Original Article

Journal of Child Neurology
Volume 23 Number 5
May 2008 536-542
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10.1177/0883073807309795
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Predictive Factors of Early Mortality in Children With Developmental Disabilities: A Case-Comparison Analysis

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The aim of this study was to identify the risk factors for early mortality in children with neurodevelopmental disabilities. Of 1000 children who were sequentially referred to the same child developmental center over the period 1975–1985, 81 children died between the ages of 6 months and 22 years (mean, 8.04 years; 6.1 SD). A group of 81 age-matched children and another group of 81 developmentally and age-matched children also referred to the center served as comparison groups. Following multivariate analysis, low developmental quotient, restricted mobility, assisted feeding, and genetic etiology were risk factors for early mortality when compared to the age-matched group ($P < .01$). In comparison to the developmentally matched group, restricted mobility, genetic etiology, and hearing deficit were identified as significant risk factors ($P < .01$). Comprehensive treatment at the child development center was demonstrated to be a significant protective factor ($P = .004$). Socioeconomic variables were not significant in predicting an increased mortality risk in disabled individuals. In conclusion, in addition to mobility and feeding skills, a genetic etiology and hearing deficit are risk factors for early mortality, whereas socioeconomic variables are not. A comprehensive treatment program was found to be a protective factor.

Keywords: mortality; developmental disabilities

The importance of the study of life expectancy in people with mental and physical disabilities has been previously acknowledged and reported.[1,2] The results of these studies point to specific risk factors associated with short life expectancy.[2–5] For these risk factors to be generalized to different societies, studies in other countries should be performed. Culture-dependent attitudes, ethnic groups, availability of health services, and the rate of home versus institutional care may all affect longevity. In the present study, a cohort of children who were enrolled in a comprehensive child development and rehabilitative program was studied. A comprehensive list of explanatory variables has been analyzed. Earlier studies have identified ambulation, feeding ability, and cognitive level as the most important predictive variables of life expectancy in the disabled,[6] whereas other variables such as sensory deficits and social status have only recently been investigated.[7,8]

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Cohen A, Asor E, Tirosh E. Predictive factors of early mortality in children with developmental disabilities: a case-comparison analysis. *J Child Neurol*. 2008;23:536-542.

The purpose of the present study was to identify risk factors for early mortality in children with developmental disabilities who were referred to a regional child development center. We hypothesized that the sociodemographic and the child's sensory variables would contribute to the mortality risk in developmentally disabled children in addition to the risk factors confirmed in previous studies.

Methods

Subjects

The children (n = 1000) included in the cohort were admitted sequentially to the child development center between 1975 and 1985, and their expected age range at the time of final outcome was 17–30 years. Our community consists of 85% Jews and 15% Arabs.

Setup

At the time of the study, the child development center is 1 of 2 multidisciplinary ambulatory referral centers located at a general medical center. The child development center admits children between birth and 6 years of age who suffer from a variety of developmental deficits and are referred mainly by the well baby clinics in the greater Haifa area. No referral bias to the 2 centers was expected because the well baby clinics

catering for their districts were evenly divided. The screening procedure has been reported previously and is applied systematically across the district.[9] Diagnostic assessments and treatments are tailored and provided for each child. The data were systematically documented in a standardized record. The developmental assessments consist of commonly used developmental evaluations as appropriate.[10–14] Laboratory tests and special investigations were performed when deemed necessary. The duration of the program is up to the age of 6 years when the children are absorbed into appropriate educational and therapeutic programs in the community.

Procedure

The standardized records of the children who were admitted to the center were reviewed. Data pertaining to the following domains throughout their follow-up were retrieved from the charts of the 3 study groups: demographics including identify number, date of birth, gender, address, and type of residence. Family variables included parent's occupation, number of children, medical history of all family members, and psychosocial status as determined by interview and psychosocial evaluation by a social worker and a psychologist.

Developmental evaluations, medical status, eating skills, and degree of mobility were assessed and documented routinely in the charts, as part of the ongoing program. Two researchers scrutinized approximately 135 records to establish data reliability. Forty-eight (4.8%) of the records (all of individuals who were alive at the time of data collection 2004–2005) were not complete and, therefore, excluded. The Israeli Health registry did not reliably identify a further 0.5%. Therefore, 947 individuals remained in the cohort. Each death (n = 81) was confirmed with the registry of 1 of 4 funds providing health insurance to the Israeli population. Each child who did not survive until the study date was age-matched with 2 comparison children: (1) (n = 81) an age-matched child with birth dates separated up to 3 months, who was admitted following the child of the study group. No other inclusion or exclusion criteria were used, therefore, this group was expected to represent the surviving referred group; and (2) (n = 81), a developmentally matched child born in the same year and identified immediately after the child of the study group, with a developmental quotient within the category of the deceased child, that is, normal (developmental quotient >90), borderline (developmental quotient 75–89), mild (developmental quotient 50–74), moderate (developmental quotient 30–49), severe and profound intellectual disability (developmental quotient <20–29). For developmental quotient assignment, both verbal comprehension and social function were used; for cerebral palsy, only verbal comprehension was used. The data from the study and comparison groups only were computerized and used for the analysis.

The following child variables were abstracted: gender, birth order, pregnancy problems (hemorrhage, toxemia, infections, uncontrolled diabetes), mode of delivery (spontaneous, instrumental, cesarean section), prematurity (≤ 36 weeks), prenatal distress (Apgar ≤ 5 at 5 minutes), birth weight, neonatal problems (respiratory, gastrointestinal, neurological, infectious), hospitalization rate (the number related to each system, for example, respiratory, neurological adjusted for 12 months and converted to a binary level of ≥ 0), mobility (independent, assisted, no mobility), and feeding (independent, assisted, tube/gastrostomy). Neurodevelopmental diagnosis including cerebral palsy (all types combined), autism/pervasive developmental disorder, mental retardation, genetic disorder or defined syndromes (chromosomal or nonchromosomal), neurodegenerative, sensory impairment including hearing (abnormal > 40 decibels in both ears), vision (abnormal 2/6 or worse in both eyes), and epilepsy. Treatment at the child development center was defined as adherence to the intervention schedule without early interruption not accounted for by residential placement or death until the age of 6 years. The study was approved by the ethical committee of the Bnai Zion Medical Center.

Statistical Analysis

The χ^2 and a 2-tailed t test were used for the univariate analyses. Cox proportional hazard-regression analysis[15] with diagnosis, etiology, feeding, mobility, developmental quotient, gender, economic status, treatment, and residential care were included as independent variables. Age at death was the dependent variable. Early mortality was defined as death at any age until the time of data collection. Hazard ratios and their 95% confidence intervals were estimated for each predictive risk variable using the 2 comparison groups as a reference. To control for an age effect on the different risk variables such as independent feeding and mobility, the analysis was done separately for ages younger and older than 24 months. The estimated 10-year survival probabilities for different risk factors were obtained either using the age or the developmentally matched comparisons. The widely used Kaplan–Meier model was used to examine whether survival rates were improved in the past 20 years and the method of logistic regression as suggested by Strauss et al[16,17] was also applied.

Results

Of 947 children, 81 (8.5%) died between the age of 6 months and 22 years. The mean age of death was 8.04 years (6.1 SD). There was a gender difference when related to the age of death (7.9 years [6.1 SD] and 8.16 years [5.12 SD] males and females, respectively). The proportion of males, although excessive in the study group was

Table 1. Description of Variables for the Study and Comparison Groups

	Age Comparison		Developmental Comparison				
Variable	Study Group	Matched Group	$\chi^2(1)/t(df)$[a]	*P* Value[b]	Matched Group	$\chi^2(1)/t(df)$[a]	*P* Value[b]
Sex (males) (%)	62	49	2.5/	.1	54	0.9/	.3
Birth order	2.3 (1.1)	2.4 (1.1 SD)	/0.22(160)	.8	2.2(1.1)	/0.65(160)	.5
Pregnancy, problems (%), mean (SD)	27	32	0.47/	.5	31	0.27/	.6
Spontaneous birth (%)	75	72	0.28/	.6	80	0.57/	.4
Prematurity	12	22	2.7/	.1	20	1.6/	.2
Perinatal distress (%)	26	22	0.3/	.6	23	0.1/	.7
Birth weight in kg, mean (SD)	3.0 (0.6)	2.9 (0.7)	/1.7 (159)	.09	2.9(0.8)	/1.5 (159)	.1
Neonatal disease (%)	43	43	/0.0	>.999	39	0.22/	.6
Hospitalization (%)	73	43	14.6/	<.001	60	3.3/	.07
Independent mobility (%)	21	86	69.7/	<.001	44	10.1/	.002
Nonindependent feeding (%)	64	9	56/	<.001	34	15	.001
Vision deficit (%)	51	17	20.1/	<.001	31	6.5/	.01
Hearing deficit (%)	57	21	21.8/	<.001	38	5.6/	.02
Severe development delay (%)	55	10	38.4/	<.001	—	—	—
Residential care (%)	30	6	15.2/	<.001	23	0.7	.37
Treatment at CDC (%)	64	65	0.03/	.9	85	8	.004

a. $\chi^2(1)$ denotes the chi-squared test statistic (with 1 degree of freedom), and $t(df)$ is the t test statistic with degrees of freedom.
b. As compared to the study group.

Table 2. Family Variables of the Study and Comparison Groups

	Age Comparison		Developmental Comparison				
Variable	Study Group	Matched Group	$\chi^2(1)/t(df)$[a]	*P* Value[b]	Matched Group	$\chi^2(1)/t(df)$[a]	*P* Value[b]
Ethnicity (%) Arabs/Jews	28/72	9/91	10.4/	.001	25/75	0.28/	.6
Socioeconomic status, mean (SD)	2.8 (1.1)	2.9 (1.3)	/0.3 (160)	.8	3.08 (1.6)	/0.9 (160)	.4
Family problems (%)	44	40	0.18/	.7	36	0.74/	.4
Family illness (%)	21	18	0.15/	.7	28	1.19/	.3
Father's age in y, mean (SD)	30.7 (7.0)	31.8 (6)	/1(158)	.3	31.0 (6.6)	/0.32(157)	.7
Mother's age in y, mean (SD)	27.8 (6)	28.4 (5)	/0.7(158)	.5	27.0 (5.8)	/0.83(157)	.4

a. $\chi^2(1)$ denotes the chi-squared test statistic (with 1 degree of freedom), and $t(df)$ is the t test statistic with degrees of freedom.
b. As compared to the study group.

not significantly different from that in the 2 comparison groups (Table 1).

Family variables are depicted in Table 2. A significantly increased proportion of Arab children were identified in the study group as compared with the age-matched group but not to the developmentally matched group. Other family variables were similar in the 3 groups.

The rate of cerebral palsy, genetic disorders, and chronic neurological disease was significantly increased in the study group compared with the age-matched group. Genetic disorders were significantly more frequent in the study group when compared with the developmental comparison group (Table 3). A comparison of age of death in children with and without cerebral palsy revealed no significant difference (7.7 years [5.3 SD] and 8.1 years [5.8 SD], respectively). Variables related to pregnancy and delivery, were not significantly different between the study and comparison groups. Prematurity was increased but not significantly in children of the developmentally matched group as compared with the study group. The rate of hospitalization for neurological problems but not other health problems and the rate of compromised mobility were significantly increased in the study group compared with the 2 comparison groups (Table 1). This difference did not change when only children of 24 months and older were included in the analysis. Figure 1 displays the estimated survival (Kaplan–Meier) curves classified according to treatment, mobility, genetic, and feeding status. Figure 1 and Table 1 illustrate that, other than for the treatment factor, the effect of these variables is consistently stronger for the age-matched than for the developmentally matched comparison. The rate of independent feeding was significantly reduced in the study group when compared with the 2 comparison groups. This difference remained statistically significant when only children aged 24 months and older were included in the analysis. Residential care was significantly increased in the study

Table 3. Diagnostic Categories as Related to Group (%)

Variable	Age Comparison				Developmental Comparison		
	Study Group	Matched Group	$\chi^2(1)$[a]	*P* Value[b]	Matched Group	$\chi^2(1)$[a]	*P* Value[b]
Cerebral palsy	22	7	7.04	.008	11	3.6	.06
Genetic	25	2	17.1	<.001	5	12.5	<.001
Neurological deficit[c]	53	30	9.1	.002	64	2.06	.15
Developmental delay[d]	55	10	38.4	<.001	—	—	—

a. $\chi^2(1)$ denotes the chi-squared test statistic (with 1 degree of freedom).
b. As compared to the study group.
c. Other than cerebral palsy.
d. Severe and profound delay.

Table 4. Estimated 10-Year Survival Probabilities (With Confidence Limits)

Group	Treatment		Lack of Mobility		Genetic Disorder		Nonindependent Feeding	
	Yes	No	Yes	No	Yes	No	Yes	No
Study and age	0.70 (060–0.77)	0.63 (0.49–0.74)	0.37 (0.27–0.48)	0.93 (0.85–0.97)	0.55 (0.32–0.72)	0.69 (0.61–0.76)	0.37 (0.25–0.49)	0.85 (0.77–0.91)
Study and developmental quotient	0.74 (0.65–0.81)	0.48 (0.32–0.62)	0.57 (0.47–0.66)	0.89 (0.77–0.95)	0.58 (0.36–0.75)	0.69 (0.60–0.76)	0.53 (0.41–0.63)	0.81 (0.71–0.88)

group when compared with the age-matched group, but not the developmentally matched group (Table 1). Table 4 displays the estimated 10-year survival probabilities for different risk factors derived from the study and either the age- or the developmentally matched comparison groups. In most cases, the estimates were the same. However, mobility and independent feeding were more significant when compared with age comparisons, whereas treatment was significant when compared with the developmental comparison group. No significant difference was obtained in the mortality risk when the periods of up to 1985, and up to 1995, were compared with the past 10-year period of surveillance.

Cox proportional hazard regression: in comparison with the age-matched group including all the cohort, the significant variables were developmental quotient (hazard ratio 6.06 [2.618, 14.08], $P < .001$), lack of independent feeding (hazard ratio 2.459 [1.462, 4.134], $P < .001$), and genetic etiology (hazard ratio 1.735 [1.031, 2.921], $P = .04$). When only children of ages greater than 24 months were included, the significant variables were developmental quotient (hazard ratio 6.173 [2.398, 15.87], $P < .001$), lack of independent mobility (hazard ratio 3.486 [1.891, 6.428], $P < .001$), and genetic etiology (hazard ratio 2.008 [1.154, 3.493], $P = .02$). Although, there is a difference between the 2 regression models, they are very similar. In the comparison with the developmentally matched group, including all the cohort, 2 significant variables remained in the model: lack of independent feeding (hazard ratio 2.457 [1.549, 3.897], $P < .001$), and genetic etiology (hazard ratio 3.302 [1.925, 5.664], $P < .001$). In addition, treatment at the child development center yielded a hazard ratio of 0.401 (0.246, 0.652, $P < .001$). When only children of ages greater than 24 months were included, the significant variables were genetic etiology (hazard ratio 3.528 [2.008, 6.198], $P < .001$), lack of independent mobility (hazard ratio 2.150 [1.237, 3.736], $P < .01$), hearing deficit (hazard ratio 1.666 [1.035, 2.682], $P = .04$), and treatment at the child development center (hazard ratio 0.502 [0.296, 0.852], $P = .01$).

Discussion

The overall mortality rate of 8.5% found in the present cohort confirms significantly increased risk for early death associated with neurodevelopmental disabilities as reported previously. In a population study including children up to 19 years, cerebral palsy was reported as the most frequent cause of death followed by mental retardation.[15] The results of our study suggest that it is the degree of mobility rather than the diagnosis of cerebral palsy that predicts life expectancy.

Whereas male gender was found to be somewhat increased, although not significantly in the study group when compared with the comparison groups, gender differences in mortality in previous reports were found to be age-related and inconsistent.[4,18–20] Ethnicity was previously reported as a risk factor for early death among the disabled.[18,20] It seems that Arab individuals are at increased risk.

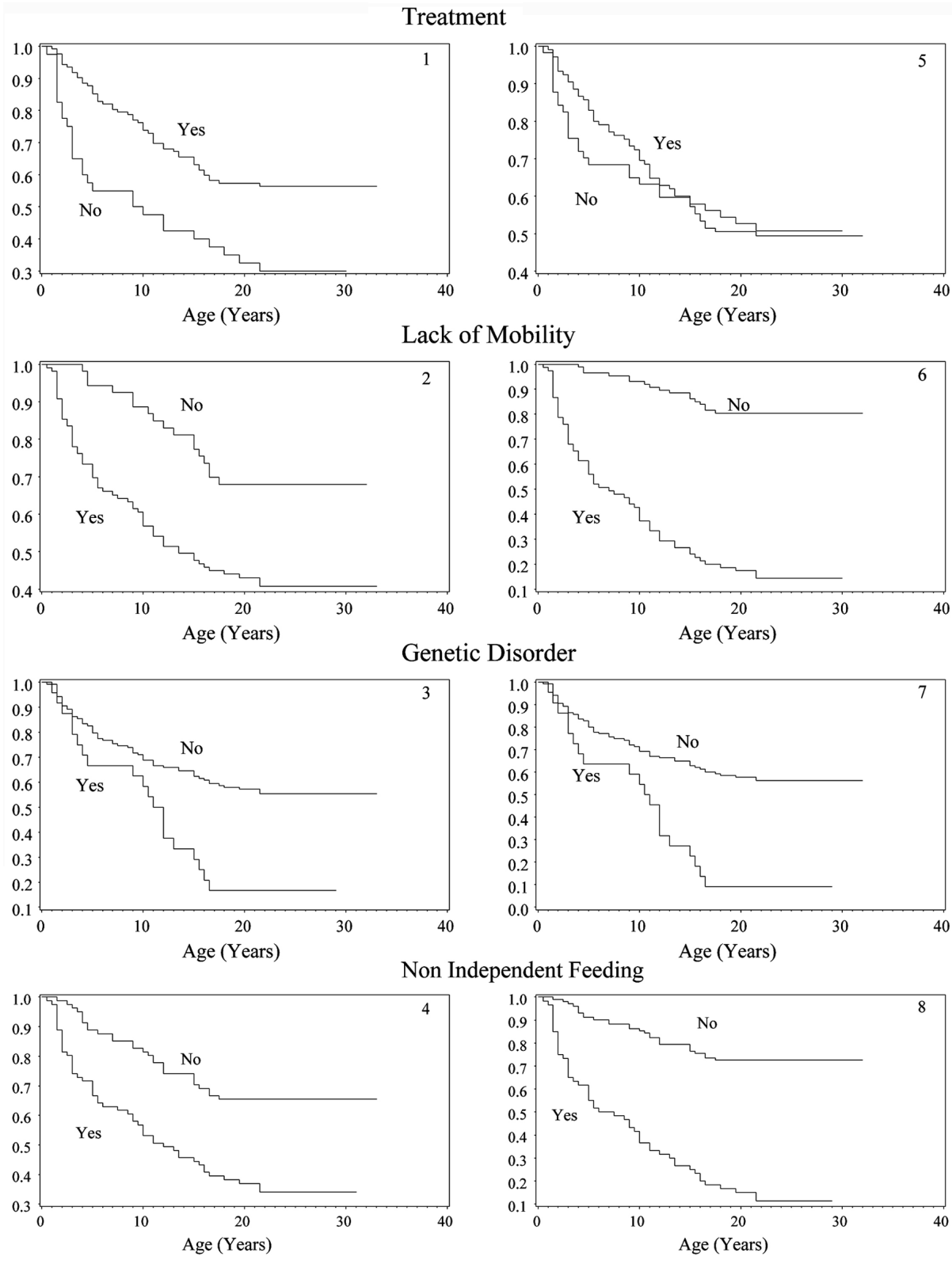

Figure 1. Survival curves (Kaplan–Meier) as related to risk factors among the study and developmental quotient (1–4) and age (5–8) comparison groups.

However, their representation in the developmental comparison group is rather similar to that in the study group. This finding is probably attributable to the over-representation of Arab children in the more severely developmentally disabled group possibly related to different attitudes toward genetic counseling, pregnancy screening, and abortions.

Our first hypothesis related to the effect of sociodemographic variables on early mortality was not substantiated. A recent study in children with cerebral palsy demonstrated a significant effect of the socioeconomic status on survival.[8] This finding, however, was highly dependent on birth weight and pertained to children aged 2 years and above. The effects of family variables on age of death have not been previously reported. The present study suggests that these variables do not contribute to early death in our community.

The increased risk of a genetic etiology in addition to compromised mobility for early death has been reported in the context of cerebral palsy[2] as well as intellectual disability.[20–22] In the present study, children with cerebral palsy and an associated neurological deficit such as epilepsy were found to have a decreased life expectancy as compared to their peers with cerebral palsy only. Chronic neurological disorders such as epilepsy were also found to be associated with early death in children with intellectual disability.[3,20]

The increased survival associated with prematurity in children with cerebral palsy has been previously reported[8,23,24] and attributed to the better mobility among these children.[23] It is also conceivable that the different underlying mechanism and the consequent type of brain damage in premature compared with full-term infants is associated with a more extensive neurophysiological disturbance in the latter resulting in early death. Eyman et al, in their study, found that lack of independent mobility and independent feeding are most consistent and significant risk factors for early death among children with cerebral palsy as well as mental retardation.[25] Lack of independent mobility and lack of independent feeding are highly correlated in the present study (83% were classified exactly the same for these 2 variables).

The degree of mobility and intellectual ability were found to predict survival in previous studies in individuals with intellectual disability[3] as well as cerebral palsy.[24] However, these studies did not consider other variables in a multivariate analysis.

Our second hypothesis related to the risk predicted by sensory deficits is supported by our data. However, in comparison to the developmentally matched children, only hearing remained statistically significant. Both vision and hearing deficits have been reported as significant predictors of poor survival among individuals with developmental disabilities.[3,8,20] It is possible that hearing deficit is more prevalent in children with disabilities other than cerebral palsy, or reflects a more extensive damage to the central nervous system.

The lack of an effect of the type of care (residential/home) is consistent with another study investigating children in a persistent vegetative state[26] but not with other studies[23,27,28] and possibly relates to the type of care provided in the communities under study. Of interest is also the significant association between longevity and treatment at the child development center. This finding controlling for the severity of developmental deficit as well as mobility and type of care is possibly a mediator for some undetected positive care practices used by some families which affect survival. We cannot detect a specific type of intervention that would have a selective effect in prolonging survival, neither can we speculate on other factors mediated by this variable such as family characteristics other than socioeconomic status or family problems found not to be significant in our research.

In conclusion, our study highlights the importance of the underlying etiology, that is, genetic versus nongenetic in the prediction of life expectancy as well as the possible role of a systematic developmental rehabilitative treatment program. The first and foremost limitation of our study is the possible bias introduced by inclusion criteria, for example, children who were referred to the child development center. It is possible that this group of children represents the more disabled end of the spectrum previously reported.[29] However, the referral policy as explained in the Methods section does not lend support to such a bias. Although the relatively small sample size is another limitation of our study, the results, being in consensus with other population-based studies, support their validity. This study is also limited by the length of follow-up, because the final outcome of interest is censored at a maximum age of 30 years, and predictive variables were not ascertained following the age of 6 years. Different communities should, therefore, investigate the specific risk factors for early death in the disabled, and use a multivariate design to account for the variability in risk as well as in protective factors.

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