Journal of Intellectual Disability Research

SYSTEMATIC REVIEW OPEN ACCESS

Shorter Telomeres and Faster Telomere Attrition in Individuals With Five Syndromic Forms of Intellectual Disability: A Systematic Review and Meta-Analysis

Sarah M. Hanley[1] | Nicola S. Schutte[1] | Jessica Bellamy[2,3] | Joshua Denham[4,5]

[1]School of Psychology, University of New England, Armidale, New South Wales, Australia | [2]School of Medical, Indigenous and Health Sciences, Faculty of Science, Medicine and Health, University of Wollongong, Wollongong, New South Wales, Australia | [3]Department of Developmental Disability Neuropsychiatry (3DN), School of Clinical Medicine, UNSW Sydney, Sydney, New South Wales, Australia | [4]School of Health and Medical Sciences, University of Southern Queensland, Toowoomba, Queensland, Australia | [5]Centre for Health Research, Toowoomba, Queensland, Australia

Correspondence: Joshua Denham (josh.denham@unisq.edu.au)

Received: 26 September 2024 | **Revised:** 8 April 2025 | **Accepted:** 9 April 2025

Funding: The authors received no specific funding for this work.

Keywords: biological ageing | down syndrome | gene dosage | Hoyeraal–Hreidarsson syndrome | telomerase

ABSTRACT

Background: People with intellectual disability suffer complex challenges due to adaptive functioning limitations, high rates of chronic diseases and shortened lifespans compared with the general population. Telomere shortening is a hallmark of ageing, and short telomeres are linked to neurological disorders. The main objective of this systematic review and meta-analysis was to identify any differences in telomere length and the rate of telomere attrition in leukocytes and fibroblasts from people with intellectual disability and controls.

Methods: PubMed, Scopus and ScienceDirect were searched. Articles that compared telomere length in individuals with intellectual disability to apparently healthy age-matched controls were included. Risk of bias was assessed using the AXIS tool and data were analysed using CMA.

Results: Fifteen studies comprised of 17 comparisons provided data and were included in meta-analyses. Compared with healthy controls ($N = 481$), people with intellectual disability ($N = 366$) from a known genetic syndrome (Cri du chat, Down, Hoyeraal–Hreidarsson, Williams or Nicolaides–Baraitser) possessed shorter leukocyte telomeres (SMD: −0.853 [95% CI: −1.622 to −0.084], $p = 0.03$). Similarly, relative to controls ($N = 16$), people with syndromic intellectual disability ($N = 21$) possessed shorter fibroblast telomeres (−1.389 [−2.179 to −0.599], $p = 0.001$). Furthermore, people with syndromic forms of intellectual disability also demonstrated a faster rate (2.09-fold) of telomere shortening.

Conclusions: Consistent with epidemiological findings on mortality and morbidity risk, people with syndromic intellectual disability appear to undergo a faster rate of biological ageing compared to the general population. These findings emphasise the need for healthy ageing lifestyle (i.e., exercise and stress management) and therapeutic interventions for people with syndromic intellectual disability.

1 | Introduction

People with intellectual disability exhibit cognitive impairments (intellectual quotient < 70) and face challenges with adaptive functioning (e.g., social skills, abstract thinking, planning, communication and many activities of daily living) that precipitates during the early developmental period (American Psychiatric Association 2013). The severity of intellectual disability is assessed from mild to profound across three domains: conceptual, social and practical (American Psychiatric Association 2013). Although acquired brain injury, chromosomal trisomy and some rare genetic syndromes cause intellectual disability, the aetiology of most patients remains unclear (e.g., in utero grown restriction and germline de novo mutations) (Patel et al. 2020; Vissers et al. 2016). Considering that aetiology are often unknown and the current medical technology is limited, treatment remains scarce for individuals with intellectual disability. Therefore, therapeutic efforts involve modifying the environment, providing support and life skills to mitigate impairments and enable them to thrive to the best of their abilities.

This can, however, be challenging regarding the high prevalence of chronic and complex health concerns. Indeed, people with intellectual disability suffer more physical and mental health conditions—that manifest at an earlier age—than people from the general population (Cooper et al. 2015; Van Den Bemd et al. 2022; Van Schrojenstein Lantman-De Valk et al. 2000). Most people with intellectual disability over the age of 50 years (80%) will suffer multiple chronic conditions (Hermans and Evenhuis 2014). Despite progress in life expectancy of people with intellectual disability in recent years, these individuals appear to experience premature biological ageing that culminates in early death (Florio and Trollor 2015; Trollor et al. 2017). Consistent with observations from the United Kingdom (Heslop et al. 2014; Tyrer et al. 2007), work from Australia highlighted that the median age of death (interquartile range) of individuals with intellectual disability was 54 (42–64) years, significantly lower than those from the general population—81 (70–92) years (Trollor et al. 2017). For example, people with intellectual disability suffered a higher death rate from potentially avoidable diseases (31%) compared with the general population (17%), circulatory disease being the highest contributor (Trollor et al. 2017). Although the genetic and environmental factors contributing to the early death of those with intellectual disability compared with the general population are unclear, mitigating them will be a crucial goal to address the inequalities in health and life expectancy.

Telomere shortening is a hallmark of ageing (Chakravarti et al. 2021; Lopez-Otin et al. 2023), and short telomeres are linked to several chronic diseases (e.g., heart disease [Brouilette et al. 2007; Haycock et al. 2014; Ogami et al. 2004; Willeit et al. 2010]; dementia and Alzheimer's disease [Forero et al. 2016; Honig et al. 2012; Topiwala et al. 2023]; and obesity [Mundstock et al. 2015; Zannolli et al. 2008])—comorbidities that are often observed in those with intellectual disability (Antonarakis et al. 2020; Hermans and Evenhuis 2014; Trollor et al. 2017). Telomeres are a repeat DNA sequence at the distal ends of chromosomes that, together with the shelterin protein complexes, maintain genomic stability (Blackburn et al. 2015; Lim and Cech 2021). Recent discoveries have demonstrated the clinical utility and the importance of telomere-based therapies for extending health and lifespan, such that telomere-targeted gene therapies are currently demonstrating promise in treating age-related diseases in rodent studies (Bar et al. 2016; Bernardes De Jesus et al. 2012; Martinez and Blasco 2017; Povedano et al. 2018), including heart (Yeh et al. 2019) and neurodegenerative diseases (Whittemore et al. 2019). Given the increased prevalence of age-related diseases (Cooper et al. 2015; Van Den Bemd et al. 2022; Van Schrojenstein Lantman-De Valk et al. 2000) and premature death in individuals with intellectual disability (Heslop et al. 2014; Trollor et al. 2017; Tyrer et al. 2007), the purpose of this systematic review was to examine the association between intellectual disability and telomere length and telomere shortening.

2 | Methods

2.1 | Search Strategy and Selection Criteria

This systematic review and meta-analysis was conducted according to the PRISMA guidelines. The study protocol was prospectively registered with PROSPERO (ID: CRD42023394008). This study was a systematic review and meta-analysis designed to answer the following questions: (1) 'Is the average telomere length different between those with intellectual disability and age-matched apparently healthy controls?' (2) 'Is the rate of telomere length change over time accelerated in individuals with an intellectual disability compared to apparently healthy controls?' Finally, (3) 'are there any differences in telomere length between intellectual disability diagnostic categories?'

Author JD searched three electronic databases (PubMed, Scopus and ScienceDirect) for relevant literature using the registered hierarchical search strategy (commenced on 17/2/23 and concluded on 28/2/23). During the review process (28/2/25), the search was repeated to retrieve relevant papers published between 2023 and 2025. PubMed was searched with 'intellectual disability', 'telomere' and 'telomere shortening' as a Mesh heading (mh). Searches were used with a combination of Boolean operators, 'AND' and 'OR' the following terms: intellectual disability, neurodevelopmental disorder, intellectual impairment, Down syndrome, trisomy, dyskeratosis congenita, Hoyeraal–Hreidarsson (HH) syndrome, Revesz syndrome, telomere, telomere length and telomere shortening. The Scopus search involved filters for document type (article), source type (journal) and language (English), whereas filters for research articles, case reports and short communications applied to ScienceDirect searches (File S1). As an example, the following searches were performed in Scopus: 'Intellectual disability' AND 'telomere length'; 'telomere length' OR telomere OR telomeres OR 'telomere shortening' AND 'intellectual disability'; 'Intellectual disability' OR 'neurodevelopmental disorder' OR 'intellectual impairment' AND 'telomere length'; 'Intellectual disability' OR 'neurodevelopmental disorder' OR 'intellectual impairment' AND telomere; 'Down syndrome' OR trisomy OR 'intellectual disability' AND 'telomere length'; 'dyskeratosis congenita' OR 'Hoyeraal–Hreidarsson syndrome' OR 'Revesz syndrome' AND 'intellectual disability' AND 'telomere length'.

Records were exported from electronic databases and managed in Endnote (version X9.3.3), screened by author JD according to the inclusion/exclusion criteria and independently confirmed by author SH. Conflicting findings were resolved by discussion until agreement. Title and abstract were initially screened before full-text version of included studies were read in full and assessed. The reference lists of eligible studies were also reviewed to source additional papers. Records were screened according to the following criteria: cross-sectional studies, case–control studies, case studies (that included an age- and sex-matched neurotypical control/s) and cohort studies (Criterion 1). Prospective studies, as well as randomised controlled and crossover trials, were also eligible if they included an apparently healthy (neurotypical) control group. Conference proceedings, abstracts, books and other published works that were not necessarily peer-reviewed were not included in this review. Participants with an intellectual disability, diagnosed by a qualified health professional according to the DSM-5 or individuals with a neurodevelopmental disorder that causes a cognitive impairment or disability (e.g., Down syndrome and Hoyeraal–Hreidarsson syndrome) were required to confirm the diagnosis of intellectual disability (Criterion 2). Since the symptoms of dyskeratosis congenita vary and not all patients exhibit intellectual disability, we restricted the inclusion of telomere biology disorders (aka telomeropathies or telomere syndromes) to HH syndrome, as intellectual disability is a typical trait (Aalfs et al. 1995; Glousker et al. 2015; Hoyeraal et al. 1970; Hreidarsson et al. 1988). Studies that included the analysis of unborn foetuses (e.g., with trisomy) were excluded from this systematic review and meta-analysis, as foetal tissue expresses relatively high telomerase activity compared with adult cells (Bekaert et al. 2004). Studies must have included apparently healthy individuals without a diagnosed intellectual disability age-matched to the cases with intellectual disability, as indicated by a lack of statistical significance between the age of cases and controls (Criterion 3). Researchers were asked to share individual data when it was unclear if they were age- and sex-matched. In these cases, they were confirmed, modified to meet the eligibility criteria (age-matched) or excluded from the analyses. Studies must have measured telomere length and/or rate of telomere length changes over time expressed in arbitrary or absolute units (e.g., kilobase pairs or nucleotides) assessed using molecular biology techniques (e.g., quantitative PCR, fluorescence in situ hybridisation [FISH], terminal restriction fragments [TRF] measured by Southern blot and DNA methylation–based estimator of telomere length [DNAmTL]) (Criterion 4). Studies were excluded if they did not measure telomere length, if cases and controls were not age-matched, if telomere length data were missing or unavailable after multiple email requests to the authors, or if they were compared with a reference population (pay-for-service company). This was to ensure consistency in telomere length measurements and avoid batch effects. Eligibility concerns were resolved by discussion.

2.2 | Data Processing

Data were extracted from eligible studies by JD. Data extraction was verified by author SH, and conflicting findings were resolved by discussion until agreement. Extracted data consisted of mean and standard deviation (SD) of telomere length and/or rate of telomere length changes over time (primary outcomes), along with frequencies and median and interquartile range for other variables: participant numbers, age, biological sex (male or female) of cases and controls. We also attempted to extract height and weight and obtain disaggregated data for males and females, yet these data were missing or unavailable in most studies. The citation, study design, tissue sample/s analysed and telomere length quantification method were also obtained (summarised in Table 1). When data were missing or uncertainty surrounded the eligibility of the work, an email request was sent to the corresponding author on two separate occasions (several weeks apart) to confirm and/or share individual patient-level data. If data were still unavailable (i.e., if the researcher no longer possessed the files), it required age-matching cases and controls, and if it was feasible, Plot Digitizer (version 2.6.9) was used for data acquisition (Du et al. 2007; Holmes et al. 2006; Kimura et al. 2005; Vaziri et al. 1993). Papers that met the eligibility criteria but had missing, or duplicate data were referenced but not included in analyses. The PRISMA flow diagram is displayed in Figure S1. The main outcome measure was telomere length expressed in arbitrary units (e.g., telomere [T] to single copy gene (S) ratio—T/S ratio) or kilobase pairs (kbp)/nucleotides (nt).

2.3 | Risk of Bias

Risk of bias was assessed using the appraisal tool for cross-sectional studies (AXIS) (Downes et al. 2016), as studies must have included cross-sectional analyses between individuals with intellectual disability and controls. This was independently performed by authors JD and JB. Studies were not excluded based on their risk of bias. The overall risk of bias (total possible score of 60) was assessed by 20 criteria, ranging from high, unclear or low risk of bias, scored 3, 2 and 1, respectively. Overall study risk of bias was presented.

2.4 | Analyses

The primary data analysis aimed to compare telomere length between individuals with intellectual disability and healthy age-matched controls, and several preplanned secondary analyses were performed as per our prospective PROSPERO registration (CRD42023394008). Specifically, meta-regression was performed to examine moderating relationships between categorical covariates (diagnosis, telomere length assessment method and developmental stage—early and middle childhood, adolescence and adults) and effect sizes. All data were analysed using Comprehensive Meta-Analysis (version 4). Since data from three manuscripts were included for fibroblasts and to improve the generalisability of the leukocyte findings, we used fixed and random effects meta-analyses, respectively. Effect size estimates were expressed as the standardised difference in the mean with 95% confidence intervals. Heterogeneity was assessed using I^2 and Q-statistics (k [number of studies] − 1 degree of freedom)—large I^2 and Q-values indicated high heterogeneity. Publication bias was assessed using funnel plots. Data were visualised using GraphPad Prism. Statistical significance was set at $p < 0.05$.

TABLE 1 | Telomere length in individuals with intellectual disability.

Reference	Country	Condition	Participants[a,b,c]	Tissue sample/s	Telomere length quantification method	Major finding
Vaziri et al. (1993)	Canada	Down syndrome	Patients: 21, 0–45 years, ? Controls: 140, 0–107 years, ?	PBMCs	Southern blot	Faster annual telomere attrition in Down syndrome patients compared with controls (133 vs. 43 bp)
Zhang et al. (2003)	Sweden	Cri du chat/5p− syndrome	Patients: 8, 1–14 years, ? Controls: 8, age-matched, ?	PBMCs	Q-FISH	Patients possessed shorter telomeres compared with controls (11 668 ± 5337.2 vs. 34 208 ± 8267.5).
De Arruda Cardoso Smith et al. (2004)	Brazil	Down syndrome	Patients: 11, 31.5 ± 18 years, ? Controls: 11, 29.3 ± 28 years, ?	PBMCs & fibroblasts (gingival)	FISH	More lost telomere signals in patients compared with controls in both cell types (0.64 ± 0.18 vs. 0.169 ± 0.05 and 0.51 ± 0.13 vs. 0.13 ± 0.003, respectively)
Kimura et al. (2005)	USA	Down syndrome	Patients: 5, 5.95 years, M Controls: 5, 5.8 years, M	Fibroblasts (skin)	Southern blot	The rate of telomere attrition after population doubling is similar in cultured cells from patients and controls.
Holmes et al. (2006)	UK	Down syndrome	Patients: 4, 23–35 weeks, ? Controls: 6, 23–32 weeks, ?	Whole blood leukocytes	Southern blot	Shorter telomeres in patients compared with age-matched controls
Du et al. (2007)	USA	Cri du chat/5p− syndrome DC	Patients (5p−): 44, ?, ? Patients (DC): 9, ?, ? Controls: 105, 3–94 years, ?	PBMCs	Southern blot Flow-FISH	Shorter telomeres in patients with 5p− syndrome and much shorter telomeres in DC patients compared with controls
Lamm et al. (2009)	Israel	HH	Patients: 4, 10.3 years, 1 M/2 F Controls: 2, 3.25 years, ?	Whole blood leukocytes Primary fibroblasts	Southern blot	Shorter leukocyte telomeres but similar fibroblast telomeres in patients with HH compared with controls
Touzot et al. (2012)	France	DC/HH	Patients: 5, 1.3 years, 1 M/4 F Controls: 4, ?, ?	Fibroblasts Whole blood leukocytes	Southern blot	Shorter telomeres in patients compared with controls

(Continues)

TABLE 1 | (Continued)

Reference	Country	Condition	Participants[a,b,c]	Tissue sample/s	Telomere length quantification method	Major finding
Wenger et al. (2014)	USA	Trisomy 21	Patients: 3, ?, ? Controls: 7, ?, ?	PBMCs	Q-FISH	Shorter telomeres in patients compared with controls
Bhaumik et al. (2017)	India	Down syndrome	Patients: 170, 1 week, ? Controls: 186, 1 week, ?	Whole blood leukocytes	Southern blot	Longer telomeres in newborns with Down syndrome compared with age-matched controls
Bhattacharya et al. (2020)	India	Down syndrome	Patients: 63, 1 year, M/F Controls: 77, 1 year, M/F	Whole blood leukocytes	Southern blot	Similar telomere lengths, but faster annual telomere attrition in patients compared with controls (58 vs. 39 bp each year)
Norris et al. (2021)	UK	DC HH	Patients (DC): 73, 21.0 ± 16 years, 58 M/15 F Patients (HH): 15, 2.8 ± 2.8 years, 11 M/4 F Controls: 171, 35.85 ± 21.5 years, 63 M/74 F/34 ?	Whole blood leukocytes	HT-STELA	DC and HH patients possess shorter telomeres compared with age-matched controls.
Holland et al. (2022)	Norway	Cri du chat/5p− syndrome	Patients: 8, ?, ? Controls: 8, ?, ?	Whole blood leukocytes (DBS)	Illumina EPIC array	Similar telomeres between patients and controls (7.97 ± 0.59 vs. 7.92 ± 0.45, respectively)
Okazaki et al. (2022)	Japan	Williams syndrome	Patients: 32, 24.3 ± 7.9 years, 15 M/17 F Controls: 32, 24.8 ± 5.9 years, 15 M/13 F	Whole blood leukocytes	Illumina 450K array	Patients possessed shorter telomeres compared with controls.
Shinko et al. (2022)	Japan	Nicolaides–Baraitser syndrome	Patients: 12, 8.5 (4, 14) years, 5 M/7 F Controls: 27, 7 (4, 11) years, 14 M/13 F	Whole blood leukocytes	Illumina EPIC array	Patients possessed shorter telomeres compared with controls.

Note: All studies involved cross-sectional designs. Legend: [a] *N*; [b] age; [c] sex; ? not reported/unknown/unclear.
Abbreviations: DC, dyskeratosis congenita; HH, Hoyeraal–Hreidarsson syndrome; HT-STELA, high-throughput single telomere length analysis; DBS, dried blood spots; kbp, kilobase pairs; MDPL, mandibular hypoplasia, deafness, progeroid features, and lipodystrophy; *NHP2*, NHP2 ribonucleoprotein; PBMCs, peripheral blood mononuclear cells; Q-FISH, quantitative fluorescent in situ hybridisation; qPCR, quantitative polymerase chain reaction; TINF2, TERF1 interacting nuclear Factor 2.

3 | Results

3.1 | Search Results

Figure S1 outlines the search strategy according to PRISMA. The search identified 5165 records, which included 3267 duplicates that were deleted. The title and abstract of 1898 articles were screened according to our inclusion criteria, and 1815 were subsequently removed because of ineligibility. The full texts of the remaining 83 articles were downloaded and read in full to assess their eligibility, and 59 articles were subsequently excluded, leaving 24 (Figure S1). An additional 24 records were identified from the bibliography of the 83 articles, which were retrieved and read in full. Twenty-one were ineligible. Twenty-seven manuscripts were eligible for inclusion in this systematic review, and meta-analyses data were available or obtained from 15 studies, involving 17 comparisons. Studies where data were unavailable or concerns around data replication occurred are summarised in Table S1. The updated search did not reveal any additional articles that met the inclusion criteria for this systematic review and meta-analysis (Figure S2).

3.2 | Study Characteristics

Data from 15 studies composed of 17 comparisons were available or obtained from the researchers. Of these, 12 studies examined leukocytes (whole blood or PBMCs) (Bhattacharya et al. 2020; Bhaumik et al. 2017; Du et al. 2007; Holland et al. 2022; Holmes et al. 2006; Lamm et al. 2009; Norris et al. 2021; Okazaki et al. 2022; Shinko et al. 2022; Vaziri et al. 1993; Wenger et al. 2014; Zhang et al. 2003). One analysed fibroblasts (Kimura et al. 2005), and two analysed fibroblasts and leukocytes (Kimura et al. 2005; Touzot et al. 2012). Studies were published between 1993 and 2022 and were from the United States (Du et al. 2007; Kimura et al. 2005; Wenger et al. 2014), the United Kingdom (Holmes et al. 2006; Norris et al. 2021), Sweden (Zhang et al. 2003), Norway (Holland et al. 2022), Japan (Okazaki et al. 2022; Shinko et al. 2022), Israel (Lamm et al. 2009), India (Bhattacharya et al. 2020; Bhaumik et al. 2017), France (Touzot et al. 2012), Canada (Vaziri et al. 1993) and Brazil (De Arruda Cardoso Smith et al. 2004). Participants were individuals with genetic syndromes (Cri du chat syndrome [Du et al. 2007; Holland et al. 2022; Zhang et al. 2003]; Down syndrome [Bhattacharya et al. 2020; Bhaumik et al. 2017; De Arruda Cardoso Smith et al. 2004; Holmes et al. 2006; Kimura et al. 2005; Vaziri et al. 1993; Wenger et al. 2014]; HH syndrome [Lamm et al. 2009; Norris et al. 2021; Touzot et al. 2012]; Williams syndrome [Okazaki et al. 2022]; or Nicolaides–Baraitser syndrome [Shinko et al. 2022]) that cause intellectual disability and age-matched apparently healthy controls. Since age-matched participants were required, data from 371 people with intellectual disability and 486 healthy controls were used in analyses. Six studies included female and male participants with intellectual disability, one included males only, and the biological sex of the other eight were unclear. The biological sex of healthy controls was unclear in 10 studies, four included male and female volunteers, and one only involved males. The average age of participants ranged from newborns (Wenger et al. 2014) to 31.6 ± 17.9 years (De Arruda Cardoso Smith et al. 2004). Seven studies used Southern blot (Bhattacharya et al. 2020; Bhaumik et al. 2017; Holmes et al. 2006; Kimura et al. 2005; Lamm et al. 2009; Touzot et al. 2012; Vaziri et al. 1993)—the current gold standard—for measuring telomere length, four used fluorescence in situ hybridisation (FISH) experiments (De Arruda Cardoso Smith et al. 2004; Du et al. 2007; Wenger et al. 2014; Zhang et al. 2003), three used Illumina arrays (EPIC or 450K) (Holland et al. 2022; Okazaki et al. 2022; Shinko et al. 2022) to estimate telomere length from DNA methylation status, and one used high-throughput single telomere length analysis (HT-STELA) (Norris et al. 2021).

3.3 | Risk of Bias

Figure 1 illustrates the risk of bias for each study according to the AXIS tool. Overall, studies included in meta-analyses exhibited an average risk of bias of 29.8 ± 4.8 out of a possible score of 57. Because of the nature of the work, Criterion 14 was not applicable (Downes et al. 2016). All studies exhibited low risk of bias for study design, defined target population and justified discussion/conclusions (Criteria 2, 4 and 17, respectively). The bias of all studies was unclear for criteria pertaining to nonresponders (7 and 13), because of a lack of information (Figure 1).

3.4 | Shorter Leukocyte Telomeres in Individuals With Syndromic Intellectual Disability Compared With Controls

The meta-analysis included fourteen studies comprised of 16 comparisons of leukocyte telomere length between individuals with intellectual disability and healthy controls ($N = 366$ and 481, respectively). The meta-analysis indicated that individuals with intellectual disability possessed shorter leukocyte telomeres compared with controls (SMD [95% CI]: −0.853 [−1.622 to −0.084], $Z = -2.173$, $p = 0.03$; Figure 2). The studies showed considerable heterogeneity with I^2 and Q-values 95% and 318.30 ($p < 0.001$), respectively. The funnel plot indicated the possibility of publication bias, as 11 of 15 studies deviated markedly from the centre (Figure S3). Meta-regression indicated that diagnosis alone explained 39% of the variance, which was increased to 52% when developmental stage was included as a covariate. Meta-regression indicated that telomere length assessment method, diagnosis and developmental stage had a statistically significant influence on the magnitude of the effect size (all $p < 0.05$; Table S2). Subgroup analysis indicated that HH only, as well as individuals with syndromic intellectual disability without the HH and DS patients (i.e., Nicolaides–Baraitser, Williams and Cri du chat syndrome people only), had shorter telomeres than age-matched controls (Table S3). The other subgroups did not show statistically significant differences in telomere length between individuals with syndromic intellectual disability and controls (all $p > 0.05$). All subgroup analyses demonstrated large heterogeneity, according to I^2 and Q-statistics.

3.5 | Shorter Fibroblast Telomeres in Individuals With Syndromic Intellectual Disability Compared With Controls

Three studies examined fibroblast telomere length from individuals with intellectual disability and healthy controls ($N = 21$ and 16, respectively) (De Arruda Cardoso Smith et al. 2004; Kimura

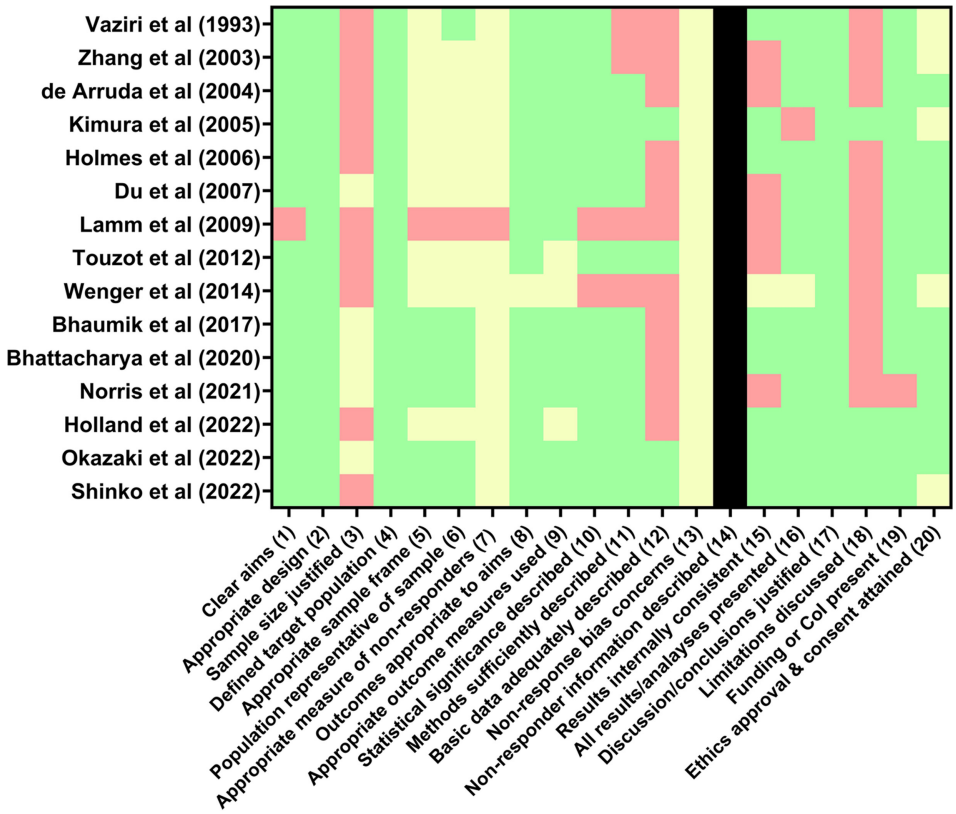

FIGURE 1 | Risk of bias. Risk of bias was assessed using the AXIS tool. CoI, conflict of interest. Green = low risk (1); yellow = unclear (2); red = high risk (3); black = not applicable. Each criterion from the AXIS tool is provided in parentheses.

et al. 2005; Touzot et al. 2012). This meta-analysis also indicated that individuals with intellectual disability possessed shorter fibroblast telomeres compared with healthy controls (SMD [95% CI]: −1.389 [−2.179 to −0.599], $Z = -3.445$, $p = 0.001$; Figure 3). These studies also showed marked heterogeneity ($Q = 12.058$, $p = 0.002$).

3.6 | Accelerated Telomere Attrition in Individuals With Syndromic Intellectual Disability

Three investigations calculated the age-related telomere shortening in individuals with Down syndrome (Bhattacharya et al. 2020; Vaziri et al. 1993) and HH syndrome (Norris et al. 2021) compared with healthy controls. This was performed by conducting linear regression to generate an annual rate of telomere shortening estimate. Relative to healthy controls ($N = 299$), individuals with intellectual disability ($n = 84$) exhibited a 2.09-fold (± 0.87) accelerated rate of annual leukocyte telomere shortening (−77 ± 49 vs. −35 ± 10; Figure 4).

4 | Discussion

Despite decades of progress in modern societies, the health and well-being inequalities remain a critical issue for individuals with intellectual disability. Our novel findings emphasise that individuals with syndromic genetic conditions with intellectual disability possess shorter telomeres (leukocyte and fibroblast) compared with age-matched healthy controls (large effect sizes). The shorter telomeres in individuals with intellectual disability syndromes are possibly, at least partly, explained by a faster rate of annual telomere shortening. The heterogeneity of the intellectual disability syndrome cohort, consistency between cell types, unique effects of covariates (diagnosis, developmental stage and telomere length method) and the biological interpretation of the findings are profound.

The five syndromes included in this study all commonly exhibit some level of intellectual disability, yet they have distinct genetic aetiologies. This offers an opportunity to examine the genetic contribution responsible for short telomeres. Alternatively, shared lifestyle factors, such as inactivity, diet and psychosocial concerns, may accelerate telomere attrition independently or in combination with genetic vulnerabilities and requires further investigation. Typically, individuals with intellectual disability suffer more ailments (Cooper et al. 2015; Van Den Bemd et al. 2022; Van Schrojenstein Lantman-De Valk et al. 2000) and earlier death (Heslop et al. 2014; Trollor et al. 2017; Tyrer et al. 2007). Physical activity levels amongst adults with intellectual disability are much lower than the general population (Borland et al. 2020; Dairo et al. 2016). For instance, a systematic review indicated that only 9% of adults with intellectual disability met the minimum physical activity guidelines (Dairo et al. 2016). Furthermore, cardiorespiratory fitness levels of those with intellectual disability are typically well below average (Boer and Moss 2016; Oviedo et al. 2014; Rimmer et al. 2004; Tsimaras et al. 2003) compared with normative data (Kaminsky et al. 2022). This is an important point since exercise training and cardiorespiratory fitness are associated with longer leukocyte telomeres (Denham, O'Brien,

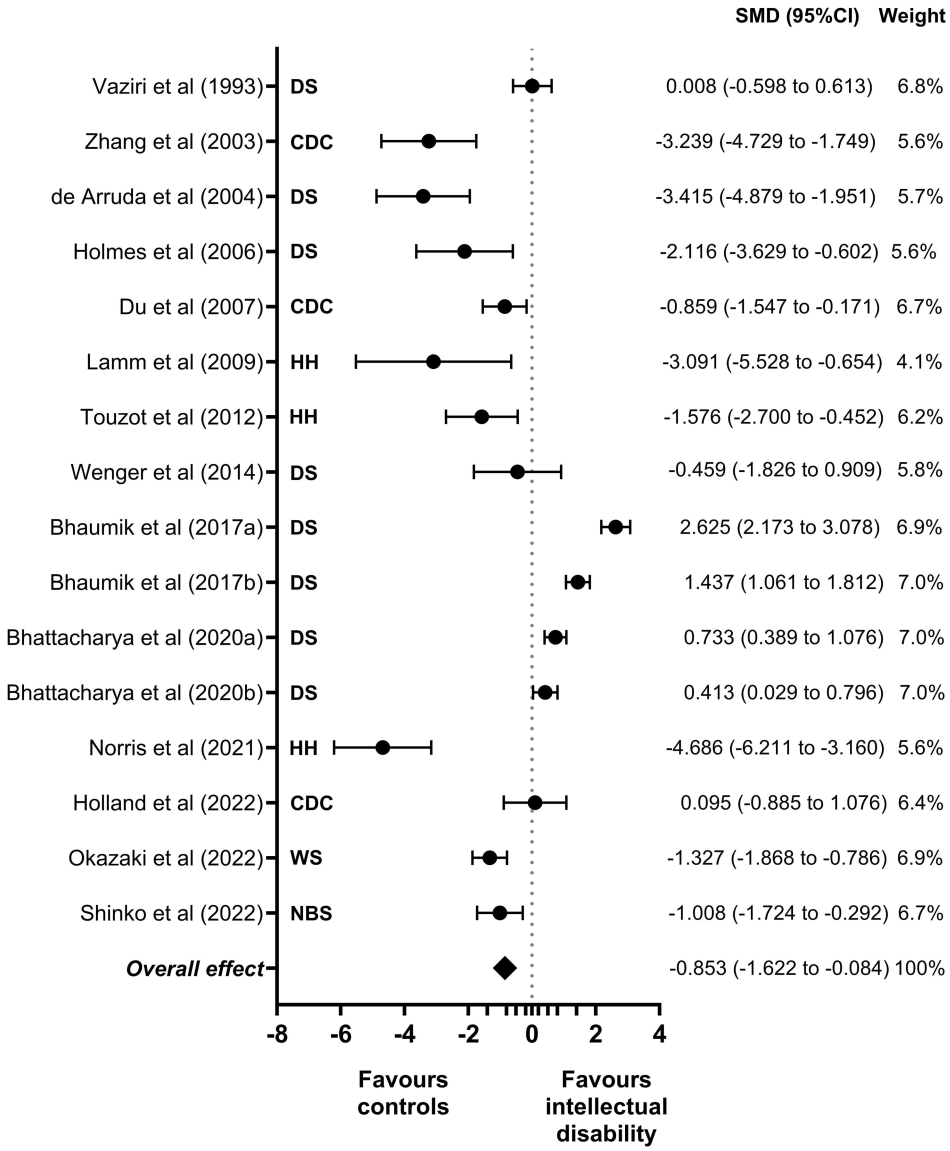

FIGURE 2 | Forest plot of leukocyte telomere length differences between individuals with intellectual disability and healthy controls. Random model. X-axis ticks indicate small, moderate, large and very large effect sizes (0.20, 0.50, 0.80 and 1.40, respectively). CDC, Cri du chat syndrome; CI, confidence interval; DS, Down syndrome; HH, Hoyeraal–Hreidarsson syndrome; NBS, Nicolaides–Baraitser syndrome; SMD, standardised mean difference; WS, Williams syndrome.

Prestes, et al. 2016; Kumar et al. 2021; Larocca et al. 2010; Shin and Kim 2023). Comorbidities in adults with intellectual disability commonly include heart disease, Type 2 diabetes and mental health concerns (Antonarakis et al. 2020; Cooper et al. 2015; Van Den Bemd et al. 2022)—conditioned linked to short leukocyte telomeres (Brouilette et al. 2007; Chakravarti et al. 2021; Honig et al. 2012; Rossiello et al. 2022). Importantly, lifestyle interventions, such as increasing physical activity and exercise, are accessible and relatively inexpensive strategies that reduce the risk of conditions linked to telomere shortening and are associated with telomere length maintenance (Denham 2023; Denham, O'Brien, and Charchar 2016; Kim et al. 2023). A salient point from the results of the present meta-analysis is that it would be important to provide more support for people with intellectual disability syndromes to combat accelerated biological ageing and maximise their life enrichment and well-being.

Individuals with intellectual disability in this meta-analysis were comprised of five syndromes with known genetic aberrations (i.e., Cri du chat, Down, Nicolaides–Baraitser, Williams and HH syndromes). Regarding the latter, it was not unexpected to find much shorter telomeres in leukocytes and fibroblasts (Touzot et al. 2012), as HH is the most severe form of the telomere biology disorder, dyskeratosis congenita (Glousker et al. 2015). The disease causes early death in infancy and ranging clinical characteristics owing to critically short and dysfunctional telomeres that ultimately leads to bone marrow failure (Niewisch et al. 2022; Ozdemir et al. 2004). Short telomeres in HH are caused by mutations in genes telomere-binding proteins, those directly responsible for telomere length regulation (*TINF2*, *ACD*, *RTEL1* and *PARN*) or telomerase-mediated telomere synthesis (i.e., its protein or RNA components—*DKC1*, *TERT* and *TERC*) (Revy et al. 2023). Convincing evidence supports rare autosomal dominant, x-linked and autosomal recessive mutations as

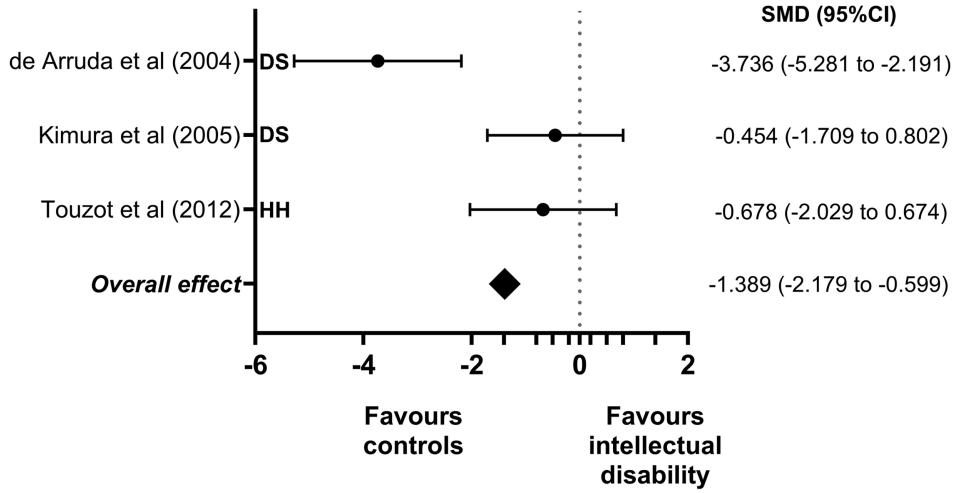

FIGURE 3 | Forest plot of fibroblast telomere length differences between individuals with intellectual disability and healthy controls. Fixed model. X-axis ticks indicate small, moderate, large and very large effect sizes (0.20, 0.50, 0.80 and 1.40, respectively). CI, confidence interval; DS, Down syndrome; HH, Hoyeraal–Hreidarsson syndrome; SMD, standardised mean difference.

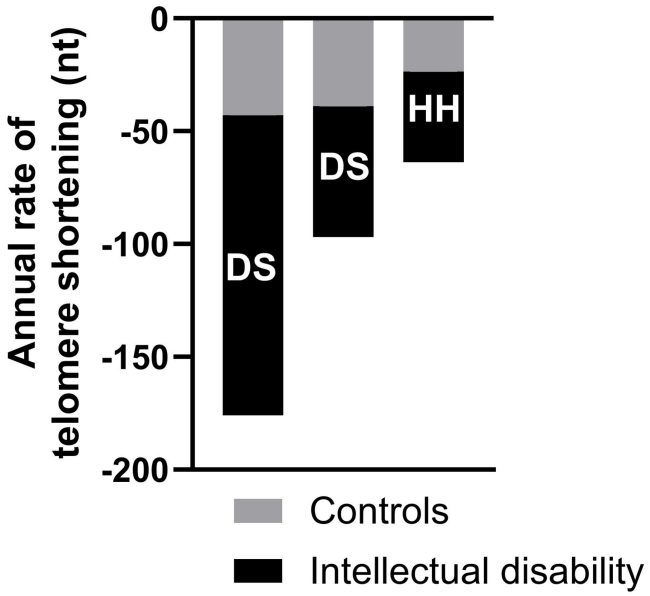

FIGURE 4 | Annual rate of telomere shortening in individuals with intellectual disability and controls. Grey (controls) and black (intellectual disability) bars indicate the telomere shortening rate in nucleotides (nt). DS, Down syndrome; HH, Hoyeraal–Hreidarsson syndrome.

the proximal cause of HH and short telomeres (Higgs et al. 2019; Niewisch and Savage 2019). Indeed, HH contributed the largest impact in our meta-regression (Table S2), was statistically significant in subgroup analyses (Table S3) and demonstrated a faster rate of telomere attrition compared with healthy individuals (Figure 4). Our findings further highlight the short leukocyte telomeres and accelerated rate of shortening at the extreme end of telomere biology disorders, HH.

The genetic contributions responsible for the shorter telomeres and accelerated telomere shortening observed in patients with intellectual disability and other diagnoses are less understood. Nicolaides–Baraitser syndrome is caused by de novo missense mutations in *SMARCA2* (aka BRM) (Van Houdt et al. 2012), one of two ATPases responsible for chromatin remodelling via the SWI/SNF complex (the other, SMARCA4/BRG1). TERT interacts with BRG1 to control Wnt signalling and subsequently stem cell maintenance and cell development (Park et al. 2009). Whether SMARCA2 exerts similar interactions with TERT is unknown, yet it appears to be required for full-length *TERT* transcription, rather than shorter alternatively spliced and dysfunctional *TERT* transcripts (Ito et al. 2008). Further, BRM knockdown leads to telomere shortening and growth arrest in H1299 cells (Ito et al. 2008). It is reasonable to suggest that healthy cells that express *TERT* (albeit at very low but biologically functional levels—i.e., lymphocytes) in the presence of a dysfunctional BRM protein (SMARCA2 missense mutation) may contribute to shorter telomeres in patients with Nicolaides–Baraitser syndrome. The STRING database also indicated protein–protein associations between SMARCA2, SMARCA4 and TERT (Figure S4) (Szklarczyk et al. 2023). Further work could reveal stronger links between telomere maintenance SMARCAs and telomerase and address an underexplored area, as only one study investigated Nicolaides–Baraitser syndrome (Shinko et al. 2022).

The shortened telomeres in the remaining syndromes are likely underpinned by gene dosage issues. For instance, Cri du chat was the second largest contributor to the effect identified in our meta-regression (Table S2). These patients exhibit haplodeficiency for *TERT*, the major rate-limiting component of telomerase, as a large portion of the small arm of chromosome five—where *TERT* is located—is absent on one of two paired chromosomes (i.e., 5p− syndrome) (Du et al. 2007; Zhang et al. 2003). In in vitro experiments, *TERT* induction upon lymphocyte stimulation in Cri du chat is markedly reduced compared with healthy controls, yet the lower telomerase activity did not reach statistical significance ($N = 10$) (Zhang et al. 2003). Interestingly, children with Cri du chat (< 5 years old) have similar telomeres to their healthy peers, indicating accelerated age-related telomere shortening (Du et al. 2007) rather than the genetic inheritance of short telomeres. Notwithstanding haplo-deficiency of other genes on 5p, *TERT* exerts important non-canonical roles in addition to telomere maintenance

(Denham 2023) that could underpin shorter leukocyte telomeres in Cri du chat patients, particularly with ageing and in rapidly dividing cells. That Cri du chat syndrome lymphocytes are responsive to *TERT* induction encourages lifestyle interventions, such as exercise and meditation, as possible therapeutic strategies to attenuate telomere attrition.

Williams–Beuren syndrome, hereafter referred to as Williams syndrome, is a rare microdeletion disorder causing hemizygosity for 25–27 protein-coding genes and several non-coding RNAs on chromosome 7q11.23 (Kozel et al. 2021). It is commonly linked to serious age-related comorbidities associated with telomere shortening (e.g., obesity, Type 2 diabetes, psychiatric conditions and heart disease). None of the genes in the 7q11.23 region directly control telomere length per se, yet gene dosage studies have demonstrated that the deletions cause genome-wide differentially regulated transcripts (Adamo et al. 2015), making indirect effects possible. Of the protein-coding genes deleted in Williams syndrome, *DNAJC30* is one with a crucial role in ATP synthesis and mitochondrial function. Since mitochondria dysfunction accelerates ROS production and preferentially damages the telomeres (Passos et al. 2007; Qian et al. 2019; Vaurs et al. 2024), *DNAJC30* could contribute to accelerated age-related telomere shortening in Williams syndrome (Tebbenkamp et al. 2018). Using DAVID Kegg pathway analysis and genes affected by Williams syndrome (Kozel et al. 2021), three genes (*CLDN3*, *CLDN4* and *NCF1*) were identified as 'leukocyte trans-endothelial migration' ($p = 0.012$) that could also influence leukocyte telomere shortening. Like *DNAJC30*, the STRING database demonstrated associations between *NCF1* and several genes involved in oxidative stress and metabolism (Figure S5), which is consistent with its function as a NADPH oxidase that generates superoxide anions upon activation.

Gene dosage issues also involve genetic additions and often lead to intellectual disability, none more established than Down syndrome (i.e., Trisomy 21). Down syndrome from trisomy of Chromosome 21 can occur during Meioses I and II, with a global frequency of approximately one in 700 births (Antonarakis 2017). There are consistent traits amongst those with Down syndrome (Antonarakis et al. 2020), yet intellectual disability and other characteristics can range considerably owing to functional genomic elements on Chromosome 21 and genetic variation on 21 and other chromosomes (Antonarakis 2017). Notably, the six studies, including eight comparisons between those with Down syndrome and controls, demonstrated considerable heterogeneity (Figure 3), such that the mean SMD approached zero with a large confidence interval in the diagnosis meta-regression (data not shown) (Bhattacharya et al. 2020; Bhaumik et al. 2017; De Arruda Cardoso Smith et al. 2004; Holmes et al. 2006; Vaziri et al. 1993; Wenger et al. 2014). Although not eligible for inclusion in this meta-analysis, several groups have observed shorter telomeres in amniocytes of Trisomy 21 compared with normal—karyotype—pregnancies (Sukenik-Halevy et al. 2011; Zhao and Bai 2024). Our meta-regression involving diagnosis and stage of development indicated that Down syndrome and HH, particularly in adulthood, were negatively associated with the SMD. This finding emphasises that those diagnoses and age tend to inflate telomere length differences between individuals with intellectual disability syndrome and apparently healthy controls (i.e., they experience a faster rate of biological ageing). Two large studies including four comparisons between young children with Down syndrome (newborns, infants and early childhood) and controls demonstrated longer leukocyte telomeres in patients (Bhattacharya et al. 2020; Bhaumik et al. 2017). High maternal age at conception is associated with an elevated risk of meiotic issues and Down syndrome. Both maternal and paternal age at conception are linked with longer telomeres in the offspring (Ferlin et al. 2013; Kimura et al. 2008), yet age of reproductive partners are often correlated supporting a role of paternal age on offspring telomeres (Eisenberg and Kuzawa 2018). That meiotic issues occur with advanced maternal age, testes express high levels of telomerase that lengthen spermatocyte telomeres as men age and other cultural considerations may underpin the observed effect here. Although the overall impact of intellectual disability syndromes on fibroblast telomere length significantly favoured controls (a large effect size), marked heterogeneity was again observed in Down syndrome patients, which may be partly explained by the fibroblast source (gingival [De Arruda Cardoso Smith et al. 2004] vs. skin [Kimura et al. 2005]) and presumably interindividual environmental factors. Two studies, however, consistently indicated an accelerated annual rate of leukocyte telomere shortening in Down syndrome compared with healthy controls (Bhattacharya et al. 2020; Vaziri et al. 1993). Our findings indicate that adults with Down syndrome demonstrated accelerated telomere attrition, yet the subgroup analysis (Table S3) did not reveal statistically significant telomere length differences in individuals with Down syndrome compared with controls, possibly due to substantial heterogeneity between and within studies. Despite the lack of statistical significance in the difference between individuals with syndromic intellectual disability in the HH-removed subgroup analysis, statistical significance was reached once DS were excluded (Table S3). This highlights the influence of the discordant findings amongst papers on DS, yet emphasises that even without HH and DS, other patients with syndromic intellectual disability possess shorter telomeres than age-matched controls.

It is worth considering the potential molecular mechanisms responsible for the observed heterogeneity in telomere lengths in those with Down syndrome. Trisomy 21 not only overexpresses genes on Chromosome 21 but deregulates the entire transcriptional landscape (gene expression of genes from other chromosomes) (Antonarakis 2017). In light of the complexity in deregulated genes in Down syndrome compounded by genetic variation, it is challenging to offer plausible mechanisms here. However, the dosage of genes located on Chromosome 21 that are implicated in the severity of Down syndrome traits (Antonarakis 2017) would be attractive targets for future investigations (e.g., *GABPA* and *SOD1*). Considering that telomeres are vulnerable to mass shortening and damage from oxidative stress, these candidates warrant investigation for their role in the accelerated telomere shortening observed in adults with Down syndrome. However, $Sod^{-/-}$ mice demonstrated accelerated ageing phenotypes, increased DNA oxidative damage and cellular senescence that culminated in 30% reduced lifespan (Zhang et al. 2017). Therefore, the increased gene copy number and expression might be considered protective suggesting that other genes maybe more attractive candidates. One of the most established transcription factors responsible for *TERT*

transcription, *ETS2*, is located on Chromosome 21, along with *ERG*—another member of the erythroblast transformation specific (ETS) family of transcription factors. Although ETS2 is considered a pro-oncogene, it appears to be protective against solid tumour growth in mouse models of Down syndrome (Trisomy 21) (Sussan et al. 2008). Considering that several genes on Chromosome 21 regulate *TERT* transcription and that oxidative stress accelerated telomere shortening (Barnes et al. 2019; Von Zglinicki 2002), *TERT* expression and telomerase enzyme activity in cells from those with Down syndrome warrants attention. Notwithstanding the complex gene dosage effects left for future work, it is tempting to speculate that significant lifestyle factors (e.g., diet-induced obesity, sedentarism and stress), comorbidities and lack of opportunities could be responsible for the observed effects in Down syndrome.

Of note, the meta-regression indicated that telomere length assessment methods were associated with the difference in telomere length between patients and controls (Table S2). Four studies used Southern blot to quantify telomere length in patients with Down syndrome and controls, including six comparisons. Of those studies, five demonstrated longer telomeres in individuals with Down syndrome compared with controls. Although Southern blot has been widely accepted as the gold standard assessment for many years, terminal restriction fragments from the technique not only include the telomeres but also some subtelomeric DNA. This may have impacted telomere length comparisons between trisomy and karyotypically normal individuals. Despite other methods estimating telomere length (Illumina array) or providing telomere length in arbitrary units (FISH), they consistently demonstrated negative associations with the SMD, along with the newer and more precise method that expresses telomere in kb, HT-STELA.

There are some limitations with this work. The telomere length reported here were mean values of telomeres on all chromosomes in the cells analysed (leukocytes and fibroblasts). Short telomeres on one or a few chromosomes are sufficient to cause cellular senescence or apoptosis. However, studies provided no data on the shortest telomeres, with one exception (Norris et al. 2021). Moreover, the age-related telomere shortening in individuals with intellectual disability syndromes was estimated by basic scatterplot (linear regression models) data, not the actual rate of telomere shortening in longitudinal analyses. Despite this, other work has indicated that the actual rate of age-related telomere shortening is much quicker compared with predicted age-related telomere shortening (i.e., from linear regression models). We eagerly await investigations analysing telomere length with more precise techniques profiling the range of telomere lengths (i.e., TESLA or STELA) in cells over several time points during the lifespan of individuals with different diagnoses causing intellectual disability. Data were not obtained from all eligible studies. We used Plot Digitizer to include as many studies as possible in our analysis to aid completeness. Although data from all eligible studies were not obtained because of their unavailability or lack of response from researchers, the inclusion of these papers was unlikely to detract from the major findings (see Table S1). Finally, the severity of intellectual disability in patients with the genetic syndromes was unclear. The potential impact of intellectual disability severity deserves attention in future investigations, as severity correlates with impairments, mortality, morbidity and opportunities in these people.

Regardless, our novel work highlights that those with intellectual disability syndromes possess shorter telomeres and exhibit faster rates of telomere shortening—one of the hallmarks of ageing. The accelerated biological ageing in people with intellectual disability syndromes requires further attention to address this inequality in ageing. We also encourage others to examine the potential of lifestyle (e.g., exercise training and meditation/mindfulness) and pharmacological interventions as therapeutic strategies to attenuate telomere attrition in people with intellectual disability syndromes.

Acknowledgements

The authors express their gratitude to researchers who willingly shared their data. Open access publishing facilitated by University of Southern Queensland, as part of the Wiley - University of Southern Queensland agreement via the Council of Australian University Librarians.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

Aalfs, C. M., H. Van Den Berg, P. G. Barth, and R. C. Hennekam. 1995. "The Hoyeraal-Hreidarsson Syndrome: The Fourth Case of a Separate Entity With Prenatal Growth Retardation, Progressive Pancytopenia and Cerebellar Hypoplasia." *European Journal of Pediatrics* 154: 304–308.

Adamo, A., S. Atashpaz, P. L. Germain, et al. 2015. "7q11.23 Dosage-Dependent Dysregulation in Human Pluripotent Stem Cells Affects Transcriptional Programs in Disease-Relevant Lineages." *Nature Genetics* 47: 132–141.

American Psychiatric Association. 2013. Diagnostic and Statistical Manual of Mental Disorders (5th ed.).

Antonarakis, S. E. 2017. "Down Syndrome and the Complexity of Genome Dosage Imbalance." *Nature Reviews. Genetics* 18: 147–163.

Antonarakis, S. E., B. G. Skotko, M. S. Rafii, et al. 2020. "Down syndrome." *Nature Reviews Disease Primers* 6: 9.

Bar, C., J. M. Povedano, R. Serrano, et al. 2016. "Telomerase Gene Therapy Rescues Telomere Length, Bone Marrow Aplasia, and Survival in Mice With Aplastic Anemia." *Blood* 127: 1770–1779.

Barnes, R. P., E. Fouquerel, and P. L. Opresko. 2019. "The Impact of Oxidative DNA Damage and Stress on Telomere Homeostasis." *Mechanisms of Ageing and Development* 177: 37–45.

Bekaert, S., H. Derradji, and S. Baatout. 2004. "Telomere Biology in Mammalian Germ Cells and During Development." *Developmental Biology* 274: 15–30.

Bernardes De Jesus, B., E. Vera, K. Schneeberger, et al. 2012. "Telomerase Gene Therapy in Adult and Old Mice Delays Aging and Increases Longevity Without Increasing Cancer." *EMBO Molecular Medicine* 4: 691–704.

Bhattacharya, M., P. Bhaumik, P. Ghosh, P. Majumder, and D. S. Kumar. 2020. "Telomere Length Inheritance and Shortening in Trisomy 21." *Fetal and Pediatric Pathology* 39: 390–400.

Bhaumik, P., M. Bhattacharya, P. Ghosh, S. Ghosh, and D. S. Kumar. 2017. "Telomere Length Analysis in Down Syndrome Birth." *Mechanisms of Ageing and Development* 164: 20–26.

Blackburn, E. H., E. S. Epel, and J. Lin. 2015. "Human Telomere Biology: A Contributory and Interactive Factor in Aging, Disease Risks, and Protection." *Science* 350: 1193–1198.

Boer, P. H., and S. J. Moss. 2016. "Validity of the 16-Metre PACER and Six-Minute Walk Test in Adults With Down Syndrome." *Disability and Rehabilitation* 38: 2575–2583.

Borland, R. L., N. Hu, B. Tonge, S. Einfeld, and K. M. Gray. 2020. "Participation in Sport and Physical Activity in Adults With Intellectual Disabilities." *Journal of Intellectual Disability Research* 64: 908–922.

Brouilette, S. W., J. S. Moore, A. D. Mcmahon, et al. 2007. "Telomere Length, Risk of Coronary Heart Disease, and Statin Treatment in the West of Scotland Primary Prevention Study: A Nested Case-Control Study." *Lancet* 369: 107–114.

Chakravarti, D., K. A. Labella, and R. A. Depinho. 2021. "Telomeres: History, Health, and Hallmarks of Aging." *Cell* 184: 306–322.

Cooper, S. A., G. Mclean, B. Guthrie, et al. 2015. "Multiple Physical and Mental Health Comorbidity in Adults With Intellectual Disabilities: Population-Based Cross-Sectional Analysis." *BMC Family Practice* 16: 110.

Dairo, Y. M., J. Collett, H. Dawes, and G. R. Oskrochi. 2016. "Physical Activity Levels in Adults With Intellectual Disabilities: A Systematic Review." *Preventive Medical Reports* 4: 209–219.

De Arruda Cardoso Smith, M., B. Borsatto-Galera, R. I. Feller, et al. 2004. "Telomeres on Chromosome 21 and Aging in Lymphocytes and Gingival Fibroblasts From Individuals With Down Syndrome." *Journal of Oral Science* 46: 171–177.

Denham, J. 2023. "Canonical and Extra-Telomeric Functions of Telomerase: Implications for Healthy Ageing Conferred by Endurance Training." *Aging Cell* 22: e13836.

Denham, J., B. J. O'Brien, and F. J. Charchar. 2016. "Telomere Length Maintenance and Cardio-Metabolic Disease Prevention Through Exercise Training." *Sports Medicine* 46: 1213–1237.

Denham, J., B. J. O'Brien, P. R. Prestes, N. J. Brown, and F. J. Charchar. 2016. "Increased Expression of Telomere-Regulating Genes in Endurance Athletes With Long Leukocyte Telomeres." *Journal of Applied Physiology* 1985, no. 120: 148–158.

Downes, M. J., M. L. Brennan, H. C. Williams, and R. S. Dean. 2016. "Development of a Critical Appraisal Tool to Assess the Quality of Cross-Sectional Studies (AXIS)." *BMJ Open* 6: e011458.

Du, H. Y., R. Idol, S. Robledo, et al. 2007. "Telomerase Reverse Transcriptase Haploinsufficiency and Telomere Length in Individuals With 5p− Syndrome." *Aging Cell* 6: 689–697.

Eisenberg, D. T. A., and C. W. Kuzawa. 2018. "The Paternal Age at Conception Effect on Offspring Telomere Length: Mechanistic, Comparative and Adaptive Perspectives." *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences* 373: 20160442.

Ferlin, A., E. Rampazzo, M. S. Rocca, et al. 2013. "In Young Men Sperm Telomere Length Is Related to Sperm Number and Parental Age." *Human Reproduction* 28: 3370–3376.

Florio, T., and J. Trollor. 2015. "Mortality Among a Cohort of Persons With an Intellectual Disability in New South Wales, Australia." *Journal of Applied Research in Intellectual Disabilities* 28: 383–393.

Forero, D. A., Y. Gonzalez-Giraldo, C. Lopez-Quintero, L. J. Castro-Vega, G. E. Barreto, and G. Perry. 2016. "Meta-Analysis of Telomere Length in Alzheimer's Disease." *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences* 71: 1069–1073.

Glousker, G., F. Touzot, P. Revy, Y. Tzfati, and S. A. Savage. 2015. "Unraveling the Pathogenesis of Hoyeraal-Hreidarsson Syndrome, a Complex Telomere Biology Disorder." *British Journal of Haematology* 170: 457–471.

Haycock, P. C., E. E. Heydon, S. Kaptoge, A. S. Butterworth, A. Thompson, and P. Willeit. 2014. "Leucocyte Telomere Length and Risk of Cardiovascular Disease: Systematic Review and Meta-Analysis." *BMJ* 349: g4227.

Hermans, H., and H. M. Evenhuis. 2014. "Multimorbidity in Older Adults With Intellectual Disabilities." *Research in Developmental Disabilities* 35: 776–783.

Heslop, P., P. S. Blair, P. Fleming, M. Hoghton, A. Marriott, and L. Russ. 2014. "The Confidential Inquiry Into Premature Deaths of People With Intellectual Disabilities in the UK: A Population-Based Study." *Lancet* 383: 889–895.

Higgs, C., Y. J. Crow, D. M. Adams, et al. 2019. "Understanding the Evolving Phenotype of Vascular Complications in Telomere Biology Disorders." *Angiogenesis* 22: 95–102.

Holland, P., M. Wildhagen, M. Istre, O. M. Reiakvam, J. A. Dahl, and A. Søraas. 2022. "Cri du Chat Syndrome Patients Have DNA Methylation Changes in Genes Linked to Symptoms of the Disease." *Clinical Epigenetics* 14: 128.

Holmes, D. K., N. Bates, M. Murray, et al. 2006. "Hematopoietic Progenitor Cell Deficiency in Fetuses and Children Affected by Down's Syndrome." *Experimental Hematology* 34: 1611–1615.

Honig, L. S., M. S. Kang, N. Schupf, J. H. Lee, and R. Mayeux. 2012. "Association of Shorter Leukocyte Telomere Repeat Length With Dementia and Mortality." *Archives of Neurology* 69: 1332–1339.

Hoyeraal, H. M., J. Lamvik, and P. J. Moe. 1970. "Congenital Hypoplastic Thrombocytopenia and Cerebral Malformations in Two Brothers." *Acta Paediatrica Scandinavica* 59: 185–191.

Hreidarsson, S., K. Kristjansson, G. Johannesson, and J. H. Johannsson. 1988. "A Syndrome of Progressive Pancytopenia With Microcephaly, Cerebellar Hypoplasia and Growth Failure." *Acta Paediatrica Scandinavica* 77: 773–775.

Ito, T., H. Watanabe, N. Yamamichi, et al. 2008. "Brm Transactivates the Telomerase Reverse Transcriptase (TERT) Gene and Modulates the Splicing Patterns of Its Transcripts in Concert With p54(nrb)." *Biochemical Journal* 411: 201–209.

Kaminsky, L. A., R. Arena, J. Myers, et al. 2022. "Updated Reference Standards for Cardiorespiratory Fitness Measured With Cardiopulmonary Exercise Testing: Data From the Fitness Registry and the Importance of Exercise National Database (FRIEND)." *Mayo Clinic Proceedings* 97: 285–293.

Kim, J. J., A. Ahn, J. Ying, E. Hickman, and A. T. Ludlow. 2023. "Exercise as a Therapy to Maintain Telomere Function and Prevent Cellular Senescence." *Exercise and Sport Sciences Reviews* 51: 150–160.

Kimura, M., X. Cao, J. Skurnick, M. Cody, P. Soteropoulos, and A. Aviv. 2005. "Proliferation Dynamics in Cultured Skin Fibroblasts From Down Syndrome Subjects." *Free Radical Biology & Medicine* 39: 374–380.

Kimura, M., L. F. Cherkas, B. S. Kato, et al. 2008. "Offspring's Leukocyte Telomere Length, Paternal Age, and Telomere Elongation in Sperm." *PLoS Genetics* 4: e37.

Kozel, B. A., B. Barak, C. A. Kim, et al. 2021. "Williams syndrome." *Nature Reviews. Disease Primers* 7: 42.

Kumar, D. P., A. J. Gray, J. Scott-Hamilton, A. D. Hagstrom, A. Murphy, and J. Denham. 2021. "Co-Expression Analysis Identifies Networks of miRNAs Implicated in Biological Ageing and Modulated by Short-Term Interval Training." *Mechanisms of Ageing and Development* 199: 111552.

Lamm, N., E. Ordan, R. Shponkin, C. Richler, M. Aker, and Y. Tzfati. 2009. "Diminished Telomeric 3′ Overhangs Are Associated With

Telomere Dysfunction in Hoyeraal-Hreidarsson Syndrome." *PLoS ONE* 4: e5666.

Larocca, T. J., D. R. Seals, and G. L. Pierce. 2010. "Leukocyte Telomere Length Is Preserved With Aging in Endurance Exercise-Trained Adults and Related to Maximal Aerobic Capacity." *Mechanisms of Ageing and Development* 131: 165–167.

Lim, C. J., and T. R. Cech. 2021. "Shaping Human Telomeres: From Shelterin and CST Complexes to Telomeric Chromatin Organization." *Nature Reviews. Molecular Cell Biology* 22: 283–298.

Lopez-Otin, C., M. A. Blasco, L. Partridge, M. Serrano, and G. Kroemer. 2023. "Hallmarks of Aging: An Expanding Universe." *Cell* 186: 243–278.

Martinez, P., and M. A. Blasco. 2017. "Telomere-Driven Diseases and Telomere-Targeting Therapies." *Journal of Cell Biology* 216: 875–887.

Mundstock, E., E. E. Sarria, H. Zatti, et al. 2015. "Effect of Obesity on Telomere Length: Systematic Review and Meta-Analysis." *Obesity (Silver Spring)* 23: 2165–2174.

Niewisch, M. R., N. Giri, L. J. Mcreynolds, et al. 2022. "Disease Progression and Clinical Outcomes in Telomere Biology Disorders." *Blood* 139: 1807–1819.

Niewisch, M. R., and S. A. Savage. 2019. "An Update on the Biology and Management of Dyskeratosis Congenita and Related Telomere Biology Disorders." *Expert Review of Hematology* 12: 1037–1052.

Norris, K., A. J. Walne, M. J. Ponsford, et al. 2021. "High-Throughput STELA Provides a Rapid Test for the Diagnosis of Telomere Biology Disorders." *Human Genetics* 140: 945–955.

Ogami, M., Y. Ikura, M. Ohsawa, et al. 2004. "Telomere Shortening in Human Coronary Artery Diseases." *Arteriosclerosis, Thrombosis, and Vascular Biology* 24: 546–550.

Okazaki, S., R. Kimura, I. Otsuka, et al. 2022. "Epigenetic Aging in Williams Syndrome." *Journal of Child Psychology and Psychiatry* 63: 1553–1562.

Oviedo, G. R., M. Guerra-Balic, T. Baynard, and C. Javierre. 2014. "Effects of Aerobic, Resistance and Balance Training in Adults With Intellectual Disabilities." *Research in Developmental Disabilities* 35: 2624–2634.

Ozdemir, M. A., M. Karakukcu, M. Kose, S. Kumandas, and H. Gumus. 2004. "The Longest Surviving Child With Hoyeraal-Hreidarsson Syndrome." *Haematologica* 89: ECR38.

Park, J. I., A. S. Venteicher, J. Y. Hong, et al. 2009. "Telomerase Modulates Wnt Signalling by Association With Target Gene Chromatin." *Nature* 460: 66–72.

Passos, J. F., G. Saretzki, and T. Von Zglinicki. 2007. "DNA Damage in Telomeres and Mitochondria During Cellular Senescence: Is There a Connection?" *Nucleic Acids Research* 35: 7505–7513.

Patel, D. R., M. D. Cabral, A. Ho, and J. Merrick. 2020. "A Clinical Primer on Intellectual Disability." *Translational Pediatrics* 9: S23–S35.

Povedano, J. M., P. Martinez, R. Serrano, et al. 2018. "Therapeutic Effects of Telomerase in Mice With Pulmonary Fibrosis Induced by Damage to the Lungs and Short Telomeres." *eLife* 7: e31299.

Qian, W., N. Kumar, V. Roginskaya, et al. 2019. "Chemoptogenetic Damage to Mitochondria Causes Rapid Telomere Dysfunction." *Proceedings of the National Academy of Sciences of the United States of America* 116: 18435–18444.

Revy, P., C. Kannengiesser, and A. A. Bertuch. 2023. "Genetics of Human Telomere Biology Disorders." *Nature Reviews. Genetics* 24: 86–108.

Rimmer, J. H., T. Heller, E. Wang, and I. Valerio. 2004. "Improvements in Physical Fitness in Adults With Down Syndrome." *American Journal of Mental Retardation* 109: 165–174.

Rossiello, F., D. Jurk, J. F. Passos, and F. D'adda Di Fagagna. 2022. "Telomere Dysfunction in Ageing and Age-Related Diseases." *Nature Cell Biology* 24: 135–147.

Shin, Y. A., and J. H. Kim. 2023. "Effects of Cardiorespiratory Fitness on Cardiovascular Disease Risk Factors and Telomere Length by Age and Obesity." *Journal of Obesity & Metabolic Syndrome* 32: 259–268.

Shinko, Y., S. Okazaki, I. Otsuka, et al. 2022. "Accelerated Epigenetic Age and Shortened Telomere Length Based on DNA Methylation in Nicolaides-Baraitser Syndrome." *Molecular Genetics & Genomic Medicine* 10: e1876.

Sukenik-Halevy, R., T. Biron-Shental, R. Sharony, M. D. Fejgin, and A. Amiel. 2011. "Telomeres in Trisomy 21 Amniocytes." *Cytogenetic and Genome Research* 135: 12–18.

Sussan, T. E., A. Yang, F. Li, M. C. Ostrowski, and R. H. Reeves. 2008. "Trisomy Represses Apc (Min)-Mediated Tumours in Mouse Models of Down's Syndrome." *Nature* 451: 73–75.

Szklarczyk, D., R. Kirsch, M. Koutrouli, et al. 2023. "The STRING Database in 2023: Protein-Protein Association Networks and Functional Enrichment Analyses for Any Sequenced Genome of Interest." *Nucleic Acids Research* 51: D638–D646.

Tebbenkamp, A. T. N., L. Varela, J. Choi, et al. 2018. "The 7q11.23 Protein DNAJC30 Interacts With ATP Synthase and Links Mitochondria to Brain Development." *Cell* 175: 1088–1104.e23.

Topiwala, A., T. E. Nichols, L. Z. J. Williams, et al. 2023. "Telomere Length and Brain Imaging Phenotypes in UK Biobank." *PLoS ONE* 18: e0282363.

Touzot, F., L. Gaillard, N. Vasquez, et al. 2012. "Heterogeneous Telomere Defects in Patients With Severe Forms of Dyskeratosis Congenita." *Journal of Allergy and Clinical Immunology* 129, no. 473–82: 482.e1–482.e3.

Trollor, J., P. Srasuebkul, H. Xu, and S. Howlett. 2017. "Cause of Death and Potentially Avoidable Deaths in Australian Adults With Intellectual Disability Using Retrospective Linked Data." *BMJ Open* 7: e013489.

Tsimaras, V., P. Giagazoglou, E. Fotiadou, K. Christoulas, and N. Angelopoulou. 2003. "Jog-Walk Training in Cardiorespiratory Fitness of Adults With Down Syndrome." *Perceptual and Motor Skills* 96: 1239–1251.

Tyrer, F., L. K. Smith, and C. W. Mcgrother. 2007. "Mortality in Adults With Moderate to Profound Intellectual Disability: A Population-Based Study." *Journal of Intellectual Disability Research* 51: 520–527.

Van Den Bemd, M., B. W. M. Schalk, E. Bischoff, M. Cuypers, and G. L. Leusink. 2022. "Chronic Diseases and Comorbidities in Adults With and Without Intellectual Disabilities: Comparative Cross-Sectional Study in Dutch General Practice." *Family Practice* 39: 1056–1062.

Van Houdt, J. K., B. A. Nowakowska, S. B. Sousa, et al. 2012. "Heterozygous Missense Mutations in SMARCA2 Cause Nicolaides-Baraitser Syndrome." *Nature Genetics* 44, no. 445–9: S1–S449.

Van Schrojenstein Lantman-De Valk, H. M., J. F. Metsemakers, M. J. Haveman, and H. F. Crebolder. 2000. "Health Problems in People With Intellectual Disability in General Practice: A Comparative Study." *Family Practice* 17: 405–407.

Vaurs, M., E. B. Dolu, and A. Decottignies. 2024. "Mitochondria and Telomeres: Hand in Glove." *Biogerontology* 25: 289–300.

Vaziri, H., F. Schächter, I. Uchida, et al. 1993. "Loss of Telomeric DNA During Aging of Normal and Trisomy 21 Human Lymphocytes." *American Journal of Human Genetics* 52: 661–667.

Vissers, L. E., C. Gilissen, and J. A. Veltman. 2016. "Genetic Studies in Intellectual Disability and Related Disorders." *Nature Reviews. Genetics* 17: 9–18.

Von Zglinicki, T. 2002. "Oxidative Stress Shortens Telomeres." *Trends in Biochemical Sciences* 27: 339–344.

Wenger, S. L., J. Hansroth, and A. L. Shackelford. 2014. "Decreased Telomere Length in Metaphase and Interphase Cells From Newborns With Trisomy 21." *Gene* 542: 87.

Whittemore, K., A. Derevyanko, P. Martinez, et al. 2019. "Telomerase Gene Therapy Ameliorates the Effects of Neurodegeneration Associated to Short Telomeres in Mice." *Aging (Albany NY)* 11: 2916–2948.

Willeit, P., J. Willeit, A. Brandstatter, et al. 2010. "Cellular Aging Reflected by Leukocyte Telomere Length Predicts Advanced Atherosclerosis and Cardiovascular Disease Risk." *Arteriosclerosis, Thrombosis, and Vascular Biology* 30: 1649–1656.

Yeh, J. K., M. H. Lin, and C. Y. Wang. 2019. "Telomeres as Therapeutic Targets in Heart Disease." *JACC: Basic to Translational Science* 4: 855–865.

Zannolli, R., A. Mohn, S. Buoni, et al. 2008. "Telomere Length and Obesity." *Acta Paediatrica* 97: 952–954.

Zhang, A., C. Zheng, M. Hou, et al. 2003. "Deletion of the Telomerase Reverse Transcriptase Gene and Haploinsufficiency of Telomere Maintenance in Cri du Chat Syndrome." *American Journal of Human Genetics* 72: 940–948.

Zhang, Y., A. Unnikrishnan, S. S. Deepa, et al. 2017. "A New Role for Oxidative Stress in Aging: The Accelerated Aging Phenotype in Sod1(−/)(−) Mice Is Correlated to Increased Cellular Senescence." *Redox Biology* 11: 30–37.

Zhao, X. X., and L. L. Bai. 2024. "Correlation Between Telomere Shortening in Maternal Peripheral Blood and Fetal Aneuploidy." *BMC Pregnancy and Childbirth* 24: 2.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.