



**The Prevalence, Risk Factors and Behavioural and Emotional Consequences of Acute
Seizures in a Rural Kenyan Setting**

by

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Abstract

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The incidence of acute seizures (e.g. both febrile seizures and acute symptomatic seizures) is higher in Africa than elsewhere, but most studies are based on hospital admissions. Acute seizures in children are associated with behavioural/emotional problems which may be related to the seizures, underlying aetiology, neurological impairments and/or genetic predisposition. Behavioural/emotional problems occur in up to 26% of older Kenyan children in the community, but there are no large community-based studies in preschool children in Africa to plan interventions.

I screened 7,047 children aged 1-6 years living in Kilifi, Kenya for acute seizures with a proportion of these (N=3,273) examined for behavioural/emotional problems using the Child Behaviour Checklist (CBCL). Factorial structure of the CBCL was examined using structural

equation modelling, while associations were determined using several regression analysis techniques. Prevalence of behavioural/emotional problems and acute seizures was computed as a probability of occurrence, by exponentiation of the constant term of a logit model.

The CBCL had between good and excellent psychometric properties and the seven-syndrome structure fitted well with the Kenyan preschool children. The prevalence of total behavioural/emotional problems was high (13% (95%CI, 12%-14%)) and so was that for acute seizures (6.1% (95%CI, 5.5%-6.8%)). Behavioural/emotional problems were particularly associated with seizure disorders, which explained the greatest variation in a structural equation model. Risk factors for acute seizures included family history of seizures, previous hospitalisation and snoring at night. The overall crude prevalence of behavioural/emotional problems in those with acute seizures was 27% (95%CI, 21%-34%), being significantly greater than for those without seizures (11% (95%CI, 11%-12%); X^2 $p \leq 0.001$). Acute seizures remained associated with behavioural/emotional problems (RR=2.40 (95%CI, 1.61-3.58)), externalising problems (RR=2.09 (95%CI, 1.40-3.13)) and internalising problems (RR=1.99 (95%CI, 1.36-2.91)), after accounting for potential confounders.

The prevalence of behavioural/emotional problems and acute seizures is high in preschool children in this rural area, and are associated with preventable risk factors.

Behavioural/emotional problems are associated with acute seizures and should be assessed and addressed in preschool children with seizures.

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List of publications

Original publications contributing to DPhil thesis

Kariuki SM, Abubakar A, Murray E, Stein A, Newton RJC. Evaluation of Psychometric Properties and Factorial Structure of the Pre-school Child Behaviour Checklist at the Kenyan Coast. *Child and Adolesc Psychiatry and Ment Health* 2016; 10:1

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Abbreviations

ADHD: Attention Deficit Hyperactivity Disorder

ADH: Attention Deficit Hyperactivity

AIC: Akaike Information Criteria

ASEBA: Achenbach System of Empirically Based Assessments

ASQ: Ages and Stages Questionnaire

BITSEA: Brief Infant-toddler Social Emotional Problems

BSQ: Behavioural Screening Questionnaire

CBCL: Child Behaviour Checklist

CFA: Confirmatory Factor Analysis

CI: Confidence Interval

CFI: Comparative Fit Index

CNS: Central Nervous System

CSE: Convulsive Status Epilepticus

DALYs: Disability-adjusted Life Years

DSM-TR: Diagnostic and Statistical Manual for Mental Disorders-Text Revision

DPT: Diphtheria Tetanus Toxoid Whole Blood Pertussis

EEG: Electroencephalography/Electroencephalogram/Electroencephalographic

GBD: Global Burden of Diseases

GLM: Generalised Linear Models

GWAS: Genome-wide Association Studies

HAZ: Height for Age Z-scores

HHV: Human Herpes Virus

ILAE: International League Against Epilepsy

IMCI: Integrated Management of Childhood Infections

IQR: Interquartile Range

KCH: Kilifi County Hospital

KHDSS: Kilifi Health and Demographic Surveillance System

LMIC: Low and Middle Income Countries

MMR: Mumps and Rubella Vaccine

MTS: Mesial Temporal Sclerosis

MUAC: Mid-Upper Arm Circumference

NIH: National Institute of Health

OR: Odds Ratio

PAF: Population Attributable Fraction

PCA: Principal Component Analysis

PDP: Pervasive Developmental Problems

PFC: Profile Feeling Checklist

RMSEA: Root Mean Square Error of Approximation

ROR: Ratio of Odds Ratio

RR: Risk Ratio

RRR: Ratio of Risk Ratio

RTI: Respiratory Tract Infections

SD: Standard Deviation

TLI: Tucker Lewis Index

WAZ: Weight-for-Age Z-scores

Chapter 1: General introduction

Synopsis of the thesis

Introduction

Acute febrile seizures occur in 2-5% of children in the world (Baram & Shinnar, 2002), but the incidence may be higher if acute symptomatic seizures are included (Beghi et al., 2010). Febrile seizures occur in children under 6 years and are often associated with febrile illnesses without any intracranial involvement, and the definition excludes acute symptomatic seizures (which have neurological involvement), previous unprovoked seizures and neonatal seizures (ILAE, 1989). Thus acute seizures refer to both febrile seizures and acute symptomatic seizures resulting from acute brain insult e.g. bacterial meningitis. Of these acute seizures, febrile seizures are thought to have a good prognosis, but some studies show an association with behavioural/emotional problems and neurocognitive impairments (Baram & Shinnar, 2002).

Complex febrile seizures i.e. focal, repetitive or prolonged occur in 30% of children from the West and in over 70% of children in malaria-endemic areas (Baram & Shinnar, 2002; Waruiru et al., 1996). The classification of seizures in falciparum malaria is controversial, since it is not clear that these seizures are caused by the high temperatures (febrile seizures) or the sequestration of malaria parasites into brain capillaries (symptomatic seizures) (R. Idro, Jenkins, & Newton, 2005). Acute seizures are common in children admitted to hospital in Africa but there are few data on the burden of these seizures in the community (R. Idro et al., 2008). The incidence of acute seizures based upon Kenyan children admitted to hospital only is 425/100,000/year which is at least six times greater than in the West (J. F. Annegers, Hauser, Lee, & Rocca, 1995; R. Idro et al., 2008), whilst the incidence of status epilepticus in Kenyan children is 108/100,000/year, five times greater than in the West (Chin et al., 2006;

Sadarangani et al., 2008). These measures are likely to be an underestimate since only 20% of children with acute seizures in Kilifi, Kenya access health facilities (unpublished pilot data). Childhood infections and perinatal complications are important causes of epileptic seizures in Kilifi (A. K. Ngugi et al., 2013), although genetic factors are important as well (S. M. Kariuki et al., 2013).

Behavioural/emotional problems, which are classified into socially withdrawn (emotional/internalising) or unsocialised-aggressive (behavioural/externalising) problems (Ivanova et al., 2010), are common in preschool children. The prevalence ranges from 5% to 25% and half of these problems may persist to adolescence and adulthood (A. S. Carter, Briggs-Gowan, & Davis, 2004; Egger & Angold, 2006). There are however fewer epidemiological studies of behavioural/emotional problems in preschool children than there are for older children (Egger & Angold, 2006) particularly in resource-limited countries of sub-Saharan Africa. These behavioural/emotional problems are associated with factors arising during early antenatal and perinatal periods, neurotoxins and environmental factors (Campbell, 1995; Grandjean & Landrigan, 2014).

Assessment of behavioural/emotional problems should be done in the context of the developmental changes of a child, family and environment (Njoroge & Bernhart, 2011). Additionally, the tools used should be formally validated and adapted in the local population. Once identified through assessment, these behavioural/emotional problems can be prevented and managed through strategic behavioural programmes and interventions (Charach et al., 2013). These programmes and interventions too should be culturally appropriate, affordable and address multiple outcomes including family functioning (Mazzucchelli & Sanders, 2011).

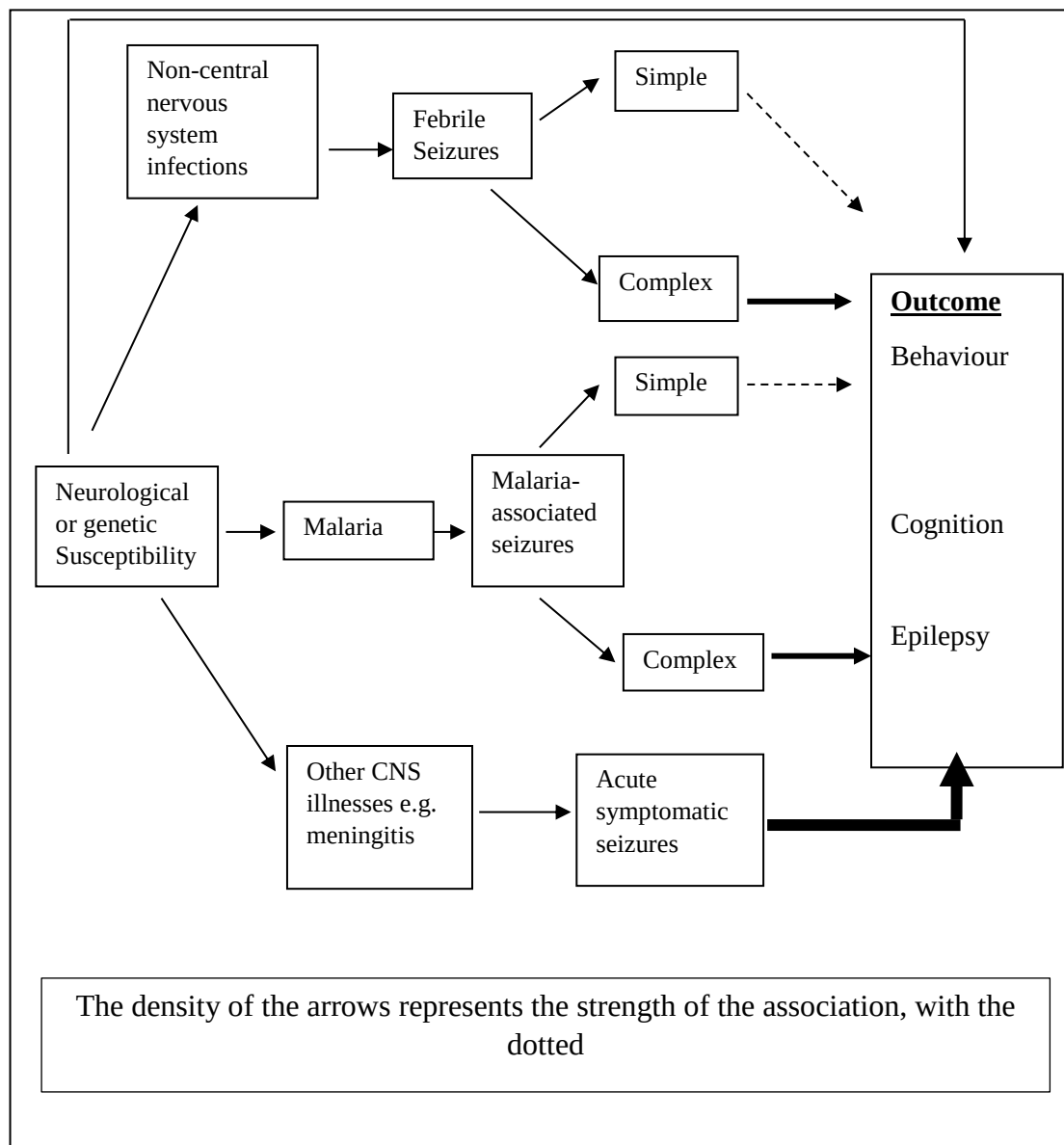
Behavioural/emotional problems were present in 26% of older Kenyan children selected from the community as controls for a study on epilepsy, and were much higher in children with

epilepsy (Symon M. Kariuki et al., 2012). This study was however a post-hoc analysis that was based on a small community sample (N=110). A large community sample would provide more accurate estimates of behavioural/emotional problems in preschool children in Kilifi, Kenya where neurological impairment, central nervous system (CNS) infections and perinatal complications are common (V. Mung'ala-Odera et al., 2006; A. K. Ngugi et al., 2013), allowing the risk factors to be examined, in particular the association with acute seizures.

Complex febrile seizures have been reported to be associated with schizophrenia, behavioural/emotional problems and epilepsy (Baram & Shinnar, 2002; Vestergaard et al., 2005). A recent study has showed evidence of shared genetic susceptibility between uncomplicated epileptic seizures and behavioural/emotional problems (Dale C. Hesdorffer, Caplan, & Berg, 2012), and it poses the question whether simple febrile seizures can also give rise to neurobehavioural problems. Acute symptomatic seizures often have a poor outcome, but it is unclear if these sequelae are due to the seizures or due to the underlying brain injury (Baram & Shinnar, 2002). Behavioural/emotional problems were reported in 10% of Kenyan children hospitalised with complex seizures associated with malaria (J. A. Carter, Mung'ala-Odera, et al., 2005), although it is unclear if the behavioural/emotional problems were caused by the malaria or the seizures *per se*.

The pathogenesis of the behavioural/emotional problems in acute seizures may be linked to a genetic predisposition, seizure-related factors, abnormal brain structure, past medical history; and family and socio-demographic characteristics (Figure 1-1) (Baram & Shinnar, 2002).

Figure 1-1: Theoretical framework of pathogenesis and outcome of acute seizures in children



Scope of the thesis

This Doctor of Philosophy (DPhil) thesis sets out to: (1) measure the prevalence of acute seizures and behavioural/emotional problems in the community, since there are no reliable estimates for either of these potentially common conditions; (2) determine the risk factors associated with acute seizures and behavioural/emotional problems in preschool children; and (3) examine the relationship between acute seizures and behavioural/emotional problems.

Three main studies were undertaken to address these objectives: Study 1; a validation and adaptation study for the Child Behaviour Checklist (CBCL) in preschool children living in Kilifi Kenya, Study 2; a cross-sectional and risk factors study of the prevalence and risk factors for acute seizures in preschool children living in Kilifi, Kenya, and Study 3; a cross-sectional and case-control study of the prevalence and risk factors for behavioural/emotional problems in preschool children living in Kilifi, Kenya. The cross-sectional and case-control studies were conducted in two phases. Phase I involved screening children in the community for both acute seizures and behavioural/emotional problems, and inviting those who screened positive for further clinical evaluation. Phase II involved clinical evaluation of those screening positive for either seizures or behavioural/emotional problems in phase I and a proportion of screen negatives selected for the case-control studies.

These studies were implemented by piloting the CBCL among 301 children aged 1-6 years from the community, by screening just over 7,000 similar aged children living in the community for acute seizures, and just over 3,000 of the 7,000 for behavioural/emotional problems. I coordinated all aspects of the study, including training of fieldworkers and clinicians, and ensured quality control of data collection. Fieldworkers were used to screen for acute seizures and behavioural/emotional problems and to obtain sociodemographic information. Clinical officers helped to conduct medical histories and clinical examination. Acute seizures were screened with a modified seizure questionnaire, previously used in

epilepsy studies in Kilifi, Kenya (T. Edwards et al., 2008), while behavioural/emotional problems were examined with the CBCL.

Null hypothesis

Acute seizures are not associated with increased prevalence of behavioural/emotional problems in pre-school children living in Kilifi, Kenya

Objectives

General objective

To estimate the prevalence, and determine risk factors for, and behavioural/emotional consequences of acute seizures in preschool children living in a rural area of Kenya.

Specific objectives:

- (1) Review the world literature on prevalence, risk factors for, and consequences of acute seizures and behavioural/emotional problems among preschool children;
- (2) To validate and adapt the CBCL in preschool children in this rural area of Kenya;
- (3) To estimate the cumulative prevalence of acute seizures and behavioural/emotional problems in preschool children living in Kilifi, Kenya;
- (4) To determine the risk factors associated with acute seizures and behavioural/emotional problems among preschool children in rural Kenya;
- (5) To examine the relationship between acute seizures and behavioural/emotional problems in preschool children in rural Kenya.

Justification of the study

The studies are motivated by the lack of community-based epidemiological studies of acute seizures and behavioural/emotional problems in Africa and by findings from previous hospital studies in this area on acute seizures and behavioural/emotional problems. We demonstrated that acute seizures are very common in children (up to 425-650/100000/year) (R. Idro et al., 2008; S. M. Kariuki et al., 2011), and that up to 10% of them develop behavioural/emotional problems following discharge from hospital (J. A. Carter, Mung'ala-Odera, et al., 2005). The risk for behavioural/emotional problems after acute seizures was greatest with complex acute seizures (focal, prolonged and/or repetitive), but studies based on a community sample are required since hospital samples may represent children with a greater morbidity.

Since only a small proportion of children (10%) are admitted to hospital for seizures (based on a pilot study), hospital data is likely to be a gross underestimate of the true prevalence. Therefore community studies are required to provide reliable estimates and risk factors for both acute seizures and behavioural/emotional problems for planning preventative and management interventions. The research project set out to understand the risk for behavioural/emotional problems following acute seizures as it is not clear whether these were related to epileptic seizures or the underlying neurological infections/conditions (J. A. Carter, Mung'ala-Odera, et al., 2005).

Febrile seizures are thought to have a good prognosis, but a few studies from high income countries have demonstrated an increase in prevalence of behaviour/emotional problems following complex febrile seizures (Kölfen, Pehle, & König, 1998). It is possible that the association between acute febrile seizures and behavioural/emotional problems is real rather than spurious since, at the least, the same underlying genetic and neurological impairments leading to seizures may also lead to behavioural/emotional problems. Understanding the

burden of and relationship between acute seizures and behavioural/emotional problems would be important in planning medical and educational interventions for preschool children.

Organisation and structure of the DPhil thesis

Chapter 2 provides a comprehensive world literature on the prevalence, risk factors for, and behavioural/emotional consequences of acute seizures in preschool children. It also contains an extensive literature review on the prevalence, risk factors/correlates and comorbidities of behavioural/emotional problems among preschool children.

Chapter 3 provides an overview on the methodology of the study, in particular, the study site, population, study design, procedures and statistical analysis in general terms. Specific procedures and statistical analysis will be mentioned in the respective subsequent chapters.

Chapter 4 focuses on the validation and adaptation of the CBCL among preschool children in Kilifi, Kenya. There are data on psychometric properties, in particular internal consistency, test-retest and inter-informant reliability and discriminant validity. The fit indices for the seven CBCL syndromes are also provided. This chapter is broadly organised into a brief background, brief methodology, main findings and summary or brief discussion of the findings.

Chapter 5 presents results on the prevalence, risk factors and medical comorbidities of emotional and behavioural problems among preschool children living in Kilifi, Kenya. This chapter is broadly organised into a brief background, brief methods and procedures, main findings and summary or brief discussion of the findings.

Chapter 6 focuses on the prevalence, risk factors and clinical features of acute seizures among preschool children living in Kilifi, Kenya. The clinical features include seizure-related factors such as onset, semiology, treatment, and duration of seizures. This chapter is broadly

organised into a brief background, brief methods and procedures, main findings and summary or brief discussion of the findings.

Chapter 7 presents results on the behavioural/emotional comorbidities of acute seizures among preschool children living in Kilifi, Kenya. I have examined if the prevalence of behavioural problems is increased in those with acute seizures by comparing with those without these seizures and determined if the association is independent of potential confounders. Factors associated with increased prevalence of behavioural problems in acute seizures and epilepsy are also discussed. This chapter is broadly organised into a brief background, brief methods and procedures, main findings and summary or brief discussion of the findings.

Chapter 8 synthesises all the content of all chapters into one discussion while pointing out similarities and contrasts of main findings with other published studies elsewhere. This chapter outlines the important additions of the DPhil studies to the literature, provides directions for future research, highlights public health value of the findings and discusses the strengths and limitations of the studies.

Chapter 2: Literature review

Prevalence of, risk factors for and assessment of behavioural/emotional problems in preschool children

Introduction

Behavioural/emotional problems are common in preschool children (defined as those aged 6 years and below), with most community studies reporting a prevalence of between 10-20% (Bauer & Webster-Stratton, 2006; A. S. Carter et al., 2004). These behavioural/emotional problems are classified into two broad categories namely externalising problems (sometimes referred to as behavioural problems) and internalising problems (sometimes referred to as emotional problems) (T. M. Achenbach, Edelbrock, & Howell, 1987). In particular preschool children experience externalising problems such as oppositional disorder, hyperactivity, and internalising problems such as dysregulated mood states, profound sadness/anxiety (Campbell, 1995; A. S. Carter et al., 2004). In this review, the term “behavioural/emotional problems” will refer to all psychological problems, while the two major subcategories will be referred to as either externalising or internalising problems.

Behavioural/emotional problems can often appear early in life and may persist into later age groups (Campbell, 1995; Horwitz et al., 2013), thus early identification is required in order to develop interventions. There is evidence that externalising problems in preschool age children are more likely to persist into adolescence than are internalising problems (Keenan & Shaw, 1997; Wilson et al., 2013). It is important to consider behavioural/emotional problems in preschool children in a developmental context since these children are growing rapidly (Campbell, 1995; Egger & Angold, 2006).

Behavioural/emotional problems in preschool children have been shown to be associated with medical comorbidities such as executive/cognitive impairments, feeding problems,

malnutrition and allergic diseases (Berlin, Lobato, Pinkos, Cerezo, & LeLeiko, 2011; Chang et al., 2013; Franz et al., 2013; Lavigne et al., 1993; Schoemaker, Mulder, Dekovic, & Matthys, 2013). Additionally, these problems may be associated with significant impairment in socialisation and overall functioning at school or family level in up to 30% of the affected children (Wilens et al., 2002). For example, parents of children with behavioural/emotional problems admit being worried about these behaviours which interferes in family activities (M. J. Briggs-Gowan, Carter, Skuban, & Horwitz, 2001; A. S. Carter et al., 2004).

Patterns, nosology and types of behavioural/emotional problems among preschool children

Behavioural/emotional problems load into two broad components: internalising and externalising problems. Items perceived to be of either component may load in different factors across studies and societies, suggesting that they co-vary with syndromes and society (T. M. Achenbach et al., 1987; Ivanova et al., 2010). Examples of internalising problems include being emotionally reactive, withdrawn, anxious and depressed, while externalising problems include aggressiveness and difficulties concentrating (T. Achenbach & Rescorla, 2000).

Internalising problems are more difficult to identify in preschool children thus most studies have focused on externalising problems such as oppositional and attention-deficit disorder (Campbell, 1995; Verlinden et al., 2012). A review of previous studies found that externalising problems such as oppositional disorders may be thrice that of internalising problems (McDonnell & Glod, 2003). However, in some societies such as Turkey, internalising problems are more likely to be reported for reasons not clearly understood (Rescorla et al., 2011).

The factor analysis of behavioural/emotional items usually loads into several syndromes or clusters depending principally on the type of tool used. The Preschool Child Behaviour Checklist (CBCL), which has 99 items and can assess behavioural/emotional problems in 1.5-5 year old children, loads into 7-syndromes (T. Achenbach & Rescorla, 2000). These are: emotionally-reactive, anxiously-depressed, somatic complaints, withdrawn, sleep problems, attention problems and aggressive behaviour. The 7 syndromes have been replicated across several settings of both high and low-income countries (Ivanova et al., 2010). The first four form the internalising problem scale while the last two form the externalising problem scale. Sleep problems, the seventh syndrome, form neither the internalising scale nor the externalising scale.

Other related preschool tools such as the Behaviour Checklist (with 19-items) developed by Richman et al (N. Richman, 1977) assesses 3 and 4 year old children, loads into 6 clusters namely: poor social adjustment, poor emotional adjustment, sleep problems, over-activity/inattention, eating problems and soiling (Sonuga-Barke, Thompson, Stevenson, & Viney, 1997). The Strength and Difficulties Questionnaire, which assesses 2-4 year old children, has five syndromes: conduct problems, emotional symptoms, hyperactivity/inattention, peer relationship problems and prosocial behaviour (Theunissen, Vogels, de Wolff, & Reijneveld, 2013).

Parents tend to report different behaviour/emotional problems depending on age of the child. For example, parents of toddlers emphasise eating, sleeping and toileting problems (Campbell, 1995), whereas those of children above two years report indiscipline issues such as disobedience, defiance, tantrums and hyperactivity (Koot & Verhulst, 1991). These differences may be context-related, where social conflicts are reported more in group settings (Chen, Fein, Killen, & Tam, 2001). Some studies have reported increased prevalence of

externalising problems among boys compared to girls (Prior, Smart, Sanson, & Oberklaid, 1993), but others report no significant differences (Hill, Degnan, Calkins, & Keane, 2006).

Prevalence of behavioural/emotional problems in preschool children

There are relatively few epidemiological studies in preschool children compared to older children (Egger & Angold, 2006) and most available estimates are for preschool and older children combined (Cortina, Sodha, Fazel, & Ramchandani, 2012). Parent reported behavioural problems range from 4-41%, with the majority rates between 10% and 20% (Table 2-1) (Lavigne et al., 1993; Paterson, Carter, Gao, & Perese, 2007). The prevalence is higher in hospital based samples (up to 37%) (Sim et al., 2013), which, unlike community samples, are not representative of true prevalence (Egger & Angold, 2006). There are no meta-analysis or systematic reviews specifically for preschool children. Meta-analytic studies combining preschool and older children had a pooled estimate of 17.6% for 33 German studies and 14.3% for 6 studies from sub-Saharan Africa (Barkmann & Schulte-Markwort, 2012; Cortina et al., 2012). Meta-analysis and systematic reviews for studies reporting prevalence of behavioural/emotional problems in preschool children are required.

A multicultural study of 23 societies, some from Asia and South America, found a prevalence of 4-13% in preschool children, but reporting of behavioural/emotional problems differed across cultures, with some problems considered normal in some cultures (Rescorla et al., 2011). Some studies show gender differences in behavioural/emotional problems in preschool children; preschool boys from Chicago scored worse than girls (10% vs. 7%) (Lavigne et al., 1996).

There are few individual population-based behavioural/emotional studies of preschool studies in low and middle income countries (LMIC). The majority of the studies in LMIC are based on clinical admissions. In Turkey behavioural/emotional problems were estimated at 9-12%

in preschool children in the community (Table 2-1) (Erol, Simsek, Oner, & Munir, 2005). A Sudanese population study found internalising complaints such as anxiety and externalising problems such as hyperactivity in up to 41% of preschool children (Rahim & Cederblad, 1986). A study in India found behavioural/emotional problems in 22% of hospital admissions aged 3-6 years (Rai, Malik, & Sharma, 1993). More epidemiological studies are required in LMIC and in particular in Africa.

Table 2-1: Examples of studies from different settings reporting prevalence of behavioural problems in preschool children

Study	Country	Age	Design	Sample size (N)	Tools	Overall prevalence
(Klein, Otto, Fuchs, Reibiger, & von Klitzing, 2015)	Germany	4-6 years	Cross-sectional	1034	SDQ	6.9%
(Fuhrmann, Equit, Schmidt, & von Gontard, 2014)	Germany	5-7 years	Cross-sectional	653	PFC	5.7%
(Sim et al., 2013)	Glasgow		Cross-sectional	543	SDQ	37%
(Karabekiroglu et al., 2013)	Turkey	1-4 years	Cross-sectional	2775	BITSEA	9.3%
(Fuchs, Klein, Otto, & von Klitzing, 2013)	Germany	3-5 years	Cohort	1738	SDQ	16%
(Brown, Copeland, Sucharew, & Kahn, 2012)	USA	3-4 years	Cross-sectional	254	ASQ	24%
(Bayer, Hiscock, Ukoumunne, Price, & Wake, 2008)	Australia	5 years	Cohort	733	CBCL	20%
(Wu et al., 2012)	Taiwan	2-6 years	Cohort	645	CBCL	25%

(Wichstrom et al., 2012)	Norway	4 years	Cohort	2475	SDQ	7.1%
(Bufferd, Dougherty, Carlson, Rose, & Klein, 2012)	USA	3-6 years	Cross-sectional	462	Early childhood inventory	13.9%
(M. M. Gleason et al., 2011)	Romania	1.5-5 years	Cohort	1003	CBCL	8.8%
(Rescorla et al., 2011)	Multisite	1.5-5 years	Multi-site	19,850	CBCL	4-13%
(Skovgaard, 2010)	Denmark	1.5 years	Cohort	6090	CBCL	18%
(A. S. Carter et al., 2010)	USA	1-3 years	Birth cohort	1329	CBCL	21.6%
(Barbarin, 2007)	USA	<6 years	Cross-sectional	5577	Questionnaire	18.4%
(Paterson et al., 2007)	New Zealand	2 years	Cross-sectional	1398	CBCL	14.2%
(Furniss, Beyer, & Guggenmos, 2006)	Germany	6 years	Cohort	1887	CBCL	12.6%
(Erol et al., 2005)	Turkey	2-3 years	Cross-sectional	673	CBCL	11.9%
(Kuschel et al., 2004)	Germany	3-6 years	Cross-sectional	809	CBCL	5%
(M. J. Briggs-Gowan et al., 2001)	USA	2-3 years	Birth cohort	1280	CBCL	11.8%
(Keenan, Shaw, Walsh, Delliquadri, & Giovannelli, 1997)	USA	5 years	Longitudinal	104	CBCL, DSM-IV-TR	26.4-29.9%
(Lavigne et al., 1996)	USA	2-5 years	Cross-sectional; descriptive	3860	CBCL, questionnaire	21.4%
(Fegert, 1996)	Germany	2.5 years	Cross-sectional	751	CBCL	11.6%
(Rai et al., 1993)	India	3-6 years	Hospital sample	200	interviews	22%
(Hooks, Mayes, &	USA	0-5 years	Descriptive	193	Interviews, Yale developme	4-32%

Volkmar, 1988)					ntal schedules	
(Kashani, 1987)	USA	1-6 years	Prospective	1,000	Interviews , DSM-III criteria	6.5%
(Cornely & Bromet, 1986)	USA	3 years	Cross-sectional	565	BSQ	11.3%
(Rahim & Cederblad, 1986)	Sudan	3-6 years	Cross-sectional	270	Interviews	41%
(Crowther, Bond, & Rolf, 1981)	USA	2-6 years	Cross-sectional	709	Vermont Behavior Checklist	20%
(Earls & Richman, 1980)	USA	3 years	Cross-sectional	100	BSQ	20%
(N. Richman, 1977)	UK	3 years	Cross-sectional	705	BSQ	7-15%

CBCL=child behaviour checklist; BSQ=behavioural screening questionnaire; DSM=diagnostic statistical manual; BITSEA=Brief-Infant Toddler Social Emotional Problems; ASQ=Ages and Stages Questionnaire; PFC=Preschool Feeling Checklist

Persistence and stability of behavioural/emotional problem in preschool children

There is substantial persistence for preschool behavioural/emotional problems in later childhood and adulthood (Bufferd et al., 2012; Campbell, 1995), with externalising problems showing more stability and homotypic continuity (same type of behavioural problems at different time points) than internalising problems (Anselmi et al., 2008). Severe preschool behavioural/emotional problems, for example those with significant impairment in social and intellectual functioning, may continue sometimes until adulthood (Anselmi et al., 2008; Egger & Angold, 2006).

In the short-term, 37% of children with behavioural/emotional problems at 18 months had similar problems at 30 months (Mathiesen & Sanson, 2000); while in another study, over half of children aged 2 and 3 years continued to have behavioural/emotional problems 2-3 years later (Lavigne et al., 1998). In the USA, 50% of those with behavioural/emotional problems at 1-year, had these problems persist at 2-years, with homotypic (same type of

behavioural/emotional problems at different time points) persistence rates ranging from 38-50% (M. J. Briggs-Gowan, Carter, Bosson-Heenan, Guyer, & Horwitz, 2006). About 60% of preschool children assessed for behavioural/emotional problems in 1989 had these problems in 2003 suggesting that they persisted over the 14-year period (Tick, van der Ende, Koot, & Verhulst, 2007). In a landmark British study, behavioural/emotional problems at 3 years persisted in 63% at age 4 years and in 62% at age 8 years (N. Richman, Graham, & Stevenson, 1982). In Brazil, of the children with behavioural/emotional problems at 4 years, 31% remained with these problems at 12 years (Anselmi et al., 2008).

Several factors predict persistence of behavioural/emotional problems. The problems tend to persist more in boys than in girls (Campbell, 1995), with prevalence declining over longer time, and maternal reports are more likely to indicate persistence than teacher reports (Gardner & Shaw, 2009; M. G. Sawyer, Mudge, Carty, Baghurst, & McMichael, 1996). Persistence of externalising and internalising problems in Swiss Kindergarten children at 6-years was predicted by poor socialisation skills and good socialisation skills at 5-years, respectively (Perren, Stadelmann, von Wyl, & von Klitzing, 2007). Parental report of co-occurring problems, high family life disruption and high parental distress are also important predictors of persistence (M. J. Briggs-Gowan et al., 2006). The more severe the behavioural/emotional problems the more it is likely that they will persist over the years (Campbell, 1995; Gardner & Shaw, 2009).

Comorbidities and outcomes of behavioural/emotional problems in preschool children

Medical and neurocognitive comorbidities of behavioural/emotional problems are common. Perception, cognitive and motor problems can co-occur with behavioural/emotional problems in preschool children (Gillberg, Rasmussen, Carlstrom, Svenson, & Waldenstrom, 1982). Impairment in language is an important comorbidity of behavioural/emotional problems and

is a common reason for most parents to be concerned about their children's developmental delay (Horwitz et al., 2003).

Complex febrile seizures are associated with increased prevalence of behavioural/emotional problems in preschool children in some studies (Rodenburg, Stams, Meijer, Aldenkamp, & Dekovic, 2005), but not in some more recent studies (Visser et al., 2012). There are however few studies examining the association between acute febrile seizures and behavioural/emotional problems. In Africa, where acute seizures are common (S. M. Kariuki et al., 2011), there are no community-based epidemiological studies on association of behavioural/emotional problems with acute seizures.

Sleeping problems were associated with internalising problems in Japanese preschool children and often resulted in a poor prognosis (Komada et al., 2011). Sleep problems were associated with behavioural/emotional problems in preschool children both at home and in day care settings in a Canadian study (Hall, Scher, Zaidman-Zait, Espezel, & Warnock, 2012). Preschool children who are registered blind are also reported to have more behavioural/emotional problems than normal-vision children (Tirosh, Shnitzer, Davidovitch, & Cohen, 1998). Preschool children with cancer have more behavioural/emotional problems than those in the community, although the association diminishes with time (M. Sawyer, Antoniou, Toogood, & Rice, 1997).

Preschool behavioural/emotional problems are associated with negative psychosocial consequences later on in life. Behavioural/emotional problems assessed at 5 years were associated with early sexual debut and risky sex at 21 years (Ramrakha et al., 2007). Behavioural/emotional problems among pre-schoolers can result in peer rejection and victimisation, which are often overlooked (Perren, von Wyl, Stadelmann, Burgin, & von Klitzing, 2006). In one study, psychosocial and clinical outcomes were determined by

sociodemographic characteristics, stressful life events and sometimes female gender (Gothelf et al., 2006).

In one study, psychopathology at 3-years was associated with the development of an asthmatic wheeze at 5-years (Calam et al., 2005). In Ontario Canada, behavioural/emotional problems during preschool problems were associated with later poor school performance (Cadman et al., 1988). Males who had externalising problems during preschool age were more likely to commit suicide at 50 years (Geoffroy, Gunnell, & Power, 2014).

Risk factors and possible causal associations for behavioural/emotional problems in preschool children

Several risk factors and/or correlates of emotional and behavioural/emotional problems have been identified, and multiple risk factors may be associated with worse outcomes. Firstly, susceptibility to behavioural/emotional problems may be determined by genes with high heritability documented in some studies (35-77%) (Bornovalova, Hicks, Iacono, & McGue, 2010; Scourfield, Van den Bree, Martin, & McGuffin, 2004). Furthermore, it is thought there are gene-environment interactions with regard to the risk for developing behavioural/emotional problems (Althoff & Hudziak, 2011). These interactions have been supported by twin studies, which have shown a role for environmental factors in the development of behavioural/emotional problems in preschool-aged twins (Saudino, Carter, Purper-Ouakil, & Gorwood, 2008).

Prenatal and perinatal factors are important in the development of behavioural/emotional problems in preschool children. Low birth-weight was associated with behavioural/emotional problems among preschool children in a recent study (Arpi & Ferrari, 2013). In Australia, pregnancy factors such as smoking and maternal stress during pregnancy were risk factors for behavioural/emotional problems in offspring during preschool age (Duazo, Avila, & Kuzawa,

2010; Robinson et al., 2008). Breastfeeding during the preschool period is associated with better neurodevelopmental outcomes, and the benefits persisted to 30 years later in a Brazilian study (Victora et al., 2015). According to a systematic review commissioned by the World Health Organization (Horta & Victoria, 2013), benefits of breastfeeding on neurodevelopment decrease with time, while in another study breastfeeding was not protective against behavioural/emotional problems in offspring after accounting for potential confounders such as sociodemographic factors (Lind, Li, Perrine, & Schieve, 2014). Heavy alcohol drinking during pregnancy can be associated with behavioural/emotional problems in offspring, while light drinking is not (Kelly et al., 2009).

Behavioural/emotional problems in preschool children can be associated with socioeconomic characteristics such as older age of child, minority status, male sex, single family, and family size (Lavigne et al., 1996; Sim et al., 2013). Another study found lack of family cohesiveness as a predictor of behavioural/emotional problems in preschool children (Lavigne et al., 1998). Low maternal age and single parenthood were associated with behavioural/emotional problems in Norwegian preschool children suggesting that parent-child interaction and socialisation are important (Javo, Ronning, Heyerdahl, & Rudmin, 2004). Intimate partner violence was associated with psychopathology in older children, but not in preschool children (McFarlane, Groff, O'Brien, & Watson, 2003). Child maltreatment or neglect may increase behavioural problems in preschool children (McDonald, Milne, Knight, & Webster, 2013). These family and parental factors are important predictors since they explained up to 25% and 17% variation of externalising and internalising problems in Australian preschool children, respectively (Bayer et al., 2008).

Parental mental health problems are also associated with the development of behavioural/emotional problems in preschool children (Einfeld, Tonge, & Clarke, 2013; Stein et al., 2014). In a UK study antenatal maternal anxiety was associated with a 2-fold increase

in behavioural/emotional problems in children at 4 years (O'Connor, Heron, Golding, Beveridge, & Glover, 2002). Poor maternal responsiveness and marital adjustment are particularly associated with externalising problems such as aggressiveness in follow up studies (Javo et al., 2004). Maternal psychopathology is associated with food insecurity and thus its association with preschool behavioural/emotional problems can easily be addressed through social policy (Whitaker, Phillips, & Orzol, 2006).

Heavy metals, chemicals and arsenics can be associated with neurodevelopmental problems according to a recent systematic review (Grandjean & Landrigan, 2014), but few studies have examined associations with behavioural/emotional problems (Rodriguez-Barranco et al., 2013). In Australia, exposure to postnatal lead was associated with adverse effects on mental development at 2-years, and strongly at 4-years (McMichael, 1989). Additionally, exposure to pesticides can be associated with pervasive developmental problems in preschool children, although some studies do not support these conclusions (Jurewicz & Hanke, 2008).

Exposure to traumatic experiences also increases the risk of behavioural/emotional problems in preschool children. In Israel, direct or indirect exposure to terrorism was associated with psychopathology in preschool children (Wang et al., 2006). Similarly, exposure to World Trade Centre attack-related events was associated with behavioural/emotional problems in preschool children from the USA (Chemtob, Nomura, & Abramovitz, 2008).

Assessment of behavioural/emotional problems in preschool children

Challenges of assessments

It is difficult to develop criteria for abnormal behaviour/emotional problems that distinguish from those of a typically growing child (Njoroge & Bernhart, 2011). There is a general misconception about behavioural/emotional problems in children. Many authors have argued

that typically developing 2 year old children are often irritable and hyperactive and this has been referred to as the “terrible twos” (A. S. Carter et al., 2004).

Much attention has focussed on a child’s neurocognitive and language abilities at the expense of behavioural/emotional problems (Egger & Angold, 2006). Furthermore, childhood is considered sacred and behavioural/emotional problems are unexpected by parents and carers alike (A. S. Carter et al., 2004; Njoroge & Bernhart, 2011).

Many behavioural/emotional problems are transient but waiting for them to pass can cause delays in the diagnosis of important conditions requiring interventions (De Giacomo & Fombonne, 1998). The delay can cause exacerbation of behavioural/emotional conditions complicating efficacy of the parenting role (Reyno & McGrath, 2006).

It is challenging to integrate behavioural/emotional data from multiple sources and informants since results may vary depending on who is providing the information (Rescorla et al., 2011). However, multiple informants from the same societal background can give more reliable assessments of the child’s behaviour/emotional status (Egger & Angold, 2006).

Guidelines for identifying behavioural/emotional problems in preschool children

Behavioural/emotional problems are better assessed taking into consideration a child’s caregiver context, broader family, cultural and community factors (M. J. Briggs-Gowan et al., 2001). It is also helpful to consider the parenting approach and family distress that are secondary to the child’s behavioural/emotional status (Egger & Angold, 2006). Furthermore, behavioural/emotional problems should be assessed within the linguistic and cognitive development of these children since they may be associated with each other (Campbell, 1995).

Assessment of behavioural/emotional problems across different cultures and or races may require adaptation and validation (Rescorla et al., 2011). Tools for assessing

behavioural/emotional development should be relatively brief, easy to administer and interpret, and should possess acceptable psychometric properties (Egger & Angold, 2006; Njoroge & Bernhart, 2011). Assessment tools should also focus on positive aspects of child functioning to reduce parental response bias, as bias often results in overestimation of a child's behavioural and emotional problems (Campbell, 1995).

Tools for measuring behavioural problems in preschool children

Earliest efforts to assess behavioural/emotional problems

In the 1970s Richman *et al.* developed the Behaviour Screening Questionnaire (BSQ) for 3 year olds. It consisted of 12 questions and was used in both British (N. Richman & Graham, 1971; N. Richman et al., 1982) and American studies (Cornely & Bromet, 1986). Soon thereafter Richman developed a 19-item version of the BSQ called Behaviour Checklist for mothers to be completed independently (N. Richman et al., 1982) and a 22-item preschool behaviour checklist for completion by teachers (McGuire & Richman, 1986). Then in 1987 Achenbach *et al* developed the CBCL (T. M. Achenbach et al., 1987), which revolutionised the assessment of behavioural/emotional problems in preschool children.

Common tools for assessment of behavioural/emotional problems in preschool children

Several tools used to assess behavioural/emotional problems in preschool children and their corresponding psychometric properties are shown in table 2-2 below. Of note is the preschool CBCL which has gained international recognition culminating in its translation and use in several settings (T. Achenbach & Rescorla, 2000; Ivanova et al., 2010). The CBCL is popular because it is easier to administer and has retained acceptable psychometric properties even after use in different cultural environments (T. Achenbach, Dumenci, & Rescorla, 2003).

Preschool CBCL assesses total, internalising and externalising problems (T. Achenbach & Rescorla, 2000). Preschool CBCL started with an earlier version that assessed children aged 2-3 years, and had fewer items (T. M. Achenbach et al., 1987). This was then upgraded to the current version for 1.5-5 year old children which has 99 items. The current CBCL can be used for children between 1-6-years without compromising validity and reliability (van Zeijl et al., 2006). The extensive use of the CBCL for defining behavioural/emotional problems has led to the development of the diagnostic and statistical manual for mental disorders (DSM)-IV-oriented scales of the CBCL (T. Achenbach et al., 2003; Keenan et al., 1997).

The CBCL has a sub-clinical cut-off of 60 which corresponds to the 90th percentile score in an American sample and a clinical cut off of 63 or more corresponding to 93rd percentile of the same sample (T. Achenbach & Rescorla, 2000). It possesses good psychometric properties (internal consistency Cronbach alpha and test-retest correlation values >0.90) and retained a consistent seven-syndrome structure across 23 different societies (Ivanova et al., 2010). In this study (Ivanova et al., 2010), the Root Mean Squared Error of Approximation was <0.05, which confirms configural invariance of CBCL across many countries and settings. In a Chinese study (Liu, Cheng, & Leung, 2011), the psychometric properties of preschool CBCL were acceptable and comparable to those of the American sample described above. I have adapted and validated the CBCL to the local populations in Kilifi, Kenya (S. M. Kariuki, Abubakar, Murray, Stein, & Newton, 2016), where it has demonstrated acceptable psychometric properties and fit indices for the seven-syndromes measured by the tool (results are provided and discussed in chapter 4 of this thesis).

In addition to the CBCL, there are other tools commonly used with preschool children but these have some limitations. The SDQ is widely used in assessing behavioural/and emotional problems in preschool children aged 2-4 years (Ezpeleta, Granero, de la Osa, Penelo, & Domenech, 2013), an age-range which is narrower than that for CBCL. Preschool Feelings

Checklist screens depression in 3-6 year olds (Luby, Heffelfinger, Koenig-McNaught, Brown, & Spitznagel, 2004), but it focuses on internalising problems but not externalising problems. Early Childhood Screen Assessment for emotional/behavioural problems in 1.5-5 year olds (Mary Margaret Gleason, Zeanah, & Dickstein, 2010) and Disruptive Behavioural Rating Scale- Parent Version for externalising problems including ADHD (Friedman-Weieneth, Doctoroff, Harvey, & Goldstein, 2009) have not been widely used across different cultural settings. The psychometric properties for these additional tools are summarised in table 2-2 below.

Table 2-2: Psychometric properties of various assessment tools for preschool children

Tools	Study	Coefficient alpha	Test-retest	Inter-informant	Discriminative validity	Predictive validity
Strengths and difficulties Questionnaire (SDQ)	(Sveen, Berg-Nielsen, Lydersen, & Wichstrom, 2013)	0.87	N/A	N/A	N/A	0.76
Child Behaviour Checklist (CBCL)	(Rescorla et al., 2011)	0.91	0.76-0.91	0.47-0.58	good	0.52-0.63
Diagnostic Infant Preschool Assessment (DIPA)	(Scheeringa & Haslett, 2010)	N/A	0.69	N/A	good	N/A
Preschool Feeling Checklist (PFC)	(Luby et al., 2004)	0.76	N/A	N/A	0.90	N/A
Brief-Infant-Toddler Socio-Emotional Assessment (BITSEA)	(M. J. Briggs-Gowan, Carter, Irwin, Wachtel, & Cicchetti, 2004)	0.79	0.87	0.68	good	good
Devereux Early Childhood Assessment (DECA)	(LeBuffe & Naglieri, 1999)	0.80	0.80	0.77	N/A	N/A
Infant Toddler Social and Emotional Assessment (ITSEA)	(Margaret J. Briggs-Gowan & Carter, 1998)	0.69	0.79-0.91	N/A	good	N/A
Ages and Stages Questionnaire (ASQ)	(Squires, Bricker, & Potter, 1997)	0.68-0.87	0.94	0.94	good	good
Toddler Behaviour Screening Inventory (TBSI)	(Mouton-Simien, McCain, & Kelley, 1997)	0.88	0.89	N/A	0.79	N/A

N/A=not available

Conclusions

Behavioural/emotional problems are common in preschool children and may persist into adolescence and adulthood. They manifest as both internalising and externalising problems, but the latter are more salient in preschool children and can persist longer than the former. There are fewer epidemiological behavioural/emotional studies on preschool children than there are for older children probably because of challenges in definition criteria, lack of appropriate assessment tools, stigma associated with these problems in preschool children, rapid developmental changes and overemphasis on neurocognitive and language development in preschool children. In particular, there is a paucity of community-based prevalence studies on psychopathology from LMIC particularly those from Africa.

Behavioural/emotional problems can be associated with genetic factors, antenatal and perinatal problems, environmental factors, parenting approach and family situation, parental psychopathology, heavy metal toxins and nutrition. Some of these factors may be associated with the persistence or stability of behavioural/emotional problems into older age groups, but persistence diminishes with time. These risk factors may interact with each other and presence of many risk factors is associated with worse behavioural/emotional problems and poorer outcomes in preschool children. Behavioural/emotional problems are associated with medical and neurocognitive comorbidities, which should be assessed and addressed.

Comprehensive assessment of behavioural/emotional problems is advised and should be done with instruments validated and adapted to the local population to ensure their reliability and cultural acceptability. The assessments should be done in the context of the child's developmental stage, family functioning and surrounding environment.

Further studies on prevalence, risk factors and course of behavioural/emotional problems in preschool children are required and particularly in LMIC of sub-Saharan Africa. These

studies should use assessment tools such as the CBCL, which have been used in different cultural backgrounds. The CBCL should be first piloted through adaption and validation. Administration of these tools can be done by trained assessors with basic secondary school education.

Prevalence of, risk factors for, and behavioural/emotional outcomes of acute (febrile) seizures

Introduction

Seizures occurring with fever or in a febrile illness are usually referred to as febrile seizures, and these are the most common seizure disorders in preschool children (Hauser, 1994). Both National Institute of Health (NIH) (Freeman, 1980) and International League Against Epilepsy (ILAE) (ILAE, 1993) define febrile seizures as seizures associated with fever or a febrile illness, although they differ slightly on age limit and exclusion criteria (table 2-3). However, this definition does not exclude febrile seizures in children with developmental delays unrelated to the febrile illness (Shinnar & Glauser, 2002). The definition for febrile seizures excludes children with previous unprovoked seizures and neonatal seizures, and those with febrile infections that affect the central nervous system such as meningitis, encephalitis and malaria, which causes acute symptomatic seizures (Beghi et al., 2010).

Table 2-3. Definition of febrile seizures according to International League Against Epilepsy (ILAE) and National Institute of Health (NIH)

ILAE	NIH
A seizure occurring in childhood	Event in infancy or childhood
Occurs between 1 month and 5 years	Occurs between 3 months and 5 years
Associated with afebrile illness	Associated with fever
Excludes CNS infections, neonatal seizures and acute symptomatic seizures	Excludes intracranial infections or seizures with defined causes

Prevalence

The cumulative incidence (lifetime prevalence) of febrile seizures in children aged ≤ 6 years is 2-5% in American and European studies (Beghi et al., 2010; Verity, Butler, & Golding,

1985), and is up to 8% in Japan and 14% in Marians Island and Guam (Shinnar & Glauser, 2002; Stanhope, Brody, Brink, & Morris, 1972). Prevalence was higher in boys than girls in one Japanese study (Tsai 1984), while in an American study, it was significantly higher in black children compared to white (Nelson 1978). There is limited population-based data on the burden of febrile seizures in resource-limited countries with available studies focusing on underlying common causes of admission to hospital with little attention to incidence of acute seizures. The few hospital-based studies in Africa have either grossly underestimated prevalence (less than 1%) probably because they focused on hospitalised children only (R. Idro et al., 2008) or overestimated prevalence (up to 20%) probably by inclusion of acute symptomatic seizures (Obi, Ejeheri, & Alakija, 1994).

Variation in prevalence of febrile seizures

Globally, the incidence of febrile seizures varies across the world (Baram & Shinnar, 2002), which may be explained by several factors. Case definitions may differ depending on whether one follows the ILAE or NIH definitions, which have different age criteria. Case ascertainment is related to the methodology used to identify cases, where hospital registers are used in high-income countries, but these may be underestimated in low and middle income countries (LMIC) where rates of hospital use are low. Geographical variation may explain underlying risk factors, for example poor areas with more infections are likely to register more febrile seizures and so forth. Cultural factors may contribute to variation in the number of febrile seizure by underreporting cases in areas where seizures are stigmatised, for example in sub-Saharan African countries (Mbuba, Abubakar, Odermatt, Newton, & Carter, 2012).

Pathophysiology: Age of onset and the role of fever

The median onset of febrile seizures is usually from 18-24 months, but a few (up to 15%) may occur after 48 months (C Waruiru & R Appleton, 2004). Most studies allude to the maturing brain's sensitivity to fever, but the mechanism underlying this susceptibility remains unclear. Fever related to a febrile illness is thought to cause the seizures, but the seizures may occur before or after the febrile illness (Sadleir & Scheffer, 2007), complicating the attribution of seizures to fever. The fact that use of antipyretic medication does not appear to prevent risk of seizures (Strengell et al., 2009) suggests that other mechanisms may be involved, for example, proinflammatory molecules such as interleukins and tumour necrosis factor, which have been shown to be elevated in febrile seizures in some studies (Choy, Dube, Ehrenguber, & Baram, 2014).

Temperatures of $\geq 38^{\circ}\text{C}$ are associated with these seizures, and the role of the rate of temperature rise and peak temperature are contentious (Sadleir & Scheffer, 2007).

Paradoxically, low febrile temperatures may increase the risk of focal or repetitive febrile seizures according to some studies (Sadleir & Scheffer, 2007). Recent evidence shows that febrile seizures can also be caused by fever-induced hyperventilation and alkalosis (Schuchmann et al., 2011).

Risk factors, causes and genetic susceptibility of febrile seizures

Risk factors for febrile/acute seizures

Febrile seizures are genetically complex often with no single mode of inheritance (Mittal, 2014). Heritability for seizures is high (up to 70%), and the risk of febrile seizures is up to three times in monozygotic compared to dizygotic twins suggesting genetic susceptibility (Kjeldsen, Kyvic, Friis, & Christensen, 2002; T. Tsai, 1987). Six febrile seizure susceptibility loci (FEB1-6) on various chromosomes have been identified (Nakayama & Arinami, 2006).

In particular, mutations in the sodium channel and gamma amino-butyric genes have been identified in children with febrile seizures alone or as a broader phenotype of generalised epilepsy with febrile seizures (Scheffer & Berkovic, 1997; Wallace et al., 1998), suggesting febrile seizures may be related to the genes that code for ion channels. However there is no definitive evidence that these genes alone increases the risk for febrile seizures. Other genes associated with febrile seizures including interleukins and acetyl choline receptors have also been identified (Table 2-4).

Table 2-4. Genes associated with acute (febrile) seizures

Genes	Effect (Susceptibility or protective)	Study design	Country
FEB1-6 loci	Susceptibility/protective	Linkage, GWAS	Multiple countries(Nakayama & Arinami, 2006)
IL-1Beta	Susceptibility	Case control	Finland(Virta, Hurme, & Helminen, 2002)
IL-10:rs3024500	Susceptibility	Case control	4 African sites(S. M. Kariuki et al., 2013)
IL-17: rs708567	Protective	Case control	4 Africa sites(S. M. Kariuki et al., 2013)
IL-1RN	Susceptibility	Case control	China(F. J. Tsai, Hsieh, Chang, Lin, & Tsai, 2002)
GABRG2	Susceptibility	Case control	China(Chou, Peng, et al., 2003)
CHRNA4	Susceptibility	Case control	China(Chou, Lee, et al., 2003)
CSNK1G2	Susceptibility	Case control	Japan(Yinan et al., 2004)
IMPA2	Susceptibility	Case control	Japan(Nakayama & Arinami, 2006)
SCN1B	Susceptibility	Linkage	Australia(Wallace et al., 1998)
SCN1A	Protective	Case control	Japan(Fujiwara et al., 2003)
SCN2A	Susceptibility	Linkage	Belgium(Ceulemans, Claes, & Lagae, 2004)

GWAS=genome-wide association study

Risk factors for febrile seizures include developmental delay, family history of febrile seizures, neonatal care discharge after 28 days, history of day care and some vaccinations (Table 2-5) (Sadleir & Scheffer, 2007; C Waruiru & R Appleton, 2004). A hospital based study from United Arab Emirates identified duration and the extent of fever as risk factors (Gururaj, Bener, Al-Suweidi, Al-Tatari, & Khadir, 2001). Family history of febrile seizures is reported in up to 40% of those affected, and the risk increases with the number of family members affected (Mittal, 2014; Veisani, Delpisheh, & Sayehmiri, 2013).

Causes of febrile/acute seizures

The potential causes include infections (viral, bacterial or parasitic), zinc and iron deficiencies, and vaccinations (Cendes & Sankar, 2011; Mittal, 2014). The viruses mentioned in several febrile seizure studies include human herpes (HHV) 6 and 7, influenza, adenovirus, respiratory syncytial virus and parainfluenza (Millichap & Millichap, 2006). These viruses can account for 50% of febrile seizures in Asian countries such as Japan, Hong Kong and China, but are very infrequent in USA and Europe (Millichap & Millichap, 2006). Viruses such as respiratory syncytial viruses are rather infrequent cause of febrile seizures (occurring in about 10% of Italian children), but may reactivate HHV6 or 7 (Bertolani et al., 1996). Gastroenteritis was an important cause of febrile seizures in Turkish children (Ghorashi, Nezami, Soltani-Ahari, & Ghorashi, 2010), but non-febrile seizures were also documented (Ghorashi et al., 2010). Malaria is observed in 25-50% of children with acute seizures in Africa (R. Idro et al., 2008; Obi et al., 1994), although sequestration of parasites into the brain may occur in a proportion of children with falciparum malaria (R. Idro et al., 2005). It is thought that vaccinations can be associated with febrile seizures (Baram & Shinnar, 2002), but it is unclear if the seizures are due to the fever or to the vaccine itself. However, vaccines are only associated with febrile seizures in less than 1% of cases, and are sometimes

repetitive febrile seizures. (Mittal, 2014). The most common vaccinations associated with febrile seizures include Diphtheria, Tetanus Toxoid and Whole blood Pertusis (DPT), influenza trivalent inactivated vaccine (Fluvax) and Measles, and Mumps and Rubella Vaccine (MMR) (Barlow et al., 2001; Cendes & Sankar, 2011). Two genetic loci for MMR vaccine-induced febrile seizures have recently been identified (Feenstra et al., 2014), supporting a causal role for these vaccines on febrile seizures. Further studies are still required to understand the relationship between vaccination and febrile seizures. Lower levels of iron and zinc have been reported in children with seizures compared to those without, for example in Iranian children (Fallah, Tirandazi, Akhavan Karbasi, & Golestan, 2013), while other studies did not find significant differences (R. Idro et al., 2010).

Table 2-5. Risk factors for onset and recurrence of febrile seizures and neurodevelopmental outcomes

Risk factor	Onset of febrile seizures	Recurrence of febrile seizures	Poor Developmental outcome
Attendance at day care	Yes	Yes	No
High temperature	Yes	No	No
Prolonged stay at neonatal care	Yes	No	No
Family history of seizures	Yes	Yes	Yes
Early onset of febrile seizures	NA	Yes	No
Low temperature during seizure	NA	Yes	No
Short duration of fever	NA	Yes	No
Neurological abnormality	Yes	No	Yes
Prolonged febrile seizure	NA	No	Yes
Focal febrile seizures	NA	No	Yes
Family history of epilepsy	NA	No	Yes
Inflammatory molecules	Yes	No	Yes

NA=not applicable

Phenotypes and duration of febrile seizures.

Most febrile seizures are generalised tonic-clonic seizures which are short (<15 minutes) and few recur (Mittal, 2014; Sadleir & Scheffer, 2007). Febrile seizures recur in up to 30% of children, are focal in up to 15% and are prolonged in 9% of children, which are often referred to as complex seizure phenotypes (Mittal, 2014; Sadleir & Scheffer, 2007; C Waruiru & R Appleton, 2004). Febrile status epilepticus occurs in 5% of children with febrile seizures, but form about 25% of all status epilepticus in childhood (Maytal & Shinnar, 1990). Studies from malaria endemic areas have documented a higher incidence of complex seizures (up to 60% of all acute seizures) (S. M. Kariuki et al., 2011; Waruiru et al., 1996), most of which could be non-febrile seizures related to the intracranial infections such as malaria and meningitis (James A. Berkley et al., 2009). Complex phenotypes of febrile seizures (focal, repetitive or prolonged) are associated with poorer outcomes in particular further prolonged attacks, epilepsy and neurodisability (Sadleir & Scheffer, 2007; C Waruiru & R Appleton, 2004).

Recurrence and risk of epilepsy after febrile seizures

At least a third of febrile seizures recur. In a Turkish study, febrile seizures recurred in those with a family history of febrile seizures, in first degree relatives and in complex phenotypes (Yakinci, Kutlu, Durmaz, Karabiber, & Egri, 2000). Other risk factors for recurrence include temperatures less than 38°C during the seizures, short duration of fever before the seizure and attendance at day care (Table 2-2). Febrile seizures may recur in up to 75% of children with multiple risk factors, compared to 4% in those without any risk (Sadleir & Scheffer, 2007). In endemic areas, malaria is associated with repetitive seizures (S. M. Kariuki et al., 2011) and the risk for recurrence may be genetically determined (S. M. Kariuki et al., 2013).

Epilepsy occurs after febrile seizures in 2-8% of children according to reviews and population based studies from America and Europe (John F. Annegers, Hauser, Elveback, & Kurland, 1979; Chungath & Shorvon, 2008; Verity & Golding, 1991), although this may be due to underlying causes rather than the seizures (Verity, Ross, & Golding, 1993). The risk is higher in hospitalised febrile seizures (up to 40% develop epilepsy) (Mittal, 2014; Nelson & Ellenberg, 1978), which may be biased towards severe morbidity, and in complex febrile seizures (20-40%) (Chungath & Shorvon, 2008). Generalised epilepsy is more common than focal epilepsy after febrile seizures (Camfield, Camfield, Gordon, & Dooley, 1994). It is thought the risk of epilepsy is related to the mesial temporal sclerosis (MTS) following febrile seizures often documented by retrospective studies (Mittal, 2014). It is unclear if MTS is caused by febrile seizures, a pre-existing MTS or an interaction between genes and environmental factors (Cendes, 2004).

The duration of follow-up in studies measuring epilepsy after febrile seizures varies, and this latency may affect the proportion that develop epilepsy (Shinnar, 2003). Predictors of epilepsy after febrile seizure include abnormal developmental status, complex febrile seizures (Mittal, 2014), family history of seizures (Lee & Ong, 2004) and serum proinflammatory molecules (Choy et al., 2014) (Table 2-2). There is no compelling evidence that prophylactic antiepileptic drugs reduce the risk of epilepsy after febrile seizures (Temkin, 2001) and further studies may be required to clarify this supposition.

Behavioural/emotional and neurocognitive outcomes of febrile seizures

Most studies observe that febrile seizures have a favourable prognosis in terms of neurocognitive performance and behavioural/emotional problems, although a few have documented poor outcomes. Poor neurocognitive development and behavioural/emotional problems are likely to occur in those with complex febrile seizures, underlying neurological

abnormality and increased risk of afebrile seizures (Nelson & Ellenberg, 1978). Poor neurocognitive outcomes are often reported more than behavioural/ emotional problems after febrile seizures (M. L. Tsai, Hung, Tsan, & Tung, 2015). Recently, familial clustering of febrile seizures and behavioural/emotional problems was demonstrated in American populations (Dale C. Hesdorffer et al., 2012), suggesting a shared underlying genetic predisposition to both conditions. Behavioural/emotional problems after febrile seizures are more likely to occur in children with a family history of mental health problems (Mitchell & Hauser-Cram, 2009).

Behavioural/emotional problems were reported in 22% of German children with febrile seizures compared to 6% of the controls (Kölfen et al., 1998). In the USA, 18% of 120 children with febrile seizures, who did not receive prophylactic phenobarbital, still developed behavioural/emotional problems, 11% of which were externalising problems (Wolf & Forsythe, 1978). Although the occurrence of behavioural/emotional problems in this cohort was significantly less than in those who received phenobarbital (18% vs. 42%), a drug which is known to increase hyperactivity, the results suggest a role for febrile seizures on behavioural/emotional problems. During a round table discussion organised by the Danish Neurological Society in 1971 in Germany, Doctor Esther Franzten reported behavioural/emotional problems such as concentration difficulties in 70/208 (34%) children with febrile seizures (Hein-Sorensen, 1971). The odds for behavioural/emotional problems were increased in Kenyan children previously admitted with malarial seizures (odds ratio=1.8) (J. A. Carter, Ross, et al., 2005), but it is unclear if the poor behavioural/emotional outcomes were due to the seizures or malaria *per se*. Some of the previous studies in high-income countries have not been able to replicate these results (Verity, Greenwood, & Golding, 1998), but more studies on this subject from poorer countries are still required.

Febrile seizures can affect neurocognitive function, particularly when seizures are complex (focal, repetitive or prolonged). In a recent long-term follow up study in China, complex febrile seizures were associated with impairment in cognitive function but not behavioural/emotional problems (M. L. Tsai et al., 2015). In this same study, pen and paper neurocognitive tests were, surprisingly, more sensitive than event-related potentials in detecting cognitive impairments. In a population-based study in America, poor intelligence scores were documented in children with febrile seizures with a history of developmental delay, compared to those without such history (Dale C. Hesdorffer et al., 2012). In a recent population based study in Rotterdam, repetitive febrile seizures were associated with delayed language development, but not with behavioural/emotional problems and impairment in executive function (Visser et al., 2012). However, executive function was impaired in Kenyan children hospitalised with malarial seizures (S. Kariuki, A. Abubakar, C. Newton, & M. Kihara, 2014), which may not qualify as febrile seizures because of the potential sequestration of malaria parasites in the cerebral vasculature. Another population-based study in Britain found a benign course for febrile seizures (Verity et al., 1998).

Several factors increase the risk for poor outcomes after febrile seizures. A hospital-based study conducted in Wales which assessed neurocognitive development but not behaviour, found that children hospitalised with febrile seizures had intellectual impairment if they experienced subsequent febrile seizures (Smith & Wallace, 1982). In the same study, anti-epileptic drugs were thought not to affect development in these children, suggesting these may have been related to seizures (Smith & Wallace, 1982). In a similar German study, behavioural problems occurred more in repetitive febrile seizures, while lower intelligence scores were associated with prolonged seizures (Kölfen et al., 1998). Kenyan children hospitalised with complex malarial seizures had worse scores for cognition and behaviour persisting several years after admission (J. A. Carter, Mung'ala-Odera, et al., 2005),

suggesting seizures which are focal, repetitive and/or prolonged are associated with poorer outcomes. Cognitive abnormalities after hospitalisation with febrile seizures may persist into young adulthood according to a Danish study (Norgaard et al., 2009). There is few or no population-based data on these behavioural and neurocognitive outcomes from resource poor settings, where febrile/acute seizures may be more common than in high-income countries. Studies on behavioural and neurocognitive outcomes of acute febrile seizures are warranted in resource-poor countries of sub-Saharan Africa.

Acute (febrile) seizures in sub-Saharan Africa

Acute seizures is a term used to refer to both febrile seizures and acute symptomatic seizures. Febrile seizures are caused by febrile diseases or fever without neurological involvement, while acute symptomatic seizures are caused by factors with neurological involvement such as bacterial meningitis or metabolic perturbations including hypoglycaemia. There are few studies of febrile seizures in sub-Saharan Africa and most of these are hospital-based and have only focused on the incidence and outcomes. These studies often do not distinguish between acute symptomatic seizures and possible febrile seizures, since falciparum malaria and invasive bacterial meningitis are often included as causes.

Community-based studies of acute (febrile) seizures in Africa

There is only one community study from Tanzania (Storz, Meindl, Matuja, Schmutzhard, & Winkler, 2015). This study estimated the prevalence of febrile seizures at 2.1%, which is surprisingly low considering some sites were malaria endemic, where the incidence of acute seizures is usually common (Serem, Newton, & Kariuki, 2015). Important causes of febrile seizures were respiratory infections and malaria. The study however had several limitations. Firstly, the use of term “febrile seizures” was probably not ideal in the context, rather the term “acute seizures”, would have been better to capture both febrile seizures and acute

symptomatic seizures (due to malaria or meningitis) (S. M. Kariuki et al., 2011). Secondly, the study was not conducted in a demographic surveillance area and thus vital statistics may not have been routinely updated. Finally, there was no data on risk factors for acute seizures and it is not clear how causes of seizures for those not hospitalised were determined. While this study provides a range of useful information, a proper community-based epidemiological study on acute seizures is still required in Africa.

Hospital-based studies of acute (febrile) seizures in Africa

In a Benin study of hospitalised children, the prevalence of what was described as “febrile seizures” was 5% in children aged 5-60 months, but acute symptomatic seizures from malaria were included and accounted for 33% of all cases (Obi et al., 1994). Another study in Nigeria found intracranial infections such as malaria and meningitis in 38% of children admitted with seizures (G. O. Akpede, P. O. Abiodun, & R. M. Sykes, 1993), although they inappropriately referred to these as febrile seizures. Three studies in Kenya used the term acute (symptomatic) seizures (R. Idro et al., 2008; S. M. Kariuki et al., 2011; Serem et al., 2015), as recommended by ILAE (Beghi et al., 2010) and both found malaria as an important cause of seizures. One of the studies (S. M. Kariuki et al., 2011), attempted to define febrile seizures by excluding those with parasitaemia and meningitis, but the rates were a gross underestimate probably because most seizures in the community are not admitted to hospital owing to cultural reasons and inaccessibility of the few hospitals available.

Causes of acute (febrile) seizures in Africa

Causes of acute seizures are not fully understood in Africa and there are often misconceptions about the causes of febrile seizures, with up to 80% of Nigerian parents attributing febrile seizures to witchcraft (Oche & Onankpa, 2013). Several studies showed that seizure onset is at around 24 months and the causes appear to be seasonal (R. Idro et al.,

2008). The most important causes of acute seizures in these areas are malaria and respiratory tract infections and bacterial sepsis (George O. Akpede, Phillip O. Abiodun, & Roger M. Sykes, 1993; R. Idro et al., 2008; Obi et al., 1994), while hypoglycaemia and hypoxic-ischaemic are important risk factors in the neonatal period (Serem et al., 2015). Vaccines are infrequently reported in these settings perhaps because attention is paid on more serious infectious causes, although their role in seizures with fever can be investigated in future community studies. Viruses complicate bacterial and malarial illnesses in Africa, and may have a role in acute seizures (Mallewa et al., 2013).

The role of fever in acute seizures from malaria-endemic areas is unclear since most seizures occur when the child is non-febrile (Waruiru et al., 1996), suggesting an intracranial underlying cause. Genes related to pro-inflammation and sequestration are also implicated in the risk for acute seizures in Africa (S. M. Kariuki et al., 2013). Community-based studies should be set up in Africa to clarify the risk factors and causes of acute seizures in preschool children.

Phenotypes of acute (febrile) seizures in Africa

The proportion of complex (focal, prolonged and/or repetitive) acute seizures in Africa is twice that in resource rich countries (>60% vs. 30%) (C Waruiru & R Appleton, 2004), but the complex phenotypes are based on hospital data and could therefore be overestimated. The high incidence of complex phenotypes, however, may be ascribed to the intracranial infections such as malaria (S. M. Kariuki et al., 2011). These complex seizures can form useful phenotypes for susceptibility or protective genes (Baram & Shinnar, 2002) and formed the bases for a genetic study of acute seizures in Africa (S. M. Kariuki et al., 2013).

Outcomes of acute (febrile) seizures in Africa

Both neurological deficits and mortality have been documented after acute seizures in Africa (Prins et al., 2014; Sadarangani et al., 2008), but no study has systematically examined behaviour and cognition. In a Kenyan study (R. Idro et al., 2008), neurological deficits were reported in 15% of those with acute seizures on discharge, and this was greatest in status epilepticus. Several years later behavioural/emotional problems and other neurodevelopmental problems developed in a third of children with status epilepticus, while 8% died (Prins et al., 2014). Complex acute seizures increased the odds of behavioural/emotional problems by two times in Kenyan children hospitalised with falciparum malaria (J. A. Carter, Ross, et al., 2005), and these seizures also affected executive function (S. Kariuki et al., 2014). It is likely these poor outcomes are related to the acute seizures, but the outcome may also depend on the underlying cause/neurological damage or genetic predisposition to these acute seizures (S. M. Kariuki et al., 2013).

Conclusions and directions for future research on acute (febrile) seizures in Africa

This review demonstrates that there is a paucity of population-based studies on the prevalence of and risk factors for acute febrile seizures in sub-Saharan Africa. Community-based studies on acute seizures in preschool children are therefore required in sub-Saharan Africa to provide reliable estimates for planning purposes.

It is likely that the causes of and risk factors for acute (febrile) seizures in Africa are different between preschool children admitted to hospital and those not hospitalised, a hypothesis which should be investigated through community-based studies. It is challenging to determine the causes of acute seizures in children in the community not admitted to hospital; recall of causes using World Health Organization clinical algorithms for Integrated

Management of Childhood Infections may be an option, but the reliability of this method may be poor (Mwangi, Mohammed, Dayo, Snow, & Marsh, 2005).

There is little data on behavioural/emotional outcomes of preschool children with acute seizures in Africa, and most available studies are hospital-based, and combine both preschool and older children. Few studies from developed countries that have documented poor behavioural/emotional outcomes in children with acute (febrile) seizures, show a particular association with complex seizures, which are very common in Africa. The different pattern of acute seizures and underlying aetiologies seen in sub-Saharan Africa may be associated with a poor behavioural/emotional outcome. Thus community studies examining prevalence of, risk factors for, and behavioural/emotional outcomes of acute seizures in preschool children from sub-Saharan Africa are required, to compare with other settings in the world.

Chapter 3: General methodology and study design

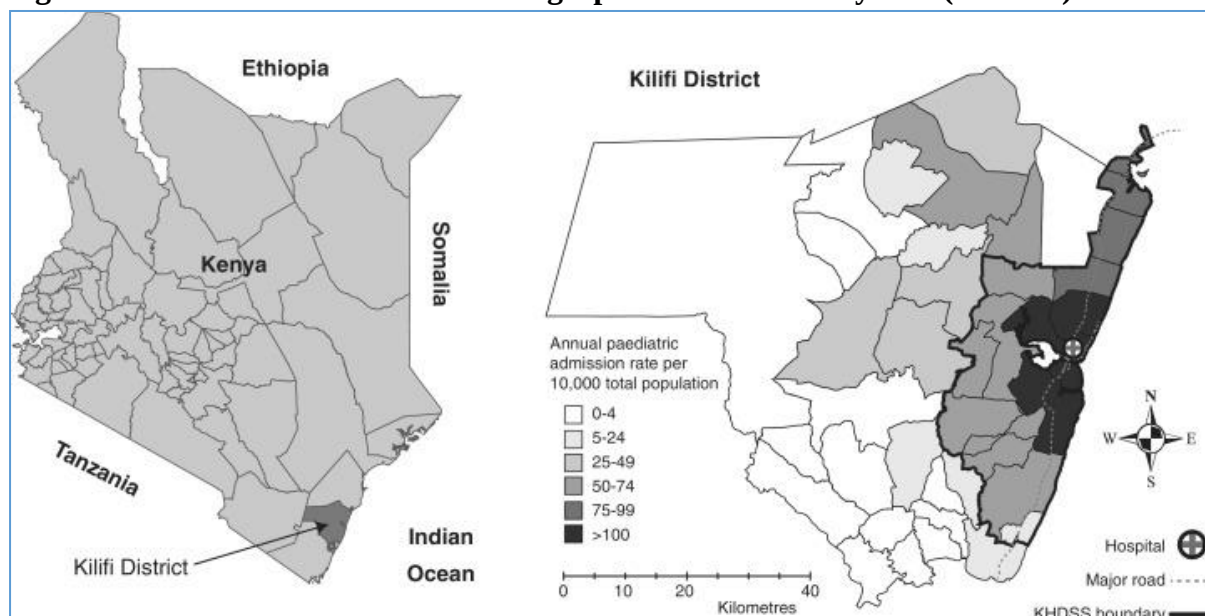
Study area and population

The study was conducted in the Kilifi Health and Demographic Surveillance System (KHDSS) on the Kenyan coast located about 60 KM North of Mombasa city (J. A. G. Scott et al., 2012) (Figure 3-1). During the study period, there were about 270,000 residents within the KHDSS, of whom about 50,000 were children aged 1-6 years. Vital statistics such as births, deaths, and migration events are updated regularly via a four-monthly census performed by fieldworkers on motorbikes or by foot. The residents are mainly Mijikenda, a Bantu group of nine tribes with Giriama (45%), Chonyi (33%), and Kauma (11%) dominating. The average per household-head income is about 700 Kenyan Shillings (US\$8) per month in 2003 and 55% of the population is regarded as absolutely poor. Because of the low literacy rate (45%) (Kenya National Bureau of Statistics, 2015), the consenting process requires that the fieldworkers read out questions to participants in the local language (Kiswahili or Giriama), and the participant makes an informed choice by appending a thumb print (or a signature for those who can write). Most people (80%) depend on subsistence farming, which is constrained by the low agricultural potential of the land (only 19% is arable).

The common causes of childhood admissions to Kilifi County Hospital (KCH) (the only referral hospital in the area) are malaria, bacterial and viral infections (J. A. Berkley et al., 2005; James A. Berkley et al., 2010; O'Meara et al., 2008). The transmission intensity of malaria is heterogeneous in the KHDSS; being high in southern areas and low in northern areas (Mbogo et al., 2003). Neurological conditions are common in the KHDSS occurring in up to 6% of children according to a previous epidemiological survey (V. Mung'ala-Odera et al., 2006). The incidence of acute seizures admitted to hospital range from 425-650 per

100,000/year (R. Idro et al., 2008; S. M. Kariuki et al., 2011), while the prevalence of active convulsive epilepsy according to a recent multisite study was 7 per 1,000 population (A. K. Ngugi et al., 2013).

Figure 3-1: The Kilifi Health and Demographic Surveillance System (KHDSS)

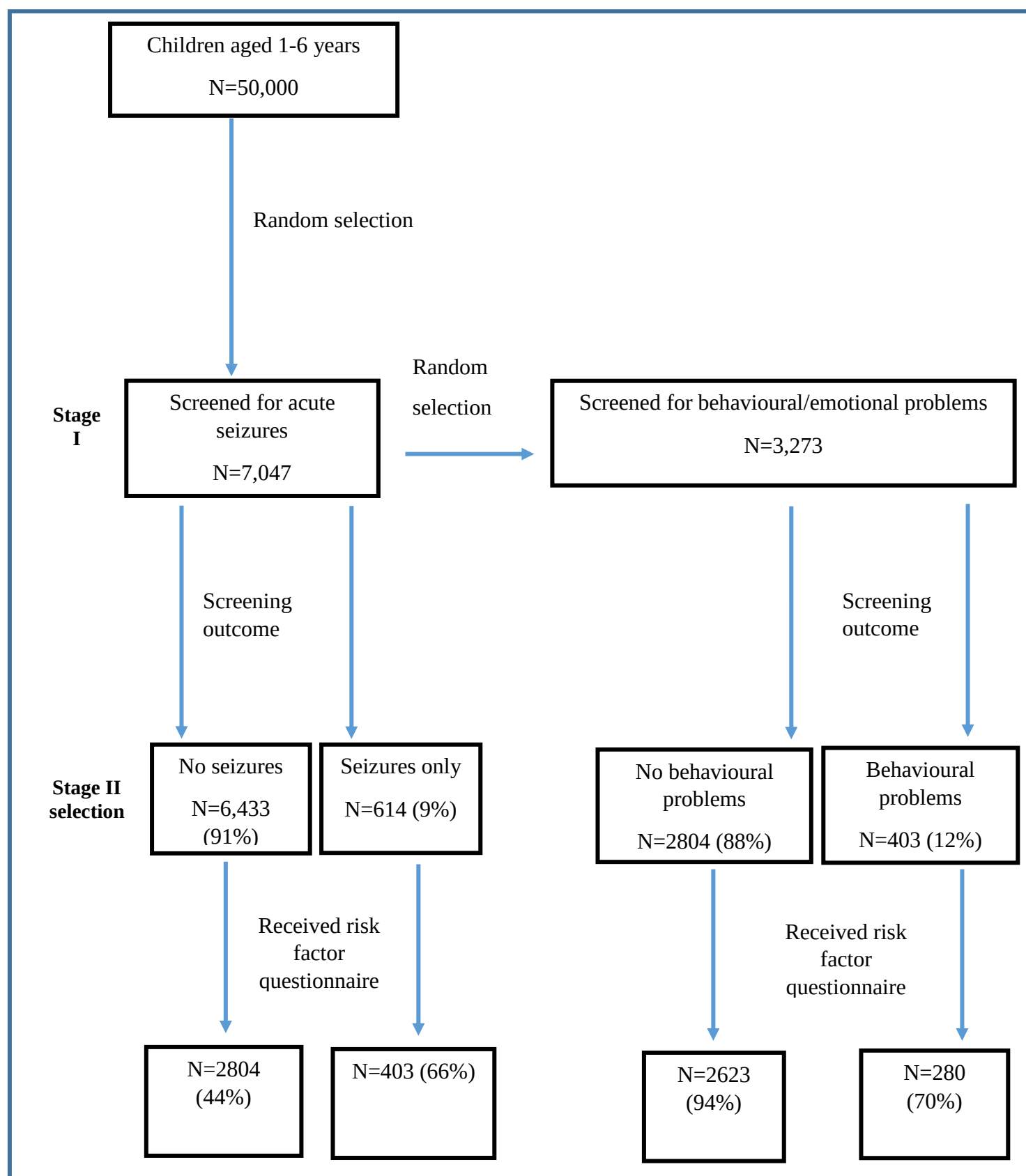


Study design

This study was both a cross-sectional and a nested case-control study to: estimate the prevalence of acute seizures and behavioural/emotional problems; determine the risk factors for and comorbidities of acute seizures and behavioural/emotional problems, and examine the relationship between behavioural/emotional problems and acute seizures (Figure 3-2). In stage I, children aged 1-6 years were randomly selected from a total population of 50,000 preschool children for screening of acute seizures and behavioural/emotional problems (Figure 3-2). The random selection was done using the RAND() command in MySQL (Oracle, Redwood Shores, CA, USA). Those screening positive for seizures and

behavioural/emotional problems, as well as a predetermined sample of those without these conditions, were invited for further clinical evaluation in stage II. Acute seizures were diagnosed by a clinician in stage II following a detailed clinical history and examination on those screening positive for seizures in stage I.

Figure 3-2 Flow chart for the study design



Sample size determination

With an estimated prevalence of seizures of 43/1,000 (R. Idro et al., 2008), screening about 7,500 children would detect a prevalence of acute seizures with a precision of 10% at 95% confidence interval. Screening behavioural/emotional problems in 3,500 of the children already screened for acute seizures would detect behavioural/emotional problems with a precision of 1.6% at 95% confidence intervals assuming a prevalence of 10% in pre-school children (Egger & Angold, 2006). Screening for seizures in 7,500 children would provide at least 250 children with acute seizures and 250 children without seizures, which would detect an odds ratio of 2 at 5% significance level with at least 80% power, assuming a prevalence of 10% of risk factors such as a family history of seizures in the population (Huang et al., 1999).

Assessing for behaviour/emotional problems in 3,500 children would provide at least 250 children with behavioural/emotional problems, and 250 children without behavioural/emotional problems, which would detect a risk ratio of 2 at 5% significant level with a 90% power, assuming a prevalence of 20% of risk factors of adverse perinatal events in the population (Kurita, Guo, Miyake, Ze, & Huilong, 1999).

The relationship between acute seizures and behavioural/emotional problems was based on the outcomes from the 3,500 children screened for both acute seizures and behavioural/emotional problems as described above. In particular the occurrence of behavioural/emotional problems in those with seizures was compared with those without seizures, and vice versa. Risk factors associated with comorbidity of acute seizures and behavioural/emotional problems were also identified from these 3,500 children, by comparing the frequency of a risk factor between those with the condition of interest and those without.

Prevalence and risk factor study in the Community

A cross-sectional survey was conducted to estimate the life-time prevalence of acute seizures and behavioural/emotional problems in children in the community. Five specifically trained fieldworkers aimed to visit households of approximately 7,500 children to screen them for seizures (5-10 minutes questionnaire) and a subset of these (n=3,500) for behavioural/emotional problems (takes about 30 minutes). The household visits and screening of acute seizures and behavioural/emotional problems took a year, from 17th February 2014 to 28th February 2015 (see table 3-1).

Table 3-1: Estimated time for assessment

Assessment	Number seen a day	Number seen a week	Estimated time
Seizure & behaviour (N=7500)	30 (by 5 fieldworkers)	150 (by 5 fieldworkers)	52 weeks
Clinical and neurological examination (N=1200)	6 (by two assessors and 2 clinicians)	30 (by 2 assessors and 2 clinicians)	52 weeks

NB: The two assessments were run concurrently, with the first starting 2 weeks earlier

Neurological and clinical examination and/or assessment

All children with a positive history of seizures and a predetermined number of those with behavioural/emotional problems (plus an equal number of children without seizures and behavioural/emotional problems, respectively, matched for age-group and sex (randomly selected from the population database)) were then seen by a clinician at the neuro-assessment clinic of KCH for a detailed medical history and full physical examination. An electroencephalogram (EEG) was performed in those with repetitive epileptic seizures. The medical and neurological examination took 2 hours for each case each day, and thus a year to assess all of the children (about 1,000) eligible for further clinical evaluation (Table 3-1).

Hospital admissions

All children aged 1-6 years admitted to KCH with acute seizures, starting 6 years before the cross-sectional study were documented, and clinical and laboratory features associated with the seizures were collected to provide more detailed and reliable description of seizures in the community study. Hospital data was useful in determining causes of acute seizures and assigning a diagnosis for acute seizures for those who did not turn up for clinical evaluation after screening positive for seizures in stage I. The hospital data was also used to estimate the proportion of children with seizures in the community who were hospitalised at KCH as well as the risk factors associated with hospitalisation.

Procedures: phase one

Training

Fieldworkers and neuropsychological assessors were trained how to recruit and consent patients through lectures and role plays. In particular the fieldworkers were trained on the study design and the process of consenting and tool administration, often referring to experiences from previous epidemiological studies. Additionally, the fieldworkers and neuropsychological assessors were taught about the ethical principles of conduct of human research including respect for study participants, confidentiality and doing no harm (whether physical or psychological). Fieldworkers and neuropsychological assessors were advised against assigning a diagnosis for conditions for which they are not specialists, and were told to refer such questions to myself for appropriate action. I planned simulation exercises for fieldworkers to do actual data collection in the community. The aim for role plays and simulation exercises on consenting and administration of questionnaires was to ensure standardised data collection. Proper handling and coding of questionnaires was also

emphasised during the training. The training was conducted over two weeks by myself in consultation with the supervisors.

Community engagement

Members of this research group and the community liaison team of the KEMRI-Wellcome Trust Research Programme formed an advisory group to develop a community engagement strategy for this study; given that it was a large scale study (involving 7,500 preschool children) that included quite sensitive information on mental health problems which are stigmatised in this community. The aim was to raise awareness of the project in advance of its commencement, to clarify where community members could report their concerns while the study was on-going, and to develop a plan for feeding back individual and study wide results to parents and community representatives. It was agreed that findings should be shared with implementing agencies who have the potential to strengthen preventative and treatment interventions for acute seizures and behavioural/emotional problems such as the ministry of medical services.

Translation and initial validation of the Child Behaviour Checklist

We used the Child Behaviour Checklist (CBCL) to detect behavioural/emotional problems, since it had been used and validated across many cultural contexts and identified different behavioural/emotional problems (Ivanova et al., 2010). Studies in low-income countries showed that the CBCL has good reliability (Cronbach alpha coefficient >0.71) and validity (content validity >0.54) (Nakamura, Ebesutani, Bernstein, & Chorpita, 2009). The initial validation of the CBCL was done in two stages. Firstly, we conducted a focused group discussion of parents and teachers of children with and without epilepsy to understand the community perception of behavioural/emotional problems in this area (Abubakar et al., 2015). This helped in understanding the idioms and culturally appropriate terms for

describing behavioural/emotional problems in this rural population. The second stage involved translation of the English version of the CBCL into Kiswahili by a linguistic specialist, and a back-translation into English by an independent linguistic specialist, a method that was utilized in a previous study in the area (V. Mung'ala-Odera et al., 2004). The back-translated version was reviewed by a psychologist from Department of Psychiatry, University of Oxford (Doctor Elizabeth Murray) who recommended revisions until the questions therein retained their original meaning. The translated CBCL and the back-translated version were shared with the developers of the tool, including Professor Thomas Achenbach, who reviewed and requested modifications which were addressed and the tool finally approved. I then piloted the CBCL for reliability (internal consistency, discriminant validity, and test-retest or inter-informant reliability) and fitness of the 7-syndrome model. The results on the psychometric properties and factorial structure of the CBCL are discussed in details in chapter 4 of this thesis.

Assessment of acute seizures and behaviour/emotional problems in the main study

Seizures were screened using a modified seizure questionnaire used in a previous study in this area (A. Ngugi et al., 2012). According to a pilot study the seizures screening questionnaire had a sensitivity of 96% and a specificity of 98% when used on previous hospital admissions with and without seizures. Behavioural/emotional problems were examined using a validated and adapted CBCL (age 12-60 months) which is a parent interview (T. Achenbach & Rescorla, 2000; Ivanova et al., 2010). It took the fieldworkers an estimated time of 25-30 minutes to administer the CBCL and 10 minutes for the seizure questionnaire, including obtaining consent. After the screening in the field, those with seizures and/or behavioural problems were invited for further clinical evaluation. Children matched for sex, age-group and neighbourhood proximity were also invited for clinical

evaluation and this group comprised those without seizures and without behavioural/emotional problems.

Procedures: Phase two

Clinical history and neurological information

Children testing positive for either behavioural/emotional problems or seizures and their matched controls were invited to the neuro-assessment epilepsy clinic at the KCH to undergo clinical history and examination and EEG (for those with repetitive seizures). The medical history for those with seizures included date of onset, seizure semiology, duration and the possible causes. Paediatric neurological examination was also performed which included evaluation of limb function, sensation, gross and fine motor function, cranial nerve function, hearing and visual function, mental status and skin integrity. These seizure details were used by experienced clinicians, often in consultation with an epileptologist, to diagnose acute seizures.

Ethics, consent and permissions

This study was approved by the Kenyan National Ethical Review Committee (SSC No 2599) and parents or caretakers of all children gave written informed consent to participate. The data used in this study are part of the neurodevelopmental studies at KEMRI-Wellcome Trust Research Programme <http://www.kemri-wellcome.org/index.php/en/researcharea/26> and are under the custody of the Data Governance Committee of the KEMRI-Wellcome Trust Research Programme, because of agreements with study participants during the consenting process. However the data can be availed to scientists wishing to use them for non-commercial purposes upon formal request from the Data Governance Committee.

Data management and statistical analysis

Data storage

Data was entered twice by two different people and verified in MySQL Version 5 open source database (Oracle Corporation, Redwood Shores, CA, USA). Some EEG were stored in external hard drives. The data storage was managed by a database manager (Ms Rachael Odhiambo), who is experienced in managing databases for other epilepsy studies across multiple sites in Africa.

Statistical data analysis

All statistical analysis was performed with STATA version 11 and 13 (Stata corporation, Texas, USA), and R statistical software (www.r-project.org). Pearson's Chi-square test was used to examine whether the prevalence of behavioural/emotional problems was increased in those with acute seizures. Confirmatory factor analysis of the seven CBCL syndromes was implemented with structural equation modelling. The unadjusted prevalence of acute seizures and behavioural/emotional problems per 1,000 was calculated by dividing the number with the condition (seizure or behavioural/emotional problems) over the screened population and multiplying by 1,000, accounting for loss to follow up between the screening phase (phase one) and clinical evaluation phase (phase two) of the study. In particular, multiple imputation was used to account for attrition between phase one and two using sociodemographic information and seizure factors collected in phase one. The prevalence was adjusted for age and sex through fitting a logit model followed by exponentiation of the coefficients from the constant term using the formula ($probability = \frac{\exp(coefficient)}{1 + \exp(coefficient)}$). The constant term of a logit model measures the probability of the dependent variable, thus the prevalence if expressed per 100 population.

Generalised linear models of the logistic regression family (for binary response variables) were used to compute odds ratios for acute seizures since it is reliable for conditions with a prevalence of less than 10% (Viera, 2008). Generalised linear models of the Gaussian family with an identity link (if the outcome is continuous behaviour/emotional scores), or binomial family and a log link (for calculating risk ratios of behavioural/emotional problems) were used to identify the risk factors associated with behavioural/emotional problems. Two approaches were used in identifying risk factors. The first approach involved accounting for age (as a fractional polynomial), sex, education level, ethnicity, religion, region of residence, marital and economic status in the generalised linear models with behavioural/emotional problems scores as the dependent variable. In this approach, all statistically significant risk factors were used to construct a multivariable structural equation model, to determine the variability explained by each risk factor in the model. The second approach involved building a multivariable analysis of variables reaching a cut-off p-value of ≤ 0.05 in the univariable analysis. In this approach, population-attributable fractions were modelled from the final generalised linear models, with the hypothetical assumption that the risk factor of interest is completely eliminated or living conditions are absolutely perfect. Multiple imputation chained equations were used to deal with missing data (Seaman, White, Copas, & Li, 2012), and more details about this approach are provided in respective chapters.

Chapter 4: Child Behaviour Checklist Study

Evaluation of psychometric properties and factorial structure of the pre-school child behaviour checklist at the Kenyan coast

Background

Behavioural/emotional problems are common in children, and externalising problems such as attention deficit hyperactivity disorder occur in up to 10% of preschool children (Froehlich et al., 2007). It is difficult to identify these behavioural disorders in very young children since these children are developing rapidly, and there are few child psychologists or psychiatrists, particularly in resource-poor settings (Omigbodun, 2008). Nonetheless, the past decade has seen increased focus on diagnosis and description of behavioural/emotional problems in very young children using screening tools that have simpler items, and which can reliably identify behavioural/emotional problems with excellent sensitivity and specificity.

The Child Behaviour Checklist (CBCL) is one such tool which was originally developed in the USA under the auspice of Achenbach System of Empirically Based Assessment (ASEBA) (T. Achenbach & Rescorla, 2000). While the CBCL is applicable for children aged between 1.5-5.5 years (T. Achenbach & Rescorla, 2000), the preschool Strength and Difficulty Questionnaire and Rutter Child Behaviour Problem scales are not extended to children under 2 or 3 years of age (Jefferis & Oliver, 2006; Theunissen et al., 2013). The CBCL has been validated in 23 other societies some from low and middle-income countries such as Kosovo, Taiwan and Turkey, where it has shown good psychometric properties (Ivanova et al., 2010). In this landmark study, the CBCL identified behavioural problems in preschool children with a sensitivity and specificity (>90%) compared to a psychiatrists diagnosis (Ivanova et al., 2010). In these validation studies, factor analysis demonstrated that the 100 items of the CBCL measures seven CBCL components which correlate well with

DSM-IV syndromes, based upon experts' evaluations (T. Achenbach et al., 2003). The CBCL also discriminates children at risk of medical conditions such as epilepsy compared to those not at risk of the condition, underlining its discriminant validity (T. Achenbach & Rescorla, 2000). However, none of these studies were conducted in Africa, where risk factors for neuropsychiatric conditions are common (R. Idro et al., 2007; V. Mung'ala-Odera, Snow, & Newton, 2004).

We have documented behavioural/emotional problems in 26% of 110 community controls aged 6-9 years selected for an epilepsy study in Kilifi, Kenya (Symon M. Kariuki et al., 2012). However, psychopathology in older children cannot be generalised to very young children (Njoroge & Bernhart, 2011; Parry, 2005). Infections with a neurological involvement such as malaria are important causes of admissions to Kilifi County Hospital (the main district level referral hospital in this area (R. Idro et al., 2007); and these may be important risk factors for mental health illnesses and behavioural disorders in children. To date no behavioural studies have been conducted in preschool children in Kenya, largely because of a lack of appropriate tools for this group of children. There are no data in Africa on the reliability of the preschool CBCL in assessing behavioural problems, but the school-age CBCL was adapted for use in Uganda and was found to be reliable (Bangirana et al., 2009).

We examined the psychometric properties of the CBCL in a community sample of preschool children living on the Kenyan coast to compare its performance with that in other countries. We investigated the applicability of the 7-syndrome CBCL structure in these preschool children. We further developed CBCL score ranges that can be used in epidemiological and intervention studies within rural Kenya.

Methods and procedures

Translation of the CBCL into local languages

We used a systematic approach of translation and adaptation. The initial translation was done by two independent translators fluent in the original language (English) and the target language (Kiswahili). These translations were then back translated into English by two independent translators. The third step involved evaluation of the translation by a panel of five people fluent in Kiswahili. We conducted focused group discussions and in-depth interviews involving 90 parents and teachers of children with epilepsy (in whom behavioural problems are common) to elicit phrases and idioms to be used in the translated version; most of the CBCL items were perceived as problems that occur in their children (Abubakar et al., 2015).

The agreed version was tested in the community with 50 mothers (who were not among the 90 parents who participated in the focused group discussions) and participants were requested to provide feedback for each item. The feedback from participants (largely on item wording) was collated and used to create the next version of the questionnaire. Following this evaluation the questionnaire was tested again to ensure that the language used was understandable to the community members. The last stage involved back-translation from Kiswahili into English by an experienced linguist. The back translated version was evaluated by Doctor Elizabeth Murray, a psychologist, for consistency of meaning with the original CBCL. The few issues raised through this process were resolved through consensus across all the groups involved in the translation process. Our translation process indicated that with adequate consultation it was possible to achieve semantic equivalence; however we did find that literacy levels of participants presented a methodological challenge.

The CBCL was originally designed to be a written questionnaire, however, with the low literacy levels in our population and restricted reading culture, most of our parents cannot fill in the questionnaires themselves. Consequently, a trained fieldworker read out the behaviour problem items to the respondents and documented the respondents rating of the child's behaviour. An additional problem consistently observed was with the use of a Likert rating scale. To simplify the procedure and enhance accuracy in our population we performed a two stage approach. Firstly we asked if the child had a problem; if the answer was yes we then asked about its frequency or severity to enable a score of 1 or 2.

A signed permission to translate the CBCL was obtained from the developers of the tool (ASEBA) from the University of Vermont's Research Centre for Children, Youth and Families, Inc.; a non-profit Corporation (Appendix: licence #912-10-21-2013). Our translation was shared with ASEBA, who used it to update an earlier translation.

Sample size determination

Our sample size determination was based on the principle that alpha coefficients are the most widely used measure for internal consistency in neuropsychological studies and that an adequate sample should be one that produces stable sample coefficient alpha, which provides a precise estimate of the population coefficient alpha (Charter, 2003). Since sample alpha coefficient is dependent on the first largest *eigenvalue* from Principal Component Analysis (PCA) on the dataset, we estimated that a sample size of at least 100 preschool children will be associated with *eigenvalues* of ≥ 6 according to a simulation study that utilised a Monte-Carlo method (Yurdugul, 2008), and therefore a sample size of 301 preschool children available in our study would provide unbiased estimator of coefficient alpha.

Administration of the CBCL

The CBCL was administered to 301 parents (mothers, fathers and/or caretakers) of children aged 1-6 years residing within the KHDSS, in the initial phase of the pilot study. The study participants were randomly selected from the KHDSS census database. Based on the multiple caregiving practice in Kilifi we asked the mother to nominate another person who knows the child well to have them respond to the CBCL; 29 alternative caregivers were used in this sub-study and these data were used to evaluate inter-informant reliability. Similarly, 17 mother-father dyads were also interviewed. For test-retest reliability we administered the CBCL to 38 randomly selected respondents after 2 weeks following the initial administration.

Statistical analysis

The data was analysed using STATA (Version 11). Student t-test or Man-Whitney test (where appropriate) was used to compare the scores between sexes. Generalised linear model of the Gaussian family and with an identity link was used to measure associations between log-transformed behavioural/emotional scores and pregnancy/birth or socioeconomic information or medical factors. Cohen's kappa coefficients determined the inter-informant agreements between the mother and either fathers or other caretakers for children with behavioural/emotional problems, defined as those with scores $\geq 90^{\text{th}}$ percentile, considered as the cut off for severe or abnormal CBCL total scores (T. Achenbach & Rescorla, 2000). The test and retest reliability of the before and after assessments was investigated using pairwise correlation coefficients. Cronbach's alpha was used to evaluate reliability coefficients of the items for the entire tool and for the specific 7-syndrome subscales. The item reliability coefficients first used data from all children, and then for boys and girls separately. Confirmatory factor analysis was used to test the fit index of the 7-syndrome model described by ASEBA in this rural population, using structural equation modelling; which provides

standardised factor loading coefficients, and goodness of fit statistics such as Root Mean Squared Error of Approximation (RMSEA), Comparative Fit Index (CFI) and Tucker-Lewis Index (TLI). The confirmatory factor analysis was done using raw CBCL scores. RMSEA was considered the primary fit index because it performed more robustly in a Monte-Carlo simulation study (Yuh & Muthen, 2002); while CFI and TLI were considered secondary. Models with modest data fit were modified by allowing correlation of error terms with the largest modification indices (>10) to improve goodness of fit statistics. The cut for acceptable fit indices was ≤ 0.09 for RMSEA and ≥ 0.90 for CFI and TLI (Browne & Cudeck, 1993).

Internalising scores were formed from emotionally reactive, anxiously depressed, withdrawn and somatic complaints subscales of the CBCL (T. Achenbach & Rescorla, 2000).

Externalising scores were derived from attention problems and aggressive behaviour subscales of the CBCL.

Results

General description

The CBCL was administered to 301 parents and/or caretakers of preschool children. The 301 respondents comprised of 224 (74.1%) mothers, 23 fathers (7.6%) 54 other caregivers (17.9%). Of the 301 children in the study, 161 (53.5%) were males. The overall median age was 29 months (Interquartile range (IQR), 10-52), with no differences between males and females ($p=0.827$).

School attendance was reported in 85/301 (28%) children. Pregnancy and birth information could be recalled by 185 mothers of whom 22 (12%) reported pregnancy problems and 10 (5%) perinatal complications. Socioeconomic and sociodemographic data showed that 116/301 (39%) mothers were educated, while 118/301 (39%) mothers were employed.

Employment was more common in educated mothers (74/116 (64%)) than in uneducated mothers (44/185) (24%)); $p < 0.001$. Seizures were diagnosed by a clinician in 17/204 (8%) children who were invited to come to our clinic for diagnostic evaluation.

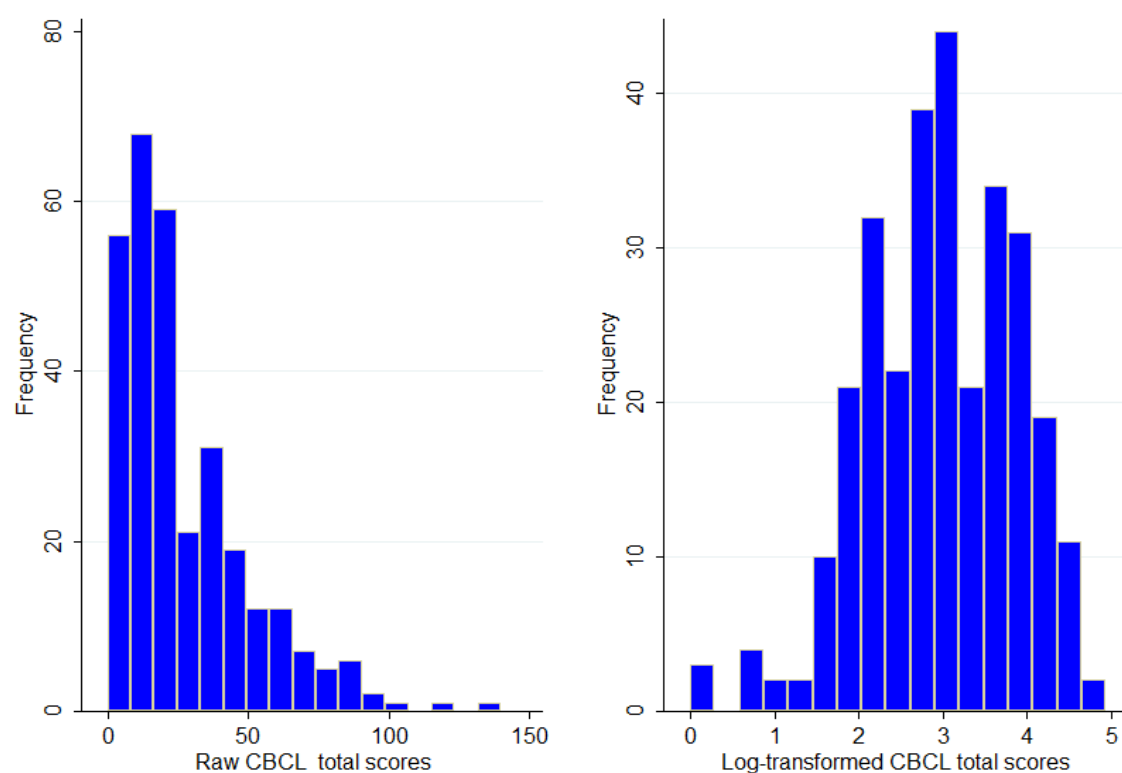
CBCL median scores

The median raw CBCL total problems scores for all items was 20 (IQR: 10-38) and were similar between males and females ($p = 0.730$). The 90th percentile raw total problems score was 60 (95%CI, 52-69). The median raw CBCL score for internalising subscales was 7 (IQR: 3-14) while that for externalising subscales the median score was 6 (IQR: 3-12). The median raw externalising scores were similar in males and females (6 (IQR: 3-11) vs. 6 (IQR: 3-14); $Z = -0.12$, $p = 0.898$), and so were raw internalising scores (7 (IQR: 3-12) vs. 7 (IQR: 4-15); $Z = 1.01$; $p = 0.312$). The median scores for the specific CBCL subscales are shown in table 4-1. The raw CBCL total scores were skewed to the left and were therefore log-transformed to achieve a Gaussian distribution for further regression analysis. The distribution of raw and log-transformed CBCL total scores are shown in Figure 4-1.

Table 4-1: Median CBCL scores by subscales and sex

Subscales	Scores for all children (IQR)	Scores for Boys (IQR)	Scores for Girls (IQR)	P-value*
Emotionally reactive	1.0 (0-2.0)	1.0 (0-2.0)	1.0 (0-3.0)	0.286
Anxiously depressed	2.0 (0-5.0)	2.0 (0-5.0)	2.0 (0-5.0)	0.419
Somatic complaints	2.0 (0-4.0)	2.0 (0-3.0)	2.0 (0-4.0)	0.363
Withdrawn	2.0 (0-3.0)	1.0 (0-2.0)	2.0 (0-3.0)	0.198
Sleep problems	2.0 (0-3.0)	2.0 (0-3.0)	2.0 (0-3.0)	0.841
Attention problems	2.0 (1.0-4.0)	2.0 (1.0-4.0)	2.0 (1.0-4.0)	0.453
Aggressive behaviour	4.0 (1.0-9.0)	4.0 (1.0-9.0)	4.0 (1.0-9.0)	0.992
Internalising subscales	7.0 (3.0-14.0)	7.0 (3.0-12.0)	7.0 (4.0-15)	0.312
Externalising subscales	6.0 (3.0-12.0)	6.0 (3.0-11.0)	6.0 (3.0-14.0)	0.898

*Mann-Whitney U test.

Figure 4-1. Distribution of raw and log-transformed CBCL scores for 301 preschool children.

Associations of perinatal, socioeconomic and medical factors with behavioural/emotional scores

In a linear regression model accounted for age and sex, only pregnancy complications ($\beta=0.44$ (95%CI, 0.07-0.81); $p=0.021$) and adverse perinatal events ($\beta=0.61$ (95%CI, 0.09-1.13); $p=0.023$) showed a significant association with behavioural/emotional scores. Maternal education ($\beta=0.15$ (95%CI, -0.10, 0.40); $p=0.233$), employment ($\beta=0.16$ (95%CI, -0.09, 0.41); $p=0.216$) and history of seizures ($\beta=0.26$ (95%CI, -0.16, 0.68); $p=0.223$) were not associated with behavioural/emotional scores.

Test-retest reliability

Of the 301 children who were initially assessed with the CBCL, 38 were assessed again after at least two weeks. The initial median CBCL total problems score for these 38 children was 9 (IQR: 7-17), and remained similar with scores after two weeks (8 (IQR: 6-11)). The before and after CBCL scores were significantly correlated (Pearson correlation coefficient (r)=0.76; $p<0.0001$).

Inter-informant agreement

For 17 children, the CBCL was administered to both mothers and the alternative caretaker. There was an excellent inter-informant agreement between the CBCL scores for the mother and those for the caretaker ($r=0.89$; $p<0.0001$). For 29 children, the CBCL was administered to both mothers and fathers. The inter-informant agreement between the mother's and father's CBCL scores was excellent too ($r=0.81$; $p<0.0001$).

Internal consistency

The internal consistency of the CBCL as measured by Cronbach's alpha was 0.95 (95% CI, 0.93-0.97) and was 0.95 (95% CI, 0.94-0.96) for boys and 0.94 (95% CI, 0.92-0.96) for girls.

All the subscales of the CBCL had acceptable to excellent Cronbach's coefficient alphas (0.65-0.86), except for the withdrawn subscale (0.53) and attention problem subscale (0.57) (Table 2). The Cronbach coefficient alpha was 0.86 (95% CI, 0.84-0.88) for externalising scores and 0.87 (95% CI, 0.85-0.89) for internalising scores. The Cronbach's coefficient alpha for males (0.95) appeared higher than those for females (0.93).

Table 4-2: Scale reliability coefficients for CBCL item scales and goodness of fit statistics for CBCL seven-syndrome structure

Subscales	Cronbach's alpha: all children (95% CI)	Cronbach's alpha: boys (95% CI)	Cronbach's alpha: girls (95% CI)	RMSEA: all children	CFI: all children	TLI: all children
Emotionally reactive	0.70 (0.65-0.75)	0.71 (0.64-0.78)	0.68 (0.61-0.75)	0.039	0.97	0.96
Anxiously depressed	0.74 (0.70-0.77)	0.77 (0.72-0.82)	0.69 (0.62-0.76)	0.050	0.97	0.95
Somatic complaints	0.69 (0.65-0.73)	0.67 (0.61-0.73)	0.71 (0.65-0.77)	0.054	0.94	0.92
Withdrawn	0.53 (0.46-0.59)	0.50 (0.40-0.60)	0.55 (0.45-0.65)	0.000	1.00	1.00
Sleep problems	0.65 (0.60-0.70)	0.72 (0.67-0.77)	0.49 (0.37-0.61)	0.061	0.97	0.93
Attention problems	0.57 (0.50-0.64)	0.59 (0.50-0.68)	0.57 (0.47-0.67)	0.000	1.00	1.00
Aggressive behaviour	0.86 (0.84-0.88)	0.87 (0.85-0.89)	0.84 (0.80-0.88)	0.077	0.83	0.80
Internalising subscales	0.87 (0.85-0.89)	0.87 (0.85-0.89)	0.87 (0.84-0.90)	0.030	0.97	0.95
Externalising subscales	0.86 (0.84-0.88)	0.88 (0.85-0.91)	0.85 (0.81-0.89)	0.039	0.92	0.90

CI=confidence interval; RMSEA=root mean squared error of approximation; CFI=Comparative Fit Index; TLI=Tucker-Lewis Index. Acceptable coefficient alpha were those >0.60, while acceptable fit indices were those <0.09 for RMSEA and those >0.90 for CFI and TLI

Standard coefficients and fit indices of the seven-syndrome CBCL structure

All of seven-syndromes of the CBCL reached the mean acceptable cut-off standardised item loadings of 0.35, with “withdrawn” having the lowest at 0.38 (Table 4-3), although it was still

within the ranges reported previously (Table 4-4) (T. Achenbach & Rescorla, 2000). All the RMSEA, CFI and TLI for the seven-syndrome CBCL structure reached acceptable fit levels, except aggressive behaviours which were slightly below the cut-off (Table 4-2).

Table 4-3: Standardised item loading coefficients for Child Behaviour Checklist in a Kenyan preschool community sample

Syndrome items	Standardised Item loading coefficients (95% CI)
Emotionally reactive	Overall: 0.47 (0.36-0.58)
Disturbed by any change in routine	0.35 (0.23-0.47)
Nervous Movements or twitching	0.33 (0.21-0.45)
Shows panic for no good reason	0.58 (0.48-0.68)
Rapid shifts between sadness and excitement	0.23 (0.11-0.36)
Sudden changes in mood or feelings	0.53 (0.42-0.63)
Sulks a lot	0.63 (0.54-0.72)
Upset by new people or situations	0.42 (0.30-0.53)
Whining	0.59 (0.49-0.68)
Worries	0.60 (0.50-0.70)
Anxious depressed	Overall: 0.53 (0.43-0.63)
Clings to adults or too dependent	0.44 (0.32-0.55)
Feelings are easily hurt	0.53 (0.43-0.63)
Gets too upset when separated from parents	0.50 (0.40-0.61)
Looks unhappy without good reason	0.68 (0.60-0.77)
Nervous, high-strung, or tense	0.51 (0.41-0.59)
Self-conscious or easily embarrassed	0.41 (0.29-0.52)
Too fearful or anxious	0.59 (0.50-0.69)
Unhappy, sad, or depressed	0.58 (0.48-0.68)
Somatic complaints	Overall: 0.46 (0.35-0.57)
Aches or pains (without medical cause)	0.35 (0.24-0.48)
Can't stand having things out of place	0.31 (0.19-0.43)
Constipated, doesn't move bowels (when not sick)	0.51 (0.41-0.62)

Diarrhoea or loose bowels (when not sick)	0.59 (0.49-0.68)
Doesn't eat well	0.27 (0.15-0.39)
Headaches (without medical cause)	0.63 (0.54-0.72)
Nausea, feels sick (without medical cause)	0.58 (0.48-0.68)
Painful bowel movements (without medical cause)	0.49 (0.37-0.58)
Stomach-aches or cramps (without medical cause)	0.70 (0.62-0.78)
Too concerned with neatness or cleanliness	0.20 (0.07-0.32)
Vomiting, throwing up (without medical cause)	0.44 (0.33-0.55)
Withdrawn	Overall: 0.38 (0.28-0.52)
Acts too young for age	0.04 (0.00-0.18)
Avoids looking other in the eye	0.42 (0.28-0.55)
Doesn't answer when people talk to him or her	0.38 (0.24-0.51)
Refuses to play active games	0.32 (0.18-0.45)
Seems unresponsive to affection	0.47 (0.33-0.61)
Shows little affection toward people	0.58 (0.44-0.73)
Shows little interest in things around her	0.48 (0.33-0.63)
Withdrawn, doesn't get involved with others	0.32 (0.17-0.47)
Sleep problems	Overall: 0.51 (0.40-0.61)
Doesn't want to sleep alone	0.22 (0.09-0.34)
Has trouble getting to sleep	0.48 (0.37-0.59)
Nightmares	0.51 (0.40-0.62)
Resists going to bed at night	0.47 (0.36-0.58)
Sleeps less than most kids during and/or night	0.49 (0.37-0.60)
Talks or cries out in sleep	0.70 (0.61-0.80)
Wakes up often at night	0.67 (0.57-0.76)
Attention problems	Overall: 0.45 (0.31-0.60)
Can't concentrate, can't pay attention for long	0.59 (0.46-0.73)
Can't sit still, restless, or hyperactive	0.62 (0.48-0.76)
Poorly coordinated or clumsy	0.39 (0.24-0.54)
Quickly shifts from one activity to another	0.41 (0.27-0.55)

Wanders away	0.26 (0.11-0.40)
Aggressive behaviour	Overall: 0.50 (0.40-0.59)
Can't stand waiting; wants everything now	0.53 (0.44-0.62)
Defiant	0.52 (0.43-0.62)
Demands must be met immediately	0.52 (0.43-0.61)
Destroys things belonging to his/her family or other children	0.59 (0.51-0.68)
Disobedient	0.36 (0.25-0.47)
Doesn't seem to feel guilty after misbehaving	0.49 (0.39-0.59)
Easily frustrated	0.51 (0.42-0.61)
Gets in many fights	0.62 (0.54-0.70)
Hits others	0.67 (0.60-0.74)
Hurts animals or people without meaning to	0.20 (0.08-0.31)
Angry moods	0.62 (0.54-0.70)
Physically attacks people	0.53 (0.44-0.63)
Punishment doesn't change his/her behaviour	0.30 (0.19-0.42)
Screams a lot	0.61 (0.53-0.69)
Selfish or won't share	0.54 (0.44-0.63)
Stubborn, sullen or irritable	0.60 (0.51-0.68)
Temper tantrums or hot temper	0.52 (0.43-0.61)
Uncooperative	0.27 (0.15-0.49)
Wants a lot of attention	0.38 (0.27-0.49)

Standardised item loading computed with Confirmatory factor analysis implemented with structural equation modelling. Individual item loadings were averaged to produce mean loadings for a specific syndrome. Acceptable factor loadings were those >0.40 for the overall subscale. CI=confidence interval.

Table 4-4: Comparison of the seven-syndrome correlated CFA model of this present study with ranges from Achenbach and Rescorla, 2000.

Syndrome	Items	Mean loadings: present study	Range of mean loadings: Achenbach and Rescorla
Emotionally reactive	9	0.47	0.33-0.73
Anxious depressed	8	0.53	0.21-0.76
Somatic complaints	11	0.46	0.38-0.96
Withdrawn	8	0.38	0.28-0.86
Sleep problems	7	0.51	0.44-0.76
Attention problems	5	0.45	0.39-0.59
Aggressive behaviours	19	0.50	0.16-0.79

Discussion

This study aimed to examine the utility and validity of the CBCL in assessing behavioural problems in a rural Kenyan preschool sample. After translation and slight adaptation of the CBCL, overall internal consistency properties were excellent, the test-retest correlation coefficients were good, and the inter-informant agreements with mothers were acceptable for other close caretakers, as well as for fathers. Additionally, most factor loadings and fit statistics for the seven-syndrome CBCL structure were acceptable, establishing the use of these behavioural constructs in this population.

CBCL scores and cut-off ranges

The 75th percentile median CBCL score of 38 in this sample is comparable to 33 from an American sample (T. Achenbach & Rescorla, 2000), but lower than those in a Taiwanese (42) (Wu et al., 2012) and Chinese sample (45); although the latter included adopted children

who may have more psychopathology than in the general population (Tan, Dedrick, & Marfo, 2007). Parents may have underreported the extent of behaviour problems considering the stigma associated with mental health illnesses (Sartorius, 2007), particularly as this was the first psychopathology survey of preschool children in this area. Behavioural scores were similar between sexes and between externalising and internalising scales, consistent with some previous studies (T. Achenbach & Rescorla, 2000; Tan et al., 2007), but not others (Wu et al., 2012).

The cut-off CBCL scores for use in epidemiological and intervention studies based on the 90th percentile as recommended by Achenbach and Rescorla (T. Achenbach & Rescorla, 2000) is comparable to those of 50-65 reported in other countries (T. Achenbach & Rescorla, 2000; Wu et al., 2012). This cut-off score likely represents those at risk of severe behavioural/emotional problems rather than a clinical diagnosis of mental health problems since it is derived from a random rather than a normative sample. The high behavioural scores in our study are consistent with a high prevalence of neuropsychiatric conditions in this area (V. Mung'ala-Odera et al., 2006); the prevalence of behavioural problems may be higher than the 8-15% reported in most studies from high income countries (Froehlich et al., 2007).

Associations for discriminant validity

Behavioural/emotional scores were associated with pregnancy complications and adverse perinatal events, supporting the discriminant validity of the CBCL in differentiating at-risk children from those not at risk (T. Achenbach & Rescorla, 2000). No significant associations were observed with seizures and socioeconomic information, but this may be explained by the smaller number screening for seizures, for example. Nonetheless, all these factors investigated should be accounted in associations with behavioural/emotional since they can

be potential confounders. The CBCL may therefore be used by clinicians to identify children at risk of behavioural/emotional problems, following medical conditions or early life exposures, who would benefit from behavioural/emotional interventions.

Test retest and inter-informer reliability

The good test-retest reliability scores asserts the stability of the CBCL in assessing behaviour over time, although psychopathology can change in developing children (Egger & Angold, 2006). Our test-retest reliability was better than that reported from a Luganda version of the CBCL (0.76 vs. 0.67), but the Uganda study used the school-aged CBCL (Bangirana et al., 2009). Inter-informant agreement was acceptable for both fathers and caretakers, although the former was lower than the latter; which is similar to UK studies using the strength and difficulty questionnaire (Griffith, Hastings, & Petalas, 2014). Indeed in anecdotal reports from the field team a number of fathers noted that they were not very familiar with their children's behavioural patterns. On the contrary, caretakers such as grandmothers, stepmothers and/or aunts showed good inter-informant agreement with the mothers; as they spend more time caring for these children.

Internal consistency

All empirically-based seven-syndromes, as defined by ASEBA (T. Achenbach & Rescorla, 2000), were associated with acceptable to excellent reliability coefficient alphas, underscoring the value of the CBCL in assessing behavioural patterns in this Kenyan rural population. A Luganda version of the school-aged CBCL had good reliability coefficient alpha (0.83) (Bangirana et al., 2009), which is slightly lower than in our preschool CBCL (0.95). Total problem coefficient alpha of 0.95 is highly similar with those documented in the USA (0.95) (T. Achenbach & Rescorla, 2000), China (0.93) (Tan et al., 2007), and Taiwan (0.95) (Wu et al., 2012). The coefficient alpha for “withdrawn” and “attention problems”

were slightly lower than in other studies (T. Achenbach & Rescorla, 2000; Tan et al., 2007; Wu et al., 2012), perhaps because in this population emotional behaviours are considered less serious than disruptive behaviours. This finding may suggest that some items describing withdrawn and aggressive behaviours are understood differently in Kenya than in the USA.

Seven-syndrome structure and fit indices

Our Confirmatory Factor Analysis, implemented with structural equation modelling, supported the seven-syndrome CBCL structure, whose fit indices were acceptable. In particular, the standardised factor loadings are comparable to the ranges provided by Achenbach and Rescorla who first validated the CBCL in the USA (T. Achenbach & Rescorla, 2000). The slightly smaller loadings in a few items in our study (withdrawn and attention problems) are in part explained by performing polychoric (for 3-point response scales) rather than tetrachoric (for 2-point response scales) item correlations; the former is deemed appropriate for the CBCL but may be associated with lower factor loadings (Yuh & Muthen, 2002). The few items with very low standardised coefficients may have been misunderstood by parents and should be investigated further in future studies before they omitted from future assessments using CBCL to examine behavioural/emotional problems in Kenyan populations. All RMSEA and most CFI and TLI indices suggested an acceptable to good fit for the seven-syndrome CBCL structure in our population. In particular, our overall RMSEA of 0.035 is better than the 0.06 from the USA (T. Achenbach & Rescorla, 2000), 0.053 from China (Ivanova et al., 2010), 0.055 in Taiwan (Wu et al., 2012) and up to 0.059 from 23 other societies (Ivanova et al., 2010), probably because we allowed item error terms to correlate (Browne & Cudeck, 1993). These findings support configural invariance of the CBCL and its application across diverse societies, including rural Kenya. Since the internal structure of the CBCL in this population is satisfactory, future studies can evaluate other

properties, in particular the predictive validity as these children grow older (Njoroge & Bernhart, 2011).

Strengths and limitations

The strength of this study is the careful translation of the CBCL into the local languages and use of a trained and experienced field assistant to administer the tool. Training of fieldworkers by one psychologist and comparison of their scoring for concordance before collection of the CBCL data helped avoid introduction of inter-rater bias. The sample size was acceptable to run confirmatory factor analysis and overall internal consistency. The sample size may however have been small for some sub-analysis. Withdrawn and attention problems scales were associated with low internal consistency. Test-retest reliability and inter-informant agreement were not performed for subscales of the CBCL, since these scales had low scores which were skewed, and these factors would overinflate the correlation coefficients. The derived cut-off score doesn't represent a clinical diagnosis of a mental health problem since it is based on a random rather than a normative sample.

Conclusion

A culturally and contextually adapted CBCL possesses good to excellent psychometric properties and has acceptable fit indices for the seven-syndrome structure; and thus can be used to assess behaviour in preschool children in this rural area of Kenya. However, these findings should be validated in other African settings since cultural and socioeconomic differences may exist which can influence behavioural assessments and outcomes. Future studies should develop clinical cut-offs for behavioural/emotional problems based on normative samples of children without neuropsychiatric problems, and examine the predictive validity of the CBCL when these children grow older. Epidemiological studies to

estimate reliable estimates of psychopathology in this area are justified to inform the development of appropriate behavioural interventions.

Chapter 5: Behavioural/emotional problems study

Burden, risk factors and comorbidities of behavioural/emotional problems in Kenyan preschool children: a population-based study

Background

Behavioural and emotional problems are common in preschool children aged under 6 years (usually 10-20 %) (Sim et al., 2013), but few epidemiological studies have been carried out.

Behavioural/emotional problems in preschool children are classified into two broad categories: (1) externalising problems such as aggressive behaviours, and (2) internalising problems such as emotional disturbances (T. Achenbach & Rescorla, 2000).

Epidemiological and meta-analysis studies on behavioural/emotional problems in children often combine preschool estimates with those of older children (Cortina et al., 2012), which contributes to a lack of data in preschool children. Most of the epidemiological studies in the literature have been conducted after 2000, suggesting an increased recognition of behavioural/emotional problems in preschool children in the past decade. The prevalence of behavioural/emotional problems in high-income countries (HIC) range from 3-40% (Kuschel et al., 2004; Sim et al., 2013). There are however few epidemiological studies of behavioural/emotional problems in low- and middle-income countries (LMIC). Two Turkish studies estimated a prevalence of about 10% (Erol et al., 2005; Karabekiroglu et al., 2013) suggesting that behavioural/emotional problems are as common as in HIC. Higher prevalence of behavioural/emotional problems were reported in studies in India (22%) (Rai et al., 1993), Hong Kong (13-28%) (Luk, Leung, Bacon-Shone, & Lieh-Mak, 1991), and Brazil (24%) (Anselmi, Piccinini, Barros, & Lopes, 2004), but the Indian study was based on a hospital sample, which may be biased towards greater morbidity. However, in Africa there are no reliable studies on the prevalence of behavioural/emotional problems in preschool children. One Sudanese study found behavioural/emotional problems in 22% of children aged 3-6 years (Rahim & Cederblad, 1986), but this data were collected in 1965, were based on a small sample size of preschool children (n= 673), and behavioural disturbances were assessed with a questionnaire rather than with a validated

assessment tool. There are no epidemiological studies of behavioural/emotional problems in Africa, studies in preschool children are required to allow comparison with other settings in the world.

It is possible to identify risk factors for behavioural problems and many of these can be addressed through public health interventions and social policy change. The risk factors include antenatal/perinatal factors (Arpi & Ferrari, 2013; Duazo et al., 2010); sociodemographic characteristics such as minority status and male gender (Lavigne et al., 1996), family factors such as intimate partner violence and child abuse (Bayer et al., 2008); and environmental factors such as heavy metals and pesticide poisoning (Rodriguez-Barranco et al., 2013). These risk factors are very common in African countries; for example, in Kenya, most births occur at home (with adverse perinatal events) and low socioeconomic status is common (J. A. Scott et al., 2012). It is therefore important to design epidemiological studies in LMIC aimed at identifying risk factors associated with behavioural/emotional problems in preschool children.

Behavioural/emotional problems in preschool children are associated with medical and neurocognitive comorbidities which may affect prognosis. Behavioural/emotional problems occur in up to 20% of preschool children with acute febrile seizures, particularly the complex phenotypes (Kölfen et al., 1998). Neurocognitive impairments, sleep problems and malnutrition are common in children with behavioural/emotional problems (Horwitz et al., 2003; Metcalfe, Harvey, & Laws, 2013). The causal association between these conditions and behavioural/emotional problems is often unclear. Seizure disorders, neurocognitive impairments and malnutrition are common in young African children (R. Idro et al., 2008; V. Mung'ala-Odera et al., 2004; Ngare & Muttunga, 1999), and could be comorbid with behavioural/emotional problems in this region. Thus it is important to know the common comorbidities of behavioural/emotional problems in preschool children to inform development of a comprehensive package of care.

Identification of behavioural/emotional problems in preschool is challenging because these children are developing rapidly (A. S. Carter et al., 2004). Few tools have been developed to assess behavioural problems in preschool children but the most common ones are the Child Behaviour Checklist (CBCL) (T. Achenbach & Rescorla, 2000), Strength and Difficulties Questionnaire (SDQ)

(Theunissen et al., 2013), and Preschool Feelings Checklist (PFC) (Luby et al., 2004). The SDQ has excellent psychometric properties, and is used for 2-4 year old children (Theunissen et al., 2013). The PFC assesses 3-6 year old children, but it assesses internalising problems at the expense of externalising problems. The CBCL is internationally recognised for assessing externalising and internalising in children between 1.5 to 5.5 years (T. Achenbach & Rescorla, 2000), and has been used on 1-6 year old children in some studies (van Zeijl et al., 2006). It identifies seven syndromes and has been used in at least 23 different societies (Ivanova et al., 2010). In Kenya, I have demonstrated that it has acceptable psychometric properties in a sample of preschool children (S. M. Kariuki et al., 2016).

In order to estimate the prevalence of behavioural/emotional problems and the associated risk factors in preschool children living in a defined demographic surveillance area on the Kenyan coast, I conducted a population-based study. The first stage of this community survey involved the assessment of behaviour/emotional problems and screening of acute seizures. Those who screened positive for acute seizures and a proportion of those with behavioural/emotional problems were invited to our clinics for further clinical and anthropometric evaluation. Clinical evaluation involved assessment of comorbidities associated with behavioural/emotional problems.

Methods and procedures

Sampling

As outlined in chapter 3, this was a two stage cross-sectional study, where eligible children were assessed for behavioural/emotional problems and screened for seizures in the stage I. We had estimated that randomly selecting and screening approximately 3,500 children from 50,000 children aged 1-6 years would be sufficient to identify a prevalence of psychopathology of 10% with a precision of 1%. During stage I, a parental risk factor questionnaire (sociodemographic, socioeconomic and medical history information) was administered to the parents/guardians of almost all children screened and/or who consented.

The stage II was a clinical evaluation study to determine medical comorbidities of behavioural/emotional problems. The plan was to invite 20% of the children assessed for behavioural/emotional problems in stage I for further clinical evaluation. Of the children invited, at least 250 children would have high behavioural/emotional scores, while the remainder would be controls with low behavioural scores. This sample size can measure an odd/risk ratio of at least two for comorbidities such as seizures with at least 80% power at 5% significant level.

Procedures and definitions

Assessment of behavioural problems

Behavioural/ emotional problems were assessed with the CBCL, which was adapted and piloted in the local population ("The global burden of mental and neurological problems. Geneva, World Health Organization, 1999 (WHO Fact Sheet No. 217)."; S. M. Kariuki et al., 2016). During the validation, the CBCL items had excellent internal consistency (Cronbach's alpha of 0.95) and the fit indices of the seven-CBCL syndromes were satisfactory in the confirmatory factor analysis (a Root mean square error of approximation <0.09 , Tucker Lewis Index >0.90 and comparative fit index of >0.90). The Pearson's correlation coefficients (r) for test-retest and inter-rater CBCL scores were all acceptable ($r>0.70$) (S. M. Kariuki et al., 2016). Because of the literacy challenges in this area, questions were read out to the respondents (parents or guardians) by trained neuropsychological assessors fluent in the local languages: Kiswahili and Giriama. The language of administration was primarily Kiswahili (lingua franca), but for a few who could not comprehend Kiswahili, administration was done in Giriama. Translations of the CBCL had been done and piloted during the validation process.

If the respondent answered 'No' to a behavioural/emotional question the score was "0", and if they answered 'Yes' to a question, the fieldworker asked about severity status response to which was scored "1" for moderate problems and "2" for severe problems.

Approximately 2,903/3273 (89.0%) parents and carers of children assessed with the CBCL were interviewed using a parental questionnaire to help with identifying the risk factors associated with behavioural/emotional problems. The risk factor questionnaire consisted of the following items (i) parental sociodemographic information such as employment, schooling religion and ethnicity (ii) antenatal and perinatal histories such as age at first birth and adverse perinatal events; (iii) socioeconomic status histories such as housing status, water availability, and livestock ownership; (iv) medical histories such as seizure disorders/other chronic illnesses, use of bednet and hospital services; and (v) child health and nutrition habits such as food types consumed, eating soil and snoring at night.

Definition and levels of risk factors

Ethnicity was categorised as Chonyi and Giriama, Kauma, other Mijikendas, and other tribes.

Religion was classified into none, traditional, Islam and Christian. Levels of education were none, primary, secondary and tertiary. Water availability was categorised as infrequent, available weekly, available daily and always available. Toilet facilities were classified into none or use of bushes/fields, traditional pit latrines, ventilated pit latrines and flush toilets. House status was classified into completely dilapidated, needing major repairs, incomplete/under construction, and needing no repair or minor repairs. Source of cooking fuel was classified into solid fuels (wood, charcoal and coal), and clean fuels (liquid fuels, gaseous fuels and electricity). Ownership of livestock was classified into none, some (≤ 5 animals) and many (> 5 animals).

Adverse perinatal events were defined as delays in crying, breathing and breastfeeding after birth.

Delivery place was either at home or hospital/clinic. Abnormal pregnancy was defined as premature/prolonged labour, post-dated pregnancy, pre-eclampsia/eclampsia or any other health problems during pregnancy. A seizure-screening questionnaire with seven questions was used to screen for any seizure disorders in stage I of the survey. Those screening positive for any seizure disorder were invited for further clinical examination in stage II to determine if their seizures met the definition for acute (febrile) seizures, epilepsy or otherwise. Some of those who did not turn up in Stage II had the diagnosis of acute seizures or epilepsy confirmed from the Kilifi Health and Demographic Surveillance System database of hospital admissions during the last six years. Acute

(febrile) seizures defined as seizures associated with a febrile illness or fever in those under 6 years, and epilepsy as a history of two unprovoked seizures (ILAE, 1989).

Clinical evaluation and anthropometric assessments

About 20% of the children were invited to take part, comprising of at least 250 high CBCL scorers and 250 low CBCL scorers, were seen by a clinician. The clinician asked questions on the history of seizure disorders to determine whether the seizures were acute seizures or epilepsy. The clinician was blinded to the status of the children screening positive for seizures in stage I in the community. The clinician performed a clinical examination to assess for gross and fine motor deficits, sensation function, abnormal activity, cognitive/mental status, cranial nerve function, sensory ability and skin integrity. Intellectual disability was assessed by a clinician by observing young children perform standardised test of a locally adapted developmental inventory (Abubakar, Holding, van Baar, Newton, & van de Vijver, 2008) and/or asking older children standardised questions to evaluate the child's awareness of person, place, and time.

Anthropometric measures of the child were also taken and included head circumference, mid-upper arm circumference (MUAC), height and weight. Malnutrition was defined as a weight for age (WAZ) or height for age (HAZ) z-score value of ≤ -2 or a mid-upper arm circumference < 11.5 cm.

Grouping of the CBCL scores and definition of behavioural/emotional problems

The scoring system used and the grouping of the CBCL items into syndromes and externalising and internalising subscales followed recommendations by the Achenbach System of Empirically Based Assessments (T. Achenbach & Rescorla, 2000), and cut-offs derived from a validation study conducted in Kilifi, Kenya. The total score for the CBCL was formed by summing ratings from all of the 99 items. Summation of specific items outlined in table 5-1 below formed the seven syndromes of the CBCL namely: emotionally-reactive, anxious-depressed, somatic complaints, withdrawn, attention problems and aggressive behaviour. Externalising problems consisted of two syndromes: attention problems and aggressive behaviours. Internalising problems consisted of four syndromes:

emotionally-reactive, anxious-depressed, somatic complaints and withdrawn. The syndrome of sleep problems does not fit into either of the two problems.

Behavioural/emotional problems cut-offs were developed from a normative sample of 301 preschool children randomly selected from the KHDSS for validation and adaptation of the CBCL before the main epidemiological study (S. M. Kariuki et al., 2016). The 90th percentile was used as the cut-off according to recommendations from the developers of the tool. The percentile corresponded to a CBCL score of 60 for the total problems scale, 21 for externalising problems and 15 for internalising problems.

Table 5-1. Criteria for constructing CBCL syndromes and DSM-IV-oriented scales using the 99 items

CBCL syndromes							DSM-oriented scales				
Emotionally-reactive	Anxious-depressed	Somatic complaints	Withdrawn	Sleep problems	Attention problems	Aggressive behaviour	Affective problems	Anxiety problems	Pervasive developmental problems	ADH problems	Oppositional defiant problems
Disturbed by change	Clings	Aches	Acts too young	Doesn't want to sleep alone	Can't concentrate	Can't stand waiting	Cries	Clings	Afraid to try new	Can't concentrate	Defiant
Twitches	Feelings hurt	Can't stand things out of place	Avoids eye contact	Trouble sleeping	Can't sit still	Defiant	Doesn't eat well	Doesn't want to sleep alone	Avoids eye contact	Can't sit still	Disobedient
Panics	Upset by separation	Constipated	Doesn't answer	Nightmares	Clumsy	Demands met	Trouble sleeping	Doesn't leave home	Can't stand things out of place	Can't stand waiting	Angry moods
Swifts between sad-excite	Looks unhappy	Diarrhoea	Refuses active games	Resists bed	Quickly shifts	Destroys other's	Looks unhappy	Fears	Disturbed by change	Demands must be met	Stubborn
Moody	Nervous	Doesn't eat well	Unresponsive to affection	Sleeps little	Wanders away	Disobedient	Overeating	Upset by separation	Doesn't answer	Gets into everything	Temper
Sulks	Self-conscious	Headaches	Little affection	Talks, cries in sleep		Lacks guilt	Overtired	Nervous	Doesn't get along with peers	Quickly shifts	Uncooperative
Upset by new	Fearful	Nausea	Little interest	Wakes often		Easily frustrated	Little interest	Nightmares	Rocks head, body		
Whining	Sad	Painful bowel	Withdrawn			Fights	Sleeps little	Panics	Unresponsive to affection		
Worries		Stomach aches				Hits others	Underactive	Fearful	Little affection		
		Too concerned with neat/clean				Hurts accidentally	Sad	Worries	Speech problem		
		Vomits				Angry moods			Strange behaviour		
						Attacks people			Upset by new		
						Punishment doesn't change			Withdrawn		
						Screams					
						Selfish					
						Stubborn					
						Temper					
						Uncooperative					

						Wants attention					
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ADH=attention-deficit hyperactivity

Statistical analysis

All analyses were performed using STATA (version 13, Stata Corp, Texas, USA) and R statistical software (www.r-project.org). We tested if the CBCL scores had a Gaussian distribution by plotting a histogram (Figure 5-2) and performing skewness and kurtosis statistical tests. Comparison of discrete variables between those with and without behavioural/emotional problems was done using Pearson's Chi-square tests, or Fishers exact tests where observations in a cell were less than 5. Student t-test or Mann-Whitney U test was used to compare distribution of behavioural/emotional scores, while providing positive effect sizes of the comparison using Cohen's *d* statistics. Effect sizes provide the magnitude of the differences between the groups, with a *d*-value of ≤ 0.2 considered small, *d*-value of 0.5 medium and *d*-value of ≥ 0.8 large (Sullivan & Feinn, 2012).

Prevalence of behavioural problems was computed as a probability (where CBCL problems are treated as "positive" and the comparison group without CBCL problems as "negative") by exponentiation of coefficients on the constant term of a logit model using the formula:

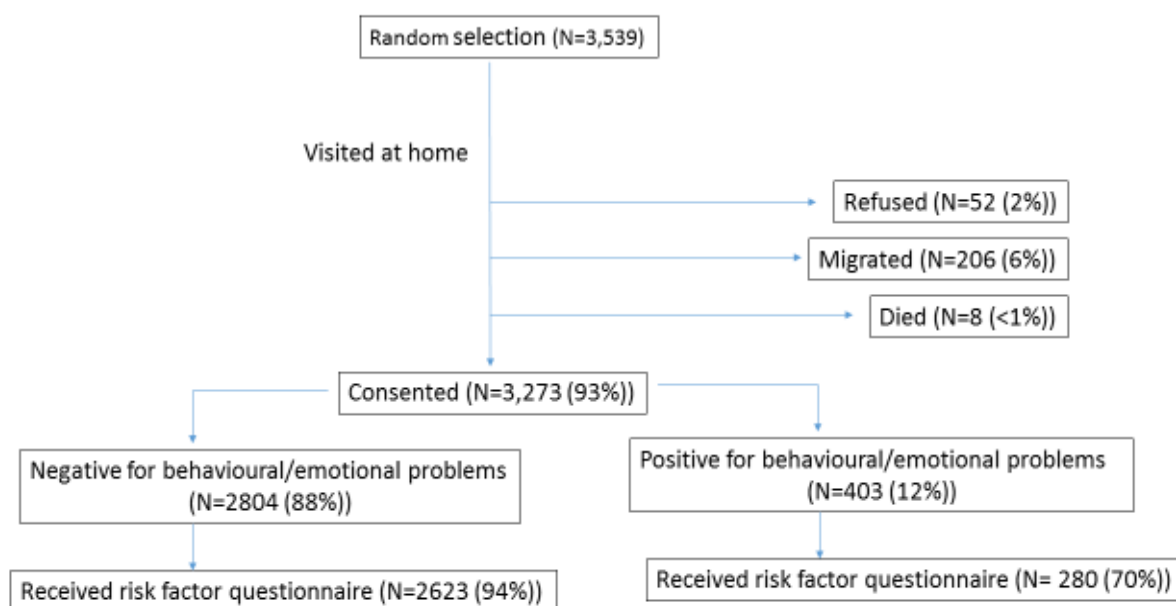
$(probability = \frac{\exp(coefficient)}{1 + \exp(coefficient)})$. The probability was multiplied by 100 to obtain the prevalence.

The overall prevalence was adjusted for age and sex in the logit model described above before exponentiation of the coefficients on the constant term. Prevalence estimates stratified by age-group and sex were also computed. The 95% confidence intervals (95%CI) around the prevalence were based on the Binomial distribution, a discrete probability distribution of the cases of behavioural/emotional problems in the total children screened (A. W. Edwards, 1960). We also calculated the Disability-adjusted Life Years (DALYs) as Years Lived with Disability, with Years of Life Lost assumed as zero since this was a cross-sectional study and follow up is usually required to measure premature mortality. The DALYs were calculated as a product of prevalence and the disability weights for anxiety and attention/deficit hyperactivity problems provided in the GBD studies (Salomon et al., 2012). The DALYs were neither age-weighted nor discounted since they were based on young children who have not yet reached their production age (Devleesschauwer et al., 2014).

Risk factors associated with behavioural/emotional problems were determined using log binomial regression model implemented in a generalised linear model, with a log link and a robust variance-covariance matrix of the estimators. Log binomial regression model computes reliable risk ratios in a population with common conditions such as behavioural/emotional problems. Beta coefficients for each risk factor above were then computed with continuous CBCL scores as the dependent variable in a generalised linear model that assumes a Gaussian distribution and has an identity link function, and a robust variance-covariance matrix of the estimators; the model is the equivalent of a linear regression model. All variables investigated were identified from the literature as potential risk factors and each one appeared in a penultimate adjusted model that accounted for child factors (age, sex, schooling, and region of residence) and a final adjusted model that accounted for both child factors (age, sex, schooling, and region of residence) and maternal factors (age, marital status, economic/employment status, education level, ethnicity and religion). A test for linear trend was performed for risk factors categorised into three or more levels. Age for the child and mother were entered into the risk factor models as first degree fractional polynomials. Adjusted risk ratios and beta coefficients were computed separately for total CBCL problems, externalising problems and internalising problems. A multivariable structural equation model, implemented in R statistical software, was used to determine the variability of behavioural/emotional problems explained by each significant risk factor (measured as R-squared) (Hu & Bentler, 1999). A p-value of 0.05 or less was considered significant.

Results

We administered the CBCL to 3273/3539 (93%) of the parents/guardians of preschool children visited in the community who were randomly selected to take part in this study. The flow diagram of how the sample was derived is shown in figure 5-1.

Figure 5-1. Derivation of the behavioural/emotional survey sample

Of the 3273 children, 1671 (51%) were males and the median age was 4 (interquartile range (IQR), 3-5) years. The sex and median age did not differ by region of the KHDSS (table 5-2). However, statistically significant differences between the northern and southern region of the KHDSS were observed for some sociodemographic, socioeconomic and medical history factors among the 2,903 (89%) children who completed a risk factor questionnaire (Table 5-2).

Table 5-2. Sociodemographic, socioeconomic and medical characteristics of study participants by study demographic surveillance area

Characteristics	Demographic surveillance region		Total (N=3,273)	p-value ^a
	Northern (N=1,437)	Southern (N=1,836)		
Child's age in months: median (IQR)	47 (31-64)	48 (32-64)	48 (32-64)	0.2636
Child's male sex	731 (51%)	934 (51%)	1671 (51%)	0.813
Mother's age in years: median (IQR)	29 (25-35)	30 (25-35)	30 (25-35)	0.1564
Administered a risk factor questionnaire				
	N=1300	N=1600	N=2903	
Sociodemographic information				

Mother's marital status				0.017
Single	178 (14%)	188 (12%)	366 (13%)	
Separated/divorced	80 (6%)	73 (5%)	153 (5%)	
Widowed	8 (1%)	22 (1%)	30 (1%)	
Married	1037 (80%)	1317 (82%)	2354 (81%)	
Mother's religion				<0.0001
None	318 (24%)	373 (23%)	691 (24%)	
Traditional	77 (6%)	111 (7)	188 (6%)	
Islam	116 (9%)	227 (14%)	343 (12%)	
Christian	792 (61%)	889 (56%)	1681 (58%)	
Mother's education level				0.720
None	447 (34%)	558 (35%)	1005 (35%)	
Primary	753 (58%)	930 (58%)	1683 (58%)	
Secondary	83 (6%)	86 (5%)	169 (6%)	
Tertiary	20 (2%)	26 (2%)	46 (2%)	
Mother's ethnicity				<0.0001
None-Mijikenda	59 (5%)	97 (6%)	156 (5%)	
Other Mijikenda	55 (4%)	120 (8%)	175 (6%)	
Kauma	72 (6%)	198 (12%)	270 (9%)	
Chonyi	183 (14%)	693 (43%)	876 (30%)	
Giriama	934 (72%)	492 (31%)	1426 (49%)	
Economic activity: mother	955 (73%)	1159 (72%)	2114 (73%)	0.607
Economic activity: father	1111/1196 (93%)	1371/1488 (92%)	2482/2684 (92%)	0.461
Number of children: median (IQR)	4 (3-6)	4 (3-6)	4 (3-6)	0.8413
Socioeconomic status and household information				
Water availability				<0.0001
Infrequent	328 (25%)	487 (30%)	815 (28%)	
Weekly	153 (12%)	48 (3%)	201 (7%)	
Daily	328 (25%)	364 (23%)	692 (24%)	
Always	494 (38%)	701 (44%)	1195 (41%)	
House status				
Dilapidated	130 (10%)	178 (11%)	308 (11%)	0.053
Major repairs needed	90 (8%)	84 (5%)	183 (6%)	
Incompletely build	24 (2%)	25 (2%)	49 (2%)	
Minor/no repairs needed	1050 (81%)	1313 (82%)	2363 (81%)	
Toilet type				<0.0001
Bush/none	522 (40%)	479 (30%)	1001 (34%)	
Traditional pit	624 (48%)	913 (57%)	1537 (53%)	
Ventilated pit	86 (7%)	133 (8%)	219 (8%)	
Flush	71 (5%)	75 (5%)	146 (5%)	
Livestock owned				<0.0001
None	516 (40%)	841 (53%)	1357 (47%)	
<5	324 (25%)	265 (17%)	589 (20%)	
>5	463 (36%)	494 (31%)	957 (33%)	
Pregnancy and birth history				
Pregnancy problems	112 (9%)	78 (5%)	190 (7%)	<0.0001
Mother's age at birth	18 (17-20)	18 (17-20)	18 (17-20)	0.3338

Delivery at home	833 (64%)	923 (58%)	1756 (60%)	0.001
Adverse perinatal events	37 (3%)	28 (2%)	65 (2%)	0.048
Medical history				
Family history of seizures	127 (10%)	125 (8%)	252 (9%)	0.066
Family history of febrile seizures	95 (7%)	147 (9%)	242 (8%)	0.066
Previous hospitalisation	124 (10%)	146 (9%)	270 (9%)	0.718
Head injury	24 (2%)	24 (2%)	48 (4%)	0.472
Dogs and cats in compound	541 (42%)	697 (44%)	1238 (43%)	0.268
Eats cassava	990 (76%)	1179 (74%)	2169 (75%)	0.158
Eats soil	175 (13%)	153 (10%)	328 (11%)	0.001
Bednet use	1116 (86%)	1329 (83%)	2445 (84%)	0.057
Snore at night	259 (20%)	319 (20%)	578 (20%)	0.968
Deceased father	35/1110 (3%)	43/1362 (3%)	78/2472 (3%)	0.966

^a**Comparison of characteristics between the Northern demographic surveillance area and Southern demographic surveillance area. The questionnaire for sociodemographic characteristics, socioeconomic status and medical history was administered to 89% (N=2,903) of the sample screened with CBCL (N=3,273). IQR=interquartile range.**

The total CBCL mean scores were 33.6 (standard deviation, 22.9), and did not differ between the sexes (Cohen's $d=-0.04$ (-0.11 (95%CI, -0.11, 0.03))). The median scores were 27 (IQR, 18-42) and again did not differ between sexes ($p=0.593$). The median and mean CBCL scores for specific CBCL syndromes and diagnostic and statistical manual for mental disorders (DSM)-oriented scales are shown in table 5-3. The distribution of raw CBCL scores was non-parametric (Skewness=1.70; Kurtosis=6.63; joint p -value <0.0001), but log transformation appeared to normalise the scores (Figure 5-2).

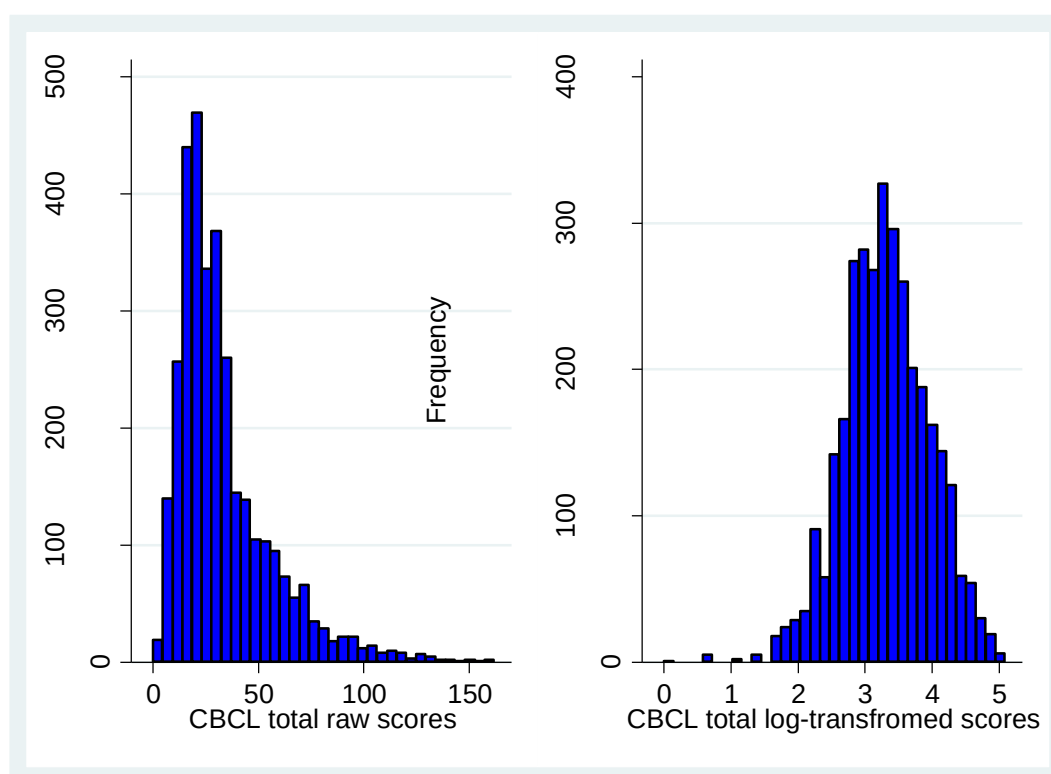
Table 5-3. Behavioural/emotional scores and problems for the CBCL 7-syndrome scales and the DSM-IV-oriented scales

Scales	Median scores, IQR	Mean scores, SD	Problems (%) N=3273
CBCL syndromes			
Emotionally-reactive	2 (1-3)	2.4 (2.4)	331 (10%)
Anxious/depressed	2 (0-4)	2.8 (3.1)	417 (13%)
Somatic problems	2 (1-3)	3.1 (2.6)	695 (21%)
Withdrawn	2 (0-3)	2.1 (2.0)	360 (11%)
Sleep problems	2 (1-3)	2.3 (2.2)	114 (4%)
Attention problems	3 (2-5)	3.4 (2.0)	507 (15%)
Aggressive behaviour	6 (3-10)	7.5 (6.6)	189 (6%)
DSM-IV-oriented			

Affective problems	1 (0-3)	1.9 (2.5)	189 (6%)
Anxiety problems	4 (2-6)	4.5 (3.5)	413 (13%)
Pervasive developmental problems	2 (1-4)	3.1 (2.9)	173 (5%)
ADH problems	5 (3-7)	5.5 (2.9)	163 (5%)
Oppositional problems	2 (0-3)	2.2 (2.3)	76 (2%)

ADH=attention-deficit hyperactivity; DSM=diagnostic and statistical manual for mental disorders; IQR=interquartile range; SD= standard deviation.

Figure 5-2. Distribution of CBCL behavioural/emotional scores among the 3,273 preschool children.



Skewed CBCL scores are shown on the left graph while the right graph shows the CBCL scores after log-transformation

Internal consistency of the CBCL

The internal consistency of the 99 items of CBCL was excellent (Cronbach's $\alpha=0.95$ (95% confidence interval (95%CI), 0.94-0.96)), and remained excellent when administered in either Kiswahili (Cronbach's $\alpha=0.95$ (95%CI, 0.94-0.95)) or Giriama (Cronbach's $\alpha=0.94$ (95%CI,

0.93-0.95)). Similarly, the internal consistency was excellent for externalising problems scale (Cronbach's $\alpha=0.86$ (95%CI, 0.84-0.88)) and internalising problems scale (Cronbach's $\alpha=0.88$ (95%CI, 0.87-0.89)) of the CBCL. The internal consistency of the six CBCL syndromes and the five DSM-oriented scales are shown in table 5-4 and are comparable to those of an earlier pilot study from the same area (S. M. Kariuki et al., 2016).

Table 5-4. Internal consistency Cronbach's alpha for the CBCL total scale, externalising scale, internalising scale and seven-syndromes scale by local language

CBCL scale	Kiswahili (N=3,037)	Giriamia (N=236)	All children (N=3,273)
Total scale	0.95 (0.94-0.96)	0.94 (0.93-0.95)	0.95 (0.94-0.96)
Externalising scale (95%CI)	0.86 (0.84-0.86)	0.86 (0.83-0.87)	0.86 (0.84-0.88)
Internalising scale (95%CI)	0.89 (0.87-0.91)	0.86 (0.84-0.88)	0.88 (0.87-0.89)
CBCL syndrome scales			
Emotionally-reactive (95%CI)	0.68 (0.67-0.69)	0.60 (0.53-0.67)	0.68 (0.66-0.70)
Anxious-depressed (95%CI)	0.76 (0.75-0.77)	0.76 (0.72-0.80)	0.76 (0.74-0.76)
Somatic problems (95%CI)	0.69 (0.67-0.71)	0.67 (0.61-0.73)	0.68 (0.66-0.70)
Withdrawn (95%CI)	0.55 (0.53-0.57)	0.55 (0.47-0.63)	0.55 (0.52-0.58)
Sleep problems (95%CI)	0.65 (0.64-0.66)	0.71 (0.65-0.77)	0.66 (0.64-0.68)
Attention problems (95%CI)	0.50 (0.48-0.52)	0.58 (0.51-0.65)	0.50 (0.48-0.52)
Aggressive behaviour (95%CI)	0.85 (0.84-0.86)	0.85 (0.83-0.87)	0.85 (0.84-0.86)
DSM-Oriented scales			
Affective problems	0.67 (0.64-0.70)	0.65 (0.59-0.71)	0.67 (0.66-0.68)
Anxiety problems	0.73 (0.71-)	0.69 (0.65-0.73)	0.73 (0.71-0.75)
Pervasive developmental problems	0.60 (0.58-0.62)	0.62 (0.56-0.68)	0.63 (0.61-0.64)
Attention deficit/hyperactivity problems	0.62 (0.60-0.64)	0.62 (0.55-0.69)	0.63 (0.60-0.66)
Oppositional defiant problems	0.65 (0.63-0.67)	0.73 (0.68-0.78)	0.66 (0.64-0.68)

CI=confidence interval

Prevalence of behavioural/emotional problems

Total CBCL problems

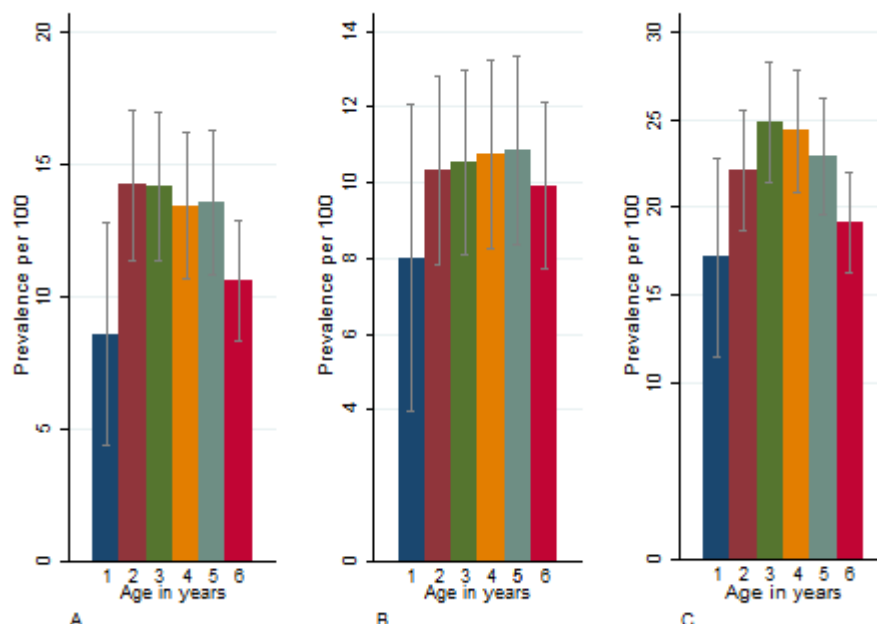
Total behavioural/emotional problems occurred in 420 (13%) children assessed with the CBCL, which is a crude overall prevalence of 13% (95%CI, 12%-14%); the distribution of prevalence across the age years is shown in Figure 5-3. The overall age and sex adjusted prevalence of behavioural/emotional problems was 11% (95%CI, 10%-13%). Occurrence of these problems was similar in younger (≤ 3 years) and older (> 3 years) children (239/1920 (13%) vs. 181/1353 (13%)), and appeared to be more frequent in males than females (231/1671 (14%) vs. 189/1602 (12%), $p=0.083$) though this was not statistically significant.

Prevalence of externalising and internalising problems

Externalising problems occurred in 338/3273 (10%) of children assessed with the CBCL, which is a crude prevalence of 10% (95%CI, 9%-11%); the distribution of prevalence across the age years is shown in Figure 5-3. The age and sex adjusted prevalence of externalising problems was 9% (95%CI, 10%-11%). Externalising problems were significantly more frequent in boys than in girls (204/1671 (12%) vs. 134/1602 (8%), $p<0.0001$), but were similar in children ≤ 3 years and in older children (> 3 years) (137/1353 (10%) vs. 201/1920 (11%), $p=0.751$).

Internalising problems occurred in 728 (22%) children, which is a crude prevalence of 22% (95%CI, 21%-24%); the distribution of prevalence across the age years is shown in Figure 5-3. The age and sex adjusted prevalence of internalising problems was 23% (95%CI, 20%-25%). The occurrence of internalising problems was similar in males and females (367/1602 (23%) vs. 361/1671 (22%), $p=0.369$), and in children ≤ 3 years and in older children (> 3 years) (306/1353 (23%) vs. 422/1920 (22%), $p=0.666$).

Figure 5-3. Prevalence of total CBCL problems, externalising problems and internalising problems among 3,273 preschool children living on the Kenyan coast



A=Total CBCL problems; B=Externalising problems, which appeared to increase with age; C= Internalising problems

CBCL syndromes and DSM-oriented scales

The two most common CBCL syndromes were somatic problems (21% (95%CI, 20%-23%)) and attention problems (16% (95%CI, 14%-17%)), while the two least frequent syndromes were aggressive behaviour (6% (95%CI, 5%-7%)) and sleep problems (4% (95%CI, 3%-4%)). The prevalence of other CBCL syndromes are shown in table 5-3 above. The most common DSM-oriented scale was anxiety problems (13% (95%CI, 12%-14%)) and the least common was oppositional defiant problems (2% (95%CI, 2%-3%)).

Disability-adjusted life years

The DALYs were computed as Years Lived with Disability for anxiety problems and attention-deficit hyperactivity (ADH) problems, the two mental health problems with published disability weights in the GBD studies (Salomon et al., 2012). The total DALYs lost to anxiety problems were 4.9 (95%CI, 4.5-5.4) per 1,000 population, while those lost to ADH problems were 2.4 (95%CI, 2.1-2.8) per 1,000 population. The age specific DALYs for anxiety were higher than those for ADH problems (table 5-5).

Table 5-5. Disability-adjusted life years by age-group

Age	DALYs per 1000 population	
	Anxiety problems	ADH problems
1 year	3.8 (95%CI, 2.1-5.5)	1.9 (95%CI, 0.5-3.4)
2 years	5.1 (95%CI, 4.0-6.1)	2.2 (95%CI, 1.4-3.1)
3 years	6.1 (95%CI, 5.1-7.2)	2.6 (95%CI, 1.8-3.5)
4 years	4.8 (95%CI, 3.8-5.8)	2.7 (95%CI, 1.8-3.6)
5 years	3.8 (95%CI, 3.0-4.6)	1.9 (95%CI, 1.2-2.6)

ADH=attention-deficit hyperactivity; CI=confidence interval; DALYs=disability adjusted life years

Risk factors for behavioural/emotional problems

Among the pregnancy and birth factors, adverse perinatal events (adjusted risk ratio (RR)=4.34 (95%CI, 3.21-5.87)) and problems during pregnancy (RR=2.11 (95%CI, 1.55-2.88)) were the most important risk factors. Epilepsy (RR=4.71 (95%CI, 2.65-8.35)) and acute seizures (RR=2.62 (1.89-3.64)) were associated with total CBCL behavioural/emotional problems among the seizure factors. Of the medical history factors, cassava consumption (RR=5.68 (95%CI, 3.22-10.03)), head injury (RR=3.11 (95%CI, 2.19-4.43)) and eating of soil (RR=2.80 (95%CI, 2.16-3.64)) were particularly associated with total problems. House status, water availability and toilet type were associated with total problems and the risk ratios for each are shown in table 5-6. Externalising and internalising

factors were associated with similar risk factors identified for total problems, but the size of the estimates were smaller (table 5-7 and 5-8). Seizure disorders, which were not mutually exclusive, explained almost all the variation of the risk of behavioural/emotional problems in a multivariable structural equation model (table 5-6, 5-7 and 5-8).

Table 5-6. Factors associated with total behavioural/emotional problems among 2,903 children who received the risk factor questionnaire

	Frequency distribution		Penultimate adjusted model ^a	Final adjusted model ^b	Penultimate adjusted model ^a	Final adjusted model ^b	
Factor	No total problem (N=2623)	Total problems (N=280)	Risk ratio (95%CI)	Risk Ratio (95%CI)	β Coefficient (95%CI)	β Coefficient (95%CI)	Variance (R-squared) ^d
Pregnancy and birth information							
Primigravida age	18 (17-20)	18 (16-20)	0.98 (0.96-1.01)	1.01 (0.98-1.06)	-0.01 (-0.01, 0.00)	0.00 (-0.01, 0.01)	N/A
Abnormal pregnancy	155 (6%)	35 (13%)	2.03 (1.46-2.81)	2.11 (1.55-2.88)	0.25 (0.15, 0.36)	0.27 (0.17, 0.38)	0.2%
Delivery at home	1583 (60%)	173 (62%)	1.07 (0.85-1.34)	1.00 (0.78-1.29)	0.00 (-0.05, 0.04)	-1.57 (-3.34, 0.20)	N/A
Adverse perinatal events	34 (1%)	31 (11%)	5.41 (4.07-7.20)	4.34 (3.21-5.87)	0.69 (0.55, 0.84)	0.67 (0.53, 0.82)	0%
Seizures information							
Any seizure disorder	157 (6%)	68 (24%)	3.83 (3.02-4.85)	2.90 (2.24-3.77)	0.42 (0.33, 0.51)	0.39 (0.30-0.49)	61.9%
Acute seizures	85/2546 (3%)	35/245 (14%)	3.72 (2.74-5.08)	2.62 (1.89-3.64)	0.36 (0.24, 0.49)	0.33 (0.21, 0.46)	88.9%
Epilepsy	11/2476 (<1%)	11/223 (5%)	6.31 (4.11-9.70)	4.71 (2.65-8.35)	0.68 (0.38, 0.99)	0.60 (0.28-0.93)	62.2%
Family history of seizures	204 (8%)	48 (17%)	2.19 (1.65-2.91)	2.00 (1.46-2.62)	0.18 (0.10, 0.27)	0.21 (0.11, 0.30)	2.1%
Family history of febrile seizures	146 (6%)	96 (34%)	5.73 (4.65-7.07)	4.07 (3.21-5.18)	0.63 (0.55, 0.71)	0.61 (0.52, 0.70)	7.8%
Medical history information							
Previous hospitalisation	211 (8%)	59 (21%)	2.63 (2.03-3.41)	2.25 (1.72-2.95)	0.25 (0.17, 0.33)	0.24 (0.15-0.34)	2.5%
Head injury	26 (1%)	22 (8%)	5.14 (3.68-7.19)	3.11 (2.19-4.43)	0.64 (0.47, 0.81)	0.56 (0.38, 0.74)	0.1%
Eats cassava	1905 (73%)	264 (94%)	5.58 (3.40-9.18)	5.68 (3.22-10.03)	0.30 (0.26, 0.35)	0.33 (0.28, 0.39)	0%

Dogs/cats in compound	1103 (42%)	135 (48%)	1.25 (0.99-1.56)	1.30 (1.04-1.64)	0.06 (0.02, 0.11)	0.06 (0.01, 0.12)	0.1%
Eats soil	251 (10%)	77 (28%)	3.14 (2.44-4.03)	2.80 (2.16-3.64)	0.42 (0.35, 0.50)	0.40 (0.32, 0.48)	0.1%
Snores at night	462 (18%)	116 (41%)	2.83 (2.28-3.53)	2.23 (1.77-2.81)	0.32 (0.26, 0.38)	0.29 (0.23, 0.37)	0.7%
Eats pork	228 (9%)	40 (14%)	1.65 (1.21-2.52)	1.74 (1.28-2.37)	0.13 (0.04, 0.22)	0.06 (0.02-0.11)	0%
Bednet use	2198 (84%)	247 (88%)	1.38 (0.97-1.97)	1.35 (0.91-1.99)	0.07 (0.01, 0.14)	0.02 (-0.05, 0.09)	N/A
Socioeconomic information							
Water availability							0.3%
Infrequent	662 (25%)	153 (55%)	1.00	1.00^c	0.00	0.00^c	
Weekly	167 (6%)	34 (12%)	0.90 (0.63-1.29)	1.41 (0.99-2.00)	-0.25 (-0.36, -0.13)	-0.13 (-0.24, -0.02)	
Daily	670 (26%)	22 (8%)	0.17 (0.11-0.26)	0.25 (0.15-0.41)	-0.38 (-0.44, -0.32)	-0.36 (-0.43, -0.29)	
Always	1124 (43%)	71 (25%)	0.31 (0.24-0.41)	0.42 (0.31-0.56)	-0.27 (-0.32, -0.22)	-0.23 (-0.29, -0.18)	
House status							2.0%
Dilapidated	159 (6%)	149 (53%)	1.00^c	1.00 ^c	0.00^c	0.00^c	
Needs major repair	149 (6%)	34 (12%)	0.38 (0.28-0.53)	0.51 (0.35-0.74)	-0.62 (-0.75, -0.50)	-0.58 (-0.73, -0.43)	
Under construction	45 (2%)	4 (1%)	0.17 (0.07-0.43)	0.18 (0.06-0.54)	-0.77 (-0.97, -0.57)	-0.84 (-10.5, -0.62)	
Needs Minor repair	2270 (87%)	93 (33%)	0.08 (0.06-0.10)	0.11 (0.08-0.14)	-0.84 (-0.91, -0.78)	-0.85 (-0.93, -0.78)	
Toilet type							0.1%
Bush/none	816 (31%)	185 (66%)	1.00^c	1.00 ^c	0.00^c	0.00^c	
Traditional pit	1466 (56%)	71 (25%)	0.24 (0.19-0.32)	0.31 (0.23-0.41)	-0.26 (-0.31, -0.21)	-0.27 (-0.32, -0.21)	
Ventilated pit	202 (8%)	17 (6%)	0.41 (0.25-0.65)	0.55 (0.33-0.93)	-0.28 (-0.38, -0.18)	-0.30 (-0.40, -0.19)	
Flush	139 (5%)	7 (3%)	0.25 (0.12-0.53)	0.46 (0.20-1.04)	-0.18 (-0.28, -0.09)	-0.16 (-0.27, -0.05)	
Livestock owned^c							

None	1214 (46%)	143 (51%)	1.00^c	1.00 ^c	0.00^c	0.00 ^c	N/A
<5	522 (20%)	67 (24%)	1.07 (0.82-1.42)	0.95 (0.70-1.27)	-0.04 (-0.10, 0.03)	0.05 (-0.11, 0.03)	
>5	887 (34%)	70 (25%)	0.69 (0.52-0.91)	0.66 (0.50-0.89)	-0.07 (-0.12, -0.02)	-0.05 (-0.11, -0.00)	
No of siblings	4 (3-6)	4 (3-6)	1.01 (0.97-1.05)	0.95 (0.88-1.01)	0.00 (-0.01, 0.01)	-0.02 (0.03, 0.00)	N/A
Deceased father	73 (3%)	5 (4)	1.15 (0.48-2.73)	1.49 (0.61-3.61)	-0.09 (-0.22, 0.04)	0.04 (-0.15, 0.23)	N/A

Significant associations are highlighted in bold. ^aAdjusted for child factors (age, sex, schooling and region of residence). ^bAdjusted for both child factors (age, sex, schooling, region of residence) and maternal factors (age, marital status, education level, economic/employment status, religion and ethnicity). ^cThe test for linear trend for the levels of the factor was statistically significant. ^dDerived from a structural equation model. NA=not done, usually if it did not meet the set statistical criteria. The variable “any seizure disorders” was based on questions from the seizure-screening questionnaire; “epilepsy” and “acute seizures” from both clinical examination at stage II, hospital records and multiple imputation; and “family history of seizures” from the parental risk factor questionnaire.

Table 5-7. Factors associated with externalising problems among 2,903 children who received the risk factor questionnaire

	Frequency distribution		Penultimate adjusted model ^a	Final adjusted model ^b	Penultimate adjusted model ^a	Final adjusted model ^b	
Factor	No externalising problem (N=2666)	Externalising problems (N=237)	Risk ratio (95%CI)	Risk ratio (95%CI)	β Coefficient (95%CI)	β Coefficient (95%CI)	Variance (R-Squared) ^d
Pregnancy and birth information							
Primigravida age	18 (17-20)	18 (16-20)	0.97 (0.94-1.00)	1.02 (0.97-1.07)	-0.01 (-0.02, 0.00)	-0.01 (-0.02, 0.00)	N/A
Abnormal pregnancy	162 (6%)	28 (12%)	1.91 (1.32-2.76)	2.02 (1.42-2.87)	0.17 (0.05, 0.28)	0.18 (0.06, 0.31)	0.2%
Delivery at home	1616 (61%)	140 (59%)	0.95 (0.74-1.21)	0.75 (0.57-0.97)	0.03 (-0.02, 0.09)	0.01 (-0.05, 0.07)	N/A
Adverse perinatal events	43 (1%)	22 (9%)	4.41 (3.05-6.39)	3.45 (2.42-4.92)	0.60 (0.42, 0.79)	0.55 (0.35, 0.74)	0%
Seizures information							
Any seizure disorder	175 (7%)	50 (21%)	3.71 (2.40-4.20)	2.37 (1.76-3.19)	0.39 (0.29, 0.50)	0.38 (0.27-0.49)	63.1%
Acute seizures	91/2577 (3%)	29/214 (14%)	3.47 (2.46-4.91)	2.48 (1.73-3.56)	0.40 (0.26, 0.54)	0.37 (0.23, 0.52)	89.0%
Epilepsy	11/2504 (1%)	8/195 (4%)	5.23 (2.96-9.23)	3.80 (1.98-7.30)	0.64 (0.36, 0.92)	0.55 (0.25-0.84)	62.1%
Family history of seizures	209 (8%)	43 (17%)	2.35 (1.74-3.19)	2.18 (1.60-2.96)	0.17 (0.06, 0.27)	0.19 (0.07, 0.30)	2.1%
Family history of febrile seizures	166 (6%)	76 (32%)	5.19 (4.09-6.59)	3.83 (2.89-5.08)	0.62 (0.53, 0.71)	0.58 (0.48, 0.69)	7.8%
Medical history information							
Previous hospitalisation	224 (8%)	46 (19%)	2.32 (1.72-3.13)	1.94 (1.42-2.66)	0.19 (0.09, 0.29)	0.18 (0.07-0.29)	2.5%
Head injury	30 (1%)	18 (8%)	4.73 (3.16-7.08)	2.61 (1.63-4.21)	0.67 (0.47, 0.86)	0.54 (0.33, 0.75)	0.1%
Eats cassava	1946 (73%)	223 (94%)	5.38 (3.15-9.16)	4.67 (2.63-8.27)	0.33 (0.27, 0.39)	0.18 (0.07, 0.29)	0%

Dogs/cats in compound	1124 (42%)	114 (48%)	1.25 (0.98-1.60)	1.26 (0.98-1.63)	0.05 (-0.01, 0.10)	0.04 (-0.02, 0.10)	N/A
Eats soil	270 (10%)	58 (24%)	2.75 (2.06-3.66)	2.32 (1.71-3.13)	0.32 (0.23, 0.40)	0.29 (0.19, 0.38)	0.1%
Snores at night	475 (18%)	103 (43%)	3.06 (2.41-3.90)	2.32 (1.79-3.00)	0.29 (0.22, 0.36)	0.25 (0.17, 0.33)	0.6%
Eats pork	233 (9%)	35 (15%)	1.69 (1.21-2.37)	1.91 (1.37-2.66)	0.04 (-0.06, 0.15)	0.04 (-0.07-0.16)	N/A
Bednet use	2235 (84%)	210 (89%)	1.45 (0.98-2.13)	1.44 (0.93-2.22)	0.07 (0.01, 0.14)	-0.02 (-0.10, 0.06)	N/A
Socioeconomic information							
Water availability							0.3%
Infrequent	684 (26%)	131 (55%)	1.00^c	1.00^c	0.00^c	0.00^c	
Weekly	172 (6%)	29 (12%)	0.89 (0.60-1.31)	1.44 (0.98-2.13)	-0.08 (-0.19, 0.03)	-0.01 (-0.13, -0.10)	
Daily	672 (25%)	20 (8%)	0.18 (0.11-0.28)	0.26 (0.15-0.43)	-0.56 (-0.63, -0.49)	-0.56 (-0.64, -0.48)	
Always	1138 (43%)	57 (24%)	0.29 (0.22-0.40)	0.39 (0.28-0.54)	-0.42 (-0.48, -0.36)	-0.40 (-0.46, -0.33)	
House status							2.0%
Dilapidated	182 (7%)	126 (53%)	1.00^c	1.00^c	0.00^c	0.00^c	
Needs major repair	152 (6%)	31 (13%)	0.41 (0.29-0.58)	0.51 (0.33-0.79)	-0.63 (-0.77, -0.48)	-0.57 (-0.74, -0.41)	
Under construction	45 (2%)	4 (1%)	0.21 (0.08-0.58)	0.23 (0.08-0.68)	-0.75 (-1.00, -0.51)	-0.83 (-1.10, -0.56)	
Needs Minor repair	2287 (86%)	76 (32%)	0.08 (0.06-0.10)	0.11 (0.08-0.15)	-0.84 (-0.91, -0.76)	-0.84 (-0.92, -0.76)	
Toilet type							N/A
Bush/none	845 (32%)	156 (66%)	1.00^c	1.00^c	0.00^c	0.00^c	
Traditional pit	1471 (55%)	66 (28%)	0.27 (0.20-0.36)	0.35 (0.27-0.48)	-0.29 (-0.35, -0.23)	-0.30 (-0.37, -0.24)	
Ventilated pit	207 (8%)	12 (5%)	0.34 (0.19-0.61)	0.45 (0.23-0.86)	-0.45 (-0.58, -0.34)	-0.53 (-0.67, -0.39)	
Flush	143 (5%)	3 (1%)	0.13 (0.04-0.40)	0.30 (0.09-0.93)	-0.26 (-0.39, -0.14)	-0.29 (-0.44, -0.14)	
Livestock owned^c							
None	1232 (46%)	125 (53%)	1.00^c	1.00^c	0.00	0.00^c	N/A

<5	532 (20%)	57 (24%)	1.05 (0.77-1.42)	1.02 (0.75-1.40)	0.00 (-0.08, 0.08)	-0.01 (-0.10, 0.07)	
>5	902 (34%)	55 (23%)	0.62 (0.46-0.84)	0.66 (0.50-0.89)	-0.05 (-0.10, 0.02)	-0.04 (-0.11, 0.02)	
No of siblings	4 (3-6)	4 (3-6)	1.00 (0.95-1.05)	0.92 (0.85-1.00)	0.00 (-0.01, 0.02)	-0.01 (-0.03, 0.01)	N/A
Deceased father	73 (3%)	5 (4%)	1.31 (0.55-3.13)	1.66 (0.70-3.93)	-0.11 (-0.30, 0.08)	-0.01 (-0.03, 0.01)	N/A

Significant associations are highlighted in bold. ^aAdjusted for child factors (age, sex, schooling and region of residence). ^bAdjusted for both child factors (age, sex, schooling, region of residence) and maternal factors (age, marital status, education level, economic/employment status, religion and ethnicity). ^cThe test for linear trend for the levels of the factor was statistically significant. ^dDerived from a structural equation model. NA=not done, usually if it did not meet the set statistical criteria. The variable “any seizure disorders” was based on questions from the seizure-screening questionnaire; “epilepsy” and “acute seizures” from both clinical examination at stage II, hospital records and multiple imputation; and “family history of seizures” from the parental risk factor questionnaire.

Table 5-8. Factors associated with internalising problems among 2,903 children who received the risk factor questionnaire

	Frequency distribution		Penultimate adjusted model ^a	Final adjusted model ^b	Penultimate adjusted model ^a	Final adjusted model ^b	
Factor	No internalising problem (N=2368)	Internalising problems (N=535)	Risk ratio (95% CI), p-value	Risk ratio (95% CI), p-value	β Coefficient (95% CI)	β Coefficient (95% CI)	Variance (R-squared) ^d
Pregnancy and birth information							
Primigravida age	18 (17-20)	18 (16-20)	0.99 (0.97-1.01)	1.02 (0.99-1.05)	-0.01 (-0.02, 0.00)	0.02 (0.00, 0.03)	N/A
Abnormal pregnancy	117 (5%)	73 (14%)	2.22 (1.82-2.72)	2.25 (1.84-2.76)	0.42 (0.30, 0.53)	0.46 (0.34, 0.58)	0.2%
Delivery at home	1423 (60%)	333 (62%)	1.06 (0.91-1.25)	0.86 (0.73-1.03)	-0.05 (-0.11, 0.01)	-0.11 (-0.18, -0.04)	0%
Adverse perinatal events	28 (1%)	37 (7%)	3.22 (2.56-4.03)	2.94 (2.36-3.65)	0.76 (0.58, 0.94)	0.79 (0.61, 0.97)	0%
Seizures information							
Any seizure disorder	128 (5%)	97 (18%)	2.68 (2.25-3.19)	2.27 (1.88-2.74)	0.51 (0.40, 0.63)	0.51 (0.39-0.64)	67.0%
Acute seizures	70/2305 (3%)	50/486 (14%)	2.61 (2.07-3.30)	2.08 (1.62-2.68)	0.41 (0.26, 0.56)	0.39 (0.22, 0.56)	88.7%
Epilepsy	7/2246 (1%)	15/453 (3%)	4.15 (3.08-5.61)	3.47 (2.42-4.99)	0.80 (0.43, 1.17)	0.76 (0.37-1.15)	62.5%
Family history of seizures	180 (8%)	72 (13%)	1.62 (1.31-2.01)	1.60 (1.28-1.99)	0.21 (0.10, 0.31)	0.23 (0.11, 0.36)	2.1%
Family history of febrile seizures	106 (4%)	136 (25%)	3.79 (4.09-6.59)	3.11 (2.62-3.67)	0.73 (0.63, 0.83)	0.75 (0.63, 0.86)	7.8%
Medical history information							
Previous hospitalisation	184 (8%)	86 (16%)	1.90 (1.56-2.31)	1.76 (1.44-2.16)	0.35 (0.25, 0.45)	0.39 (0.28-0.50)	2.5%
Head injury	18 (1%)	30 (6%)	3.76 (2.99-4.73)	2.80 (2.18-3.59)	0.72 (0.54, 0.89)	0.68 (0.49, 0.87)	0.1%
Eats cassava	1702 (72%)	467 (87%)	2.32 (1.82-2.95)	2.44 (1.85-3.21)	0.21 (0.15, 0.27)	0.20 (0.13, 0.27)	0%

Dogs/cats in compound	978 (41%)	260 (49%)	1.27 (1.09-1.47)	1.31 (1.11-1.54)	0.13 (0.08, 0.19)	0.14 (0.07, 0.20)	0.1%
Eats soil	199 (8%)	129 (24%)	2.48 (2.10-2.94)	2.33 (1.96-2.78)	0.47 (0.37, 0.56)	0.48 (0.37, 0.59)	0.1%
Snores at night	388 (16%)	190 (36%)	2.22 (1.90-2.58)	1.93 (1.64-2.26)	0.34 (0.27, 0.42)	0.34 (0.26, 0.42)	0.7%
Eats pork	197 (8%)	71 (13%)	1.51 (1.22-1.88)	1.56 (1.24-1.95)	0.28 (0.19, 0.38)	0.33 (0.22-0.43)	N/A
Bednet use	1979 (84%)	466 (87%)	1.26 (0.99-1.58)	1.08 (0.84-1.38)	0.09 (0.02, 0.18)	0.10 (0.00, 0.10)	N/A
Socioeconomic information							
Water availability							N/A
Infrequent	592 (25%)	233 (42%)	1.00 ^c	1.00 ^c	0.00 ^c	0.00	
Weekly	155 (7%)	46 (9%)	0.82 (0.61-1.09)	1.17 (0.88-1.55)	-0.14 (-0.28, 0.00)	-0.04 (-0.18, 0.11)	
Daily	615 (26%)	77 (14%)	0.40 (0.31-0.51)	0.54 (0.41-0.70)	-0.09 (-0.17, -0.01)	-0.03 (-0.12, 0.06)	
Always	1006 (42%)	189 (35%)	0.57 (0.48-0.67)	0.72 (0.60-0.86)	-0.08 (-0.16, -0.01)	-0.04 (-0.13, 0.04)	
House status							2.0%
Dilapidated	96 (4%)	212 (40%)	1.00 ^c	1.00 ^c	0.00 ^c	0.00 ^c	
Needs major repair	130 (5%)	53 (10%)	0.41 (0.32-0.52)	0.51 (0.39-0.66)	-0.59 (-0.73, -0.44)	-0.59 (-0.76, -0.41)	
Under construction	41 (2%)	8 (2%)	0.23 (0.12-0.43)	0.24 (0.13-0.51)	-0.80 (-1.04, -0.56)	-0.87 (-1.12, -0.61)	
Needs Minor repair	2101 (89%)	262 (49%)	0.16 (0.14-0.18)	0.18 (0.15-0.23)	-0.94 (-1.03, -0.84)	-1.00 (-1.11, -0.90)	
Toilet type							0.1%
Bush/none	699 (30%)	302 (56%)	1.00 ^c	1.00 ^c	0.00 ^c	0.00 ^c	
Traditional pit	1357 (57%)	180 (34%)	0.39 (0.33-0.46)	0.43 (0.36-0.52)	-0.28 (-0.35, -0.21)	-0.28 (-0.36, -0.20)	
Ventilated pit	185 (8%)	34 (6%)	0.51 (0.37-0.71)	0.64 (0.45-0.90)	-0.12 (-0.22, -0.11)	-0.04 (-0.16, -0.08)	
Flush	127 (5%)	19 (4%)	0.43 (0.28-0.67)	0.49 (0.28-0.84)	-0.19 (-0.32, -0.07)	-0.12 (-0.26, -0.02)	
Livestock owned^c							
None	1107 (47%)	250 (47%)	1.00	1.00	0.00	0.00	N/A

<5	463 (20%)	126 (24%)	1.13 (0.93-1.38)	1.07 (0.87-1.33)	0.02 (-0.06, 0.10)	0.01 (-0.08, 0.10)	
>5	798 (34%)	159 (30%)	0.89 (0.74-1.06)	0.90 (0.73-1.09)	-0.06 (-0.13, 0.00)	-0.07 (-0.15, 0.00)	
No of siblings	4 (3-6)	4 (3-6)	1.01 (0.98-1.05)	0.95 (0.91-0.99)	0.00 (-0.01, 0.01)	-0.02 (-0.04, 0.00)	N/A
Deceased father	67 (3%)	11 (3%)	1.08 (0.62-1.88)	1.39 (0.78-2.47)	-0.02 (-0.19, 0.16)	0.11 (-0.12, 0.34)	N/A

Significant associations are highlighted in bold. ^aAdjusted for child factors (age, sex, schooling and region of residence). ^bAdjusted for both child factors (age, sex, schooling, region of residence) and maternal factors (age, marital status, education level, economic/employment status, religion and ethnicity). ^cThe test for linear trend for the levels of the factor was statistically significant. ^dDerived from a multivariable structural equation model. NA=not done, usually if it did not meet the set statistical criteria. The variable “any seizure disorders” was based on questions from the seizure-screening questionnaire; “epilepsy” and “acute seizures” from both clinical examination at stage II, hospital records and multiple imputation; and “family history of seizures” from the parental risk factor questionnaire.

Medical comorbidities of behavioural/emotional problems

Any seizure disorder (as assessed by seizure screening questionnaire in stage I) occurred in 289/ 3273 (9%) of all children screened with the CBCL in the community, with seizures occurring in 89/420 (21%) of all children with a CBCL total score of ≥ 60 compared to only 200/2893 (7%) of those with CBCL scores < 60 ($p < 0.0001$). Similarly, seizures disorders were more frequent in those with externalising (59/338 (17%) vs. 230/2935 (8%), $p < 0.0001$) and internalising problems (129/728 (18%) vs. 160/2545 (6%), $p < 0.001$) compared to those without these problems. There was an increased prevalence of clinically confirmed acute seizures (acute seizures confirmed by clinical history in stage II and hospital records) (35/364 (10%) vs. 86/2733 (3%), $p < 0.0001$) and epilepsy (11/342 (3%) vs. 11/2663 ($< 1\%$), $p < 0.0001$) in those with total CBCL problems compared to those without, despite attrition between screening in stage I and clinical evaluation in stage II.

In stage II of the study, a total of 620/3273 (19%) preschool children attended the clinical history and neurological examinations. The commonest comorbidities were general/fine motor deficits (86/620 (14%)), burns (65/620 (10%)) and hypoesthesia (reduced sensation) (29/620 (11%)). Occurrence of other comorbidities is shown in table 5-9 below. In addition to seizure disorders above, few other comorbidities were significantly more frequent in those with behavioural/emotional problems compared to those without: burns for total problems (33/243 (14%) vs. 32/377 (8%), $p = 0.043$) and externalising problems (33/196 (17%) vs. 32/424 (2%), $p < 0.0001$); skin bruises and scars for total problems (12/243 (5%) vs. 8/377 (2%), $p = 0.053$) and respiratory problems for internalising problems (10/354 (3%) vs. 1/266 ($< 1\%$), $p = 0.023$). The frequency of other comorbidities between those with and without behavioural/emotional problems is shown in table 5-9 below.

Table 5-9. Medical and neurocognitive comorbidities of behavioural/emotional problems by age group among the 348 children randomly selected for clinical evaluation

Comorbidities	All children (620)	Total problems			Externalising problems			Internalising problems		
		No (N=377)	Yes (N=243)	p-value	No (N=424)	Yes (N=196)	p-value	No (N=266)	Yes (N=354)	p-value
Hypoesthesia ^a	29 (5%)	13 (3%)	16 (6%)	0.071	17 (4%)	12 (6%)	0.247	8 (3%)	21 (6%)	0.088
Abnormal limb function ^b	8 (1%)	3 (1%)	5 (2%)	0.174	4 (1%)	4 (2%)	0.260	2 (1%)	6 (2%)	0.303
Motor impairments ^c	86 (14%)	46 (12%)	40 (16%)	0.134	56 (13%)	30 (15%)	0.482	36 (14%)	50 (15%)	0.833
Intellectual disability	27 (4%)	12 (3%)	15 (6%)	0.075	15 (4%)	12 (6%)	0.143	8 (3%)	19 (5%)	0.154
Otitis & ear canal abnormalities	26 (4%)	18 (5%)	8 (3%)	0.418	22 (5%)	4 (2%)	0.084	12 (5%)	14 (4%)	0.840
Cardiovascular problems	4 (1%)	3 (1%)	1 (<1%)	1.000	4 (1%)	0 (0%)	0.313	1 (<1%)	3 (1%)	0.639
Respiratory problems	11 (2%)	6 (2%)	5 (2%)	0.759	6 (1%)	5 (3%)	0.337	1 (<1%)	10 (3%)	0.023
Malnutrition	19 (3%)	13 (3%)	6 (2%)	0.490	16 (4%)	3 (2%)	0.132	9 (4%)	10 (3%)	0.690
Skin scars/bruises	20 (3%)	8 (2%)	12 (5%)	0.053	11 (3%)	9 (5%)	0.191	7 (4%)	13 (4%)	0.468
Burn marks	65 (10%)	32 (8%)	33 (14%)	0.043	32 (8%)	33 (17%)	<0.0001	26 (10%)	39 (11%)	0.619

^aReduced sensation to touch or painful stimuli; ^bReduced or increased reflex activity; ^cBoth general and fine motor skills assessed

Discussion

This is the largest epidemiological study of behavioural/emotional problems in African preschool children and the findings show a substantial burden of mental health problems explained by multiple underlying risk factors. In particular, total CBCL problems occurred in 13% of preschool children while internalising problems were more frequent than externalising problems (22% vs. 10%). Behavioural/emotional problems were associated with multiple risk factors, particularly seizure disorders. Respiratory problems, burns and skin bruises were particularly common comorbidities of behavioural/emotional problems in preschool children. The CBCL was equally reliable when administered in Kiswahili or Giriama.

Prevalence of behavioural/emotional problems

The prevalence of total CBCL problems (13%) is comparable to that of other settings in low and middle income countries such as Turkey (11.9%) (Erol et al., 2005) and high income countries such as Germany (12.4%) (Furniss et al., 2006). The prevalence remained above 10% even after accounting for age and sex, suggesting behavioural/emotional problems are common in Kenyan preschool children. The prevalence was higher than in Romania (8.8%) (M. M. Gleason et al., 2011), and Norway (7.1%) (Wichstrom et al., 2012), and the differences may be explained by the high incidence of infectious and perinatal risk factors in the Kenyan rural population. The prevalence could be as high as in a Brazilian study (24%) (Anselmi et al., 2004), considering that some parents could have concealed their children's psychological status owing to stigma and that this is the first epidemiological study on mental health problems in this area. The prevalence was high in children aged 6 years, after which period behavioural/emotional problems may persist (Campbell, 1995).

Internalising problems were more prevalent than externalising problems (22% vs. 10%), a difference which is similar to other CBCL studies from New Zealand (18% vs. 7%) (Paterson et al., 2007) and Germany (5% vs. 1%) (M. M. Gleason et al., 2011). These differences are plausible since the CBCL has more questions and syndromes dedicated to internalising problems (T. Achenbach et al., 2003; T. Achenbach & Rescorla, 2000), which improves the sensitivity of detecting these problems. This is a strength of the CBCL, since internalising problems are less dramatic and visible, and thus are more likely to be under reported by parents compared to externalising problems as in a Taiwanese study by Wu et al (11% vs 25%) (Wu et al., 2012).

There was a heterogeneous prevalence of specific syndromes and DSM-oriented scales as found in other studies. Somatic problems were commonest in the CBCL syndromes, but this may be exaggerated by, or confused with, the episodes of febrile illnesses, which are common in this rural population (Bejon et al., 2014). The prevalence of ADH problems based on the DSM-oriented scale was 5%, which is similar to estimates from previous studies (5.3%) (Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007). Prevalence of ADH symptoms in Japanese children as rated by teachers was 4.3%, but parents in the same study disproportionately overestimated the problems (31%) (Soma, Nakamura, Oyama, Tsuchiya, & Yamamoto, 2009). Pervasive Developmental Problems (PDP) were reported in 5% of preschool children in our study, which is significantly higher than the epidemiological estimates from specific PDP assessment tools (~1%) (Fombonne, 2009). While these estimates may suggest an increased prevalence of PDP symptoms such as autism in this rural population, the use of the CBCL to examine autism in preschool children must be viewed with caution, since the tool is not designed for this condition and adjustment of cut-off scores based on a clinical sample or supplementation with the teacher version of the CBCL will be required to improve specificity (So et al., 2013). Children screened with autism questions in

the CBCL should be followed up further with specific Autism Spectrum tools such as Modified Checklist for Autism in Toddlers and Social Communication Questionnaire (Snow & Lecavalier, 2008).

Disability-adjusted life years

Anxiety problems and ADH problems were associated with substantial DALYs, which were greater for the former than the latter. The computed DALYs represent the Years Lived with disability since premature mortality could not be measured within the cross-sectional design of this study. The DALYs for ADH problems (2.1-2.8 per 1000) are similar to the central sub-Saharan estimates by Erskine et al (~1-2 per 1000) (Erskine et al., 2014). Our study's estimates are significantly greater than those of GBD (~1 per 1000 for childhood behavioural/emotional problems), probably because (i) this study used a screening tool (CBCL) to estimate prevalence, and (ii) GBD extrapolated the Africa estimates based on studies from high-income countries which can underestimate. There is need to set up mental health services with adequate resources in African countries in order to reduce the significant burden of childhood behavioural/emotional problems.

Risk factors for behavioural/emotional problems

Seizure disorders

Seizure disorders, including epilepsy and acute seizures were important risk factors for behavioural/emotional problems, explaining almost all the variability in the risk of these problems in a multivariable structural equation model. This association was established in previous epidemiological and case-control studies of epilepsy (Symon M. Kariuki et al., 2012; Russ, Larson, & Halfon, 2012), and the poor outcomes were often attributed to the seizures, underlying neurological impairment, the anti-epileptic drugs or a shared genetic susceptibility (Dale C. Hesdorffer et al., 2012; Rodenburg, Stams, Meijer, Aldenkamp, &

Deković, 2005; Russ et al., 2012). Risk ratios for epilepsy were significantly greater than those for acute seizures, which would be expected since acute seizures resolve when the underlying aetiology is treated, while epilepsy is a chronic condition with serious health and psychosocial consequences (S. M. Kariuki, W. Matuja, et al., 2014).

Only a few studies in high-income countries have associated behavioural/emotional problems with febrile seizures (Kölfen et al., 1998; Wolf & Forsythe, 1978), but these studies are old. Acute seizures in our study could be symptomatic of an underlying central nervous system causes such as malaria (S. M. Kariuki et al., 2011), which can increase the risk of developing behavioural/emotional problems. Part of the explanation for the association between acute seizures and behavioural/emotional problems may be a common genetic susceptibility as supported by the significant association of behavioural/emotional problems with a family history of febrile seizures. Risk factors for behavioural/emotional comorbidity of acute seizures in Africa are not fully understood, but these are investigated and discussed in details in chapter 7 of this thesis.

Other risk factors

Other risk factors for behavioural/emotional problems explained little or no variability in a multivariable structural equation model with seizure disorders, perhaps because they moderate the association between seizures and behavioural/emotional problems. It is possible that the association of antenatal and perinatal problems with behavioural/emotional problems is moderated by seizures or underlying neurological impairment (Hille et al., 2001; van Handel, Swaab, de Vries, & Jongmans, 2010). The association of consumption of cassava and soil with behavioural/emotional problems are likely mediated through social disadvantage and neurological impairments including seizures, although both behaviours may be directly neurotoxic (Grandjean & Landrigan, 2014; Oluwole, Onabolu, Link, & Rosling,

2000). Additionally, soil consumption could be a marker of iron deficiency (Kettaneh et al., 2005) or a consequence of the behavioural/emotional problems.

History of hospitalisation with febrile illnesses and head injury were associated with behavioural/emotional problems, and could reflect that these problems are related to neurological insults including those from infections such as falciparum malaria (Newton, 2012). Pets are intermediate hosts for parasitic infections such as *Toxoplasma gondii*, which are associated with mental health problems in humans (Flegr, 2013). House status is an important marker of social disadvantage and inequalities in health care access which can moderate other risk factors for behavioural/emotional problems discussed above.

Comorbidities of behavioural/emotional problems

Comorbidities were common in behavioural/emotional problems, but only few showed significant differences when compared with those without these problems. Seizure disorders including epilepsy and acute seizures were particularly common in behavioural/emotional problems occurring in about 20% of children, and were important risk factors for development of behavioural/emotional problems, as discussed above (Russ et al., 2012).

Respiratory problems were more frequent in those with internalising problems, and a similar association was reported in 19% of older Brazilian children with behavioural/emotional problems (Feitosa et al., 2011). Since respiratory problems such as asthma are common in preschool children (Haby, Peat, Marks, Woolcock, & Leeder, 2001), their treatment should be included in the mental health care for children. Skin problems and burns were associated with behavioural/emotional problems, similar to preschool children in other settings (De Young, Kenardy, Cobham, & Kimble, 2012). Children with externalising problems are often restless increasing the risk of injuries including burns (Schwebel et al., 2011). Common

comorbidities of behavioural/emotional problems should be assessed and addressed in preschool children.

Strengths and limitations

This study is based on a large randomly selected community sample that is adequately powered to estimate prevalence and identify underlying risk factors. The assessment was performed using the CBCL which is an internationally recognised tool that was formally adapted and validated in the local population. The study estimates both prevalence and DALYs, thereby providing a reliable measure of true burden of behavioural/problems in this area that could guide planning of mental health services. Risk factors for behavioural/emotional problems were identified with robust statistical techniques that utilised continuous scores and empirical cut- offs, resulting in reliable effect estimates.

The study is not without limitations. This is a cross sectional study, in which the causal inference of associations is difficult without prospective longitudinal studies. We did not assess the maternal mental health status which may influence behavioural/emotional outcomes of children, although we adjusted for other maternal-related factors.

Conclusions

There is substantial burden of behavioural/emotional problems in Kenyan preschool children. These problems are as common as in high-income countries, but further studies are required in other settings in Africa. There are multiple risk factors, with the most important ones being perinatal complications and seizure disorders. Most of the risk factors can be addressed using simple public health interventions such as creation of awareness about prevention and treatment of seizures. Respiratory problems, skin bruises, and burns are important comorbidities of behavioural/emotional problems and should be assessed and addressed. There is need to set up future studies to: (i) understand the role of genetic and maternal

mental health status in the risk of developing behavioural/emotional problems in preschool children; and (ii) evaluate effective parent-family interventions for addressing these mental health problems.

Chapter 6: Acute seizures study

Prevalence, risk factors, proximate causes and clinical features of acute seizures in

Kenyan preschool children: a population-based study

Background

Acute seizures are often provoked by events such as febrile infections, metabolic disorders, toxins or brain insults (Beghi et al., 2010); and comprise febrile seizures and acute symptomatic seizures (Baram & Shinnar, 2002; S. M. Kariuki et al., 2011). Febrile seizures are the most common seizure disorders in preschool children and they occur in 2-8% of the children aged between 6 months and 6 years in the general population (Baram & Shinnar, 2002). They are considered benign, but are associated with risk for epilepsy and behavioural/emotional problems in some studies (Kölfen et al., 1998). Acute symptomatic seizures, by definition, occur in close temporal association with CNS insults such as toxins or CNS infections (Beghi et al., 2010); and the prognosis is thought to be poorer than for febrile seizures. Since it is difficult to differentiate between acute symptomatic and febrile seizures in Africa, it is proposed that seizures with fever in sub-Saharan Africa be referred to as acute seizures (R. Idro et al., 2008), (S. M. Kariuki et al., 2011).

There are few epidemiological studies of acute (febrile) seizures in low and middle income countries (LMIC) particularly those of sub-Saharan Africa, where febrile illnesses are common. Most of the estimates of acute seizures in Africa are based on hospital studies, which provides unreliable estimates considering only a proportion of Africans visit hospitals due to cultural reasons (S. M. Kariuki et al., 2015a). Nevertheless, hospital incidence of acute seizures in Kenyan children aged 0-13 years is between 425 and 650 per 100,000/year (R. Idro et al., 2008; S. M. Kariuki et al., 2011), which is higher than similar studies in the West (J. F. Annegers et al., 1995). Epidemiological studies are required to provide accurate measurements of the burden of these seizures in the community. A recent community-based study in Tanzania (Storz et al., 2015) estimated the prevalence of febrile seizures at 2.1%, but the denominator population could have been inaccurate since it was not from a demographic surveillance system. Additionally, the study did not identify risk factors. Another

Togolese study estimated febrile seizures at 8.4% (Assogba, Balaka, Touglo, Apetse, & Kombate, 2015), but this estimate was based on a hospital sample which may be biased towards severe morbidity, and some febrile seizures may have been acute symptomatic seizures since malaria was a cause in 52%. Clearly, large epidemiological studies in Africa are required to provide reliable estimates and identify risk factors for planning preventative and therapeutic interventions.

Febrile seizures are classified into simple and complex phenotypes, with the later occurring in about 30% of children with febrile seizures (Baram & Shinnar, 2002). Simple phenotypes comprise generalised tonic-clonic seizures that are short i.e. lasts <15 minutes. Complex phenotypes are febrile seizures that are focal (involves one body part), repetitive (>1 seizure in one illness or 24 hours) and prolonged (lasts $\geq$ 15 minutes including status epilepticus) (Beghi et al., 2010). These phenotypes are clinically important in that they are associated with poorer psychiatric outcome, epilepsy and mortality (Baram & Shinnar, 2002). The proportion of complex seizures in Kenyan studies is >60% (S. M. Kariuki et al., 2013; Waruiru et al., 1996), probably since some of these seizures are acute symptomatic seizures. The onset of acute (febrile) seizures in studies throughout the world including in Africa, occur in the second year of life (R. Idro et al., 2008). In Africa these complex phenotypes and age at onset of seizures are based on hospital studies, but it is not clear what happens in the community.

Recognised risk factors for febrile seizures include history of developmental delay, family history of seizures and day care especially during the neonatal period (Baram & Shinnar, 2002). Important infectious causes include respiratory illnesses due to either viral, bacterial or parasitic infections; vaccinations; and low levels of iron/zinc (Mittal, 2014). Viral infections such as parainfluenza are more important in febrile seizures in Asian countries (Millichap & Millichap, 2006), while malaria is important in seizures in sub-Saharan Africa (S. M. Kariuki et al., 2011). There is little data on the underlying risk factors for acute (febrile) seizures in sub-Saharan Africa, where studies have focused mostly on infectious causes of these seizures.

It is unclear what determines poor outcome in acute (febrile) seizures. It may be related to the seizures themselves, or a shared underlying genetic susceptibility or a common neurological impairment. In a

German study, 20% of children with febrile seizures had behavioural/emotional problems, compared to 2% of controls (Kölfe et al., 1998). In The Netherlands, neurocognitive impairments were more common in febrile seizures, specifically language impairments. Epilepsy may occur in up to 15% of children with febrile seizures (Chungath & Shorvon, 2008), but the causal pathway remains controversial since most studies are retrospective. Behavioural/emotional outcomes are worse with complex phenotypes of febrile seizures (Baram & Shinnar, 2002; Kölfe et al., 1998).

Behavioural/emotional problems and cognitive impairments were common in Kenyan children hospitalised with acute seizures from malaria (J. A. Carter, Mung'ala-Odera, et al., 2005), but it was unclear if these poor outcomes were due to the seizures or the malaria illness. Population-based studies are therefore required in sub-Saharan Africa to clarify the association of acute seizures with behavioural/emotional and medical comorbidities.

I conducted a community survey on preschool children living on the Kenyan coast to estimate the prevalence of acute seizures, identify the associated risk factors and causes, and characterise the clinical features of these seizures. I further measured the associations between acute seizures and other behavioural/emotional and medical comorbidities.

Materials and methods

Sampling

This study involved screening children aged 1-6 years from within the KHDSS for acute seizures and behavioural/emotional problems in stage I as discussed in detail in chapter 3. Those positive for seizures in the first stage were invited for further clinical, neurological and anthropometrical evaluation to make the diagnosis of acute seizures; after excluding unprovoked and non-epileptic seizures in the second stage (stage II). I had estimated that screening 7,500 children randomly selected from a population of 50,000 children aged 1-6 years would detect acute seizures with a precision of 1% assuming a prevalence of acute seizures of 5% in the community.

A parental risk factor questionnaire with items on socio-demographic, socioeconomic and medical history information was administered to all those with acute seizures and to a predetermined sample of those without seizures, who served as controls. Assuming a prevalence of 10% of risk factors (for example family history of febrile seizures in the population), I estimated that at least 250 children with acute seizures and 250 without seizures would be sufficient to identify an odds/risk ratio of 2 with 80% power at 5% significant level.

Procedures

Seizures were screened in stage I by trained fieldworkers using a 7-question questionnaire which was piloted before the study (appendices). The questions were based upon previous screening questionnaires for epilepsy studies (T. Edwards et al., 2008), but were modified to capture seizures with fever occurring in the childhood period. The modified questionnaire was piloted on 50 children who had been admitted to hospital with seizures in the past one year and on a similar number admitted without seizures during the same period. It was found to detect previous admission with acute seizures with a sensitivity of 96% (95%CI, 94-99%) and a specificity of 98% (95%CI, 96-100%). Additional seizure details on onset, duration, localisation and family history were obtained in stage I just in case some of those screening positive failed to turn up for clinical evaluation in stage II (referred to as “attrition” subsequently), when most of the seizure information was to be obtained by a clinician.

Based on the sample size calculation for the behavioural/emotional survey (chapters 3 and 5), about 3,500 of the children screened for seizures in stage I were also assessed for behavioural/emotional problems using the Child Behaviour Checklist (CBCL), which had been adapted and validated for use in this rural population (discussed in detail in chapter 4) (S. M. Kariuki et al., 2016). To help determine risk factors associated with acute seizures in the community, about half of the children screened also received a parental questionnaire of risk factors which included questions about family background and historical aspects of the child and mother. Specifically the information in this risk factor questionnaire included: (i) maternal and child prenatal/perinatal history such as pregnancy and birth events, immunization and breastfeeding status; (ii) socioeconomic status information such as housing, parental education/economic activity and lifestyle; (iii) medical history information such as

history of seizure disorders/other chronic illnesses, use of bednet and hospital services and (4) child habits such as eating soil and snoring at night, both which may be associated with delayed neurodevelopment.

Clinical/neurological evaluation and anthropometric assessments

Children with a history of seizures and a proportion of those without seizures were seen by a clinician in stage II for further clinical evaluation. Assuming a prevalence of 30% of comorbidities in acute seizures and 10% in those without seizures, we estimated that about 100 children with acute seizures and an equal number of those without seizures were sufficient to differentiate occurrence of comorbidities with an odds ratio of 2 with 80% power at 5% significance level.

The clinician, who was blinded to seizures status in stage I, asked questions on the history of seizure disorders and determined whether the seizures were acute seizures or established epilepsy. The clinician obtained further information on onset of seizures, seizure type/frequency and duration. Acute seizures were defined as seizures occurring with a febrile illness or associated with a recorded fever ($>38.5^{\circ}\text{C}$). Epilepsy was defined as a history of two unprovoked seizures with those having one of the seizures in the past one year considered to have active epilepsy (ILAE, 1989). A clinician assessed cognitive impairments by observing how children performed on a number of items in a standardised developmental inventory (Abubakar et al., 2008) or by asking older children (aged > 36 months) standardised questions about the child's awareness of person, place, and time. As explained above, behavioural/emotional problems were assessed in stage I using the CBCL.

Neurological examination was performed on all children invited for further review. This involved assessment of mental status, reflex activity, cranial nerve function, sensation, ear-nose-throat integrity and skin integrity.

Causes of acute seizures were identified by asking the parent about the febrile illness that was associated with the seizures, and the surrounding circumstance (Table 6-1). This followed the WHO algorithms for Integrated Management of Child Infections (IMCI) (WHO, 1995), which is followed by primary health care workers from resource limited countries to identify, grade and treat common

childhood illnesses such as malaria, diarrhoea and pneumonia. The IMCI algorithms for falciparum malaria were piloted in Kilifi among children admitted with malaria and correctly identified majority of these children for treatment (Mwangi et al., 2005). The community data on acute seizures were linked with hospital admissions to identify additional causes of acute seizures.

Anthropometric measures of the child were also taken and included head circumference, mid-upper arm circumference, height and weight. Malnutrition was defined as a weight for age (WAZ) or height for age (HAZ) z-score value of ≤ -2 .

Table 6-1: Identification and classification of febrile and non-febrile causes of children with acute seizures based on the WHO's Integrated Management of Childhood Infections (IMCI)

Febrile Illness/cause	Description
Malaria	Any fever without running nose, since Kilifi is a high risk area
Very severe febrile disease e.g. meningitis	Fever with stiff neck and crying a lot or irritability
Upper respiratory tract infection (RTI)	Fever with running nose and a mild cough
Lower RTI (pneumonia)	Fever with severe cough, fast breathing ($>40/\text{min}$) and chest indrawing
Diarrhoea e.g. gastroenteritis	Fever or no fever with 3 or 4 loose stools in 24 hours, lethargy or not able to feed properly
Ear infections	Fever with ear discharge, ear pain and/or swelling behind ear
Measles	History of fever and eye discharge and/or mouth ulcers with or without respiratory and ear infections or diarrhoea or rash
Undetermined cause	Neither of the above

NB: For infants: history of presence of a bulging of fontanelle and a red umbilicus draining pus may suggest febrile illness e.g. bacterial infections

Characterisation of acute seizures

Acute seizures were febrile seizures if they were not associated with a diagnosis of malaria, meningitis or encephalopathy as identified with IMCI guidelines or hospital admissions,

while the remainder were presumed to be acute symptomatic seizures. I classified convulsive seizures into either focal or generalised, with focal seizures being those that involved one body part, and generalised seizures those involving the entire body (ILAE, 1989). Seizures were considered prolonged if they lasted 15 minutes or more, including convulsive status epilepticus (Trinka et al., 2015). Repetitive seizures were 2 or more seizures in the same illnesses or within 24 hours (ILAE, 1989). Complex acute seizures were defined as those acute seizures that were either focal, prolonged or repetitive.

Statistical analysis

All analyses were performed using STATA (version 13, Stata Corp, Texas, USA). Pearson's Chi square compared discrete variables between groups, while student's t-test or Mann-Whitney U test compared continuous variables such as age and behavioural scores between groups, while providing positive effect sizes of the comparison using Cohen's *d* statistics (Sullivan & Feinn, 2012).

Prevalence of acute seizures was computed as a probability (where those with acute seizures are treated as "positive" and those without acute seizures as "negative") by exponentiation of coefficients in the constant term of a logit model using the formula: ($probability = \frac{\exp(coefficient)}{1+\exp(coefficient)}$). Prevalence was obtained by multiplying the probability by 100.

The overall prevalence was adjusted for age and sex at the logit model level before exponentiation of the coefficients. Prevalence estimates stratified by age group and sex were also computed. Prevalence was also accounted for attrition between stage I and II, using multiple imputation by chained equations (Azur, Stuart, Frangakis, & Leaf, 2011), implemented in STATA by constructing a model with age, and seizure variables obtained in stage I. The attrition between stage I and II was expected since acute seizures are viewed as relatively benign in this community and are not treated at hospital (Serem et al., 2015). The

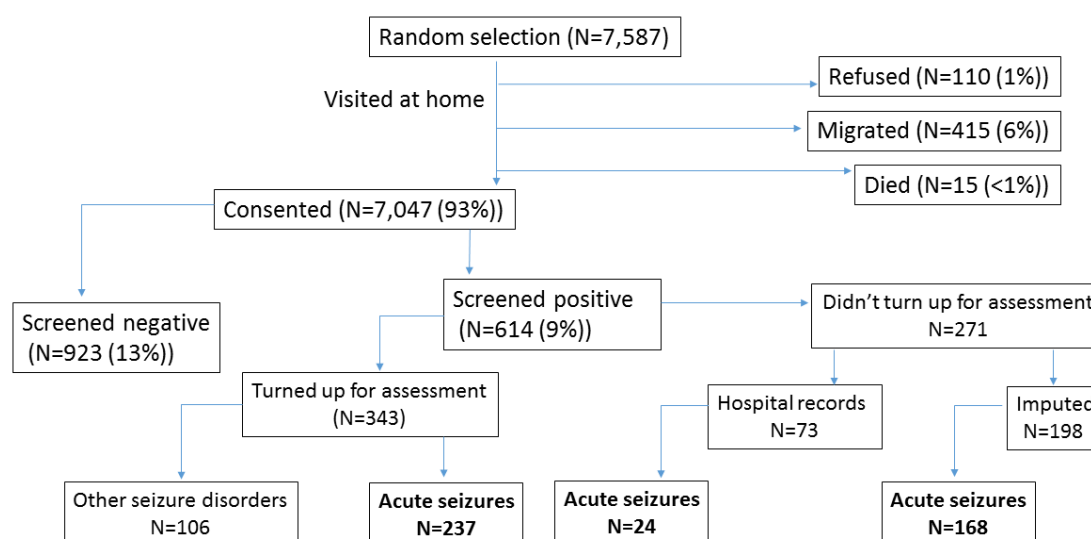
95% confidence intervals (95%CI) around the prevalence are based on the Binomial distribution.

Risk factors associated with acute seizures were determined using logistic regression model applied in a univariable and multivariable analysis. Logistic regression model obtains odds ratios (OR) which closely approximates risk ratios when the outcome is relatively rare (<10%) (Diaz-Quijano, 2012), otherwise for very common conditions odds ratios may overestimate the relative risk of the condition (Zou, 2004). Variables reaching a p-value ≤ 0.25 were entered into a multivariable logistic regression model; if two variables showed evidence for multi-collinearity, one of the two was randomly selected for inclusion into the model. Age was entered into the model as fractional polynomial. Hosmer-Lemeshow test was used to test the goodness-of-fit of the multivariable logistic regression model (Paul, Pennell, & Lemeshow, 2013). Population-attributable fractions (PAF) for modifiable risk factor investigated in the multivariable model were computed, with the assumption that the risk factor was completely eliminated or the living conditions were absolutely perfect. However, the computed PAF add up to >1 in scenarios where some individuals with more than one risk factor can have conditions prevented in more than one way, and the prevented cases of these individuals could be counted more than once (Rowe, Powell, & Flanders, 2004). Frequencies of comorbidities were compared between: (i) those with acute seizures and those without seizures; and (ii) those with complex seizures and those with simple seizures, while providing ORs adjusted for child's age and sex in a logistic regression model. Factors associated with hospitalisation of acute seizures were identified using a logistic regression model adjusted for child's age and sex. I further tested if statistically significant associations of comorbidities with complex seizures were greater than with simple seizures by computing ratios of the corresponding odds ratios (ROR) (Altman & Bland, 2003). Confidence intervals for the ROR were calculated on the log scale followed by exponentiation using the formula (log

$ROR \pm 1.96 * \log SE(d)$), where $SE(d)$ is the square root of the sum of the squares of the logarithm of separate standard errors of the two associations i.e. $(\log SE_1^2 + \log SE_2^2)^{0.5}$ (Altman & Bland, 2003). A p-value of 0.05 or less was considered significant while ROR value of >1.0 signified a greater association.

Results

A history of seizures was screened in 7047/7587 (93%) children visited in the community who had been randomly selected from the KHDSS database (Figure 6-1). The median age of the 7047 children screened was 46 months (inter-quartile range 30-62), while 51% were males (Table 6-1). Sociodemographic, socioeconomic and medical characteristics for the children according are shown in table 6-2.

Figure 6-1. The flowchart for the acute seizures study during the stage I & II.**Table 6-2. Socio-demographic and medical characteristics of study participants**

Characteristics	Younger children (4539)	Older children (2508)	Total (N=7047)	p-value
Child's age in years: median (IQR)	25 (19-31)	57 (47-68)	46 (30-62)	<0.0001
Male	2315 (51%)	1279 (51%)	3594 (51%)	0.996
Mother's age in years: median (IQR)	28 (23-34)	30 (25-36)	29 (25-35)	<0.0001
Administered a risk factor questionnaire				
	N=1122	N=2085	N=3207	
Socio-demographic information				
Mother's marital status				0.089
Single	57 (5%)	95 (5%)	152 (5%)	
Separated/divorced	62 (6%)	139 (7%)	201 (6%)	
Widowed	13 (1%)	46 (2%)	59 (2%)	
Married	990 (88%)	1805 (87%)	2795 (87%)	
Mother's religion				0.631
None	266 (24%)	532 (26%)	798 (25%)	
Traditional	64 (6%)	108 (5%)	172 (5%)	
Islam	133 (9%)	254 (12%)	387 (12%)	
Christian	659 (59%)	1191 (57%)	1850 (58%)	
Mother's education level				0.515
None	326/1120 (34%)	631/2080 (30%)	957/3200 (35%)	
Primary	707/1120 (63%)	1288/2080 (62%)	1995/3200 (62%)	
Secondary	67/1120 (6%)	135/2080 (6%)	202/3200 (6%)	
Tertiary	20/1120 (2%)	26/2080 (2%)	46/3200 (2%)	
Mother's ethnicity				0.049
None-Mijikenda	51 (5%)	115 (6%)	166 (5%)	

Other Mijikenda	77 (7%)	117 (6%)	194 (6%)	
Kauma	121 (11%)	190 (9%)	311 (10%)	
Chonyi	303 (27%)	643 (31%)	946 (30%)	
Girama	570 (51%)	1018 (49%)	1588 (50%)	
Economic activity: mother	761/1121 (68%)	1515/2080 (73%)	2276/3201 (71%)	0.003
Economic activity: father	958/1031 (93%)	1786/1937 (92%)	2744/2968 (92%)	0.483
Number of children: median (IQR)	4 (2-6)	5 (3-6)	4 (3-6)	<0.0001
Socioeconomic status and household information				
Water availability				0.494
Infrequent	205 (18%)	419 (20%)	624 (19%)	
Weekly	138 (12%)	242 (12%)	380 (12%)	
Daily	231 (21%)	447 (21%)	678 (21%)	
Always	548 (49%)	977 (47%)	1525 (48%)	
House status				
Dilapidated	76 (7%)	107 (5%)	183 (6%)	0.294
Major repairs needed	105 (9%)	195 (9%)	300 (9%)	
Incompletely build	29 (3%)	58 (3%)	87 (3%)	
Minor/no repairs needed	912 (81%)	1723 (83%)	2635 (82%)	
Toilet type				0.212
Bush/none	309/1121 (28%)	585/2082 (28%)	894/3203 (28%)	
Traditional pit	651/1121 (58%)	1161/2082 (56%)	1812/3203 (57%)	
Ventilated pit	105/1121 (9%)	195/2082 (9%)	300/3203 (9%)	
Flush	71 (5%)	75 (5%)	146 (5%)	
Livestock owned				0.210
None	507 (45%)	1004 (48%)	1511 (47%)	
<5	242 (22%)	406 (19%)	648 (20%)	
>5	373 (33%)	675 (32%)	1048 (33%)	
Pregnancy and birth history				
Pregnancy problems	88/1121 (8%)	140/2083 (8%)	228/3204 (7%)	0.236
Caffeine/smoking/alcohol in pregnancy	11/161 (7%)	26/335 (8%)	37/496 (7%)	0.712
Mother's age at birth	18 (17-20)	18 (17-20)	18 (17-20)	0.023
Delivery at home	646 (58%)	1332 (64%)	1978 (62%)	<0.0001
Premature birth	109/162 (67%)	214/334 (64%)	323/496 (65%)	0.481
Adverse perinatal events	42/1121 (4%)	48/2082 (2%)	90/3203 (2%)	0.019
Medical history				
Family history of seizures	127 (11%)	254 (12%)	381 (12%)	0.066
Family history of febrile seizures	102 (9%)	218 (10%)	320 (10%)	0.217
Previous hospitalisation	103/1119 (10%)	288/2076 (14%)	391/3195 (12%)	<0.0001
Head injury	12/1122 (1%)	54/2083 (3%)	66/3205 (4%)	0.004
Dogs and cats in compound	506/1075 (47%)	913/1983 (46%)	1419/3058 (46%)	0.586
Eats cassava	832 (74%)	1673 (80%)	2505 (75%)	<0.0001
Eats soil	211 (19%)	167 (8%)	378 (12%)	<0.0001
Bednet use	975 (87%)	1769 (85%)	2744 (86%)	0.122
Snores at night	253 (23%)	477 (23%)	730 (23%)	0.837

Deceased father	34/1051 (3%)	65/1967 (3%)	99/3018 (3%)	0.919
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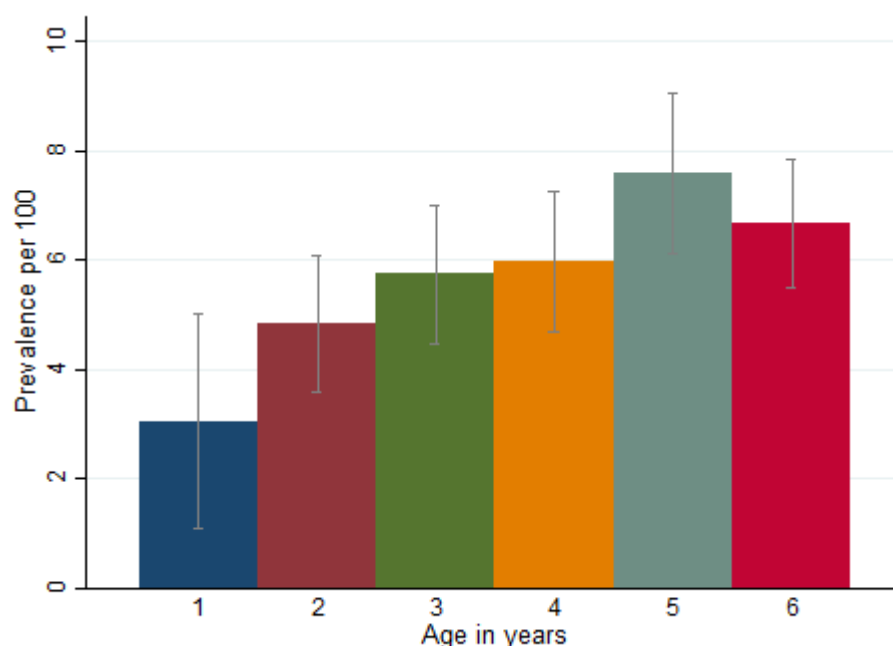
Younger children are those aged 36 months and below, while those >36 are older children. The risk factors questionnaire was administered to 3207 (46%) of the 7047 children screened, and included all acute seizures. IQR=interquartile range.

Overall prevalence of acute seizures

Of the 7047 children screened, 614 (9%) had a history of seizures in stage I, and were invited for further clinical evaluation in stage II. A clinician evaluated over half of these children with seizures in stage II (N=343 (56%)), of whom 261 were diagnosed with acute seizures (237 from clinical history in stage II and 24 from hospital records), an unadjusted prevalence of 3.7 (95%CI, 3.3-4.2) per 100 population of the children screened in stage I. The unadjusted prevalence was 4.0 per 100 (95%CI, 3.4-4.7) for males compared to 3.1 per 100 (2.8-4.1) for females, but the difference was not statistically significant ($X^2=2.20$, $p=0.138$). The total number of acute seizures after accounting for attrition (between stage I and II) was 409 (261 from clinical history or hospital records, and 168 from multiple imputation of seizure variables obtained in stage I), which is an overall prevalence of 6.1 per 100 (95%CI, 5.5-6.8). The lowest prevalence of acute seizures was 3.8 per 100 (95%CI, 2.9-5.1) after further adjusting the attrition-accounted prevalence for age and sex. Prevalence of acute seizures appeared to increase with age of the child (Figure 6-2).

Prevalence of febrile seizures and acute symptomatic seizures

Of the 261 acute seizures confirmed by a clinician, 126 (48%) met the definition for probable febrile seizures, while the remainder were acute symptomatic seizures. This translates to a prevalence of 2.9 per 100 (95%CI, 2.6-3.3) for febrile seizures and 3.2 (95%CI, 2.9-3.5) for acute symptomatic seizures after accounting for attrition.

Figure 6-2. Prevalence of acute seizures in preschool children by age group

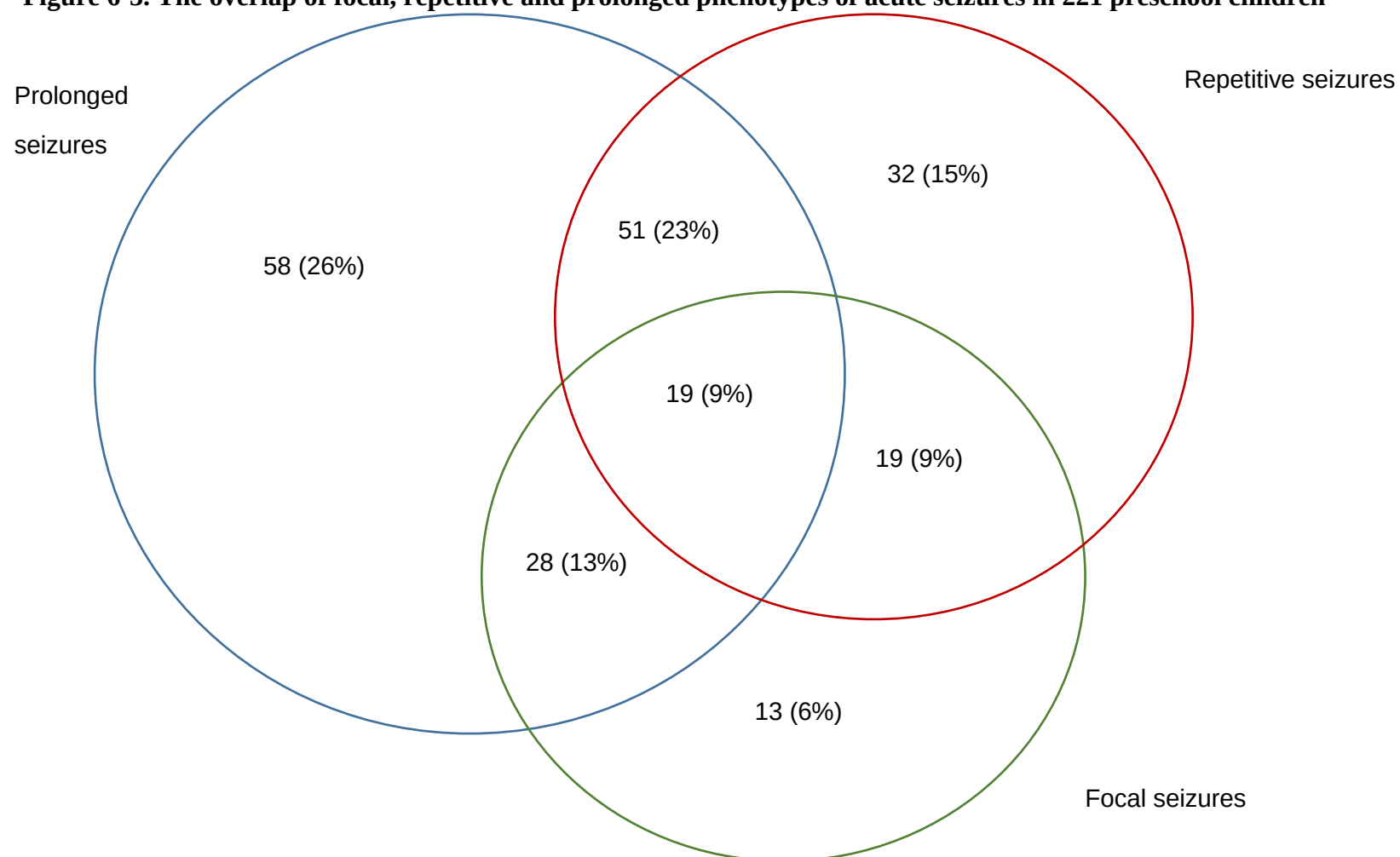
Clinical features of acute seizures

The median age of onset of all acute seizures was 13 months (IQR, 6-25), being earlier for acute symptomatic seizures (11 months (IQR, 6-24)) than for febrile seizures (13 months (IQR, 6-32)). Most of the seizures occurred during both the day and at night (135/261 (52%)), while few occurred either just at night (4/261 (2%)) or just during the day (2/261 (<1%)); period of occurrence could not be established for the remainder. The number of all acute seizures experienced ranged from 1-10, and were similar for acute symptomatic seizures and febrile seizures ($p=0.839$). Most children experienced one seizure type, specifically generalised tonic-clonic seizures (221/261 (85%)), few had multiple seizure types (17/261 (7%)), while seizure type could not be established in the remainder.

Of the 261 children diagnosed with acute seizures by a clinician, complex acute seizures occurred in 240/261 (84%) of all seizures, in 114/135 (84%) of acute symptomatic seizures and in 106/126 (84%) of febrile seizures. Prolonged acute seizures were the most common

complex acute seizure (156/220 (71%)), followed by repetitive acute seizures (121/220 (55%)) and focal acute seizures (79/220 (36%)). The frequency of specific phenotypes of complex acute seizures is shown in figure 6-3, and there was significant overlap between the phenotypes. Acute seizures were co-diagnosed with epilepsy in 30/261 (11%), with the acute seizures almost always preceding the unprovoked seizures. The co-diagnosis of epilepsy was similar between acute symptomatic seizures and febrile seizures (18/135 (13%) vs. 12/126 (10%); $p=0.335$).

Figure 6-3. The overlap of focal, repetitive and prolonged phenotypes of acute seizures in 221 preschool children



Causes of acute seizures

Among the causes of acute seizures, falciparum malaria was the most important cause of acute seizures (112/261 (43%)), followed by respiratory tract infections (68/261 (26%)), gastroenteritis (18/261 (7%)) and meningitis (3/261 (1%)). Other causes are shown in table 6-3. The causes were not statistically different between complex and simple seizures.

Table 6-3. Causes of acute seizures by phenotype in preschool children

Diagnosis	Focal phenotype (N=79)	Repetitive phenotype (N=121)	Prolonged phenotype (N=156)	All Complex phenotype (N=221)	All Simple seizures (N=40)	All acute seizures (N=261)	P-value*
Malaria	35 (44%)	56 (46%)	68 (44%)	96 (43%)	16 (40%)	112 (43%)	0.686
Respiratory tract infections	19 (24%)	32 (26%)	43 (28%)	57 (26%)	11 (28%)	68 (26%)	0.821
Gastroenteritis/diarrhoea	3 (4%)	10 (8%)	11 (7%)	17 (8%)	1 (3%)	18 (7%)	0.324
Meningitis	1 (1%)	3 (2%)	2 (1%)	3 (1%)	0 (0%)	3 (1%)	1
Measles	0 (0%)	1 (1%)	0 (0%)	1 (<1%)	0 (0%)	1 (<1%)	1

*Pearson's Chi-square comparison of the causes between the complex phenotypes versus simple phenotypes. The causes are not mutually exclusive. Fishers exact was used to compared infrequent observations (<5 in a cell)

Risk factors for acute seizures

Several risk factors were associated with acute seizures in the univariable analysis (table 6-4).

In the multivariable analysis, the most important risk factors were family history of febrile seizures (OR)=3.19 (95%CI, 2.03-5.01)), previous hospitalisation (OR=6.65 (95%CI, 4.60-9.63)), snoring at night (OR=1.60 (95%CI, 1.10-2.32)), use of bednets (OR=1.97 (1.03-3.75)), consumption of cassava (OR=5.15 (95%CI, 2.28-11.63)) and pets (dogs or cats) in the compound (OR=1.65 (1.14-2.37)). Maternal employment was associated with reduced risk for acute seizures (OR=0.64 (95%CI, 0.44-0.92)). Other risk factors in the multivariable analysis are shown in table 6-4.

The population-attributable fractions (PAF) associated with these risk factors in the multivariable analysis were variable, and were largest in the most frequent risk factors in the community. The highest PAF was observed for consumption of cassava (0.69 (95%CI, 0.41-0.84)), followed by bednet use (0.37 (95%CI, 0.00-0.60)). Other PAFs for other risk factors are shown in table 6-4.

Table 6-4. Univariable and multivariable results for the factors associated with acute seizures for all children

Factor	Univariable analysis				Multivariable analysis		
	No seizures (N=2907)	Acute seizures (N=245)	Odds ratio (95%CI)	p-value	Odds ratio (95%CI)	p-value	PAF (95%CI)
Child's age in months: median(IQR)	46 (30-62)	50 (34-67)	1.01 (0.99-1.01)	0.054	1.00 (0.99-1.01)	0.446	-
Child's sex	1452 (50)	141 (55%)	1.17 (0.90-1.52)	0.239	1.02 (0.72-1.45)	0.901	-
Maternal age	30 (25-35)	27 (24-33)	0.99 (0.98-1.02)	0.734	-	-	-
Mother's marital status							2% (0-7%)
Single	142 (5%)	8 (3%)	1.00		1.00		
Separated/divorced	178 (6%)	18 (7%)	1.79 (0.76-4.25)	0.183	2.25 (0.76-6.61)	0.142	
Widowed	51 (2%)	8 (3%)	2.75 (0.99-7.80)	0.052	2.57 (0.68-9.82)	0.162	
Married	2536 (87%)	211 (86%)	1.48 (0.71-3.05)	0.292	1.45 (0.59-3.58)	0.442	
Mother's religion							NA
None	714 (25%)	70 (29%)	1.00		1.00		
Traditional	167 (6%)	2 (1%)	0.12 (0.03-0.50)	0.004	0.09 (0.01-0.81)	0.031	
Islam	346 (12%)	30 (12%)	0.88 (0.57-1.38)	0.590	1.13 (0.61-2.07)	0.704	
Christian	1680 (58%)	148 (58%)	0.87 (0.64-1.17)	0.354	1.10 (0.73-1.65)	0.661	
Mother's education level							
None	867/2904 (30%)	76/241 (32%)	1.00		-	-	-
Primary	1812/2904 (62%)	147/241 (61%)	0.93 (0.69-1.23)	0.599	-	-	-
Secondary	183/2904 (6%)	15/241 (6%)	0.94 (0.53-1.66)	0.819	-	-	-
Tertiary	42/2904 (1%)	3/241 (1%)	0.81 (0.25-2.69)	0.7371	-	-	-
Mother's ethnicity							

None-mijikenda	149 (5%)	13/243 (5%)	1.00 ^b		-	-	-
Other mijikenda	173 (6%)	16/243 (7%)	1.06 (0.49-2.28)	0.881	-	-	-
Kauma	273 (9%)	34/243 (14%)	1.43 (0.73-2.79)	0.298	-	-	-
Chonyi	847 (29%)	81/243 (33%)	1.10 (0.60-2.01)	0.769	-	-	-
Giriama	1465 (50%)	99/243 (41%)	0.77 (0.42-1.41)	0.406	-	-	-
Economic activity: mother	2086/2902 (72%)	149/244 (61%)	0.61 (0.47-0.80)	<0.0001	0.64 (0.44-0.92)	0.016	11% (1-20%)
Economic activity: father	2487/2687 (93%)	209/228 (92%)	0.88 (0.54-1.45)	0.625	-	-	-
Number of children: median (IQR)	4 (3-6)	3 (2-6)	1.02 (0.97-1.07)	0.458	-	-	-
Water availability							36% (2-59%)
Infrequent	594 (20%)	21 (9%)	1.00 ^b		1.00		
Weekly	318 (11%)	61 (25%)	5.43 (3.24-9.07)	<0.0001	2.42 (1.19-4.94)	0.016	
Daily	643 (22%)	21 (9%)	0.92 (0.50-1.71)	0.801	1.20 (0.56-2.56)	0.642	
Always	1352 (47%)	142 (58%)	2.97 (1.85-4.75)	<0.001	2.09 (1.11-3.92)	0.022	
House status							13% (4-22%)
Dilapidated	136/2906 (5%)	41/244 (17%)	1.00 ^b		1.00		
Major repairs needed	245/2906 (8%)	53/244 (22%)	0.72 (0.45-1.13)	0.156	0.95 (0.48-1.87)	0.879	
Incompletely build	77/2906 (3%)	7/244 (3%)	0.30 (0.13-0.70)	0.006	0.39 (0.12-1.11)	0.075	
Minor/no repairs needed	2448/2906 (84%)	143/244 (57%)	0.19 (0.13-29)	<0.0001	0.46 (0.26-0.83)	0.009	
Toilet type							0% (0-18%)

Bush/none	819/2906 (28%)	64/244 (26%)	1.00^b		1.00		
Traditional pit	1647/2906 (57%)	130/244 (54%)	1.01 (0.74-1.38)	0.950	0.89 (0.59-1.33)	0.564	
Ventilated pit	272/2906 (9%)	25/244 (10%)	1.18 (0.73-1.90)	0.509	0.98 (0.50-1.91)	0.954	
Flush	168/2906 (6%)	24/244 (10%)	1.83 (1.11-3.01)	0.017	1.25 (0.64-2.45)	0.516	
Livestock owned							
None	1364 (47%)	116 (47%)	1.00				-
<5	595 (20%)	44 (18%)	0.87 (0.61-1.25)	0.447	-	-	-
>5	948 (33%)	85 (35%)	1.05 (0.79-1.41)	0.722	-	-	-
Pregnancy and birth history							
Pregnancy problems	189 (7%)	35/242 (15%)	2.43 (1.65-3.58)	<0.0001	1.34 (0.78-2.28)	0.286	
Mother's age at birth	18 (17-20)	18 (17-20)	1.00 (0.96-1.03)	0.784	-	-	-
Delivery at home	1793/2906 (62%)	151 (62%)	1.00 (0.76-1.31)	0.983	-	-	-
Adverse perinatal events	73/2906 (3%)	13/242 (5%)	2.20 (1.20-4.04)	0.011	0.74 (0.33-1.68)	0.477	0% (0-0%)
Medical history							
Family history of seizures	277 (10%)	97% (40%)	6.28 (4.66-8.45)	<0.0001	2.52 (1.64-3.88)	<0.0001	17% (9-24%)
Family history of febrile seizures	223/2906 (8%)	84 (34%)	6.22 (4.68-8.27)	<0.0001	3.19 (2.03-5.01)	<0.0001	17% (8-25%)
Previous hospitalisation	265/2903 (9%)	111/237 (47%)	8.77 (6.60-11.65)	<0.0001	6.65 (4.60-9.63)	<0.0001	NA
Head injury	54/2905 (2%)	10 (4%)	2.25 (1.13-4.47)	0.021	0.91 (0.36-2.25)	0.883	0.00 (0-2%)
Dogs and cats in compound	1264/2823 (45%)	125/185 (68%)	2.57 (1.87-3.53)	<0.0001	1.65 (1.14-2.37)	0.008	20% (0-33%)

Eats cassava	2225 (77%)	234 (96%)	6.52 (3.54-12.01)	<0.0001	5.15 (2.28-11.63)	<0.0001	69% (41-84%)
Eats soil	327 (11%)	40/244 (16%)	1.55 (1.08-2.21)	0.017	1.25 (0.78-2.00)	0.360	3% (0-9%)
Bednet use	2472 (85%)	227 (93%)	2.35 (1.42-3.89)	0.001	1.97 (1.03-3.75)	0.040	37% (0-60%)
Snores at night	612/2906 (21%)	101/244 (41%)	2.65 (2.02-3.47)	<0.0001	1.60 (1.10-2.32)	0.013	11% (2-20%)
Deceased father	90/2734 (3%)	9/234 (4%)	1.17 (0.58-2.36)	0.651	-	-	-

^aIncludes univariate risk factors with a p-value ≤ 0.25 in a logistic regression model with child's age and sex. ^bStatistically significant linear trend for the categories. Cells marked with dash (-) represents the variables which did not qualify for the multivariable analysis. PAF=population-attributable fraction; CI=confidence interval. PAF should not be summed up as some cases can be eliminated through control of many risk factors, which interact, and some cases could be counted more than twice when computing PAF. Negative point PAF were rounded to zero. Approximately 16/261 (6%) children with clinically confirmed acute seizures did not receive the risk factor questionnaire and were excluded from the risk factor analysis. Approximately 55 children with a risk factor questionnaire (but without acute seizures) had other seizures disorders e.g. epilepsy and hence were excluded from the comparison group in the risk factor analysis.

Comorbidities of acute seizures

Behavioural/emotional problems were the most common comorbidity of acute seizures, occurring in 28% of all acute seizures, 28% of complex acute seizures and 28% of simple acute seizures (table 6-5). Behavioural/emotional problems were similar in those with acute symptomatic seizures and febrile seizures (21/69 (30%) vs. 15/59 (25%); $p=0.530$). The mean CBCL behavioural/emotional scores were significantly higher in those with acute seizures than those without seizures (43.3 (standard deviation (SD)=26.8) vs. 32.9 (SD=22.3), $p<0.0001$), and the effect sizes were moderate (Cohens $d=-0.46$ (95%CI, -0.64 to -0.329)). The second most common comorbidity were motor deficits (16% for all acute seizures, 17% for complex acute seizures and 12% for simple acute seizures), followed by burns (12% for all acute seizures, 10% complex acute seizures and 21% for simple acute seizures) (Table 6-5). Other comorbidities were relatively infrequent (Table 6-5).

In logistic regression models, acute seizures were significantly associated with behavioural/emotional problems (adjusted OR=2.92 (95%CI, 1.96-4.37)) and motor deficits (adjusted OR=1.70 (95%CI, 1.08-2.67)) after accounting for child's age and sex. Complex acute seizures were significantly associated with behavioural/emotional problems (adjusted OR=2.94 (95%CI, 1.91-4.52)), peer-relationship problems (adjusted OR=2.66 (95%CI, 1.03-6.87)), and motor deficits (adjusted OR=2.02 (95%CI, 1.00-4.07)) after accounting for age and sex. Simple seizures were weakly associated with behavioural/emotional problems (adjusted OR=2.84 (95%CI, 1.01-8.05)) and burns (adjusted OR=2.45 (95%CI, 1.02-5.86)), after accounting for child's age and sex. Other comorbidities are shown in table 6-5.

Since behavioural/emotional problems were associated with both complex and simple acute seizures, in order to examine whether the associations were similar (i.e. not significantly different from each other) the ratio of the two odds ratios i.e. ROR was run. The ROR value

was 1.03, with the 95%CI being 0.61-1.70. The lower CI for the ROR included 1.0, which is the null hypothesis that the associations are similar.

Table 6-5. Medical and neurocognitive comorbidities of acute seizures by in preschool children examined by a clinician

Feature/comorbidity	No seizures	Acute seizures	Odds ratios (95% CI) ^a	Simple seizures	Odds ratios (95% CI) ^b	Complex seizures	Odds ratio ^c
Behavioural problems ^d	357/3041 (12%)	36/128 (28%)	2.92 (1.96-4.37)	5/18 (28%)	2.84 (1.01-8.05)	31/110 (28%)	2.94 (1.91-4.52)
Peer-relationship problems	7/254 (3%)	13/227 (6%)	2.20 (0.86-5.64)	0 (0%)	-	13/193 (7%)	2.66 (1.03-6.87)
Intellectual disability	22/645 (3%)	15/220 (7%)	1.85 (0.93-3.66)	1/33 (3%)	0.91 (0.12-7.05)	14/187 (7%)	2.02 (1.00-4.07)
Malnutrition	15/656 (2%)	5/222 (2%)	1.02 (0.37-2.86)	1/32 (3%)	0.80 (0.08-7.61)	4/190 (2%)	0.94 (0.31-2.90)
Developmental delay	13/256 (5%)	19/235 (8%)	1.65 (0.80-3.46)	2/36 (6%)	1.38 (0.18-10.78)	17/199 (9%)	1.78 (0.84-3.79)
Respiratory problems	11/667 (2%)	5/236 (2%)	1.33 (0.45-3.89)	1/34 (3%)	1.79 (0.22-14.37)	4/202 (2%)	1.25 (0.39-3.99)
Cardiovascular problems	5/667 (1%)	0 (0%)	-	0 (0%)	-	0 (0%)	-
Burns	65/668 (10%)	28/236 (12%)	1.26 (0.79-2.03)	7/34 (21%)	2.45 (1.02-5.86)	21/202 (10%)	1.08 (0.64-1.83)
Skin bruises	24/669 (4%)	9/237 (4%)	1.06 (0.48-2.32)	0 (0%)	-	9/203 (4%)	1.24 (0.57-2.74)
Motor deficits	86/668 (13%)	38/234 (16%)	1.70 (1.08-2.67)	4/34 (12%)	0.95 (0.29-3.11)	34/200 (17%)	1.93 (1.19-3.11)
Abnormal reflexes	10/667 (2%)	4/234 (2%)	1.09 (0.34-3.55)	1/34 (3%)	2.02 (0.25-16.33)	3/200 (2%)	0.94 (0.26-3.49)
Hypoesthesia	30/586 (5%)	8/161 (5%)	0.93 (0.42-2.09)	1/21 (5%)	0.92 (0.12-7.20)	7/140 (5%)	0.94 (0.40-2.19)

Comorbidities were identified through clinical evaluation. ^aComparison between all acute seizures and those without seizures. ^bComparison of the comorbidities between simple and no seizures. Statistically significant associations are highlighted in bold. ^cComparison between complex seizures and no seizures. ^dBehavioural/emotional problems were assessed in over 3,000 children as part of a larger study. All odds ratios are adjusted for child's age and sex. CI=confidence intervals. The comparisons are based on a maximum of 237/261 (91%) cases of acute seizures that were confirmed by a clinician through clinical history/examination, but that the denominator for some questions varied because of missing data.

Hospital use and acute seizures

Of the 261 children with clinically confirmed acute seizures, 81 (31%) reported having been treated at hospital for their seizures, while 44 (17%) sought treatment from a traditional healer. Half of those with a history of treated acute seizures (40/81 (49%)) sought treatment at KCH, while the remainder sought treatment elsewhere. Of the 180 children who did not report seeking treatment for their seizures, 37 (21%) had sought treatment at KCH for non-seizure related medical problems, bringing the total admissions/hospitalisations (both from KCH database and self-reported hospitalisation) of the acute seizures to 118/261 (45%).

Factors significantly associated with hospitalisation among children with acute seizures were employment for the mother (adjusted OR=1.81 (95%CI, 1.05-3.12)), non-traditional religion for the mother (adjusted OR=2.44 (95%CI, 1.33-4.49)), history of pregnancy problems (adjusted OR=2.37 (95%CI, 1.11-5.05)), motor deficits (adjusted OR=2.18 (95%CI, 1.01-4.69)) and co-diagnosis of epilepsy (adjusted OR=2.36 (95%CI, 1.06-5.25)). As expected, children of parents who visited traditional healers were least likely to be hospitalised for seizures (adjusted OR=0.50 (95%CI, 0.26-0.96)). Frequency distribution of factors in those hospitalised and those not hospitalised are shown in table 6-6.

Table 6-6. Factors associated with hospitalisation among children with acute seizures in the community

Characteristic	Not hospitalised (N=143)	Hospitalised (N=118)	Adjusted odds ratio (95% CI)*
Socioeconomic factors			
Maternal economic activity	78/142 (55%)	71/102 (70%)	1.81 (1.05-3.12)
Paternal economic activity	117/130 (90%)	92/98 (94%)	1.76 (0.64-4.85)
Maternal age: median (IQR)	28 (23-35)	29 (25-37)	1.03 (0.99-1.07)
Educated mother	103/141 (73%)	62/100 (62%)	0.61 (0.35-1.07)
Non-traditional religion	92/142 (65%)	83/103 (81%)	2.44 (1.33-4.49)
Medical history			
Pregnancy problems	15/140 (11%)	20/102 (20%)	2.37 (1.11-5.05)
Child delivered at home	84/142 (59%)	67/103 (65%)	1.23 (0.72-2.11)
Perinatal complications	7/141 (5%)	6/101 (6%)	1.27 (0.40-4.02)
Visits traditional healers	38/139 (27%)	17/112 (15%)	0.50 (0.26-0.96)
Previous hospitalisation	23/136 (17%)	88/101 (87%)	32.51 (15.52-68.11)
Head injury	4/142 (3%)	20/102 (20%)	2.10 (0.57-7.81)
Seizure factors			
Family history of seizures	52/142 (37%)	45/103 (44%)	1.28 (0.76-2.18)
Age of onset of seizures	13 (5-34)	15 (6-23)	0.98 (0.94-1.02)
Prolonged seizures	83/143 (58%)	73/118 (62%)	1.26 (0.76-2.11)
Repetitive seizures	62/143 (43%)	59/118 (50%)	1.25 (0.72-2.11)
Focal seizures	45/143 (31%)	34/118 (29%)	0.88 (0.51-1.52)
All complex seizures	119/143 (83)	101/118 (86%)	1.20 (0.60-2.39)
Epilepsy	13/143 (9%)	17/95 (18%)	2.36 (1.06-5.25)
Medical examination status			
Behavioural problems	17/66 (26%)	19/62 (31%)	1.22 (0.56-2.66)
Cognitive impairment	9/133 (7%)	6/87 (7%)	0.86 (0.29-2.57)
Motor deficits	19/139 (14%)	19/95 (20%)	2.18 (1.01-4.69)
Malnutrition	4/133 (3%)	1/89 (1%)	0.48 (0.05-4.42)
Burn scars	15/140 (11%)	13/96 (14%)	1.28 (0.57-2.84)

The odds ratios are adjusted for child's age and sex; IQR=interquartile range; CI=confidence interval. Statistically significant associations are highlighted in bold.

Discussion

This epidemiological study provides prevalence estimates of acute seizures and their associated risk factors and clinical features using population data of preschool children from a demographic surveillance system on the Kenyan coast. The prevalence of acute seizures was high (6.1%), being 2.9% for febrile seizures and 3.2% for acute symptomatic seizures. The onset age for these seizures was 13 months (IQR, 6-25), being similar for febrile seizures and acute symptomatic seizures. About 85% had complex phenotypes (prolonged, repetitive and/or focal acute seizures). Most acute seizures were probably caused by falciparum malaria (43%), respiratory tract infections (26%) or gastroenteritis (7%). Several risk factors for acute seizures were identified, including family history of seizures, previous hospitalisation and snoring at night. The most important comorbidities of acute seizures were behavioural/emotional problems, learning disability and motor deficits, which showed particular association with complex acute seizures. Under half (45%) of acute seizures were admitted to hospital; with maternal employment, non-traditional beliefs, co-diagnosis of epilepsy, motor deficits and pregnancy complications being associated with hospitalisation.

Prevalence of acute seizures

The prevalence of acute seizures in this study was high (6.1%). The prevalence of febrile seizures (2.9%) was higher than for febrile seizures in Tanzania (2.1%) (Storz et al., 2015), England (2.3%), but lower than in America (3.9%) (Nelson & Ellenberg, 1978), Japan (8%) and Guan, Mariana Islands (>10%) (Stanhope et al., 1972). High estimates in Asian countries have not been documented elsewhere, and may be explained by easier recognition as Asian families live together or by genetic susceptibility (Baram & Shinnar, 2002). Since our study and Tanzanian study were conducted in similar rural settings including malaria-endemic areas, their low estimates are probably explained by challenges with case ascertainment probably related to conduct of their study within administrative boundaries rather than within

demographic surveillance systems. The lower prevalence of febrile seizures in our study compared to the American study is because acute symptomatic seizures were excluded from the definition of febrile seizures. It may also be related to under-reporting of febrile seizures by parents, owing to stigma associated with seizures in this area (Mbuba et al., 2012).

The high prevalence of acute seizures in our study even after adjusting for age and sex can be explained by the high incidence of infectious aetiologies in this area, especially falciparum malaria (Bejon et al., 2014) and possible genetic susceptibility (S. M. Kariuki et al., 2013).

The estimates are reliable since the screening tool has excellent sensitivity (96%) and specificity (98%) to detect acute seizures, and acute seizures were diagnosed by epilepsy clinicians during stage II of the study. These estimates are consistent with substantial burden of other neurological problems in children from this area (V. Mung'ala-Odera et al., 2006).

The prevalence estimates confirm a prior hypothesis that hospital incidence (R. Idro et al., 2008; Serem et al., 2015) grossly underestimates true prevalence of acute seizures by up to 90% (6.1% vs. 0.5%).

Clinical features of acute seizures

The onset for seizures was early (IQR=6-25 months), and is within the onset range of around 24 months for most febrile studies in the literature (C. Waruiru & R. Appleton, 2004). The relatively low range of onset in our study, compared to other studies, reflects the susceptible period for the infectious causes of acute seizures in this area, in particular falciparum malaria (R. Idro et al., 2008; Serem et al., 2015). Generalised tonic-clonic seizures were the single most common seizures type reported (85%), which is a widely recognised finding in most studies of febrile seizures (Sadleir & Scheffer, 2007). Complex acute seizures were very common, in similar occurrence with previous studies in the same area (S. M. Kariuki et al., 2013; Waruiru et al., 1996). However, the complex phenotypes of febrile seizures in our

study were significantly higher than in a Tanzanian study (42%) (Storz et al., 2015) and in studies from America and Europe (15-30%) (Shinnar & Glauser, 2002). The prolonged and repetitive acute seizures were particularly common in our study (71% and 55%), consistent with previous studies in the area (Crawley et al., 1996; Sadarangani et al., 2008). The complex acute seizures may be attributable to malaria (S. M. Kariuki et al., 2011) and underlying genetic susceptibility (Baram & Shinnar, 2002; S. M. Kariuki et al., 2013). Complex acute seizures increase the risk for neurodisabilities (J. A. Carter, Ross, et al., 2005; S. M. Kariuki, A. Abubakar, C. R. Newton, & M. Kihara, 2014) and thus should be managed appropriately.

Acute seizures preceded unprovoked seizures in 11% of children, which is similar to rates of 8% reported in high income countries (HIC) (Chungath & Shorvon, 2008). While acute seizures may predispose to unprovoked seizures, the underlying causes or shared genetic susceptibility may cause the two conditions (Baram & Shinnar, 2002). Both NIH and ILAE in their definition of febrile seizures (Freeman, 1980; ILAE, 1989), noted that underlying developmental delay may increase susceptibility to acute febrile seizures. Neurological impairments and developmental delay are usually not excluded from the definition of febrile seizures (Shinnar & Glauser, 2002).

Causes of acute seizures

We determined causes by linking our cases with clinical admissions in the past six years before the study. For children whose seizures were not treated at hospital, causes were determined using WHO's IMCI guidelines/algorithms since most acute seizures in the community are untreated (Serem et al., 2015), but some parents can recall signs and symptoms of the associated febrile illnesses (Mwangi et al., 2005). Malaria was the most common cause of acute seizures (43%), which is not surprising since this study was

conducted in an endemic area. Among parasitaemic children, >93% of seizures are attributable to malaria (S. M. Kariuki et al., 2011). The reported malaria rate is comparable to a recent hospital study (Serem et al., 2015)), despite the widely recognised previous decline in malaria (Okiro et al., 2007). Respiratory infections were important (26%), but it is not easy to distinguish if they were related to viral or bacterial aetiologies, both of which are common in this area (James A. Berkley et al., 2009). Parainfluenza and human herpes 6/7 are particularly important aetiologies (Millichap & Millichap, 2006), but these are identifiable only with an extensive battery of tests, which are unavailable in most low-income settings such as ours. Future studies are required to investigate role of iron/zinc, although iron was not associated with hospitalised acute seizures in a study in the same setting (R. Idro et al., 2010). Causes were not different between complex and simple seizures, which should be interpreted carefully because of significant overlap between individual phenotypes and possible poor recall of duration of seizures and underlying febrile illnesses by parents. Nonetheless, this study confirms that aetiologies of acute seizures are still prevalent in the community and should be addressed.

Risk factors of acute seizures

Family history of seizures, particularly febrile seizures were associated with a threefold risk for acute seizures. Like in febrile seizure studies from resource rich countries (Veisani et al., 2013) family history of febrile seizures was documented in up to 40% of children with acute seizures. Since the heritability for febrile seizures is high (70%) (Kjeldsen et al., 2002), our results suggest that acute seizures may be heritable in Kenyan children, supported by polymorphisms associations with acute seizures in the same population (S. M. Kariuki et al., 2013) and increased seizure disorders in relatives of children hospitalised with malaria (Versteeg, Carter, Dzombo, Neville, & Newton, 2003). However genetic studies of acute

seizures using community data are required in Kilifi since seizures are genetically complex with no single mode of inheritance.

Previous hospitalisation was an important risk factor for acute seizures, which could be a marker of admission with infections such as malaria which cause seizures (R. Idro et al., 2008; Serem et al., 2015). The moderate association between use of bednets and acute seizures is difficult to explain but there are two parsimonious explanations. The permethrin in insecticide treated bednets may have adverse neurodevelopmental effects according to animal studies (Nasuti et al., 2014), but human studies are required to establish this association.

Bednets are likely to be used in high malaria-transmission areas, where the risk for malarial seizures is also expected to be high. Snoring was also associated with acute seizures, and has previously been linked to behavioural problems in a study of American preschool children (Beebe, Rausch, Byars, Lanphear, & Yolton, 2012), suggesting snoring can impair neurodevelopment. The mechanisms underlying neurodevelopmental problems are not well understood, but it is thought that obstructive sleep apnoea can result in hypoxia that affects nervous circuitry (Rosenzweig, Williams, & Morrell, 2014).

Association between cassava consumption and acute seizures is an interesting finding especially as cassava consumption was also associated with behavioural/emotional problems in chapter 5 of this thesis. While cassava consumption may be a marker of poverty or social disadvantage, which is often associated with neuropsychiatric problems (Davis, Sawyer, Lo, Priest, & Wake, 2010), the socioeconomic variables were accounted for in the multivariable models, suggesting a possible neurotoxic role for cassava. Raw cassava contains linamarin, a cyanogenic glycogen which is thought to be neurotoxic (Rivadeneira-Dominguez, Vazquez-Luna, Rodriguez-Landa, & Diaz-Sobac, 2013). However these adverse effects can be avoided through the use of proper methods for processing cassava such as fermentation and drying (Oluwole et al., 2000).

Socio-economic factors, for example maternal employment and water availability, were associated with acute seizures. While maternal employment reduced the risk of acute seizures, paradoxically, water availability increased the risk. Through the ‘social causation’ hypothesis (Peterlin & Scher, 2013), employment may generally lead to improved nutrition and improved health accessibility, thus the reduced risk for seizures. The surprising association of water availability with seizures raises questions as to whether water reservoirs in Kilifi are contaminated with heavy metals that could be neurotoxic (Grandjean & Landrigan, 2014), which can be investigated in future studies. It is also possible that these socioeconomic factors moderates other risk factors discussed above (Kramer, 1987).

Comorbidities of acute seizures

All acute seizures were associated with behavioural/emotional problems and motor deficits; while complex acute seizures were associated with behavioural/emotional problems, peer-relationship problems and intellectual disability. Behavioural/emotional problems were reported in 22% of German children (Kölfen et al., 1998) and in 18% of American children (Nelson & Ellenberg, 1978), being significantly more frequent than in controls. Recent studies in Britain did not report increased behavioural/emotional problems in febrile seizures (Verity et al., 1998), although few such studies have been conducted recently.

Behavioural/emotional problems may be related to underlying neurological impairments and shared genetic susceptibility rather than from the febrile seizures as supported in part by the association between complex seizures and intellectual disability. Acute seizures may create anxiety in mothers, which affects their child’s behaviour (Stein et al., 2014). Complex acute seizures could explain some of these behavioural/emotional problems in our study given the association with peer relationship problems. However, the lower confidence intervals for the ROR of the behavioural associations with complex and simple seizures crossed below one, suggesting no significant difference for associations with combined complex acute seizures.

The lack of association between seizure factors and behavioural/emotional comorbidity is documented in some epilepsy studies (Reilly et al., 2014). Other risk factors for behavioural/emotional problems comorbidity of acute seizures, which have not been studied before in this area, are discussed in details in Chapter 7 of this thesis.

Motor deficits were important comorbidities of acute seizures, which could imply that seizures are a spectrum of neurodevelopment in young children (Gillberg, 2010). In preschool children, motor function is a reliable measure of psychomotor development, and is a vital component of most neuropsychological assessment tools for the young children (Abubakar et al., 2008; Tieman, Palisano, & Sutlive, 2005). Additionally, complex acute seizures in our study were associated with learning disability, and were more frequently reported than behavioural/emotional problems in children with complex febrile seizures in England (Visser et al., 2012), America (Nelson & Ellenberg, 1978) and in Japan (M. L. Tsai et al., 2015). These findings taken together suggests that neurological deficits should be identified and addressed in children with acute seizures.

Hospital use among children with acute seizures

Acute seizures were treated in hospital in 45% of children, while 17% visited traditional healers. Over two thirds of those hospitalised were traced in the admission records of KCH, where admissions are linked to a demographic surveillance database.

Acute seizures in children of employed mothers were more likely to be hospitalised probably because these parents can afford infrastructure and health costs. Non-traditional beliefs were associated with more admissions to hospital, consistent with fewer admissions in those who visit traditional healers. The severity of the acute seizures influenced hospitalisation, as supported by the association with motor deficits and history of epilepsy. Motor deficits but not seizures *per se* may also prompt parents to seek disability support from the hospital. As

expected, children with acute seizures were more likely to be admitted if they had been previously hospitalised suggesting easy accessibility and/or positive attitude towards biomedical treatment in this group. There is need to create awareness of the medical benefits of hospital services for children with acute seizures as these seizures may be associated with other medical comorbidities as discussed above.

Strengths and limitations

To our knowledge, this is the largest epidemiology study to provide reliable estimates of prevalence, risk factors and features of acute seizures within a demographic surveillance system in Africa. The two stage methodology ensured that acute seizures were diagnosed by a clinician, to avoid misdiagnosis due to confusion with unprovoked seizures and other non-epileptic psychogenic seizures. I attempted to define febrile seizures and acute symptomatic seizures, which may have different prognosis. The linked clinical and demographic surveillance data, helped identify causes of acute seizures, and confirm acute seizure status of some cases that did not turn up for clinical evaluation. Additionally, attrition was accounted for using a robust statistical approach, to avoid underestimation of the burden of acute seizures. The study not only provides the burden of acute seizures but also determines its associations with medical and behavioural/emotional comorbidities.

The observed attrition rate is explained by the parents' belief that acute (febrile) seizures have a favourable prognosis; which could prompt some parents not to turn up for clinical evaluation. However, we attempted to obtain additional seizure details in stage I for describing positive cases that failed to turn up for further clinical evaluation in stage II. It was difficult to conclusively identify causes of some acute seizures since the WHO's IMCI guidelines/algorithms for febrile illnesses may be subject to recall bias. This epidemiological study did not measure laboratory assessments of serum levels of iron which are thought to

explain pathogenesis of some acute seizures (R. Idro et al., 2010). Additionally, the genetic susceptibility to acute seizures was not investigated as it was not the focus for this study.

Conclusion

This epidemiological study provides reliable estimates of acute seizures, which are higher than in Europe and African countries even when febrile seizures alone are considered. These estimates can be used to guide planning of preventative and management interventions for acute seizures in Kenya and in similar settings in Africa, especially for the 30% of children at risk of behavioural/emotional and learning comorbidities. Most causes of acute seizures can be prevented including falciparum malaria, which is endemic in this area and caused just under half of the seizures. Family history of seizures was common in children with acute seizures (40%), and highlights the need to identify underlying genes using genetic trios or genome-wide association studies. The mechanisms underlying some risk factors such as cassava consumption and snoring remains largely unclear and further studies are justified. Behavioural/emotional problems were particularly common in acute seizures and should be studied further in this population including the associated risk factors. The low rates of hospital admission among children with acute seizures, calls for creation of awareness about the hospital treatment of these seizures since complex seizures or the underlying aetiology may complicate the prognosis.

Chapter 7: Behavioural/emotional comorbidity of acute seizures study

Behavioural/emotional comorbidity of acute seizures in Kenyan preschool children: a population-based study

Background

Acute seizures comprise febrile seizures and acute symptomatic seizures (Baram & Shinnar, 2002; S. M. Kariuki et al., 2011) and occur within the context of febrile illnesses, without neurological involvement for febrile seizures and with neurological involvement for acute symptomatic seizures (ILAE, 1989). Acute seizures may be associated with mental health problems, which may be linked to seizures or separate mechanisms (Jensen, 2011). Although febrile seizures are the commonest seizure disorder in childhood (occur in 2-8%), there are very few studies on behavioural/emotional outcomes in children with these seizures (Baram & Shinnar, 2002).

Febrile seizure in resource-rich countries have been found to be associated with behavioural/emotional problems, epilepsy and neurocognitive impairments, with the latter being most frequently reported (M. L. Tsai et al., 2015). Behavioural/emotional problems were reported in 22% of German children with febrile seizures compared to 6% of the controls (Kölfen et al., 1998). In the USA, behavioural/emotional problems developed in 18% of 120 children with febrile seizures, 11% of which were externalising problems (Wolf & Forsythe, 1978). During a meeting for the Danish Neurological Society in 1971 in Germany, Doctor Esther Franzten reported behavioural/emotional problems in 70/208 (34%) children with febrile seizures (Hein-Sorensen, 1971). Recent studies have reported impairments in intelligence (Dale C. Hesdorffer et al., 2012) and language (Visser et al., 2012), but not behavioural/emotional problems (Verity et al., 1998). It is possible that these behavioural/emotional comorbidities of febrile seizures are related to either the seizures, the

shared genetic susceptibility or underlying neurological impairment. Evidence for familial clustering of behavioural/emotional problems and epileptic seizures is documented in American children (Dale C. Hesdorffer et al., 2012). Complex febrile seizures are associated with poor outcomes, for example, behavioural/emotional problems were associated with repetitive febrile seizures in a Germany study (Kölfen et al., 1998). The risk for poor neurobehavioural outcomes after febrile seizures is increased fourfold in hospitalised children compared to those not hospitalised (Chungath & Shorvon, 2008). Use of prophylactic phenobarbital in febrile seizures increased behavioural/emotional problems two folds (48% vs. 18%) compared to febrile seizures without prophylaxis (Wolf & Forsythe, 1978).

In sub-Saharan Africa, a significantly greater proportion of acute seizures are complex seizures (60-70%) (S. M. Kariuki et al., 2013; Waruiru et al., 1996), which may increase the risk of behavioural/emotional problems in affected children. These acute seizures are either acute symptomatic seizures or febrile seizures, but the hospital incidence of febrile seizures is low (S. M. Kariuki et al., 2011). Acute symptomatic seizures with underlying illnesses such as malaria and meningitis, are associated with neurological damage which can add to the risk for poor behavioural/emotional and neurocognitive outcomes (J. A. Carter et al., 2004; J. A. Carter, Ross, et al., 2005; S. M. Kariuki, A. Abubakar, et al., 2014). It is unclear if the behavioural/emotional comorbidities of acute symptomatic seizures were due to the seizures, or the underlying malarial illness. Some of the genetic polymorphisms associated with the risk of acute seizures in Africa (S. M. Kariuki et al., 2013) may be also associated with behavioural/emotional problems. However, these Kenyan estimates are based on hospital data and should be interpreted carefully since can be biased towards severe disease. Community studies of behavioural/emotional comorbidities of acute seizures are required in African countries to understand the extent and spectrum of these behavioural/emotional problems.

I conducted a population-based study to understand the relationship between acute seizures and behavioural/emotional problems among preschool children residing in a rural area on the Kenyan coast. Factors associated with behavioural/emotional comorbidities of acute seizures were also investigated.

Methods and procedures

Sampling

This was a population based cross-sectional study, in which children were visited and screened for seizures and behavioural/emotional problems in the community (stage I), with a proportion of these children invited for further clinical evaluation at the Neuroassessment clinic affiliated with Kilifi County Hospital (stage II). Acute seizures and behavioural/emotional problems were assessed in 3,273 children as part of an epidemiological study to determine the burden and risk factors for behavioural/emotional problems, discussed in detail in chapters 5 and 6. It was estimated that this sample size would generate at least 100 cases of acute seizures, which if compared with at least an equal number of those without seizures could measure a prevalence ratio for behavioural/emotional problems of at least 2 with 80% power and at 5% significance level, assuming a frequency of 25% in those with acute seizures and 10% in those without seizures.

Assessment of behavioural/emotional problems

The preschool Child Behavioural Checklist (CBCL) was used to screen for behavioural/emotional problems as described in chapters 4 and 5. The CBCL was administered to all 3273 children of whom 13% had behavioural/emotional problems as reported in chapter 5. Behavioural/emotional were classified into externalising and internalising problems, the former occurring in 10% and the latter in 22% of the 3,273

children screened, as reported in chapter 5. Behavioural/emotional problems were also classified into seven CBCL syndromes namely emotionally-reactive, anxious-depressed, somatic complaints, withdrawn, attention problems and aggressive behaviour; the first four form the internalising scale and the last two the externalising scale, with sleep problems excluded from either scales. There were 5 diagnostic and statistical manual for mental disorders (DSM)-oriented scales to identify problems in: affective, anxiety, pervasive developmental problems (PDP), attention deficit hyperactivity (ADH) problems and oppositional defiant problems. Additional details on the CBCL syndromes and DSM-oriented scales are discussed in chapter 5.

Screening and definition of seizure disorders

Acute seizures were identified in a two stage process, with those screening positive in stage I invited for further clinical evaluation in stage II. In stage II the clinician made a diagnosis of acute seizures and epilepsy. Some of those who did not turn up in Stage II had the diagnosis of acute seizures or epilepsy confirmed from the Kilifi Health and Demographic Surveillance System database of hospital admissions during the last six years. Acute seizures were defined as seizures associated with fever or a febrile illness. Epilepsy was defined as history of two unprovoked seizures. Definitions for acute seizures and epilepsy followed the ILAE recommendations including those of ILAE commission on epidemiology (ILAE, 1989; Thurman et al., 2011).

In chapter 6, the prevalence of acute seizures was 3.8% before accounting for attrition between stages I and II, and 6.1% after accounting for attrition. Seizures were broadly classified into generalised (start at some point within bilaterally connected networks involving both cerebral hemispheres, so convulsive movements involves the entire body parts) and focal (begin within networks limited to one hemisphere and thus convulsive movements usually involve one body part) (Berg et al., 2010). Repetitive seizures were two or more seizures in the same illness or within 24 hours, whereas prolonged seizures were

those lasting 15 minutes or more. Complex seizures were defined as focal, repetitive and/or prolonged seizures. Other clinical features of acute seizures are described in details in chapter 6

Administration of the parental risk factor questionnaire

2903 (89%) of the 3273 children who completed the CBCL were interviewed with a parental risk factor questionnaire. The questionnaire had the following items: (i) parental sociodemographic information such as employment, schooling religion and ethnicity; (ii) antenatal and perinatal histories such as age at first birth and adverse perinatal events; (iii) socioeconomic status histories such as housing status, water availability, and livestock ownership; (iv) medical histories such as seizure disorders/other chronic illnesses, use of bednet and hospital services; and (v) child health and nutrition habits such as food types consumed, eating soil and snoring at night.

Paediatric medical examination

Of the 3273 children who completed the CBCL, 620 (19%) comprising those positive for acute seizures and/or behavioural problems and those without either condition also had a paediatric medical examination by a clinician (explained in detail in chapter 5). Paediatric examination involved the assessment of mental status, cranial nerve function, limb function, sensation, ear-nose-throat status and skin integrity. Learning disability was assessed by a clinician by observing young children perform a standardised test of a locally adapted developmental inventory (Abubakar et al., 2008) and/or asking older children standardised questions about their awareness of person, place, and time.

Statistical analysis

Data analysis was done using STATA (version 13, Stata Corp, TX). The Gaussian distribution of the CBCL scores and age were explored using formal tests of normality such

as skewness and kurtosis and by plotting histograms. For 5% of the children who completed the CBCL data, acute seizures and epilepsy status was part of the data imputed using multiple imputation chained equations described in chapter 6 (Azur et al., 2011). The association of acute seizures with behavioural/emotional problems was determined by fitting generalised linear models (GLM) of the binomial family and with a log link since acute seizures were a binary outcome. The risk ratios from the GLM models were initially adjusted for child's age and sex, and region of residence, and additionally for known non-seizure risk factors for behavioural/emotional problems namely antenatal problems, perinatal complications, maternal age, maternal employment, house status and head injury. In the adjusted GLM models, a relatively smaller Akaike Information Criteria (AIC) suggested a better goodness of fit of the model. Effect estimates for the association of behavioural/emotional problems with acute symptomatic seizures was hypothesised to be greater than that with febrile seizures in the same dataset, which was tested by computing ratios of the risk ratios (RRR). Confidence intervals for the RRR were calculated on the log scale followed by exponentiation using the formula $(\log \text{RRR} \pm 1.96 * \log \text{SE}(d))$, where $\text{SE}(d)$ is the square root of the sum of the squares of the logarithm of separate standard errors of the two associations i.e. $(\log \text{SE}_1^2 + \log \text{SE}_2^2)^{0.5}$ (Altman & Bland, 2003).

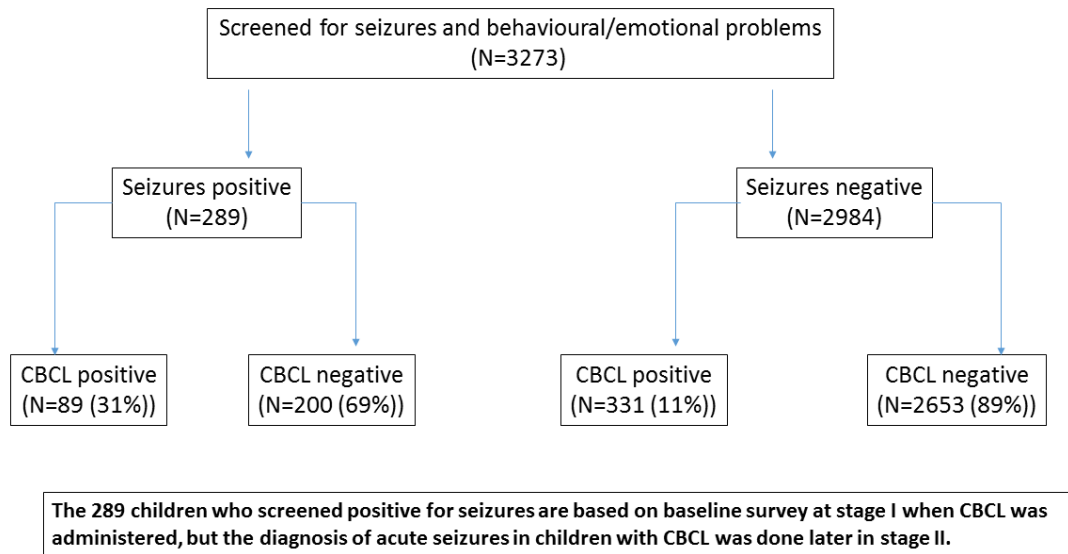
Using a two separate/different model techniques, the risk factors associated with behavioural/emotional comorbidity of acute seizures were identified using binomial regression with a log link function when the behavioural/emotional problems were a binary outcome variable or in a GLM model of the Gaussian family with an identity link function when continuous behavioural/emotional problems were the outcome variable. In the two GLM models, each one of the investigated risk factors was first adjusted for child factors specifically age, sex and region of residence. Risk factors reaching a cut-off p-value of ≤ 0.25 in the adjusted models were entered into a standard multivariable GLM model that also

included the child variables (age, sex and region of residence). MacFadden's pseudo R² was used to test the variance of behavioural/emotional comorbidity of acute seizures explained by risk factors significant in the standard multivariable model using the formula: $(1 - \frac{\ln L(Mic)}{\ln L(Mi)})$, where the numerator function represents the log likelihood from the GLM models with all the predictors *in situ*, while the denominator represents the log likelihood for the intercept only model. Linear trend of prevalence of behavioural/emotional problems across ordered age-groups in years was tested using GLM model that considered age-groups as continuous. Linear trend of continuous behavioural/emotional scores was tested with non-parametric test for trend in Stata (*nptrend*), which is an extension of Wilcoxon rank-sum test.

Results

General description

Both behavioural/emotional problems and seizures were assessed in 3,273 children (Figure 7-1), of whom 1671 (51%) were males while the median age was 48 (Interquartile range, 32-64) months. Most of these children resided in the south of the KHDSS than in the north, and sociodemographic, socioeconomic and medical history information of these children by area of residence are shown in table 5-2.

Figure 7-1. Flowchart of children screened for behaviour/emotional problems and seizures

Distribution of behavioural/emotional scores by acute seizure status.

The mean and median scores were significantly higher in those with acute seizures than those without acute seizures for total behavioural/emotional scores and for the six CBCL syndromes and five DSM-oriented scales (Table 7-1 and Figure 7-2). However, effect sizes were variable for comparisons between acute seizures and those without these seizures, and appeared greater for internalising problems (Cohens $d=0.44$ (95%CI, 0.29-0.58)) than for externalising problems (Cohens $d=0.38$ (95%CI, 0.24-0.52)). Among the six CBCL syndromes, effect sizes were greatest for somatic problems (Cohens $d=0.47$ (0.32-0.62)) and smallest for attention problems (Cohens $d=0.23$ (95%CI, 0.08-0.37)). Among the five DSM-oriented scales the effect sizes were greatest for affective problems (Cohens $d=0.43$ (95%CI, 0.28-0.57)) and lowest for pervasive developmental problems (Cohens $d=0.20$ (95%CI, 0.06-0.35)).

The median total behavioural/emotional scores for children with acute symptomatic seizures (37 (IQR, 23-63)) and febrile seizures (35 (IQR, 23-62)) were higher than for those without seizures (27 (IQR, 18-21)); $p<0.0001$ for both comparisons. The effect sizes for acute symptomatic seizures (Cohens $d=0.59$ (95%CI, 0.32-0.80)) were greater than those for febrile seizures (Cohens $d=0.35$ (95%CI, 0.10-0.61)).

Among the children with acute seizures, the median scores did not differ between males and females for total behavioural/emotional scores (39 (IQR, 23-64) vs. 32 (IQR, 19-61); $p=1496$) or internalising scores (11 (IQR, 6-21) vs. 10 (IQR, 6-18); $p=0.4454$), but differed for externalising scores (13 (IQR, 8-21) vs. 11 (IQR, 6-11); $p=0.0327$). The non-parametric test for trend across ordered age-groups showed that the median scores in those with acute seizures did not increase with age for total behavioural/emotional scores ($p=0.347$), externalising problems ($p=0.520$) and internalising problems ($p=0.872$) (Figure 7-3).

Table 7-1. Effect sizes and distribution of behavioural/emotional scores between those with and without acute seizures

Behavioural/emotional scores	Median scores (IQR)		p-value^a	Mean scores (SD)		p-value^b	Cohens <i>d</i> (95%CI)
	No acute seizures (N=3073)	Acute seizures (N=200)		No acute seizures (N=3073)	Acute seizures (N=200)		
Total	27 (18-41)	35 (22-62)	<0.0001	33.0 (22.5)	43.2 (27.1)	<0.0001	0.44 (0.30-0.59)
Internalising	8 (4-13)	11 (6-20)	<0.0001	10.0 (8.4)	13.8 (10.5)	<0.0001	0.44 (0.29-0.58)
Externalising	9 (5-14)	12 (6-19)	<0.0001	10.7 (7.7)	13.6 (8.9)	<0.0001	0.38 (0.24-0.52)
CBCL syndromes							
Emotionally-reactive	2 (1-3)	2 (1-5)	0.0094	2.3 (2.4)	3.0 (3.1)	0.0002	0.27 (0.13-0.41)
Anxious-depressed	2 (0-4)	3 (1-7)	<0.0001	2.8 (2.7)	4.1 (3.6)	<0.0001	0.43 (0.28-0.57)
Somatic problems	2 (1-4)	4 (2-6)	<0.0001	3.0 (2.6)	4.3 (3.5)	<0.0001	0.47 (0.32-0.62)
Withdrawn	1 (0-3)	2 (1-4)	0.0009	1.9 (2.1)	2.4 (2.4)	0.0010	0.24 (0.10-0.38)
Sleep problems	2 (1-3)	2 (1-4)	<0.0001	2.2 (2.2)	2.9 (2.5)	<0.0001	0.32 (0.17-0.46)
Attention problems	3 (2-5)	4 (2-5)	0.0023	3.4 (2.1)	3.8 (2.1)	0.0019	0.23 (0.08-0.37)
Aggressive behaviour	6 (3-10)	8 (4-15)	<0.0001	7.3 (6.5)	9.8 (7.5)	<0.0001	0.38 (0.24-0.52)
DSM-oriented scales							
Affective problems	1 (0-3)	2 (1-4)	<0.0001	1.9 (2.4)	3.0 (2.9)	<0.0001	0.43 (0.28-0.57)
Anxiety problems	4 (2-6)	5 (2-8)	0.0001	4.4 (3.5)	5.6 (4.0)	<0.0001	0.32 (0.18-0.47)
Pervasive developmental problems	2 (1-4)	3 (2-5)	0.0049	3.1 (2.9)	3.7 (3.3)	0.0054	0.20 (0.06-0.35)
Attention deficit/hyperactivity problems	5 (3-7)	6 (4-8)	0.0044	5.4 (2.9)	6.0 (3.0)	0.0031	0.22 (0.07-0.36)
Oppositional defiant problems	2 (0-3)	3 (1-4)	<0.0001	2.2 (2.3)	2.9 (2.4)	<0.0001	0.32 (0.18-0.46)

^aMann-Whitney U test comparison of median behavioural/emotional scores. ^bStudent t-test comparison of behavioural/emotional scores; CI=confidence interval; IQR=interquartile range; SD=standard deviation; DSM=diagnostic and statistical manual for mental disorders. Effect sizes were a function of mean scores and standard deviation.

Figure 7-2. Distribution of behavioural/emotional problem scores by acute seizure status

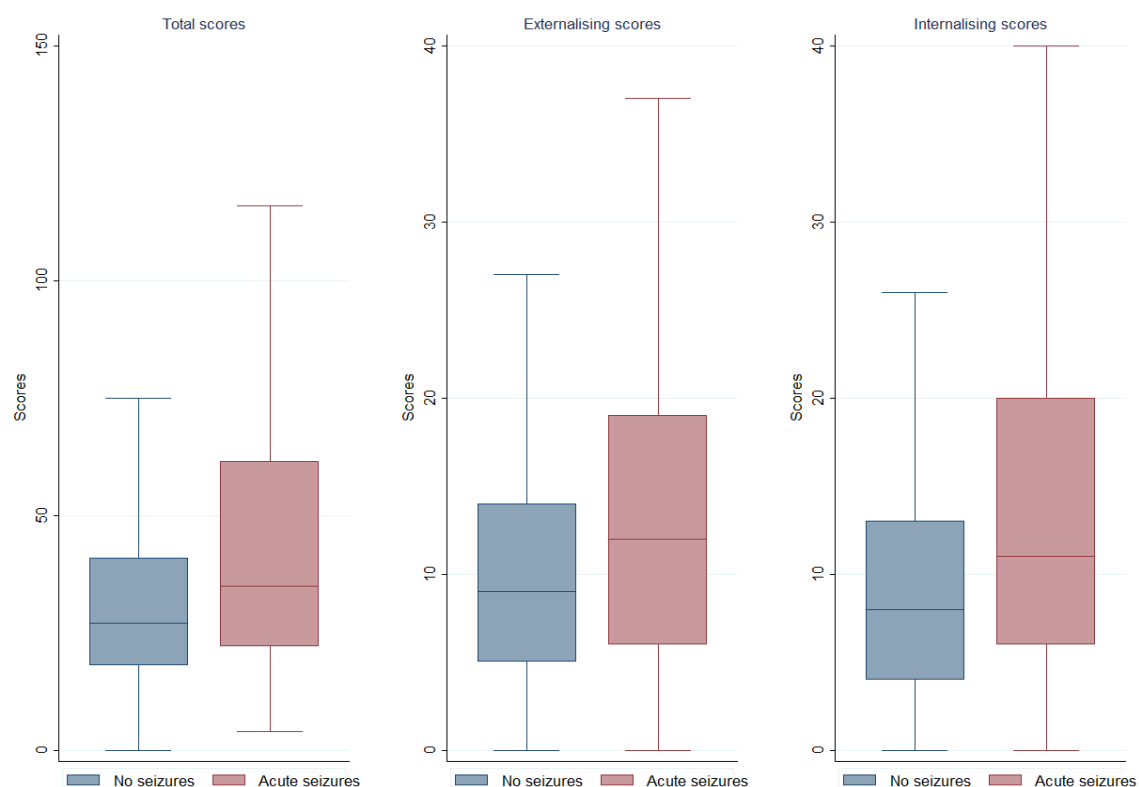
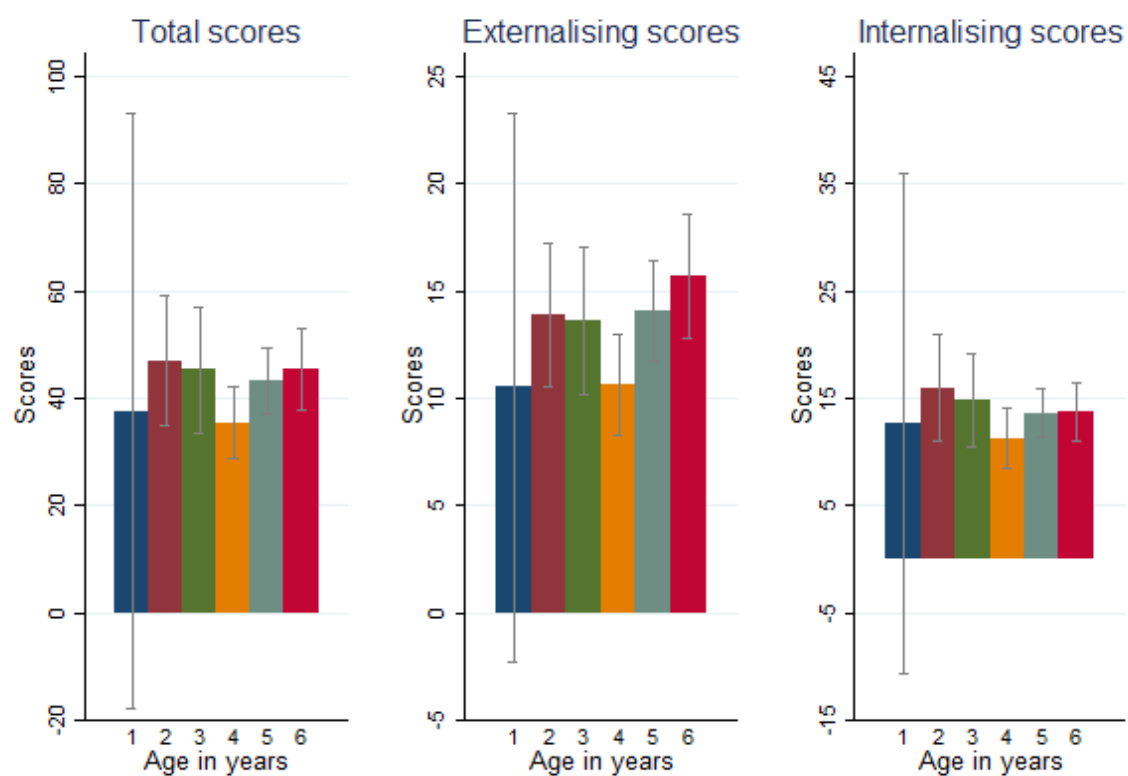


Figure 7-3. Distribution of CBCL scores by age in children with acute seizures



Prevalence of behavioural/emotional problems by acute seizure status

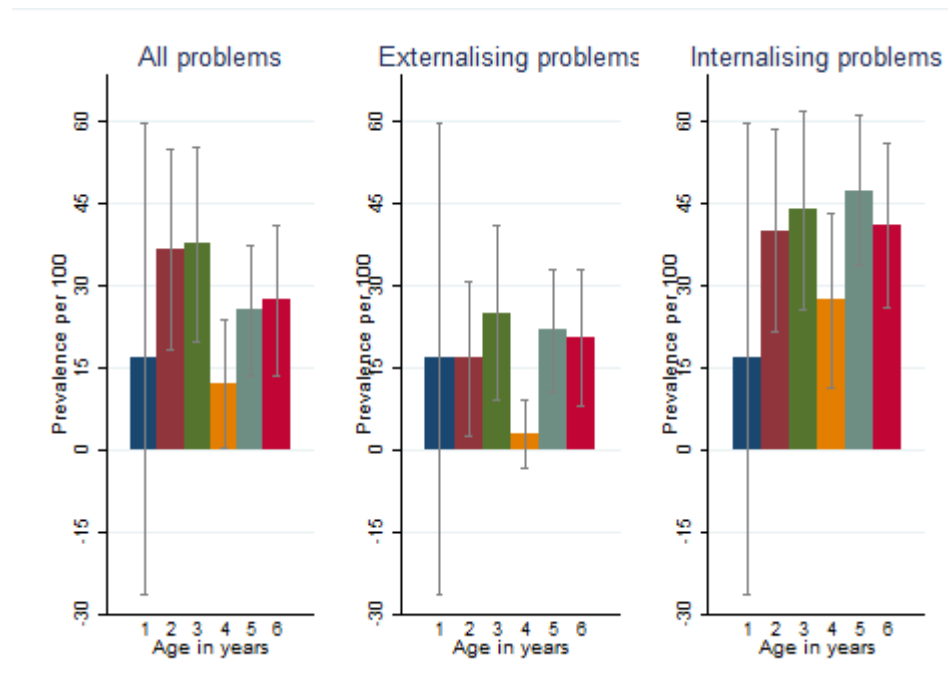
The crude prevalence of total behavioural/emotional problems was 27% (95%CI, 21%-34%) for those with acute seizures, 30% (95%CI, 20%-43%) for those with acute symptomatic seizures and 25% (95%CI, 15%-38%) for those with febrile seizures; all being significantly greater than for those without seizures (11% (95%CI, 11%-12%); Chi-squared $p \leq 0.001$). The crude prevalence of externalising problems was significantly greater in acute seizures (18% (95%CI, 13%-24%)), in acute symptomatic seizures (23% (95%CI, 14%-35%)), and in febrile seizures (22% (95%CI, 12%-35%)) than in those without seizures (12% (95%CI, 11%-13%)); Chi-squared $p < 0.0001$ for all comparisons.

The crude prevalence of total behavioural/emotional problems was 27% (95%CI, 22%-34%) for complex acute seizures combined, 35% (95%CI, 23%-48%) for repetitive acute seizures, 35% (95%CI, 24%-46%) for focal acute seizures, 26% (95%CI, 20%-34%) for prolonged acute seizures and 28% (95%CI, 16%-42%) for simple seizures. None of these proportions was significantly greater than in the simple acute seizures. The prevalence of externalising problems was similar for complex seizures and simple seizures (17% (12%-23%) vs. 20% (10%-34%); Chi-squared $p = 0.624$) and so was the prevalence for internalising problems (40% (95%CI, 34%-47%) vs. 44% (95%CI, 30%-59%); Chi-squared $p = 0.631$). The prevalence of total behavioural/problems was 31% (95%CI, 20%-44%) in hospitalised acute seizures and 26% (95%CI, 16%-38%) in acute seizures not hospitalised, but the difference was not statistically significant (Chi-squared $p = 0.539$).

The prevalence of total behavioural/emotional problems in those with acute seizures did not differ by sex for total behavioural/emotional problems (27% vs. 27%; Chi-squared $p = 0.895$), internalising problems (43% vs. 36%; Chi-squared $p = 0.349$) and externalising problems (21% vs 13%; Chi-squared $p = 0.141$). Similarly, the prevalence did not differ with age-group in years

for total behavioural/emotional problems (prevalence ratio (PR)=0.97 (95%CI, 0.92-1.03)), and for externalising (PR=1.01 (95%CI, 0.95-1.08)) and internalising problems (PR=0.98 (95%CI, 0.95-1.02)) (Figure 7-4).

Figure 7-4. Prevalence of behavioural/emotional problems by age in children with acute seizures



Association of behavioural/emotional problems and acute seizures

Binary behavioural/emotional problems and acute seizures

Acute seizures were significantly associated with total behavioural/emotional problems (RR=2.47 (95%CI, 1.84-3.31)), externalising problems (RR=1.39 (95%CI, 1.39-2.56)) and internalising problems (RR=2.35 (95%CI, 1.80-3.08)) after accounting for child's age, sex and region of residence. In addition, after accounting for non-seizure factors such as pregnancy/birth complications, head injury, house status and maternal age and unemployment, acute seizures remained associated with total behavioural/emotional problems (RR=2.40 (95%CI, 1.61-3.58)), externalising problems (RR=2.09 (95%CI, 1.40-

3.13)) and internalising problems (RR=1.99 (95%CI, 1.36-2.91)). Additional accounting of potential confounders was associated with smaller AIC, suggesting goodness-of-fit of the adjusted GLM models (Table 7-2).

Association of binary CBCL syndromes with acute seizures

Association of acute seizures with each of the 6 CBCL syndromes were strongest with anxious/depressed problems (RR=2.18 (95%CI, 1.50-3.18)) after accounting for non-seizure factors such as pregnancy/birth complications, head injury, house status and maternal age and unemployment (Table 7-2). Similarly, the association of acute seizures with specific DSM-oriented scales was strongest with affective problems (RR=2.07 (95%CI, 1.28-3.34)) after accounting for non-seizure factors such as pregnancy/birth complications, head injury, house status and maternal age and unemployment.

Association of binary behavioural/emotional problems with acute symptomatic seizures or febrile seizures

In a final model accounting for non-seizure factors such as pregnancy/birth complications, house status and maternal age and unemployment and head injury; acute symptomatic seizures were associated with behavioural/emotional problems (RR=3.64 (95%CI, 1.94-6.84)), externalising problems (RR=2.97 (95%CI, 1.58-5.60)) and internalising problems (RR=2.45 (95%CI, 1.30-4.62)). In a similar model, febrile seizures also showed a modest association with behavioural/emotional problems (RR=2.00 (95%CI, 1.02-3.92)) and internalising problems (RR=1.98 (95%CI, 1.06-3.69)), but not with externalising problems (RR=1.89 (95%CI, 0.95-3.75)). The RRR for the association between acute symptomatic seizures and behavioural/emotional problems compared to that between febrile seizures and behavioural/emotional problems was 1.82 (95%CI, 1.31-2.53)), suggesting the former association was greater.

Association of continuous CBCL scores with acute seizures

Acute seizures were associated with continuous total scores (RR=1.01 (95%CI, 1.00-1.02)), externalising scores (RR=1.03 (95%CI, 1.02-1.05)) and internalising scores (RR=1.03 (95%CI, 1.01-1.04)) (scores used as the explanatory variable) in a GLM model (Table 7-3). Use of continuous behavioural/emotional scores as the main explanatory variable in a GLM model elucidated further significant associations with CBCL syndromes and DSM-oriented scales (Table 7-3).

Table 7-2. Association of acute seizures with binary behavioural/emotional problems

Behavioural/e motional problems	No seizures (N=3073)	Acute seizures (200)	Adjusted RR (95% CI)^a	AIC^b	Adjusted RR (95% CI)^b	AIC^b	AIC^b< AIC^a
Total problems	366 (12%)	54 (27%)	2.47 (1.84-3.31)	0.45	2.40 (1.61-3.58)	0.41	Yes
Externalising problems	302 (10%)	36 (18%)	1.82 (1.39-2.56)	0.46	2.09 (1.40-3.13)	0.41	
Internalising problems	648 (21%)	80 (40%)	2.35 (1.80-3.08)	0.45	1.99 (1.40-2.91)	0.41	Yes
CBCL syndromes							
Emotionally- reactive	299 (10%)	32 (16%)	1.71 (1.20-2.44)	0.46	1.38 (0.86-2.21)	0.41	Yes
Anxious- depressed	362 (12%)	55 (28%)	2.63 (1.97-3.52)	0.45	2.18 (1.50-3.18)	0.41	Yes
Somatic problems	622 (20%)	73 (37%)	2.07 (1.58-2.72)	0.45	2.15 (1.52-3.05)	0.41	Yes
Withdrawn	327 (11%)	33 (17%)	1.63 (1.15-2.33)	0.46	1.27 (0.78-2.05)	0.41	Yes
Sleep problems	100 (3%)	14 (7%)	1.99 (1.19-3.32)	0.46	1.82 (1.00-3.35)	0.41	Yes
Attention problems	461 (15%)	41 (21%)	1.38 (1.00-1.91)	0.46	1.52 (1.04-2.23)	0.41	Yes
Aggressive behaviour	166 (5%)	23 (12%)	2.02 (1.36-3.02)	0.46	1.87 (1.19-2.94)	0.41	Yes
DSM-oriented scales							
Affective problems	163 (5%)	26 (13%)	2.38 (1.64-3.46)	0.46	2.07 (1.28-3.34)	0.41	Yes
Anxiety problems	363 (12%)	45 (23%)	2.05 (1.50-2.81)	0.45	1.82 (1.23-2.70)	0.41	Yes

Pervasive developmental problems	157 (5%)	16 (8%)	1.60 (0.97-2.53)	0.46	0.93 (0.49-1.78)	0.41	Yes
Attention deficit/hyperactivity problems	146 (5%)	17 (8%)	1.69 (1.07-2.70)	0.46	1.53 (0.84-2.78)	0.41	Yes
Oppositional defiant problems	71 (2%)	5 (3%)	1.01 (0.43-2.39)	0.46	1.12 (0.40-3.14)	0.41	Yes

AIC=Akaike's information criterion; CI= confidence interval; RR=risk ratio; ^aModel one; ^bModel two; RR^a is adjusted for child's age and sex and region of residence while RR^b is adjusted for known non-seizure risk factors for behavioural/emotional problems namely pregnancy problems, perinatal complications, maternal age, maternal employment, house status and head injury; in addition to those adjusted in RR^a. Behavioural/emotional problems were entered into the model as binary variables.

Table 7-3. Association of acute seizures with continuous behavioural/emotional scores

Behavioural/emotional scores	Adjusted RR (95%CI)	AIC ^a	Adjusted RR (95%CI)	AIC ^b	AIC ^b <AIC ^b
Total problems	1.01 (1.00-1.02)	0.45	1.01 (1.00-1.02)	0.41	Yes
Externalising problems	1.04 (1.02-1.05)	0.45	1.03 (1.02-1.05)	0.41	Yes
Internalising problems	1.04 (1.03-1.04)	0.45	1.03 (1.01-1.04)	0.41	Yes
CBCL syndromes					
Emotionally-reactive	1.08 (1.04-1.13)	0.46	1.05 (0.99-1.11)	0.41	Yes
Anxious-depressed	1.11 (1.07-1.15)	0.45	1.09 (1.04-1.13)	0.41	Yes
Somatic problems	1.12 (1.09-1.16)	0.45	1.11 (1.06-1.16)	0.41	Yes
Withdrawn	1.10 (1.05-1.15)	0.46	1.06 (1.00-1.13)	0.41	Yes
Sleep problems	1.11 (1.06-1.16)	0.46	1.08 (1.01-1.15)	0.41	Yes
Attention problems	1.09 (1.03-1.16)	0.46	1.10 (1.02-1.18)	0.41	Yes
Aggressive behaviour	1.04 (1.03-1.06)	0.45	1.04 (1.02-1.06)	0.41	Yes
DSM-oriented scales					
Affective problems	1.13 (1.10-1.17)	0.45	1.12 (1.07-1.17)	0.41	Yes
Anxiety problems	1.08 (1.04-1.11)	0.45	1.05 (1.01-1.10)	0.41	
Pervasive developmental problems	1.05 (1.02-1.10)	0.46	1.02 (0.98-1.07)	0.41	Yes

Attention deficit/hyperactivity problems	1.07 (1.02-1.12)	0.46	1.06 (1.00-1.13)	0.41	Yes
Oppositional defiant problems	1.11 (1.06-1.15)	0.46	1.09 (1.03-1.15)	0.41	Yes

AIC=Akaike's information criterion; RR=risk ratio; CI=confidence interval; ^aModel one; ^bModel two; RR^a is adjusted for child's age and sex and region of residence while RR^b is adjusted for known non-seizure risk factors for behavioural/emotional problems namely pregnancy problems, perinatal complications, maternal age, maternal employment, house status and head injury; in addition to those adjusted in RR¹. All behavioural/emotional scores were entered into the model as continuous variables.

Risk factors for behavioural/emotional comorbidity of acute seizures

In the univariable analysis, antenatal/perinatal complications, seizure disorders and past medical history were particularly associated with behavioural/emotional problems among children with acute seizures (Table 7-4). Factors in the multivariable analysis that were associated with increased risk for behavioural/emotional problems among children with acute seizures were family history of febrile seizures (RR=3.36 (95%CI, 1.34-8.41)), head injury (RR=2.46 (95%CI, 1.00-6.10)), eating soil/geophagia (RR=2.19 (95%CI, 1.04-4.59)) and snoring (with outcome as continuous behavioural/emotional problems) (β =0.23 (95%CI, 0.02-0.45))). Water being available on a daily basis was associated with reduced risk for behavioural/emotional comorbidity in the multivariable analysis (RR=0.13 (95%CI, 0.03-0.64)) of children with acute seizures. According to MacFadden's pseudo R²-squared value, these five significant risk factors explained 30% of variation of the behavioural/emotional problems among children with acute seizures.

Table 7-4. Risk factors associated with all behavioural/emotional comorbidity of acute seizures

			Binary behavioural/emotional problems		Continuous behavioural/emotional scores	
Risk factor	No behavioural problems	Behavioural problems	Adjusted RR (95%CI)^a	Multivariable RR (CI)	Adjusted β coefficient (95%CI)^b	Multivariable β coefficient (95%CI)
Mother's age in years: median (IQR)	27 (24-34)	26 (23-35)	1.00 (0.97-1.04)	-	-0.00 (-0.02, 0.01)	-
Sociodemographic information	N=115	N=41				
Mother's marital status				-		
Single	6 (5%)	1 (2%)	1.00	1.00	0.00	
Separated/divorced	6 (5%)	7 (17%)	4.00 (0.62-25.92)	Large SE	0.05 (-0.49, 0.59)	-
Widowed	4 (3%)	1 (2%)	1.45 (0.12-18.02)	Large SE	-0.16 (-0.71, 0.39)	-
Married	99 (86%)	32 (78%)	1.75 (0.28-10.97)	Large SE	-0.15 (-0.50, 0.19)	-
Mother's religion						
None	35 (30%)	10 (24%)	1.00	-	0.00	0.00
Traditional	2 (2%)	0 (0%)	-	-	0.11 (-0.50, 0.71)	-
Islam	13 (11%)	6 (15%)	1.42 (0.59-3.44)	-	0.23 (-0.10, 0.56)	0.10 (-0.31, 0.50)
Christian	65 (57%)	25 (61%)	1.30 (0.68-2.46)	-	0.10 (-0.14, 0.33)	-0.03 (-0.27, 0.21)
Mother's education level						
None	39 (34%)	11 (27%)	1.00	-	0.00	0.00

Primary	64 (56%)	27 (66%)	1.35 (0.73-2.50)	-	0.20 (-0.03, 0.44)	-0.05 (-0.43, 0.69)
Secondary	9 (8%)	2 (5%)	0.87 (0.22-3.34)	-	0.17 (-0.25, 0.58)	0.13 (-0.43, 0.69)
Tertiary	3 (3%)	1 (2%)	1.04 (0.18-5.91)	-	0.13 (-0.42, 0.68)	-0.37 (-1.07, 0.32)
Economic activity: mother	78 (68%)	23 (56%)	0.67 (0.39-1.14)	0.69 (0.37-1.30)	-0.21 (-0.42, 0.01)	-0.22 (-0.50, 0.06)
Economic activity: father	98/108 (91%)	36/39 (92%)	1.17 (0.41-3.32)	-	0.05 (-0.36, 0.46)	-
Number of children: median (IQR)	4 (2-6)	4 (2-6)	1.01 (0.91-1.12)	-	-0.02 (-0.06, 0.02)	-
Socioeconomic status and household information	N=115	N=41				
Water availability						
Infrequent	10/115 (9%)	5/41 (12%)	1.00	1.00	1.00	-
Weekly	23/115 (20%)	9/41 (22%)	0.87 (0.35-2.14)	0.58 (0.17-1.94)	0.01 (-0.33, 0.35)	-
Daily	24/115 (21%)	3/41 (7%)	0.34 (0.10-1.21)	0.13 (0.03-0.64)	-0.23 (-0.60, 0.14)	-
Always	58/115 (50%)	24/41 (59%)	0.91 (0.42-1.97)	0.60 (0.21-1.73)	-0.05 (-0.37, 0.27)	-
House status						
Dilapidated	18 (16%)	9 (22%)	1.00	-	1.00	0.00
Major repairs needed	16/115 (14%)	9 (22%)	1.16 (0.54-2.47)	-	0.15 (-0.19, 0.50)	-0.16 (-0.50, 0.17)
Incompletely build	7 (6%)	0 (0%)	-	-	-0.23 (-0.55, 0.09)	-0.12 (-0.60, 0.37)
Minor/no repairs needed	74 (64%)	23 (56%)	0.74 (0.39-1.40)	-	-0.07 (-0.31, 0.16)	-0.16 (-0.50, 0.18)
Toilet type						

Bush/none	29 (25%)	12 (29%)	1.00	-	1.00	
Traditional pit	65 (57%)	20 (49%)	0.79 (0.43-1.45)	-	-0.07 (-0.31, 0.17)	-
VIP pit	9 (8%)	5 (12%)	1.22 (0.52-2.88)	-	0.01 (-0.42, 0.45)	-
Flush	12 (10%)	4 (10%)	0.81 (0.31-2.12)	-	0.01 (-0.37, 0.38)	-
Livestock owned						
None	52 (45%)	23 (56%)	1.00	-	1.00	0.00
<5	20 (17%)	6 (15%)	0.75 (0.35-1.61)	-	-0.19 (-0.48, 0.08)	0.06 (-0.23, 0.35)
>5	43 (37%)	12 (29%)	0.74 (0.40-1.37)	-	-0.19 (-0.42, 0.04)	-0.05 (-0.44, 0.33)
Pregnancy and birth history						
Pregnancy problems	16 (14%)	7 (17%)	1.22 (0.61-2.45)	-	-0.05 (-0.39, 0.28)	-
Mother's age at birth	18 (17-20)	18 (17-19)	0.95 (0.87-1.03)	0.94 (0.86-1.03)	-0.02 (-0.05, 0.02)	-
Delivery at home	72 (63%)	23 (56%)	0.83 (0.49-1.38)	-	-0.10 (-0.31, 0.11)	-
Adverse perinatal events	6 (5%)	4 (10%)	1.54 (0.68-3.51)	-	0.15 (-0.17, 0.48)	-
Medical history						
Previous hospitalisation	N=115 54 (47%)	N=41 17 (41%)	0.84 (0.49-1.44)	-	-0.08 (-0.28, 0.12)	-
Head injury	4 (3%)	4 (10%)	2.02 (0.91-4.49)	2.46 (1.00-6.10)	0.48 (0.15, 0.81)	0.25 (-0.29, 0.80)
Dogs and cats in compound	65 (57%)	18 (44%)	0.70 (0.41-1.21)	0.60 (0.29-1.25)	-0.07 (-0.27, 0.14)	-
Eats cassava	105 (91%)	40 (98%)	2.98 (0.46-19.32)	0.42 (0.08-2.12)	0.17 (-0.13, 0.46)	-

Eats soil	14 (12%)	11 (27%)	2.14 (1.22-3.76)	2.19 (1.04-4.59)	0.53 (0.25, 0.80)	0.26 (-0.05, 0.56)
Bednet use	102 (89%)	35 (85%)	0.86 (0.40-1.86)	-	0.19 (-0.13, 0.51)	0.02 (-0.45, 0.50)
Snores at night	40 (35%)	19 (46%)	1.46 (0.87-2.47)	1.38 (0.79-2.41)	0.16 (-0.06, 0.37)	0.23 (0.02, 0.45)
Deceased father	5 (5%)	1 (3%)	0.65 (0.10-4.24)	-	0.11 (-0.36, 0.57)	-
Seizure factors	N=146	N=54				
Family history of seizures	36/115 (31%)	19/41 (46%)	1.55 (0.91-2.63)	1.30 (0.65-2.61)	0.24 (0.04, 0.44)	0.04 (-0.23, 0.31)
Family history of febrile seizures	76/115 (66%)	36/41 (88%)	2.91 (1.20-7.05)	3.36 (1.34-8.41)	0.31 (0.11, 0.51)	0.39 (0.06, 0.72)
Prolonged seizures	84/120 (70%)	29/41 (71%)	0.94 (0.50-1.7)	-	-0.02 (-0.24, 0.20)	-
Repetitive seizures	37/128 (29%)	17/51 (33%)	1.49 (0.94-2.36)	1.18 (0.57-2.43)	0.14 (-0.05, 0.34)	0.22 (-0.02, 0.46)
Focal seizures	39 (27%)	21 (39%)	1.22 (0.75-1.99)	-	0.09 (-0.11, 0.29)	-
All complex seizures	110 (75%)	40 (74%)	0.97 (0.58-1.62)	-	-0.06 (-0.27, 0.16)	-
Epilepsy co-diagnosis	15 (10%)	11 (20%)	1.69 (0.99-2.86)	1.73 (0.92-3.26)	0.22 (-0.03, 0.48)	0.06 (-0.26, 0.37)
Medical examination	N=84	N=39				
Developmental delays	5/80 (6%)	6/34 (18%)	2.03 (1.11-3.72)	1.27 (0.65-2.50)	0.49 (0.18, 0.81)	-0.20 (-0.61, 0.21)
Motor deficits	15 (18%)	8 (21%)	1.36 (0.67-2.75)	-	0.30 (-0.04, 0.65)	0.10 (-0.24, 0.44)
Intellectual disability	4 (5%)	3 (8%)	1.31 (0.57-2.98)	-	0.30 (0.10, 0.50)	0.59 (0.12, 1.06)
Peer-relationship problems	5/78 (6%)	3/34 (9%)	1.40 (0.52-3.82)	-	0.38 (-0.04, 0.79)	-0.32 (-0.74, 0.11)

Sensation problems	3 (4%)	1 (3%)	0.72 (0.12-4.50)	-	0.10 (-0.64, 0.85)	-
Malnutrition	3 (4%)	1 (3%)	0.85 (0.14-5.13)	-	-0.29 (-0.96, 0.37)	-

Highlighted adjusted RR or β and multivariable RR or β reached the cut-off p-value of ≤ 0.25 and ≤ 0.05 , respectively. ^aModel one; ^bModel two; RR^a and β^a are adjusted for child's age and sex and region of residence. CI=confidence interval; IQR=interquartile range; RR=risk ratio; SE=standard error

Externalising problems in children with acute seizures were associated with antenatal/perinatal complications, seizure disorders and past medical history in the univariable analysis (Table 7-5). In the multivariable analysis, externalising problems (as a binary variable) were associated with family history of febrile seizures (RR=3.26 (95%CI, 1.38-6.73)) and water being available weekly (RR=0.32 (95%CI, 0.11-0.99)), daily (RR=0.12 (95%CI, 0.03-0.33)) and always (RR=0.27 (95%CI, 0.09-0.81)). Continuous externalising scores in children with acute seizures were further associated with repetitive acute seizures ($\beta=0.36$ (95%CI, 0.15-0.57)), intellectual disability ($\beta=0.49$ (95%CI, 0.15-0.82)), academic difficulties ($\beta=1.01$ (95%CI, 0.31-1.72)), number of siblings ($\beta=0.12$ (95%CI, 0.06-0.17)), eating soil ($\beta=0.55$ (95%CI, 0.21-0.89)), developmental delay ($\beta=-0.63$ (95%CI, -1.08, -0.17)) and home delivery ($\beta=-0.29$ (95%CI, -0.52, -0.07)). According to Mac Fadden's pseudo R^2 -value, these nine significant risk factors explained 79% of variation of the externalising problems in children with acute seizures.

Table 7-5. Risk factors for externalising problems in children with acute seizures

Factors	Externalising problems		Binary externalising problems		Continuous externalising scores	
	No	Yes	Adjusted RR (95%CI)	Multivariable RR (95%CI)	Adjusted β coefficient (95%CI)	Multivariable β coefficient (95%CI)
Mother's age in years: median (IQR)	27 (24-32)	29 (23-35)	1.01 (0.97-1.05)	-	0.00 (-0.01, 0.02)	-
Sociodemographic information	N=124	N=32				
Mother's marital status						
Single	6 (5%)	1 (3%)	1.00	1.00	0.00	-
Separated/divorced	7 (6%)	6 (19%)	3.97 (0.50-31.32)	5.95 (0.94-37.58)	0.06 (-0.54, 0.66)	-
Widowed	4 (3%)	1 (3%)	1.82 (0.12-27.50)	2.63 (0.19-36.54)	-0.15 (-0.85, 0.54)	-
Married	107 (86%)	24 (75%)	1.50 (0.20-10.95)	1.13 (0.23-5.55)	-0.15 (-0.56, 0.26)	-
Mother's religion						
None	39 (31%)	6 (19%)	1.00	1.00	0.00	0.00
Traditional	1 (1%)	1 (3%)	4.25 (0.82-22.24)	18.35 (0.79-425.72)	0.53 (0.00, 1.06)	Large SE
Islam	13 (10%)	6 (19%)	2.25 (0.81-6.27)	1.93 (0.49-7.56)	0.13 (-0.29, 0.54)	-0.11 (-0.64, 0.41)
Christian	71 (57%)	19 (59%)	1.76 (0.78-3.99)	2.26 (0.21-23.85)	0.09 (-0.17, 0.35)	-0.09 (-0.34, 0.15)
Mother's education level						
None	40 (32%)	10 (31%)	1.00	1.00	0.00	0.00
Primary	72 (58%)	19 (59%)	1.05 (0.54-2.06)	0.65 (0.30-1.42)	0.13 (-0.15, 0.41)	-0.04 (-0.30, 0.23)
Secondary	10 (8%)	1 (3%)	0.53 (0.07-3.88)	0.26 (0.02-4.33)	0.27 (-0.24, 0.78)	-0.36 (-0.18, 0.90)
Tertiary	2 (2%)	2 (2%)	2.80 (0.82-9.54)	2.26 (0.21-23.88)	0.38 (-0.30, 1.07)	-0.62 (-1.28, 0.05)
Economic activity: mother	84 (68%)	17 (53%)	0.59 (0.32-1.10)	0.55 (0.24-1.26)	-0.17 (-0.44, 0.10)	-0.01 (-0.30, 0.28)
Economic activity: father	107/118 (91%)	27/29 (93%)	1.32 (0.35-4.96)	-	0.02 (-0.41, 0.45)	-

Number of children: median (IQR)	4 (2-6)	4 (3-7)	1.02 (0.90-1.16)	-	-0.04 (-0.08, 0.01)	0.12 (0.06, 0.17)
Socioeconomic status and household information	N=124	N=32				
Water availability						
Infrequent	10 (8%)	5 (16%)	1.00	1.00	0.00	0.00
Weekly	24 (19%)	8 (25%)	0.88 (0.36-2.18)	0.32 (0.11-0.99)	0.05 (-0.37, 0.47)	-0.04 (-0.48, 0.39)
Daily	25 (20%)	2 (6%)	0.25 (0.06-1.11)	0.12 (0.03-0.33)	-0.46 (-0.94, 0.02)	-0.46 (-0.91, -0.01)
Always	65 (52%)	17 (53%)	0.70 (0.32-1.53)	0.27 (0.09-0.81)	-0.08 (-0.45, 0.29)	-0.37 (-0.71, -0.02)
House status						
Dilapidated	22 (18%)	5 (16%)	1.00	-	0.00	-
Major repairs needed	17 (14%)	8 (25%)	1.82 (0.69-4.84)	-	0.24 (-0.18, 0.66)	-
Incompletely build	7 (6%)	0 (0%)	Large SE		-0.02 (-0.40, 0.36)	-
Minor/no repairs needed	78 (63%)	19 (59%)	1.15 (0.49-2.72)	-	-0.12 (-0.42, 0.18)	-
Toilet type						
Bush/none	32 (26%)	9 (28%)	1.00	-	0.00	-
Traditional pit	70 (56%)	15 (47%)	0.74 (0.36-1.54)	-	-0.10 (-0.39, 0.19)	-
VIP pit	9 (7%)	5 (16%)	1.56 (0.62-3.95)	-	0.11 (-0.36, 0.58)	-
Flush	13 (10%)	3 (9%)	0.77 (0.24-2.40)	-	-0.11 (-0.60, 0.38)	-
Livestock owned						
None	56 (45%)	19 (59%)	1.00	1.00	0.00	0.00
<5	21 (17%)	5 (16%)	0.76 (0.33-1.77)	0.40 (0.13-1.20)	-0.24 (-0.57, 0.09)	0.23 (-0.12, 0.58)
>5	47 (38%)	8 (25%)	0.62 (0.29-1.33)	0.93 (0.38-2.32)	-0.22 (-0.49, 0.05)	0.04 (-0.26, 0.33)
Pregnancy and birth history						
Pregnancy problems	16 (13%)	7 (22%)	1.77 (0.86-3.66)	1.26 (0.36-4.43)	-0.09 (-0.49, 0.31)	-
Mother's age at birth	18 (17-20)	18 (16-20)	0.98 (0.90-1.07)	-	-0.01 (-0.05, 0.03)	-
Delivery at home	80 (65%)	15 (47%)	0.59 (0.32-1.09)	0.95 (0.42-2.15)	-0.24 (-0.48, 0.01)	-0.29 (-0.52, -0.07)
Adverse perinatal events	8 (6%)	2 (6%)	0.91 (0.24-3.46)	-	0.26 (-0.05, 0.58)	-0.11 (-0.53, 0.31)
Medical history	N=124	N=32				
Previous hospitalisation	57 (46%)	14 (44%)	0.93 (0.50-1.73)	-	-0.12 (-0.36, 0.13)	-

Head injury	5 (4%)	3 (9%)	2.17 (0.79-6.02)	2.09 (0.16-26.59)	0.70 (0.44, 0.97)	0.06 (-0.45, 0.57)
Dogs and cats in compound	70 (56%)	13 (41%)	0.60 (0.32-1.14)	0.43 (0.17-1.08)	-0.16 (-0.40, 0.08)	-0.10 (-0.37, 0.18)
Eats cassava	70 (56%)	13 (41%)	1.12 (0.31-3.97)	-	0.14 (-0.28, 0.56)	-
Eats soil	18 (15%)	7 (22%)	1.75 (0.86-3.58)	1.40 (0.41, 4.76)	0.56 (0.28, 0.83)	0.55 (0.21, 0.89)
Bednet use	108 (87%)	29 (91%)	1.70 (0.54-5.31)	-	0.30 (-0.09, 0.70)	0.44 (-0.01, 0.87)
Snores at night	46 (37%)	13 (41%)	1.18 (0.63-2.20)	-	0.10 (-0.15, 0.36)	-
Deceased father	6/120 (5%)	0/28 (0%)	Large SE	-	0.03 (-0.44, 0.50)	-
Seizure factors	N=164	N=36				
Family history of seizures	38/124 (31%)	17/32 (53%)	1.96 (1.05-3.65)	3.26 (1.58-6.73)	0.30 (0.06, 0.54)	0.16 (-0.10, 0.42)
Family history of febrile seizures	84/124 (68%)	28/32 (88%)	2.79 (1.03-7.54)	1.21 (0.39-3.75)	0.40 (0.15, 0.66)	0.31 (-0.03, 0.64)
Prolonged seizures	97/137 (71%)	16/24 (67%)	0.85 (0.38-1.92)	-	0.09 (-0.18, 0.35)	-
Repetitive seizures	42 (26%)	18 (50%)	2.32 (1.31-4.10)	1.47 (0.68-3.15)	0.24 (0.01, 0.46)	0.36 (0.15, 0.57)
Focal seizures	42/145 (29%)	12/34 (35%)	1.40 (0.75-2.61)	-	-0.10 (-0.36, 0.16)	-
All complex seizures	124 (76%)	26 (72%)	0.96 (0.50-1.83)	-	-0.10 (-0.32, 0.12)	-
Epilepsy co-diagnosis	19 (12%)	7 (19%)	1.58 (0.76-3.30)	0.96 (0.46-2.02)	0.18 (-0.13, 0.48)	-
Medical examination	N=92	N=31				
Developmental delays	5/86 (6%)	6/28 (21%)	2.66 (1.50-4.71)	1.27 (0.32-5.03)	0.39 (-0.03, 0.82)	-0.63 (-1.08, -0.17)
Motor deficits	16 (17%)	7 (23%)	1.77 (0.88-3.56)	2.04 (0.47-8.92)	0.05 (-0.34, 0.44)	-
Intellectual disability	4 (4%)	3 (10%)	1.56 (0.71-3.46)	-	0.37 (-0.01, 0.74)	0.49 (0.15, 0.82)
Academic difficulties	3/58 (5%)	2/17 (12%)	1.79 (0.66-4.81)	-	0.55 (0.24, 0.87)	1.01 (0.31, 1.72)
Peer-relationship problems	5/83 (6%)	3/29 (10%)	1.80 (0.67-4.84)	1.83 (0.51-6.54)	0.43 (-0.02, 0.89)	-0.24 (-0.86, 0.37)
Sensation problems	3 (3%)	1 (3%)	0.77 (0.12-5.13)	-	0.09 (-0.59, 0.77)	-
Malnutrition	4 (4%)	0 (0%)	Large SE	-	-0.29 (-0.94, 0.37)	-

Highlighted adjusted RR or β and multivariable RR or β reached the cut-off p-value of ≤ 0.25 and ≤ 0.05 , respectively. ^aModel one; ^bModel two; RR^a and β^a are adjusted for child's age and sex and region of residence. CI=confidence interval; IQR=interquartile range; RR=risk ratio; SE=standard error

Internalising problems occurring in the context of acute seizures were associated with antenatal/perinatal complications, seizure disorders and past medical history in the univariable analysis (Table 7-6). In the multivariable analysis, internalising problems (as a binary variable) were associated with focal acute seizures (RR=1.80 (95%CI, 1.05-3.08)). Continuous internalising scores were associated with repetitive acute seizures ($\beta=0.53$ (95%CI, 0.23, 0.83)), intellectual disability ($\beta=0.62$ (95%CI, 0.01, 1.24)) and maternal tertiary education level ($\beta=-0.35$ (95%CI, -0.70, -0.01)). These four significant risk factors explained 48% of variability in internalising problems in children with acute seizures according to Mac Fadden's pseudo R^2 -value.

Table 7-7. Risk factors for internalising problems in children with acute seizures

Factors	Internalising problems		Binary internalising problems		Continuous internalising scores	
	No	Yes	Adjusted RR (95%CI)	Multivariable RR (95%CI)	Adjusted β coefficient (95%CI)	Multivariable β coefficient (95%CI)
Mother's age in years: median (IQR)	30 (25-35)	28 (24-35)	0.99 (0.97-1.02)	-	-0.01 (-0.02, 0.01)	-
Mother's marital status						
Single	4/96 (4%)	3/60 (5%)	1.00	-	0.00	-
Separated/divorced	6/96 (6%)	7/60 (12%)	1.39 (0.53-3.60)	-	0.15 (-0.65, 0.96)	-
Widowed	2/96 (2%)	3/60 (5%)	1.64 (0.57-4.72)	-	0.01 (-0.94, 0.96)	-
Married	84/96 (88%)	47/60 (78%)	0.93 (0.40-2.15)	-	-0.01 (-0.60, 0.57)	-
Mother's religion						
None	28/96 (29%)	17/60 (28%)	1.00	-	0.00	-
Traditional	2/96 (2%)	0	-	-	-0.75 (-2.17, 0.67)	-
Islam	12/96 (13%)	7/60 (12%)	0.98 (0.48-1.98)	-	0.18 (-0.25, 0.60)	-
Christian	54/96 (56%)	36/60 (60%)	1.15 (0.73-1.80)	-	0.08 (-0.22, 0.37)	-
Mother's education level						
None	33/96 (34%)	17/60 (28%)	1.00	1.00	0.00	0.00
Primary	51/96 (53%)	40/60 (67%)	1.32 (0.85-2.07)	1.33 (0.71-2.48)	0.23 (-0.07, 0.53)	0.20 (-0.22, 0.63)
Secondary	9/96 (9%)	2/60 (3%)	0.61 (0.16-2.29)	0.44 (0.09-2.19)	0.11 (-0.35, 0.56)	-0.13 (-0.87, 0.61)
Tertiary	3/96 (3%)	1/60 (2%)	0.70 (0.13-3.88)	1.80 (0.34-9.43)	-0.01 (-0.67, 0.66)	-0.44 (-1.37, 0.50)
Economic activity: mother	69/96 (72%)	32/60 (53%)	0.61 (0.41-0.90)	0.61 (0.35-1.08)	-0.28 (-0.54, -0.03)	-0.35 (-0.70, -0.01)
Economic activity: father	82/91 (90%)	52/56 (93%)	1.24 (0.52-2.94)	-	0.15 (-0.37, 0.68)	-
Number of children: median (IQR)	4 (3-6)	4 (3-6)	1.00 (0.93-1.09)	-	-0.01 (-0.06, 0.04)	-

Socioeconomic status and household information						
Water availability						
Infrequent	10/96 (10%)	5/60 (8%)	1.00		0.00	-
Weekly	19/96 (20%)	13/60 (22%)	1.41 (0.64-3.10)	-	-0.15 (-0.56, 0.27)	-
Daily	21/96 (22%)	6/60 (10%)	0.72 (0.27-1.92)	-	-0.11 (-0.51, 0.29)	-
Always	46/96 (48%)	36/60 (60%)	1.45 (0.71-2.93)	-	0.00 (-0.39, 0.39)	-
House status						
Dilapidated	15/96 (16%)	12/60 (20%)	1.00	1.00	0.00	0.00
Major repairs needed	9/96 (9%)	16/60 (27%)	1.53 (0.93-2.52)	1.74 (0.74-4.09)	0.34 (-0.10, 0.77)	-0.22 (-0.75, 0.31)
Incompletely build	6/96 (6%)	1/60 (2%)	0.30 (0.04-2.08)	0.82 (0.13-5.26)	-0.20 (-0.64, 0.23)	-0.45 (-1.01, 0.11)
Minor/no repairs needed	66/96 (69%)	31/60 (52%)	0.77 (0.47-1.25)	1.13 (0.49-2.63)	0.02 (-0.32, 0.35)	-0.36 (-0.79, 0.07)
Toilet type						
Bush/none	24/96 (25%)	17/60 (28%)	1.00	-	0.00	-
Traditional pit	52/96 (54%)	33/60 (55%)	0.89 (0.58-1.39)	-	-0.07 (-0.37, 0.24)	-
VIP pit	9/96 (9%)	5/60 (8%)	0.82 (0.37-1.86)	-	-0.07 (-0.54, 0.40)	-
Flush	11/96 (11%)	5/60 (8%)	0.72 (0.32-1.58)	-	0.00 (-0.44, 0.43)	-
Livestock owned						
None	43/96 (45%)	32/60 (53%)	1.00		0.00	-
<5	17/96 (18%)	9/60 (15%)	0.82 (0.46-1.44)	-	-0.11 (-0.45, 0.22)	-
>5	36/96 (38%)	19/60 (32%)	0.86 (0.55-1.34)	-	-0.10 (-0.38, 0.19)	-
Pregnancy and birth history						
Pregnancy problems	15/96 (16%)	8/60 (13%)	0.96 (0.53-1.73)	-	0.04 (-0.32, 0.40)	-
Mother's age at birth	18 (17-20)	18 (16-20)	0.94 (0.88-1.01)	0.98 (0.89-1.06)	-0.03 (-0.07, 0.01)	-
Delivery at home	59/96 (61%)	36/60 (60%)	0.99 (0.66-1.46)	-	-0.02 (-0.28, 0.24)	-
Adverse perinatal events	5/96 (5%)	5/60 (8%)	1.28 (0.64-2.55)	-	-0.07 (-0.58, 0.46)	-
Seizure factors						
Family history of seizures	32/96 (33%)	23/60 (38%)	1.09 (0.73-1.63)	-	0.10 (-0.18, 0.38)	-

Family history of febrile seizures	60/96 (63%)	52/60 (87%)	2.64 (1.38-5.04)	2.61 (0.88-7.70)	0.34 (0.06, 0.61)	0.26 (-0.17, 0.68)
Prolonged seizures	72/101 (71%)	41/60 (68%)	0.90 (0.58-1.39)	-	-0.17 (-0.47, 0.12)	0.28 (-0.21, 0.76)
Repetitive seizures	31/120 (26%)	29/80 (36%)	1.31 (0.93-1.84)	1.15 (0.63-2.07)	0.23 (-0.02, 0.47)	0.53 (0.23, 0.83)
Focal seizures	29/108 (27%)	25/71 (35%)	1.33 (0.92-1.93)	1.80 (1.05-3.08)	0.34 (0.09, 0.58)	0.33 (-0.06, 0.72)
All complex seizures	92/120 (77%)	58/80 (73%)	0.90 (0.62-1.31)	-	-0.12 (-0.40, 0.16)	-
Epilepsy co-diagnosis	12/120 (10%)	14/80 (18%)	1.40 (0.92-2.11)	1.60 (0.83-3.07)	0.18 (-0.20, 0.56)	-
Medical examination						
Developmental delays	4/64 (6%)	7/50 (14%)	1.58 (1.01-2.45)	0.64 (0.29-1.44)	0.54 (0.20, 0.88)	-0.35 (-0.82, 0.12)
Motor deficits	13/67 (19%)	10/56 (18%)	1.16 (0.69-1.95)	-	0.20 (-0.23, 0.64)	-
Intellectual disability	2/67 (3%)	5/56 (9%)	1.48 (0.95-2.32)	1.60 (0.64-3.96)	0.23 (-0.02, 0.48)	0.62 (0.01, 1.24)
Academic difficulties	2/40 (5%)	3/35 (9%)	1.23 (0.56-2.70)	-	0.26 (-0.06, 0.59)	0.14 (-0.41, 0.69)
Peer-relationship problems	3/62 (5%)	5/50 (10%)	1.69 (0.96-2.97)	1.60 (0.77-3.35)	0.44 (-0.04, 0.92)	-0.36 (-0.93, 0.21)
Sensation problems	2/67 (3%)	2/56 (4%)	0.92 (0.30-2.79)	-	0.17 (-0.73, 1.07)	-
Malnutrition	3/67 (5%)	1/56 (2%)	0.60 (0.10-3.63)	-	-0.46 (-1.45, 0.53)	-
Medical history						
Previous hospitalisation	45/96 (47%)	26/60 (43%)	0.91 (0.61-1.35)	-	-0.05 (-0.30, 0.20)	-
Head injury	3/96 (3%)	5/60 (8%)	1.81 (0.94-3.45)	2.16 (0.82-5.67)	0.32 (-0.19, 0.83)	-0.48 (-1.74, 0.78)
Dogs and cats in compound	52/96 (54%)	31/60 (52%)	0.96 (0.64-1.43)	-	-0.11 (-0.37, 0.14)	-
Eats cassava	86/96 (90%)	59/60 (98%)	4.37 (0.70-27.17)	Large SE	0.12 (-0.17, 0.42)	-
Eats soil	11/96 (11%)	14/60 (23%)	1.84 (1.21-2.79)	1.85 (0.93-3.68)	0.46 (0.08, 0.85)	-0.29 (-0.74, 0.16)
Bednet use	86/96 (90%)	51/60 (85%)	0.93 (0.54-1.59)	-	0.16 (-0.27, 0.61)	-
Snores at night	35/96 (36%)	24/60 (40%)	1.12 (0.75-1.68)	-	0.09 (-0.19, 0.36)	-
Deceased father	2/92 (2%)	4/56 (7%)	1.82 (1.06-3.12)	0.45 (0.19-1.06)	0.22 (-0.54, 0.99)	-

Highlighted adjusted RR or β and multivariable RR or β reached the cut-off p-value of ≤ 0.25 and ≤ 0.05 , respectively. ^aModel one; ^bModel two; RR^a and β^a are adjusted for child's age and sex and region of residence. CI=confidence interval; IQR=interquartile range; RR=risk ratio; SE=standard error

Discussion

This population-based study, examined the behavioural/emotional comorbidities of acute seizures in preschool children and demonstrated that behavioural/emotional problems occur in at least a third of children with acute seizures. Behavioural/emotional scores were significantly higher in children with acute seizures than those without seizures, with moderate effect sizes, highest in acute symptomatic compared to febrile seizures. Acute seizures remained independently associated with behavioural/emotional problems after accounting for non-seizure risk factors, with the association significantly greater in acute symptomatic seizures than febrile seizures. Among those children with acute seizures, the most important risk factors were family history of febrile seizures for total behavioural/emotional problems and externalising problems, repetitive acute seizures for externalising and internalising problems and focal acute seizures for internalising problems.

Prevalence and effect size of behavioural/emotional comorbidity of acute seizures

The prevalence of total behavioural/emotional problems was significantly greater in acute seizures (27%) than in those without seizures (11%), being 30% in acute symptomatic and 25% in febrile seizures. The prevalence was highest in repetitive (35%) and focal seizures (35%), but surprisingly lower in prolonged seizures (26%). Our estimate for behavioural comorbidity of febrile seizures of 25% compares with a febrile seizure study in Germany (22%) (Kölfen et al., 1998), but is slightly greater than in an American febrile seizure study (18%) (Wolf & Forsythe, 1978). Although two recent European studies have not reported increased prevalence of behavioural/emotional problems after febrile seizures (Verity et al., 1998; Visser et al., 2012), our findings support the need to conduct more studies on this subject as mental health problems may have shared underlying causes with febrile seizures (Baram & Shinnar, 2002). Acute symptomatic seizures had a higher prevalence of behavioural/emotional comorbidity as expected since they can cause neurological damage (J.

A. Carter, Ross, et al., 2005). In a Kenyan hospital study, the prevalence of behavioural/emotional problems of acute symptomatic seizures due to malaria was twice that of those without seizures (J. A. Carter, Mung'ala-Odera, et al., 2005). Complex seizures can interfere with maturation of neuronal networks or damage parts of the brain (Baram & Shinnar, 2002), thus their association with increased prevalence of behavioural/emotional comorbidity in this study is not surprising.

The prevalence of internalising problems was higher than externalising problems in acute seizures. There are two explanations to these differences. Firstly, the baseline survey of behavioural/emotional problems reported in chapter 5 showed a significantly higher prevalence of internalising problems, a difference which may remain apparent in a subset of children with acute seizures. The CBCL has significantly more items for internalising problems than for externalising problems, which improves sensitivity for detection of the former problems (T. Achenbach & Rescorla, 2000). Secondly, in the literature the association between internalising problems and epileptic seizures is widely recognised (Rodenburg, Stams, Meijer, Aldenkamp, & Deković, 2005), which could have been replicated in our findings. While behavioural/emotional problems may increase with age due to improvement in detection and manifestations (A. S. Carter et al., 2004), in children with acute seizures the prevalence remained unchanged with age, suggesting a uniform risk in this group of children.

Effect sizes quantified the differences in behavioural/emotional scores between those with acute seizures and those without, suggesting that most of them were moderately large (i.e. Cohens $d > 0.2$). The behavioural/emotional comorbidity differences as measured with effect sizes are consistent with prevalences discussed above, for example the effect sizes were larger for acute symptomatic seizures (Cohens $d = 0.59$) compared to febrile seizures (Cohens $d = 0.35$) and for internalising problems (Cohens $d = 0.44$) compared to externalising problems (Cohens $d = 0.38$). The moderately large effect sizes that are based on continuous scores

further supports the observed increased prevalence for behavioural/emotional problems in acute seizures.

Independent association between acute seizures and behavioural/emotional problems

Acute seizures remained associated with behavioural/emotional problems, externalising problems and internalising problems after accounting for potential non-seizure confounders. This important finding suggests an independent association between acute seizures and behavioural/emotional problems, but may not imply a causal association as this was a cross-sectional study in which it is difficult to establish whether acute seizures were antecedents of behavioural/emotional problems. There is evidence that behavioural/emotional problems may precede the onset of seizures (Austin et al., 2001), which complicates the bi-directionality of the association between the two conditions. We however asked parents about behavioural/emotional problems in the past two months, when most children had already experienced their first acute seizures, thus most seizures could have preceded the onset of behavioural/emotional problems. Alternatively, acute seizures can create anxiety in mothers, which affects the behaviour of their children (Stein et al., 2014).

Associations of acute seizures with internalising problems were more striking than with externalising problems, suggesting a particular association of the former with acute seizures as in other studies of epileptic seizures (Rodenburg, Stams, Meijer, Aldenkamp, & Deković, 2005). Acute symptomatic seizures contributed significantly greater behavioural/emotional comorbidities than febrile seizures since the RRR and its corresponding lower confidence interval were greater than 1. This may have underestimated the strength of the association considering that some parents with febrile seizures may not have recalled the symptomatic causes such as malaria. Falciparum malaria and bacterial meningitis, the two important causes of acute symptomatic seizures in this area (R. Idro et al.,

2008), are associated with neurological damage (J. A. Carter, Mung'ala-Odera, et al., 2005; S. M. Kariuki, A. Abubakar, et al., 2014) that can result in increased burden of behavioural/emotional problems in children with these seizures. These associations suggest that behavioural/emotional problems should be assessed and addressed in children with acute seizures particularly acute symptomatic seizures. This is important since none of the parents with children with behavioural/emotional problems had received psychological support before the study, notwithstanding that only 45% of acute seizures were treated in hospital as discussed in chapter 6.

Risk factors of behavioural comorbidity of acute seizures

Several risk factors in the multivariable analysis explained substantial a proportion of behavioural/emotional comorbidity of acute seizures of up to 80% for externalising problems, for example. Family history of febrile seizures was associated with total behavioural/emotional problems and externalising problems in children with acute seizures. This could suggest that both acute seizures and behavioural/emotional problems have shared genes considering that heritability for both conditions is high (Kjeldsen et al., 2002; Pappa et al., 2015). Only two complex phenotypes of acute seizures (i.e. focal and repetitive acute seizures) were independent risk factors for externalising and internalising problems, consistent with a German study which identified repetitive seizures as important risk factors for behavioural/emotional comorbidity of febrile seizures (Kölfen et al., 1998). These two phenotypes of complex acute seizures are particularly attributable to malaria (S. M. Kariuki et al., 2011), and can damage parts of the brain or affect maturation of neuronal networks, which may explain the association with behavioural/emotional problems (J. A. Carter et al., 2004; S. M. Kariuki, A. Abubakar, et al., 2014).

Surprisingly, prolonged acute seizures were not independent risk factors for behavioural/emotional comorbidity of acute seizures, but this should be interpreted carefully since timing of seizures may have been problematic as most parents do not have watches (S. M. Kariuki et al., 2015b; Newton & Kariuki, 2013). Acute seizures are also dramatic (C. Waruiru & R. Appleton, 2004), which could have prompted some parents to exaggerate the duration of short seizures thereby diluting associations with behavioural/emotional problems. Seizure factors are usually not important predictors of behavioural/emotional comorbidity in studies of childhood epilepsy (Reilly et al., 2014).

Head injury, and learning disability could be markers of underlying neurological damage (Schwartz et al., 2003) that can increase the risk for behavioural problems in acute seizures or for both conditions. Snoring, when caused by upper airway obstruction, was associated with behavioural/emotional problems in a previous study (Beebe et al., 2012; Rosenzweig et al., 2014); a similar mechanism could apply in children with acute seizures. The role of eating soil in behavioural/emotional comorbidity of acute seizures is unclear, but this could be a consequence of behavioural/emotional problems, reflecting underlying neurological abnormality. Alternatively, both acute seizures and/or behavioural/emotional problems could be associated with neurological abnormality related to the possible neurotoxins in soils (Grandjean & Landrigan, 2014) or perhaps micronutrients deficiency from intestinal worm infested soils (de Gier, Campos Ponce, van de Bor, Doak, & Polman, 2014). Developmental delays appeared to reduce the risk for externalising problems, which was perhaps because this group of children had severe deficits in motor skills that may suppress manifestation of externalising problems (Crnic, Hoffman, Gaze, & Edelbrock, 2004). Co-diagnosis of epilepsy with acute seizures was not an independent risk factor for behavioural/emotional problems, underpinning the detrimental impact of acute seizures on behaviour/emotional development of children.

Few socioeconomic and sociodemographic factors were associated with behavioural/emotional comorbidity of acute seizures. Water availability and education are makers of social disadvantage, which has been implicated in occurrence of behavioural/emotional in general, through social causation or selection (Peterlin & Scher, 2013). Through social causation, social advantaged families may have improved health accessibility (Peterlin & Scher, 2013) and subsequently fewer behavioural/emotional comorbidities of acute seizures. Number of siblings can increase family/parental distress (Neece, Green, & Baker, 2012), that can exacerbate behavioural/emotional comorbidity in acute seizures.

Strengths and limitations

The strength of this study is that it was based on a community sample, and the seizure semiology was well defined. Additionally, behavioural/emotional problems were assessed with an internationally applied behavioural/emotional assessment tool (the CBCL), which was validated and adapted to the local population (S. M. Kariuki et al., 2016). Associations between acute seizures and behavioural/emotional problems were accounted for potential confounders, and were therefore robust. Risk factors investigated, which were selected based on evidence from the literature, explained a substantial variability of behavioural/emotional comorbidity of acute seizures in regression models.

Maternal mental health status, quality of parenting process and family functioning may influence behavioural/emotional outcomes (Neece et al., 2012; Stein et al., 2014), but they were not assessed in our study. These are modifiable factors and could be targeted during future behavioural/emotional interventions. Developmental delay and intellectual disability reported in this study were evaluated by a clinician by observing a child perform a subset of tasks of a developmental inventory, and may not be as reliable as performing all tasks or a

battery of standardised neuropsychological tests. It is difficult to perform neuropsychological tests on all children in a cross-sectional study since it is labour intensive.

Recommendations and future direction

These findings suggest that there may be a biological association between acute seizures and behavioural/emotional problems, with the association being greatest for acute symptomatic seizures. There is need for clinicians to identify and address behavioural/emotional problems in children presenting with acute seizures to improve outcome. Parenting programmes should be initiated to support parents of children with behavioural/emotional problems associated with seizures. Control of risk factors and causes of acute seizures in the community may reduce the burden of behavioural/emotional problems in preschool children.

Future longitudinal studies are however required to understand the direction of causality in the association between acute seizures and behavioural/emotional problems. Acute seizures and behavioural/emotional problems may be partly explained by genes, a hypothesis which can be investigated in future genetic studies.

Conclusions

Acute seizures are associated with substantial behavioural/emotional problems. Such problems should be assessed and addressed in children with these seizures in this rural area of Kenya. There is an independent association between acute seizures and behavioural/emotional problems, but it is difficult to establish directionality of the relationship in a cross-sectional study such as ours; future longitudinal studies should clarify this association. The prevalence of behavioural/emotional comorbidity is greatest in acute symptomatic seizures suggesting control of infections such as falciparum malaria, which are endemic in this area, could reduce the burden of neuropsychiatric problems in this area. Behavioural/emotional comorbidities of acute seizures in this area is mainly determined by

underlying neurological abnormality and repetitive or focal seizures, prevention of which may improve behavioural/emotional outcomes. Family history of febrile seizures was an important risk factor for behavioural/emotional comorbidity of acute seizures highlighting the need to study the genetic determinants of both acute seizures and behavioural/emotional problems in this area. A history of epilepsy in those acute seizures was not an independent risk factor for behavioural/emotional comorbidity of acute seizures, underlining the association between acute seizures and these behavioural/emotional problems. Parental distress and family functioning, which can influence behavioural/emotional comorbidity of acute seizures, were not examined in this study, but could be still targeted for modification by future behavioural/emotional interventional studies for parents.

Chapter 8: Summary of the thesis

Synthesised discussion

Background

This thesis measures the prevalence of acute seizures and behavioural/emotional problems in preschool children living in Kilifi, Kenya. It also determines the risk factors for acute seizures and behavioural/emotional problems and examines their relationship. The study was motivated by the observation that risk factors for behavioural/emotional problems and acute seizures are prevalent in preschool children in the community, but there are no epidemiological studies of behavioural/emotional problems and acute seizures in this community. Some risk factors for behavioural/emotional problems and acute seizures include adverse perinatal events due to home deliveries and poor obstetric services (Victor Mung'ala-Odera & Newton, 2001), central nervous infections such as malaria (R. Idro et al., 2007; Newton & Warrell, 1998), and other underlying neurological impairments (V. Mung'ala-Odera et al., 2006). One Kenyan study showed a prevalence of 26% for behavioural/emotional problems in controls selected for an epilepsy study (Symon M. Kariuki et al., 2012), but this sample was small and older children were recruited. The incidence of complex acute seizures in Kilifi is double that of in America and England (Serem et al., 2015; C. Waruiru & R. Appleton, 2004; Waruiru et al., 1996) and these complex phenotypes may increase the risk of behavioural/emotional problems in Kilifi, Kenya, as complex seizures were associated with poor neurobehavioural outcomes in other areas (Baram & Shinnar, 2002). I therefore conducted an epidemiological study of acute seizures and behavioural/emotional problems in 7,047 preschool children living in Kilifi, Kenya to determine if there is an independent association between acute seizures and behavioural/emotional problems.

Overview of main findings from this thesis

The findings from this study show that the Child Behaviour Checklist (CBCL) (T. Achenbach & Rescorla, 2000) possesses acceptable psychometric properties and that its seven syndrome factor model is applicable in the Kilifi population. There is a high life-time prevalence of acute seizures (6%) and total behavioural/emotional problems (13%) in children aged 1-6 years. The most important risk factors for acute seizures were socio-economic factors, antenatal and perinatal complications and past medical history; while seizure disorders explained the greatest variability for behavioural/emotional problems in multivariable structural equation models. Acute seizures were independently associated with behavioural/problems even after accounting for potential confounders such as history of head injury and antenatal and perinatal complications.

Psychometric properties of the CBCL

The Cronbach's alpha was excellent for all 99 items of the CBCL and for the seven syndromes, supporting the conclusion of good internal consistency of the CBCL. The Cronbach's alpha was lower for the withdrawn and attention scales, suggesting that some items of these scales may be understood differently in Kenya compared to North America (T. Achenbach & Rescorla, 2000). These findings are supported by the low standardised coefficients for some items that form these scales. These items have been discriminatory in other settings (Rescorla et al., 2011), and should be evaluated further before they are omitted from future assessments. The test-retest reliability was excellent, supporting the stability of behavioural/emotional problems over time in this area. However, this re-assessment was performed after only two weeks, and it is unclear if the findings would remain stable over a longer period. The inter-informant reliability of the mother's scores was excellent when compared with both the fathers and the guardians, but it was higher in the former than in the latter. This is not surprising as the guardians in this area, including the grandmothers, spend

more time with children than the fathers, who are often away for economic reasons. These findings support use of other informants in assessing behavioural/emotional problems when the mother is unavailable.

Factorial structure of the CBCL

We investigated whether the 7-factorial structure of the CBCL was applicable in the Kilifi population as in other non-American societies (Rescorla et al., 2011). Most of the syndromes had acceptable fit indices in terms of root mean squared error of approximation (RMSEA) (<0.05), Tucker Lewis index (TLI) (>0.90), and comparative fit index (CFI) (>0.90) (Browne & Cudeck, 1993; Yuh & Muthen, 2002), with aggressive behaviours being borderline (>0.85). The relatively lower fit indices for aggressive behaviour could be in part explained by the use of polychoric (for 3-point response scales) rather than tetrachoric (for 2-point response scales) approach in the confirmatory factor analysis (Yuh & Muthen, 2002). Polychoric approach is deemed appropriate for the CBCL, but may be associated with lower factor loadings (Yuh & Muthen, 2002). Additionally, aggressive behaviours are considered unpleasant in this community, and concealing of some items may lower fit indices for that scale (Abubakar et al., 2015). The findings support the use of the 7-syndrome model of the CBCL in describing behavioural/emotional problems in Kilifi.

Discriminant validity

The CBCL scores were significantly higher in those with antenatal complications (adjusted beta coefficient (β) = 0.44 (95 % CI, 0.07–0.81)) and in those with perinatal complications (β = 0.61 (95 % CI, 0.09–1.13)) compared to those without these conditions, confirming its discriminant validity. This is important since adverse perinatal events are important causes of development impairments (V. Mung'ala-Odera et al., 2006), including behavioural/emotional problems which can be detected by the CBCL. The lack of association between the CBCL scores and seizures may be related to the small number of seizures in the 301 children

included in this pilot study. These findings suggest that the CBCL scores can be used to discriminate children with a history of pregnancy/perinatal complications from those without these exposures. The findings also highlight the need to account for antenatal and perinatal complications in statistical models with behavioural/emotional problems as an explanatory or dependent variable.

Prevalence of behavioural/emotional problems

Total behaviour/emotional problems occurred in 13% of preschool children living in Kilifi, with internalising problems being more common than externalising problems (22% vs. 10%). The CBCL includes more items for internalising problems which may increase the sensitivity for detecting these problems and thus resulting in a higher prevalence. This has been reported in other studies from New Zealand (Paterson et al., 2007) and Germany (M. M. Gleason et al., 2011). The high prevalence of behavioural/emotional problems are comparable to those in studies from Turkey (11.9%) (Erol et al., 2005), and Germany (12.4%) (Furniss et al., 2006) suggesting behavioural/emotional problems are as common in Kilifi as in any other part of the world. The CBCL's diagnostic statistical manual for mental illnesses (DSM)-oriented scales appeared more conservative than its 7-syndrome model, possibly because the former comprises few items, only those which fitted the DSM diagnosis as judged by an international panel of experts in psychiatry (T. Achenbach et al., 2003).

While the prevalence of attention-deficit hyperactivity disorder (ADHD) symptoms in Kilifi (5%) was comparable to estimates in the literature (Polanczyk et al., 2007), pervasive developmental symptoms were overestimated (>1%) (Fombonne, 2009), supporting use of autism spectrum specific tools in future epidemiological studies. The disability-adjusted life years (DALYs) were only computed for ADHD and anxiety problems, for which disability weights were available in the Global Burden of Disease Study (Salomon et al., 2012). The DALYs results confirmed a substantial burden for ADHD symptoms (2.4 (95%CI, 2.1-2.8)

per 1,000 population) and anxiety problems (4.9 (95%CI, 4.5-5.4) per 1,000 population), similar to other reported studies (Erskine et al., 2014).

Important comorbidities of behavioural/emotional problems were seizures and other medical conditions such as respiratory illnesses and burns. Behavioural/emotional problems are known to be associated with epilepsy, often with a bidirectional relationship (Rodenburg, Stams, Meijer, Aldenkamp, & Deković, 2005), which could indicate a shared genetic susceptibility for both conditions. Respiratory problems were common in Brazilian preschool children with behavioural/emotional problems (Feitosa et al., 2011), but it is possible this is a coincidental association due to susceptibility to both conditions in young children (Haby et al., 2001). All of these medical comorbidities should be included in the package of care for preschool children with behavioural/emotional problems.

Risk factors for behavioural/emotional problems

Several risk factors were associated with behavioural/emotional problems, particularly seizure disorders which explained the greatest variability in a multivariable structural equation model. Adverse perinatal events such as hypoxic ischaemic encephalopathy may be associated with brain damage or social disadvantage (Lai & Yang, 2011) both of which can be associated with behavioural/emotional problems. Both epilepsy and acute seizures were associated with behavioural/emotional problems, with the risk ratios for the former being greater than the latter, as would be expected. The role of epilepsy in behavioural/emotional problems is well recognised in the literature (Davies, Heyman, & Goodman, 2003), but for acute seizures its role is unclear and is discussed further below.

Other risk factors such as socioeconomic status and antenatal and perinatal complications for behavioural/emotional problems were also significant in adjusted generalised linear models. However, they explained little or no variability in a multivariable structural equation model

with seizure disorders, probably because they moderate or mediate the association between seizures and behavioural/emotional problems. Nevertheless, adverse perinatal events such as hypoxic-ischaemic encephalopathy may be associated with brain damage (Lai & Yang, 2011) that is associated with behavioural/emotional problems. It is likely that eating of cassava and soil are markers of poverty/deprivation, which was measured by house status in this study, or is a consequence of the behavioural/emotional problems themselves. Cassava and soil may be directly neurotoxic (Grandjean & Landrigan, 2014; Oluwole et al., 2000; Rivadeneyra-Dominguez et al., 2013) or are associated with learning disability and iron deficiency.

Prevalence and clinical features of acute seizures

The prevalence of acute seizures was high (6.1%), being 2.9% for febrile seizures and 3.2% for acute symptomatic seizures. The febrile seizure estimates are comparable with those of studies from England (2.3%) (Verity et al., 1985) and Tanzania (2.1%) (Storz et al., 2015), but lower than those from America (3.9%) (Nelson & Ellenberg, 1978). The Tanzanian study was conducted in the administrative boundaries rather than in a demographic surveillance system; the lack of regular enumeration in the former may be associated with inaccurate prevalence. Most studies in Africa did not separate acute symptomatic seizures from other acute seizures (Storz et al., 2015), making comparison difficult with this present study. The prevalence of acute seizures remained high even after accounting for age and sex, suggesting that there are common risk factors for these seizures, for example infections, in this area. The results confirm a previous observation that hospital estimates grossly underestimate the true burden of acute seizures in children (Sabbagh, Soria, Escolano, Bulteau, & Dellatolas, 2006; Serem et al., 2015).

The age at onset of acute seizures was 6-25 months, which is within the two year period when most febrile seizures in other settings begin (C. Waruiru & R. Appleton, 2004). The very early onset of seizures at 6 months probably represents the susceptibility age for infections

such as malaria in this area (Bejon et al., 2014). Most acute seizures were generalised tonic-clonic in nature (85%). However complex phenotypes were common (84%) and higher than in a Tanzanian study (Storz et al., 2015) and in studies from England (Verity et al., 1985) and America (Nelson & Ellenberg, 1978). These complex phenotypes can be attributable to malaria or underlying genetic susceptibility (S. M. Kariuki et al., 2011; S. M. Kariuki et al., 2013). Acute seizures co-occurred with epilepsy in 11% of children, and often preceded the onset of epilepsy. Acute seizures may have a shared underlying cause or genetic susceptibility with epilepsy (Thomas & Berkovic, 2014), but it is thought that acute seizures are a risk factor for the development of epilepsy, especially when they are complex and symptomatic (J. A. Carter et al., 2004).

Causes and risk factors for acute seizures

Causes were determined using IMCI clinical algorithms or by linking community data with hospital admissions during the same period. Malaria was the commonest cause (43%) of acute seizures followed by respiratory tract infections (26%). The proportion of malarial acute seizures is similar to hospital studies (R. Idro et al., 2008; Serem et al., 2015) and is high because the study was conducted in a malaria endemic area. These results suggest that control of infectious causes of acute seizures in the community may reduce the burden.

The most important risk factors for acute seizures were family history of febrile seizures, previous hospitalisation (mostly due to malaria), use of bednets, snoring, water availability, consumption of cassava, and socioeconomic status. Family history of seizures is established in the literature as a risk factor for febrile seizures and may suggest genetic susceptibility for acute seizures (Sadleir & Scheffer, 2007). Previous hospitalisation and use of bednets could be markers of falciparum malaria infection/exposure which is known to cause brain damage (R. Idro et al., 2007; Newton & Warrell, 1998). However, bednets contain permethrin that can be neurotoxic (Nasuti et al., 2014), a hypothesis that could not be tested within the study.

Snoring could be related to upper airway obstruction, and has been associated with behavioural/emotional problems in resource rich countries (Beebe et al., 2012). Water availability was a surprising risk factor for acute seizures, raising questions as to whether water in Kilifi is contaminated with heavy metals, which can be neurotoxic. Unprocessed cassava may be a marker of socioeconomic disadvantage which is also a risk factor for febrile seizures (Aydin, Ergor, & Ozkan, 2008), but cassava also contains linamarin which can be neurotoxic (Oluwole et al., 2000). Measures of socioeconomic status were associated with acute seizures similar to previous studies (Aydin et al., 2008).

Medical comorbidities and treatment of acute seizures

Behavioural/emotional problems were prevalent in acute seizures (acute symptomatic and febrile seizures combined) (28%), similar to a study from Germany which reported behavioural/emotional problems in 22% of febrile seizures (Kölfen et al., 1998); both of these prevalences are greater than in controls. It is possible that the acute seizures and behavioural/emotional problems are due to shared underlying causes or genetic susceptibility (Baram & Shinnar, 2002). The association between acute seizures and motor deficits suggests that these seizures could be in the spectrum of neurodevelopment (Gillberg, 2010), Complex acute seizures are also associated with learning disability and peer-relationship problems in this thesis further supporting this hypotheses. These medical comorbidities should be identified and addressed in preschool children with acute seizures.

Only 45% of children with acute seizures were admitted to Kilifi County Hospital during the study period and 6 months before the study started. Admission to hospital was associated with: maternal employment (probably because these mothers can afford transport and user fee costs) (Mwabu, Mwanzia, & Liambila, 1995); non-traditional beliefs which would support the use of biomedical treatment (Kendall-Taylor, Kathomi, Rimba, & Newton, 2008); and comorbidity with epilepsy and motor deficits which are a likely to be a markers of severe

acute seizures. Awareness of the benefits of biomedical treatment for acute seizures in Kilifi, Kenya needs to be improved especially as complex phenotypes could be associated with neurodevelopmental disorders including behavioural/emotional problems (Baram & Shinnar, 2002; Crino, Miyata, & Vinters, 2002).

Associations of behavioural/emotional problems with acute seizures

Behavioural/emotional problems were significantly more common in acute seizures (28%) than in controls without seizures (11%), and slightly higher in acute symptomatic seizures (30%) than febrile seizures (25%). The prevalence of behavioural/emotional problems in febrile seizures is comparable to studies from Germany (22%) (Kölfen et al., 1998) and America (18%) (Nelson & Ellenberg, 1978). Contrary to our study, there were no significant differences in the overall mean scores between febrile seizures and controls in an English study (Verity et al., 1998). Our study was conducted in a malaria endemic area, where it is difficult to distinguish febrile seizures from acute symptomatic seizures (S. M. Kariuki et al., 2011), which are associated with more brain damage (J. A. Carter, Ross, et al., 2005). The prevalence of internalising problems in acute seizures was greater than that for externalising problems, consistent with the greater prevalence of internalising problems in the baseline prevalence estimates discussed in chapter 5 of this thesis. The greater prevalence of internalising problems in acute seizures is consistent with that of repetitive unprovoked seizures in the literature (Rodenburg, Stams, Meijer, Aldenkamp, & Deković, 2005). The Cohen's *d* effect sizes that were based on continuous scores were consistent with the observed increased prevalence for behavioural/emotional problems in acute seizures.

After accounting for potential confounders, such as head injury and antenatal/perinatal complications, all acute seizures, acute symptomatic seizures and febrile seizures remained independently associated with behavioural/emotional problems. These results suggest that there is a biological association between acute seizures and behavioural/emotional problems.

However it is difficult to establish the direction of causality since this was a cross-sectional study. It is possible that some seizures were antecedent to the behavioural/emotional problems, since the CBCL screened for behavioural/emotional problems which occurred in the last two months when most acute seizures may have occurred. Acute symptomatic seizures accounted for more behavioural/emotional problems than febrile seizures since the lower confidence interval for the ratio of risk ratios for the two was greater than one (Altman & Bland, 2003). This finding is not surprising considering acute symptomatic seizures are mainly caused by falciparum malaria which is known to cause neurological damage (Newton & Warrell, 1998). The adjusted association for internalising problems with acute seizures was greater than for externalising problems, similar to the prevalence/frequency differences discussed above. These results support the hypothesis that there is an association between internalising problems and seizures, as is highlighted in the literature (Rodenburg, Stams, Meijer, Aldenkamp, & Deković, 2005).

Risk factors for behavioural/emotional comorbidity in acute seizures

Several risk factors were associated with behavioural/emotional comorbidity of acute seizures, explaining up to 80% variability for externalising problems in the final regression model. A family history of febrile seizures was associated with total behavioural/emotional problems and externalising problems suggesting a shared genetic susceptibility (Baram & Shinnar, 2002). Focal and repetitive acute seizures increased the risk for internalising and externalising problems (Figure 8-1), but prolonged seizures did not show an association. Repetitive acute seizures were important risk factors for behavioural/emotional comorbidity of febrile seizures in Germany (Kölfen et al., 1998). Lack of association with prolonged acute seizures may be in part explained by poor timing of seizures in Kenya since most parents do not own watches (Newton & Kariuki, 2013).

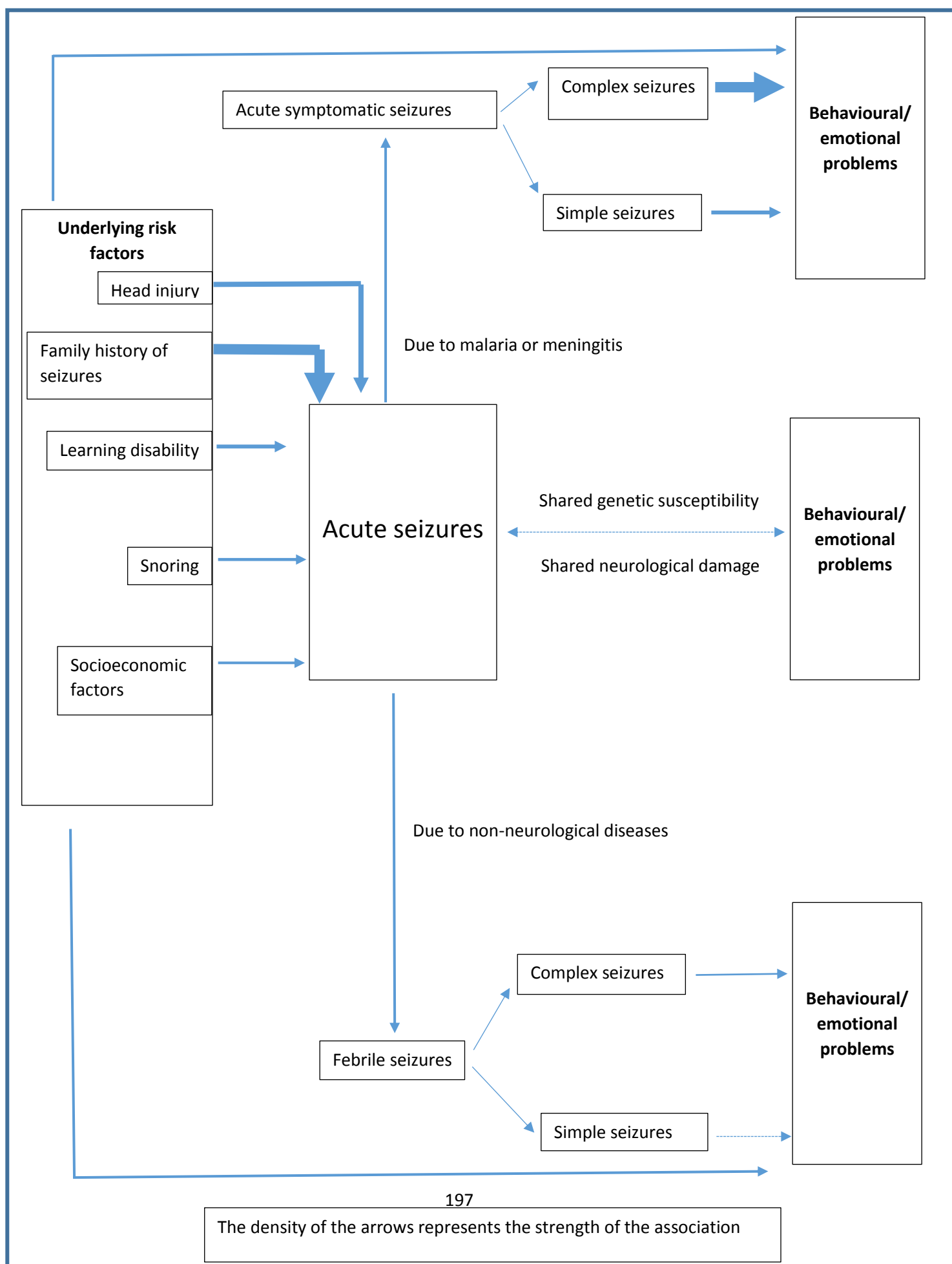
Head injuries and learning disability could be markers of neurological damage thus they are associated with behavioural/emotional comorbidity of acute seizures. Snoring could be a marker of upper airway obstruction (Beebe et al., 2012), resulting in hypoxia that may be associated with behavioural/emotional problems in acute seizures (Figure 8-1). The role of eating soil in behavioural/emotional comorbidity of acute seizures is unclear, but it could be associated with learning disability and iron deficiency, or is a consequence of behavioural/emotional problems. Socioeconomic status factors represent social disadvantage which is a recognised risk factor for behavioural/emotional problems (Rijlaarsdam et al., 2013), and these were also associated with acute seizures. An increasing number of siblings can affect the quality of parenting process (Neece et al., 2012) resulting in behavioural/emotional problems in children with acute seizures (Stein et al., 2014).

Explanations for the association between seizures and behavioural/emotional problems

Taken together, the findings presented here suggest several pathogenic mechanisms for the association between acute seizures and behavioural/emotional problems (Figure 8-1). There may be a common underlying genetic susceptibility for both acute seizures and behavioural/emotional problems; supported by the association with a family history of febrile seizures (Brooks-Kayal, 2011). The association of head injury with behavioural/emotional comorbidity of acute seizures, suggests that shared underlying neurological damage is related to both conditions (Baram & Shinnar, 2002). Environmental factors such as poverty and its correlates may determine the underlying neurological damage (Abubakar, Holding, Van de Vijver, Newton, & Van Baar, 2010), which is then associated with behavioural/emotional problems in acute seizures in preschool children. The increased prevalence of behavioural/emotional problems in acute seizures may be a direct effect of seizures on the brain as suggested by the association with recurrent and focal acute seizures, (Baram & Shinnar, 2002). Acute seizures are a dramatic event which can make parents anxious and

more protective/restrictive about their children which can affect child's behaviour (Stein et al., 2014). A bidirectional relationship between acute seizures and behavioural/emotional is possible, due to the cross sectional design of this study, where either condition may precede the other (D. C. Hesdorffer et al., 2004).

Figure 8-1. Pathogenesis for behavioural/emotional comorbidity of acute seizures



Study strengths and limitations

The strengths of this study are the use of : (i) a community sample drawn from a health demographic surveillance system area that is very representative of a resource-poor setting;(ii) an adequate sample size that provides reliable prevalence and risk factors of behavioural/emotional problems and acute seizures in order to plan preventative and therapeutic interventions; (iii) an internationally recognised behavioural/emotional assessment tool (the CBCL) which was adapted and validated to ensure it had acceptable psychometric properties for assessing behavioural/emotional problems in a rural population; (iv) a robust statistical approach to account for attrition thereby reducing the underestimation of prevalence of behavioural/emotional problems and (v) International League Against Epilepsy criteria for the description of clinical features of seizures including distinguishing between acute symptomatic seizures and febrile seizures.

The limitations of this study are: (i) cross-sectional design which cannot establish direction of causality, especially for the association between acute seizures and behavioural/emotional problems; (ii) cultural beliefs in this area may be associated with stigma and under-reporting of behavioural/emotional problems; (iii) use of Integrated Management of Childhood infections clinical algorithms to identify causes of acute seizures in some children may be subject to recall bias; and (iv) data on maternal well-being was not obtained which may have influenced the behavioural/emotional outcomes of the children.

Public health significance of the findings

These studies have several important public health implications: (i) promotes use of behavioural/emotional assessment tools such as the CBCL in identifying mental health problems in poor regions of the world where there are very few or no qualified child and adolescent psychiatrists, (ii) provides data on the prevalence of acute seizures and mental health problems in preschool children which can inform policy on preventative and

therapeutic interventions for these children, (iii) identifies some preventable risk factors for acute seizures and behavioural/emotional problems that can be easily addressed using simple interventions, (iv) focuses on the preschool period, a time when children can maximally benefit from early preventative or therapeutic interventions before they enrol for schooling, and (v) recommends screening and management of behavioural/emotional problems in preschool children with acute seizures since the two conditions co-exist.

Unique contributions to the literature

The results from the epidemiological studies in this thesis provide the first robust evidence that (i) the prevalence of mental health problems in preschool children is high in a rural Kenyan population and this prevalence is comparable to estimates published from other regions of the world, (ii) the prevalence of acute seizures in preschool children living in rural Kenya is higher than in Europe and America and both febrile seizures and acute symptomatic seizures contribute to this prevalence (iii) acute seizures in preschool children are independently associated with at least two fold-risk of behavioural/emotional problems, and the risk is significantly greater with acute symptomatic seizures than with febrile seizures; and (iv) both acute seizures and behavioural/emotional problems are associated with preventable risk factors such as pregnancy/perinatal complications and socioeconomic disadvantage, which can easily be addressed or prevented by simple public health interventions.

Conclusions

This epidemiological study provides robust evidence that the prevalence of behavioural/emotional problems and acute seizures is high in preschool children living in the community in Kilifi, Kenya. It also shows that the CBCL can be utilised to screen for behavioural/emotional problems in Kenyan preschool children since it has acceptable psychometric properties. Control of infections, improvements in the standard of living and

provision of obstetric services may help reduce the prevalence of behavioural/emotional problems and acute seizures in preschool children. There may be a genetic susceptibility to behavioural/emotional problems and acute seizures as shown by their striking association with a family history of febrile seizures, but future genetic studies are required to confirm this hypothesis.

Behavioural/emotional problems are significantly increased in children with acute seizures and the association between these two conditions is independent of potential confounders. Internalising problems are particularly associated with acute seizures. Acute symptomatic seizures account for most of the behavioural/emotional comorbidity probably because most of these seizures are caused malaria or bacterial meningitis which can cause brain damage. Complex acute seizures, socioeconomic factors, snoring, head injury and learning disability were the most important risk factors for behavioural/emotional comorbidity of acute seizures. A co-diagnosis of epilepsy was not an independent risk factor for behavioural/emotional problems in those with acute seizures, supporting an independent association between acute seizures and behavioural/emotional problems in preschool children from rural Kenya.

These findings support the need to develop preventative and therapeutic interventions for preschool children with behavioural/emotional problems and acute seizures.

Directions for future research

Future studies are required to: (i) clarify the bidirectional relationship between behavioural/emotional problems and acute seizures, preferably by designing community-based longitudinal cohort studies, (ii) examine the role of genetics in the risk for behavioural/emotional problems and acute seizures through genome-wide association studies and (iii) to understand the role of maternal factors particularly depression and quality of

parenting process on the development of behavioural/emotional problems in preschool children.

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Appendices

Appendix 1: Informed consent form

Informed Consent forms

KEMRI Wellcome Trust Research Programme: Patient Information Sheet and Consent Form

A Study of Convulsions/fits and Behaviour Disorders in Younger Children in the Community

KEMRI Kilifi	Symon M Kariuki (principal investigator), Amina Abubakar, Michael Kihara, Anthony K Ngugi, Rachael Odhiambo, Martha Kombe, Evasius Bauni, Charles R Newton
Kilifi District Hospital	Leonard Nasoro
Kings College London	Jacqueline Phillips-Owen
Department of Psychiatry, University of Oxford	Alan Stein

What is KEMRI?

KEMRI is a government institution that carries out medical research to find better ways of preventing and treating illness in the future for everybody's benefit. All research at KEMRI has to be approved before it begins by several national and international committees who look carefully at planned work. They must agree that the research is important, relevant to Kenya and follows nationally and internationally agreed research guidelines. This includes ensuring that all participants' safety and rights are respected.

What is this study?

We would like to find out what proportion of children in the community has epilepsy and behavioural problems, and what the possible causes are. This is important because convulsions/fits are very common in children with infections with fever. Very rarely convulsions may affect the brain of children leading to disruptions in the way a child behaves (for example how they concentrate on household tasks and school work, and how active they are), or lead to epilepsy (a common condition affecting the brain that causes children to have seizures/convulsions from time to time). Learning more about how many children these problems have can help to develop better ways of helping people with similar problems in future.

Why me and what are you asking of me?

Your child is one of 7,500 participants randomly selected from all the children in the area aged 1-6 years. All the participants will be screened for convulsions/fits. Of the 7500 children, about half of them (3,500) will also be screened for behavioural disorders. The children who are screened for behavioural disorders as well as convulsions/fits will be chosen using a system based on chance, without any preference.

If you agree to participate in this study, we will:

Visit your home and ask you questions about your child's history of convulsions/fits and behaviour problems. If you do not want to answer any of the questions you may say so and the interviewer will move on to the next question.

For all participants, if the answers to the questions suggest a history of acute convulsions/fits, we will invite you and your child to attend a special check-up (neuro-assessment clinic) at Kilifi District Hospital to do some more detailed checks to see if there really is any problem. For those participants who have been screened for behavioural problems, if the answers to the questions suggest any behavior that might suggest a need for further checks, we will also invite you and your child to attend this clinic to check if there really is any problem.

If your child is asked to come to the clinic, they will be observed taking part in indoor games for about an hour, and the activity of the brain will be measured using painless leads placed on the top of the head (show photo). You will also be asked for information about your family situation more generally, such as your husband/wife's education, employment and medical history.

We will also ask some parents whose answers do NOT suggest a history of convulsions/fits or any behavior problems to come for further checks, to allow us to compare what is learned with those whose answers do suggest a problem. This will help us learn whether we are measuring convulsions/fits and behavioural disorders properly.

If you agree, we will video-record your child during the second interview so that another doctor can check the assessment the first doctor makes. With your permission these videos may be used in future for teaching purposes.

Are there any risks or disadvantages to me or my child taking part?

The disadvantages of participating in this study are the time taken for interviews at home and – for some – to attend the clinic once or – for even fewer people – twice. You will have to travel to Kilifi to attend the clinic at Kilifi District Hospital, but we will reimburse your transport costs in full. If there are questions that you, or your child, find distressing or too personal or private, you are free to not answer those questions or to withdraw from participating.

Are there any benefits to me/my child of taking part?

By taking part in this study, your child will help us to understand better the extent of convulsions/fits and behaviour problems in this community, and the types of behaviour problems that children with a history of convulsions/fits have. This we hope will improve treatment for children with epileptic seizures in the future.

If we find your child has difficulties concentrating, you and your child will have an opportunity to ask questions about how best to help him or her concentrate and control behaviour. As part of this study we are working on providing formal ways of helping children with these problems. At present, this will be through available psychiatric services in Kilifi District Hospital but in the future we may be able to offer medication or special training to help child with such difficulties and their families.

Those requiring medication for their convulsions will be enrolled at KEMRI epilepsy clinic which provides these drugs in collaboration with the ministry of health. We will also offer you and your

child snacks and a drink on arrival, and children will be offered exercise books and pencils to thank them for participating.

Who will have access to the information I give?

We will not share individual information about you or your child collected as part of this research with anyone beyond a few people who are closely concerned with the study. All of our documents and recordings are stored securely in locked cabinets and on password protected computers.

The knowledge gained from this research may be shared in summary form, without revealing individuals' identities.

At the end of the study, information in this study may be shared with other researchers outside this project, without revealing individuals' identities.

With your permission the videos may be used in future for teaching purposes but confidentiality will be ensured by protecting the identity of the children involved.

What will happen if I refuse to participate?

All participation in research is voluntary. You are free to decide if you want to take part or not. If you do agree you can change your mind at any time without any consequences.

What if I have any questions?

You are free to ask me any question about this research. If you have any further questions about the study, you are free to contact the research team using the contacts below:

Mr Symon Kariuki, KEMRI Wellcome Trust Research Programme, P.O. Box 230, Kilifi. Telephone: 0723 926 339, 041 7522063

If you want to ask someone independent anything about this research please contact:

Community Liaison Manager, KEMRI – Wellcome Trust, P.O.Box 230, Kilifi. Telephone: 0723 342 780/0738 472 281 or 041 7522 063

And

The Secretary – KEMRI/National Ethics Review Committee, P. O. BOX 54840-00200, Nairobi, Tel number: 020 272 2541 Mobile: 0722 205 901 or 0733 400 003

KEMRI-Wellcome Trust Research Programme consent form for: A Study of Convulsions/fits and Behaviour Disorders in Pre-school Children in the Community

I have had the study explained to me. I have understood all that has been read/explained and had my questions answered satisfactorily.

- ☐ **Yes please tick I agree to be interviewed**
- ☐ **Yes please tick I agree for my child to participate in this study**
- ☐ **Yes please tick I agree for my child's interview to be video recorded**
- ☐ **Yes please tick I agree for my child's video to be used in future for teaching purposes**

I understand that I can change my mind at any stage and it will not affect me/my child in any way.

Signature: _____ **Date:** _____

Participant/guardian Name: _____ **Time:** _____

(please print name)

Where a parent/guardian cannot read, a witness* may observe consent process and sign below if needed:

I attest that the information concerning this research was accurately explained to and apparently understood by the subject/parent/guardian and that informed consent was freely given by the subject/parent/guardian.

Witness' signature: _____ **Date** _____

Witness' name: _____ **Time** _____

**A witness is a person who is independent from the trial or a member of staff who was not involved in gaining the consent.*

Thumbprint of the parent as named above if they cannot write:

Investigator/designee statement:

I have followed the study SOP to obtain consent from the [participant/guardian]. S/he apparently understood the nature and the purpose of the study and consents to the participation [of the child] in the study. S/he has been given opportunity to ask questions which have been answered satisfactorily.

Designee/investigator's signature: _____ **Date** _____

Designee/investigator's name : _____ **Time** _____

(Please print name)

THE PARENT/GUARDIAN SHOULD NOW BE GIVEN A SIGNED COPY TO KEEP

KEMRI Wellcome Trust Research Programme: Controls Information Sheet and Consent Form

A Study of Convulsions/fits and Behaviour Disorders in Pre-school Children in the Community: Healthy Children

KEMRI Kilifi	Symon M Kariuki (principal investigator), Amina Abukakar, Michael Kihara, Anthony K Ngugi, Rachael Odhiambo, Martha Kombe, Evasius Bauni, Charles R Newton
Kilifi District Hospital	Leonard Nasoro
Kings College London	Jacqueline Phillips-Owen
Department of Psychiatry, University of Oxford	Alan Stein

About your child and this study

You recently agreed for your child to participate in a KEMRI study on conditions where children have convulsions/fits and/or behavioural problems. As you know, your child was found to be completely well. However, we are now inviting you and your child to take part in the next stage of this study to help us to learn more about convulsions/fits and/or behavioural problems. Your child does not have these problems but, as part of our study, we are asking your child to participate in order to compare children with these problems with other children who do not have them. In this way, your child's participation will help us to understand more about an illness affecting many other children.

What is KEMRI and what is this study about?

KEMRI is a government organisation that carries out medical research to find better ways of preventing and treating illness in the future for everybody's benefit.

All research at KEMRI has to be approved before it begins by several national and international committees who look carefully at planned work. They must agree that the research is important, relevant to Kenya and follows nationally and internationally agreed research guidelines. This includes ensuring that all participants' safety and rights are respected.

Overall, in this study, we aim to compare healthy children and those with convulsions and/or behavioural problems in their behavior and their reactions to different kinds of noises and pictures.

Why do you want to talk to me and what does it involve?

We have used a system based on chance, without preference, to choose the healthy children invited to participate in this study, from all those who participated in the first stage recently. Approximately up to 300 children between the ages of 1 and 6 years have been chosen from a list of all the children

interviewed recently in a previous stage of this study and who did not have either convulsions or behaviour disorders

If you agree to participate in this study, we will:

Ask you questions about your child's sociodemographic information (such as age, schooling and number of siblings and economic situation of the family) and medical history such as previous illnesses and history of hospitalisation. Questions about education will be useful in helping us understand if these two conditions under investigations negatively impact educational performances of those children enrolled in school. If you do not want to answer any of the questions you may say so and the interviewer will move on to the next question. The interview with you will take place at home. No-one else but the interviewer will be present unless you would like someone else there.

Invite you and your child to attend a special clinic (neuroassessment clinic) at Kilifi District Hospital to talk to a doctor in more detail and have a neurological examination. At the clinic, your child will be observed taking part in indoor games for about an hour, and the activity of the brain will be measured using painless leads placed on the top of the head (show photo). You will also be asked for information about your family situation more generally, such as your husband/wife's education, employment and medical history.

Videos will be recorded in the second stage of the study so that another doctor can use them to make an independent assessment of your child's behaviour. With your permission these videos may be used in future for teaching purposes.

Are There Any Risks or Disadvantages to Me or My Child Taking Part?

We do not think there are any risks involved in participating in this study. If there are questions that you, or your child, find distressing or too personal or private, you are free to not answer those questions or to withdraw from participating. The main disadvantage is the time taken to participate in the study. You will have to travel to Kilifi to attend the clinic at Kilifi District Hospital, but we will reimburse your transport costs in full.

Are there any benefits to me/my child of taking part?

There are no individual benefits to taking part in this study but you will help us to understand better the things that cause some children to develop convulsions/fits and behavioural problems, which may improve prevention and treatment for children with convulsions/fits and behavioural problems in future.

If your child is found to have any problems through the assessments we are doing, we will let you know about this and discuss with you what can be done to help. Children requiring medication for convulsions will be enrolled in the KEMRI epilepsy clinic which provides these drugs in collaboration with the ministry of health. Those with behavioural problems will be seen by professionals from Kilifi District hospital who are trained in dealing with these problems. We will also offer you and your child snacks and a drink on arrival. Children will be offered pencils and exercise books to thank them for participating.

Who will have access to the information I give?

We will not share individual information about you or your child collected as part of this research with anyone beyond a few people who are closely concerned with the study. All of our documents and recordings are stored securely in locked cabinets and on password protected computers.

The knowledge gained from this research may be shared in summary form, without revealing individuals' identities.

At the end of the study, information in this study may be shared with other researchers outside this project, without revealing individuals' identities.

With your permission the recorded videos may be used in future for teaching purposes but confidentiality will be ensured by protecting the identity of the children involved.

What will happen if I refuse to participate?

All participation in research is voluntary. You are free to decide if you want to take part or not. If you do agree, you can later change your mind at any time without any consequences.

What if I have any questions?

You are free to ask me any question about this research. If you have any further questions about the study, you are free to contact the research team using the contacts below:

Mr Symon Kariuki, KEMRI Wellcome Trust Research Programme, P.O. Box 230, Kilifi. Telephone: 0723 926339, 041 7522063

If you want to ask someone independent anything about this research please contact:

Community Liaison Manager, KEMRI – Wellcome Trust, P.O.Box 230, Kilifi. Telephone: 0723 342 780/0738 472 281 or 041 7522 063

Or

The Secretary - KEMRI/National Ethics Review Committee, P. O. BOX 54840-00200, Nairobi, Tel number: 020 272 2541 Mobile: 0722 205 901 or 0733 400 003

KEMRI-Wellcome Trust Research Programme consent form for: A Study of Convulsions/fits and Behavior Disorders in Pre-school Children in the Community

I have had the study explained to me. I have understood all that has been read/explained and had my questions answered satisfactorily.

- ☐ **Yes please tick I agree to be interviewed**
- ☐ **Yes please tick I agree for my child to participate**
- ☐ **Yes please tick I agree for my child's interview to be video recorded**
- ☐ **Yes please tick I agree for my child's video to be used in future for teaching purposes**

I understand that I can change my mind at any stage and it will not affect me/my child in any way.

Signature: _____ **Date:** _____

Participant/guardian Name: _____ **Time:** _____
(please print name)

Where a parent/guardian cannot read, a witness* may observe consent process and sign below if needed:

I attest that the information concerning this research was accurately explained to and apparently understood by the subject/parent/guardian and that informed consent was freely given by the subject/parent/guardian.

Witness' signature: _____ **Date** _____

Witness' name: _____ **Time** _____

**A witness is a person who is independent from the trial or a member of staff who was not involved in gaining the consent.*

Thumbprint of the parent as named above if they cannot write:

Investigator/designee statement:

I have followed the study SOP to obtain consent from the [participant/guardian]. S/he apparently understood the nature and the purpose of the study and consents to the participation [of the child] in the study. S/he has been given opportunity to ask questions which have been answered satisfactorily.

Designee/investigator's signature: _____ **Date** _____

Designee/investigator's name : _____ **Time** _____

(Please print name)

Appendix 2: Acute seizure screening questionnaire

Today's Date		Y Y Y Y M M D D	TDATE
Study Number			STNO
PID			PID
RESID			RESID
Name and Surname			NAME
Age (estimated if date of birth unknown)		Y Y Y Y M M D D	AGE
Gender		Male/ Female	SEX
For all children in the study aged 0-6 years/ unable respondents.			
Mother/Guardian's Name			MOTHNAME
Who will answer questions about the index?		1 = Self 2 = Self and other 3 = The Index's mother 4 = The Index's father 5 = Index's grandmother 6 = Index's sibling 7 = Another relative 8 = Other	QCHILD
For all children in the study aged 0-6 years/ unable respondents.			
Is the informant one who mainly takes care of the Index patient?		Yes/ No	INFORM
Answer Yes(Y) or No (N)			
1. Vidze mwanao adzangwe kufitika hangu azhalwe? <i>Has your child ever had a fit?</i>		Yes/ No	HAVEFITS
2. Mutu adzangwe kukwambira kukala mwanao wafitika? <i>Has someone ever told you that your child had fits?</i>		Yes/ No	SOMEFITS
3. Udzangwe kwambirwa kukala mwanao ana vitsala hedu kufitika kwa vitsala? <i>Have you ever been told that your child had epileptic fits?</i>		Yes/ No	EPIFITS
4. Mwanao adzangwe kukala na vipindi ambazho anagwa hotsi na kungamiza fahamu <i>Has your child ever had attacks in which (s)he fall to the ground with loss of consciousness?</i>		Yes/ No	CONSC
5. Mwanao adzangwe kugwa hotsi bila sababu yoyosi na <i>Has your child ever fallen to the ground without reason and experienced:</i>			
Kupigwa ni zhoyo <i>Twitching</i>		Yes/ No	TWITCH
Kuthethemwa ni mikono yosi hedu magulu gosi bila kudziunya <i>Shaking of the arms or legs without control</i>		Yes/ No	SHAKING
Na kudzikodzolera <i>Wetting him(er)self</i>		Yes/ No	WETTING
Kuluma luthimi <i>Biting of the tongue</i>		Yes/ No	BITING
6. Udzangwe kwambirwa ni dakitari kukala mwanao ana vitsala hedu kufitika kwa vitsala?		Yes/ No	DRHAVE

Have you ever been told by a doctor that your child has epileptic fits?

7. Kufitika kungine kwa sababishwa ni mwiri moho
Did some seizures occur with a febrile illness or fever?

Yes/ No

☐ 1

SZ_FILL

If yes to any of the above 7 questions:

I. Wafitika rini mwanzo? *When did the seizures start?*

 Y Y Y Y M M D D

SZ_START

II. Wafitika rini mwisho? *When was the last seizure?*

 Y Y Y Y M M D D

LAST_SZ

III. Kufitika kwahusisha sehemu mwenga ya mwiri?

Did the seizures involve one body part?

Yes/ No

☐ 1

SZ_FOC

IV. Kufitika kwahusisha sehemu zosi za mwiri ?

Did the seizures involve all body parts?

Yes/ No

☐ 1

SZ_GEN

V. Kufitika kwahala muda wani

How long did the seizures last

Yes/ No

☐ 1

SZ_DUR

VI. Kufitika kwahala Zaidi ya dakikat 30

Did the seizures last ≥ 30 minutes

Yes/ No

☐ 1

SZ_SE1

VII. Kufitika kwahala Zaidi ya muda wa kuchemusha nyungu ya matsere

Did the seizures last longer than boiling a pot of maize

Yes/ No

☐ 1

SZ_SE2

VIII. Kufitika kwahala Zaidi ya muda wa ibada kanisani

Did the seizures last longer than a sermon in church or mosque

Yes/ No

☐ 1

SZ_SE3

IX. Kufitika na/au wo mwiri moho watibiwa sipitali?

Were the seizures and/or the febrile illness treated at a hospital?

Yes/ No

☐ 1

SZ_HOS

X. Unahumira madawa gogosi ga kufitika kwa wakathi uno?

Are you currently using any drugs for convulsions?

Yes/ No

☐ 1

MEDIC

XI. Udzangwe kwenda kwa muganga kwa kulagulwa kufitika?

Have you ever visited a traditional healer for treatment of seizures?

Yes/ No

☐ 1

TRAD_H

Family and Community seizure information

Vidze hana mutu yeyosi kwenye familiya ambaye anafitika

Does any other member of the family have seizures?

Yes/ No

☐ 1

FAM_SZ

Ikikala ahaha ni hani? IfWho?

Name		Relationship	Agincourt No.						
1.									
2.									
3.									

Unamanya muhoho yeyosi (9 months-6 years) ambaye anafitika *Do you know of other child(9-6years)with seizures?* ☐ **ANYB_SZ**
Yes/ No

Ikikala a haho ni hani? *Who?*

Name	Relationship	Kilifi No.
1.		☐ ☐ ☐ ☐ ☐ ☐ ☐
2.		☐ ☐ ☐ ☐ ☐ ☐ ☐
3.		☐ ☐ ☐ ☐ ☐ ☐ ☐

Interviewer:

Answer the question below by ticking the appropriate answer. An individual will only be referred if the answer to ANY of the above 7 questions **YES**

Should this person be referred for further evaluation? Yes/ No ☐ **REF_EVAL**

Interviewer:

Has the information sheet been read to the respondent? Yes/ No ☐ **COM_SHT**

Has the respondent consented to participate in the study? Yes/ No ☐ **CONSENT**

If NO consent is given, what are the reasons given for the decline?

1	
2	
3	

REAS_NOC1

REAS_NOC2

REAS_NOC3

Interviewer:

Answer the questions below by ticking the appropriate answer. An individual will only be referred as a control for Phase III if they answer **NO** to all the first 6 questions. Please proceed to recruit the controls as follows;

Are you willing to be a control in this study (please explain what a control is if need be)? ☐ **CTRL_ST**
Yes/ No

If the individual responds YES to the above 2 question, please notify them of the intention to invite them to the assessment centre for assessments.

Has this person agreed to come for assessment? Yes/ No ☐ **AGREED**

Sign if you have checked that the form is complete _____.

Appendix 3: Kiswahili version of the Child Behaviour Checklist

Today's Date	Y Y Y Y M M D D	TDATE
Study Number	B S K 1 4	STNO
PID	1 1 1 1 1 1 1 1 1 1	PID
RESID	1 1 1 1 1 1 1 1 1 1	RESID
Name and Surname		NAME
Age (estimated if date of birth unknown)	Y Y Y Y M M D D	AGE
Gender	Male/ Female	SEX

Score	Number of items	Total score
0		
1		
2		
Total (TOT_SCORE)		

Should this person be referred for further evaluation? Yes/ No **REF_EVAL**

Referral Date **REF_DATE**

Katika sehemu hii tutaongea au nitakuuliza maswali kuhusu tabia za mwanao. Ikiwa kutakuwa na swali ambalo utakuwa hukuelewa tafadhali uwe huru kuniuliza. Katika kila swali taangalia kama kitu au kitendo hicho kilifanyika ndani na miezi miwili iliyopita.

Uliza jina la mtoto ili ujue unaongea kuhusu nani.

Katika kila swali utajibu kulingana na hivi vipengele;

A) NI KWELI au SI KWELI

B) KWELI KIASI au MARA NYINGI

Start Time: [:]

		Hapana	Ndio
1	Huumwa au huwa na maumivu (bila sababu yoyote ya kiafya, na wala sio kuumwa na tumbo au kichwa)	0	1 2
2	Hujifanya mdogo(mchanga) kwa umri wake	0	1 2
3	Huogopa kujaribu vitu vipya (kama kubembea,kupanda ngamia)	0	1 2
4	Huepuka kuangalia watu machoni	0	1 2
5	Hawezi kumakinika au kuwa makini kwa muda mrefu	0	1 2
6	Hawezi kuketi akatuliza, yuko juujuu, yuko mbio mbio kila wakati na utukutu mwingi	0	1 2
7	Hukasirika vitu vikiwa havijapangwa kama kawaida yake (kwa mfano huwa ana mahali anaweka vitabu/vitu vya kuchezea)	0	1 2
8	Hawezi kungoja au kusubiri, akitakacho hukitaka wakati huo huo	0	1 2
9	Hutafuna vitu ambavyo si vya kuliwa (kama karatasi au mchanga)	0	1 2
10	Hujigandamiza au anategemea sana watu wazima	0	1 2
11	Hutafuta usaidizi mara kwa mara	0	1 2
12	Huvimbiwa,hapati choo (ijapokuwa si mgonjwa)	0	1 2
13	Hulia sana	0	1 2
14	Ni katili kwa wanyama (kama kupiga wanyama, kuchukuwa mnyama na kumuangusha chini)	0	1 2
15	Mjeuri	0	1 2
16	Matakwa yake lazima yatekelezwe saa hiyo hiyo	0	1 2

17	Huharibu vitu vyake mwenyewe	0	1	2
18	Huharibu vitu vya familia yake au vya watoto wengine	0	1	2
19	Huharisha au hupata choo cha maji maji (ijapokua) si mgonjwa	0	1	2
20	Huwa si mtiifu	0	1	2
21	Husumbuliwa na mabadiliko yoyote ya kawaida/ratiba yake ya kawaida (mfano: asubuhi hadi apige mswaki ndio anywe chai)	0	1	2
22	Hapendi kulala peke yake	0	1	2
23	Huwa hajibu watu wanapoongea naye	0	1	2
24	Hali vizuri (eleza)_____	0	1	2
25	Haelewani na watoto wenzake	0	1	2
26	Hajui kufurahika,hana utoto huonyesha tabia za kiutu uzima (mahali kwa kufurahi yeye huwa haonyeshi)	0	1	2
27	Haoni ana hatia hata baada ya kukosa adabu	0	1	2
28	Hapendi kutoka nje ya nyumba/mji (kucheza mbali na nyumbani)	0	1	2
29	Yeye huvunjika moyo kwa haraka kama hawezi kitu fulani	0	1	2
30	Huona wivu kwa haraka	0	1	2
31	Hula au hunywa vitu ambavyo si chakula (lakini si peremende) (kama mafuta ya taa, nguo au rubber) (eleza)_____	0	1	2
32	Huogopa baadhi ya wanyama,hali fulani au pahali (sehemu) K.M(_____)	0	1	2
33	Hisia zake huudhiwa kwa urahisi	0	1	2
34	Huumia mara kwa mara,hupata ajali kwa urahisi	0	1	2
35	Huhusika katika kupigana mara kwa mara	0	1	2
36	Hujihusisha katika kila kitu (akiona mtu anafanya kitu yeye pia hutaka kufanya)	0	1	2
37	Hukasirika sana anapotengwa kutoka kwa wazazi wake	0	1	2
38	Ana shida ya kupata usingizi	0	1	2
39	Huumwa na kichwa(bila sababu yoyote ya kiafya)	0	1	2
40	Hupiga wengine	0	1	2
41	Huzuia pumzi zake (kuvuta pumzi ndani na kuzuia)	0	1	2
42	Huumiza wanyama au watu bila kukusudia (bila kujua analofanya)	0	1	2
43	Huonekana hana raha bila sababu	0	1	2
44	Huwa katika hali za hasira	0	1	2
45	Huhisi kutapika, huhisi ugonjwa (bila sababu yoyote ya kiafya)	0	1	2
46	Kutetemeka kwa sehemu fulani za mwili (kama kwa jicho au kiganja cha mkono)(eleza)_____	0	1	2
47	Ana wasi wasi, ni mwoga ,anashtuka shtuka	0	1	2
48	Hupata ndoto mbaya (za kutisha)	0	1	2
49	Hula kupita kiasi	0	1	2
50	Huchoka kupita kiasi	0	1	2
51	Huonyesha hofu bila sababu yoyote	0	1	2
52	Huhisi uchungu anapokwenda haja kubwa (bila sababu yoyote ya kiafya)	0	1	2
53	Hushambulia watu	0	1	2
54	Huchokoa pua, ngozi au sehemu nyenginezo za mwili	0	1	2
55	Huchezea sehemu zake za siri sana	0	1	2
56	Hana umakini au utaratibu	0	1	2
57	Huwa na shida ya macho (bila sababu yoyote ya kiafya) (eleza)_____	0	1	2
58	Hata ukimuadhibu habadilishi tabia yake	0	1	2

59	Hubadilisha kwa haraka kutoka mchezo/shughuli moja hadi nyingine	0	1	2
60	Huwa na harara au matatizo mengine ya ngozi (bila sababu yoyote ya kiafya)	0	1	2
61	Hukataa kula	0	1	2
62	Hukataa kucheza michezo ya kutumia nguvu	0	1	2
63	Hutikisa kichwa au mwili mara kwa mara	0	1	2
64	Hukataa kwenda kitandani usiku	0	1	2
65	Hukataa kufundishwa jinsi ya kwenda haja (eleza)	0	1	2
66	Hupiga mayowe sana	0	1	2
67	Huonyesha kutojali au kutorejesha ule upendo anao onyeshwa (kama kutoa shukurani anapopewa kitu)	0	1	2
68	Hajiamini au huona aibu kwa urahisi	0	1	2
69	Ni Mchoyo au hapendi kugawana	0	1	2
70	Huonyesha upendo kidogo kwa watu (haonyeshi shukurani)	0	1	2
71	Huonyesha kutoshughulika na vitu vilivyo karibu naye	0	1	2
72	Huonyesha kutokuwa na woga wa kuumia	0	1	2
73	Ana haya	0	1	2
74	Hulala muda mfupi kuliko watoto wengine wakati wa mchana /au usiku	0	1	2
75	Hujipaka au huchezea kinyesi	0	1	2
76	Ana shida ya kuongea (eleza)	0	1	2
77	Huonekana amezubaa au mwenye mawazo	0	1	2
78	Huumwa na tumbo (bila sababu yoyote ya kiafya)	0	1	2
79	Hubadilika haraka kutoka kuwa na huzuni hadi (mfano amechapwa hasira zake huchukua muda gani)	0	1	2
80	Ana tabia za ajabu (eleza)	0	1	2
81	Ni mkaidi au mwenye kuudhika kwa urahisi	0	1	2
82	Hubadili hisia kwa gafla	0	1	2
83	Hununa wakati mwingi	0	1	2
84	Huzungumza au hulika akiwa usingizini	0	1	2
85	Mwepesi wa hasira au hupiga mayowe na kugaagaa chini anapokua na hasira	0	1	2
86	Yeye hujali sana kuwa msafi au nadhifu	0	1	2
87	Huwa mwoga sana na mwenye hofu	0	1	2
88	Hapendi ushirikiano	0	1	2
89	Si mchangamfu huenda pole pole au hukosa nguvu	0	1	2
90	Hana raha ana huzuni, mnyong'onyevu (kuwa mnyonge)	0	1	2
91	Huwa na kelele zisizo za kawaida	0	1	2
92	Hukasirishwa na watu asiowajua au hali mpya (akiona watu asiowajua hukasirika au mahali kama hajapazoea) Eleza	0	1	2
93	Hutapika (bila sababu zozote za kiafya)	0	1	2
94	Huamka mara kwa mara wakati wa usiku	0	1	2
95	Hutembea mbali huranda randa ovyo ovyo	0	1	2
96	Hupenda kushughulikiwa/kuonekana sana (kutengezewa vitu)	0	1	2
97	Hulalamika au kunungunika	0	1	2
98	Anajitenga na wenzake hataki kuhusika nao	0	1	2
99	Huwa na wasi wasi	0	1	2
100	Tafadhali niambie shida zozote ambazo mwanao yuko nazo ambazo hatujazizungumzia			

--	--

Tafadhali hakikisha umejibu vipengele vyote. Piga mstari kwa lolote ambalo una wasi wasi nalo

Wasi wasi wako mkubwa kuhusu mtoto wako ni nini

Tafadhali eleza vitu vizuri zaidi kuhusu mtoto wako

Kuna jambo ambalo mwanao anafanya linalo kutia wasiwasi

Kuna jambo ambalo unatarajia mwanao aweze kufanya katika umri wake lakini hawezi au hajafanya

Comments:

End time: [:]

Checked by: _____

Entry 1: _____

Entry 1: _____

Appendix: 4: Parental risk factor questionnaire

Today's Date		Y Y Y Y M M D D	TDATE
Study Number			STNO
PID		1 1 1 1 1 1 1 1	PID
RESID		1 1 1 1 1 1 1 1	RESID
Name and Surname			NAME
Age (estimated if date of birth unknown)	Y Y Y Y M M D D	DOB	1 1
			AGE
Gender	Male/ Female		SEX
		1	

Does s/he attend school?		Yes/ No	☐	SCH
Mother/Guardian's Name:				GDNAME
Who will answer questions about the index?	1 = Self	5 = Index's grandmother	☐	RESP
	2 =Self and other	6 = Index's sibling		
	3 = The Index's mother	7 = Another relative		
	4 = The Index's father	8 = Other		
Is the informant one who mainly takes care of the Index patient?		Yes/ No	☐	INFCT

Interviewer:

Has the information sheet been read to the respondent?		Yes/ No	☐	COMSHT
Has the respondent consented to participate in the study?		Yes/ No	☐	CONSENT
If NO consent is given, what are the reasons given for the decline?	1	REAS_NOC1		
	2	REAS_NOC2		
	3	REAS_NOC3		

Mother's Socio-demographic Information

Q1	Mother's date of birth	Y Y Y Y M M D D	MDOB
Q2	Age in completed in years	1	MOMAGE
Q3	Mother's religious affiliation	1.Catholic 2.Protestant 3.Islam 4.Traditional 5.None 6.Other(Specify	MOMREL
Q4	Marital status	1. Never married 2.Married 3.Separated 4. Divorced 5. Widowed	MOMMST
Q5	Mother's ethnic group	1. Giriama 2. Chonyi 3.Kauma	MOMEG

4. Other Mijikendas 5. Luos 6.Others			
Q6	Has the mother ever attended school?	1.Yes 2.No 3. Do not know	MOMSCH
Q7	If YES, what is the mother's highest level of education?	1. Primary incomplete 2. Primary 3. Secondary incomplete 4. Secondary 5.High school/A-level 6. Post-secondary 7. Other (specify)	MOMLED U
Q8	If other, please specify		
Q9	Has the mother's partner ever attended school?	1.Yes 2.No 3. Do not know	PATSCH
Q10	Partner's level of education	(Use codes in Q7)	PATLED U
Q11	If other, please specify		
Q12	Has the Caregiver ever attended school?	1. Yes 2.No 3. Do not know	CARESC H
Q13	Caregiver's level of education	(Use codes in Q7)	CARELE DU
Q14	Does the mother do anything to earn cash?	1. Yes 2.No 3. Do not know	MOMEAC AC
Q15	If YES, what is the mother's occupation?	1. Prof /Technical 2.Adm/Mngt 3.Clerical 4. Agric 5.Production/ 6.Services 7.Crafts 8. Others (specify)_____	MOMOC C
Q16	If other, please specify		
Q17	Does her partner do anything to earn cash?	1. Yes 2.No 3. Do not know	PATECA C
Q18	If YES, what is his occupation?	(Use codes in Q15)	PATOCC
Q19	Does the caregiver do anything to earn cash?	1. Yes 2.No 3. Do not know	CAREEC AC
Q20	If YES, what is his occupation?	(Use codes in Q15)	CAREOC C
Q21	If other, please specify		
Q22	Mother's age at first birth		AGEBIRT H1
Q23	Number of children ever born		CEB
Q24	Number of children living with mother		CLWM
Q25	Number of children living elsewhere		CELSE

Q26	Number of children dead		CDEAD
Q27	Is the father alive?	Yes/ No	FALIVE
Q28	If he died, what did he die from?		FCADE

SOCIO – ECONOMIC STATUS

Water Source:	Piped water		
a) What is the source of water for members of the household?	1. Piped into dwelling 2. Piped into compound or plot 3. Public tap 4. Open well in compound or plot 5. Open public well 6.Spring, 7. River 8. Pond/ lake 9. Dam 10. Rainwater 11. Bottled water		WATER
b) How long does it take you to go there, get water and come back?	1. On premises 2. Minutes.		LWATER
c) How frequently is water available from this source?	1. Usually / always available, 2. Several hours per day 3. Once or twice a week 4. Infrequently		FWATER
Toilet facilities	1. Flush toilet		
a) What kind of toilet facilities does your household have?	2. Traditional pit latrine 3. Ventilated pit (VIP) latrine 4. No facilities/ bush/ field 5. Others-----		TOILET
b) Do you share this toilet with other households?	1. Yes 2. No		STOILET
c) How many other households use this toilet?	1. Less than 5, 2. 5-9 3. 10 or more		HTOILET
House	1. Earth/ mud/ dung/ sand 2.Wood planks		
a) Main material of the floor (observation)?	3. Palm, bamboo 4. Parquet/ polished wood 5. Vinyl or asphalt strips 6. Ceramic tiles 7. Carpet 8. Other ----- (specify)		FLOOR
b) Main material of the roof?	1. Grass/thatch 2.Tins, cans, 3. Corrugates iron 4.Asbestos sheets, 5. Concrete 6.Tiles 7. Other -----(specify)		ROOF
c) State of repair of the building	1.Completely dilapidated shack 2.Needs major repairs 3.Needs no or minor repairs 4.Being repaired now 5.Under construction		SREPAIR

d) Window type	1. Glass, 2. Shutters, 3. Wire mesh 4. Open, 5. None		WINDOW												
e) Does your household have	<table border="1"> <tr> <td>Electricity</td> <td> </td> </tr> <tr> <td>Solar</td> <td> </td> </tr> <tr> <td>Radio</td> <td> </td> </tr> <tr> <td>Television</td> <td> </td> </tr> <tr> <td>Telephone/mobile</td> <td> </td> </tr> <tr> <td>Refrigerator</td> <td> </td> </tr> </table>	Electricity		Solar		Radio		Television		Telephone/mobile		Refrigerator			ELECTRICITY SOLAR RADIO TELEVISION TELEPHONE REFRIGERATOR
Electricity															
Solar															
Radio															
Television															
Telephone/mobile															
Refrigerator															
Livestock	Write how many														
a) How many animals (e.g. sheep, goats, cows, 999=don't know)	1. None 2. Some (less than 5) 3. Many (more than 5)		ANIMALS												
b) How many chickens and ducks? 999=don't know			CHICK_D UCKS												
Fuel	1. Electricity 2. LPG/natural gas, 3. Biogas 4. Paraffin/kerosene, 5. Coal, lignite 6. Charcoal from wood, 6. Firewood/straw 7. Dung 8. Other.....(specify)		FUEL												
a) What type of fuel does your household mainly use for cooking?															
Ownership	1. Bicycle 2. Motorcycle/scooter 3. Car/truck		OWN												
a) Does any member of your household own:															
b) Does your household own this structure (house, flat, and shack), do you rent it, or do you live here without paying?	1. Owns, 2. Pays rent/lease 3. No rent, w. Consent of owner 4. No rent, squatting		STRUCT URE												
c) Does your household own the land on which the structure (house, flat, and shack) sits?	1. Owns, 2. Pays rent/lease 3. No rent, w. Consent of owner 4. No rent, squatting		LAND												
Waste disposal	1. Regular collection by government 2. Infrequent collection by government 3. Pays for private collection, 4. Composted, 5. Dump, bury, burn in compound 6. Dump in street/empty plot, 7. Other...(specify)		WDISPOS E												
a) How does this household dispose of kitchen waste and trash?															

PAST MEDICAL HISTORY

Family Seizure History			
Does anyone have seizures (fits) in the family?	Yes/ No	☐	SF
If so, who?			WHOSD
Has anyone in the family ever had seizures (fits) in the past?	Yes/ No	☐	SFP
Who?			WHOSF P
Do any of the brothers or sisters have seizures?	Yes/ No	☐	BSS
Has your mother had seizures?	Yes/ No	☐	MS
Has your father had seizures?	Yes/ No	☐	FS
Does anyone of your family have seizures associated with fevers?	Yes/ No	☐	SAF
Please describe:			
Pregnancy	Normal/ Abnormal	☐	NP
If abnormal, what was the problem?			NPP
Where was the delivery?	1 = Hospital, 2 = Clinic 3 = Home 4 = Don't Know	☐	DL
Delivery	Normal/ Abnormal	☐	NAD
If abnormal, what was the problem?			NADP
Were there any problems after delivery?	Yes/ No	☐	PAD
If so, what?			
Did the baby have difficulties in breathing after delivery?	Yes/ No	☐	DBR
Did the baby have difficulties in crying after delivery?	Yes/ No	☐	DCRY
Did the baby have difficulties in breast-feeding after delivery?	Yes/ No	☐	DFEED
Are you still breast feeding?	Yes/ No	☐	DFC
How many times did/ do you breastfeed in a day?		☐	BFND
If stopped breastfeeding, how long(mnths) did you breastfeed?		☐	BFL
Has s/he been admitted to hospital previously?	Yes/ No	☐	HAP
For what?			DGS
When?			DOA
Has s/he ever had a head injury?	Yes/ No/ Don't Know	☐	HI
If YES, did s/he loses consciousness at the time of the head injury?	Yes/ No/ Don't Know	☐	HIC

Was s/he admitted into the hospital at the time of the head injury?	Yes/ No/ Don't Know	☐	HIA
Does s/he often eat cassava?	Yes/ No/ Don't Know	☐	ECAS
Has s/he ever used drugs?	Yes/ No/ Don't Know	☐	UDRGS
Are there any dogs in your household?	Yes/ No/ Don't Know	☐	DC
Are there any cats in your household?	Yes/ No/ Don't Know	☐	CC
Does your child eat pork?	Yes/ No/ Don't Know	☐	EP
Does your child eat soil?	Yes/ No/ Don't Know	☐	ES
Does your child snore more than 3 nights per week?	Yes/ No/ Don't Know	☐	SW
Does your child use or has s/he used bed nets?	Yes/ No	☐	BNET
For how long has s/he slept under bed nets?		☐	DBNET
Is the bed net frequently replaced or treated?	Yes/ No	☐	TBNET
Other relevant history?	Yes/ No	☐	ORH
Please describe	☐		

Road to Health Card Details

Birth weight	☐	☐	☐	☐	BW
Birth weight at first visit to clinic	☐	☐	☐	☐	BWC
Completed Immunization	☐				CIM
Growth Curve	☐				GC
Any special comments on the road to health card	☐				SCOMM
How long have you lived in your current location (in years)?	☐	☐	☐	☐	KDURY

Sign if you have checked that the form is complete _____.

Appendix 5: Clinical history form

Study Number	B S K 1 4									
PID	1 1 1 1 1 1 1									
Date of Assessment	Y Y Y Y M M D D									
Name and Surname										
Gender	Male/Female 1									
Date of Birth	Y Y Y Y M M D D									

Clinical History Summary			
Does s/he have acute (febrile) seizures	Yes/ No	1	AFS
Does s/he have Epilepsy?	Yes/ No	1	HE
If YES, is it Active Epilepsy?	Yes/ No	1	AE
Does s/he need an EEG?	Yes/ No	1	EEG
If YES, when done?	Y Y Y Y M M D D	EEGDATE	

NB: EEG for those with repetitive acute (febrile) seizures, and/or those with epilepsy

Does s/he have a history of acute illnesses?	Yes/ No	1	AIL
HIV	Yes/ No	1	HIV
Sickle cell disease?	Yes/ No	1	SCD
Stroke?	Yes/ No	1	STK
Other, specify			

Pregnancy, Birth and Developmental History			
Pregnancy History			
Were there maternal health problems during pregnancy?	Yes/ No	1	MHP
Did the mother smoke and/or take alcohol or caffeine during pregnancy?	Yes/ No	1	SAC
Birth History			
Did the mother deliver before 40 weeks?	Yes/ No	1	DEL
Was the birth difficult or labor prolonged?	Yes/ No	1	DBL
Developmental History			
Are age-specific milestones delayed?	Yes/ No	1	ASM
Is the school grade inappropriate for age?	Yes/ No	1	SGA

Does child have problems with peer relationships?	Yes/ No	☐	PRS
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ACUTE (FEBRILE) SEIZURE OR EPILEPSY RECORD

Answer **Yes (Y)** or **No (N)** or **Unknown (U)**

Has s/he ever had a fit	Yes/ No/ Unknown	☐	CF
Has s/he ever had episodes when s/he loses consciousness	Yes/ No/ Unknown	☐	CLC
Has s/he ever fallen to the ground without a reason	Yes/ No/ Unknown	☐	CFG
and the arms or legs twitch/shake	Yes/ No/ Unknown	☐	ALT
and bites the tongue	Yes/ No/ Unknown	☐	BT
and wets him/herself	Yes/ No/ Unknown	☐	WH
Have you ever noticed that s/he has episodes of			
shaking, trembling of one arm or one leg or the face	Yes/ No/ Unknown	☐	ST
becoming stiff	Yes/ No/ Unknown	☐	BS
loses contact with the surroundings	Yes/ No/ Unknown	☐	LCS
frequent loss memory from a short period of time	Yes/ No/ Unknown	☐	FLM
jerkings which move up your arm, leg or body	Yes/ No/ Unknown	☐	JALB
Has s/he had episodes when s/he appears dazed	Yes/ No/ Unknown	☐	CD
complains of tummy aches	Yes/ No/ Unknown	☐	TA
smells an odd smell	Yes/ No/ Unknown	☐	OS
sees something strange	Yes/ No/ Unknown	☐	SS
Have you ever been told that s/he has had a fit	Yes/ No/ Unknown	☐	TCF

*Description of Child's Seizures as narrated by the
parent/ caretaker*

Date of onset of seizures	Y Y Y Y M M D D	DOS
Number of different seizure types	1	NST
When was the last seizure?	Y Y Y Y M M D D	LS
How many seizures in the last year?	1 1	SY
When does s/he have seizures?	Daytime/ Nighttime/ Both	1 WS
How many seizures has s/he ever had?	0-9, Frequent	1 NS
How many times per month?	0-9, Frequent	1 PM
How many times per week?	0-9, Frequent	1 PW
How many times per day?	0-9, Frequent	1 PD
Is the seizure provoked?	1	SZP
If YES, is it by fever or febrile illness?	1	SZF
If NO, what are the precipitating factors?		
Have you had unprovoked seizures before?	1	PPS
If provoked by febrile illness, was the child admitted to hospital?	1	HOSP
If hospitalised, which health facility?	1	HFAC
If hospitalised, when was this?	1	DHOSP
If provoked by febrile illness, tick the possible illness in the table below		

Table: Identification and classification of febrile illnesses associated with acute seizures

Illness	Description	Yes/No	
Malaria	Any fever without running nose, since Kilifi is a high risk area		MAL
Very severe febrile disease e.g. Meningitis	Fever with stiff neck and crying a lot or irritability		SFEB
Upper respiratory tract infection (RTI)	Fever with running nose and a mild cough		URTI
Lower RTI (Pneumonia)	Fever with severe cough, fast breathing (>40/min) and chest indrawing		LRTI
Diarrhoea e.g. gastroenteritis	Fever or no fever with 3 or 4 loose stools in 24 hours, lethargy or not able to feed properly		DIAR
Ear infections	Fever with ear discharge, ear pain and/or swelling behind ear		EARI
Measles	History of fever and eye discharge and/or mouth ulcers with or without respiratory and ear infections or diarrhea or		MEAS
Undetermined			UNDET

NB: For infants: history of presence of a bulging of Fontanele and a red umbilicus draining pus may suggest febrile illness e.g. bacterial infections.

Current anti-epileptic drugs

Any Medication?		Yes/ No	☐	AM	
If yes which one(s)		Phenobarbitone(PB); Phenytoin(PH); Carbamazepine (CB); Sodium Valproate (NN)			
taken:	First drug taken:	☐	AE1	Dose per day ☐ ☐ ☐ AED1	
	Second drug	☐	AE2	Dose per day ☐ ☐ ☐ AED2	
Previous anti-epileptic drug history					
taken:	First drug taken:	☐	AEP1	Dose per day ☐ ☐ ☐ AEPD1	
	Second drug	☐	AEP2	Dose per day ☐ ☐ ☐ AEPD2	
Any drug reactions or unacceptable side effects from anti-epileptic drugs?		Yes/ No	☐	DR	
Describe					
Did you consult a Traditional Healer for the child's seizures		Yes/ No	☐	TH	
If so what did the traditional healer suggest?					
Did they suggest Traditional Medicine?		Yes/ No	☐	PTRM	
Descriptions of Seizure Types: (Clinicians Summary)					
Before the episode			1 st Seizure	2 nd Seizure	3 rd Seizure
Does s/he know it is going to occur (Ex. Goes to another person)?	Yes/ No	KO	☐	☐	☐
Abnormal Behavior?	Yes/ No	AB	☐	☐	☐
During the episode					
Becomes unresponsive (not answer questions, disobey commands)	Yes/ No	BU	☐	☐	☐
Falls to the ground	Yes/ No	FG	☐	☐	☐
Talks nonsense	Yes/ No	TN	☐	☐	☐
Does not know where s/he is	Yes/ No	DW	☐	☐	☐
Hallucinations; parasthesiae	Yes/ No	HP	☐	☐	☐
Automatisms: Swallowing, grimacing, fiddling, gestures, vocalisations, walking	Yes/ No	AM	☐	☐	☐

Other phenomena: Fear, weeping abdominal, déjà vu	Yes/ No	OP	☐	☐	☐
Convulsive movements					
Which side?	Both/ Right/ Left/ Unsure CS		☐	☐	☐
Which limb?	Both/ Arms/ Legs CM		☐	☐	☐
Partial	Face/ Lips/ Hands CP		☐	☐	☐
Eyes involved:					
Blank Stare	Yes/ No BK		☐	☐	☐
Stares Ahead	Yes/ No SA		☐	☐	☐
Deviate:	Upwards/Right/ Left/ Unsure ED		☐	☐	☐
Jerking movements					
Lips involved	No/ Smacking/ Licking LI		☐	☐	☐
Bites tongue	Yes/ No BG		☐	☐	☐
Wets self	Yes/ No WE		☐	☐	☐
Soils self	Yes/ No SO		☐	☐	☐
Duration (in minutes)	DU		☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐
Duration episode ≥ 30 minutes	Yes/ No SE		☐	☐	☐
Did the episode last a news bulletin or longer	Yes/ No SB		☐	☐	☐
Did the episode last a church/mosque sermon or longer	Yes/ No SS		☐	☐	☐
After the episode					
Drowsy	Yes/ No DY		☐	☐	☐
Sleeps	Yes/ No SP		☐	☐	☐
Headache	Yes/ No HE		☐	☐	☐

Abnormal behavior	Yes/ No AN	☐	☐	☐
Paralysis	Yes/ No PA	☐	☐	☐
Disturbance of sleep	Yes/ No DS	☐	☐	☐
Speech and language difficulties (Aphasia)	Yes/ No SL	☐	☐	☐
Does s/he remember the episode?	Yes/ No RE	☐	☐	☐
Since onset of seizures, is there stagnation behavior and cognition and language development	Yes/ No SD	☐	☐	☐

Sign if you have checked that the form is complete _____.

Appendix 6: Paediatric neurological examination form

Study Number			
Name and Surname			
Date of Assessment			Y Y Y Y M M D D
Gender	Male/ Female		
Date of Birth			
Weight	In Kg		WT
OFC	In cm		HC
MUAC	In cm		MUAC
Height	In cm		HT
Handedness	Right/ Left/ Undetermined		HD
Skull shape	Normal/Abnormal		SKS
Facial Appearance	Normal/ Dysmorphic		FA
<u>Skin</u>			
Any features of neurofibromatosis?	Yes/ No		NCF
Any features of tuberous sclerosis?	Yes/ No		NCT
Any scars or bruises?	Yes/ No		NCS
Jaundice	Yes/ No		JAN
Lymphadenopathy	Yes/ No		LYM
If so, describe			
BCG scar	Yes/ No		BCG
Hand	Normal/Abnormal		HAN D
Feet	Normal/Abnormal		FEE T
Blood Pressure (BP) (in mmHg)			BP
Respiratory system	Normal/Abnormal		RPS
Cardiovascular System	Normal/Abnormal		CDS
<u>Mental State Exam</u>	Yes/ No/NA		MSN

Can the child tell you his/her name?			
Does s/he know where you are now (e.g. Is the hospital?)	Yes/ No/NA	☐	MSP
Can he/ she tell you the names of his/ her siblings and friends?	Yes/ No/NA	☐	MSN R
Can he/she tell you what time of the day it is?	Yes/ No/NA	☐	MSN T
Does the child call 'mama', 'baba' appropriately (in younger infants)?	Yes/ No/NA	☐	MST
Does the child respond to his/her name when the parent calls (in younger infants)?	Yes/ No/NA	☐	MSR C
Does s/he have any burn marks?	Yes/ No	☐	ABM
If so, where?			

Examination of Cranial Nerves

<u>Cranial Nerve II</u>			
Ptosis	Yes/ No	☐	PT
Pupils	Normal/Abnormal	☐	PU
Cranial Nerves III, IV, and VI; V and VII			
Eye Movements	Cranial Nerves III, IV, and VI		
Squint?	Yes/ No	☐	SQ
Which eye?	Right/ Left/ Both	☐	SWE
Nystagmus?	Yes/ No	☐	NY
The Face: Muscles of facial expression	Cranial Nerve VII		
Facial weakness?	Yes/ No	☐	FW
Forehead stronger than lower face?	Yes/ No	☐	FS
Cranial Nerves IX and X; XII			

The mouth, pharynx, and larynx	Cranial nerves IX, X, XII			
Uvula	a.	Is central?	Yes/ No	☐ UM C
	b.	Deviates to:	Right/ Left/ None	☐ UD
Tongue	a.	Deviation?	Yes/ No	☐ TD
	b.	Size of tonsils	Enlarged/ Normal	☐ ST
Motor System				
<u>General Motor Skills</u>				
Can s/he support his neck?		Yes/ No/ NS	☐	GM N
Can s/he roll back to belly or bell to back when laid down?		Yes/ No/ NS	☐	GM R
Can s/he sit upright without support?		Yes/ No/ NS	☐	GMS
Can s/he crawl?		Yes/ No/ NS	☐	GM C
Can s/he pull her/himself to stand?		Yes/ No/ NS	☐	GM P
Can s/he walk with support?		Yes/ No/ NS	☐	GM W
Does s/he have a stable, symmetrical gait?		Yes/ No/ NS	☐	GM G
Can s/he run without falling?		Yes/ No/ NS	☐	GM RW
Can s/he jump or hop?		Yes/ No/ NS	☐	GMJ
Can s/he walk on tip toe or heels for 5-10 steps?		Yes/ No/ NS	☐	GM T
<u>Fine Motor Skills</u>				
Can s/he grip a finger?		Yes/ No/ NS	☐	FM G
Can s/he reach towards object and grasps with whole hand?		Yes/ No/ NS	☐	FMR
Can s/he see a small piece of object like rice grain/ a bean or bead on the ground and pick it up with the thumb and finger?		Yes/ No/ NS	☐	FMS
Can s/he transfer objects from one hand to the other?		Yes/ No/ NS	☐	FMT
Does s/he have a pincer grasp?		Yes/ No/ NS	☐	FMP

Can s/he poke or point with index finger?	Yes/ No/ NS		FMI
Reflexes for Newborns and Infants			
Parachute reflex	Normal/Abnormal/ NA		PR
Moro's reflex	Normal/Abnormal/ NA		MR
Palmar and plantar grasp	Normal/Abnormal/ NA		PG
Arms Wasting?	Yes/ No		AW
If so, where?			
Tone?	Normal/ Increased/ Decreased		AT
If abnormal please describe			
Contractures?	Yes/ No		AC
If so, where?			
Power (MRC 0-5)	Normal/ Abnormal/ Grossly Abnormal		AP
If abnormal	Right	Left	
Upper arm			
Lower arm			
Hand			
Legs Wasting?	Yes/ No		LW
If so, where?			
Tone?	Normal/ Increased/ Decreased		LT
If abnormal please describe			
Contractures?	Yes/ No		LC
If so, where?			
Power (MRC 0-5)	Normal/ Abnormal/ Grossly Abnormal		LP
If abnormal	Right	Left	
Upper leg			

Lower leg	☐	☐
Foot	☐	☐

<u>Reflexes</u>		Right	Left
Decreased/ Normal/ Increased	Biceps	☐ BR	☐ BL
	Knee	☐ KR	☐ KL
	Ankle	☐ AR	☐ AL
Down going/ Up going	Plantar	☐ PR	☐ PL

<u>Co-ordination (NA in younger Children)</u>			
Finger-nose	Normal/Abnormal /NA	☐	FN
Piano-playing	Normal/Abnormal /NA	☐	PP
Dysdiadochokinesia	Yes/No/NA	☐	DDK
Trunkal ataxia	Yes/No/Ns	☐	TA
Fog Test	Positive/Negative /NA	☐	FT
Gait	Normal/Abnormal	☐	GN
If abnormal, describe			

Sensory Examination (Please check all dermatomes)	Normal/Abnormal /NA	☐	SEN
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Is there any evidence of abnormal sensation? If yes, please out a full sensory examination and document your findings:

In younger Children and Infants, please check the following:			
Does the child respond to tickling or touching?	Yes/ No/ NA	☐	TSE N
Does the child withdraw limbs in response to pain (Scratching with the sharp end of spatula)?	Yes/ No/ NA	☐	PSE N
Does the child withdraw from a warm stimulus (eg: warm water in a closed bottle)	Yes/ No/ NA	☐	WSE NS

Ears					
Auroscope Examination	a	Right	Normal/ Abnormal/ Wax	☐	UR
	b	Left	Normal/ Abnormal/ Wax	☐	UL
Otitis Media	a	Right	Yes/ No/ Wax	☐	OM R
	b	Left	Yes/ No/ Wax	☐	OM L
Otitis Externa	a	Right	Yes/ No/ Wax	☐	OER
	b	Left	Yes/ No/ Wax	☐	OEL
Eyes					
Cataracts			Yes/ No	☐	CT
If so, which eye?			Right/ Left/ Both/ None	☐	CW E
Other abnormality?			Yes/ No	☐	EAB
If so, describe.					
Fundoscope Examination	Fundi seen		Yes/ No	☐	FE
	Right		Normal/ Abnormal/ Impossible	☐	FR
	Left		Normal/ Abnormal/ Impossible	☐	FL
Any other Observation and medical history?					
AOM					
Diagnosis 1	DIAG1				
Diagnosis 2	DIAG2				
Investigations 1	INVST1				
Investigations 2	INVST2				
Treatment 1	TREAT1				
Treatment 2	TREAT2				

Follow – up			FUP
Summary			
Does s/he have evidence of learning difficulties?	Yes/ No	☐	ELD
Does s/he have any neurological deficits?	Yes/ No	☐	EXN D
Does s/he need a CT scan?	Yes/ No	☐	EXC T

Sign if you have checked that the form is complete _____.