

# Impact of Hospitalizations due to Chronic Health Conditions on Early Child Development

Joanna E. Fardell<sup>1,2</sup>, PhD, Nan Hu<sup>3</sup>, PhD, Claire E. Wakefield<sup>1,2</sup>, PhD, Glenn Marshall<sup>2</sup>, PhD, Jane Bell<sup>4</sup>, PhD, Raghu Lingam<sup>3</sup>, PhD, and Natasha Nassar<sup>1,4</sup>, PhD

<sup>1</sup>Behavioural Sciences Unit, School of Women's and Children's Health, UNSW Sydney, Australia,

<sup>2</sup>Kids Cancer Centre, Sydney Children's Hospital, Australia,

<sup>3</sup>Population Child Health Research Group, School of Women's and Children's Health, University of New South Wales, Australia and

<sup>4</sup>Child Population and Translational Health Research, Children's Hospital at Westmead Clinical School, University of Sydney, Australia

All correspondence concerning this article should be addressed to Joanna E. Fardell, PhD, Kids Cancer Centre, Level 1 South, Sydney Children's Hospital, High Street, Randwick, NSW 2031, Australia. E-mail: j.fardell@unsw.edu.au

Joanna E. Fardell and Nan Hu are joint first authors.

Raghu Lingam and Natasha Nassar are joint senior authors.

## Abstract

**Objective:** To assess the impact of hospitalization for chronic health conditions on early child development and wellbeing at school start.

**Methods:** We conducted a longitudinal cohort study of children starting school using population-based record linkage of routinely collected admitted hospital data and standardized assessment of early childhood development (Australian Early Developmental Census: AEDC). Developmental vulnerability (DV) was defined as children scoring <10th centile in any one of five developmental domains. Children scoring <10th centile on two or more domains were considered developmentally high-risk (DHR). Children hospitalized with chronic health conditions were compared to children without hospitalizations prior to school start.

**Results:** Among 152,851 children with an AEDC record, 22,271 (14.6%) were hospitalized with a chronic condition. Children hospitalized with chronic health conditions were more likely to be DHR (adjusted odds ratio 1.25, 95% CI: 1.18–1.31) compared to children without hospitalizations. Children hospitalized more frequently (>7 times) or with longer duration (>2 weeks) had a 40% increased risk of being DHR (1.40, 95% CI: 1.05–1.88 and 1.40, 95% CI: 1.13–1.74, respectively). Children hospitalized with mental health/behavioral/developmental conditions had the highest risk of DHR (2.23, 95% CI: 1.72–2.90). Developmental vulnerability was increased for physical health (1.37, 95% CI: 1.30–1.45), language (1.28, 95% CI: 1.19–1.38), social competence (1.22, 95% CI: 1.16–1.29), communication (1.17, 95% CI: 1.10–1.23), and emotional maturity (1.16, 95% CI: 1.09–1.23).

**Conclusions:** Frequent and longer duration hospitalizations for chronic health conditions can impact early childhood development. Research and interventions are required to support future development and well-being of children with chronic health conditions who are hospitalized.

**Keywords:** chronic illness; infancy and early childhood; preschool children; public health

## Introduction

The first years of life form the foundation of a child's health and mental wellbeing. Critical childhood development occurs across all domains of functioning: physical, cognitive, social, and emotional. School readiness has been used to describe children who are developmentally ready for the experiences afforded by school (including sensory, social and developmental experiences), who are able and ready to participate in school activities and engage with learning (Peterson et al., 2018). As a marker of early childhood development, measurement of school readiness has varied with regard to what developmental domains to include, but typically includes cognitive development, physical development, language development, social-emotional development, and approaches to learning (Peterson et al., 2018). Children with low school readiness have fewer developed skills for classroom engagement and potentially academic success (Bell et al., 2016; Peterson et al., 2018). Known risk factors to development and school readiness include ethnic and racial minority status, and

low socioeconomic status (SES), exposure to violence, lack of stimulation, parental health and mental health and infection during pregnancy (McCoy et al., 2017; Romano et al., 2010; Walker et al., 2011).

Children with low school readiness are more likely to have worse academic performance, are more likely to repeat a grade, and less likely to graduate from secondary school (McCoy et al., 2017; Peterson et al., 2018; Romano et al., 2010). Conversely, children ready for school start have lower incarceration rates, teen pregnancy and better mental and physical health later in life (Campbell et al., 2014; Reynolds et al., 2011). The cost of impact to early child development and consequently school readiness is therefore significant to individuals, communities and governments, and highlights how essential preventative measures, such as interventions promoting school readiness, in early childhood are to negate these negative outcomes (Bierman et al., 2018; Reynolds et al., 2011).

With increasing neonatal survival, the number of children living with chronic health conditions is increasing (Keogh

et al., 2018; Van Der Lee et al., 2007), and many will live with significant effects of their disease and treatment (Robison & Hudson, 2014; Steiner & Kovacs, 2018). Childhood health has the potential to impact early development (Peterson et al., 2018). Children with health conditions prior to school commencement can have difficulties with and engaging in learning, are more likely to display disruptive behavior, and report reduced quality of life (Delaney & Smith, 2012; Quach & Barnett, 2015).

Terminology, conceptualizations and operationalization of chronic health conditions among children varies in the literature (Bethell et al., 2008). Systematic review has highlighted commonalities between the terms *chronic health conditions*, *children with special health needs*, and *children with medical complexity* (Van Der Lee et al., 2007). Sustained health and wellbeing impact, that may be incurable, and ongoing health service usage or reliance on medical technologies are defining characteristics for this population of children (Rogers et al., 2021; Van Der Lee et al., 2007). Van Der Lee et al. (2007) provide a framework for identifying children with health impacts based on diagnosis, limitations (impact) and health care use, and a final group of children with special health care needs “who have or are at increased risk of a chronic physical, developmental, behavioral, or emotional condition and who also require health care and related services of a type or amount beyond that required by children generally” (p. 2749). Here we use chronic health conditions for those requiring at least 1 year of medical care, including follow-up appointments, hospitalization, or medication (Hardelid et al., 2014). Examples include, but are not limited to, epilepsy, attention-deficit/hyperactive disorder, cancer, and congenital heart disease (Hardelid et al., 2014).

Like school readiness and education, health disparities exist. Children with chronic health conditions from diverse race and ethnicity groups have difficulties accessing timely and targeted health care due to racism borne out through institutional structures, and interpersonal relationships (Trent et al., 2019). Children from migrant families’ experiences are compounded by lack of availability of culturally competent and linguistically appropriate care (Chang, 2019). Children living in disadvantaged socioeconomic circumstances experience reduced access to healthcare services and also worse health outcomes (Pearce et al., 2019). These disparities and impacts have been worsened by the COVID-19 pandemic (Saatci et al., 2021).

While several studies have reported on disease specific impacts on early development, for example cancer (Morris et al., 2021), few studies have considered all chronic health conditions to capture overall impacts. Data from a small cohort study indicated children with chronic health conditions ( $N = 2,879$ ) are 17–34% more likely to be classified as developmentally vulnerable on all domains of a standardized measure of school readiness (Bell et al., 2016). Parent report data suggest children with longer duration and more severe chronic health conditions prior to school have reduced school readiness as indicated by teacher rated learning outcomes (mathematics and literacy) and approach to learning (Quach & Barnett, 2015). However, further work is needed to examine the impact of hospitalizations on school readiness.

Chronic health conditions in early childhood may impact early development and school readiness in multiple ways. The chronic condition or its treatment may directly impact development of school readiness (e.g. neurological conditions or

CNS directed treatment, Lum et al., 2017). Children with chronic health conditions may also miss out on opportunities for development, particularly in social and communication domains, offered through participation in formalized child-care or preschool programs due to the requirement for ongoing medical appointments and treatments (Ehrlich et al., 2014), or parental perceptions of child vulnerability (Anthony et al., 2003). Many children with chronic health conditions, particularly those with medical complexity, experience recurrent hospital admissions (Coller et al., 2016), and may be a proxy marker for condition severity. Yet no studies have considered the impact on early development of children with chronic health conditions who are hospitalized and how the impact varies by frequency and duration of hospitalization.

Understanding how the burden of managing chronic health conditions and hospitalizations experienced during the first 5 years of life impact on school readiness is critical to informing development of interventions to support children to achieve their potential. Therefore, this study aimed to (i) identify the number of children with chronic health conditions who experience hospitalizations prior to school start, and (ii) determine the impact of hospitalization frequency and duration of stay on school readiness for children with chronic health conditions. To address these aims we used standardized definitions of developmental status obtained through objective and national census of children starting school in New South Wales (NSW) Australia and linkage with longitudinal hospitalization data obtained prior to developmental assessment. We hypothesized children with chronic health conditions who are hospitalized, especially with more frequent and longer duration hospitalizations, experience greater disruption in early development.

## Methods

### Study Design and Data Sources

We conducted a population-based longitudinal cohort study of linkage records of all children born in NSW, Australia, who had a school readiness assessment at school entry in 2009 and 2012. The study cohort was identified via record linkage of birth (NSW Perinatal Data Collection, PDC), hospital (NSW Admitted Patient Data Collection, APDC) and early child development (Australian Early Development Census, AEDC) datasets. The study was approved by the NSW Population and Health Services Research Ethics Committee. The NSW Centre for Health Record Linkage probabilistically linked individual records across datasets and provided de-identified data to the researchers. The data underlying this article cannot be shared publicly due to privacy and ethical requirements of data custodian.

### Study Outcomes

We used the AEDC as a measure of early development prior to school start. The AEDC is implemented nationally every 3 years in Australia from 2009 for children in their first year of formal full-time schooling (normally at 5 or 6 years of age). Coverage is almost universal in NSW, with 99.9% of children enrolled to begin school in 2009 having a record for the AEDC and 96.5% in 2012 (Australian Government, 2013). Only AEDC data in 2009 and 2012 were available in the linkage records analyzed in this study. The AEDC data are collected using the Australian version of the Early Development

Instrument (AvEDI), adapted from the Canadian Early Development Instrument. Teachers complete the AvEDI, individually assessing each child in their class (Brinkman et al., 2014). More than 100 items cover five domains; physical health and wellbeing, social competence, emotional maturity, language and cognitive skills, communication skills and general knowledge. The AvEDI has demonstrated reliability and validity (Brinkman et al., 2014), and AvEDI teacher ratings have been shown to predict later educational outcomes (Brinkman et al., 2013). Children with a domain score in the lowest 10% of the population were considered developmentally vulnerable (DV) on that domain, and those in the lowest 10% of the population on at least two domains were classified as developmentally high risk (DHR). These cut-off percentiles are based on the baseline AEDC data collected in 2009 and remain the same across each collection cycle to provide a reference point against which later AEDC results can be compared (Australian Government, 2019). Children with medical evidence of diagnosis of chronic medical, physical or intellectual disabilities that require special assistance at school are identified as having special needs, and did not have AEDC domains or developmental risk (i.e., DV and DHR) determined as this scoring has not been validated (Australian Government, 2019).

### Study Exposures

We used the APDC to identify all hospital admissions with chronic health conditions that occurred from birth to before AEDC school readiness assessment. We excluded admissions that occurred within 29 days of birth as these were likely to be associated with the birth. The APDC contains up to 50 diagnosis fields associated with the hospitalization, coded using the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification (ICD-10-AM) system.

We considered children to be hospitalized with a chronic condition if they had at least one hospital admission related to chronic health conditions identified using ICD codes from Hardelid et al.'s (2014) classification system. This system defines a chronic condition as "any health problem likely to require follow-up for more than 1 year, where follow-up could be repeated hospital admissions, specialist follow-ups through outpatient department visits, medication or use of support services" (Hardelid et al., 2014: 2). The ICD codes were classified by clinicians and included validated code lists for chronic health conditions in children. Eight mutually exclusive categories affecting different body systems were created: mental health/behavioral/developmental (e.g. conduct disorder, developmental delays), cancer/blood disorders (e.g. leukemia), chronic infections (e.g. HIV), respiratory (e.g. asthma, cystic fibrosis), metabolic (e.g. diabetes), musculoskeletal (e.g. juvenile idiopathic arthritis), neurological (e.g. epilepsy, cerebral palsy), cardiovascular (e.g. congenital heart disease), and one category for non-specific chronic condition (e.g. lack of expected normal physiological development). Supplementary Table 1 shows each diagnostic code included in each category, and see Hardelid et al. (2014) for further methods on classification system development. We identified condition-specific hospitalizations based on all the 50 diagnosis fields; thus, a child may be in multiple diagnostic categories of chronic conditions. Children without any hospital admission records were the comparison group. Total frequency (1, 2–3, 4–6, and  $\geq 7$ ), total duration of

hospitalizations (1–2, 3–4, 5–7, 8–14, and  $\geq 15$  days), and types of chronic condition diagnosis prior to school readiness assessment were determined.

### Potential Confounders

We grouped potential confounders into five categories for progressive adjustment in analyses (specific variables shown in Table I): (1) child sex; (2) perinatal factors; (3) maternal and familial socio-demographic factors at child's birth; (4) cultural and linguistic diversity (CALD); and (5) child age at school enrolment (used to control for cohort difference). Maternal postcode-level area socioeconomic disadvantage was determined using the Index of Relative Socioeconomic Disadvantage (IRSD), developed by the Australian Bureau of Statistics. The IRSD is a summary measure of a range of socioeconomic factors, including income, educational and occupational status, of the people and the households within a postcode-level area (Australian Bureau of Statistics, 2008). The Accessibility/Remoteness Index of Australia (ARIA) was used to categorize geographic accessibility to services for the residents within a postcode-level area (Australian Bureau of Statistics, 2008).

### Statistical Analysis

We used logistic regression analysis to examine how the occurrence, frequency, and duration of hospitalizations with a chronic condition influence the odds of each school readiness outcome. Crude odds ratios (ORs) were estimated using univariable logistic regression analysis (Model 1). Adjusted ORs (aORs) were estimated by cumulatively controlling for the various categories of potential confounders (Model 2–Model 5, Supplementary Table 2). Each exposure variable (i.e., occurrence, frequency, duration, and diagnosis of hospitalizations) was treated as a dummy variable in the regression analyses. We controlled for teacher-based clustering of outcomes using generalized estimating equations (GEE) approach. The standard errors of the regression coefficients were estimated using the empirical estimation method to construct 95% confidence intervals (Zeger et al., 1988). Where there was a greater than 10% change in estimates between models we assessed potential interaction with chronic health conditions and relevant variables. All analyses were conducted using SAS (Enterprise Guide) statistical software version 7.1 (SAS Institute Inc., Cary, NC, USA).

### Results

A total of 152,851 children had an AEDC record either in the year 2009 ( $n = 72,758$ ) or 2012 ( $n = 80,093$ ). Of these children, 22,271 (14.6%) were hospitalized with a chronic condition, 45,406 (29.7%) were hospitalized without any chronic condition, and 85,174 (55.7%) had no hospital admission records and were included as the comparison group in this analysis (Table I). Nearly three-quarters of the children were 5 years old at school entry. Just over half (51.5%) of the children were male, and most (91.7%) were born full-term. Among those hospitalized with chronic conditions there were more boys (59.6% vs. 46.9%), children born pre-term (10.2% vs. 5.1%), children whose language was English (85.5% vs. 81.3%) or whose mother was born in Australia (76.8% vs. 70.9%), and who were older than 6 years at school entry (30.5% vs. 24.7%) compared to children without hospitalizations. Other available socio-demographic,

**Table 1.** Maternal, Perinatal and School Characteristics of Children With and Without Hospitalization for Chronic Health Conditions

Sociodemographic, perinatal, and childhood characteristics	Number of children <sup>a</sup>	Hospitalizations with chronic health conditions			<i>p</i> values
		Children with no hospitalizations (comparison group)	Children hospitalized without any CC	Children hospitalized with a chronic condition	
	<i>N</i> (column %)	<i>n</i> (column %)	<i>n</i> (column %)	<i>n</i> (column %)	
All	152,851 (100)	85,174 (100)	45,406 (100)	22,271 (100)	
Child sex					
Male	78,657 (51.5)	39,949 (46.9)	25,444 (56.0)	13,264 (59.6)	<.001 <sup>d</sup>
Female	74,095 (48.5)	45,169 (53.0)	19,935 (43.9)	8,991 (40.4)	<.001 <sup>e</sup>
Unknown	99 (0.1)	56 (0.1)	27 (0.1)	16 (0.1)	<.001 <sup>f</sup>
Child perinatal factors					
Gestational age (weeks)					
Pre-term birth (gestational age ≤36)	9,992 (6.5)	4,359 (5.1)	3,360 (7.4)	2,273 (10.2)	<.001 <sup>d</sup>
Term birth (gestational age: 37–41)	140,120 (91.7)	79,185 (93.0)	41,281 (90.9)	19,654 (88.3)	<.001 <sup>e</sup>
Post-term birth (gestational age ≥42)	2,710 (1.8)	1,610 (1.9)	757 (1.7)	343 (1.5)	<.001 <sup>f</sup>
Missing	29 (0.0)	20 (0.0)	8 (0)	1 (0.0)	
Birthweight by gestation					
Small for gestation (<10%)	15,756 (10.3)	8,421 (9.9)	4,836 (10.7)	2,499 (11.2)	<.001 <sup>d</sup>
Birthweight by gestation: 10–<90%	121,266 (79.3)	68,008 (79.9)	35,838 (78.9)	17,420 (78.2)	<.001 <sup>e</sup>
Large for gestation (≥90%)	15,516 (10.2)	8,593 (10.1)	4,635 (10.2)	2,288 (10.3)	.064 <sup>f</sup>
Missing	313 (0.2)	152 (0.2)	97 (0.2)	64 (0.3)	
Plurality					
Singleton	148,266 (97.0)	82,974 (97.4)	43,851 (96.6)	21,441 (96.3)	<.001 <sup>d</sup>
Twins or others	4,585 (3.0)	2,200 (2.6)	1,555 (3.4)	830 (3.7)	<.001 <sup>e</sup>
Apgar score (5 min)					
5 min Apgar: <7	1,725 (1.1)	822 (1.0)	498 (1.1)	405 (1.8)	.024 <sup>d</sup>
5 min Apgar: 7–10	150,759 (98.6)	84,139 (98.8)	44,804 (98.7)	21,816 (98.0)	<.001 <sup>e</sup>
Missing	367 (0.2)	213 (0.3)	104 (0.2)	50 (0.2)	<.001 <sup>f</sup>
Maternal and familial socio-demographic factors at child's birth					
Maternal parity					
First born child	62,756 (41.1)	34,182 (40.1)	19,028 (41.9)	9,544 (42.9)	<.001 <sup>d</sup>
Second born child	52,236 (34.2)	29,508 (34.6)	15,172 (33.4)	7,556 (33.9)	<.001 <sup>e</sup>
Third born child or younger	37,291 (24.4)	21,177 (24.9)	11,029 (24.3)	5,085 (22.8)	<.001 <sup>f</sup>
Missing	568 (0.4)	307 (0.4)	175 (0.4)	86 (0.4)	
Gestational weeks at 1st antenatal visit					
Antenatal care < 20 weeks	135,252 (88.5)	75,069 (88.1)	40,314 (88.8)	19,869 (89.2)	<.001 <sup>d</sup>
Antenatal care ≥20 weeks	15,765 (10.3)	9,089 (10.7)	4,551 (10)	2,125 (9.5)	<.001 <sup>e</sup>
Missing	1,834 (1.2)	1,016 (1.2)	541 (1.2)	277 (1.2)	.051 <sup>f</sup>
Maternal smoking during pregnancy					
Yes	21,550 (14.1)	11,041 (13.0)	7,192 (15.8)	3,317 (14.9)	<.001 <sup>d</sup>
No	130,224 (85.2)	73,529 (86.3)	37,917 (83.5)	18,778 (84.3)	<.001 <sup>e</sup>
Unknown	1,077 (0.7)	604 (0.7)	297 (0.7)	176 (0.8)	.002 <sup>f</sup>
Maternal age (years)					
<20	5,720 (3.7)	2,844 (3.3)	2,030 (4.5)	846 (3.8)	<.001 <sup>d</sup>
20–24	21,485 (14.1)	11,281 (13.2)	7,051 (15.5)	3,153 (14.2)	<.001 <sup>e</sup>
25–34	93,431 (61.1)	52,366 (61.5)	27,450 (60.5)	13,615 (61.1)	<.001 <sup>f</sup>
35–39	26,636 (17.4)	15,405 (18.1)	7,360 (16.2)	3,871 (17.4)	
≥40	5,537 (3.6)	3,254 (3.8)	1,498 (3.3)	785 (3.5)	
Missing	42 (0.0)	24 (0.0)	17 (0)	1 (0.0)	
Maternal postcode-level residential SES <sup>b</sup>					
≤25% (most disadvantaged)	31,237 (20.4)	17,460 (20.5)	9,613 (21.2)	4,164 (18.7)	<.001 <sup>d</sup>
25<–50%	37,276 (24.4)	20,792 (24.4)	11,340 (25)	5,144 (23.1)	<.001 <sup>e</sup>
50<–75%	39,924 (26.1)	22,320 (26.2)	11,847 (26.1)	5,757 (25.9)	<.001 <sup>f</sup>
>75% (least disadvantaged)	44,288 (29.0)	24,520 (28.8)	12,576 (27.7)	7,192 (32.3)	
Missing	126 (0.1)	82 (0.1)	30 (0.1)	14 (0.1)	
Maternal postcode-level residential remoteness/accessibility <sup>c</sup>					
Major cities of Australia	118,902 (77.8)	67,041 (78.7)	34,271 (75.5)	17,590 (79.0)	<.001 <sup>d</sup>
Inner regional Australia	25,309 (16.6)	13,654 (16.0)	8,115 (17.9)	3,540 (15.9)	.11 <sup>e</sup>
Outer regional Australia	7,621 (5.0)	3,990 (4.7)	2,636 (5.8)	995 (4.5)	<.001 <sup>f</sup>
Remote and very remote Australia	920 (0.6)	425 (0.5)	360 (0.8)	135 (0.6)	
Unknown	99 (0.1)	64 (0.1)	24 (0.1)	11 (0.1)	

(continued)



Table I. (continued)

Sociodemographic, perinatal, and childhood characteristics	Number of children <sup>a</sup>  N (column %)	Hospitalizations with chronic health conditions			<i>p</i> values
		Children with no hospitalizations (comparison group) <i>n</i> (column %)	Children hospitalized without any CC <i>n</i> (column %)	Children hospitalized with a chronic condition <i>n</i> (column %)	
Cultural and linguistic diversity					
Language background other than English					
Yes	26,205 (17.1)	15,962 (18.7)	7,017 (15.5)	3,226 (14.5)	<.001 <sup>d</sup>
No	126,646 (82.9)	69,212 (81.3)	38,389 (84.6)	19,045 (85.5)	<.001 <sup>e</sup> .001 <sup>f</sup>
Maternal country of birth					
Australia born	112,099 (73.3)	60,358 (70.9)	34,644 (76.3)	17,097 (76.8)	<.001 <sup>d</sup>
Non-Australia born	40,752 (26.7)	24,816 (29.1)	10,762 (23.7)	5,174 (23.2)	<.001 <sup>e</sup> .18 <sup>f</sup>
Child's age at school entry					
<5 years	1,344 (0.9)	796 (0.9)	368 (0.8)	180 (0.8)	<.001 <sup>d</sup>
5–5.5 years	38,760 (25.4)	22,800 (26.8)	10,958 (24.1)	5,002 (22.5)	<.001 <sup>e</sup>
5.5–6 years	71,985 (47.1)	40,542 (47.6)	21,144 (46.6)	10,299 (46.2)	<.001 <sup>e</sup>
≥6 years	40,762 (26.7)	21,036 (24.7)	12,936 (28.5)	6,790 (30.5)	
Year of AEDC					
2009	72,758 (47.6)	40,172 (47.2)	22,191 (48.9)	10,395 (46.7)	<.001 <sup>d</sup>
2012	80,093 (52.4)	45,002 (52.8)	23,215 (51.1)	11,876 (53.3)	<.19 <sup>e</sup> <.001 <sup>e</sup>

<sup>a</sup> Comprises of children without any hospitalizations (*n* = 85,174), children hospitalized for conditions other than chronic health conditions (*n* = 45,406), and children hospitalized with a chronic health conditions (CC) (*n* = 22,271).

<sup>b</sup> Maternal postcode-level residential SES was measured using the Index for Relative Socioeconomic Disadvantage score.

<sup>c</sup> Maternal postcode-level residential remoteness was determined using the Accessibility/Remoteness Index of Australia (ARIA) classification.

<sup>d</sup> *p* value for the statistical significance of distributional difference of each factor between every two groups using the Chi-square tests: *p* values between children with no hospitalizations and children hospitalized without any chronic condition.

<sup>e</sup> *p* value for the statistical significance of distributional difference of each factor between every two groups using the Chi-square tests: *p* values between children with no hospitalizations and children hospitalized with a chronic condition.

<sup>f</sup> *p* value for the statistical significance of distributional difference of each factor between every two groups using the Chi-square tests: *p* values between children hospitalized with and without a chronic condition.

perinatal, and childhood characteristics were broadly similar across the groups with and without chronic health conditions. Among children with chronic health conditions, children were mostly hospitalized for respiratory conditions (52.4%), followed by neurological conditions (32.1%. Table II).

A higher proportion of children hospitalized with chronic health conditions (10.9%), and hospitalized without chronic health conditions (10.5%) were identified as DHR compared with those without any hospitalizations (8.5%) (Table II). On crude analysis, children hospitalized with chronic health conditions had 37% (odds ratio [OR] 1.37; 95% confidence interval [CI] 1.30–1.43) increased odds of being DHR, although after controlling for covariates the odds were attenuated slightly (adjusted (a)OR 1.25, 95% CI: 1.18–1.31, Table II). The change in odds was mostly attributable to child sex (Supplementary Table 2: Model 2) and after stratifying the analysis we found greater odds for DHR for girls (aOR 1.32; 95% CI 1.20–1.46) compared with boys with chronic health conditions (aOR 1.21; 95% CI 1.14–1.29) (test for interaction, *p* = .07, Supplementary Table 3). Table II also shows that being hospitalized with a chronic condition only once or for only 1–2 days was associated with 20% increased risk of DHR. The adjusted odds of DHR rose progressively, with increased frequency or duration of hospitalizations with a chronic condition, such that children hospitalized more than 7 times or more than 2 weeks before starting school had 40% increased risk of being DHR (aOR 1.40; 95% CI: 1.05–1.88, and 1.40; 95% CI: 1.13–1.74, respectively). Both these associations were most influenced by child sex, and perinatal factors played an additional role in slightly attenuating the

association for duration of stay in hospital (Supplementary Table 2). Additionally, children hospitalized with chronic health conditions had 9% increased odds of DHR than those hospitalized without a chronic condition (aOR 1.09; 95% CI 1.03–1.15, Supplementary Table 5).

Children with mental health/behavioral/developmental conditions who were hospitalized were more likely to be identified as DHR with the highest odds of 2.23 (95% CI: 1.72–2.90). Other chronic health conditions associated with increased odds of being DHR included childhood cancer (aOR 1.46; 95% CI: 1.18–1.81), musculoskeletal (aOR 1.39; 95% CI: 1.15–1.68), neurological (aOR 1.34; 95% CI: 1.23–1.46), and respiratory (aOR 1.23; 95% CI: 1.15–1.31) conditions (Table II). Regardless of chronic condition, odds of DHR was attenuated after controlling for child sex (Supplementary Table 4: Model 2). The impact of other covariates varied by chronic health conditions. Perinatal factors were relevant for mental health/behavioral, cancer and cardiovascular conditions. Maternal and socio-demographic factors affected estimates for chronic infections, neurological and non-specific chronic health conditions. Age at school entry impacted the association for mental health/behavioral/developmental conditions (Supplementary Table 4).

Children hospitalized with and without chronic health conditions had increased odds of being developmentally vulnerable on each AEDC domain, compared to those without any hospitalizations (Tables III and IV). Overall, the odds of being developmentally vulnerable for children hospitalized with chronic health conditions were 1.37 for physical health and wellbeing (95% CI: 1.30–1.45), 1.28 for language and

**Table II.** Association Between Having a Hospitalization With a Chronic Condition and the Risk of Developmentally High Risk (DHR)

	Number of children	Developmentally high risk (DHR)		
	N (column %)	No. of children DHR (row %)	Crude OR (95% CI) <sup>a</sup>	Adjusted OR (95% CI) <sup>b</sup>
Without hospital admissions (comparison group)	82,200 (56.7)	6,955 (8.5)	Reference	Reference
Had hospitalizations but none with CC	43,228 (29.8)	4,558 (10.5)	1.26 (1.21, 1.31)	1.15 (1.10, 1.19)
Had $\geq 1$ CC-related admission	19,589 (13.5)	2,139 (10.9)	1.37 (1.30, 1.43)	1.25 (1.18, 1.31)
Number of CC-related hospital admissions				
1	13,150 (9.1)	1,408 (10.7)	1.32 (1.25, 1.40)	1.20 (1.13, 1.28)
2–3	5,037 (3.5)	568 (11.3)	1.45 (1.33, 1.57)	1.34 (1.22, 1.46)
4–6	996 (0.7)	114 (11.5)	1.50 (1.25, 1.78)	1.34 (1.11, 1.63)
$\geq 7$	406 (0.3)	49 (12.1)	1.56 (1.18, 2.04)	1.40 (1.05, 1.88)
Duration of CC-related hospital admissions (days)				
1–2	12,824 (8.8)	1,313 (10.2)	1.28 (1.21, 1.36)	1.19 (1.12, 1.27)
3–4	3,004 (2.1)	352 (11.7)	1.49 (1.34, 1.65)	1.32 (1.18, 1.47)
5–7	1,943 (1.3)	234 (12.0)	1.49 (1.31, 1.70)	1.35 (1.17, 1.55)
8–14	1,094 (0.8)	138 (12.6)	1.54 (1.30, 1.84)	1.38 (1.14, 1.66)
$\geq 15$	724 (0.5)	102 (14.1)	1.72 (1.41, 2.10)	1.40 (1.13, 1.74)
Types of chronic condition <sup>c</sup>				
Mental health/behavioral/developmental	405 (2.1)	76 (18.8)	2.43 (1.91, 3.09)	2.23 (1.72, 2.90)
Cancer/blood disorders	777 (4.0)	102 (13.1)	1.66 (1.36, 2.02)	1.46 (1.18, 1.81)
Chronic infections	98 (0.5)	12 (12.2)	1.48 (0.83, 2.62)	1.15 (0.61, 2.19)
Respiratory	10,260 (52.4)	1,194 (11.6)	1.43 (1.35, 1.52)	1.23 (1.15, 1.31)
Metabolic <sup>d</sup>	2,414 (12.3)	234 (9.7)	1.25 (1.10, 1.41)	1.14 (0.99, 1.30)
Musculoskeletal/skin	1,214 (6.2)	141 (11.6)	1.38 (1.16, 1.65)	1.39 (1.15, 1.68)
Neurological	6,287 (32.1)	640 (10.2)	1.34 (1.24, 1.45)	1.34 (1.23, 1.46)
Cardiovascular	710 (3.6)	79 (11.1)	1.39 (1.12, 1.71)	1.17 (0.93, 1.47)
Non-specific chronic condition	1,141 (5.8)	121 (10.6)	1.42 (1.20, 1.68)	1.45 (1.20, 1.75)

<sup>a</sup> Crude ORs were derived from the univariable logistic regression analyses controlling for teacher-level clustering only.

<sup>b</sup> Adjusted ORs were generated from the multivariable logistic regression analyses controlling for all the groups of confounders including child's sex, child's perinatal factors, maternal and familial socioeconomic factors, child's age at school entry, and year of AEDC assessment, as well as teacher-level clustering.

<sup>c</sup> A child may be hospitalized for multiple types of chronic health conditions, thus the sum of the numbers of children hospitalized for different types of chronic health conditions is greater than the total number of children hospitalized for any chronic health conditions.

<sup>d</sup> Metabolic/endocrine/digestive/renal/genitourinary conditions.

cognitive skills (95% CI: 1.19–1.38), 1.22 for social competence (95% CI: 1.16–1.29), 1.17 for communication skills and general knowledge (95% CI: 1.10–1.23), and 1.16 for emotional maturity (95% CI: 1.09–1.23). Increasing number of hospitalizations with a chronic condition was associated with increased odds of developmental vulnerability (DV) for two domains: physical health and wellbeing (trend aOR 1.18; 95% CI: 1.11–1.26) and communication skills and general knowledge (trend aOR 1.09; 95% CI: 1.01–1.17). The odds for the other three domains dropped at the last level when children had the highest frequency of hospitalizations, likely due to the small sample sizes (Tables III and IV). Children with mental health/behavioral/developmental conditions consistently had greater than twofold increased odds of being developmentally vulnerable on all AEDC domains. Children with respiratory (aORs ranged from 1.12 to 1.33) and neurological diseases (aORs generally above 1.30) had increased odds of being developmentally vulnerable on all domains (Tables III and IV). Children hospitalized with chronic health conditions had higher odds of being developmentally vulnerable than those hospitalized without a chronic condition, especially on physical health and wellbeing (aOR 1.21; 95% CI: 1.15–1.29) and social competence domains (aOR 1.07; 95% CI: 1.01–1.13, Supplementary Table 5).

Table V shows that 11.7% of children hospitalized with a chronic condition and 4.3% of children hospitalized without

a chronic condition had special needs (these children did not have an AEDC assessment), compared to 3.0% of children without any hospitalizations. More boys than girls hospitalized with a chronic condition had special needs identified (13.3% vs. 9.3%). The proportion of children reported to have special needs increased as the frequency and the duration of hospitalizations related to chronic conditions increased, with 48% for those hospitalized  $\geq 7$  times and 39% for those hospitalized for  $\geq 15$  days. Of children hospitalized with mental health/behavioral/developmental conditions prior to school start, nearly 60% had special needs. Specific mental health diagnoses differed by child age. At age 3 the most common diagnoses were developmental (e.g. 48.7% were speech and language or autism diagnoses). At 4 and 5 years the most common diagnoses were related to behavioral disorders (e.g. oppositional defiant disorder). After mental health/behavioral/developmental conditions, 27% of children hospitalized with cardiovascular diseases had special needs.

## Discussion

This study sought to investigate the impact of frequency and duration of hospitalization among children with chronic health conditions on early development using a dataset of over 100,000 children. Our analysis found almost 15% of children with chronic health conditions had been hospitalized

**Table III.** Association Between Frequency and Duration of Hospitalizations and Developmental Vulnerability of AEDC Domains

	AEDC domains										
	Number of children	Physical health and wellbeing	Social competence		Emotional maturity		Language and cognitive skills		Communication skills and general knowledge		
	N (column %)	n (row %)	Adjusted OR (95% CI) <sup>a</sup>	n (row %)	Adjusted OR (95% CI)	n (row %)	Adjusted OR (95% CI)	n (row %)	Adjusted OR (95% CI)	n (row %)	Adjusted OR (95% CI)
Without hospital admissions (comparison group)	82,596 (56.7)	6,146 (7.4)	Reference	6,289 (7.6)	Reference	4,829 (5.9)	Reference	3,663 (4.4)	Reference	6,360 (7.7)	Reference
Had hospitalizations but none with CC	43,457 (29.8)	3,918 (9.0)	1.13 (1.08, 1.18)	4,067 (9.4)	1.14 (1.10, 1.19)	3,307 (7.6)	1.15 (1.09, 1.20)	2,561 (5.9)	1.22 (1.15, 1.29)	3,755 (8.6)	1.11 (1.06, 1.16)
Had ≥ 1 CC-related admission	19,674 (13.5)	2,028 (10.3)	1.37 (1.30, 1.45)	1,911 (9.7)	1.22 (1.16, 1.29)	1,499 (7.6)	1.16 (1.09, 1.23)	1,137 (5.8)	1.28 (1.19, 1.38)	1,691 (8.6)	1.17 (1.10, 1.23)
Number of CC-related hospital admissions											
1	13,206 (9.1)	1,301 (9.0)	1.29 (1.21, 1.38)	1,264 (9.6)	1.19 (1.12, 1.26)	987 (7.5)	1.13 (1.05, 1.21)	754 (5.7)	1.26 (1.16, 1.37)	1,110 (8.4)	1.11 (1.04, 1.19)
2–3	5,055 (3.5)	535 (10.6)	1.44 (1.31, 1.58)	501 (9.9)	1.29 (1.18, 1.42)	399 (7.9)	1.22 (1.10, 1.36)	300 (5.9)	1.36 (1.20, 1.54)	448 (8.9)	1.26 (1.14, 1.40)
4–6	999 (0.7)	120 (12.0)	1.70 (1.41, 2.05)	107 (10.7)	1.35 (1.11, 1.64)	84 (8.4)	1.33 (1.06, 1.67)	61 (6.1)	1.29 (0.98, 1.69)	88 (8.8)	1.26 (1.02, 1.56)
≥7	414 (0.3)	72 (17.4)	2.54 (1.96, 3.29)	39 (9.4)	1.23 (0.91, 1.66)	29 (7.0)	1.05 (0.72, 1.53)	22 (5.3)	1.09 (0.71, 1.68)	45 (10.9)	1.53 (1.12, 2.09)
Duration of CC-related hospital admissions (days)											
1–2	12,872 (8.8)	1,199 (9.3)	1.25 (1.17, 1.34)	1,192 (9.3)	1.18 (1.11, 1.26)	947 (7.4)	1.13 (1.05, 1.22)	668 (5.2)	1.21 (1.11, 1.33)	1,046 (8.1)	1.14 (1.06, 1.22)
3–4	3,016 (2.1)	321 (10.6)	1.39 (1.23, 1.56)	313 (10.4)	1.30 (1.16, 1.45)	239 (7.9)	1.20 (1.05, 1.37)	203 (6.7)	1.43 (1.23, 1.67)	273 (9.1)	1.15 (1.02, 1.31)
5–7	1,955 (1.3)	229 (11.7)	1.58 (1.37, 1.82)	196 (10.0)	1.24 (1.07, 1.43)	165 (8.4)	1.26 (1.07, 1.49)	131 (6.7)	1.38 (1.14, 1.67)	180 (9.2)	1.22 (1.05, 1.43)
8–14	1,100 (0.8)	149 (13.6)	1.75 (1.47, 2.09)	121 (11.0)	1.37 (1.14, 1.66)	88 (8.0)	1.17 (0.93, 1.46)	72 (6.6)	1.29 (1.01, 1.67)	107 (9.7)	1.24 (1.01, 1.52)
≥15	731 (0.5)	130 (17.8)	2.37 (1.94, 2.90)	89 (12.2)	1.40 (1.13, 1.74)	60 (8.2)	1.17 (0.89, 1.55)	63 (8.6)	1.47 (1.11, 1.94)	85 (11.6)	1.40 (1.12, 1.76)

<sup>a</sup> Adjusted ORs were generated from the multivariable logistic regression analyses controlling for all the groups of confounders including child’s sex, child’s perinatal factors, maternal and familial socioeconomic factors, child’s age at school entry, and year of AEDC assessment, as well as teacher-level clustering. For each regression analysis, there was only one comparison/reference group, which was “children without hospital admissions”, and each other group was compared with the reference group separately, not simultaneously.

**Table IV.** Association Between Type of Hospitalizations With a Chronic Condition and Developmental Vulnerability of AEDC Domains

	AEDC domains										
	Number of children	Physical health and wellbeing		Social competence		Emotional maturity		Language and cognitive skills		Communication skills and general knowledge	
	N (column %)	No. of children (row %)	Adjusted OR (95% CI) <sup>a</sup>	No. of children (row %)	Adjusted OR (95% CI)	No. of children (row %)	Adjusted OR (95% CI)	No. of children (row %)	Adjusted OR (95% CI)	No. of children (row %)	Adjusted OR (95% CI)
Types of chronic health conditions											
Mental health/behavioral/developmental	408 (2.07)	73 (18.0)	2.65 (2.06, 3.41)	60 (14.8)	1.87 (1.41, 2.47)	55 (13.6)	2.12 (1.6, 2.82)	40 (9.9)	2.26 (1.62, 3.16)	70 (17.2)	2.58 (1.95, 3.40)
Cancer/blood disorders	785 (3.99)	105 (13.5)	1.81 (1.47, 2.23)	78 (10.0)	1.24 (0.99, 1.55)	54 (7.0)	0.99 (0.74, 1.32)	67 (8.6)	1.88 (1.45, 2.44)	82 (10.5)	1.35 (1.08, 1.69)
Chronic infections	99 (0.50)	12 (12.2)	1.32 (0.7, 2.47)	10 (10.2)	1.14 (0.61, 2.12)	9 (9.2)	1.43 (0.76, 2.71)	7 (7.1)	1.06 (0.4, 2.76)	12 (12.2)	1.58 (0.85, 2.94)
Respiratory	10,302 (52.36)	1,102 (10.7)	1.33 (1.24, 1.42)	1,027 (10.0)	1.19 (1.11, 1.27)	809 (7.9)	1.13 (1.04, 1.22)	657 (6.4)	1.29 (1.18, 1.41)	950 (9.3)	1.12 (1.05, 1.21)
Metabolic <sup>c</sup>	2,431 (12.36)	250 (10.3)	1.40 (1.23, 1.6)	227 (9.4)	1.25 (1.1, 1.43)	184 (7.7)	1.19 (1.03, 1.39)	110 (4.6)	0.99 (0.81, 1.22)	181 (7.5)	1.00 (0.86, 1.16)
Musculoskeletal/skin	1,218 (6.19)	147 (12.1)	1.73 (1.45, 2.06)	127 (10.5)	1.34 (1.1, 1.63)	89 (7.4)	1.19 (0.94, 1.49)	78 (6.4)	1.57 (1.24, 1.99)	116 (9.6)	1.40 (1.15, 1.70)
Neurological	6,310 (32.07)	610 (9.7)	1.45 (1.33, 1.58)	595 (9.5)	1.3 (1.19, 1.41)	489 (7.8)	1.27 (1.16, 1.40)	310 (4.9)	1.30 (1.15, 1.46)	491 (7.8)	1.33 (1.21, 1.46)
Cardiovascular	719 (3.65)	90 (12.6)	1.60 (1.28, 20)	73 (10.2)	1.27 (1.02, 1.58)	59 (8.3)	1.22 (0.92, 1.60)	44 (6.2)	1.19 (0.88, 1.63)	58 (8.1)	0.99 (0.76, 1.28)
Non-specific chronic condition	1,146 (5.82)	133 (11.6)	1.85 (1.55, 2.2)	117 (10.2)	1.46 (1.22, 1.77)	84 (7.4)	1.26 (1.00, 1.58)	59 (5.2)	1.37 (1.05, 1.80)	98 (8.6)	1.42 (1.15, 1.74)

<sup>a</sup> Adjusted ORs were generated from the multivariable logistic regression analyses controlling for all the groups of confounders including child's sex, child's perinatal factors, maternal and familial socioeconomic factors, child's age at school entry, and year of AEDC assessment, as well as teacher-level clustering. The comparison group is "children without any hospital admissions" for all types of chronic health conditions to facilitate comparison of the effect sizes.

<sup>b</sup> Metabolic/endocrine/digestive/renal/genitourinary conditions.



**Table V.** Characteristics of Children With Special Needs in Relation to Hospitalizations With a Chronic Condition

Hospital admissions with a chronic condition (CC)	Number of children			
	Total N (column %)	Children with special needs (row %)		
		Total	Boys	Girls
Without hospital admissions	85,174 (55.7)	2,578 (3.0)	1,777 (4.5)	799 (1.8)
Had hospitalizations but none with CC	45,406 (29.7)	1,949 (4.3)	1,443 (5.7)	506 (2.5)
Had $\geq 1$ CC-related admission	22,271 (14.6)	2,597 (11.7)	1,761 (13.3)	834 (9.3)
Number of CC-related hospital admissions				
1	14,293 (9.4)	1,087 (7.6)	773 (9.1)	314 (5.4)
2–3	5,826 (3.8)	771 (13.2)	533 (15.2)	236 (10.2)
4–6	1,357 (0.9)	358 (26.4)	228 (29.0)	130 (22.8)
$\geq 7$	795 (0.5)	381 (47.9)	227 (47.6)	154 (48.7)
Duration of CC-related hospital admissions (days)				
1–2	14,027 (9.2)	1,155 (8.2)	849 (10.0)	306 (5.5)
3–4	3,388 (2.2)	372 (11.0)	257 (12.7)	113 (8.3)
5–7	2,269 (1.5)	314 (13.8)	214 (16.1)	100 (10.7)
8–14	1,388 (0.9)	288 (20.8)	179 (23.3)	109 (17.7)
$\geq 15$	1,199 (0.8)	468 (39.0)	262 (39.6)	206 (38.4)
Types of chronic condition <sup>a</sup>				
Mental health/behavioral/developmental	973 (4.4)	565 (58.1)	381 (62.6)	183 (50.4)
Cancer/blood disorders	941 (4.2)	156 (16.6)	96 (17.7)	60 (15.1)
Chronic infections	115 (0.5)	16 (13.9)	9 (14.3)	7 (13.5)
Respiratory	11,339 (50.9)	1,037 (9.2)	744 (10.6)	292 (6.8)
Metabolic <sup>b</sup>	2,915 (13.1)	484 (16.6)	310 (17.4)	173 (15.4)
Musculoskeletal/skin	1,519 (6.8)	301 (19.8)	168 (22.9)	133 (17.0)
Neurological	7,687 (34.5)	1,377 (17.9)	886 (19.4)	491 (15.7)
Cardiovascular	985 (4.4)	266 (27.0)	148 (27.8)	118 (26.1)
Non-specific chronic condition	1,599 (7.2)	453 (28.3)	265 (31.4)	188 (24.9)

<sup>a</sup> A child may be hospitalized for multiple types of chronic health conditions, thus the sum of the numbers of children hospitalized for different types of chronic health conditions is greater than the total number of children hospitalized for any chronic health conditions.

<sup>b</sup> Metabolic/endocrine/digestive/renal/genitourinary conditions.

at school start, and 30% of children had been hospitalized without a chronic condition. Hospitalization prior to school start was associated with increased risk to development, for children with and without chronic health conditions. Among children with chronic health conditions, risk of reduced development increased with increasing frequency of hospitalizations and longer duration in hospital. Children with the most frequent (more than 7 times) and longest duration of hospitalization (more than 2 weeks) had 1.4-fold increased risk of being DHR at school start. Early development was compromised across all developmental domains for children who had been hospitalized prior to school start, with and without chronic health conditions. Those hospitalized with chronic health conditions were at particular increased risk compared to those hospitalized without chronic health conditions. The domains of physical health and communication skills exhibited the strongest decrements related to hospitalization severity. Children hospitalized with mental health/behavioral/developmental conditions were more likely to be identified as DHR and having special needs than children hospitalized with other chronic health conditions.

Severe and chronic health conditions during childhood have the potential to impact the child, their family and society (Kazak, 2006; Piquart & Teubert, 2012). Our findings highlight that this impact may be further exacerbated with extended periods in hospital. Further, our results show that

when factors known to impact on early child development are statistically controlled for (such as maternal education level, familial socio-demographic factors at child's birth and cultural and linguistic diversity), hospitalization with chronic health conditions further impacts early development and school readiness. There is well documented evidence of socioeconomic and racial disparities in both health and early child developmental outcomes (Newacheck et al., 2002; Peterson et al., 2018), and factors that also affect child developmental outcomes, and are associated with suboptimal chronic health condition management, such as SES, family structure, available support, parental health and mental illness, access to service which may compound impacts on both health and education outcomes (Newacheck et al., 2002). For example, management of chronic health conditions and accessing healthcare (Newacheck et al., 2002) and high-quality preschool programs (Bassok & Galdo, 2016) are likely to be more challenging for families from disadvantaged socioeconomic backgrounds. Future work investigating these interactions is therefore warranted for development of services and interventions that consider the whole of child context.

Time away from usual activities and opportunities to develop school readiness due to chronic health conditions can lead to life-long reductions in academic performance, social and emotional wellbeing (Lum et al., 2017; Maslow et al., 2012; Peterson et al., 2018). The cost of chronic health

conditions born out across the lifespan is significant with high health care utilization and costs observed at school entry (Nasuuna et al., 2016; Quach & Barnett, 2015), persisting into adulthood (Delaney & Smith, 2012). The needs of this population are under-recognized, and are therefore not yet well addressed by either health or education systems (Goldfeld et al., 2012; Peterson et al., 2018). The combined cost of chronic health conditions and missed education opportunities on productivity has not been quantified, but the individual level impact of reduced academic performance, lower graduation rates, and low rates of further training, can culminate in higher rates of unemployment (Lum et al., 2017).

As observed elsewhere (Pinquart, 2020), physical health was compromised in children hospitalized with chronic health conditions. Early development of communication, language and social competence were also affected. Chronic health conditions may act as a specific barrier to social interactions through disruption to friendships and impact on development of social cognitive skills in early life (Janin et al., 2018; Lum et al., 2017). Communication and social-emotional skills are critical to academic success (Maslow et al., 2012; Romano et al., 2010), and particularly social success which can protect against negative impacts on health, mental health and overall quality of life (Dalton et al., 2016; Jones et al., 2015; Maslow et al., 2012). Reduced development in these skills at school start may preclude establishing strong social support networks to protect against mental health difficulties in later life (Jones et al., 2015). For young adults and adults with childhood-onset chronic health conditions, social and emotional well-being are areas of life-long vulnerability, contributing to overall decreased quality of life, physical health problems, and increased healthcare costs (Dalton et al., 2016).

Our data indicate hospitalization with any chronic condition in the first 5 years of life can impact early development and school readiness, however there were some differences across domains by chronic health conditions. For children hospitalized with metabolic, musculoskeletal and skin, neurological, or cardiovascular chronic health conditions, physical health and wellbeing had greater odds of DV compared to other domains assessed. Children with mental health/behavioral/developmental conditions early in life were more likely to be developmentally vulnerable across all domains assessed, potentially due to the AEDC focus on social and emotional development. For children hospitalized with cancer and other blood disorders, respiratory chronic health conditions both physical health and wellbeing and language and communication were at increased odds of DV compared to other domains. Consistent with others, boys were more likely to have identified special needs (Goldfeld et al., 2012). In contrast, girls had slightly greater odds of DV, possibly because boys were more likely identified as having special needs and therefore not included in the AEDC assessment of DV. However, sample sizes were small with increasing severity of hospitalization, and this result requires cautious interpretation and further research.

Early developmental health difficulties are likely to be long lasting in the absence of intervention (Dekker et al., 2007), and emotional and behavioral difficulties at school entry are predictive of later education and learning outcomes (Barnett et al., 2018). Early intervention, and support in developing school readiness skills with these young children is especially warranted. This may be even more critical in the context of the global COVID-19 pandemic. Children with chronic health

conditions may be at increased risk of contracting COVID-19 and severe negative impacts (Tsankov et al., 2021; Woodruff et al., 2022), and as a result may face greater limitations on their engagement with childcare and other early childhood school readiness programs. While COVID-19, associated social distancing requirements, and school and childcare closures have caused increased stress on families (Kerr et al., 2021; Rao et al., 2021), family stress may be particularly elevated in the homes of children with chronic health conditions as the burden of managing a chronic health conditions is compounded by fears of increased risk of infection and reduced access to medical care and psychological support (Davies et al., 2022; Wauters et al., 2022).

Clinicians and health care providers who have regular contact with children with chronic health conditions and their families are ideally placed to identify and refer these children to programs for promoting school readiness (Peterson et al., 2018). However, clinicians report unmet training needs in understanding and managing the implications of health on schooling (Ellis et al., 2019). These unmet needs may limit referrals to appropriately trained pediatric psychologists who are well-suited to deliver evidence-based interventions across all domains of development to support school readiness in the context of chronic health conditions. Preschool interventions that promote school readiness, self-regulation, and early learning have the potential to reduce burden on health services and reduce the need for later remedial interventions (Bierman et al., 2018). Innovative approaches to delivering evidence-based mental health treatments, such as parent-child interaction therapy, at the hospital bedside may support both mental health and health status of children with chronic health conditions, and importantly can be tailored address care disparities (Christian-Brandt & Santacrose, 2020). Future research focusing on identifying potential for developmental impact and developing interventions targeting the unique developmental domains impacted by specific chronic health conditions will support practice, health, and education outcomes. For example, implementing developmental assessments for children with cancer in hospital clinics supported timely access to developmental domain specific, age appropriate, play-based, family-centered intervention services to support early childhood development (Harman et al., 2021). Integration and systemic implementation of developmental testing can reduce barriers to accessing timely, clinically, and developmentally appropriate support across the silos of health, psychology, and education for children with chronic health conditions to ultimately support optimal development in the first 5 years of life in the context of health (Harman et al., 2021).

While our study has several strengths, there were limitations. Our study cannot account for individual and family level differences including parent health, lifestyle, health behaviors and parent education. Our data also do not account for approaches to learning and parenting style, previously shown to predict academic performance for children with and without chronic health conditions (Barnett et al., 2018). Due to confidentiality and ethics agreements, we were not able to identify and report on the outcomes of children identifying as Aboriginal and Torres Strait Islander, and the data we do have on ethnicity/race are limited (i.e. language background other than English and maternal country of birth which we do have are not good measures of ethnicity). Further, as we used hospitalization data, we could not identify children who

had chronic health conditions but did not have any hospitalization records where their chronic health condition was noted in the APDC. Many of these children may receive care from primary and community-based healthcare providers. A further limitation is children with special needs did not have AEDC domain or vulnerability risk determined (according to scoring and administration instructions: [Australian Government, 2019](#)), yet this cohort may be most in need of early identification of developmental needs and tailored support services. Thus, the lack of the AEDC outcome for children reported to have special needs may result in underestimated effects of hospitalizations with chronic conditions on school readiness found in this study. This may be particularly an issue for children admitted with mental health diagnoses, given 60% of these children had identified special needs. We did not examine hospitalization of comorbidity (i.e., hospitalization for multiple chronic conditions) in this study, due to the complex pattern of comorbidity (e.g., various types, numbers and durations of comorbid chronic conditions). This warrants a separate investigation. Our study importantly demonstrates the impact of more severe chronic health conditions on school readiness across an entire population and is consistent with other studies using parent report ([Nasuuna et al., 2016](#)). In a study of an Australian cohort of 24,678 children starting school, over 50% were identified by their parents as having a health condition such as allergy, sensory, dental, intellectual, behavioral, and physical health conditions ([Nasuuna et al., 2016](#)). [Nasuuna et al. \(2016\)](#) found more serious or complex conditions, which are more likely to require hospitalization (e.g. epilepsy, cystic fibrosis), and intellectual, developmental conditions impacted on later academic performance, while less serious health problems (e.g. dental problems, asthma) did not. However, given we found hospitalization with and without chronic health conditions prior to school start was associated with impacts to early development, further research is needed to better support children requiring hospitalization prior to school start.

## Conclusions

Children hospitalized with chronic health conditions are at risk of compromised early development and school readiness compared to children without hospitalizations in the first 5 years of life. Children with the most serious and severe chronic health conditions as indicated by increasing frequency and duration of hospitalizations increases the risk of poor school readiness. Our data also indicate chronic health conditions in the first 5 years of life impact more than physical health. Caring for these children must therefore consider the impact on developmental domains crucial for school readiness, particularly social, emotional, and language development. Pediatric psychologists with interdisciplinary expertise across physical, cognitive, social, and emotional development and health and illness issues in children, adolescents, and families are therefore well positioned to work with healthcare providers and educators to support school readiness and life-long academic success for children with chronic health conditions.

## Supplementary Data

Supplementary data can be found at: <https://academic.oup.com/jpepsy>.

## Author Contributions

Joanna E. Fardell (Conceptualization [lead], data curation [supporting], formal analysis [supporting], investigation [equal], methodology [equal], project administration [supporting], resources [equal], writing – original draft [lead], writing – review & Editing [lead]), Nan Hu (Conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, validation, visualization, writing – original draft, writing – review & Editing [equal]), Claire E. Wakefield (Conceptualization, methodology, supervision, writing – review & Editing [equal]), Glenn Marshall (Conceptualization, supervision, writing – review & Editing [equal]), Jane Bell (Data curation, formal analysis, methodology, project administration, resources, software, writing – review & Editing [equal]), Raghu Lingam (Conceptualization, funding acquisition, methodology, supervision, writing – review & Editing [equal]), and Natasha Nassar (Conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, writing – review & Editing [equal])

## Acknowledgements

The authors would like to thank the NSW Ministry of Health for access to the population health data used in this study, and the NSW Centre for Health Record Linkage for linking the datasets. We also acknowledge the use of data from the Australian Early Development Census (AEDC) for this study. The AEDC is funded by the Australian Government Department of Education, Skills and Employment. The findings and views reported are those of the author and should not be attributed to the Department or the Australian Government.

## Funding

The authors acknowledge the support of the Maridulu Budyari Gumal, The Sydney Partnership for Health, Education, Research & Enterprise (SPHERE) Kids to Adults (K2A) Clinical Academic Group. Dr. J. E. Fardell is a Maridulu Budyari Gumal (SPHERE) Cancer CAG Senior Research Fellow and is supported by a Cancer Institute NSW Research Capacity Building Grant (2021/CBG003) and the Kids Cancer Project. Prof C. E. Wakefield is supported by a Career Development Fellowship from the National Health and Medical Research Council (NHMRC) of Australia (APP1143767). Prof R. Lingam and Prof N. Nassar are funded by the Financial Markets Foundation for Children. The other authors received no funding relevant to this article.

## Conflicts of interest

None declared.

## References

- Anthony, K. K., Gil, K. M., & Schanberg, L. E. (2003). Brief report: Parental perceptions of child vulnerability in children with chronic illness. *Journal of Pediatric Psychology*, 28(3), 185–190. <https://doi.org/10.1093/jpepsy/jsg005>

- Australian Bureau of Statistics. (2008). *An introduction to socio-economic indexes for areas (SEIFA) 2006*. Australian Bureau of Statistics.
- Australian Government. (2013). A snapshot of early childhood development in Australia 2012 – AEDI National Report Re-issue November 2013. Australian Government.
- Australian Government. (2019). *Australian Early Development Census (AEDC) data guidelines*. Australian Government. <https://www.aedc.gov.au/resources> Retrieved 24 April 2023.
- Barnett, T., Giallo, R., Kelaher, M., Goldfeld, S., & Quach, J. (2018). Predictors of learning outcomes for children with and without chronic illness: An Australian longitudinal study. *Child: care, Health and Development*, 44(6), 832–840. <https://doi.org/10.1111/cch.12597>
- Bassok, D., & Galdo, E. (2016). Inequality in preschool quality? Community-level disparities in access to high-quality learning environments. *Early Education and Development*, 27(1), 128–144. <https://doi.org/10.1080/10409289.2015.1057463>
- Bell, M. F., Bayliss, D. M., Glauert, R., Harrison, A., & Ohan, J. L. (2016). Chronic illness and developmental vulnerability at school entry. *Pediatrics*, 137(5), e20152475. <https://doi.org/10.1542/peds.2015.2475>
- Bethell, C. D., Read, D., Blumberg, S. J., & Newacheck, P. W. (2008). What is the prevalence of children with special health care needs? Toward an understanding of variations in findings and methods across three national surveys. *Maternal and Child Health Journal*, 12(1), 1–14. <https://doi.org/10.1007/s10995-007-0220-5>
- Bierman, K. L., Welsh, J., Heinrichs, B. S., & Nix, R. L. (2018). Effect of preschool home visiting on school readiness and need for services in elementary school: A randomized clinical trial. *JAMA Pediatrics*, 172(8), e181029. <https://doi.org/10.1001/jamapediatrics.2018.1029>
- Brinkman, S., Gregory, T., Harris, J., Hart, B., Blackmore, S., & Janus, M. (2013). Associations between the early development instrument at age 5, and reading and numeracy skills at ages 8, 10 and 12: A prospective linked data study. *Child Indicators Research*, 6(4), 695–708. <https://doi.org/10.1007/s12187-013-9189-3>
- Brinkman, S. A., Gregory, T. A., Goldfeld, S., Lynch, J. W., & Hardy, M. (2014). Data resource profile: The Australian early development index (AEDI). *International Journal of Epidemiology*, 43(4), 1089–1096. <https://doi.org/10.1093/ije/dyu085>
- Campbell, F., Conti, G., Heckman, J. J., Moon, S. H., Pinto, R., Pungello, E., & Pan, Y. (2014). Early childhood investments substantially boost adult health. *Science (New York, N.Y.)*, 343(6178), 1478–1485. <https://doi.org/10.1126/science.1248429>
- Chang, C. D. (2019). Social determinants of health and health disparities among immigrants and their children. *Current Problems in Pediatric and Adolescent Health Care*, 49(1), 23–30. <https://doi.org/10.1016/j.cppeds.2018.11.009>
- Christian-Brandt, A. S., & Santacrose, D. (2020). Adapting PCIT to address mental health care disparities among underserved families impacted by pediatric illness: A case series of bedside PCIT. *Clinical Practice in Pediatric Psychology*, 8(2), 164–175. <https://doi.org/10.1037/cpp0000322>
- Coller, R. J., Lerner, C. F., Eickhoff, J. C., Klitzner, T. S., Sklansky, D. J., Ehlenbach, M., & Chung, P. J. (2016). Medical complexity among children with special health care needs: A two-dimensional view. *Health Services Research*, 51(4), 1644–1669. <https://doi.org/10.1111/1475-6773.12416>
- Dalton, E. D., Hammen, C. L., Brennan, P. A., & Najman, J. M. (2016). Pathways maintaining physical health problems from childhood to young adulthood: The role of stress and mood. *Psychology & Health*, 31(11), 1255–1271.
- Davies, J., O'Connor, M., Halkett, G. K. B., Kelada, L., & Gottardo, N. G. (2022). Parents' experiences of childhood cancer during the COVID-19 pandemic: An Australian perspective. *Journal of Pediatric Psychology*, 47(2), 148–157. <https://doi.org/10.1093/jpepsy/jsab125>
- Dekker, M. C., Ferdinand, R. F., van Lang, N. D., Bongers, I. L., van der Ende, J., & Verhulst, F. C. (2007). Developmental trajectories of depressive symptoms from early childhood to late adolescence: Gender differences and adult outcome. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, 48(7), 657–666. <https://doi.org/10.1111/j.1469-7610.2007.01742.x>
- Delaney, L., & Smith, J. P. (2012). Childhood health: Trends and consequences over the life course. *The Future of Children*, 22(1), 43–63. <https://doi.org/10.1353/foc.2012.0003>
- Ehrlich, S. B., Gwynne, J. A., Stitzel Pareja, A., Allensworth, E. M., Moore, P., Jagesic, S., & Soric, E. (2014). *Preschool attendance in Chicago Public Schools: Relationships with learning outcomes and reasons for absences*. ERIC.
- Ellis, S. J., Fardell, J. E., Wakefield, C. E., Schilstra, C. E., Burns, M. A., Donnan, B., Walwyn, T., Lum, A., Marshall, G., Carter, A., Barton, B., & Cohn, R. J. (2019). Are we meeting the training needs of healthcare and education professionals supporting children with cancer in their return to school? *Pediatric Blood & Cancer*, 66(4), e27575. <https://doi.org/10.1002/pbc.27575>
- Goldfeld, S., O'Connor, M., Sayers, M., Moore, T., & Oberklaid, F. (2012). Prevalence and correlates of special health care needs in a population cohort of Australian children at school entry. *Journal of Developmental and Behavioral Pediatrics : JDBP*, 33(4), 319–327. <https://doi.org/10.1097/DBP.0b013e31824a7b8e>
- Hardelid, P., Dattani, N., & Gilbert, R. Child Death Overview Working Group (2014). Estimating the prevalence of chronic conditions in children who die in England, Scotland and Wales: A data linkage cohort study. *BMJ Open*, 4(8), e005331.
- Harman, J. L., Molnar, A. E., Jr, Jacola, L. M., Corr, A., Scott, A., Potter, B., Schwartzberg, S., Boyer, H., Greear, J., & Willard, V. W. (2021). Establishing a hospital-based early intervention program for young children with cancer: A quality improvement initiative. *Clinical Practice in Pediatric Psychology*, 9(4), 323–333. <https://doi.org/10.1037/cpp0000375>
- Janin, M. M. H., Ellis, S. J., Lum, A., Wakefield, C. E., & Fardell, J. E. (2018). Parents' perspectives on their child's social experience in the context of childhood chronic illness: A qualitative study. *Journal of Pediatric Nursing*, 42, e10–e18.
- Jones, D. E., Greenberg, M., & Crowley, M. (2015). Early social-emotional functioning and public health: The relationship between kindergarten social competence and future wellness. *American Journal of Public Health*, 105(11), 2283–2290. <https://doi.org/10.2105/ajph.2015.302630>
- Kazak, A. E. (2006). Pediatric Psychosocial Preventative Health Model (PPPHM): Research, practice, and collaboration in pediatric family systems medicine. *Families, Systems, & Health*, 24(4), 381–395.
- Keogh, R. H., Szczesniak, R., Taylor-Robinson, D., & Bilton, D. (2018). Up-to-date and projected estimates of survival for people with cystic fibrosis using baseline characteristics: A longitudinal study using UK patient registry data. *Journal of Cystic Fibrosis : Official Journal of the European Cystic Fibrosis Society*, 17(2), 218–227. <https://doi.org/10.1016/j.jcf.2017.11.019>
- Kerr, M. L., Fanning, K. A., Huynh, T., Botto, I., & Kim, C. N. (2021). Parents' self-reported psychological impacts of COVID-19: Associations with parental burnout, child behavior, and income. *Journal of Pediatric Psychology*, 46(10), 1162–1171. <https://doi.org/10.1093/jpepsy/jsab089>
- Lum, A., Wakefield, C. E., Donnan, B., Burns, M. A., Fardell, J. E., & Marshall, G. M. (2017). Understanding the school experiences of children and adolescents with serious chronic illness: A systematic meta-review. *Child: Care, Health and Development*, 43(5), 645–662. <https://doi.org/10.1111/cch.12475>
- Maslow, G., Haydon, A. A., McRee, A. L., & Halpern, C. T. (2012). Protective connections and educational attainment among young adults with childhood-onset chronic illness. *The Journal of School Health*, 82(8), 364–370. <https://doi.org/10.1111/j.1746-1561.2012.00710.x>
- McCoy, D. C., Yoshikawa, H., Ziol-Guest, K. M., Duncan, G. J., Schindler, H. S., Magnuson, K., Yang, R., Koepp, A., & Shonkoff, J. P. (2017). Impacts of early childhood education on medium- and long-term educational outcomes. *Educational Researcher (Washington, D.C.: 1972)*, 46(8), 474–487. <https://doi.org/10.3102/0013189x17737739>



- Morris, J. N., Roder, D., Turnbull, D., & Hunkin, H. (2021). The impact of cancer on early childhood development: A linked data study. *Journal of Pediatric Psychology*, 46(1), 49–58. <https://doi.org/10.1093/jpepsy/jsaa084>
- Nasuuna, E., Santoro, G., Kremer, P., & de Silva, A. M. (2016). Examining the relationship between childhood health conditions and health service utilisation at school entry and subsequent academic performance in a large cohort of Australian children. *Journal of Paediatrics and Child Health*, 52(7), 750–758.
- Newacheck, P. W., Hung, Y.-Y., & Wright, K. K. (2002). Racial and ethnic disparities in access to care for children with special health care needs. *Ambulatory Pediatrics*, 2(4), 247–254. [https://doi.org/10.1367/1539-4409\(2002\)002<0247:RAEDIA>2.0.CO;2](https://doi.org/10.1367/1539-4409(2002)002<0247:RAEDIA>2.0.CO;2)
- Pearce, A., Dundas, R., Whitehead, M., & Taylor-Robinson, D. (2019). Pathways to inequalities in child health. *Archives of Disease in Childhood*, 104(10), 998–1003. <https://doi.org/10.1136/archdis-child-2018-314808>
- Peterson, J. W., Loeb, S., & Chamberlain, L. J. (2018). The intersection of health and education to address school readiness of all children. *Pediatrics*, 142(5), e20181126. <https://doi.org/10.1542/peds.2018-1126>
- Pinquart, M. (2020). Health-related quality of life of young people with and without chronic conditions. *Journal of Pediatric Psychology*, 45(7), 780–792. <https://doi.org/10.1093/jpepsy/jsaa052>
- Pinquart, M., & Teubert, D. (2012). Academic, physical, and social functioning of children and adolescents with chronic physical illness: A meta-analysis. *Journal of Pediatric Psychology*, 37(4), 376–389. <https://doi.org/10.1093/jpepsy/jsr106>
- Quach, J., & Barnett, T. (2015). Impact of chronic illness timing and persistence at school entry on child and parent outcomes: Australian longitudinal study. *Academic Pediatric*, 15(1), 89–95. <https://doi.org/10.1016/j.acap.2014.08.004>
- Rao, N., Fisher, P. A., & Editors, C.-S. S.; COVID-19 Special Section Editors (2021). The impact of the COVID-19 pandemic on child and adolescent development around the world. *Child Development*, 92(5), e738–e748. <https://doi.org/10.1111/cdev.13653>
- Reynolds, A. J., Temple, J. A., White, B. A. B., Ou, S.-R., & Robertson, D. L. (2011). Age 26 cost-benefit analysis of the child-parent center early education program. *Child Development*, 82(1), 379–404. <https://doi.org/10.1111/j.1467-8624.2010.01563.x>
- Robison, L. L., & Hudson, M. M. (2014). Survivors of childhood and adolescent cancer: Life-long risks and responsibilities. *Nature Reviews Cancer*, 14(1), 61–70.
- Rogers, J., Reed, M. P., Blaine, K., & Manning, H. (2021). Children with medical complexity: A concept analysis. *Nursing Forum*, 56(3), 676–683. <https://doi.org/10.1111/nuf.12559>
- Romano, E., Babchishin, L., Pagani, L. S., & Kohen, D. (2010). School readiness and later achievement: Replication and extension using a nationwide Canadian survey. *Developmental Psychology*, 46(5), 995–1007.
- Saatci, D., Ranger, T. A., Garriga, C., Clift, A. K., Zaccardi, F., Tan, P. S., Patone, M., Coupland, C., Harnden, A., Griffin, S. J., Khunti, K., Dambha-Miller, H., & Hippisley-Cox, J. (2021). Association between race and COVID-19 outcomes among 2.6 million children in England. *JAMA Pediatrics*, 175(9), 928–938. <https://doi.org/10.1001/jamapediatrics.2021.1685>
- Steiner, J. M., & Kovacs, A. H. (2018). Adults with congenital heart disease – Facing morbidities and uncertain early mortality. *Progress in Pediatric Cardiology*, 48, 75–81. <https://doi.org/10.1016/j.pped-card.2018.01.006>
- Trent, M., Dooley, D. G., Dougé, J., Cavanaugh, R. M., Lacroix, A. E., Fanburg, J., Rahmandar, M. H., Hornberger, L. L., Schneider, M. B., Yen, S., Chilton, L. A., Green, A. E., Dilley, K. J., Gutierrez, J. R., Duffee, J. H., Keane, V. A., Krugman, S. D., McKelvey, C. D., Linton, J. M., ... Wallace, S. B., Section on Adolescent Health (2019). The impact of racism on child and adolescent health. *Pediatrics*, 144(2), e20191765. <https://doi.org/10.1542/peds.2019-1765>
- Tsankov, B. K., Allaire, J. M., Irvine, M. A., Lopez, A. A., Sauvé, L. J., Vallance, B. A., & Jacobson, K. (2021). Severe COVID-19 infection and pediatric comorbidities: A systematic review and meta-analysis. *International Journal of Infectious Diseases : IJID : Official Publication of the International Society for Infectious Diseases*, 103, 246–256. <https://doi.org/10.1016/j.ijid.2020.11.163>
- Van Der Lee, J. H., Mokkink, L. B., Grootenhuys, M. A., Heymans, H. S., & Offringa, M. (2007). Definitions and measurement of chronic health conditions in childhood: A systematic review. *JAMA: The Journal of the American Medical Association*, 297(24), 2741–2751.
- Walker, S. P., Wachs, T. D., Grantham-McGregor, S., Black, M. M., Nelson, C. A., Huffman, S. L., Baker-Henningham, H., Chang, S. M., Hamadani, J. D., Lozoff, B., Gardner, J. M. M., Powell, C. A., Rahman, A., & Richter, L. (2011). Inequality in early childhood: Risk and protective factors for early child development. *The Lancet (London, England)*, 378(9799), 1325–1338. [https://doi.org/10.1016/S0140-6736\(11\)60555-2](https://doi.org/10.1016/S0140-6736(11)60555-2)
- Wauters, A., Vervoort, T., Dhondt, K., Soenens, B., Vansteenkiste, M., Morbée, S., Waterschoot, J., Haerynck, F., Vandekerckhove, K., Verhelst, H., Van Aken, S., Raes, A., Schelstraete, P., Walle, J. V., & Van Hoecke, E. (2022). Mental health outcomes among parents of children with a chronic disease during the COVID-19 pandemic: The role of parental burn-out. *Journal of Pediatric Psychology*, 47(4), 420–431. <https://doi.org/10.1093/jpepsy/jsab129>
- Woodruff, R. C., Campbell, A. P., Taylor, C. A., Chai, S. J., Kawasaki, B., Meek, J., Anderson, E. J., Weigel, A., Monroe, M. L., Reeg, L., Bye, E., Sosin, D. M., Muse, A., Bennett, N. M., Billing, L. M., Sutton, M., Talbot, H. K., McCaffrey, K., Pham, H., ... Havers, F. (2022). Risk factors for severe COVID-19 in children. *Pediatrics*, 149(1), e2021053418. <https://doi.org/10.1542/peds.2021-053418>
- Zeger, S. L., Liang, K. Y., & Albert, P. S. (1988). Models for longitudinal data: A generalized estimating equation approach. *Biometrics*, 44(4), 1049–1060. <https://www.ncbi.nlm.nih.gov/pubmed/3233245>