2-26-2014

Low socioeconomic status is associated with worse survival in children with cancer: A systematic review

Sumit Gupta
Hospital for Sick Children University of Toronto

Marta Wilejto
Hospital for Sick Children University of Toronto, marta.wilejto@lhsc.on.ca

Jason D. Pole
Pediatric Oncology Group of Ontario

Astrid Guttmann
University of Toronto

Lillian Sung
Hospital for Sick Children University of Toronto

Low Socioeconomic Status Is Associated with Worse Survival in Children with Cancer: A Systematic Review

Sumit Gupta[1,2,6,7]*, Marta Wilejto[1,6], Jason D. Pole[3,4], Astrid Guttmann[2,4,5,7], Lillian Sung[1,2,6,7]

1 Division of Haematology/Oncology, the Hospital for Sick Children, Toronto, Ontario, Canada, 2 Department of Paediatrics, University of Toronto, Toronto, Ontario, Canada, 3 Pediatric Oncology Group of Ontario, Toronto, Ontario, Canada, 4 Institute for Clinical and Evaluative Sciences, Toronto, Ontario, Canada, 5 Division of Paediatric Medicine, Hospital for Sick Children, Toronto, Ontario, Canada, 6 Program in Child Health Evaluative Sciences, the Hospital for Sick Children, Toronto, Ontario, Canada, 7 Institute for Health, Policy Management and Evaluation, University of Toronto, Toronto, Ontario, Canada

Abstract

Background: While low socioeconomic status (SES) has been associated with inferior cancer outcome among adults, its impact in pediatric oncology is unclear. Our objective was therefore to conduct a systematic review to determine the impact of SES upon outcome in children with cancer.

Methods: We searched Ovid Medline, EMBASE and CINAHL from inception to December 2012. Studies for which survival-related outcomes were reported by socioeconomic subgroups were eligible for inclusion. Two reviewers independently assessed articles and extracted data. Given anticipated heterogeneity, no quantitative meta-analyses were planned *a priori*.

Results: Of 7,737 publications, 527 in ten languages met criteria for full review; 36 studies met final inclusion criteria. In low- and middle-income countries (LMIC), lower SES was uniformly associated with inferior survival, regardless of the measure chosen. The majority of associations were statistically significant. Of 52 associations between socioeconomic variables and outcome among high-income country (HIC) children, 38 (73.1%) found low SES to be associated with worse survival, 15 of which were statistically significant. Of the remaining 14 (no association or high SES associated with worse survival), only one was statistically significant. Both HIC studies examining the effect of insurance found uninsured status to be statistically associated with inferior survival.

Conclusions: Socioeconomic gradients in which low SES is associated with inferior childhood cancer survival are ubiquitous in LMIC and common in HIC. Future studies should elucidate mechanisms underlying these gradients, allowing the design of interventions mediating socioeconomic effects. Targeting the effect of low SES will allow for further improvements in childhood cancer survival.

Introduction

Socioeconomic status (SES), a multi-dimensional construct encompassing economic resources, power and social standing, has been associated with a number of health outcomes.[1–4] Understanding the mechanisms behind such associations is necessary in order to reduce health disparities. Among adult patients, strong evidence exists supporting socioeconomic gradients in cancer mortality. [5]

By contrast, the equivalent pediatric literature is sparse and predominantly restricted to low- and middle-income countries (LMIC). [6,7] High-income country (HIC) studies have yielded seemingly contradictory results.[8–10] Given differences in cure rates and developmental position, adult socioeconomic gradients cannot be extrapolated to children with cancer.

We therefore undertook the first systematic review of the literature examining the impact of SES upon pediatric oncology outcomes. Our primary objective was to determine the impact of income- and education-based measures of SES on event-free survival (EFS), overall survival (OS) and disease-free survival (DFS) among children with cancer. Secondary objectives included determining the effect of other SES measures, as well as the effect of SES on treatment-related mortality (TRM), relapse and abandonment of therapy.

Methods

The conduct of the review followed the PRISMA framework. [11] Both the PRISMA Checklist and the initial protocol can be found in Checklist S1 and Text S1.

Data Sources

We performed electronic searches of Ovid Medline, EMBASE and CINAHL from inception to December 10th, 2012 with the assistance of a library scientist. The Medline search strategy is illustrated in Table 1, with complete strategies illustrated in Text S2.

Table 1. Medline Search Strategy.

Set	History	Results	Comments
1	"emigration and immigration"/or residence characteristics/or "catchment area (health) "/or housing/or public housing/or health status disparities/or Healthcare Disparities/or rural health services/or suburban health services/or urban health services/or exp Insurance/or exp Health Services Accessibility/or exp Socioeconomic Factors/	54,3627	SES Terms
2	Exp Neoplasms/	2,416,057	Neoplasm terms
3	1 and 2	3,227,924	Base clinical set
4	limit 3 to "all child (0 to 18 years)"	4,042	Age group limit
5	(infan* or child* or adolescen* or youth* or teen* or pediatric* or paediatric*).mp.	2,961,284	Age group textword terms
6	4 or (3 and 5)	4,533	FINAL Results

doi:10.1371/journal.pone.0089482.t001

Study Selection

Inclusion and exclusion criteria were defined *a priori*. Inclusion criteria were: (1) ecologic, cross-sectional, cohort, case-control or randomized control trial designs; (2) pediatric data available, with pediatric ages defined by authors, and (3) at least one pre-specified survival-related outcome reported by subgroups defined by a pre-specified socioeconomic variable (see below). Biologic factors may account for a portion of the disparities in outcome seen between different ethnic groups. [12] Since the independent effects of biology and SES cannot be disentangled when ethnicity is the sole proxy of SES, such studies were excluded. There was no restriction by language. Two reviewers (SG, MW) independently evaluated identified titles and abstracts, retrieved any potentially relevant manuscript and determined eligibility; discrepancies were resolved through consensus. Agreement between reviewers was assessed using the kappa statistic. [13] Non-English articles were assessed with the assistance of pediatric oncologists whom were native speakers of the relevant language.

Data Abstraction

Two reviewers (SG, MW) independently abstracted data using standardized forms. The primary outcomes were EFS, OS and DFS; secondary outcomes were specific causes of treatment failure (TRM, relapse, abandonment). Relative survival was assumed to be comparable to OS. Multiple measures of SES exist in the literature, reflecting three main domains: material resources, knowledge related assets and social standing. [14] Though income and education (including measures of occupation) were the key variables of interest in this study, we included a broad range of SES measures reflecting these domains: material possession (e.g. car ownership), family composition (e.g. marital status), health insurance status, health care accessibility and immigrant status. Both ecologic and individual-level variables were included. When measures over multiple time periods were available, only the most contemporaneous time period was recorded. Study authors were contacted to solicit missing data.

Study quality was assessed using a framework of potential biases developed by Hayden et?al to evaluate prognosis studies. [15] Four key indicators of study quality relevant for studies examining the impact of SES were identified *a priori*: (1) the degree to which study samples reflected underlying populations, (2) whether loss to follow-up was associated with socioeconomic characteristics, (3) whether potential confounders were accounted for and (4) the appropriateness of the analysis. Further details are provided in the online supplemental data. When assessing the degree to which study samples represented the general population, samples derived from clinical trials were judged to be only partly representative of
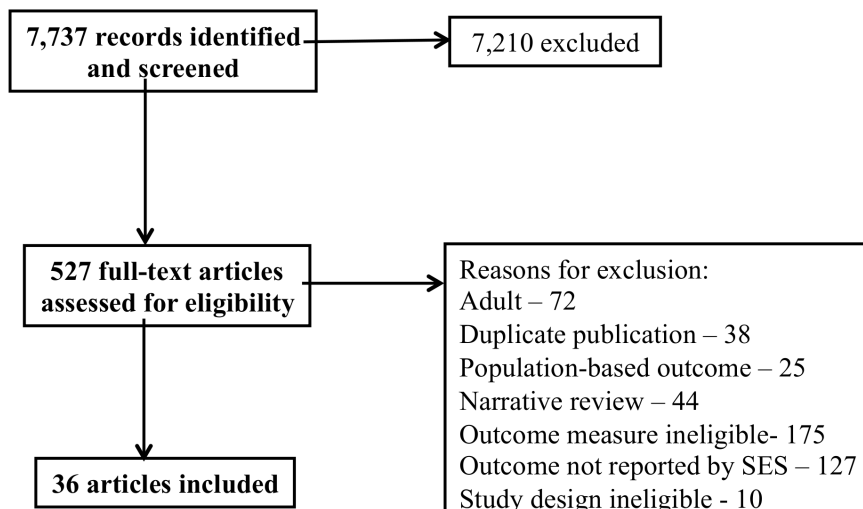
Figure 1. PRISMA flow diagram.
doi:10.1371/journal.pone.0089482.g001

Table 2. Characteristics of included studies.

Characteristic	Studies, N (%)	
	LMIC (N = 10)	HIC (N = 26)
Malignancy		
All cancers	0 (0.0)	8 (30.8)
Leukemia or lymphoma	9 (90.0)	15 (57.7)
Solid tumor	1 (10.0)	1 (3.8)
Central nervous system tumor	0 (0.0)	2 (7.7)
Type of socioeconomic variable examined		
Ecologic	1 (10.0)	13 (50.0)
Income-based	7 (70.0)	2 (7.7)
Education-based[a]	6 (60.0)	10 (38.5)
Other[b]	5 (50.0)	10 (38.5)
Sample Size		
<100	1 (10.0)	4 (15.4)
100–999	9 (90.0)	9 (34.6)
1,000–9,999	0 (0.0)	12 (46.2)
≥10,000	0 (0.0)	1 (3.8)
Restricted to adolescents/young adults[c]		
Yes	0 (0.0)	2 (7.7)
No	10 (100.0)	24 (92.3)
Study sample adequately reflective of general population[d]		
Yes	8 (80.0)	21 (80.7)
No/Partial/Unsure	2 (20.0)	5 (19.2)
Loss to follow-up unrelated to socioeconomic status[d]		
Yes	3 (30.0)	21 (80.7)
No/Partial/Unsure	1 (10.0)	5 (19.2)
Not applicable	6 (60.0)	0 (0.0)
Potential confounders accounted for[d]		
Yes	6 (60.0)	12 (46.2)
No/Partial/Unsure	4 (40.0)	14 (53.8)
Analysis appropriate[d]		
Yes	8 (80.0)	18 (69.2)
No/Partial/Unsure	2 (20.0)	8 (30.8)

HIC – high-income countries; LMIC – low- and middle-income countries.
[a]Also included occupation-based measures of socioeconomic status.
[b]Included measures of material possession, family composition, insurance status, immigrant status, and health care accessibility.
[c]As defined by study authors.
[d]See supplemental data for definitions of study quality variables.
doi:10.1371/journal.pone.0089482.t002

the overall population, as patients of low SES who consent to trials may be systematically different than those who do not. [16,17] Single institution studies were also assessed as only partly representative. The loss to follow-up quality indicator was judged not applicable for settings in which abandonment of therapy constituted a significant cause of treatment failure. [18] As various indicators measure different domains of socioeconomic position, accounting for confounding was assessed as adequate if both a measure of disease risk and a second SES indicator were included. Analyses that were not based on time-to-event data were assessed as partially adequate.

Analysis

Given the anticipated heterogeneity in settings, SES measures and malignancies, no quantitative meta-analyses were planned. The magnitude and underlying mechanisms of any association between SES and outcome are likely to differ between developing and developed countries. The results were therefore summarized separately for LMIC and for HIC, as defined by the World Bank using Gross National Income per capita (LMIC <$12,616 vs. HIC ≥$12,616). [19].

As the unit of analysis varied markedly even among studies investigating a common SES variable (e.g. per unit of monthly income vs. per income quintile), we could not compare magnitudes of association across studies. Consequently, measures of association between SES and outcome were plotted on a single

Table 3. Eligible studies examining the impact of socioeconomic status upon outcome in children with cancer in low- and middle-income countries.

Country	Malignancy	N	Outcome Measure	Ecologic Measures	Income Measures	Education Measures[a]	Other SES Measures
Bonilla 2010 El Salvador	Standard risk ALL	260	EFS	-	**HR 0.84; Per $100 increase**	**HR 0.49; ≥Secondary vs. ≤primary**	Telephone ownership NS
-	-	-	-	-	-	-	Mode of transport NS
-	High risk ALL	183	EFS	-	Monthly income NS	Parental education NS	Telephone ownership NS
-	-	-	-	-	-	-	Mode of transport NS
Mostert 2010 Indonesia	ALL	283	EFS	-	**HR 2.6; 2nd/3rd class ward vs. VIP/1st class ward, based on income**	.	.
Tang 2008 China	ALL	346	EFS	-	.	-	**5-year EFS 61.2% urban vs. 30.3% rural; p<0.0001[c]**
Dinand 2007 India	Hodgkin Lymphoma	145	EFS	-	**HR 5.4; Low vs. high Kuppuswami score[b]**	-	-
Pedrosa 2007 Brazil	Non-Hodgkin Lymphoma	110	OS	-	Family income NS	Maternal education NS	-
Carlos 2002 Mexico	Retinoblastoma	552	OS	**HR 2.38; Most marginalized vs. least**	-	-	-
Viana 1998 Brazil	ALL	167	DFS	-	**5-year DFS 58% for those >0.4 × minimum wage vs. 8% for those <0.4 × minimum wage; p<0.0001**	-	**>4 kw hours daily electric consumption vs. <4 kw hours; p=0.0003**
-	-	-	-	-	-	-	**Very poor vs. fair-good housing conditions; p=0.006**
Gupta 2009 El Salvador	AML	78	TRM	-	Monthly income NS	Parental education NS	Telephone ownership NS
-	-	-	-	-	-	-	Number of family members NS
-	-	-	-	-	-	-	Cost to travel to clinic NS
Wang 2011 China	ALL	323	Abandonment	-	-	Paternal education NS	**32.5% abandonment good housing conditions vs. 83.3% poor; p<0.001**
-	-	-	-	-	-	Maternal education NS	-
Kulkarni 2010 India	ALL	532	Abandonment	-	Kuppuswami score NS[b]	-	-

ALL – acute lymphoblastic leukemia; AML – acute myeloid leukemia; DFS – disease free survival; EFS – event free survival; HR – hazard ratio; N – number; NS – non-significant; OS – overall survival; SES – socioeconomic status; TRM – treatment related mortality.

Bolded variables indicate statistically significant associations. Magnitudes of non-significant associations and confidence intervals of significant associations can be found in Table S1, along with definitions of each variable.

[a]Education measures also include occupation-based measures.

[b]Aggregate score based on income, education and occupation.

[c]Urban residents also had medical insurance while rural residents did not.

doi:10.1371/journal.pone.0089482.t003
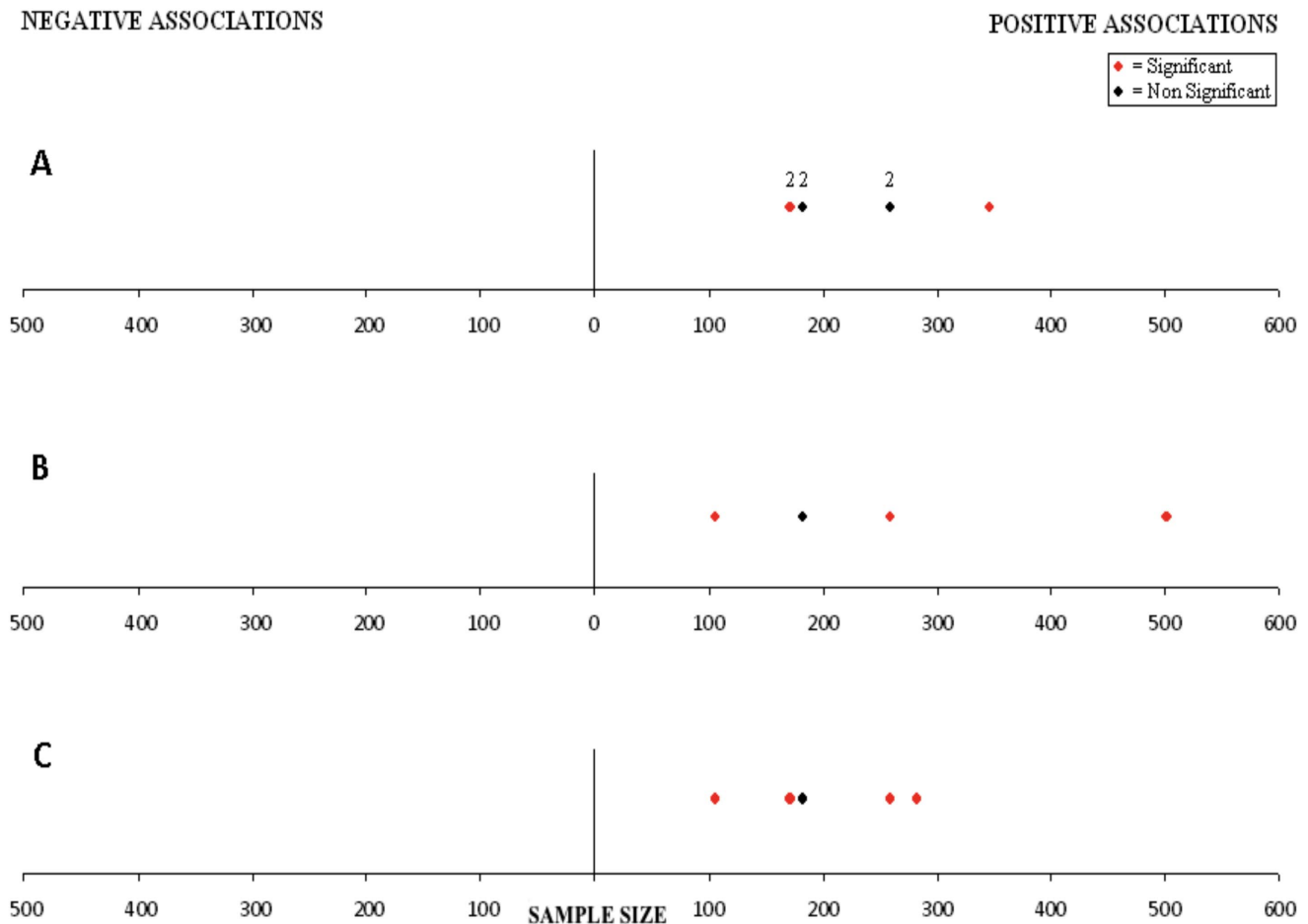
Figure 2. Associations between socioeconomic measures and event-free and overall survival in low- and middle-income countries.
A. Measures of material possession, family composition, insurance status, immigrant status, and health care accessibility. B. Measures of education and occupation. C. Measures of income. Positive = lower socioeconomic status associated with inferior outcome; Negative = lower socioeconomic status associated with superior outcome. Magnitudes of association are not plotted. Statistically significance is denoted in red. Data points with a number above represent multiple socioeconomic variables.
doi:10.1371/journal.pone.0089482.g002

graph in which sample size was represented on the x-axis. Positive associations (defined as higher SES associated with better outcome) were placed to the right of the y-axis while negative associations (defined as higher SES associated with worse outcome) were placed to the left, regardless of statistical significance or magnitude. Points more distal from the y-axis therefore do not represent greater degrees of association. When the SES measure was categorical (e.g. income quintiles), the direction of the association was determined by comparing outcomes between the highest and lowest SES categories. For each study, associations for only the highest aggregation of cancers were presented. Statistically significant associations were displayed in red and non-significant associations in black.

For studies describing the effect of dichotomous measures of income or insurance upon EFS, OS or DFS in acute lymphoblastic leukemia (ALL) or Hodgkin lymphoma (HL), the proportion of adverse outcomes attributable to low SES (attributable risk) was calculated by the following formula (p_e = proportion of the population exposed to the adverse prognosticator; RR = ratio of the cumulative incidence of adverse outcome in the two groups): [20] $p_e(RR-1)/[p_e(RR-1)+1]$ ALL and HL were chosen as they account for a significant percentage of incident cases of childhood cancer. The concept of attributable risk assumes that

the relationship is causal and that no significant bias or confounding exists. Attributable risks were also calculated for recently discovered biologic prognosticators as comparators. These prognosticators were chosen by the authors based on their prominence in either clinical practice (e.g. minimally residual disease) or laboratory research (e.g. CRLF2 expression).

Ethics Statement

Institutional review board approval was not required as only group-level, and not individual-level data were obtained from already published studies.

Results

Figure 1 illustrates the flow of study identification and selection. A total of 7,737 abstracts were identified by the search strategy; 527 articles in ten languages were retrieved for full evaluation. Of these, 36 met eligibility criteria. The kappa statistic of agreement between the two reviewers was 0.82 (95% confidence interval (CI) 0.72–0.91). Characteristics of the included studies, including indicators of study quality, are shown in Table 2. Though most studies were of acceptable quality, only half accounted for potential confounders.

Table 4. Eligible studies examining the impact of socioeconomic status upon outcome in children with cancer in high-income countries.

	Country	Outcome Measure	Malignancy	N	Ecologic Measures	Income Measures	Education Measures[a]	Other SES Measures
Metzger 2008	USA	EFS	Hodgkin lymphoma	327	**HR 1.9; High poverty county vs. low**	–	–	–
Bhatia 2002	USA, Canada	EFS	ALL	1596	–	Annual household income NS	Paternal education NS	–
	–	–	–	–	–	–	Maternal education NS	–
Hann 1981	England	5 year EFS	ALL	209	–	–	Paternal occupation NS	–
Lightfoot 2012	England, Scotland, Wales	OS	ALL	1559	**HR 1.29; Deprived vs. affluent**	–	Paternal occupation NS	–
Syse 2012	Norway	OS	Cancers	6280	–	Household income NS	**OR 1.2; ≤High school vs. ≥College**	Marital status NS
	–	–	–	–	–	•	–	Number of children NS
Rondelli 2011	Italy	OS	ALL	3522	–	•	–	**HR 1.70; Immigrant vs. non-immigrant**
Walsh 2011[b]	Ireland	5 year OS	All Cancers	1440	SAHRU deprivation index NS	–	–	–
Youlden 2011	Australia	5 year OS	Cancers	6289	Disadvantage index NS	–	–	**HR 1.55; Remote vs. Major city**
Crouch 2009[c]	UK	5 year OS	All cancers	654	**Affluent 70% OS to deprived 64%; trend p<0.5**	–	–	–
Hsieh 2009	USA	OS	NB	1777	–	–	–	**5-year OS Urban county 63% OS vs. rural county 55%; p = 0.04**
Kent 2009	USA	OS	Leukemias	4158	Census-based deprivation index NS	–	–	**HR 1.56; Any insurance vs. none/unknown**
Birch 2008[b,c]	England	5 year OS	All Cancers	31722	**Affluent 71% to deprived 70%; trend p=0.001**	–	–	–
Moschovi 2007	Greece	OS	MB	50	–	–	Maternal education NS	Place of residence NS
Perez-Martinez 2007[d]	Spain	5 year OS	All cancers	90+	–	•	–	Immigrant status NS
Tseng 2006	England, Wales	5 year OS	Malignant CNS	3169	Carstairs index NS	–	–	–
Charalampopolou 2004	Greece	OS	ALL	293	–	–	Maternal education NS	**HR 2.85; Other vs. married**

Table 4. Cont.

	Country	Outcome Measure	Malignancy	N	Ecologic Measures	Income Measures	Education Measures[a]	Other SES Measures
	-	-	-	-	-	-	-	-
Coleman 1999	England, Wales	5 year OS	Hodgkin lymphoma	189	Carstairs index NS	-	-	HR 0.63; Per child
	-	-	NHL	273	Carstairs index NS	-	-	-
	-	-	CNS	1050	Carstairs index NS	-	-	-
	-	-	Wilms	257	Carstairs index NS	-	-	-
	-	-	OST	117	Carstairs index NS	-	-	-
	-	-	ES	97	Carstairs index NS	-	-	-
	-	-	STS	319	Carstairs index NS	-	-	-
	-	-	GCT	121	Carstairs index NS	-	-	-
McKinney 1999[e]	UK	OS	All Cancers	1979	Carstairs index NS	-	-	-
Schillinger 1999	England, Wales	5 year OS	ALL	5566	Carstairs index NS	-	-	-
Coebergh 1996	Netherlands	5 year OS	Standard-risk ALL	367	-	-	Parental education NS	-
	-	-	High-risk ALL	141	-	-	Parental education NS	-
	-	-	AML	67	-	-	Parental education NS	-
Hord 1996	USA	5 year OS	ALL	178	-	-	-	OR 0.61; Total insurance coverage vs. at least partially uncovered
Petridou 1994	Greece	OS	Leukemias	120	-	.	Paternal occupation NS	HR 0.29; Private car vs. none
	-	-	-	-	-	-	Paternal education NS	Maternity hospital type NS
	-	-	-	-	-	-	Maternal education NS	Ability to choose doctor NS
McWhirter 1983	Australia	5 year OS	ALL	70	-	-	High social class 59% OS vs. low 27%	-
Szklo 1978	USA	2 year OS	ALL	55	High rental value 51% OS vs. low rental value 28%; p<0.005	-	-	-

Table 4. Cont.

	Country	Outcome Measure	Malignancy	N	Ecologic Measures	Income Measures	Education Measures[a]	Other SES Measures
Byrne 2011	USA	Median duration	AML (Age 0–9)	84	Community poverty level NS	–	–	–
	–		AML (Age 10–19)	102	Community poverty level NS	–	–	–
Walters 1972[f]	USA	Median duration	ALL	334	–	–	16.2 months lowest SES vs. 24.3 months highest	–

ALL – acute lymphoblastic leukemia; AML – acute myeloid leukemia; CNS – central nervous system tumors; EFS – event free survival; ES – Ewing sarcoma; GCT – germ cell tumors; HR – hazard ratio; LR – log rank; MB – medulloblastoma; N – number; NB – neuroblastoma; NHL – non-Hodgkin lymphoma; OR – odds ratio; OS – overall survival; OST – osteosarcoma; RR – relative risk; SES – socioeconomic status; STS – soft tissue sarcoma; UK – United Kingdom; USA – United States of America.
Bolded variables indicate statistically significant associations. Magnitudes of non-significant associations and confidence intervals of significant associations can be found in Table S2, along with definitions of each variable.
[a]Education measures also include occupation-based measures.
[b]Individual malignancies within the overall category showed no significant association between SES and outcome.
[c]Adolescent and young adult population.
[d]Immigrant patients from one center were compared to a historical control.
[e]Within the overall malignancy category, leukemias did show a significant association between lower SES and inferior outcome.
[f]No statistical analysis was presented, though the authors state that survival was "directly related to SES".
doi:10.1371/journal.pone.0089482.t004

Low- and Middle-income Country Studies

The results of the ten eligible LMIC studies are shown in Table 3, with full details available in Table S1. Of the ten, seven found at least one measure of low SES to be significantly associated with inferior outcome.[21–27] The remaining three found no significant association.[28–30] When restricted to studies examining the primary outcomes of EFS, OS or DFS, 6/7 (85.8%) studies showed at least one statistically significant association where lower SES was associated with worse survival.

Figure 2 illustrates each association between a socioeconomic variable and outcome plotted by study sample size, restricted to LMIC studies examining EFS, OS or DFS. One Brazilian study of non-Hodgkin lymphoma provided log rank p values of without information on the directions of association; none of these were statistically significant. [30] Regardless of the SES measure chosen, lower SES was always associated with inferior EFS/OS/DFS, with the majority of associations statistically significant. There were no studies that showed that lower SES was associated with better survival irrespective of statistical significance.

High-income Country Studies

The results of the 26 eligible studies conducted in HIC are shown in Table 4, all of which used EFS or OS as their outcome. Full details are available in Table S2. Individual-level and ecologic measures of SES were used by 13 (50.0%) and 10 (38.5%) studies respectively; three studies (11.5%) used both. Of the 26, 14 (53.8%) showed at least one measure of low SES to be significantly associated with inferior outcome.[10,31–43].

Figure 3 illustrates each HIC association plotted by the study sample size. Of the 21 measures of association between ecologic SES variables and outcome, 15 (71.4%) showed lower SES to be associated with worse survival, five of which were statistically significant. The remaining six (28.6%) showed that lower SES was associated with superior outcome, none of which were statistically significant.

Of the 15 measures of association between individual parental education and outcome, ten (66.7%) showed that lower parental education was associated with worse survival, three of which were statistically significant. None of the five (38.5%) associations in which higher parental education was associated with worse survival were statistically significant.

Two studies examined the impact of family income. In one study, there was no association between annual income categorized above and below $30,000 and EFS (HR = 1.0). [44] The second study found that lower income was associated with worse OS though the association was not statistically significant. [42].

Of the 14 associations between the remaining individual-level SES variables and outcome, 12 (85.7%) showed that worse SES was associated with inferior outcome, seven of which were statistically significant. Two (14.3%) studies showed that better SES was associated with worse outcome. One of these two was statistically significant; among children with ALL in Greece, a higher number of siblings was associated with a lower risk of death (HR 0.63 per child; 95% CI 0.40–0.99). [10].

Figure S1 illustrates all associations between SES measures (individual or ecologic) and outcome from the subset of HIC studies conducted in the United States. Of eleven associations, eight (72.7%) showed that lower SES was associated with worse outcome; two were statistically significant. There were three associations in which better SES was associated with worse survival; none were statistically significant.
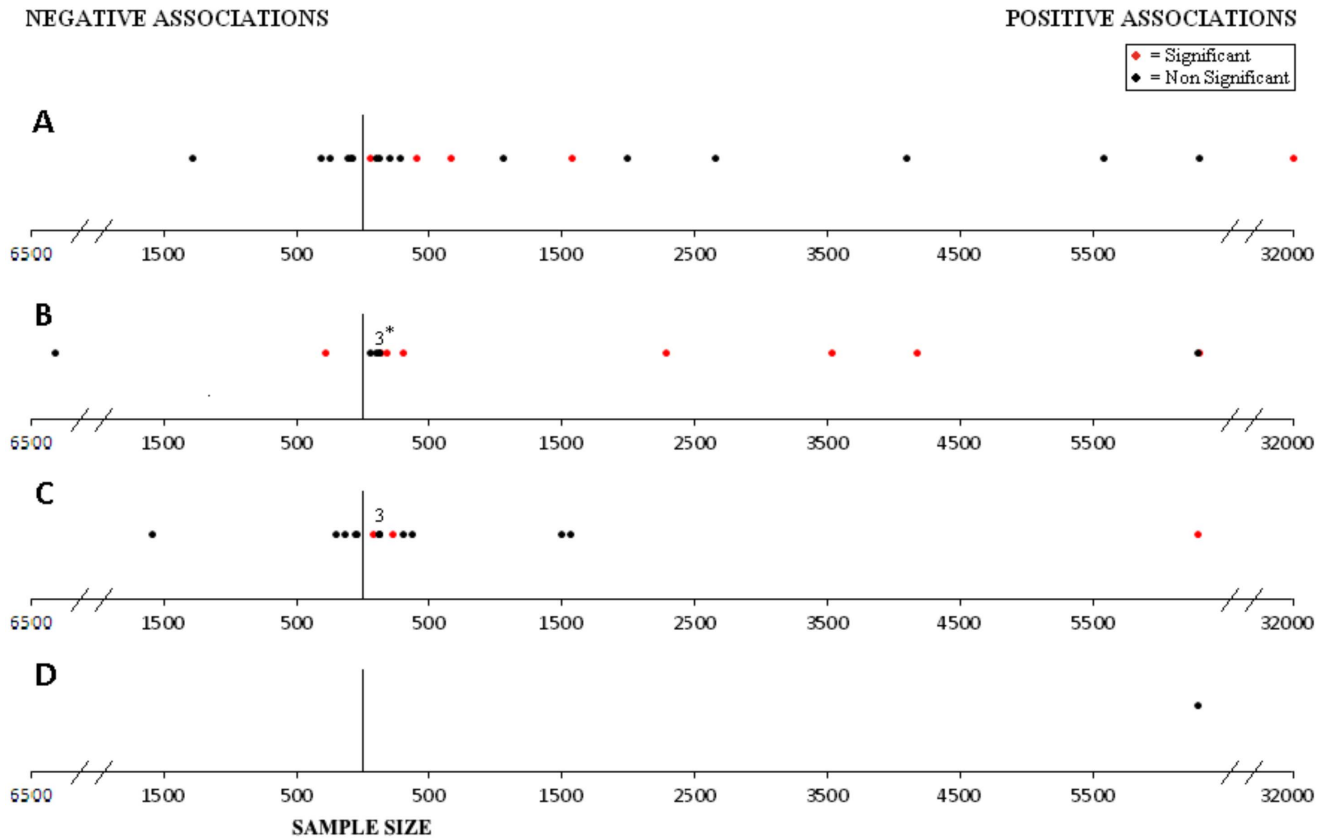
Figure 3. Associations between socioeconomic measures and event-free and overall survival in high-income countries. A. Ecologic measures B. Measures of material possession, family composition, insurance status, immigrant status, and health care accessibility. C. Measures of education and occupation. D. Measures of income. Positive = lower socioeconomic status associated with inferior outcome; Negative = lower socioeconomic status associated with superior outcome. Magnitudes of association are not plotted. Statistically significance is denoted in red. Data points with a number above represent multiple socioeconomic variables. 3* indicates 2 non-significant associations and one significant association.
doi:10.1371/journal.pone.0089482.g003

Attributable Risk

Table 5 shows the proportion of adverse outcomes attributable to low socioeconomic measures of income or insurance as calculated from LMIC and HIC studies. Based on the selected studies, and assuming both causality and the absence of significant bias or confounding, eliminating the adverse effect of low socioeconomic status would result in a theoretical 22.9% to 74.8% reduction in adverse outcome among LMIC children. Among HIC children, 0.0% to 31.9% of adverse outcomes could be avoided.

Discussion

In this systematic review, we found that among children with cancer in LMIC, measures of low SES were uniformly associated with inferior outcome. The majority of these associations were statistically significant. The results in HIC were less uniform although the majority of associations (including all but one of the statistically significant associations) also linked lower SES and worse outcome.

We chose to include multiple measures of SES in this systematic review, as SES indicators measure "different, often related aspects of socioeconomic stratification and may be more or less relevant to different health outcomes." [45] This issue may be particularly pronounced in pediatric oncology, where mechanisms linking SES and outcome are likely complex and inter-related, as illustrated in Figure 4. These mechanisms have been suggested by previous authors as outlined in the figure legend, but are often theoretical with little empiric basis.

Based on this framework, our finding that all measures of low SES in LMIC were associated with inferior outcome implies that in these settings, many mechanisms link SES and outcome. Interventions targeting a particular mechanism in LMIC are therefore likely to decrease but not erase socioeconomic gradients in outcome. For example, while the provision of free treatment, accommodation and transport to families in El Salvador resulted in a decrease in abandonment rates to 13%, socioeconomic variables remained the strongest predictors of abandonment. [46] Multi-faceted interventions are thus required in order to completely eliminate the negative influence of poor SES in LMIC.

Turning to studies conducted in HIC, income-based measures of SES were not significantly associated with outcome, though were infrequently investigated. By contrast, measures encompassing paternal education, material possession, and insurance status were often statistically associated with inferior outcome. This contrast to the LMIC findings has several potential explanations. First, a negative influence of low SES in HIC may be present but weaker than in LMIC, such that HIC studies were more likely to be underpowered. As the majority of non-significant associations were in the direction of low SES being associated with inferior outcome, this hypothesis is plausible.

Alternatively, only some of the pathways illustrated in Figure 4 may be relevant in HIC. Interestingly, both American studies examining the effect of insurance coverage found the lack of full coverage to be significantly associated with inferior survival. [34,47] In HIC, measures of access to health care may therefore be more

Table 5. Proportion of adverse outcomes (attributable risk) due to poor socioeconomic prognosticators in studies of the effect of dichotomous measures of income and insurance in acute lymphoblastic leukemia and Hodgkin lymphoma, as well as of selected biologic prognosticators by way of comparison.

	Malignancy	Country	Category	Adverse Prognosticator	p_e	RR	AR
Dinand 2007	HL	India	LMIC	Low SES, based on aggregate score including income	0.67	5.4	74.8%
Mostert 2010	ALL	Brazil	LMIC	Monthly per capita income <0.4 ×minimum wage	0.25	1.2	22.9%
Viana 1998	ALL	Indonesia	LMIC	2nd/3rd class ward, based on income	0.76	2.6	55.0%
Tang 2008	ALL	China	LMIC	Rural residence/no insurance	0.74	1.8	37.1%
Bhatia 2002	ALL	USA, Canada	HIC	Annual household income <$30,000	0.56	1.0	0.0%
Hord 1996	ALL	USA	HIC	At least partially uncovered by insurance	0.29	1.6	15.7%
Lightfoot 2012	ALL	England, Scotland, Wales	HIC	Deprived area, based in part on income	0.39	1.3	10.2%
Metzger 2008	HL	USA	HIC	County with high % children in poverty	0.52	1.9	31.9%
Borowitz 2008	SR-ALL	Multiple	HIC	MRD>0.01%	0.14	7.2	45.6%
Borowitz 2008	HR-ALL	Multiple	HIC	MRD>0.01%	0.30	3.2	39.4%
Loken 2012	AML	Multiple	HIC	Residual disease by flow cytometry	0.22	2.17	20.5%
Chen 2012	ALL	Multiple	HIC	High CRLF2 expression	0.18	1.86	13.1%

ALL – acute lymphoblastic leukemia; AML – acute myeloid leukemia; AR – attributable risk; HIC – high-income country; HL – Hodgkin lymphoma; LMIC – low- to middle-income country; MRD – minimal residual disease; p_e – proportion of population exposed to the adverse prognosticator; RR – risk ratio; SES – socioeconomic status.

doi:10.1371/journal.pone.0089482.t005

relevant than, for example, measures of income. It is also likely that the impact of different aspects of SES will vary between settings and malignancies. For example, different measures of SES are likely to be relevant in countries with universal access to health care than in those without. Compliance will have a greater potential effect upon outcome in malignancies for which outpatient oral chemotherapy plays a major role than those involving mainly inpatient therapy.

Implications for Future Studies

Future studies must move beyond choosing socioeconomic variables and outcomes based simply on what data are easily available to the investigators. Instead, authors should posit specific mechanisms and potential confounders in advance, identify measures of SES and outcomes consistent with the hypothesis, and only then examine for significant associations. For example, Bhatia et?al. measured rates of compliance to oral chemotherapy among American children with ALL. Low rates of compliance were linked to single mother households and associated with higher rates of relapse. [48] Demonstrating the role of a particular pathway thus not only leads to a deeper understanding of the impact of SES, but also to plausible interventions mediating the pathway.

While such studies are likely to be complex, their impact may be significant. We have shown that improving the outcome of children of low SES to that of their high SES brethren would result in the elimination of up to 74.8% of adverse outcomes in LMIC and up to 31.9% of adverse outcomes in HIC. By way of comparison, minimal residual disease accounts for a theoretical 39.4% of relapse in high-risk ALL, while the novel feature of high CRLF2 expression accounts for 13.1% of relapse among all children with ALL. [49,50] Consequently, debate on how low SES can be targeted is warranted, both in LMIC and HIC. Targeted interventions could encompass more frequent follow-up, intensive compliance monitoring, or other stratagems.

Strengths and Limitations

This study represents the first comprehensive assessment of the effect of SES on children with cancer. Other strengths include the lack of language-based restrictions and the exclusion of ethnicity,

allowing for the role of biologic confounders to be minimized. Our main limitation was the inability to compare magnitudes of associations across studies. Even when multiple studies used both the same outcome (e.g. EFS) and exposure (e.g. income), different units of analysis were used (richest income quintile vs. poorest income quintile, per $100 monthly income). In previous work we showed the effect of monthly income upon EFS in children with ALL in El Salvador was HR = 0.81 per $100. [28] Comparing the richest quartile to the poorest in the identical population would have resulted in a HR of 0.45. Thus meaningful comparisons can only be made when the analysis unit is identical. This also rendered the use of Forest plots inappropriate. Our figures instead were restricted to illustrating effect direction and significance. In the future, individual-level meta-analyses may be useful in this regard as long as the non-categorized covariate (e.g. monthly income) was collected. Secondly, it is possible that publication bias is present, particularly in studies of LMIC. Finally, the incidence of ALL has itself been linked to high SES in some studies. [51] For this to explain the findings of our systematic review, the biologic driver behind this association would have to be specific to a low-risk form of ALL across multiple populations. While we cannot rule this possibility out, this would not explain the association between SES and outcome seen in other cancers.

In conclusion, low SES is uniformly associated with poorer outcomes among LMIC children with cancer, and widespread among HIC children. Future studies should identify specific mechanisms underlying these gradients, as well as evaluate interventions aimed at improving the outcome of children with cancer with socioeconomic risk factors.

Supporting Information

Figure S1 Associations between socioeconomic measures and event-free and overall survival in studies conducted in the United States. Positive = lower socioeconomic status associated with inferior outcome; Negative = lower socioeconomic status associated with superior outcome. Magnitudes of association are not plotted. Thus points distal from the y-
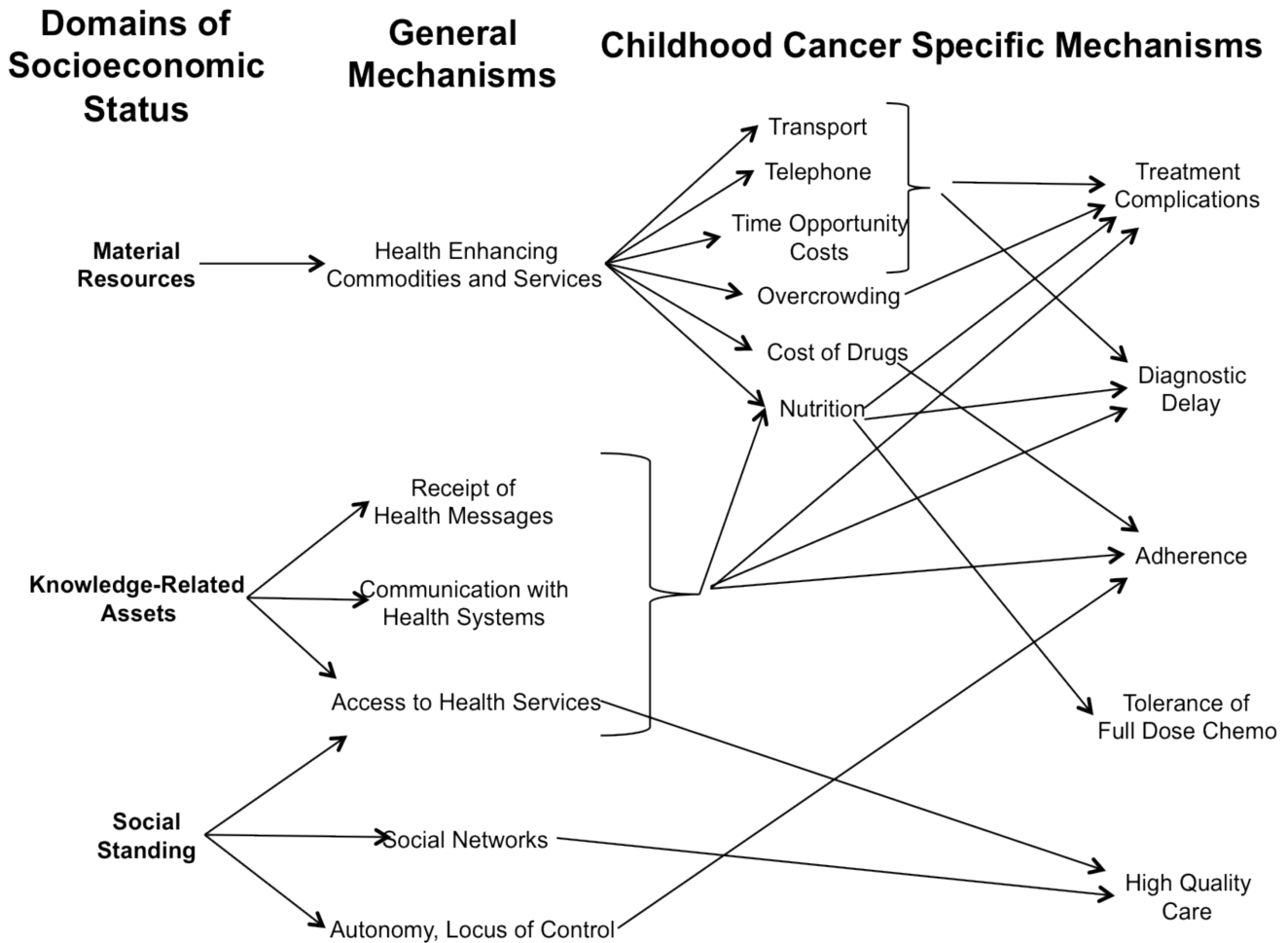
Figure 4. Mechanisms linking socioeconomic status domains to both general and childhood cancer specific health outcomes. Domains and general mechanisms are adapted from the work of Galobardes et?al., Braveman et?al., Krieger et?al. and Marmot. Several childhood specific mechanisms are suggested by Bhatia et?al., Gage, Viana et?al. and Gupta et?al. These mechanisms are often theoretical with little empiric basis.

doi:10.1371/journal.pone.0089482.g004

axis may represent stronger, weaker or equivalent associations than proximal points.
(DOCX)

Table S1 Eligible studies examining the impact of socioeconomic status upon outcome in children with cancer in low- and middle-income countries. ALL – acute lymphoblastic leukemia; AML – acute myeloid leukemia; DFS – disease free survival; EFS – event free survival; HR – hazard ratio; N – number; OS – overall survival; SES – socioeconomic status; TRM – treatment related mortality. Bolded variables indicate statistically significant associations. [a]The marginalization index used by Carlos et?al. is an ecologic measure of SES; all other variables in the table are measures of individual-level SES.
(DOCX)

Table S2 Eligible studies examining the impact of socioeconomic status upon outcome in children with cancer in high-income countries. ALL – acute lymphoblastic leukemia; AML – acute myeloid leukemia; CNS – central nervous system tumors; EFS – event free survival; ES – Ewing sarcoma; GCT – germ cell tumors; HR – hazard ratio; MB – medulloblastoma; N – number; NB – neuroblastoma; NHL – non-Hodgkin lymphoma; OR – odds ratio; OS – overall survival;

OST – osteosarcoma; RR – relative risk; SES – socioeconomic status; STS – soft tissue sarcoma; UK – United Kingdom; USA – United States of America. Bolded variables indicate statistically significant associations. [a]Individual malignancies within the overall category showed no significant association between SES and outcome. [b]Adolescent and young adult population. [c]Within the overall malignancy category, leukemias did show a significant association between lower SES and inferior outcome. [d]Immigrant patients from one center were compared to a historical control. [e]No statistical analysis was presented, though the authors state that survival was "directly related to SES". [f]HR is per level of occupation.
(DOCX)

Text S1 Study Protocol.
(DOCX)

Text S2 Search Strategies.
(DOCX)

Text S3 Data Abstraction Form.
(DOCX)

Checklist S1 PRISMA Checklist.
(DOC)

Acknowledgments

Author Contributions

Conceived and designed the experiments: SG JP AG LS. Performed the experiments: SG MW. Analyzed the data: SG LS. Wrote the paper: SG MW JP AG LS.

References

1. Braveman PA, Cubbin C, Egerter S, Chideya S, Marehi KS, et al. (2005) Socioeconomic status in health research: One size does not fit all. JAMA 294: 2879–2888.
2. Rabi DM, Edwards AL, Svenson LW, Graham MM, Knudston ML, et al. (2010) Association of median household income with burden of coronary artery disease among individuals with diabetes. Circ Cardiovasc Qual Outcomes 3: 48–53.
3. Frederiksen BL, Osler M, Harling H, Danish Colorectal Cancer Group, Ladelund S, et al. (2009) The impact of socioeconomic factors on 30-day mortality following elctive colorectal cancer surgery: a nationwide study. Eur J Cancer 45: 1248–1256.
4. Luo ZC, Wilkins R, Kramer MS (2006) Effect of neighbourhood income and maternal education on birth outcomes: A population-based study. CMAJ 174: 1415–1421.
5. Woods LM, Rachet B, Coleman MP (2006) Origins of socio-economic inequalities in cancer survival: a review. Annals of Oncology 17: 5–19.
6. Tang Y, Xu X, Song H, Yang S, Shi S, et al. (2008) Long-term outcome of childhood acute lymphoblastic leukemia treated in China. Pediatr Blood Cancer 51: 380–386.
7. Mostert S, Sitaresmi MN, Gundy CM, Sutaryo, Veerman AJ (2006) Influence of socioeconomic status on childhood acute lymphoblastic leukemia treatment in Indonesia. Pediatrics 118: e1600–1606.
8. McWhirter WF, Smith H, McWhirther KM (1983) Social class as a prognostic variable in acute lymphoblastic leukemia. Med J Aust 2: 319–321.
9. Schillinger JA, Grosclaude PC, Honjo S, Quinn MJ, Sloggett A, et al. (1999) Survival after acute lymphoblastic leukaemia: Effects of socioeconomic status and geographic region. Arch Dis Child 80: 311–317.
10. Charalampopoulou A, Petridou E, Spyridopoulos T, Dessypris N, Oikonomou A, et al. (2004) An integrated evaluation of socioeconomic and clinical factors in the survival from childhood acute lymphoblastic leukaemia: a study in Greece. European Journal of Cancer Prevention 13: 397–401.
11. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009) Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. PLoS Medicine 6.
12. Harvey RC, Mullighan CG, Chen IM, Wharton W, Mikhail FM, et al. (2010) Rearrangement of CRLF2 is associated with mutation of JAK kinases, alternation if IKZF1, Hispanic/Latino ethnicity, and a poor outcome in pediatric B-progenitor acute lymphoblastic leukemia. Blood 115: 5312–5321.
13. Landis R, Koch GG (1977) The measurement of observer agreement for categorical data. Biometrics 33: 159–174.
14. Marmot MG (2003) Understanding social inequalities in health. Persp Biol Med 46: S9–S23.
15. Hayden JA, Cote P, Bombardier C (2006) Evaluation of the quality of prognosis studies in systematic reviews. Ann Intern Med 144: 427–437.
16. Simon C, Zyzanski SJ, Eder M, Raiz P, Kodish ED, et al. (2003) Groups potentially at risk for making poorly informed decisions about entry into clinical trials for childhood cancer. J Clin Oncol 21: 2173–2178.
17. Drotar D, Miller V, Willard V, Anthony K, Kodish E (2004) Correlates of parental participation during informed consent for randomized clinical trials in the treatment of childhood leukemia. Ethics Behav 14: 1–15.
18. Mostert S, Arora RS, Arreola M, Bagai P, Friedrich P, et al. (2011) Abandonment of treatment for childhood cancer: Position statement of a SIOP PODC Working Group. Lancet Oncol 12: 719–720.
19. The World Bank (2012) Data - A Short History. The World Bank.
20. Rockhill B, Newman B, Weinberg C (1998) Use and misuse of population attributable fractions. Am J Public Health 88: 15–19.
21. Bonilla M, Gupta S, Vasquez R, Fuentes SL, deReyes G, et al. (2010) Predictors of outcome and methodological issues in children with acute lymphoblastic leukaemia in El Salvador. European Journal of Cancer 46: 3280–3286.
22. Carlos L-L, Roberto R-L, Victor T-G, Carlos H-G, Eduardo L-P (2002) Risk of dying of retinoblastoma in Mexican children. Medical & Pediatric Oncology 38: 211–213.
23. Dinand V, Dawar R, Arya LS, Unni R, Mohanty B, et al. (2007) Hodgkin's lymphoma in Indian children: Prevalence and significance of Epstein-Barr virus detection in Hodgkin's and Reed-Sternberg cells. European Journal of Cancer 43: 161–168.
24. Mostert S, Sitaresmi MN, Gundy CM, Janes V, Sutaryo, etal. (2010) Comparing childhood leukaemia treatment before and after the introduction of a parental education programme in Indonesia. Archives of Disease in Childhood 95: 20–25.
25. Tang Y, Xu X, Song H, Yang S, Shi S, et al. (2008) Long-term outcome of childhood acute lymphoblastic leukemia treated in China. Pediatric Blood & Cancer 51: 380–386.
26. Viana MB, Fernandes RA, de Carvalho RI, Murao M (1998) Low socioeconomic status is a strong independent predictor of relapse in childhood acute lymphoblastic leukemia. International Journal of Cancer - Supplement 11: 56–61.
27. Wang YR, Jin RM, Xu JW, Zhang ZQ (2011) A report about treatment refusal and abandonment in children with acute lymphoblastic leukemia in China, 1997–2007. Leukemia Research 35: 1628–1631.
28. Gupta S, Bonilla M, Fuentes SL, Caniza M, Howard SC, et al. (2009) Incidence and predictors of treatment-related mortality in paediatric acute leukaemia in El Salvador. British Journal of Cancer 100: 1026–1031.
29. Kulkarni KP, Marwaha RK (2010) Pattern and implications of therapy abandonment in childhood acute lymphoblastic leukemia. Asian Pacific Journal of Cancer Prevention: Apjcp 11: 1435–1436.
30. Pedrosa MF, Pedrosa F, Lins MM, Pontes Neto NT, Falbo GH (2007) Non-Hodgkin's lymphoma in childhood: clinical and epidemiological characteristics and survival analysis at a single center in Northeast Brazil. Jornal de Pediatria 83: 547–554.
31. Birch JM, Pang D, Alston RD, Rowan S, Geraci M, et al. (2008) Survival from cancer in teenagers and young adults in England, 1979–2003. British Journal of Cancer 99: 830–835.
32. Croucher C, Whelan JS, Moller H, Davies EA (2009) Trends in the incidence and survival of cancer in teenagers and young adults: regional analysis for South East England 1960–2002. Clinical Oncology (Royal College of Radiologists) 21: 417–424.
33. Hsieh MH, Meng MV, Walsh TJ, Matthay KK, Baskin LS (2009) Increasing incidence of neuroblastoma and potentially higher associated mortality of children from nonmetropolitan areas: analysis of the surveillance, epidemiology, and end results database. Journal of Pediatric Hematology/Oncology 31: 942–946.
34. Kent EE, Sender LS, Largent JA, Anton-Culver H (2009) Leukemia survival in children, adolescents, and young adults: influence of socioeconomic status and other demographic factors. Cancer Causes & Control 20: 1409–1420.
35. McWhirter WR, Smith H, McWhirter KM (1983) Social class as a prognostic variable in acute lymphoblastic leukaemia. Medical Journal of Australia 2: 319–321.
36. Metzger ML, Castellino SM, Hudson MM, Rai SN, Kaste SC, et al. (2008) Effect of race on the outcome of pediatric patients with Hodgkin's lymphoma. Journal of Clinical Oncology 26: 1282–1288.
37. Petridou E, Kosmidis H, Haidas S, Tong D, Revinthi K, et al. (1994) Survival from childhood leukemia depending on socioeconomic status in Athens. Oncology 51: 391–395.
38. Szklo M, Gordis L, Tonascia J, Kaplan E (1978) The changing survivorship of white and black children with leukemia. Cancer 42: 59–66.
39. Walters TR, Bushore M, Simone J (1972) Poor prognosis in Negro children with acute lymphocytic leukemia. Cancer 29: 210–214.
40. Lightfoot TJ, Johnston WT, Simpson J, Smith AG, Ansell P, et al. (2012) Survival from childhood acute lymphoblastic leukaemia: the impact of social inequality in the United Kingdom. European Journal of Cancer 48: 263–269.
41. Rondelli R, Dini G, De Rosa M, Quarello P, Bisogno G, et al. (2011) Foreign children with cancer in Italy. Italian Journal of Pediatrics 37.
42. Syse A, Lyngstad TH, Kravdal O (1870) Is mortality after childhood cancer dependent on social or economic resources of parents? A population-based study. International Journal of Cancer 130: 1870–1878.
43. Youlden DR, Baade PD, Valery PC, Ward LJ, Green AC, et al. (1649) Differentials in survival for childhood cancer in Australia by remoteness of residence and area disadvantage. Cancer Epidemiology, Biomarkers & Prevention 20: 1649–1656.
44. Bhatia S, Sather HN, Heerema NA, Trigg ME, Gaynon PS, et al. (2002) Racial and ethnic differences in survival of children with acute lymphoblastic leukemia. Blood 100: 1957–1964.
45. Galobardes B, Lynch J, Smith GD (2007) Measuring socioeconomic position in health research. British Medical Bulletin 81: 21–37.
46. Bonilla M, Rossell N, Salaverria C, Gupta S, Barr R, et al. (2009) Prevalence and predictors of abandonment of therapy among children with cancer in El Salvador. International Journal of Cancer 125: 2144–2146.
47. Hord MH, Smith TL, Culbert SJ, Frankel LS, Pinkel DP (1996) Ethnicity and cure rates of Texas children with acute lymphoid leukemia. Cancer 77: 563–569.
48. Bhatia S, Landier W, Shangguan M, Hageman L, Schaible AN, et al. (2012) Nonadherence to oral mercaptopurine and risk of relapse in Hispanic and non-Hispanic white children with acute lymphoblastic leukemia: A report from the Children's Oncology Group. J Clin Oncol 30: 2094–2101.
49. Borowitz MJ, Devidas M, Hunger SP, Bowman WP, Carroll A, et al. (2008) Clinical significance of minimal residual disease in childhood acute lympho-

blastic leukemia and its relationship to other prognostic factors: a Children's Oncology Group study. Blood 111: 5477–5485.

50. Chen I-M, Harvey RC, Mullighan CG, Gastier-Foster J, Wharton W, et al. (2012) Outcome modeling with CRLF2, IKZF1, JCK, and minimal residual

disease in pediatric acute lymphoblastic leukemia: A Children's Oncology Group Study. Blood 119: 3512–3522.

51. Stiller C, Kroll ME, Boyle PJ, Feng Z (2008) Population mixing, socioeconomic status and incidence of childhood acute lymphoblastic leukaemia in England and Wales: analysis by census ward. Br J Cancer 98: 1006–1011.