality of life” OR “Life Quality” OR HRQOL OR QOL))
CINAHL	311	1. “Down Syndrome” OR “Downs Syndrome” OR “Down's Syndrome” OR “Trisomy 21” OR “Mongolism” 2. “Quality of life” OR “Life Quality” OR “HRQOL” OR “QOL” 3. 1 AND 2

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

QOL measures using PedsQL

Fernandez Scotto et al.[1] compared the QOL of 51 children with DS aged 2 to 4 years in Argentina with TD children. Children with DS had worse total score compared to TD children (median 82.1; IQR 75-91.6 versus 88; IQR 82.1-94.0; p=0.003) with psychosocial health score faring the worst. Children with DS had statistically significant lower scores in almost all subdomains compared to TD children. Children with DS had a higher, but not statistically significant score, in the emotional functioning subdomain (median 85; IQR 75-90 versus 80; IQR 70-90; p=0.47).

Katsiana et al.[2] investigated the QOL of children, aged 5 to 10 years, in Greece. Out of which 55 had DS, 61 had Autism Spectrum Disorders (ASD), and 90 were TD children who formed the control group. Children with DS and ASD had poorer QOL than TD children irrespective of their age. The TD group scored higher than children with DS in total scores, with a mean (SD) of 88.68 (±11.49) versus 69.98 (±14.03) respectively, as well as in all subdomain scores. The QOL of DS and ASD children were not statistically different in the physical, social, and school functioning scores. However, children with DS scored significantly higher than ASD children in emotional functioning (77.11 ± 17.86 versus 69.02 ±22.23 respectively; p value not stated).

Xanthopoulos et al.[3] investigated QOL in 150 children with DS and adolescents (aged 10 – 20 years) in USA, and the role of obesity on QOL, and compared them with 59 children and adolescents without DS. Total QOL, physical health, and psychosocial health summary scores were significantly lower in the DS group versus the non-DS group. Social and school functioning were also significantly lower ($p < 0.001$), but emotional functioning did not differ between the two groups ($p = 0.31$). Notably, total QOL and subdomain scores of obese and non-obese children with DS did not show any statistical difference.

Rojnueangnit et al.[4] studied QOL of children with DS in Thailand. Four children (aged 8-12 years) completed PedsQL on their own in parallel to their caregivers; their scores were excluded from the meta-analysis. Total mean (SD) caregiver reported QOL score was 67.9 (± 14.5). The highest score was emotional functioning at 73.6 (± 12.8), while cognitive/school functioning was the lowest at 57.2 (± 25.6). The authors highlighted that total QOL score among children with DS was lower than non-DS Thai children (79 ± 12.8), but similar to that of Thai children with chronic diseases in another study.[5] Self-reported scores from the four children with DS were higher in emotional and school functioning, similar in physical health, and lower in social functioning as compared to parents' report highlighting the importance of exploring self-reported QOL among suitable patients. However, there was no difference in total score (p=0.38).[4]

Fuca et al.[6] conducted a cross-sectional study in 73 children with DS in Italy (aged 5 to 12 years), and analyzed differences between children with high and low QOL. The authors used total QOL score of 67 as the cut off to determine high versus low QOL.[7] Emotional functioning scores were higher compared to other subdomain scores ($p < 0.001$). Children in the high QOL group (n=42) had higher intelligent quotient than children in the low QOL group (n= 31) (mean 59.36, ±6.72 versus mean 54.81,±6.8, respectively). The high and low QOL groups did not differ by age or gender. Family perception of child's QOL were unaffected by parental education and occupation.

Rozensztrauch et al.[8] studied QOL of children with DS (n=53) and explored the impact of child's QOL on family's QOL. The highest and lowest QOL were in physical functioning (mean 60.14±23.82) and school functioning (51.36±18.72) respectively. The presence of poor muscle tone adversely affected child physical, emotional, psychosocial and total QOL scores ($p< 0.05$ for all). There was a positive correlation between child's QOL and family's QOL.

Ciciora et al.[9] examined whether presence of disorders of gut brain interactions such as functional constipation and irritable bowel syndrome, two associated comorbidities among children with DS, impact the QOL. All measures of QOL were lower among children with disorders of gut brain interactions. Irritable bowel syndrome negatively impacted all measures of QOL among children with DS, whereas functional constipation did not. Alqahtani et al.[10] explored the relationship between varying levels of physical activity and QOL of DS and TD children. They found QOL was poorer QOL in all domains ($p<0.001$) as compared to TD children. Interestingly, in their cohort, both children with DS and TD children spent large part in sedentary behavior or light physical activity. Although, no children met the recommended vigorous physical activity, among children with DS a moderate level of physical activity resulted in better school functioning.

QOL measures using KidsLife and KidsLife Down

Lee et al.[11] conducted a multinational survey across DS support groups from 18 countries. Of the 211 participants, 77.7% were from the US, and 96.2% were of the White race. The DS individual's mean age was 10.9 years (range 4-21 years). Participants were stratified into 3 age groups (4-5, 6-12, 13-21 years). Parent-proxy reports using KidsLife indicated moderate to favorable levels of QOL with the mean overall QOL score of 89.7 (SD 16.0) (70^{th} to 71^{st} percentile). Within the subdomains, scores were: social inclusion 84^{th} (highest), self-determination 75^{th}, material 63^{rd}, physical 50^{th}, interpersonal relation 50^{th}, personal development 50^{th}, and rights 50^{th} percentile. The emotional well-being subdomain (37^{th} percentile) had the lowest score. There were no significant differences in overall QOL and the 8 core domains by gender and age groups. Emotional well-being, interpersonal relationship, and social inclusions varied by age groups; parents of younger children (4-5

years) reported better scores in these three domains compared to parents of older age groups (13-21 years).

Moran et al.[12] studied 404 children with DS from Spain using KidsLife Down. The assessments were completed by 325 caregivers (64.3% family members; 35.7% professionals, mostly psychologists and teachers involved in the children's care). Overall QOL (308.90±31.30) exceeded the theoretical midpoint of the instrument scale and was deemed "adequate". The highest scores were observed in the material well-being (43.35±4.42), physical well-being (41.42±5.25), and rights (40.66±5.33) subdomains. The lowest scores were observed in the self-determination (31.18±6.02) and social inclusion (33.95±6.73) subdomains. Intermediate scores were observed in the personal development (39.24±5.19), interpersonal relations (40.33±5.14), and emotional well-being (38.77±5.79) subdomains. Age was positively and significantly associated with the overall QOL (R = 0.12, P ≤0.5), self-determination (R = 0.33, *P* ≤0.001), and emotional (R = 0.16, *P* ≤0.001), physical (R = 0.12, *P* ≤0.5), and material well-being (R = 10.9, *P* ≤0.001). However, correlation coefficient sizes were small (R = 0.10-0.29) to medium (0.30-0.49). On the other hand, age was negatively and significantly associated with social inclusion (R = -0.17, *P* ≤0.001).

QOL measures using KIDSCREEN

Jung et al.[13] surveyed parents of 16 children with DS (mean age 6.8years; 4-12years) and 20 TD children (mean 8years; 4-12years), using the KIDSCREEN-52 (Korean version) and a subsection of the International Classification of Functioning, Disability and Health – Children and Youth Version (ICF-CY) checklist to assess Body Function, Activity and Participation. Children with DS had significantly lower overall QOL compared to their TD peers in pre-school children (aged 4-7 years) (mean 58.9 ± 4.7 versus 91.7 ±9.4 respectively; *P* <0.001), and in school age children (aged 8-12years) (68.6 ±12.0 versus 94.5 ±6.9 respectively; *P* <

0.001). In addition, children with DS had significantly lower scores in all QOL subdomains. Moreover, among children with DS, function and activities and participation section of ICF-CY were significantly correlated with QOL ($R = -0.514$, $p<0.05$).

Rofail et al.[14] conducted a multinational survey at baseline and 24 weeks using the Acute Version (recall period 7 days: "The past week…") of KIDSCREEN-27[14] via face-to-face interviews with a clinician (psychologist). The age range of DS patients was 12-30 years; with adolescents (n=49; mean age 14.5 ± 1.6 years) and adults (n=41; mean age 22.7 ± 3.4 years). We excluded the adults from our review. Compared to European normative group, adolescents with DS had significantly higher baseline scores in the school environment ($t(48) = 3.4$, $P <0.01$), and significantly poor scores in the social support and peers domains ($t(48) = -2.81$, $P < 0.01$).

Shields et al.[15] surveyed parents of 75 children with DS in Australia (mean age 13 years; range 5-18 years) using KIDSCREEN-27. QOL scores were compared with the normative data of TD children. Mean (SD) scores for children with DS were in the normal range for 3 dimensions: psychological well-being 47.4(±7.9), autonomy and parent relation 48.5(±8.7), and school environment 51.0(±7.8). However, children with DS scored below the normal range in 2 dimensions: physical well-being 43.4(±9.6), and social support and peers 39.5(±11.0); these 2 dimensions also had the highest differences when compared to TD children (mean, 95% CI) (-8.01, -10.55 to -5.47, and - 11.24, -13.78 to -8.70 respectively). In addition, 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).

Alrayes et al.[16] studied association between QOL of children with DS and demographic characteristics of both parents and children (n=112) from Saudi Arabia. Children with DS scored highly in psychological well-being, autonomy, parental relation, school and learning

domains and relatively poorly in physical and social well-being and peer subdomains. Family income has a positive impact on all QOL domains.

QOL measures using TACQOL and TAPQOL

van Gameren-Oosterom et al.[17] investigated levels of development, problem behavior, and QOL using the TACQOL-PF in a population sample of 337 Dutch 8-year-old children with DS, compared with normative data of 8-year-old children. Children with DS had significantly lower QOL scores in gross motor skills, autonomy, social functioning and cognitive functioning ($p<0.001$). No differences were observed for physical complaints, positive and negative emotions. Mean developmental age was substantially lower than the mean calendar age, with boys more affected than girls. Compared with the general population, children with DS had more emotional and behavioral problems ($p<0.001$). However, on the anxious/depressed scale, they scored significantly more favorably ($p<0.001$).

Alhaddad et al.[18] used TAPQOL and TACQOL-PF in children with DS in Saudi Arabia with and without congenital heart disease (CHD). CHD was associated with impaired motor function in younger (1-5 years) but not older (6-15 years) children with DS, which could be attributed to activity restriction among younger children with CHD. All other QOL-related parameters were unaffected by CHD. Non-Saudi children with DS with CHD had significantly lower scores in the stomach, lung, and sleep problems and positive mood domains than those without CHD. In contrast, CHD had no effect on QOL scores in Saudi children.

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

QOL tool	Studies utilising tool	Reported by (Child self-report or Parent-proxy report)	Domains	No. of Items	Minimum and Maximum Values	Age Limits
Pediatric Quality of Life Inventor (PedsQL) Version 4.0 (PedsQL 4.0)	Fernandez Scotto et al [16] Fuca et al [24] Xanthopoulos et al [12] Rojnueangnit et al [18] Katsiana et al [23] Rozensztrauch et al [25] Ciciora et al [26] Alqahtani et al [27]	Child-self report or Parent-proxy report	Physical Emotional Social School	23	0 to 100	1-12 months 13-24 months 2-4 years 3-5 years 5-7 years 8-12 years 13-18 years 18-25 years
KidsLife and Kids Life Down Scale	Lee et al (KidsLife) [11] Moran et al (KidsLife Down) [29]	Parent-proxy report	Social Inclusion Self-determination Emotional well-being Physical well-being Material well-being Rights Personal Development Interpersonal relationships (Note: The pool of items in KidsLife Down varied by 30% (n = 29) from KidsLife. The domains that differed most from the original scale are Personal Development, Interpersonal Relationships, and Self-determination, and the most similar domain was Rights.[3] Higher scores indicate better QOL.	96	Raw score converted to corresponding standard score	4-21 years
KidsScreen	Shields et al [33] Jung et al [32] Rofail et al [21]	Child-self report or Parent-proxy report	Physical well-being Psychological well-being Moods and Emotions	52	0 to 100	8-18 years

		Alrayes et al [34]		Self-Perception Autonomy Parent Relation and Home Life Financial Resources Social Support and Peers School Environment Social Acceptance and Bullying			
				Physical well-being Psychological well-being Autonomy and Parent relations Peers and Social support School environment	27		
TNO-AZL (Netherlands Organisation for Applied Scientific Research Academic Medical Centre)	TNO-AZL Preschool Quality of Life (TAPQOL)	Alhaddad et al [38]	Parent-proxy report	Physical Social Cognitive Emotional functioning	43	0 to 100	1-5 years
	TNO-AZL Child Quality of Life Parent Form (TACQOL-PF)	van Gameren-Oosterom et al [37]	Parent-proxy report	Physical complaints (pain and symptoms) Gross motor functioning Cognitive functioning Social functioning Autonomy Positive and Negative emotional functioning	56	0 to 32	6-15 years
Personal Outcome Scale (POS)		Bermudez et al [39]	Self-Report Direct Observation	Three factors (independence, social participation, and well-being), divided over eight domains (personal development, self-determination, interpersonal relations, social inclusion, rights, and emotional, physical, and material well-being)			4 years and above

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

	Selection Bias Assessment (Maximum 5 stars)				**Comparability (Maximum 2 stars)**	**Outcome (Maximum 3 stars)**		**Total score (Maximum 10 stars)**
	Representativeness of the sample	Sample size	Non-respondents	Ascertainment of the exposure (risk factor)	Confounding factors are controlled	Assessment of the outcome	Statistical Test	
Study (Reference number)	1. Representativeness of the sample: a. Truly representative of the average in the target population. * (all subjects or random sampling) b. Somewhat representative of the average in the target group. * (non-random sampling) c. Selected group of users/ convenience sample. d. No description of the derivation of the included subjects.	2. Sample size: a. Justified and satisfactory (including sample size calculation). * b. Not justified.	3. Non-respondents: a. Comparability between respondents and non-respondents characteristics is established, and the response rate is satisfactory. * b. The response rate is unsatisfactory, or the comparability between respondents and non-respondents is unsatisfactory. c. No description of the response rate of the characteristics of the responders and the non-responders.	4. Ascertainment of the exposure (risk factor): a. Validated measurement tool. ** b. Non-validated measurement tool, but the tool is available or described * c. No description of the measurement tool.	1. Comparability of subjects in different outcome groups on the basis of design or analysis. Confounding factors are controlled. a. The study controls for the most important factor (select one). * b. The study control for any additional factor. *	1. Assessment of outcome: a. Independent blind assessment. ** b. Record linkage. ** c. Self-report. * d. No description.	2. Statistical test: a. Statistical test used to analyse the data clearly described, appropriate and measures of association presented including confidence intervals and probability level (p value). * b. Statistical test not appropriate, not described or incomplete.	Cross-sectional Studies: Very Good Studies: 9-10 points Good Studies: 7-8 points Satisfactory Studies: 5-6 points Unsatisfactory Studies: 0 to 4 points

Fernandez Scotto et al 2023 [16]	1	0	0	2	0	2	1	6
Fuca et al 2022 [24]	1	0	0	2	0	2	1	6
Xanthopoulos et al 2017 [12]	1	0	0	2	0	2	1	6
Rojnueangnit et al 2020 [18]	1	0	0	2	0	2	1	6
Katsiana et al 2020 [23]	1	0	0	2	0	2	1	6
Shields et al 2018 [33]	1	0	0	2	1	2	1	7
Jung et al 2018 [32]	1	0	0	2	0	2	1	6
Rofail et al 2017 [7]	1	0	0	2	1	2	1	7
Lee et al 2021[11]	1	0	0	2	0	2	1	6
Moran et al 2022 [29]	1	0	0	2	0	2	1	6
Van Gameren-Oosterom et al 2011 [37]	1	0	0	2	1	2	1	7
Alhaddad et al 2023 [38]	1	0	0	2	0	2	1	6
Alrayes et al 2024 [34]	1	0	0	2	0	2	1	6

Rozentauchz et al 2023 [25]	1	0	0	2	0	2	1	6
Bermudez et al 2024 [39]	1	0	0	2	0	2	1	6
Ciciora 2023 [26]	1	0	0	2	0	2	1	6
Alqahtani 2024 [27]	1	0	0	2	1	2	1	7