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Malnutrition and Associated Factors in Children With Cerebral Palsy: A Cross-Sectional Study

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Abstract

Introduction

Children with cerebral palsy are vulnerable to malnutrition because of interacting motor, feeding, and gastrointestinal difficulties. This study assessed the prevalence of malnutrition and associated clinical and dietary factors in children attending a tertiary pediatric center.

Methods

This hospital-based cross-sectional study enrolled 100 children aged 1-16 years from 160 screened at a tertiary center in New Delhi, India, between January 2023 and March 2024, using convenience sampling. Malnutrition was defined as a recorded deficit below -2 standard deviations (SD) on at least one age-appropriate anthropometric index. Bivariate comparisons used Pearson chi-square or exact tests. Adjusted associations were estimated using Firth penalized binary logistic regression.

Results

Seventy-six children (76.0%, 95% confidence interval {CI}: 66.8%-83.3%) met the composite definition. Stunting and low body mass index (BMI)-for-age were recorded in 63 (63.0%) and 34 (34.0%) children, respectively. Among 78 children eligible for weight-for-age assessment, 54 (69.2%) were underweight. In the focused adjusted model, malnutrition was associated with Gross Motor Function Classification System (GMFCS) levels III-V (adjusted odds ratio {aOR}, 4.93; 95% CI, 1.38-20.41), oropharyngeal dysfunction (aOR, 6.30; 95% CI, 1.79-26.40), and inadequate energy intake (aOR, 7.68; 95% CI, 2.30-31.81). The associations with motor impairment and inadequate energy intake persisted in the expanded model.

Conclusions

Anthropometric deficits were frequent among eligible children attending this tertiary outpatient service. Greater motor impairment and inadequate energy intake showed the most consistent adjusted associations. These findings support assessing growth, feeding function, and dietary intake together in children with cerebral palsy.

Categories: Neurology, Nutrition, Pediatrics
Keywords: cerebral palsy, childhood malnutrition, dietary adequacy, feeding dysfunction, gastrointestinal symptoms, gross motor function

Introduction

Cerebral palsy is a group of permanent disorders of movement and posture caused by nonprogressive disturbances in the developing fetal or infant brain [1]. Feeding difficulties, gastrointestinal symptoms, impaired mobility, and altered body composition can complicate nutritional care. Contractures and difficulties obtaining reliable anthropometric measurements may further hinder the recognition of poor growth [2,3].

The nutritional burden varies across populations and assessment methods. The Global Low- and Middle-Income Country Cerebral Palsy Register identified at least one form of undernutrition in 2,432 (86.1%) of 2,826 children in Bangladesh and 126 (97.7%) of 129 children in Indonesia [4]. In India, Goyal et al. reported severe malnutrition in 18 (36.0%) of 50 children aged six months to five years, including severe wasting in 12 (24.0%) and severe stunting in 12 (24.0%) [5]. Differences in age, motor severity, referral patterns, and nutritional definitions must be considered when comparing these estimates [2,4,5].

Feeding dysfunction can restrict the amount and variety of food consumed, while constipation and reflux symptoms may complicate mealtimes and nutritional management [3,6,7]. Greater motor impairment can increase dependence on caregivers for positioning and feeding. Nutritional assessment therefore requires

the consideration of feeding ability, gastrointestinal symptoms, dietary intake, and functional status together [3,6,7].

This study estimated the prevalence of malnutrition and examined its associations with sociodemographic, motor, feeding, gastrointestinal, and dietary characteristics among children with cerebral palsy attending a tertiary pediatric center in New Delhi.

Materials And Methods

Study design, setting, and participants

This hospital-based cross-sectional study was conducted at the Institute of Child Health, Sir Ganga Ram Hospital, New Delhi, India, from January 2023 to March 2024, following institutional ethics approval. Children aged 1-16 years with a clinical diagnosis of cerebral palsy attending the pediatric outpatient department were enrolled by convenience sampling. Exclusion criteria were progressive neurological disorders; congenital anomalies or musculoskeletal conditions, including congenital hip dislocation and myopathy; concurrent chronic systemic illnesses, including cardiac or renal disease; and severe contractures that prevented reliable anthropometry.

The planned sample size was 160, calculated as $n = (10 \times k)/p$, where k represented eight candidate factors and p was an anticipated malnutrition prevalence of 0.50 based on clinical experience.

Of 160 children screened, 60 were excluded: 18 with progressive neurological impairment; 24 with congenital anomalies, musculoskeletal disorders, or concurrent chronic systemic illness; and 18 with severe contractures precluding reliable anthropometry. The remaining 100 children were enrolled, assessed, and included in the analysis. Figure *1* summarizes participant flow.

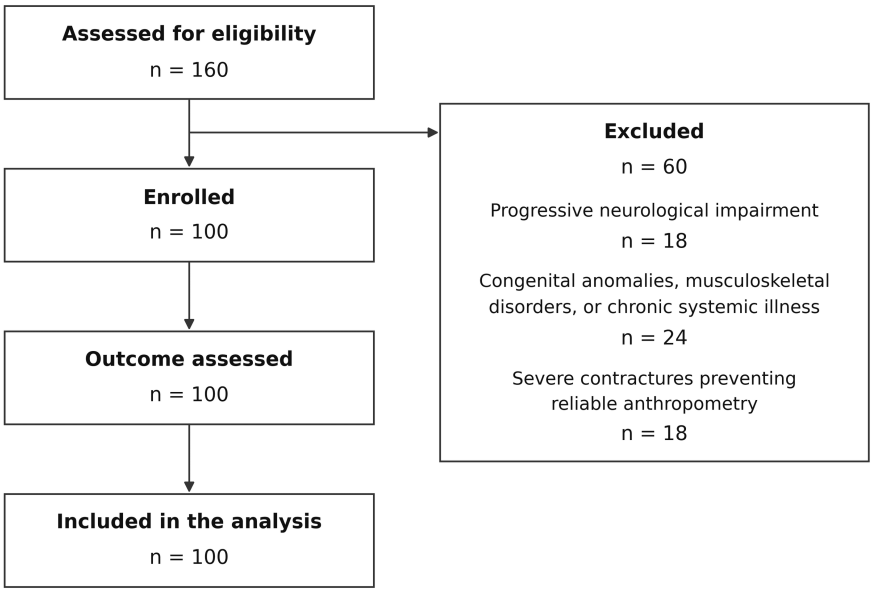


FIGURE 1: Flowchart depicting screening, enrollment, assessment, and analysis of study participants.

n: number of children

Clinical and dietary assessment

Clinical and oral-motor assessments and anthropometric measurements were performed by the principal investigator. Dietary interviews and intake calculations were completed in consultation with a dietitian. Multidisciplinary supervision was provided by specialists in pediatric gastroenterology and nutrition, developmental and behavioral pediatrics, pediatric neurology, and dietetics.

Caregivers were interviewed using a semistructured case proforma. Sociodemographic characteristics, medical history, and antiepileptic treatment were recorded. Socioeconomic status was classified using the modified Kuppuswamy scale, which incorporates the education and occupation of the head of the family and

monthly family income [8]. Gross motor function was classified into Gross Motor Function Classification System (GMFCS) levels I-V [9]. Cerebral palsy subtype was recorded clinically as spastic diplegia, spastic quadriplegia, hemiplegia, dystonic, or mixed.

Oropharyngeal dysfunction was assessed using the Schedule for Oral-Motor Assessment (SOMA), which evaluates oral-motor performance across food categories using category-specific scoring criteria [10]. Dysfunction was classified as present when the criterion for abnormal oral-motor function was met in at least one assessed food category and as absent when findings were normal across all assessed categories. Feeding route was recorded as oral or gastrostomy. The gastrostomy-fed children were included in the dysfunction group for the binary analysis. To assess the influence of this classification, the focused adjusted model was repeated among orally fed children.

Constipation was assessed using at least two of six adult Rome IV symptom components. The first five were straining, hard or lumpy stools, incomplete evacuation, anorectal blockage, and manual maneuvers, each occurring during more than one-quarter of defecations. The sixth was fewer than three spontaneous bowel movements per week [11]. These adult Rome IV components formed the study's operational definition of constipation symptoms. Caregivers provided the bowel history, including for younger children and children who could not report their symptoms. Observable features such as stool frequency and consistency could be described by caregivers, while subjective sensations such as incomplete evacuation were more difficult to assess. Clinically suspected reflux was assessed from recurrent vomiting and dental findings, including discoloration and frequent caries despite oral hygiene. This classification reflected clinical suspicion rather than confirmed gastroesophageal reflux disease [12].

Dietary intake was assessed by caregiver-reported 24-hour recall, including oral and tube feeds. Household measures were converted to raw-food equivalents, and daily energy and protein intake were estimated using the Indian Food Composition Tables [13]. Energy and protein intake were compared separately to age-specific recommendations from the National Institute of Nutrition, Indian Council of Medical Research [14]. Intake below the corresponding recommended daily amount was classified as inadequate, whereas intake meeting or exceeding that amount was classified as adequate.

Anthropometry and nutritional outcomes

Weight was measured using an electronic scale (Phoenix PAS-150, Nitiraj Engineers Limited, Dhule, India), with caregiver-assisted tare weighing for children unable to stand. Standing height was measured using a stadiometer (Phoenix PSM-101, Nitiraj Engineers Limited, Dhule, India) when feasible; otherwise, height was estimated from knee height using the equation height (cm) = 2.69 × knee height (cm) + 24.2 [15]. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared.

The WHO Child Growth Standards and the WHO growth reference for school-aged children and adolescents guided age- and sex-specific classification [16,17]. The analysis used recorded height-for-age and BMI-for-age categories for all children and weight-for-age categories for the 78 children younger than 10 years. The WHO weight-for-age reference ends at age 10 because, beyond this age, the index cannot distinguish body mass from stature during pubertal growth [17]. BMI-for-age provided a measure of weight relative to stature across the study age range. Weight-for-length/height was outside the composite, and a separate wasting estimate was omitted because of inconsistencies between some category codes and the underlying measurements.

The composite summarized the presence of any anthropometric deficit. A child met the definition if any eligible index was classified below -2 standard deviations (SD). The most severe eligible component determined the composite category. Moderate deficit corresponded to $-3\ \text{SD} \leqslant z < -2\ \text{SD}$, and severe deficit to $z < -3$ SD. Children with all eligible indices at or above -2 SD were classified as having no deficit. Stunting, underweight, and low BMI-for-age were reported separately to distinguish the component findings.

Statistical analysis

IBM SPSS Statistics version 28.0 (IBM Corp., Armonk, NY) was used for statistical analysis. Categorical variables were summarized as counts and percentages, with explicit denominators for age-restricted assessments. Bivariate association analyses included all 100 children; weight-for-age assessment included 78 age-eligible children. A Wilson 95% confidence interval (CI) was calculated for malnutrition prevalence. Pearson chi-square tests without continuity correction were used when no expected cell count was below one and no more than 20% were below five; otherwise, the two-sided Fisher-Freeman-Halton exact test was used. Pearson test statistics were reported where applicable. Effect sizes were expressed as Cramér's V, calculated from the Pearson statistic, including for exact-test tables; for two-by-two tables, this equals the absolute phi coefficient. Prevalence odds ratios (ORs) with log-Wald 95% CIs were calculated for each binary exposure without covariate adjustment. All tests were two-sided, with significance set at $p < 0.05$ before rounding. No adjustment for multiple comparisons was applied; associations were considered exploratory.

Adjacent upper and upper-middle socioeconomic categories were pooled. Hemiplegia, dystonic cerebral palsy, and mixed cerebral palsy were pooled as other subtypes for analysis, with their constituent diagnoses

reported. Firth penalized binary logistic regression was used to address sparse categories and separation [18]. The focused model included age in years, GMFCS level (III-V versus I-II), oropharyngeal dysfunction, constipation, clinically suspected reflux, and inadequate energy intake. Covariates were selected for clinical relevance during revision. An expanded exploratory model added socioeconomic status and cerebral palsy subtype. The focused model was repeated among orally fed children. Adjusted odds ratios were reported with profile penalized likelihood 95% confidence intervals and penalized likelihood ratio p-values.

A separate classification check applied WHO reference parameters to recorded age, sex, weight, and stature. Age in years was converted to months, with interpolation between monthly reference values. For children younger than 24 months, 0.7 cm was added to stature to approximate recumbent length. Extreme values were retained for this diagnostic comparison. The focused model was repeated using the recalculated composite.

Ethical approval and consent

The study received approval from the Institutional Ethics Committee of Sir Ganga Ram Hospital, New Delhi (approval letter dated December 13, 2022; reference: SGRH/Acad/DNB/1063/JAN-22). Written informed consent was obtained from a parent or guardian before enrollment.

Results

Participant characteristics and nutritional status

The analysis included 100 children: 47 (47.0%) were younger than five years, 31 (31.0%) were aged 5-10 years, and 22 (22.0%) were older than 10 years. Seventy-seven (77.0%) were male. Spastic quadriplegia, present in 49 (49.0%) children, and spastic diplegia, present in 37 (37.0%), were the most frequent subtypes. Sixty-one (61.0%) children were classified as GMFCS levels III-V. Ninety-one (91.0%) were fed orally and nine (9.0%) through a gastrostomy.

Seventy-six children (76.0%, 95% CI: 66.8%-83.3%) met the recorded composite definition. Fifty-seven (57.0%) had a severe deficit, 19 (19.0%) had a moderate deficit, and 24 (24.0%) had no deficit on any eligible index. Stunting and low BMI-for-age were recorded in 63 (63.0%) and 34 (34.0%) children, respectively. Among 78 children eligible for weight-for-age assessment, 54 (69.2%) were underweight. Figure *2* shows the distribution of moderate and severe deficits by index.

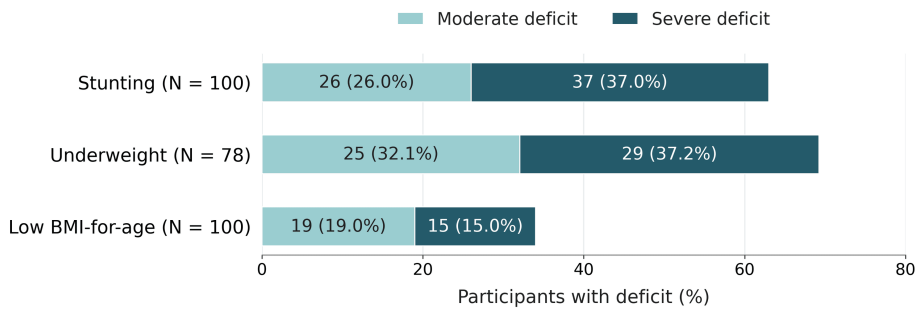


FIGURE 2: Distribution of moderate and severe anthropometric deficits.

Labels show n (%), with percentages calculated using the denominator indicated for each outcome. Moderate deficit, -3 ≤ z < -2; severe deficit, z < -3. Weight-for-age analysis was restricted to children younger than 10 years. A child could have more than one anthropometric deficit. The figure was created using Matplotlib version 3.10.8 in Python (Python Software Foundation, Fredericksburg, VA).

BMI, body mass index; N, number assessed

Sociodemographic and motor associations

In bivariate comparisons, malnutrition differed across GMFCS levels (p = 0.002). It was present in six (40.0%) children at level I, 16 (66.7%) at level II, 24 (85.7%) at level III, 11 (91.7%) at level IV, and 19 (90.5%) at level V. Malnutrition also differed across the regrouped cerebral palsy subtypes (p = 0.010) and socioeconomic categories (exact p < 0.001). The socioeconomic distribution showed no consistent gradient. Age group, sex, and antiepileptic treatment were not significantly associated with malnutrition (Table *1*).

Factor and category	N	Malnutrition n (%)	Test statistic	Cramér's V	P-value
Age group					
<5 years	47	33 (70.2)			
5-10 years	31	25 (80.6)	1.638	0.128	0.441
>10 years	22	18 (81.8)			
Sex					
Male	77	55 (71.4)	3.836	0.196	0.050
Female	23	21 (91.3)			
Socioeconomic status					
Upper/upper middle	42	36 (85.7)	NA	0.410	<0.001
Lower middle	29	17 (58.6)			
Upper lower	17	17 (100.0)			
Lower	12	6 (50.0)			
GMFCS level					
I	15	6 (40.0)	17.280	0.416	0.002
II	24	16 (66.7)			
III	28	24 (85.7)			
IV	12	11 (91.7)			
V	21	19 (90.5)			
Cerebral palsy subtype					
Spastic diplegia	37	22 (59.5)	9.313	0.305	0.010
Spastic quadriplegia	49	43 (87.8)			
Other subtypes	14	11 (78.6)			
Antiepileptic therapy					
None	26	20 (76.9)	4.857	0.220	0.088
Monotherapy	29	18 (62.1)			
Polytherapy	45	38 (84.4)			

TABLE 1: Sociodemographic and motor factors associated with malnutrition.

Percentages are within categories. Each factor includes 100 children, of whom 76 had malnutrition. Statistics and p-values apply to the entire factor. Pearson chi-square tests were used except for socioeconomic status, which used the two-sided Fisher-Freeman-Halton exact test. NA indicates that a separate test statistic is not reported for the exact test. Cramér's V was calculated from the Pearson statistic. Upper/upper middle combines the upper (n = 2) and upper-middle (n = 40) categories. Other subtypes comprise hemiplegia (n = 8), dystonic cerebral palsy (n = 4), and mixed cerebral palsy (n = 2).

N, category total; n, children with malnutrition; GMFCS, Gross Motor Function Classification System

Feeding, gastrointestinal, and dietary associations

Oropharyngeal dysfunction was recorded in 68 (68.0%) children, constipation in 62 (62.0%), and clinically suspected reflux in 41 (41.0%). Energy intake was inadequate in 55 (55.0%) children and protein intake in 40 (40.0%). Malnutrition affected 61 (89.7%) children with oropharyngeal dysfunction and 15 (46.9%) without it. Constipation, clinically suspected reflux, and inadequate energy intake were also associated with malnutrition. Protein inadequacy was not significantly associated with malnutrition (p = 0.085). Table *2* presents the group comparisons and effect sizes.

Factor	Category	N	Malnutrition, n (%)	Test statistic (df)	Cramér's V	P-value
Oropharyngeal dysfunction	Present	68	61 (89.7)	21.885 (1)	0.468	<0.001
	Absent	32	15 (46.9)			
Constipation	Present	62	55 (88.7)	14.449 (1)	0.380	<0.001
	Absent	38	21 (55.3)			
Clinically suspected reflux	Present	41	38 (92.7)	10.604 (1)	0.326	0.001
	Absent	59	38 (64.4)			
Energy intake	Inadequate	55	49 (89.1)	11.483 (1)	0.339	<0.001
	Adequate	45	27 (60.0)			
Protein intake	Inadequate	40	34 (85.0)	2.961 (1)	0.172	0.085
	Adequate	60	42 (70.0)			

TABLE 2: Feeding, gastrointestinal, and dietary factors associated with malnutrition.

Percentages are calculated within each category. All comparisons used Pearson chi-square tests. Cramér's V quantifies association strength and equals the absolute phi coefficient for these two-by-two comparisons. Each statistic, effect size, and p-value apply to the entire factor.

N, category total; n, children with malnutrition; df, degrees of freedom

Figure 3 presents crude prevalence odds ratios and 95% confidence intervals from separate bivariate comparisons of feeding, gastrointestinal, and dietary factors with malnutrition.

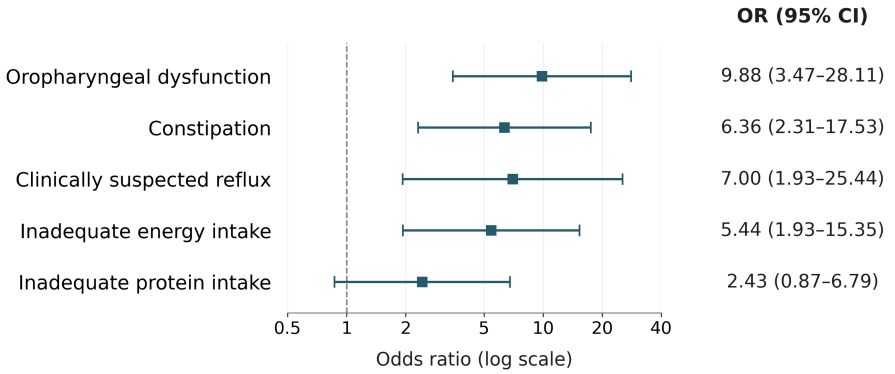


FIGURE 3: Crude prevalence odds ratios for feeding, gastrointestinal, and dietary factors associated with malnutrition.

Squares represent crude prevalence ORs from separate exposure-outcome comparisons; horizontal lines show log-Wald 95% CIs. The dashed line marks OR = 1. Oropharyngeal dysfunction, constipation, and clinically suspected reflux compare presence with absence; energy and protein comparisons use inadequate versus adequate intake. Estimates are plotted on a logarithmic scale.

OR, odds ratio; CI, confidence interval

Adjusted associations

In the focused model, GMFCS levels III-V, oropharyngeal dysfunction, and inadequate energy intake were associated with higher odds of malnutrition. The adjusted confidence intervals for constipation and clinically suspected reflux included 1. In the expanded model, the associations with GMFCS levels III-V and inadequate energy intake persisted, while the estimate for oropharyngeal dysfunction attenuated, and its confidence interval included 1 (Table 3). The overall p-values for socioeconomic status and cerebral palsy subtype in the expanded model were 0.030 and 0.780, respectively.

Variable	Focused model aOR (95% CI)	P-value	Expanded model aOR (95% CI)	P-value
Age, per year	1.09 (0.95-1.28)	0.235	1.12 (0.94-1.36)	0.224
GMFCS III-V versus I-II	4.93 (1.38-20.41)	0.014	6.31 (1.46-39.29)	0.013
Oropharyngeal dysfunction	6.30 (1.79-26.40)	0.004	3.08 (0.59-17.89)	0.180
Constipation	1.99 (0.58-7.03)	0.272	1.30 (0.27-5.94)	0.735
Clinically suspected reflux	1.32 (0.25-7.53)	0.740	0.89 (0.09-6.29)	0.909
Inadequate energy intake	7.68 (2.30-31.81)	<0.001	8.22 (2.21-41.81)	0.001
Lower-middle socioeconomic status	-	-	0.18 (0.03-0.87)	0.032
Upper-lower socioeconomic status	-	-	3.51 (0.25-532.27)	0.390
Lower socioeconomic status	-	-	0.19 (0.02-1.35)	0.098
Spastic quadriplegia	-	-	1.52 (0.20-10.69)	0.670
Other cerebral palsy subtypes	-	-	0.62 (0.06-6.07)	0.674

TABLE 3: Adjusted associations with the composite malnutrition outcome.

Both models included 100 children, of whom 76 met the composite definition. Estimates are from Firth penalized binary logistic regression. Reference categories were GMFCS I-II, the absence of the listed clinical feature, adequate energy intake, upper/upper-middle socioeconomic status, and spastic diplegia, as applicable. Dashes denote variables outside the focused model.

aOR, adjusted odds ratio; CI, confidence interval; GMFCS, Gross Motor Function Classification System

Among orally fed children (n = 91), the focused model showed a similar pattern, including an association with oropharyngeal dysfunction (aOR, 5.10; 95% CI, 1.40-21.81). The measurement-based check classified 70 children with a deficit and agreed with the recorded composite in 90 of 100 children. In the corresponding focused model, GMFCS levels III-V (aOR, 3.58; 95% CI, 1.17-11.90), oropharyngeal dysfunction (aOR, 7.08; 95% CI, 2.20-26.47), and inadequate energy intake (aOR, 4.29; 95% CI, 1.56-13.10) remained associated with the composite.

Discussion

Three-quarters of the children met the recorded composite definition of malnutrition. Greater motor impairment and inadequate energy intake showed the most consistent associations across the focused and expanded models. Oropharyngeal dysfunction was associated with malnutrition in the focused model and among orally fed children, with a less precise estimate after socioeconomic status and cerebral palsy subtype were included. The bivariate associations with constipation and clinically suspected reflux weakened after adjustment.

The high prevalence is consistent with the nutritional burden reported across the Global LMIC CP Register, although referral patterns, age distributions, and anthropometric definitions differ between settings [4]. Severe malnutrition affected 57 (57.0%) children in the present study, compared with 18 (36.0%) of 50 children in the Indian study by Goyal et al. [5]. Their cohort was limited to children aged six months to five years and classified severe malnutrition using height-for-age and weight-for-height; the present composite included height-for-age, BMI-for-age, and age-eligible weight-for-age. These estimates therefore describe different populations and outcome definitions. The prominence of stunting also supports the assessment of linear growth, alongside current weight and body composition [2,3].

In a larger Indian cohort, greater gross motor impairment and lower socioeconomic status were associated with more severe stunting and underweight [19]. Motor impairment can affect positioning, self-feeding, and the assistance needed at mealtimes. A Swedish population-based study linked poorer eating and drinking ability with lower height-for-age after accounting for gross motor function and cerebral palsy subtype [20]. A Spanish multicenter study found that dysphagia, constipation, and reflux were more frequent among children with greater motor impairment [21]. This overlap helps explain why estimates for individual feeding and gastrointestinal characteristics changed after adjustment.

Malnutrition prevalence varied across socioeconomic categories without a consistent gradient. The wide confidence intervals for several categories, particularly the upper-lower group, reflect the small numbers within strata. Differences in motor severity, feeding dependence, and referral patterns may have contributed

to the distribution. Energy inadequacy describes intake on the recalled day and should be interpreted in that context.

Strengths and limitations

The study used structured assessments, explicit denominators, and separate reporting of anthropometric components. Single-center convenience sampling and enrollment below the planned sample size restrict generalizability and precision. Excluding children with severe contractures may have lowered the prevalence estimate if nutritional deficits were more frequent among children with substantial physical impairment. By narrowing the range of motor impairment represented, this exclusion may also have altered the motor function association, although the direction is uncertain. The findings primarily apply to eligible children attending this tertiary outpatient service.

The cross-sectional design precluded establishing temporal sequence, and residual confounding remains possible after adjustment. A single dietary recall and sparse categories limit the precision and interpretation of the estimates. Estimated stature and differences in body composition can affect height-derived indices [22]. The approximate measurement-based check identified differences from some recorded classifications, so prevalence is interpreted in relation to the recorded categories. The adult Rome IV symptom components and caregiver reporting may have affected constipation classification, particularly for subjective symptoms in younger and nonverbal children.

Conclusions

Anthropometric deficits were frequent among eligible children with cerebral palsy attending this tertiary outpatient service. Greater motor impairment and inadequate energy intake showed the most consistent adjusted associations. Growth surveillance should be accompanied by the assessment of feeding function and dietary intake. Prospective studies can clarify how these factors relate to growth over time.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Apoorva Upadhyay, Nishant Wadhwa, Praveen Suman, Praveen Kumar, Radhika Kedia

Acquisition, analysis, or interpretation of data: Apoorva Upadhyay, Nishant Wadhwa, Praveen Suman, Praveen Kumar, Archit Khardenavis, Radhika Kedia

Drafting of the manuscript: Apoorva Upadhyay, Nishant Wadhwa, Praveen Suman, Praveen Kumar, Archit Khardenavis, Radhika Kedia

Critical review of the manuscript for important intellectual content: Apoorva Upadhyay, Nishant Wadhwa, Praveen Suman, Praveen Kumar, Archit Khardenavis, Radhika Kedia

Supervision: Archit Khardenavis

Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. The Institutional Ethics Committee of Sir Ganga Ram Hospital issued approval SGRH/Acad/DNB/1063/JAN-22. The study was approved by the Institutional Ethics Committee of Sir Ganga Ram Hospital, New Delhi, at its meeting on September 21, 2022, as documented in the approval letter dated December 13, 2022 (reference: SGRH/Acad/DNB/1063/JAN-22). Written informed consent was obtained from a parent or guardian before enrollment. **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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