PAEDIATRIC HEALTH-RELATED QUALITY OF LIFE IN CONGENITAL CYTOMEGALOVIRUS

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Abstract

Objective

Congenital cytomegalovirus (cCMV) is the most common congenital infection globally. This cross-sectional study aimed to describe the health-related quality of life (HRQoL) of children with cCMV and that of their parents.

Methods

Families of children with cCMV in the UK were approached through the charity CMV Action. Parents completed questionnaires about their own HRQoL and that of their child. Children who were able to self-report completed questionnaires about their own HRQoL.

Demographic characteristics of the sample were described using descriptive statistics. Questionnaire responses were scored, and domain and summary scores calculated and compared with UK population norms, where available.

Results

Seventy families participated, with children aged between 5 months and 18 years. Children with cCMV had poorer HRQoL compared to children from UK population data. HRQoL of children whose health was more severely affected by cCMV was poorer than that of children whose health was less severely affected.

Parents of children whose health was moderately or severely affected had greater psychological morbidity and poorer HRQoL in Physical, Emotional, Social, and Cognitive Functioning domains than parents of less severely affected children.

Conclusions

cCMV has a significant effect on the HRQoL of children with cCMV and their parents, with the children with the most significant health needs having the lowest HRQoL compared to those children with little or no effects on their health. This data could contribute to health economic analyses, informing resource allocation to potential interventions for the prevention and treatment of cCMV.

What is already known on this topic

There is currently very little known about how congenital cytomegalovirus (cCMV) affects the health-related quality of life (HRQoL) of affected children and their parents.

Around 25% of children with cCMV go on to have long-term adverse outcomes including sensorineural hearing loss.

What this study adds

To our knowledge, this is the first study to assess the HRQoL of children with cCMV in the UK.

The HRQoL of children with cCMV was poorer than that of children from UK population data.

Children whose health was severely affected by cCMV had significantly poorer HRQoL than children whose health had not been affected by cCMV.

How this study might affect research, practice or policy

Our findings could be used alongside economic data in health economic analyses, influencing policy decisions regarding the implementation of interventions for the prevention and treatment of cCMV.

INTRODUCTION

Congenital cytomegalovirus (cCMV) is the most common congenital infection globally and is estimated to affect 0·3% of infants born in the United Kingdom (UK).[1] Between 10-15% of infants infected with cytomegalovirus have symptoms or signs of cCMV at birth.[2,3] Overall, an estimated 25% of children born with cCMV will develop permanent sequelae such as sensorineural hearing loss, cognitive impairment, movement disorders, visual impairment, epilepsy, and autism spectrum disorders.[2,3]

Data demonstrating the impact of cCMV on health-related quality of life (HRQoL) is needed to inform policy decisions regarding the implementation of interventions to prevent and treat cCMV.[4–6] HRQoL is a multidimensional concept which considers physical, social, and psychological health and wellbeing from the patient's perspective.[7] HRQoL measures can be used to generate quality-adjusted life-years (QALYs) which are used to reflect disease burden in health economic analysis.[8]

This study aimed to describe the HRQoL of children with cCMV in the UK and that of their parents and to calculate QALYs for children with cCMV and their parents.

METHODS

Study design and participants

We used a national cross-sectional questionnaire study design, distributed through the UK charity CMV Action.

Families with at least one child (aged 1 month to 18 years) with cCMV, living within the UK, who were able to read and write in English, and able to give written informed consent, were included.

The University of Southampton Faculty of Medicine Ethics Committee granted ethical approval (ERGO reference: 61440); NHS ethics approval was not required.

Materials

Questionnaire selection was based on inclusion of HRQoL domains relevant to the cCMV population and to enable the calculation of QALYs. Full descriptions of questionnaires used are provided in Supplementary 1.

The Pediatric Quality of Life Inventory (PedsQL) modules enable comparison between different populations as well as with population norms.[9] Generic Core and Infant Scales measure domains of functioning relevant to HRQoL. The General Well-Being module measures levels of happiness the child feels about their life.[9–12]

The Strengths and Difficulties Questionnaire (SDQ) measures behavioural functioning.[13] The supplementary 'Impact Score' indicates the impact of a child's behavioural problems on the child and family.

The PedsQL Family Impact Module assesses the extent to which parent HRQoL and family functioning may be affected by having a child with cCMV.[14]

The General Health Questionnaire-12 (GHQ-12) was selected to assess the extent to which the burden of caring for a child with cCMV may affect parent psychological wellbeing.[15]

The Child Health Utility-9 Dimensions (CHU-9D) was used to calculate QALYs. QALYs have index values between 0 and 1, where 0 = death and 1 = perfect health.[16] Negative scores indicate a state valued worse than death.

The EuroQol-5 Dimensions-Youth (EQ-5D-Y) and EuroQol-5 Dimensions-3 Levels (EQ-5D-3L) enable the calculation of QALYs in paediatric and adult populations, respectively.[17,18] EQ-5D-Y was used in addition to CHU-9D to calculate QALYs for children to assess whether there was a correlation between parent QALYs and child QALYs.

Procedures

Participants were approached through the website and social media channels of CMV Action and by emails sent directly to families on the CMV Action database. Participants completed online questionnaires anonymously on Microsoft Forms. One parent from each family answered basic demographic questions, three questionnaires relating to their own HRQoL (PedsQL Family Impact Module, GHQ-12, EQ-5D-3L) and between one and five questionnaires about their child's HRQoL, dependent on the child's age (PedsQL Generic Core or Infant Scales, General Well-Being module, SDQ, CHU-9D, EQ-5D-Y). Demographic information was collected on gender and age of the parent and child, and long-term impairments and schooling for the child. Self-report HRQoL data was also collected from children if aged five years or older, if their parent reported they were able to answer questions themselves. Children eligible to self-report completed between one and five questionnaires depending on age (Supplementary 1). Total time to complete questionnaires was between 10 and 25 minutes for parents and 5 and 20 minutes for children. Informed consent was obtained. Families completing questionnaires received a gift voucher.

Statistical Analysis

Demographic characteristics were analysed using descriptive statistics. Due to the large variation in severity of sequelae in children with cCMV, HRQoL was likely to be highly varied. Therefore, to present clinically meaningful results, the sample was divided into four subgroups for statistical analyses based on parent-reported overall effect of cCMV on their child's health: no effect, mild, moderate, and severe effect. Parents were asked to rate the overall effect of congenital CMV on their child's health as part of the demographic questionnaire. This was used to split the data into subgroups, rather than using an algorithm based on which impairments the child had, because parents were likely to assess the severity of the effect of cCMV on their child's health more accurately than a generic algorithm, particularly considering the varying severity within each impairment. For example, autism spectrum disorder varies in severity, so assigning it a fixed "score" does not account for this variation, potentially resulting in less meaningful subgroups.

Descriptive statistics were performed for domain and summary scores for each HRQoL measure and compared with previously published population norms, with a preference for UK norms, where this data was available. Parent-reported data were displayed graphically using GraphPad Prism (version 9.1, March 2021). Self-reported data were analysed descriptively and presented in tables.

All data were non-parametric, so group differences were analysed using Kruskal-Wallis H tests and pairwise comparisons using Dunn's test with Bonferroni correction.[24]

QALYs were calculated for children and parents using the UK value sets for CHU-9D and EQ-5D-3L, respectively. QALYs for children were also calculated from EQ-5D-Y responses using the UK value set for EQ-5D-3L as currently there is no UK value set available for EQ-5D-Y. Intraclass correlation coefficient (ICC) estimates and their 95% confidence intervals (95% CIs) were calculated to assess inter-rater reliability between self-report and parent-report QALYs for both CHU-9D and EQ-5D-Y.[19]

IBM SPSS version 27 was used for all statistical analyses.

RESULTS

Of 96 eligible families who expressed an interest in the study, 70 (72·9%) completed the questionnaires between 08/03/2021 and 08/04/21 (Supplementary 2). Demographic data is presented in Table 1. According to parental assessment, cCMV had no effect on health for 17% of children, 17% were mildly affected, 29% were moderately affected, and 37% were severely affected.

Children whose parents reported a ‘severe effect’ of cCMV on their health had a high frequency of sequelae related to cCMV and the majority attended a school for children with additional needs. Conversely, children whose parents reported a ‘mild effect’ of cCMV on their health had a much lower frequency of cCMV-related sequelae and most were in mainstream school.

The age range of all children was 5 months to 18 years, but for self-report was older, since only children aged 5 years or older were eligible to self-report.

Child self-report data is presented in Supplementary 3 due to the small sample size (n=20).

Table 1: Demographic characteristics of study participants from whom parent proxy-report was collected, for the whole cohort and for each parent-reported severity of effect of cCMV on health subgroup

Demographics	Whole cohort, n=70 (%)	No effect, n=12 (%)	Mild effect, n=12 (%)	Moderate effect, n=20 (%)	Severe effect, n=26 (%)
Parent gender, female	61 (87)	12 (100)	9 (75)	18 (90)	22 (85)
Parent age in years, median (range)	36 (22-54)	33 (25-48)	35 (28-44)	36 (24-54)	38 (22-53)
Child age in years, median (range)	5 (0·4-18)	2 (0·5-10)	6 (2-11)	4 (0·4-16)	5 (1·3-18)
Child gender, female	34 (49)	4 (33)	6 (50)	7 (35)	11 (65)
Child ethnicity					
White British	61 (87)	10 (83)	11 (92)	16 (80)	24 (92)
Any other White background	5 (7)	1 (8)	0	2 (10)	2 (8)
Mixed or Multiple ethnic groups	4 (6)	1 (8)	1 (8)	2 (10)	0
Age at diagnosis in months, median (range)*	0.5 (0-144)	0 (0-3)	0 (0-60)	3 (0-96)	1 (0-144)
School type (n=40)					
Mainstream with no additional support	8 (20)	3 (100)	4 (44)	1 (8)	0
Mainstream with additional support	13 (33)	0	4 (44)	8 (67)	1 (6)
Non-residential special needs	17 (43)	0	1 (11)	3 (25)	13 (81)
Residential special needs	1 (3)	0	0	0	1 (6)
Other	1 (3)	0	0	0	1 (6)
Long-term impairment					
Hearing	46 (66)	3 (25)	7 (58)	14 (70)	22 (85)
Visual	18 (26)	0	3 (25)	5 (25)	10 (39)
Autism spectrum disorder	11 (16)	0	2 (17)	6 (30)	3 (12)
Attention deficit hyperactivity disorder	4 (6)	0	0	3 (15)	1 (4)
Movement or cerebral palsy	29 (41)	0	2 (17)	4 (20)	23 (89)
Balance or coordination	30 (43)	0	6 (50)	10 (50)	14 (54)
Seizures or epilepsy	17 (24)	0	0	2 (10)	15 (58)
Microcephaly	20 (29)	0	1 (8)	5 (25)	14 (54)
Cognitive impairment or learning difficulties	35 (50)	0	5 (42)	10 (50)	20 (77)
Speech and/or language	34 (49)	0	4 (33)	9 (45)	21 (81)
Other	15 (21)	4 (33)	0	7 (35)	4 (15)
Children with hearing impairment	n=46 (%)	n=3 (%)	n=7 (%)	n=14 (%)	n=22 (%)
Laterality^, bilateral	28 (61)	2 (67)	4 (57)	8 (57)	14 (64)
Severity					
Mild	5 (11)	2 (67)	1 (14)	1 (7)	1 (5)
Moderate	10 (22)	1 (33)	3 (43)	2 (14)	4 (18)
Severe	31 (67)	0	3 (43)	11 (79)	17 (77)
Hearing device					
Hearing aid	23 (50)	1 (33)	4 (57)	3 (21)	15 (68)
Cochlear implant	9 (20)	0	0	7 (50)	2 (9)
Other	1 (2)	0	0	1 (5)	0

*0 indicates antenatal diagnosis or diagnosis at birth.

^ laterality of hearing loss data was missing for 1 child in 'mild effect' subgroup.

Percentages rounded to nearest whole number. Consequently, totals may add up to more than 100.

HRQoL of children with cCMV

PedsQL Generic Core Scales and General Well-Being

Children whose health was severely affected by cCMV had statistically significantly lower (poorer) HRQoL scores across multiple domains, compared to ‘no effect’ and ‘mild effect’ subgroups (Figure 1). For both parent-report and self-report, children in ‘mild effect’, ‘moderate effect’, and ‘severe effect’ subgroups scored lower in all domains and summary scores than healthy UK population means.[12]

General Well-Being Scores (available for children ≥8 years of age) were not significantly different between subgroups, meaning cCMV may not affect children’s overall sense of wellbeing, but this score was only completed for a small number of children (n=21) (Supplementary 4). No population norms are available for the General Well-Being Score.

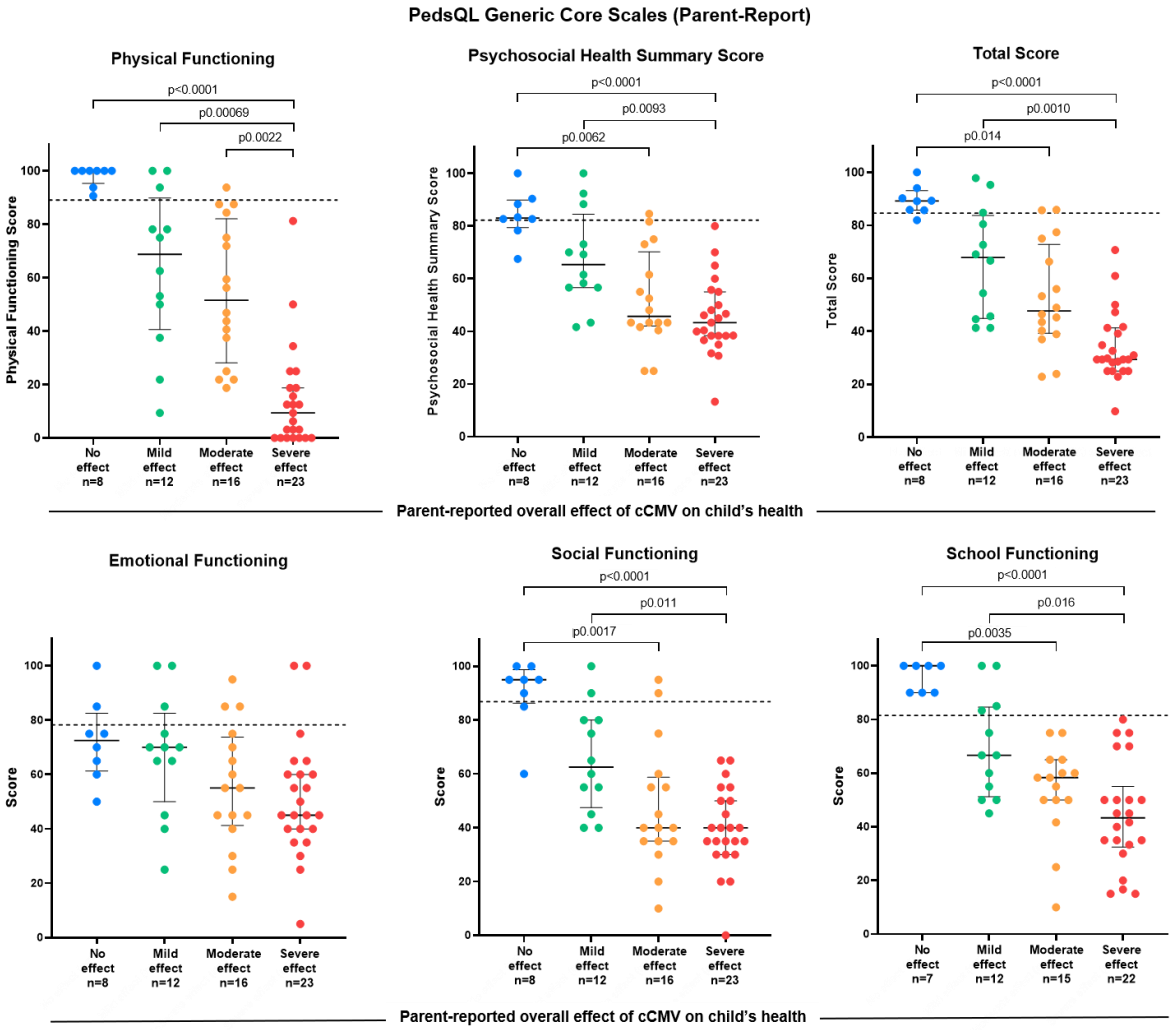

Figure 1: Comparison between children with congenital cytomegalovirus (cCMV) and the UK population in parent-reported Pediatric Quality of Life Inventory (PedsQL) Generic Core Scales Physical Functioning Score, Psychosocial Health Summary Score, Total Score, and individual domain scores (Emotional Functioning, Social Functioning, and School Functioning), by subgroups based on parent-reported overall effect of cCMV on the child's health

Higher scores indicate better HRQoL. Psychosocial Health Summary Score is the mean of Emotional, Social, and School Functioning scores. Physical Functioning score is the same as the Physical Health Summary Score, so is shown as Physical Functioning score here. Total Score is the mean of all items on the PedsQL Generic Core Scales. *Bars m*edians and interquartile ranges, *circles* individual data points, *dashed line* healthy UK population norms from Upton 2005.[12] Population norms are shown as means as there were no median or interquartile range data available. Kruskal-Wallis H test was run and pairwise comparisons were performed using Dunn's (1964) procedure with a Bonferroni correction for multiple comparisons. Lines with p values on graphs indicate statistically significant differences in pairwise comparisons. No line indicates no statistically significant difference in pairwise comparisons.

Children whose health was more severely affected by cCMV had significantly lower Physical Functioning Scores, Psychosocial Health Summary Scores, and Total Scores as well as Social Functioning and School Functioning scores, than less severely affected children. Children in 'severe effect', 'moderate effect', and 'mild effect' subgroups had lower median Physical Functioning scores, Psychosocial Health Summary Scores, and Total Scores, as well as Emotional Functioning, Social Functioning, and School Functioning scores, than healthy UK population means.

PedsQL Infant Scales

There were only 11 infants for whom data was collected. In 'moderate effect' (n=4) and 'severe effect' (n=3) subgroups, cCMV was reported to affect all domains of HRQoL particularly 'Cognitive Functioning' (Supplementary 5).

Effect of cCMV on children's behaviour

SDQ

'Hyperactivity' and 'Peer Problems' scores of children whose health was more severely affected by cCMV were higher (poorer) than children in the 'no effect' subgroup and UK population means (Figure 2).[20] Similar trends were observed in self-report (Supplementary 3). Conversely, 'Emotional Symptoms' and 'Conduct Problems' scores were similar across subgroups and to population means.[20]

'Prosocial Scale' scores were significantly lower (poorer) in the 'severe effect' subgroup than in 'no effect' and 'mild effect' subgroups. Median 'Prosocial Scale' scores in 'moderate effect' and 'severe effect' subgroups were lower (poorer) than population means.[20]

'Impact Scores' were significantly higher (more severe) in the 'severe effect' subgroup than the 'no effect' subgroup. Median 'Impact Scores' in 'moderate effect' and 'severe effect' subgroups were higher than population means.[20]

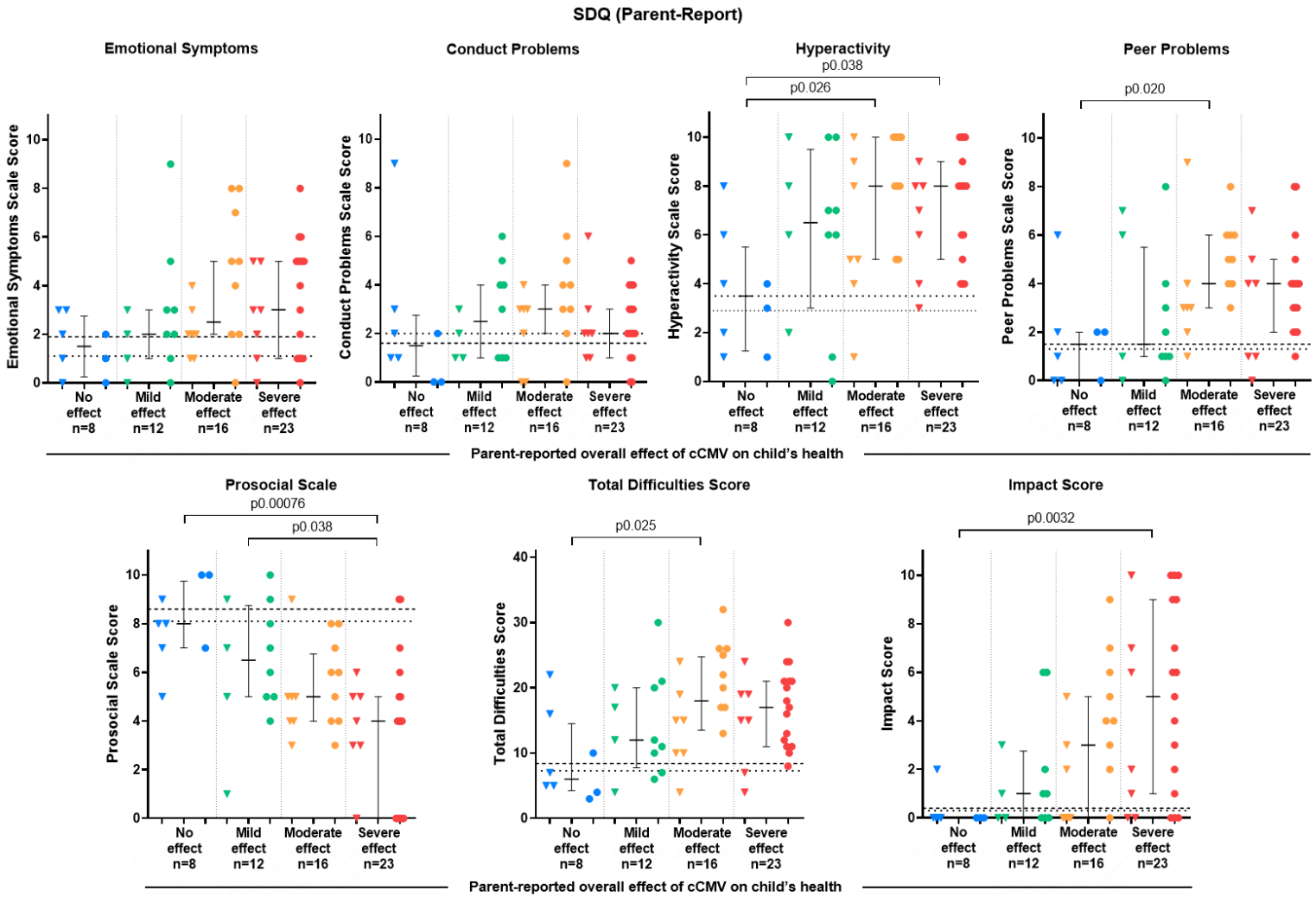

Figure 2: Comparison between children with congenital cytomegalovirus (cCMV) and the UK population in parent-report Strengths and Difficulties Questionnaire (SDQ), by subgroups based on parent-reported overall effect of cCMV on the child's health

In all domains except Prosocial Scale, higher scores indicate greater behavioural problems in that domain. Total Difficulties Score is the sum of the Emotional, Conduct, Hyperactivity, and Peer Problems scores. Higher Impact Score indicates greater impact of behavioural problems on the child and family. Higher Prosocial Scale score indicates greater prosocial behaviour. *Bars m*edians and interquartile ranges for all children in a subgroup, *triangles* individual data points for children aged 2-4, *circles* children aged 5-17, *dashed line* UK population norms for age 5-17 from SDQ website, *dotted line* UK population norms for age 2-4 from SDQ website.[21] Population norms are shown as means as there were no median or interquartile range data available. Kruskal-Wallis H test was run and pairwise comparisons were performed using Dunn's (1964) procedure with a Bonferroni correction for multiple comparisons. Lines with p values on graphs indicate statistically significant differences in pairwise comparisons. No line indicates no statistically significant difference in pairwise comparisons.

Children in the 'severe effect' subgroup had higher 'Hyperactivity' and 'Peer Problems' scores, and lower 'Prosocial Scale' scores, than children in the 'no effect' subgroup and population norms. 'Impact Scores' were significantly higher in 'severe effect' subgroup than 'no effect' subgroup.

HRQoL of parents of children with cCMV

PedsQL Family Impact Module

Median summary scores were lower (indicating more impact) in parents of children in the 'severe effect' subgroup than parents of children in the 'no effect' subgroup and UK population means (Figure 3).[21] Median scores for all domains were also lower in the 'severe effect' subgroup than the 'no effect' subgroup, particularly 'Communication', 'Worry', and 'Daily Activities' domains (Supplementary 6).

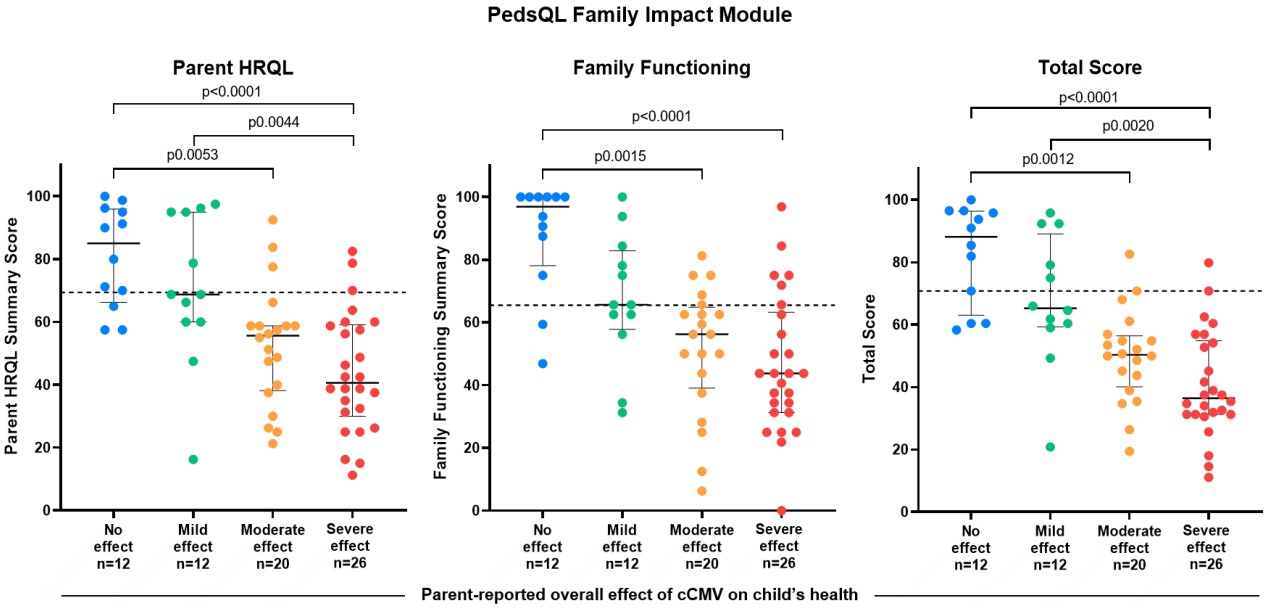

Figure 3: Comparison of parents of children with congenital CMV (cCMV) and the UK population in Pediatric Quality of Life Inventory (PedsQL) Family Impact Module Parent HRQL (Health-Related Quality of Life) Summary Score, Family Functioning Summary Score, and Total Score, by subgroups based on parent-reported overall effect of cCMV on the child's health

Higher scores indicate better HRQoL or less negative family or parental impact from the child's health. Parent HRQL is the mean of scores for items in Physical, Emotional, Social, and Cognitive Functioning domains. Family Functioning is the mean of scores for items in Daily Activities and Family Relationships domains. Total Score is the mean of all items in the PedsQL Family Impact Module. *Bars m*edians and interquartile ranges, *circles* individual data points, *dashed line* healthy UK population norms from Medrano 2013.[22] Population norms are shown as means as there were no median or interquartile range data available. Kruskal-Wallis H test was run and pairwise comparisons were performed using Dunn's (1964) procedure with a Bonferroni correction for multiple comparisons. Lines with p values on graphs indicate statistically significant differences in pairwise comparisons. No line indicates no statistically significant difference in pairwise comparisons.

Parent HRQL scores, Family Functioning scores, and Total Scores were significantly lower in parents of children in the 'severe effect' and 'moderate effect' subgroup than parents of children in the 'no effect' subgroup. Median Parent HRQL, Family Functioning, and Total Scores were lower in parents of severely affected children than population norms.

GHQ-12

In 'moderate effect' and 'severe effect' subgroups, 17/20 and 23/26 parents, respectively, met or exceeded the threshold indicative of probable psychological disorder (Supplementary 6).[15]

QALYs for children with cCMV

QALYs calculated using parent-reported CHU-9D were significantly lower (poorer) in children in the 'severe effect' subgroup than the 'no effect' subgroup (Table 2, p=0.0056); there was no significant difference in QALYs between subgroups in self-report (Supplementary 3). Inter-rater reliability between parent-report and self-report QALYs from CHU-9D was 0·804 (95% CI: 0·437-0·933), indicating good agreement in HRQoL reports between parent-proxy and child.

Similar to CHU-9D, QALYs calculated using parent-report EQ-5D-Y were significantly lower (poorer) for children in the 'severe effect' subgroup compared to 'no effect', 'mild effect', and 'moderate effect' subgroups.

Full data for parent-report CHU-9D and EQ-5D-Y domain scores is in Supplementary 7.

Table 2: Median and interquartile ranges (IQR) of quality-adjusted life-years (QALYs) for children with cCMV calculated using parent-report Child Health Utility-9 Dimensions (CHU-9D)[16] and EQ-5D-Y[17]

	No effect, n=3 **Median (IQR^)**	**Mild effect, n=8** **Median (IQR)**	**Moderate effect, n=9** **Median (IQR)**	**Severe effect, n=16** **Median (IQR)**
CHU-9D QALYs (Parent-Report)	0·952	0·797 (0·718-0·866)	0·712 (0·645-0·829)	0·628 (0·561-0·782)
	n=3	**n=9**	**n=13**	**n=16**
EQ-5D-Y QALYs (Parent-Report)	1·00 (1·00-1·00)	0·516 (0·119-0·924)	0·587 (0·041-0·710)	-0·166 (-0·290 - -0·088)

Parent-report responses for CHU-9D and EQ-5D-Y domains were used to calculate parent-report QALYs for children with cCMV. QALYs from EQ-5D-Y were also used to assess if there was a correlation between child and parent QALYs.
Kruskal-Wallis H test was conducted and pairwise comparisons were performed using Dunn's (1964) procedure with a Bonferroni correction for multiple comparisons.
IQR interquartile range, **^**No IQR due to small sample size.
For CHU-9D, children in the 'severe effect' subgroup had significantly lower QALYs than those in the 'no effect' subgroup. For EQ-5D-Y, children in the 'severe effect' subgroup had significantly lower QALYs than those in 'no effect', 'mild effect', and 'moderate effect' subgroups.

QALYs for parents of children with cCMV

QALYs calculated using EQ-5D-3L for parents of more severely affected children were lower (poorer) than that of less severely affected children and population means, although this difference was not statistically significant (Supplementary 6).

DISCUSSION

We found that children with cCMV had poorer HRQoL than healthy UK population norms in multiple domains, even when the effect of cCMV on their health was mild. Children whose health was more severely affected by cCMV had poorer HRQoL and lower QALYs than children whose health was less severely affected by cCMV. Children with cCMV had greater problems with hyperactivity and peer relations and poorer prosocial behaviour than UK population norms. Parents of children whose health was moderately or severely affected by cCMV had greater psychological morbidity and poorer HRQoL than parents of less severely affected children. Overall, our results show that cCMV has significant consequences for the HRQoL of children with cCMV and their parents.

Our results are consistent with those of Korndewal *et al.* (2017), who found that cCMV-positive children with long-term impairment had significantly lower PedsQL scores than cCMV-negative children with long-term impairment, although this trend was not seen in children without long-term impairment.[22] Children in the 'severe effect' subgroup had poorer HRQoL than previously found in studies using the PedsQL in children with cerebral palsy, children with cancer, child survivors of meningitis, and children with cochlear implants.[23–25] This is likely due to the range and severity of impairments related to cCMV.

The domain most affected by cCMV was Physical Functioning; emotional domains were least affected. This may be due to parent-report not accurately capturing subjective emotional functioning, as shown in previous studies.[26] However, it is more likely that emotional domains were less affected due to children with cCMV never experiencing a 'better' health state, so their emotional wellbeing was similar to healthy children, known as the disability paradox.[26] cCMV can be associated with ADHD and autism. A significant proportion of children in our sample had these conditions, which may explain the poorer scores in hyperactivity, peer relations and prosocial behavioural domains in our sample. This is similar to findings in extremely preterm survivors, a population with similar impairments to children with cCMV.[27]

cCMV was associated with poorer parent HRQoL, family functioning, and parent psychological wellbeing in 'severe effect' and 'moderate effect' subgroups. This contrasts with the findings of Korndewal *et al.* (2017), who found no significant difference in HRQoL between parents of children with cCMV and controls.[22] This discordance may be explained by differences in prevalence of long-term impairments (and therefore burden of care) in the samples, as all subgroups other than the 'no effect' subgroup in our study had much higher prevalence of long-term impairments than those in the Korndewal study.[3]

Our study is strengthened by the inclusion of multiple HRQoL measures, which explored multiple domains. The wide age range of children resulted in a sample more generalisable to children at different life stages. The collection of both parent-report and self-report data gave important insights from the parent and child perspective and we observed good agreement between parent- and self-report QALYs. Self-report data is considered the gold standard measure of paediatric HRQoL, but our small self-reporting sample reflects the reality that young children and children with cognitive impairment are often unable to self-report.[7,26]

The representativeness of the sample was limited by our sampling through CMV Action, which likely skewed the sample towards inclusion of more children with more severe impairments. Parents of severely affected children are more likely to engage with a patient charity than parents of children with no impairments from CMV. Therefore this may not be fully representative of all children with cCMV. However, by dividing the sample into subgroups, we attempted to mitigate this.

Another limitation was grouping the sample by parent-reported overall effect of cCMV on the child's health. Parents who report their child's health to be severely affected by cCMV are likely to also report poorer HRQoL. However, patients' perceptions of their own HRQoL often contradicts their objective health status.[26] Therefore a parent's assessment of the effect of cCMV on their child's health does not necessarily impact their perception of their child's HRQoL. Furthermore, parents are likely to more accurately assess the severity of the effect of cCMV on their child's health than an algorithm which assigns a score for each impairment, due to the variation in severity of each impairment. An algorithm would not capture this variation and could result in less meaningful subgroups.

It was not feasible to include a control group due to resource limitations, however published population norms were used for comparison. Thus, the effect on HRQoL could be attributable to other factors rather than cCMV. Future studies should include a control group, enrol participants at birth through population screening, and measure HRQoL at multiple time points to assess how HRQoL changes over time in children with cCMV.

We were unable to specifically determine the effect of hearing on HRQoL. To our knowledge, there are no widely used HRQoL instruments to measure this.

Whilst the sample size of parents was too small to give a robust measure of the 'spillover effects' of caring for a child with cCMV on parent HRQoL, the poorer PedsQL Family Impact Module scores and poorer QALYs in parents of children with cCMV indicate further research into 'spillover effects' of cCMV would be worthwhile.[28]

To our knowledge, this is the first study to assess HRQoL of children with cCMV in the UK. It contributes to the growing evidence base demonstrating the impact of cCMV from an individual and societal perspective. Disabilities related to cCMV have a significant negative impact on QALYs, which is likely to be lifelong. The QALY data could be used alongside existing economic data in health economic analyses of potential interventions for the prevention and treatment of cCMV, such as CMV vaccine candidates, hygiene-based interventions during pregnancy, and novel antiviral treatments.[4–6,29] Such evidence is necessary to build a compelling case for the implementation of interventions in the future.

Contributions

KR, CJ, and KB developed the idea and designed the study. CT and SW contributed to the design of the study. KR carried out data collection. KR and CJ verified the data. KR performed the data cleaning, data analyses, and data interpretation. KR drafted the first version of the manuscript and prepared the tables and figures. All authors (KR, KB, CT, SW, CJ) contributed to the interpretation of the findings; the revision of the manuscript, tables, and figures; and the approval of the final submitted version. All authors had full access to all the data in the study and accept responsibility for the decision to submit for publication.

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Ethical Approval

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Data Sharing Statement

Individual participant questionnaire data will be made available on appropriate request.

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Figure Legends

Figure 1: Comparison between children with congenital cytomegalovirus (cCMV) and the UK population in parent-reported Pediatric Quality of Life Inventory (PedsQL) Generic Core Scales Physical Functioning Score, Psychosocial Health Summary Score, Total Score, and individual domain scores (Emotional Functioning, Social Functioning, and School Functioning), by subgroups based on parent-reported overall effect of cCMV on the child's health

Higher scores indicate better HRQoL. Psychosocial Health Summary Score is the mean of Emotional, Social, and School Functioning scores. Physical Functioning score is the same as the Physical Health Summary Score, so is shown as Physical Functioning score here. Total Score is the mean of all items on the PedsQL Generic Core Scales. *Bars m*edians and interquartile ranges, *circles* individual data points, *dashed line* healthy UK population norms from Upton 2005.[13] Population norms are shown as means as there were no median or interquartile range data available. Kruskal-Wallis H test was run and pairwise comparisons were performed using Dunn's (1964) procedure with a Bonferroni correction for multiple comparisons. Lines with p values on graphs indicate statistically significant differences in pairwise comparisons. No line indicates no statistically significant difference in pairwise comparisons.

Children whose health was more severely affected by cCMV had significantly lower Physical Functioning Scores, Psychosocial Health Summary Scores, and Total Scores as well as Social Functioning and School Functioning scores, than less severely affected children. Children in 'severe effect', 'moderate effect', and 'mild effect' subgroups had lower median Physical Functioning scores, Psychosocial Health Summary Scores, and Total Scores, as well as Emotional Functioning, Social Functioning, and School Functioning scores, than healthy UK population means.

Figure 2: Comparison between children with congenital cytomegalovirus (cCMV) and the UK population in parent-report Strengths and Difficulties Questionnaire (SDQ), by subgroups based on parent-reported overall effect of cCMV on the child's health

In all domains except Prosocial Scale, higher scores indicate greater behavioural problems in that domain. Total Difficulties Score is the sum of the Emotional, Conduct, Hyperactivity, and Peer Problems scores. Higher Impact Score indicates greater impact of behavioural problems on the child and family. Higher Prosocial Scale score indicates greater prosocial behaviour. *Bars m*edians and interquartile ranges for all children in a subgroup, *triangles* individual data points for children aged 2-4, *circles* children aged 5-17, *dashed line* UK population norms for age 5-17 from SDQ website, *dotted line* UK population norms for age 2-4 from SDQ website.[21] Population norms are shown as means as there were no median or interquartile range data available. Kruskal-Wallis H test was run and pairwise comparisons were performed using Dunn's (1964) procedure with a Bonferroni correction for multiple comparisons. Lines with p values on graphs indicate statistically significant differences in pairwise comparisons. No line indicates no statistically significant difference in pairwise comparisons.

Children in the 'severe effect' subgroup had higher 'Hyperactivity' and 'Peer Problems' scores, and lower 'Prosocial Scale' scores, than children in the 'no effect' subgroup and population norms. 'Impact Scores' were significantly higher in 'severe effect' subgroup than 'no effect' subgroup.

Figure 3: Comparison of parents of children with congenital CMV (cCMV) and the UK population in Pediatric Quality of Life Inventory (PedsQL) Family Impact Module Parent HRQL (Health-Related Quality of Life) Summary Score, Family Functioning Summary Score, and Total Score, by subgroups based on parent-reported overall effect of cCMV on the child's health

Higher scores indicate better HRQoL or less negative family or parental impact from the child's health. Parent HRQL is the mean of scores for items in Physical, Emotional, Social, and Cognitive Functioning domains. Family Functioning is the mean of scores for items in Daily Activities and Family Relationships domains. Total Score is the mean of all items in the PedsQL Family Impact Module. *Bars m*edians and interquartile ranges, *circles* individual data points, *dashed line* healthy UK population norms from Medrano 2013.[22] Population norms are shown as means as there were no median or interquartile range data available. Kruskal-Wallis H test was run and pairwise comparisons were performed using Dunn's (1964) procedure with a Bonferroni correction for multiple comparisons. Lines with p values on graphs indicate statistically significant differences in pairwise comparisons. No line indicates no statistically significant difference in pairwise comparisons.

Parent HRQL scores, Family Functioning scores, and Total Scores were significantly lower in parents of children in the 'severe effect' and 'moderate effect' subgroup than parents of children in the 'no effect' subgroup. Median Parent HRQL, Family Functioning, and Total Scores were lower in parents of severely affected children than population norms.