UNIVERSITY OF SOUTHAMPTON

Longitudinal Studies in Sickle Cell Disease

Using a prospective cohort to examine definitions and clinical course in sickle-cell disease epidemiology.

Study participants, haematology
clinical events, and health status

Ian Richard Hambleton

Tropical Medicine Research Institute, Jamaica

and,

MRC Environmental Epidemiology Unit, United Kingdom

Submitted for the degree of Doctor of Philosophy

August 2003

Abstract

Background. The sickle-cell unit in Kingston has operated Jamaica's only comprehensive sickle-cell centre since 1973, and initiated the Jamaican cohort Study of Sickle-Cell Disease (JSSCD) in the same year. JSSCD participants (552 haemoglobinopathies and 246 AA genotype controls) were initially identified from neonatal screening of 100,000 consecutive hospital deliveries. In the 27 years to December 1999, JSSCD members had been followed for between 18 and 26 years, and 6,464 non-cohort patients had also presented to the clinic (and formed the clinic study). We have used longitudinal information from these study groups to examine three challenges facing sickle-cell disease (SCD) epidemiology: important gaps in our knowledge of the natural history of the disease, how to recruit study participants and define haematology and clinical endpoints in ways that minimise study bias, and how to define and predict SCD health-status.

Methods. We described and modelled profiles of 10 haematological indices, and 14 common clinical complications from birth to early adulthood. We additionally described childhood growth and its association with later health outcomes, we report on mortality in the JSSCD, and we model lifetime survival among people with homozygous sickle-cell disease in Jamaica. Together, these analyses meet our first challenge of describing SCD natural history, and they form the backbone of this thesis.

We estimated the proportion of the true SCD population that remain unrecruited when neonatal screening is not available. We quantified the 'late-entry' bias introduced in clinical event reporting when using a clinically ascertained population, and suggested guidelines for when to apply a statistical adjustment to reduce this bias. We developed and used a new adjustment technique to provide valid estimates of lifetime survival in the presence of this bias. We described levels of JSSCD non-response, and the role of two forms of non-response: temporary non-response (default) and permanent non-response (dropout) on invalidating research conclusions. Together, these analyses examine our second challenge: the role of bias in SCD epidemiology.

We used a systematic review to identify the literature on health status in SCD, and summarized the quality of included articles. We applied health status prediction models to the JSSCD to provide the first external validation of these tools. We described an ongoing study to develop robust prediction tools for SCD health status. Together, these analyses examine our third challenge: the role of health status in SCD epidemiology.

Findings. We present our work as four related 'books' covering study participants, haematology, clinical events, and health status. The sickle-cell unit clinic load has increased from 3,668 presentations in 1973-75 to 35,682 in 1997-99. The number of patients and the number of presentations per patient per year have both increased. Non-enrolment among people with unscreened SS disease is considerable; up to 90% will not enrol by five years of age and so will not benefit from important early-life clinical interventions, and up to half may not enrol for specialist clinical care during childhood. Among SS disease patients that do enrol, over half do so in adolescence and adulthood when clinical management is less focused on preventive care. In the JSSCD, 2.7% of participants default from the clinic for one complete calendar year, and 21.9% default from a single pre-arranged appointment. Defaulting predicts subsequent mortality, which suggests an avenue for intervention. Participants that default or dropout have different levels of haematology and different clinical expressions: defaulters that survive have a mild haematological profile, while defaulters that subsequently die exhibit increased reticulocytosis. This 'non-ignorable' non-response has far reaching consequences for how we analyse observational studies in sickle-cell disease. Health status literature remains contradictory, and from 77 identified articles just 3 met minimal criteria for acceptable design. From 16 articles offering systems for classifying health status a single article maintained some ability to minimise false-positive identification of adversely affected patients, but its general predictive ability degraded from 79% to 6%. Our clinical case studies present a range of findings and conclusions, which we present in the body of our report. Our major case study investigated lifetime survival in SS disease, and we report an encouraging median survival of 53 years (95% confidence interval 49.0 to 58.7) for men and 58.5 years (53.5 to 70.9) for women.

Table of contents

BOOK ONE. Study Participants

Chapter 3

Chapter 4

BOOK TWO. Haematology

Chapter 5

Table of Case Studies

Acknowledgements

This thesis represents four years of research on sickle-cell disease. It has been a rewarding journey, largely thanks to the many influential collaborators and friends that have accompanied me along the way.

I originally conceived of the project when working with Professor Graham Serjeant, and many of the ideas reflect the ethos of Professor Serjeant and the Jamaican Sickle-Cell Unit. His unique dedication to sickle-cell disease continues to be an inspiration.

Dr Klaas Wierenga was a major influence throughout the project. He collaborated directly on numerous areas of the thesis: notably recruiting study participants (Chapter 3), mortality and survival (Chapter 6), and defining health-status (Chapters 7 and 8). More than this, he served as my unofficial clinical supervisor throughout the project. He did this with enthusiasm, with insight, and with dedication, and the final product would not have been possible without him.

Dr Clive Osmond provided insightful and good-humoured statistical supervision throughout the project, and his help in securing additional research time for the thesis by appointing an assistant statistician in Jamaica was invaluable. Karen Drake provided administrative support beyond the call of duty when she photocopied and posted over 200 articles from the UK to Jamaica for the systematic review of sickle-cell disease health-status.

I pursued this thesis part time, and through my 'day-job' I have been lucky to collaborate with a wide range of sickle-cell disease researchers. These clinicians have shared their expertise and their enthusiasm, and I hope that a little of their passion is reflected in this thesis: Dr Stephen Magnus and recurrent bacteraemia, Mrs Beryl Serjeant and the haematological response to B19 infection, Dr Josh Wright and post-splenectomy clinical course. Dr Jennifer Thame and red blood-cell transfusions, Dr Adebayo Olujohungbe and red blood-cell antibodies, Dr Tom Walker and gallstones, Professor Alan Bird and Dr Susan Downes and proliferative sickle retinopathy, Dr Mark Ware and studies on the painful crisis, Dr Nicky Thomas and coping with the painful crisis, Dr Andrea Clare and leg-ulceration, Dr Atul Singhal and menarche, Dr Minerva Thame and pregnancy, and Dr Joanne Thompson and renal function.

This thesis represents a time of change for the Jamaican Sickle Cell Unit, as it converted from an overseas laboratory of the British Medical Research Council, to a research unit within a Caribbean-wide medical research facility (The Tropical Medicine Research Institute, or TMRI). I am grateful to those that ensured the continuation of my research programme through this sometimes turbulent process of change. Dr Diana Dunstan of the British Medical Research Council facilitated the funding of this project, and a series of MRC research coordinators eased some of the difficulties of working as a lone statistician in a

resource-poor environment: Dr David Cox, Dr Robin Buckle, and Dr Morven Roberts. The TMRI was launched in 1999 under the Directorship of Terrence Forrester, and from the first days of the Institute Professor Forrester has been a constant source of encouragement. He patiently allowed me dedicated time to complete this thesis, against a background of overwhelming demand for statistical collaboration in the Institute, the Medical Faculty, and the University, and an acute shortage of formally trained statisticians.

This thesis represents a major summary of the Jamaican Study of Sickle-Cell Disease (JSSCD), and I am grateful to the staff of the Jamaican Sickle Cell Unit, whose dedication has ensured that this 30-year study remains viable and important.

Finally, this thesis represents four years of evenings and weekends, endless late nights and early mornings. I am (and will remain) indebted to Fiona, my wife, who tackled my often unreasonable dedication to this project with her unique blend of fiery spirit and good humour.

Barman, mine's a Red Stripe...

Ian Hambleton,
Senior Lecturer in Medical Statistics,
Kingston, Jamaica.

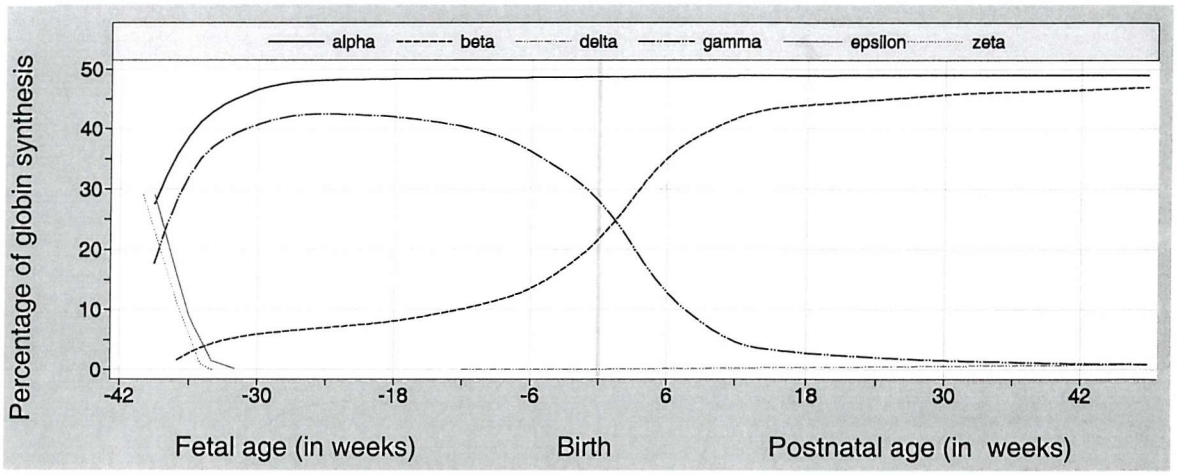
Chapter 1

Introduction

1.1 Human haemoglobin

A continuous supply of oxygen is essential for life, and this oxygen is transported from our lungs to all parts of our body by haemoglobin, which is the major protein in red blood cells. There are several human haemoglobins and they all have two pairs of globin chains (a globin chain contains amino acids - the building blocks of proteins) folded around a pocket containing the oxygen-carrying haem molecule. Globin chains vary with the stage of fetal development, and are designated the Greek letters alpha (α), beta (β), gamma (γ), delta (δ), epsilon (ε), and zeta (ξ). Alpha and gamma are the main chains in fetal life, with gamma mostly replaced by beta production in postnatal life (Figure 1.1).

Figure 1.1
Globin chain synthesis in fetal and postnatal life (adapted from (1))



In fetal life, the main haemoglobin molecule is fetal haemoglobin or HbF ($\alpha 2$-$\gamma 2$), and in postnatal life, this fetal haemoglobin is replaced by adult haemoglobin or HbA ($\alpha 2$-$\beta 2$), and by small amounts of HbA2 ($\alpha 2$-$\delta 2$) (2;3).

1.2 Haemoglobin disorders

Disorders of haemoglobin production or structure are known as haemoglobinopathies.

1.2.1 Altered haemoglobin structure: sickle-cell disease

Sickle-cell disease (SCD) is a group of inherited conditions identified by the presence of haemoglobin-S (HbS), which replaces a proportion of HbA. Haemoglobin-S is the product of a single-point mutation of the gene that regulates β-globin production. Inheriting this muta-

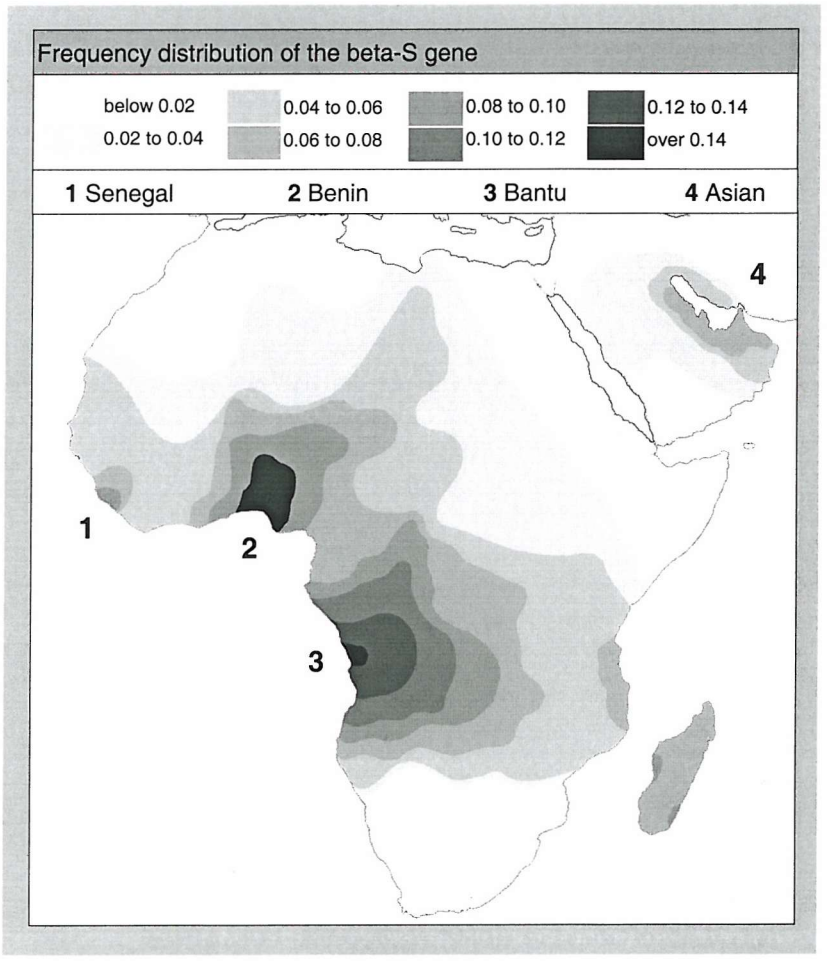
tion from both parents creates the homozygous form of the disease, known as homozygous sickle cell (SS) disease in the United Kingdom and elsewhere, and sickle-cell anaemia (SCA) in the United States. It is the most common of all haemoglobin disorders, with 230 000 new cases per year in sub-Saharan Africa, a region that accounts for 70% of worldwide prevalence (4;5). People with SS disease are the main focus of this thesis.

Other forms of SCD (known as compound heterozygous forms), combine the HbS mutation with another mutation of the beta-globin gene. Examples of compound heterozygous SCD are SC disease, $S\beta^{o}$-thalassaemia, and $S\beta^{+}$-thalassaemia (see Section 1.2.2). Most people who carry the mutated 'sickle-cell' allele have it on only one of their pair of genes. The other gene of the pair does not have the mutation and so produces normal adult haemoglobin (haemoglobin A). These carriers have the sickle cell trait, and in general suffer no adverse clinical effects.

(a) Origins

The sickle-cell mutation has occurred in at least four independent populations: three in Africa and one the Middle East and India (Figure 1.2). Each mutation has a recognisable DNA structure around the beta-globin locus (known as a beta-globin haplotype).

Figure 1.2
Geographical distribution of the sickle-cell gene in Africa and the Middle East (adapted from Bodner and Cavelli-Sforza (6)).



These mutations, if inherited from a single parent (creating the sickle-cell trait), confer a relative protection against falciparum malaria during an important phase in early childhood between the loss of passively acquired maternal immunity and the development of actively acquired immunity (7;8). They are more likely to survive and pass on their genes. This protection does not apply to sickle-cell disease; in Africa malaria is a common cause of mortality among people with SS disease (8).

(b) Distribution

Over generations the sickle cell trait has therefore reached high frequencies in malarious areas (Figure 1.2). Subsequent human movement transferred affected populations from West and Central Africa to the Caribbean, the southern United States, and Central and South America. From the 1950's secondary movements shifted southern US populations to the Northern United States and Canada, Caribbean populations to Europe and North America, and Mediterranean populations to Northern Europe.

1.2.2 Decreased haemoglobin production: the thalassaemias

Disorders of haemoglobin production result in the thalassaemia conditions. Decreased production of alpha chains (α-thalassaemia) or beta chains (β-thalassaemia) are most common, and less frequently larger genetic regions are affected, giving rise to delta-beta or gamma-delta-beta thalassaemia. Alpha-thalassaemia is usually the result of gene deletion. Beta-thalassaemia usually occurs due to a single point mutation. Sickle-cell disease is a β-globin disorder, and concidence with α-globin deletions is relatively common.

1.3 Pathophysiology

The haemoglobin-S molecule has a tendency to change its shape when it is not linked to oxygen. Collections of these molecules distort the whole red blood cell. We commonly refer to this repeated deformation process as 'sickling', and the resulting red blood cell as a sickled-cell (because of its distinctive shape). After a series of cycles of sickling and de-sickling, red blood cells with a high concentration of HbS lose the ability to de-sickle and become permanently deformed.

Sickling has two important effects: haemolysis and vaso-occlusion (9). Red cells containing HbS have a weaker structure and have a much shorter life than the normal four-months. This increased red cell destruction (increased haemolysis) leads to anaemia. By itself, anaemia may not be a big problem - people with sickle-cell disease cope well with chronically lowered levels of haemoglobin.

Secondly, red cells with HbS are less pliable and tend to adhere to blood vessel walls. These effects, along with the increased density of sickled cells can slow the blood flow in SCD, and

in extreme cases can cause complete blockage of small blood vessels. These blockages are always serious, as they deprive tissues of their oxygen and lead to local death of the tissue.

1.4 Diagnosis

Diagnosis of the major genotypes of sickle-cell disease is relatively simple and has been the subject of several reviews (10-12). Neonatal diagnosis is available and inexpensive, allowing clinical management from birth. Antenatal diagnosis is possible, but is more costly and has associated ethical, religious, and social considerations.

1.5 Clinical manifestations

SCD has a wide range of symptoms, and anyone with the disease may have any number of these complications. Some may have none but die with a single acute event. Some skip one or more 'phases' in the age-related progression of the disease. A person with sickle-cell disease would be expected to survive into the fifth or sixth decade, although there is also wide variation in survival rates (13;14). There is evidence that variation in the expression of the disease has a geographical dimension, although reports from different countries are complicated by differences in the characteristics of the populations studied (for example, many studies are cross sectional with different age structures). Based on clinical signs and symptoms, SS and $S\beta^{o}$-thalassaemia are considered the clinically serious forms of SCD, with SC and $S\beta^{+}$-thalassaemia ranked as milder diseases (15;16).

Evidence for the haemolytic anaemia in SS disease is an increased reticulocyte count, which reflects an increased bone marrow response. Complications of haemolysis relate to the high red cell turnover, and the production of excessive amounts of haemoglobin metabolites such as bilirubin. The most common associated clinical event is the production of gallstones.

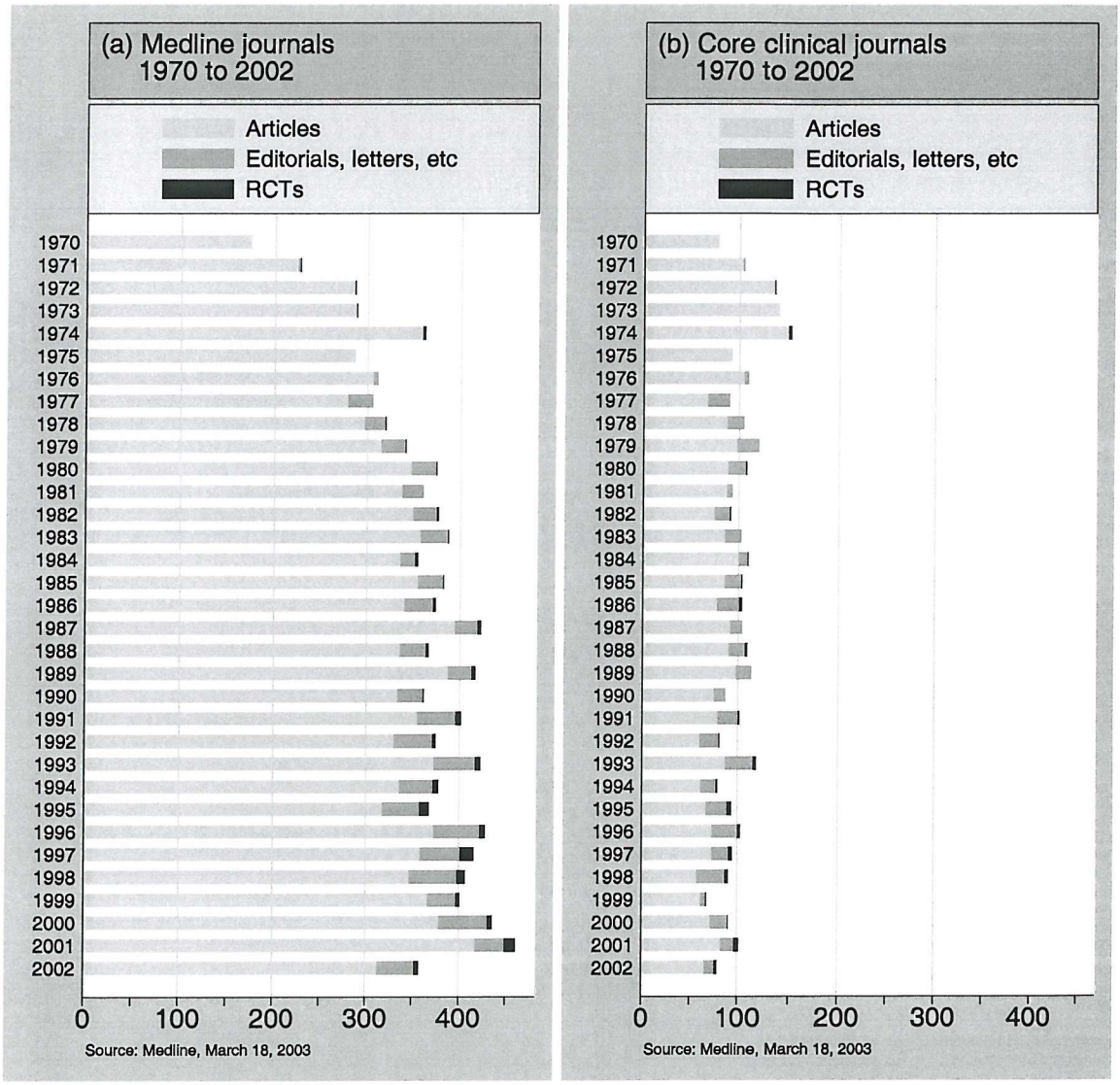
The vaso-occlusive aspect of SCD is responsible for most of the major complications; many organs of the body can be affected. In infancy, functional asplenia leads to increased susceptibility to infection, and acute splenic sequestration (ASS) can reduce the total haemoglobin to critical levels within hours. Dactylitis is common in infancy and may be a precursor to a serious clinical course (17). In childhood, infection, stroke and the acute chest syndrome (ACS) dominate as causes of morbidity and death. In adolescence, bacteraemias, dactylitis, ASS, ACS, and stroke decrease in frequency, and gallstones, episodes of severe pain, and leg ulceration increase in frequency. Although adolescence can be a time of relative clinical calm, those with the disease face the physical limitations and the psychological impact of a serious chronic condition. In adulthood, complications associated with pregnancy, the eyes, and chronic organ damage become increasingly prevalent. Throughout adolescence and early adulthood the painful crisis becomes the major cause of morbidity, placing a physical and social burden on those that it affects.

1.6 Sickle-cell disease epidemiology

The variable clinical expression of the disease is well known. A large literature has focused on defining the range of clinical events, and exploring features of study participants and their environment that might explain why and when specific clinical events occur. This is the domain of epidemiology in sickle-cell disease research. The number of sickle-cell disease publications has risen steadily in the 30-years from 1970 (Figure 1.3). The number of clinical trials remains low. Observational studies dominate the SCD literature and provide the evidence-base for most current clinical practice. There is an urgent need for randomised controlled trials of therapeutic interventions, but observational epidemiology looks likely to drive our understanding of SCD for some time to come.

Figure 1.3

Number of sickle-cell disease publications listed in Medline between 1970 and 2002



1.7 Research challenges in sickle-cell disease epidemiology

Sickle-cell disease epidemiology faces important challenges.

1.7.1 Definitions

Decisions on how we recruit study participants, and how we define clinical endpoints and haematological indices (which are often used as predictors in models of the disease) are fundamental pre-requisites in sickle-cell disease epidemiology. Despite their central importance, there is little consensus on the role of participant recruitment, and the use of haematology and clinical events in sickle-cell disease. Systematic assessment of whether currently accepted methodology and definitions are appropriate is not available. This has lead to widespread use of potentially inappropriate statistical methodology. The ability to compare and reproduce published risk factors is complicated by these variations.

1.7.2 Incomplete natural history

Many clinical events in sickle-cell disease have been well documented, and important texts are available that summarise these findings (2;18;19). Other events remain poorly described, often because appropriate study participants have not been available to allow a satisfactory description of a condition; in some cases the event is rare, in some cases an event is only seen in infants or older adults, and in some cases the described populations are missing important subgroups, which can bias conclusions. In many instances, cross-sectional information has been used to summarise implicitly age-related phenomena.

1.7.3 Predicting health-status

The possibility of identifying those most affected by the disease as primary candidates for intervention, has encouraged a vocal and persistent call for methods to inform the classification of people with SS disease according to some notion of health-status (20-24). At the same time, the barriers to such a classification are widely understood (25). For a predictive scheme to be useful in practice, it must accurately identify those people at increased risk of adverse outcomes (using a generally accepted measure of outcome). To promote clinical acceptance, the tool must then be shown to maintain its accuracy in repeated applications to different groups of participants. This level of statistical rigour is not yet available.

1.8 Thesis plan

In this thesis we use a prospective cohort and a clinically ascertained group of participants to investigate each of these research challenges. We have grouped our investigations into four books: ***study participants***, ***haematology***, ***clinical events***, and ***health-status***. In each book we present analyses in self-contained chapters, each with its own background, methods, results, and discussion. We present summaries of proposed future work in the final thesis discussion (Chapter 9).

Two chapters do not belong to any thesis book. In chapter two we introduce the study groups and provide a description of clinic utilisation among these participants, which provides information for future resource planning. In chapter nine we offer a final overarching interpretation of the thesis results.

1.8.1 ***Book One:*** *Study participants*

In Book One (chapters 3 and 4) we examine the influence of study participants on research results. It tackles research challenge one – definitions in sickle-cell disease. Methods of identifying participants, and levels of subsequent non-response among participants define the generalisability of research to other sickle-cell disease populations. Without neonatal screening, patients enrol to clinic with varying delay, and a proportion of homozygous sickle-cell births may never enrol for specialist clinical care. In chapter three, we quantify this delay, and the proportion of non-enrolled patients using a clinic-enrolled Jamaican patient population and the known haemoglobin-S allele frequency for Jamaica. The results have implications for the clinical care of the homozygous sickle-cell disease patient, for public-health policymaking, and for clinical research.

Neonatal screening for SCD is well established in industrialised countries that have significant numbers of people with the disease. The economic conditions in low and low-middle income countries makes the provision of systematic screening more challenging. In case studies 1 and 2 we explore neonatal screening programmes in two low-middle income nations: Brazil and Jamaica.

The use of clinic-ascertained patients remains common in sickle-cell disease research. We report the incidence of bacteraemia (case-study 3) and the mortality rate (case-study 5) using neonatal and clinic ascertained participants. Differences in results from these two study groups would confirm an intuitive assumption that research conclusions can be dependent on the choice of research population.

In chapter four we define and describe non-response, and explore the effect of non-response on research conclusions.

1.8.2 ***Book Two:*** *Haematology*

In book two (chapter 5) we examine the role of haematology in sickle-cell disease research. It tackles research challenge two – sickle-cell disease natural history.

Cross-sectional summaries of haematology are generally used for modelling clinical outcomes. Most haematological indices are strongly age-related, and using single summaries may be inappropriate. Published age-related descriptions of haematology are restricted to early childhood (26;27). In chapter five we describe eleven haematological parameters from birth to 18

years of age, accounting for non-linear changes with age, and the effects of participant non-response.

During modelling in sickle-cell disease, haematological indices may be included as potential risk-factors. Usually, we only use haematology collected when a patient is clinically well; the notion of 'steady-state' haematology. There is no consensus on a definition for steady-state haematology. In chapter nine, we propose a study to apply alternative definitions for the haematological 'steady-state' to the cohort study group, and to investigate the resulting variation in risk-factor study conclusions using sensitivity analysis.

Non-steady state haematology is routinely discarded as unrepresentative time periods. Yet paradoxically, it is these acute phases that define much clinical outcome. The use of non-steady state haematology may ultimately provide novel information on sickle-cell disease clinical outcome. In chapter nine we include a proposal for future development of this work.

Reference intervals are commonly used in medical research to determine whether individual values are 'normal' or 'extreme' in relation to a sampled majority. In chapter nine we describe a proposal for the development of reference intervals for haematological indices for use in the clinic setting.

1.8.3 ***Book Three:*** *Clinical events*

In book three (chapter 6) we investigate the clinical outcomes of sickle-cell disease.

Evidence on the incidence and prevalence of clinical events is available, but is widely dispersed and for many events it is incomplete. In chapter six we provide annual incidence rates for fourteen common clinical events in SS and SC disease, and present gender differences in these rates. We examine the bias introduced into clinical descriptions when we use study participants that have been clinically ascertained. We investigate the use of birth cohorts in analysing early predictors of later clinical outcome by examining the role of birthweight and childhood size on adolescent vasoocclusive events (case study 4). We finally examine mortality and survival among people with homozygous sickle-cell disease in Jamaica (case study 5).

Descriptions of haematological profiles, clinical event incidence, and of growth, mortality and survival fulfil the original aim of the JSSCD and of this thesis – to document and summarise the aetiology and natural history of sickle-cell disease.

1.8.4 ***Book Four:*** *Health status*

In book four (chapters 7 and 8) we examine the definition of health-status in sickle-cell disease. It tackles research challenge 3 – sickle-cell disease health-status.

Methods for summarising the health status of people living with SS disease are not well developed. Evidence is available, but has not received widespread clinical acceptance. In chap-

ter seven we systematically review the available evidence on health-status in SS disease for content and quality.

In this systematic review, a subset of articles offering a quantitative index to classify or predict health-status was identified. In chapter eight we apply these indices to a cohort study group to assess their ability to maintain prognostic ability when applied to an alternative population.

Biomarkers are outcomes that can represent or predict a clinical event or health-status, but can be measured earlier in the disease process, potentially reducing the length of clinical trials. A major clinical trial showed the benefit of hydroxyurea therapy for reducing the annual number of painful crises in SS disease (28). In chapter nine we propose the use of data from our cohort participants to develop prognostic models for biomarkers of painful crises. Developed models will be subjected to stringent sensitivity analyses, and will be validated using an external population from a London sickle cell disease register. This will be the first time that modelling in sickle-cell disease has been subjected to such statistical rigour.

1.8.5 Thesis study participants

All study participants in this thesis attend the Jamaican Sickle Cell Clinic, located in Kingston, Jamaica.

(a) The Jamaican Study of Sickle-Cell Disease

The Jamaican Study of Sickle-Cell Disease (JSSCD) is a longitudinal cohort study of people with sickle-cell disease, identified at birth and prospectively followed thereafter. Cohort participants were identified from neonatal screening of 100 000 consecutive live births from a single Kingston hospital between 1973 and 1981 (26). It is the longest running cohort in sickle-cell disease research, and is the only ongoing birth-cohort of adult sickle-cell disease. Importantly, although participants may subsequently drop out or temporarily default from the study, this birth cohort avoids biases associated with enrolling patients from clinics or hospitals, who may represent a more severely affected subpopulation. This prospective data collection is time consuming and costly but the resulting clinical and laboratory data possibly represent the best available observational data.

(b) The Jamaican Sickle cell unit clinic study

The clinic study participants are not actively recruited and join the study as they present to the Jamaican sickle cell clinic. The clinic study has enrolled 6326 participants in the period between January 1st 1973, and December 31st 1999.

1.9 Reference List

(1) Weatherall DJ, Clegg JB. The Thalassaemia syndromes. 3rd ed. Oxford: Blackwell Scientific Publications, 1981.

(2) Serjeant GR. Sickle Cell Disease. 2nd ed. Oxford: Oxford University Press, 1992.

(3) Dzierzak E. A developmental approach to hematopoiesis. In: Steinberg MH, Forget BF, Higgs DR, Nagal RL, editors. Disorders of hemoglobin. Genetics, pathophysiology, and clinical management. Cambridge University Press, 2001.

(4) Weatherall DJ, Clegg JB. Inherited haemoglobin disorders: an increasing global health problem. Bull World Health Organisation 2001; 79(8):704-712.

(5) World Health Organisation. Joint WHO/TIF Meeting on the Control of Haemoglobinopathies. Report of the VIIth Meeting of the WHO Working Group on the Control of Hereditary Anaemias, Nicosia, Cyprus, 3-4 April, 1994. (unpublished document WHO/HDP/TIF/HA/93.1). 1994. Geneva, WHO.

(6) Bodner J, Cavelli-Svorza LL. Genetics, Evolution and man. San Francisco: WH Freeman, 1976.

(7) Allison AC. Protection afforded by sickle-cell trait against subtertian malarial infection. BMJ 1957; 48:290-294.

(8) Aidoo M, Terlouw DJ, Kolczak MS, McElroy PD, ter Kuile FO, Kariuki S et al. Protective effects of the sickle cell gene against malaria morbidity and mortality. Lancet 2002; 359(9314):1311-1312.

(9) Nagal RL, Platt OS. General Pathophysiology of sickle cell anemia. In: Steinberg MH, Forget BF, Higgs DR, Nagal RL, editors. Disorders of hemoglobin. Genetics, pathophysiology, and clinical management. Cambridge University Press, 2001.

(10) Rosner F, Tatsis B, Calas CF. Screening for sickle cell disease and related disorders. JAMA 1972; 219(11):1478-1479.

(11) Zeuner D, Ades AE, Karnon J, Brown J, Dezateux C, Anionwu EN. Antenatal and neonatal haemoglobinopathy screening in the UK: review and economic analysis. Health Technol Assess 1999; 3(11):1-186.

(12) Davies SC, Cronin E, Gill M, Greengross P, Hickman M, Normand C. Screening for sickle cell disease and thalassaemia: a systematic review with supplementary research. Health Technol Assess 2000; 4(3):i-99.

(13) Platt OS, Brambilla DJ, Rosse WF, Milner PF, Castro O, Steinberg MH et al. Mortality in sickle cell disease. Life expectancy and risk factors for early death. N Engl J Med 1994; 330(23):1639-1644.

(14) Wierenga KJ, Hambleton IR, Lewis NA. Survival estimates for patients with homozygous sickle-cell disease in Jamaica: a clinic-based population study. Lancet 2001; 357(9257):680-683.

(15) Nagal RL, Steinberg MH. Hemoglobin SC disease and HbC disorders . In: Steinberg MH, Forget BF, Higgs DR, Nagal RL, editors. Disorders of hemoglobin. Genetics, pathophysiology, and clinical management. Cambridge University Press, 2001.

(16) Steinberg MH. Compound heterozygous and other sickle hemoglobinopathies. In: Steinberg MH, Forget BF, Higgs DR, Nagal RL, editors. Disorders of hemoglobin. Genetics, pathophysiology, and clinical management. Cambridge University Press, 2001.

(17) Miller ST, Sleeper LA, Pegelow CH, Enos LE, Wang WC, Weiner SJ et al. Prediction of adverse outcomes in children with sickle cell disease. N Engl J Med 2000; 342(2):83-89.

(18) Embury SH, Hebbel RP, Mohandas N, Steinberg MH. Sickle cell disease. Basic principles and clinical practice. New York: Raven Press, 1994.

(19) Steinberg MH, Forget BF, Higgs DR, Nagal RL. Disorders of hemoglobin. Genetics, pathophysiology, and clinical management. Cambridge University Press, 2001.

(20) Walters MC, Patience M, Leisenring W, Eckman JR, Scott JP, Mentzer WC et al. Bone marrow transplantation for sickle cell disease [see comments]. N Engl J Med 1996; 335(6):369-376.

(21) Scott JP, Hillery CA, Brown ER, Misiewicz V, Labotka RJ. Hydroxyurea therapy in children severely affected with sickle cell disease. J Pediatr 1996; 128(6):820-828.

(22) Reed WF, Vichinsky EP. Transfusion practice for patients with sickle cell disease. Curr Opin Hematol 1999; 6(6):432-436.

(23) Smith KD. Assessment of clinical severity of sickle cell disease. In: Knakoo Y, Davis H, editors. Academic Press, New York, 1978: 77-91.

(24) Powars DR. Progress in the natural history studies of the clinical severity of sickle cell disease. Academic Press, New York, 1978: 151-164.

(25) Steinberg MH. The difficulty and paradox of assessing clinical severity of sickle cell anaemia. In: Beuzard Y, Charache S, Galacteros F, editors. Approaches to the therapy of sickle cell anaemia. Paris: INSERM, 1986: 457-470.

(26) Hayes RJ, Beckford M, Grandison Y, Mason K, Serjeant BE, Serjeant GR. The haematology of steady state homozygous sickle cell disease: frequency distributions, variation with age and sex, longitudinal observations. Br J Haematol 1985; 59(2):369-382.

(27) Brown AK, Sleeper LA, Miller ST, Pegelow CH, Gill FM, Waclawiw MA. Reference values and hematologic changes from birth to 5 years in patients with sickle cell disease. Cooperative Study of Sickle Cell Disease. Arch Pediatr Adolesc Med 1994; 148(8):796-804.

(28) Charache S, Terrin ML, Moore RD, Dover GJ, Barton FB, Eckert SV et al. Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. Investigators of the Multicenter Study of Hydroxyurea in Sickle Cell Anemia [see comments]. N Engl J Med 1995; 332(20):1317-1322.

Chapter 2
The Jamaican Sickle-cell Clinic

Background

The sickle-cell unit of the University of the West Indies has operated Jamaica's only comprehensive sickle-cell centre since 1973. In the 27 years to December 31 1999, 7262 patients had presented to the clinic. In the same year the Jamaican cohort Study of Sickle Cell Disease (JSSCD) was started, to investigate the natural history of the disease. JSSCD participants have been followed prospectively for between 18 and 26 years.

Methods

JSSCD participants were initially identified from neonatal screening of 100 000 consecutive non-operative deliveries at a single hospital location; 552 cases of sickle-cell disease were identified, 315 of which were homozygous for the haemoglobin-S allele. Data on haematology, biochemistry, and anthropometry are collected according to a predefined visit schedule, and participants are encouraged to attend the day-care medical facility when sick, at which time information on clinical complications is recorded. The clinical services are also available free of charge to anyone with sickle-cell disease.

Findings

During the 27-year period there has been a steady increase in the number of registered patients (patient load) and the number of annual clinic presentations (clinic load). The clinic load has increased 10-fold, from 3668 presentations in 1973-75 to 35,682 presentations in 1997-1999. There has been an associated increase in number of presentations per patient per year (clinic rate), especially amongst young children (ages 0-4) and young adults (ages 20-39) visiting during the 1990's. The age structure of the general clinic population is stable, whilst that of the JSSCD continues to increase by design.

Interpretation

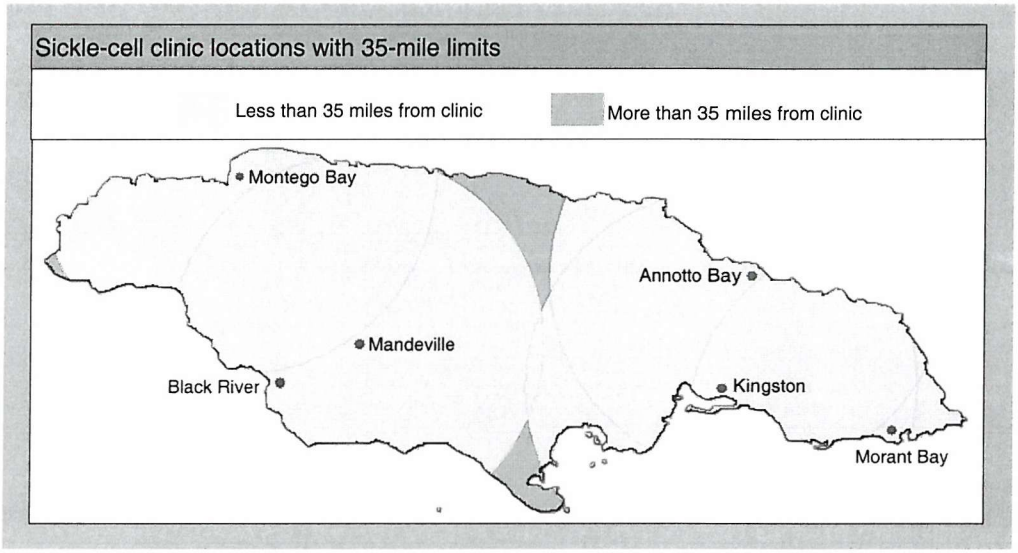
These attendance figures have implications for healthcare planning, which in turn will influence the collection of timely, relevant and quality clinical data for research.

2.1 History of the Jamaican sickle-cell clinic

Outpatient clinics of the then University College Hospital of the West Indies were initiated in 1952, and until 1965 sickle-cell patients used this general outpatient facility. An adult sickle-cell clinic was initiated in 1965 by Dr. Paul Milner of the Department of haematology, and a paediatric clinic began in 1968. These two clinics operated on different days, in different locations and were manned by different staff. At 12 years of age, patients were referred from the paediatric to adult clinic, and a high default rate during this transition has been ascribed to the apprehension of changing clinics (1). Also in 1968, a network of outreach clinics were initiated to service people with sickle-cell disease living beyond the limits of the Kingston corporate area. These clinics were located in five regional hospitals (Morant Bay, Annotto Bay, Montego Bay, Black River, and Mandeville) and were selected so that patients were rarely more than 35 miles from a clinic (Figure 2.1). In 1971, staffing reductions forced the cancellation of the outreach program and a reduction in the facilities offered by the Kingston based adult clinic.

Figure 2.1

Location of six sickle-cell clinics in Jamaica between 1968 and 1971 with 35-mile clinic limits



In 1962, the British Medical Research Council (MRC) funded the MRC Epidemiological Research Unit at a site on the University Hospital of the West Indies (UHWI) campus in Mona, Kingston for a ten-year study on hypertension and cardiomegaly. This study ended in 1972. Thereafter, sickle-cell disease became a focus of research, and the new unit, under the directorship of Professor Graham Serjeant, was known officially as the MRC Laboratories (Jamaica) and locally as The sickle-cell unit (SCU). This Unit took responsibility for the adult sickle-cell clinic, and extended an existing programme of sickle-cell research, funded by the Wellcome Trust since 1966, to study the natural history of SCD in Jamaica. In early 1973 the adult and paediatric clinics were merged and run jointly by MRC staff and the department of Child Health. This merger rationalized administration and data collection,

and removed the artificial barrier associated with the transition from child to adult healthcare. In 1977, a reduced outreach programme re-commenced, with monthly clinics at Black River and Montego Bay serving the sickle-cell population of Western Jamaica.

A dedicated clinic facility was built in 1988 using funds from an associated charity (the sickle-cell trust) and in 1990 a suite of laboratories was built on the same site with funds from the MRC. In 1994 corporate financing allowed the development of a sickle-cell education centre, again on the same physical site. In September 1999 the Unit passed into the ownership of the University of the West Indies. The SCU became one of four units of the Tropical Medicine Research Institute (TMRI), along with the Tropical Metabolism Research Unit (TMRU) and The Epidemiology Research Unit (ERU), also on the Mona campus, and the Chronic Diseases Research Centre (CDRC) on the Cave Hill campus in Barbados.

2.2 The Jamaican Study of Sickle-Cell Disease (JSSCD)

Throughout the first half of the twentieth century, SS disease was considered a severe condition of childhood and adolescence, and those with the disease were not expected to survive into adulthood. Occasional case reports of long survival appeared primarily in the early 1960's (2-5), and in 1968 the first extended presentation described 60 patients surviving beyond 30 years of age in Jamaica (6). Subsequent publications reflected an increasing awareness of the variability in clinical expression, with further descriptions of extended survival (7-9) and benign cases at younger ages (10).

Improving clinical management may have partly explained this apparent improvement in prognosis. Much early research, however, relied on symptomatic, clinic-based research participants, and this implied that people who died without presenting to clinic were being missed. Death without presentation to a healthcare provider might be ascribed to two physiological processes: mild and severe disease expression, (extremes in a spectrum of clinical severity). It might also reflect missed diagnosis when a patient presents to a healthcare provider.

In Jamaica, early attempts to reduce this symptomatic bias focused on encouraging clinic attendance, and included regional clinics, free bus fares, and a mobile clinical unit for domiciliary visits. Despite these efforts, most patients were still identified by symptomatic presentation, and the life-course of undiagnosed patients remained unknown.

The JSSCD was started to provide a group of study participants free from the symptomatic bias of clinic-recruitment. The participants were identified at birth from a population that was screened for the presence of haemoglobin-S. These participants were then followed at regular intervals.

2.2.1 Study design

The JSSCD was designed as a prospective cohort study. The assignment of participants into groups was defined at birth by genotype and gender, making patient randomisation inapplicable and categorizing the study as observational.

2.2.2 Patient ascertainment

Cord blood screening was performed on 100 000 consecutive normal deliveries at the main government maternity hospital in Kingston, Jamaica (Victoria Jubilee Hospital). Caesarean section births or other operative deliveries were excluded due to increased difficulty in obtaining blood samples. During the recruitment period the hospital had between 10 000 and 15 000 deliveries yearly, accounting for two-thirds of all deliveries in the Kingston corporate area, and approximately one-quarter of all island deliveries. It served a population of principally West African descent. The screening programme commenced on 25 June 1973 and ended on 28 December 1981. The number of births screened and haemoglobinopathies ascertained are presented by year of recruitment in Table 2.1.

The first 125 children with initial genotyping consistent with SS disease were matched with 2 controls of the same sex, born closest in time to the index case and with a normal haemoglobin (AA) genotype. Each SS patient and associated AA control pair were assigned a unique cohort identifying number.

Table 2.1

Number of patients screened, genotypes identified, and genotypes entering the JSSCD by year of screening.

Year	Screened (% / cum %)		SS	Sbeta$^+$	Sbeta^0	SC	SF	SL	SO	SV	AA	Total
1973	6472	(6.5 / 6.5)	24	2	0	16	1	0	0	1	49	93
1974	12208	(12.2 / 18.6)	38	4	2	28	0	0	0	1	87	160
1975	12031	(12.0 / 30.7)	44	9	2	23	2	0	0	0	106	186
1976	12179	(12.2 / 42.9)	38	4	1	25	1	0	0	0	4	73
1977	12030	(12.0 / 54.9)	30	5	2	20	0	0	0	1	0	58
1978	11580	(11.6 / 66.5)	35	4	0	27	2	0	1	1	0	70
1979	11516	(11.5 / 78.1)	36	5	1	16	0	0	0	0	0	58
1980	11003	(11.0 / 89.0)	37	1	2	16	0	1	1	1	0	59
1981	10981	(11.0 / 100)	33	2	1	2	1	0	0	2	0	41
Total	100,000		315	36	11	173	7	1	2	7	246	798

Some of these initial SS classifications were subsequently identified as Sβ^0 thalassaemia (n=14) or S/hereditary persistence of fetal haemoglobin (S/HPFH or SF) (n=4), leaving 107 SS patients with associated AA controls. Of the 250 controls with an AA genotype, four were subsequently shown to have the β thalassaemia trait, leaving 246 AA controls. These four re-classified controls were associated with two SS cases, one Sβ$^+$ case, and one SC case,

leaving four case-control groups with a single AA control each. Due to clinic and staffing capacity, recruitment of AA controls was stopped after cohort member 125. The last 28 cases of the 201 SC participants identified were referred directly to another institution (Bustemante Children's Hospital, Spanish Town) for follow-up, reducing the number of SC participants entering the cohort to 173. The numbers of recruited haemoglobinopathies and controls that were never traced or were untraceable after a single clinic attendance are presented in Table 2.2.

Table 2.2

Numbers of untraceable recruited JSSCD participants

Genotype	Recruited	No clinic visit	Single clinic visit
SS	315	3	1
Sβ +	36	0	1
Sβ 0	11	0	0
SC	173	6	0
SF	7	0	0
SL	1	0	0
SO	2	0	0
SV	7	0	0
AA	246	3	7
Total	798	12	9

2.2.3 Data collection

Data collected for all cohort participants are grouped into the following broad classifications: static information, routine and sick visit documentation, haematology, anthropometry, ophthalmological, ultrasound, and clinical events.

(a) Static patient information

Basic information is maintained on all participants: a unique numeric identifier, genotype, gender, date of birth, date of last visit, patient status (alive, dead, emigrated), alpha-thalassaemia status, and beta-globin haplotype.

(b) Routine visits and sick visit documentation

Study participants follow a pre-defined routine appointment schedule (see section 2.2.3(c), and are encouraged to attend the clinic whenever they are sick. Clinical event information (see section 2.2.3(h) is collected at each sick visit, along with haematology and biochemistry if necessary for patient management. All other data are collected during the pre-defined appointment schedule.

(c) Routine visit appointment schedule

Initially, two methods of follow-up were proposed so that the effects of frequent follow-up on the clinical course could be ascertained. Odd numbered cohort members were given appointments at monthly intervals from birth to six months, two monthly intervals from six to twelve months and every three months thereafter. Even numbered cohorts were given appointments at six-month intervals. This regime proved unsatisfactory, with the less frequent follow-up group providing inadequate levels of information. Infrequent follow-up was abandoned in April 1975, and thereafter, surveillance of all participants followed the more frequent attendance schedule. From six-years of age, follow-up of AA controls was reduced to intervals of six-months (Table 2.3). From 25-years of age follow-up of SC cases was reduced to intervals of six-months.

Table 2.3

Routine appointment schedule among JSSCD participants with sickle-cell disease (SCD) and normal (AA) controls.

	1973 - March 1975				**April 1975 – Dec 1981**	
	SCD (odd)	**AA controls**	**SCD (even)**	**AA controls**	**SCD (all)**	**AA controls**
Year One						
birth	✓	✓	✓	✓	✓	✓
1 month	✓	✓			✓	✓
2	✓	✓			✓	✓
3	✓	✓			✓	✓
4	✓	✓			✓	✓
5	✓	✓			✓	✓
6	✓	✓	✓	✓	✓	✓
8	✓	✓			✓	✓
10	✓	✓			✓	✓
12	✓	✓	✓	✓	✓	✓
Year Two						
15	✓	✓			✓	✓
18	✓	✓	✓	✓	✓	✓
21	✓	✓			✓	✓
24	✓	✓	✓	✓	✓	✓
Years Three to Five			**Regime amended.**			
1st q	✓	✓	Participants		✓	✓
2nd q	✓	✓	transferred to		✓	✓
3rd q	✓	✓	frequent follow-up		✓	✓
4th q	✓	✓			✓	✓
Years Six and above						
1st q	✓				✓	
2nd q	✓	✓			✓	✓
3rd q	✓				✓	
4th q	✓	✓			✓	✓

(d) haematology / biochemistry

An initial capillary blood sample was taken within 48 hours of birth. Subsequent venepunctures have been performed, and haematology and biochemistry collected according to the regime outlined in Table 2.4. Assessment of routine haematology is contra-indicated for a three-month post-transfusion period.

Table 2.4

Data collection regime of routine haematology among JSSCD participants

Age	FBC	HbA_2	HbF	Fe / Bilirubin	Folate	Storage	LFT	RFT
1	2	1	1	1	1	1	-	-
2	2	1	1	1	1	1	-	-
3	2	1	1	1	1	1	-	-
4	2	1	1	1	1	1	-	-
5	2	1	1	1	1	1	1	-
6	2	1	1	1	1	1	-	-
7	2	1	1	1	1	1	-	-
8	2	1	1	1	1	1	-	-
9	2	1	1	1	1	1	-	-
10	2	1	1	1	1	1	1	-
11 to 14	2	-	1	1	1	1	-	-
15	2	1	1	1	1	1	1	1
16 to 19	2	-	1	1	1	1	-	1
20	2	1	1	1	1	1	1	1
21 to 24	2	-	1	1	1	1	-	1
25	2	1	1	1	1	1	1	1
26 to 29	2	-	1	1	1	1	-	1
30	2	1	1	1	1	1	1	1

1 Measurement once a year, on birthday
2 Measurement twice a year, on birthday and at 6-months

Routine haematology (full blood count or FBC) consists of total haemoglobin (Hb, g/dl), red cell count (RBC, count/l), packed cell volume or haematocrit (PCV, l/l), mean cell volume (MCV, fl), mean cell haemoglobin (MCH, pg), mean cell haemoglobin concentration (MCHC, g/dl), platelet count (PLATE 10^9/l), and reticulocyte count (RETICS %). Hb and RBC were measured in an electronic counter (Coulter ZB16 or Coulter MaxM, Coulter Electronics) regularly calibrated with a commercially available control (4C, Coulter Electronics). PCV was measured as the centrifuged micro-haematocrit after centrifuging at 12,000g for 5 minutes and without correction for trapped plasma. MCV, MCH, and MCHC were derived haematological parameters calculated from Hb, RBC, and PCV (equations 2.1 to 2.3).

$$\text{MCV} = \frac{\text{PCV (\%)} \times 10}{\text{RBC (millions/}\mu\text{l)}} \text{ fl} \tag{2.1}$$

$$\text{MCH} = \frac{\text{Hb (g/dl)} \times 10}{\text{RBC (millions/}\mu\text{l)}} \text{ pg} \tag{2.2}$$

$$\text{MCHC} = \frac{\text{Hb (g/dl)}}{\text{PCV (\%)}} \times 100 \tag{2.3}$$

Platelets were counted in an electronic counter (Coulter Thrombocounter). Reticulocytes were ascertained from blood, stained 5% brilliant cresyl blue. Further red cell indices were collected less frequently. HbA_2 (g/dl) was estimated by elution after electrophoresis on

cellulose acetate (11) and fetal hemoglobin (%) by an alkali denaturation method. Serum was separated and stored at 4°C for estimation of serum iron (mmols/l) by the method of Beale *et al* (12), iron binding capacity (mmols/l), and % saturation (%). Serum was stored at -20°C for estimation of serum bilirubin (conjugated and total, mmols/l) by the method of Lathe and Ruthven (13). Serum was stored at -20°C after addition of ascorbic acid to stabilize folate, for the estimation of serum folate (mg/l). Assessment of folate levels was contra-indicated for patients on folate supplementation (14). Further serum was separated and stored at -70°C.

Liver function tests (LFTs) included total protein, albumin, globulin, alkaline phosphatase, GGT, and SGOT. Renal function tests (RFTs) include serum electrolytes, urea, creatinine, and uric acid. Stored serum allowed subsequent measurement of β_2 microglobin (an indicator of the glomerular filtration rate). Urine samples taken at annual birthday visits were tested for proteinuria, and were stored at -70°C for later measurement of microalbuminuria.

(e) anthropometry

The measurement schedule for anthropometry is presented in Table 2.5.

Height and weight

Patient height and weight (HW) were recorded by a nurse practitioner at each routine visit. Weight (kg) was measured on balance scales after removal of shoes and any heavy top clothes. Height (cm) was measured using a standing stadiometer with the person standing straight and upright, head forward and eyes level, and heels on the ground and against the back plate. Height and weight measurements were compared with previous values by the attending physician, and were repeated if necessary.

Anthropometry

Limited anthropometry (L) additionally included sitting height, arm span, arm circumference, triceps skin fold thickness and subscapular skin-fold thickness, and was collected every six months. The mean of three consecutive skin-fold measurements are taken. Full anthropometry (F) additionally included inter-acromial diameter, inter cristal diameter, chest anteroposterior and lateral diameters, chest circumference, and bicep and supra-iliac skin fold thicknessess.

Limited and full anthropometry are not used in this thesis. Measurement details are not described, and are available on request.

Table 2.5

Data collection regime of anthropometry among JSSCD patients

	SS / AA	SC	S/other
Every routine visit	HW	HW	HW
Every 6 months	L P	L P	L P
Every year (birthday)	F P	L P	L P
Once at 8 years	F P B	F P B	F P B
Once at 12 years	F P B	L P B	L P
Once at menarche	B	-	-

HW = height and weight, L = limited anthropometry, F = full anthropometry
P = pubertal staging, B = bone age.

Sexual development

Pubertal staging (P) is assessed by the Tanner method from stage 1 (prepubertal) to stage 5 (pubertal). Testicular size is assessed by Praders orchidometer palpating each testicle gently in the right hand while comparing with the orchidometer held in the left.

(f) ophthalmological studies

Each year between 1985 and 2000, a team led by Professor Alan Bird (Moorfield's Hospital, London) examined the eyes of all JSSCD patients with a haemoglobin S genotype. This examination took place over three weeks in January and February - a period known anecdotally as *the cohort eye review.* Examination included assessment of visual acuity, retinal examinations with retinal drawings, fluorescein angioscopy and angiography, and was designed to describe the natural history of proliferative sickle retinopathy. During the clinic presentation, participants were given a clinical examination, and a FBC was collected.

(g) ultrasound studies

During the cohort eye review, participants underwent annual ultrasound assessment. The gallbladder was examined for stones, sludge, thickening of the gallbladder wall, or dilation of the common bile duct. The spleen was examined for dimensions, and irregularities of splenic structure and consistency. The kidneys were examined for long and short renal dimensions, abnormalities of structure, and congenital abnormalities.

(h) sick visits

A computerised participant information system allowed attending physicians to enter details of clinical events directly into a database. The wide ranging symptoms of SCD have proven difficult to incorporate into a general clinical coding regime (e.g. ICD, READ codes (15;16)), and a dedicated coding system has been developed for use at the Jamaican sickle-cell clinic. Codes are presented in Appendix 1, organized by system involvement. A study participant is assigned one or more clinical codes at every clinic presentation. A *y1* (481) code is assigned each time a study participant presents without clinical symptoms.

2.3 Patients and methods

2.3.1 Patient groups

Newborn screening took place at a single Kingston hospital for the period of JSSCD recruitment. There was no neonatal screening between the end of JSSCD recruitment (1981) and 1994, and a geographically limited (and ongoing) programme thereafter. Full details of screening for sickle-cell disease are presented in Chapter Three. The JSSCD recruited 552 patients with a haemoglobin β^S allele, and 246 AA genotype controls. The ongoing newborn screening program has identified 138 patients with an SS genotype. The remaining 6326 patients have been symptomatically recruited to the clinic.

Participants belong to one of two distinct samples from the Jamaican sickle-cell disease population: (1) the JSSCD sample, recruited for a specific and ongoing research program, and (2) the clinic sample, not actively recruited and joining the sample as they present to the sickle-cell clinic. **Patients identified through the ongoing newborn screening program and symptomatically recruited patients are collectively considered to be *clinic-study* participants.** If analysed separately, symptomatically referred patients are known as *main-study* participants, and patients identified through the ongoing newborn screening programme are known as *screened-study* participants.

2.3.2 Patient characteristics at first visit to clinic

The clinic facilities of the Jamaican sickle-cell unit and its regular outreach clinics represent the primary health care provider for β^S haemoglobin allele patients in Jamaica. Since 01 January 1973, 7016 patients with the β^S globin chain abnormality have presented to the clinic. Along with 246 AA genotype JSSCD controls, 7262 patients have presented to clinic at least once within the study window. These patients are summarized by study group (main, JSSCD, screened), and by genotype in Table 2.6. SS disease forms the clinic majority in both the main and JSSCD study groups (main: 66.5%, JSSCD: 57.1%), with the combined patient load (see section 2.3.3) of SS and SC disease around 90% for both main study and the JSSCD (main: 91.1%, JSSCD: 88.4%). Within the JSSCD, the ten compound heterozygotes of HbS and beta chain variants (SV) include sickle-cell-HbO Arab (two), sickle-cell-HbD Punjab (two), sickle-cell-Hb Lepore-Boston (one), and combinations of the sickle-cell gene with HbD Iran (two), Hb Caribbean (one), HbK Woolwich (one), and Hb Korle Bu (one).

Among symptomatically referred study participants, median age at entry to clinic (unadjusted for clinic period) was lower in the more severe genotypes. Compared to SS disease, the age at first presentation to clinic was significantly higher among SC and $S\beta^+$ participants; the relative risk of attendance for SC (with 95% CI) was 0.69 (0.65 to 0.73), and for $S\beta^+$ it was 0.67 (0.60 to 0.75). Recruitment is considered in detail in Chapter Three. Once recruited to the clinic, the relative risk of leaving the study for any reason was

significantly higher in all genotypes compared with SS patients. Non-response is considered in detail in Chapter Four. These differences may be a feature of clinical expression across genotypes, with an increasing number of clinical complications maintaining attendance. The increased research focus on SS disease may further promote attendance among the SS patient group. Among JSSCD study participants, the pattern of follow-up was different, with recruitment at birth, and an increased length of follow-up among the milder genotypes (SC, $S\beta^+$, SF), which reflects improved survival.

Table 2.6

Number of patients enrolled, age at entry to clinic, and years of clinic follow-up by study group and genotype.

	Main study							JSSCD			Screened-study		
genotype	**N**	**age at entry**	**mad ***	**relative risk † (95 CI)**	**yrs of follow-up**	**mad ***	**relative risk ‡ (95% CI)**	**N**	**yrs of follow-up**	**mad ***	**N**	**yrs of follow-up**	**MAD***
$S\beta^+$	305 (4.82)	12.22	7.90	0.67 (0.60 to 0.75)	7.25	5.57	1.34 (1.19 to 1.50)	36 (6.52)	21.62	2.28	12 (8.7)	2.13	0.92
$S\beta^0$	198 (3.13)	8.28	4.82	0.98 (0.85 to 1.13)	7.72	4.65	1.18 (1.03 to 1.36)	11 (1.99)	18.95	3.51	8 (5.8)	0.93	1.05
SC	1567 (24.77)	12.75	7.93	0.69 (0.65 to 0.73)	6.63	4.62	1.54 (1.46 to 1.64)	173 (31.34)	21.00	2.75	-	-	-
SF	19 (0.30)	13.03	8.41	0.84 (0.54 to 1.32)	2.05	1.79	2.29 (1.46 to 3.59)	7 (1.27)	20.91	3.35	2 (1.4)	0.83	0.92
SS	4207 (66.50)	9.12	6.72	1	9.41	6.33	1	315 (57.07)	19.15	4.63	115 (83.3)	1.51	0.85
SV	30 (0.74)	9.83	5.33	1.00 (0.70 to 1.43)	6.79	6.07	1.48 (1.03 to 2,12)	10 (1.81)	3.54	7.70	1 (0.7)	0.66	-
total	6326 (100)							552 (100)			138 (100)		
AA	-	-	-		-	-		246	23.82	1.59	-	-	-

* mad: Median absolute deviation

† Relative risk of presentation to clinic (compared to SS participants)

‡ Relative risk of leaving the clinic (compared to SS participants)

2.3.3 Vital statistics: patient burden and clinic burden

Vital statistics have been described as data on the fundamental events of human life; births and deaths (17). They are generally simple constructs, usually in the form of counts or rates. We develop four vital statistics describing clinic demand: the number of people recruited to the clinic in time period t (r_t), the number of people eligible for clinic attendance in time period t (e_t), the number of people attending the clinic in time period t (a_t), and the number of clinic presentations in time period t (c_t). Recruitment occurs at birth for neonatally screened study participants and at first visit to clinic otherwise. A person is eligible for attendance at the sickle-cell clinic if that person has been recruited and has not emigrated or died since the last clinic visit. From the set of eligible participants, the number attending and the total number of presentations in any given time period are available.

To investigate healthcare demand, we develop two concepts: participant burden, measured by participant load and participant rate, and clinic burden, measured by clinic load and clinic rate. For any time period, t,

a_t = participant load

$a_t \,/\, e_t$ = participant rate

c_t = clinic load

$c_t \,/\, a_t$ = clinic rate

$r\,(e) = e\,(main) \,/\, e\,(jsscd)$ = Relative participant eligibility

$r\,(a) = a\,(main) \,/\, a\,(jsscd)$ = Relative participant load

Participant load can be used to describe the changing population structures of the clinic-study populations (clinic participants and JSSCD participants). Participant rate describes the number of eligible participants that attend the clinic, and provides a basic description of default from each study. Clinic load is a direct measure of participant demand for the healthcare facility, and clinic rate allows the direct comparison of demand from alternative study groups, controlling for the size of the attending group. Both are useful to healthcare management. Relative participant eligibility and relative participant load examine the changing contribution of the main and JSSCD studies to the overall clinic population as age and period vary. All measures are examined annually. Attendance may exhibit seasonal fluctuation, and clinic burden is also examined monthly. Data are presented by study group (clinic participants and JSSCD participants), for all genotypes, and restricting to SS disease.

2.3.4 Reference tables

For reference, we tabulate participant-burden and clinic-burden in three-year time periods (9 groups) and either five-year age groups (13 groups – clinic sample) or two-year age groups (14 groups – JSSCD). We present the average annual participant load for the clinic sample

(Table 2.7) and for the JSSCD (Table 2.8). We present the clinic load and the clinic rate for the clinic sample (Table 2.9) and for the JSSCD (Table 2.10).

2.3.5 The effect of time on attendance: age, period and cohort effects

Attendance may increase with age due to an ongoing process of symptomatic referral (main study) or conversely may decrease due to attrition of participants caused by mortality, migration (JSSCD). Attendance may depend on secular (calendar) time due to events that affect the entire clinic population at once. Examples of these period effects include the introduction of newborn screening in Jamaica (1973), the introduction (in 1977) of parental education for the detection of an enlarged spleen (18) with a subsequent increase in detected cases of acute splenic sequestration, and the introduction (in 1978) of penicillin prophylaxis (19) requiring regular medication visits to the sickle-cell clinic. Patients less than 5 years of age attending the clinic from May 1978, will have benefited from the treatment, highlighting the potential effect of period and age. Only participants recruited in the last three years of the JSSCD benefited from penicillin prophylaxis, highlighting the potential effects of period and cohort

2.3.6 Graphical display of attendance

Marginal period and age effects can be visualised using 1-dimensional line graphs, by either calendar period or age. We present these graphs in Figure 2.2 to Figure 2.4. These simple displays can provide useful information. Care is needed in interpretation, however, as alternative 1-dimensional projections of 2-dimensional data can lead to competing conclusions. Two-dimensional plots, which allow the joint assessment of alternative time bands, are more useful. Jolley and Giles suggest the use of contour plots as an alternative summary of age-period-cohort trends without the potential loss of information. Contours in the age-period projection represent regions of equal attendance (cf. contours on a topological map). Superimposed lines from lower left to upper right represent the passage of cohort groups (20). We present contour plots in Figure 2.5 and Figure 2.6.

Table 2.7

Average annual participant load for clinic participants (SS only patients in brackets).

Calender	Age group												
period	0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60+
73-75	11 (8)	18 (13)	21 (15)	22 (16)	20 (15)	14 (10)	11 (7)	7 (5)	6 (5)	3 (2)	2 (1)	2 (2)	1 (0)
76-78	10 (8)	22 (15)	26 (18)	29 (21)	26 (19)	19 (15)	10 (7)	8 (6)	6 (4)	3 (2)	1 (1)	1 (0)	1 (1)
79-81	23 (19)	29 (22)	34 (25)	36 (27)	33 (24)	27 (19)	18 (13)	10 (6)	9 (5)	5 (4)	2 (2)	1 (1)	1 (1)
82-84	40 (31)	53 (39)	70 (48)	72 (51)	56 (39)	45 (31)	30 (20)	18 (13)	14 (10)	8 (5)	4 (3)	3 (2)	1 (1)
85-87	56 (43)	61 (41)	66 (47)	79 (57)	71 (51)	51 (36)	35 (23)	25 (17)	15 (10)	11 (7)	6 (3)	3 (2)	1 (1)
88-90	62 (51)	87 (60)	67 (46)	83 (60)	79 (59)	59 (44)	45 (32)	27 (18)	20 (15)	15 (10)	11 (7)	5 (4)	1 (1)
91-93	61 (50)	97 (74)	82 (53)	71 (50)	84 (60)	70 (52)	42 (32)	31 (23)	21 (16)	12 (9)	12 (9)	6 (4)	1 (1)
94-96	75 (62)	101 (77)	107 (74)	72 (49)	82 (61)	78 (58)	53 (42)	35 (28)	24 (18)	15 (13)	11 (8)	9 (6)	1 (1)
97-99	105 (87)	120 (88)	114 (86)	90 (62)	79 (58)	87 (65)	69 (53)	44 (34)	32 (26)	18 (14)	13 (10)	10 (8)	2 (1)

Table 2.8

Average annual participant load for JSSCD participants (SS only patients in brackets).

Calender	Age group												
period	0-1	2-3	4-5	6-7	8-9	10-11	12-13	14-15	16-17	18-19	20-21	22-23	24-25	26-17
73-75	150 (44)													
76-78	139 (58)	125 (42)												
79-81	95 (59)	93 (52)	112 (46)	87 (32)										
82-84	46 (38)	68 (50)	86 (50)	112 (50)	146 (42)									
85-87		25 (23)	58 (43)	83 (49)	92 (44)	151 (47)	112 (32)							
88-90				44 (35)	68 (44)	82 (43)	115 (44)	123 (37)						
91-93					29 (25)	53 (37)	76 (43)	82 (38)	130 (40)	98 (29)				
94-96							40 (31)	59 (38)	70 (37)	94 (36)	103 (33)			
97-99								22 (18)	44 (31)	57 (32)	65 (31)	95 (33)	67 (22)	19 (8)

Table 2.9

Clinic load (c) and clinic rate (c/a), for all clinic sample participants by genotype

		Age group												
		0-4	**5-9**	**10-14**	**15-19**	**20-24**	**25-29**	**30-34**	**35-39**	**40-44**	**45-49**	**50-54**	**55-59**	**60+**
73-75	All c (c/a)	282 (1.8)	461 (1.7)	480 (1.5)	563 (1.7)	626 (2.1)	409 (2)	286 (1.8)	185 (1.9)	172 (1.8)	57 (1.5)	39 (1.7)	71 (2.1)	37 (1.9)
	SS c (c/a)	218 (1.8)	351 (1.9)	343 (1.6)	435 (1.9)	510 (2.3)	316 (2.2)	219 (2)	136 (2)	146 (2)	45 (1.6)	19 (1.7)	67 (2.2)	21 (2.6)
76-78	All c (c/a)	287 (2)	561 (1.7)	615 (1.6)	673 (1.6)	700 (1.8)	577 (2)	290 (1.8)	207 (1.7)	131 (1.5)	69 (1.4)	20 (1.5)	18 (1.3)	99 (2.5)
	SS c (c/a)	252 (2.1)	425 (1.9)	473 (1.7)	501 (1.6)	542 (1.9)	468 (2.1)	214 (1.9)	150 (1.7)	95 (1.6)	44 (1.4)	13 (1.4)	5 (1)	85 (3.1)
79-81	All c (c/a)	1037 (3)	731 (1.7)	763 (1.5)	839 (1.5)	953 (1.9)	775 (1.9)	585 (2.1)	253 (1.8)	244 (1.9)	137 (1.7)	60 (1.6)	26 (1.4)	78 (1.7)
	SS c (c/a)	912 (3.2)	587 (1.7)	587 (1.6)	656 (1.6)	752 (2.1)	582 (2)	466 (2.3)	178 (1.9)	172 (2.1)	91 (1.7)	44 (1.6)	12 (1.5)	51 (2)
82-84	All c (c/a)	1970 (3.3)	1851 (2.3)	2119 (2)	2381 (2.2)	2061 (2.5)	1722 (2.6)	1083 (2.4)	712 (2.6)	496 (2.4)	332 (2.6)	149 (2.7)	107 (2.8)	164 (2.9)
	SS c (c/a)	1606 (3.5)	1430 (2.4)	1518 (2.1)	1730 (2.3)	1530 (2.6)	1246 (2.7)	748 (2.5)	525 (2.8)	363 (2.5)	222 (2.9)	119 (2.6)	53 (2)	95 (3.4)
85-87	All c (c/a)	2794 (3.4)	2279 (2.5)	2121 (2.1)	2603 (2.2)	2612 (2.4)	1826 (2.4)	1516 (2.9)	986 (2.7)	530 (2.3)	379 (2.4)	226 (2.6)	118 (2.9)	211 (3.1)
	SS c (c/a)	2239 (3.4)	1638 (2.6)	1575 (2.2)	1973 (2.3)	2025 (2.6)	1390 (2.6)	1190 (3.5)	780 (3)	348 (2.4)	266 (2.5)	142 (2.8)	71 (2.4)	140 (3.3)
88-90	All c (c/a)	2978 (3.2)	3384 (2.6)	2307 (2.3)	3277 (2.6)	3018 (2.5)	2350 (2.7)	1709 (2.5)	1023 (2.5)	873 (2.9)	607 (2.7)	416 (2.5)	192 (2.4)	307 (3.6)
	SS c (c/a)	2589 (3.4)	2473 (2.7)	1648 (2.4)	2399 (2.7)	2376 (2.7)	1888 (2.9)	1365 (2.9)	701 (2.7)	689 (3.1)	428 (2.8)	284 (2.8)	137 (2.5)	204 (3.5)
91-93	All c (c/a)	2855 (3.1)	3505 (2.4)	2526 (2.1)	2680 (2.5)	3732 (2.9)	3358 (3.2)	1823 (2.9)	1456 (3.1)	850 (2.8)	517 (2.8)	522 (2.9)	262 (2.8)	289 (3.8)
	SS c (c/a)	2429 (3.2)	2810 (2.5)	1774 (2.2)	1950 (2.6)	2690 (3)	2717 (3.5)	1513 (3.2)	1183 (3.4)	706 (3)	379 (2.9)	439 (3.1)	164 (2.8)	172 (3.5)
94-96	All c (c/a)	3859 (3.5)	3895 (2.6)	3374 (2.1)	2466 (2.3)	4289 (3.5)	3840 (3.3)	2580 (3.2)	1765 (3.4)	1127 (3.1)	562 (2.5)	587 (3.5)	426 (3.3)	241 (2.7)
	SS c (c/a)	3411 (3.6)	2957 (2.6)	2408 (2.2)	1741 (2.4)	3164 (3.4)	3003 (3.4)	2229 (3.6)	1509 (3.6)	945 (3.5)	505 (2.7)	479 (4.1)	298 (3.4)	137 (2.4)
97-99	All c (c/a)	5739 (3.6)	4652 (2.6)	3844 (2.3)	3063 (2.3)	3777 (3.2)	4882 (3.8)	3501 (3.4)	2326 (3.5)	1599 (3.3)	774 (2.8)	603 (3)	473 (3.2)	449 (2.9)
	SS c (c/a)	5006 (3.9)	3578 (2.7)	2922 (2.3)	2170 (2.3)	2814 (3.2)	3745 (3.8)	2900 (3.6)	1983 (3.8)	1376 (3.5)	635 (3)	524 (3.5)	412 (3.5)	312 (3.3)
All years		21801 (3)	21319 (2.2)	18149 (1.9)	18545 (2.1)	21768 (2.5)	19739 (2.7)	13373 (2.6)	8913 (2.6)	6022 (2.4)	3434 (2.3)	2622 (2.4)	1693 (2.5)	1875 (2.8)
		18662 (3.1)	16249 (2.3)	13248 (2)	13555 (2.2)	16403 (2.6)	15355 (2.8)	10844 (2.8)	7145 (2.8)	4840 (2.6)	2615 (2.4)	2063 (2.6)	1219 (2.4)	1217 (3)

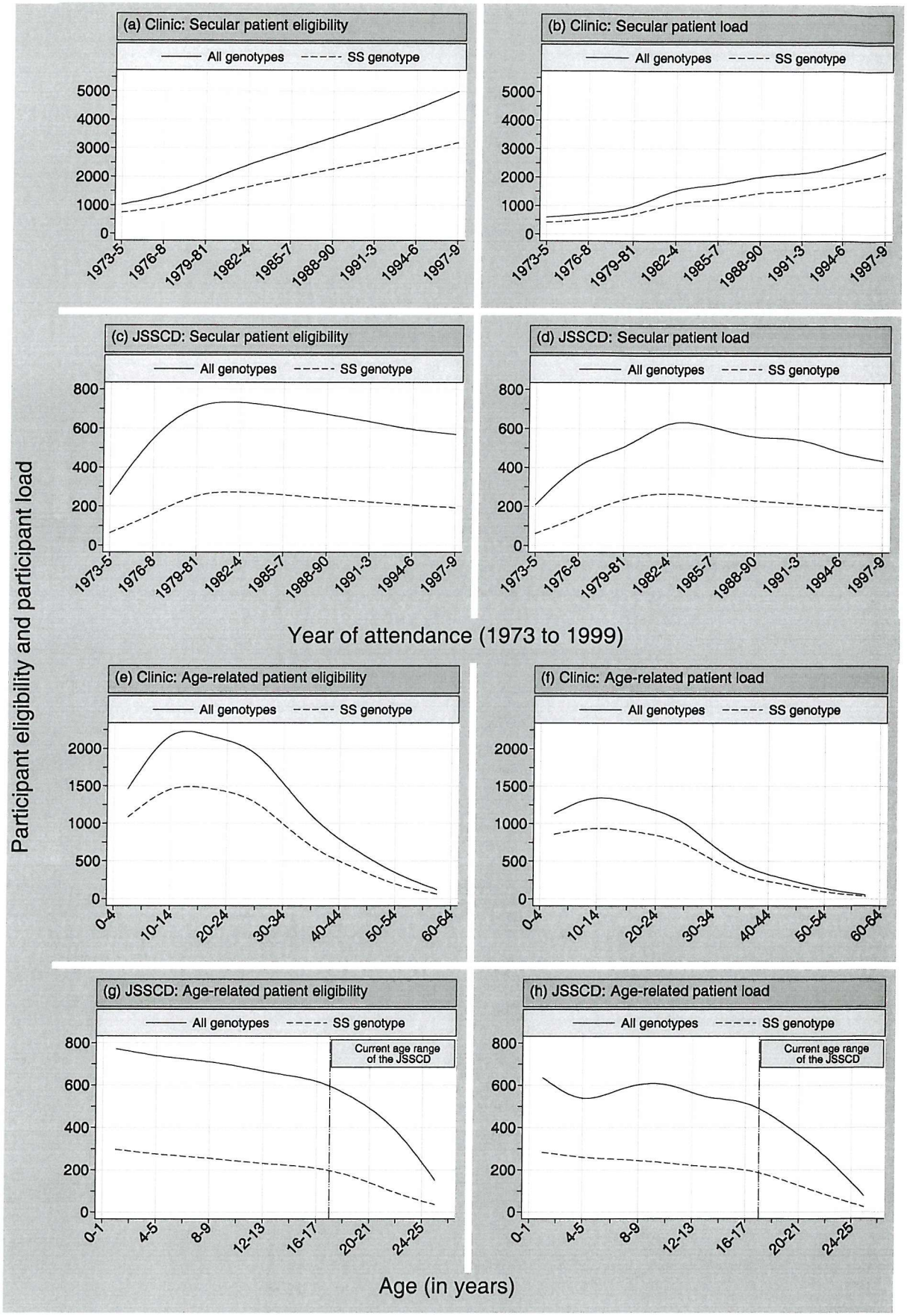
Table 2.10

Clinic load (c) and clinic rate (c/a), for all JSSCD sample participants by genotype

		Age group													
		0-1	**2-3**	**4-5**	**6-7**	**8-9**	**10-11**	**12-13**	**14-15**	**16-17**	**18-19**	**20-21**	**22-23**	**24-25**	**26-17**
73-75	All c (c/a)	2570 (3.4)	79 (2)												
	SS c (c/a)	925 (4.2)	38 (2.9)												
76-78	All c (c/a)	3820 (4.6)	2156 (2.9)	499 (2.5)											
	SS c (c/a)	2038 (5.9)	1014 (4)	266 (3.6)											
79-81	All c (c/a)	2998 (5.2)	2128 (3.8)	2039 (3)	1116 (2.6)	67 (1.9)									
	SS c (c/a)	2144 (6.1)	1454 (4.6)	1152 (4.2)	581 (3.7)	31 (2.4)									
82-84	All c (c/a)	797 (5.7)	1818 (4.4)	2013 (3.9)	2093 (3.1)	2307 (2.6)	574 (2.3)								
	SS c (c/a)	712 (6.2)	1383 (4.6)	1291 (4.3)	1182 (4)	932 (3.7)	232 (3.3)								
85-87	All c (c/a)		102 (4.1)	1175 (4.1)	1819 (3.7)	1981 (3.6)	2504 (2.8)	1456 (2.6)	60 (1.7)						
	SS c (c/a)		98 (4.3)	944 (4.4)	1181 (4)	1191 (4.5)	1055 (3.8)	585 (3.6)	37 (2.3)						
88-90	All c (c/a)				584 (4.5)	1545 (3.8)	1748 (3.6)	2150 (3.1)	1909 (2.6)	442 (2.3)					
	SS c (c/a)				503 (4.8)	1032 (3.9)	1013 (3.9)	1067 (4)	772 (3.5)	209 (2.9)					
91-93	All c (c/a)					120 (4.1)	880 (3.3)	1604 (3.5)	1579 (3.2)	2129 (2.7)	1298 (2.7)	80 (2.2)			
	SS c (c/a)					112 (4.5)	634 (3.4)	935 (3.6)	839 (3.6)	886 (3.7)	576 (4)	54 (3.2)			
94-96	All c (c/a)							414 (3.5)	1227 (3.5)	1589 (3.8)	1896 (3.3)	1988 (3.2)	500 (2.9)		
	SS c (c/a)							331 (3.6)	770 (3.4)	954 (4.3)	970 (4.4)	962 (4.9)	275 (4.2)		
97-99	All c (c/a)								90 (4.1)	824 (3.7)	1424 (4.2)	1534 (4)	2016 (3.5)	1015 (3)	48 (2.5)
	SS c (c/a)								81 (4.5)	550 (3.5)	838 (4.3)	884 (4.7)	1058 (5.4)	514 (4.6)	32 (4)
All years	c (c/a)	10185 (4.7)	6283 (3.4)	5726 (3.4)	5612 (3.5)	6020 (3.2)	5706 (3)	5624 (3.2)	4865 (3)	4984 (3.1)	4618 (3.4)	3602 (3.1)	2516 (3.2)	1015 (3)	48 (2.5)
	c (c/a)	5819 (5.6)	3987 (4.1)	3653 (4.1)	3447 (4.1)	3298 (3.8)	2934 (3.6)	2918 (3.7)	2499 (3.5)	2599 (3.6)	2384 (4.2)	1900 (4.3)	1333 (4.8)	514 (4.6)	32 (4)

Figure 2.2

Participant eligibility, and participant load at the Jamaican sickle-cell clinic



2.4 Results one: Participant burden

2.4.1 Period effects

We present the number of eligible participants, and participant-load for clinic participants (Figure 2.2 a-b) and for JSSCD participants (Figure 2.2 c-d).

(a) Clinic participants

Clinic sample eligibility increases approximately linearly throughout the study period (Figure 2.2a). The clinic sample patient load also rises throughout the study period, reaching an absolute peak in 1997-99 (all patients: 2890, SS patients: 2143) (Figure 2.2b). Annual participant rates were highest in the period 1982-84 (all genotypes: 64.8%, SS genotype: 66.0%). The crude participant rate was 58.3% among all clinic patients and 61.5% among SS clinic patients.

(b) JSSCD participants

Eligibility among the JSSCD rises to a peak soon after the close of study recruitment (1982-84), and decreases thereafter due to mortality and migration (Figure 2.2c). JSSCD participant load reached an absolute maximum during 1982-84 (all patients: 622, SS patients: 265) (Figure 2.2d). Annual patient rates were highest in the mid 1980's (all genotypes, 1985-87: 86.3%, SS genotype, 1982-84: 97.2%). The crude patient rate was 80.5% among all JSSCD patients and 95.4% among SS JSSCD patients.

(c) Relative participant eligibility and relative participant load

The relative participant eligibility, and relative participant load are presented in Figure 2.3 for all participants and for SS participants. They fall rapidly to lows toward the end of JSSCD recruitment (1979-81) and rise thereafter. The closed nature of the JSSCD cohort defines its decreasing importance over time with respect to clinic attendance. Relative participant load is generally lower than relative eligibility, highlighting the higher participant rate within the JSSCD.

Among all genotypes, relative participant load rises from a low of 1.75 (95% confidence interval 1.58 to 1.93) in 1976-78 to a high of 6.68 (6.23 to 7.16) in 1997-99. Among SS patients it rises from a low of 3.01 (2.77 to 3.26) in 1979-81 to a high of 11.90 (11.21 to 12.64) in 1997-99.

2.4.2 Age effects

We present the number of eligible participants, and participant-load for clinic participants (Figure 2.2 e-f), and for JSSCD participants (Figure 2.2 g-h).

(a) Clinic participants

Clinic sample eligibility increased from birth to a plateau between 10-24 years of age, and decreased slowly thereafter (Figure 2.2e). Participant load followed a similar pattern (Figure 2.2f).

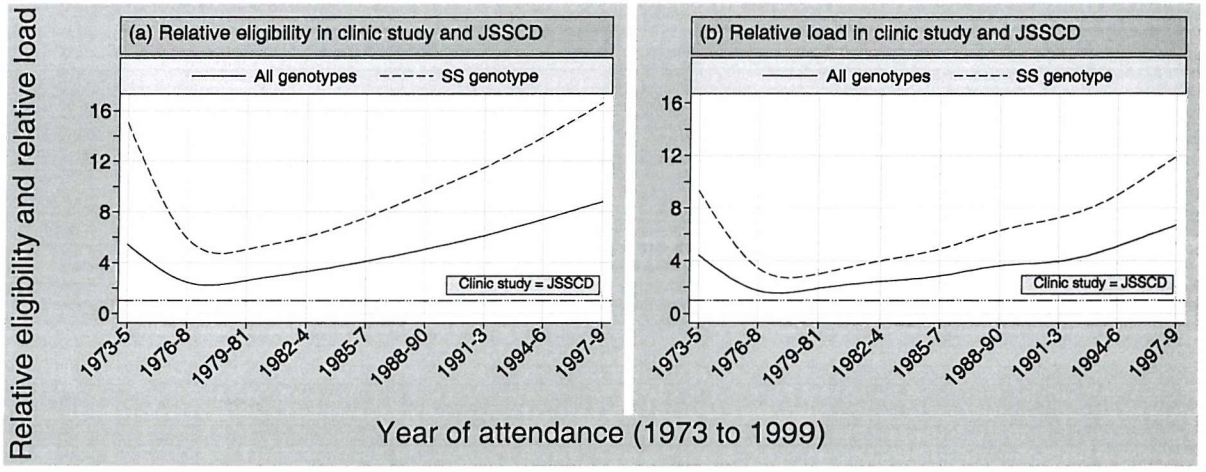
(b) JSSCD participants

JSSCD eligibility decreased steadily with age as participants died or migrated. As of December 31, 1999, JSSCD participants were between 18 and 26 years of age, and eligibility decreased sharply between these ages (Figure 2.2g). JSSCD participant load mirrors the pattern of decreasing eligibility (Figure 2.2h). Among JSSCD participants there was a dip in participant load between the ages of two and seven. This dip was not seen in SS participants.

Generally, the percentage of eligible participants presenting in any given calendar year or at any given age is increased among JSSCD participants, and among SS participants.

Figure 2.3

Relative patient eligibility and relative patient load between the clinic study and the JSSCD



2.5 Results two: Annual clinic burden

The marginal effects of calendar period and age on clinic load and clinic rate are examined using line graphs (Figure 2.4 a-h). The investigation is then extended with the examination of the joint effects of calendar period, age and cohort using contour plots (Figure 2.5 a-d and Figure 2.6 a-d).

2.5.1 Period effects

(a) Clinic participants

Clinic load rises steadily throughout the calendar period. A jump is evident at the close of JSSCD recruitment (1981), and probably represents the return of the Victoria Jubilee Hospital SCD births to the clinically ascertained population. Over the nine 3-year calendar periods, the clinic has seen a 10-fold increase in attendance (3668 presentations in 1973-75, increasing to 35682 presentations in 1997-99) (Figure 2.4 a). Clinic rate ranges between 2 and 3 presentations per participant per year, with an upward shift in clinic rate in the early 1980's (Figure 2.4 b).

(b) JSSCD participants

Clinic load peaks at the end of JSSCD recruitment (Figure 2.4 c). Clinic rate is generally stable at between 3 and 4 presentations per participant per year for the entire JSSCD sample, and between 4 and 5 presentations per patient per year among JSSCD SS participants (Figure 2.4 d).

2.5.2 Age effects

(a) Clinic participants

Among the clinic sample, clinic load has two peaks; early childhood (ages 0-4), and early adulthood (ages 20-24). Thereafter, presentations decrease rapidly due to a decreasing patient load (Figure 2.4 e). The clinic rate is highest in early childhood, dips during adolescence, before settling to values below 3 presentations per participant per year in adulthood (Figure 2.4 f).

(b) JSSCD participants

Among the JSSCD, clinic load reflects the decreasing participant eligibility with increasing age. Highs in the first 2 years of life decrease rapidly, stabilise in adolescence, and fall towards zero after 18 years of age (Figure 2.4 g). A high clinic rate of around 5 presentations per participant per year settles to values between 3 and 4 in adolescence, and rises again in early adulthood, especially among SS participants (Figure 2.4 h).

2.5.3 Age-period-cohort effects

Using contour plots, the interaction between age, period, and cohort are more evident (see Figure 2.5 and Figure 2.6).

(a) Clinic participants

The sharp rise in clinic load at the end of JSSCD recruitment (1979-1981) is seen primarily among patients aged 30 years or less, whilst the high early childhood and early adulthood clinic loads are only apparent from 1990 onwards (Figure 2.5 a). The pattern of participant load for SS participants is broadly similar (Figure 2.5 c).

The sharp rise in clinic rate seen at the end of JSSCD recruitment is seen across all ages. Clinic rates peak in early childhood (ages 0-4) for all calendar years, in early adulthood (ages 20-39) in the 1990's, and in older adults (ages 54-64) around 1990 (Figure 2.5 b and d).

(b) JSSCD participants

The passage of the JSSCD population through time is striking. The high early life clinic load (ages 0-3) persists for the 8-year window of recruitment, and this largely explains the very different period and age trends seen on the 1-dimensional projections (Figure 2.6 a,c). Clinic rates are generally stable, with a tendency for increased rates early in life (ages 0-3) and for the latter half of the JSSCD recruits (recruitment 1987-1981) (Figure 2.6 b,d). This cohort effect will be due in part to the design change of JSSCD follow-up (see Table 2.3).

Figure 2.4

Clinic load and clinic rate by calendar period (a-d) and by age (e-h)

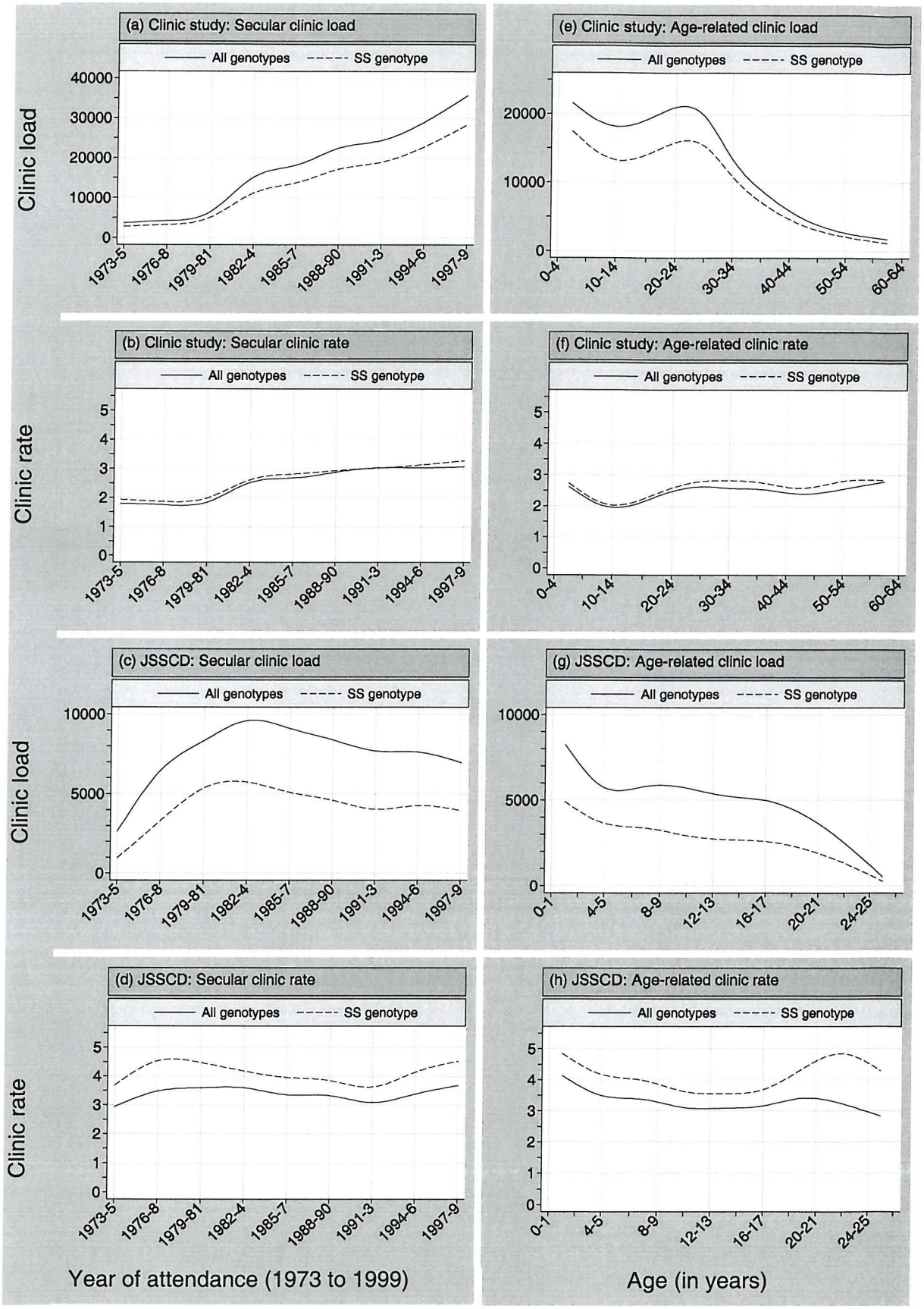


Figure 2.5

Clinic load for all participants (a) and for SS participants (c), and clinic rate for all participants (b) and for SS participants, among the clinic sample.

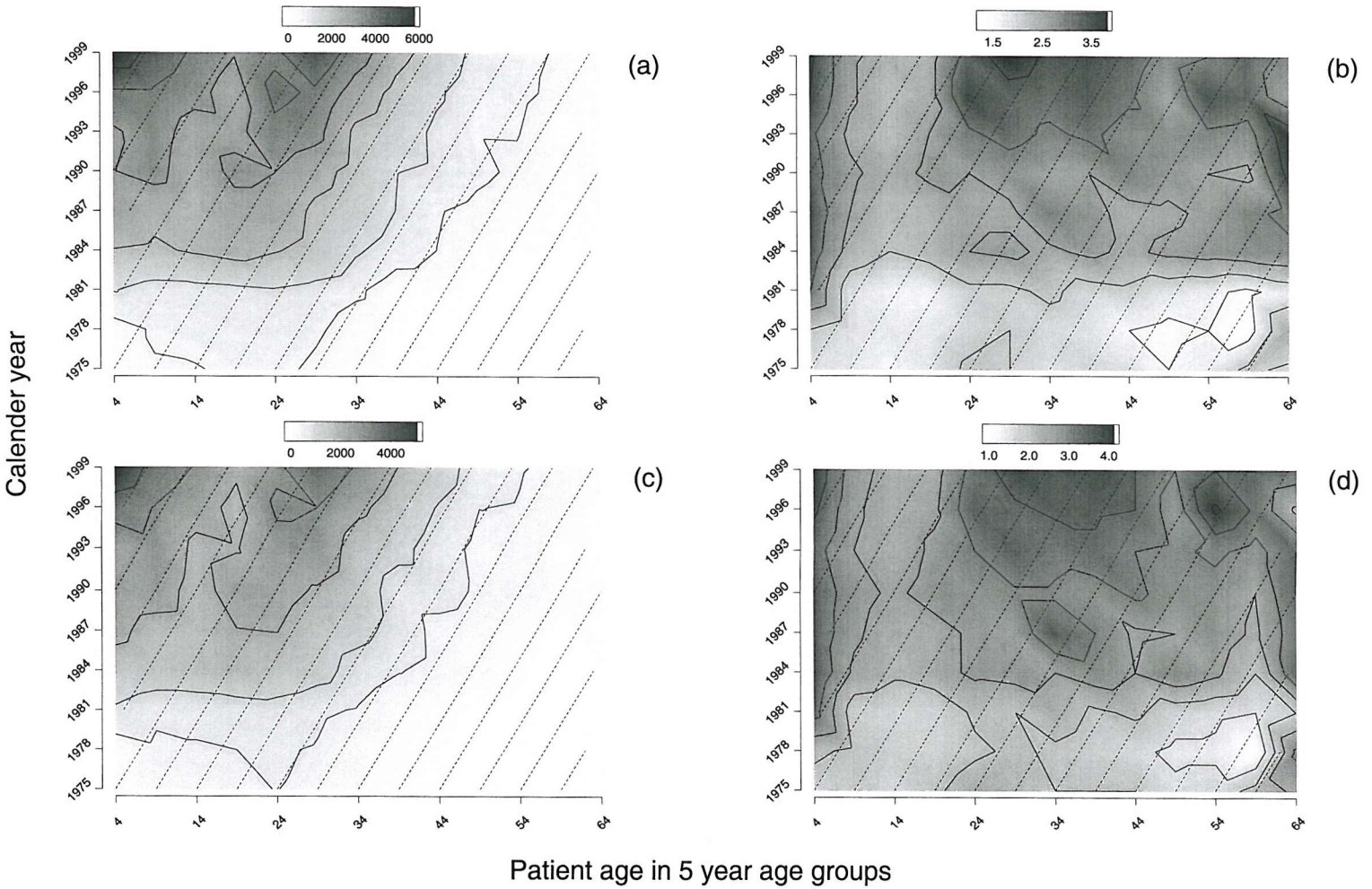
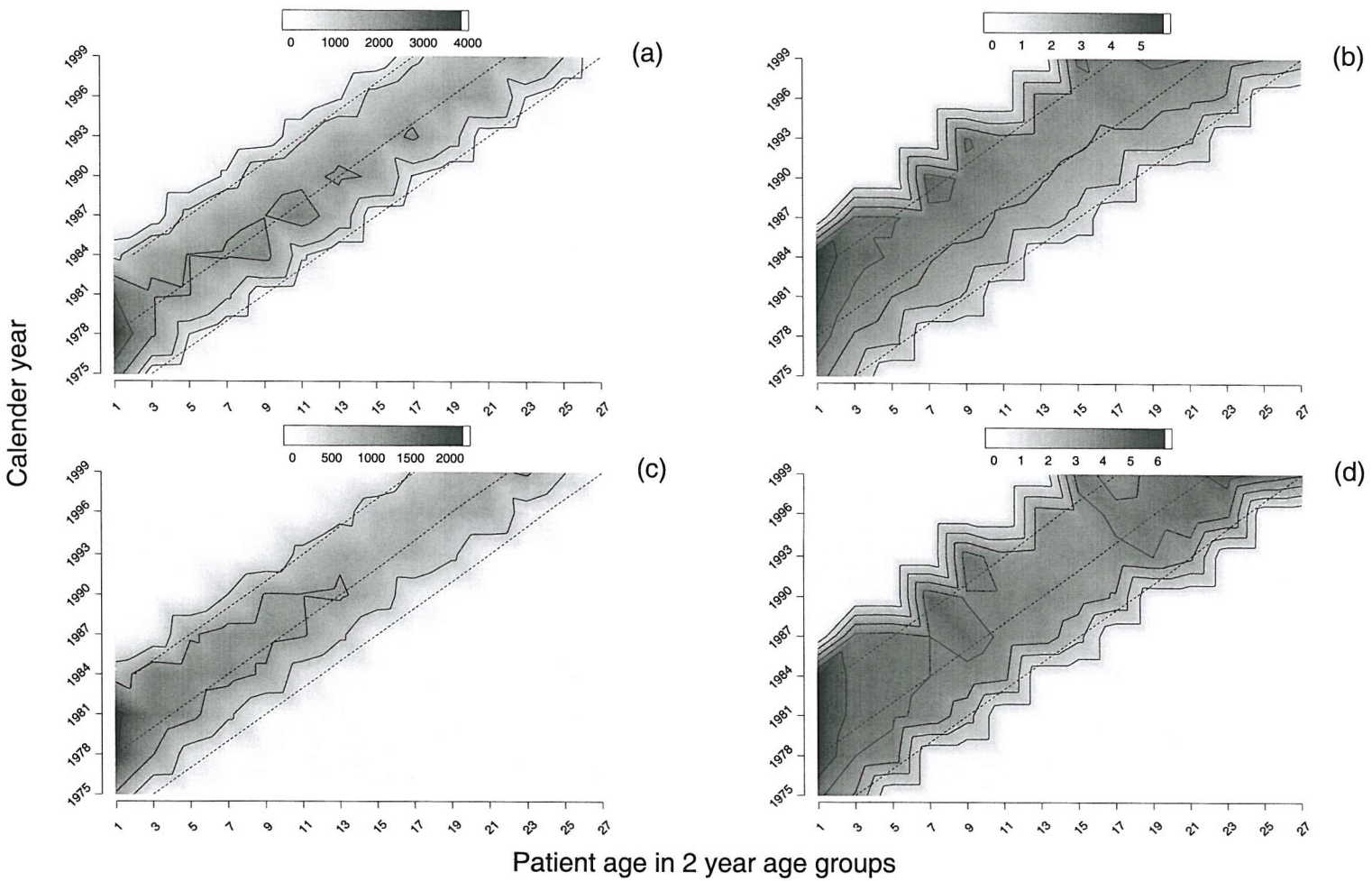


Figure 2.6

Clinic load for all participants (a) and for SS participants (c), and clinic rate for all participants (b) and for SS participants, among the JSSCD sample.



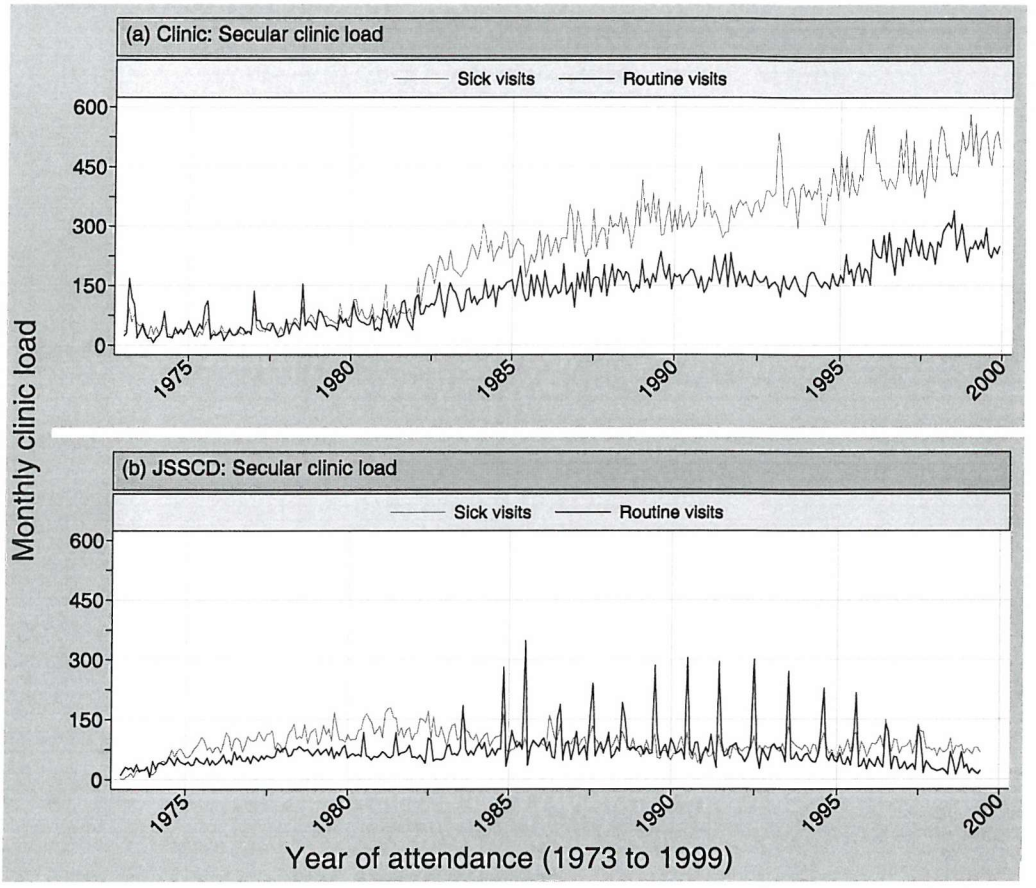
2.6 Results three: Monthly clinic burden

Seasonal fluctuations in clinic load should be expected and will be due to variation in the level of sick visits (21) and the structure of routine appointments.

2.6.1 Period effects

Figure 2.7

Monthly clinic load among (a) the clinic participants and (b) the JSSCD



(a) Clinic participants

The numbers of routine and sick visits are similar until the early 1980's and diverge abruptly thereafter (Figure 2.7 a).

(b) JSSCD participants

The numbers of routine and sick visits are roughly comparable. Routine attendance spikes from 1985 onwards highlight the annual JSSCD review of participants (Figure 2.7 b).

2.7 Discussion

We summarise some main findings from this investigation of attendance:

- During the 27-year period from 1973 to 1999, there has been a continual increase in the number of people visiting the clinic (participant load) and the number of clinic appointments (clinic load).

- Clinic load has increased 10-fold, rising from 3668 presentations in the period 1973-1975 to 35682 presentations in 1997-99. This increasing trend has been approximately linear throughout the period.

- This increase in clinic load is due to an increase in the size of the eligible participant sample and an increase in the number of visits per person per year (clinic rate).

- Clinic rate was highest among young children (ages 0-4) at all times and young adults (ages 20-39) during the 1990's

- The importance of the JSSCD at a contributor to patient and clinic burden has been decreasing since the close of JSSCD patient recruitment, and will continue to do so.

- The age structure of the clinic sample has stabilised, whilst the age structure of the JSSCD continues to increase (Table 2.11). The clinical management of SCD for the clinic sample should already be based on the correct demographic profile. Research using the JSSCD participants must continue to adapt to the emerging complications of adulthood.

Serjeant and Hutson provided the only published record of Jamaican sickle-cell clinic attendance (1952-1982) (1) and showed an aging clinic in the first 15 years of the clinic and stability thereafter. Median age with associated median absolute deviation (22) for the period 1973 to 1999 for clinic and JSSCD study groups confirms the continuing age stability for the clinic study and an increasing age structure among the JSSCD. The median JSSCD age exceeded that of the main study for the first time in 1999 and will continue to increase as the JSSCD are followed through adulthood.

Participant and clinic burden provide important basic information for healthcare provision. In particular, knowledge of how these burdens are likely to change in the near future can guide timely alterations in healthcare supply.

In SCD research, all data on disease complications are collected directly from the clinic environment. The quantity and quality of data is fundamentally dependent on the ability to accurately collect comprehensive clinical data. The changing demand on the clinical

environment, and the clinic's ability to adapt to such changes has quality implications for subsequent research.

Table 2.11

Median age (median absolute deviation) by calendar period and study group.

Calendar period	Clinic sample	JSSCD
1973-75	20.21 (8.32)	0.50 (0.33)
1976-78	20.51 (8.35)	1.75 (1.02)
1979-81	19.97 (8.92)	3.50 (2.00)
1982-84	19.55 (8.84)	6.54 (2.22)
1985-87	20.15 (9.67)	9.75 (2.00)
1988-90	20.67 (10.19)	12.75 (2.00)
1991-93	21.99 (10.49)	15.75 (2.00)
1994-96	22.83 (10.97)	18.89 (1.90)
1997-99	22.55 (11.84)	21.75 (2.00)

2.8 Appendix One

Sickle-cell Unit clinical coding system.

Code	id	Description	Code	id	Description
Infections: general					
a1	1	Chicken pox	a7	7	Unused
a2	2	Mumps	a8	8	Unused
a3	3	Measles	a9	9	Unused
a4	4	Pertussis	a0	10	Unused
a5	5	Diptheria	a-	11	Unused
a6	6	Unused	a+	12	
			a-	13	
Infections: GI tract and upper respiratory tract					
b1	21	Diarrhoea - no culture sent	b7	27	Oral Monilia
b2	22	Diarrhoea - no pathogen	b8	28	Tonsillitis
b3	23	Diarrhoea - E. coli	b9	29	URTI (without tonsillitis)
b4	24	Diarrhoea – Salmonella	b0	30	Vomiting ? cause
b5	25	Diarrhoea – Shigella	b-	31	Acute gastroenteritis
b6	26	Diarrhoea - Other	b+	32	-
			B*	33	Stool culture, pending result
Infections: Localised					
c1	41	Otitis externa	c7	47	Osteomyelitis - salmonella
c2	42	Otitis media (acute)	c8	48	Osteomyelitis – other
c3	43	conjunctivitis & eye infections	c9	49	Osteomyelitis – suspected
c4	44	Unused	c0	50	Venereal disease
c5	45	Unused	c-	51	MSU, culture sterile
c6	46	Unused	c+	52	MSU, confirmed UTI
			c*	53	MSU pending result
Dactylitis, Painful Crisis, and Avascular Necrosis of Bone (AVN)					
d1	61	Acute dactylitis	d7	67	AVN femoral head - joint damage
d2	62	Shortened small bones	d8	68	AVN femoral head - no joint damage
d3	63	Osteomyelitis of digits	d9	69	AVN other sites
d4	64	Mild bone pain	d0	70	AVN ribs or sternum
d5	65	Painful crisis requiring peth / sosegon	d-	71	-
d6	66	Abdominal painful crisis (distention ±decreased or absent bowel sounds)	d+	72	Day care admission
			d*	73	-
E.N.T					
e1	81	Perforated drum	e7	87	
e2	82	Permanent deafness, 1 or 2 ears	e8	88	
e3	83	Nosebleed	e9	89	
e4	84	Dental abcess	e0	90	Other
e5	85		e-	91	
e6	86		e+	92	
			e*	93	
Urogenital System: Male					
f1	101	Stuttering priapism	f7	107	
f2	102	Major priapism	f8	108	
f3	103	Impotence	f9	109	
f4	104	Gynaecomastia with stilboestrol	f0	110	
f5	105	Gynaecomastia without stilboestrol	f-	111	
f6	106	-	f+	112	
			f*	113	
Gastrointestinal Tract					
g1	121	Non-specific abdominal pain	g7	127	Large bowel lesion
g2	122	Pica	g8	128	Hernia
g3	123	Vomiting ? cause	g9	129	DU symptoms Endoscopy

					NAD
g4	124	Symptoms suggestive of DU	g0	130	Suspected worms
g5	125	DU (endoscopy or barium meal)	g-	131	Other GI problems
g6	126	Small bowel lesion	g+	132	Constipation
			g*	133	
Heart					
h1	141	Congenital heart disease	h7	147	
h2	142	Rheumatic heart disease	h8	148	
h3	143	Heart failure	h9	149	
h4	144	Hypertension (diastolic ≥90)	h0	150	Other heart problems
h5	145		h-	151	
h6	146		h+	152	
			h*	153	
Liver and Spleen					
i1	161	Hepatitis / hepatic abscess	i7	167	ASS (clinical)
i2	162	Hepatomegaly > 3cm	i8	168	ASS (subclinical)
i3	163	Hepatic sequestration	i9	169	Hypersplenism
i4	164	Acute cholecystitis	i0	170	Splenic Infarction
i5	165	Acute cholestasis	i-	171	
i6	166	Cholelithiasis	i+	172	
Chronic Diseases					
j1	181	Diabetes	j7	187	BMT
j2	182	SLE	j8	188	
j3	183	Cirrhosis	j9	189	
j4	184	HIV +	j0	190	
j5	185	HTLV1 +	j-	191	
j6	186	HBSAg +	j+	192	
			j*	193	
Kidney Problems					
k1	201	Enuresis	k7	207	Urinary retention
k2	202	Haematuria	k8	208	Oedema (renal or non-renal origin)
k3	203	Nephrotic syndrome	k9	209	-
k4	204	Acute nephritis	k0	210	Other
k5	205	Acute renal failure	k-	211	-
k6	206	Chronic renal failure	k+	212	-
			k*	213	-
Locomotor problems					
l1	221	Fracture of bone	l7	227	-
l2	222	Osteoarthritis	l8	228	-
l3	223	Ankle fixation from leg ulceration	l9	229	-
l4	224	Gout	l0	230	Other
l5	225	Mechanical neck and back pain	l-	231	-
l6	226	Rheumatoid arthritis	l+	232	-
			l*	233	-
Miscellaneous					
m1	241	Malnutrition	m7	247	Other psychological disorder
m2	242	Trauma	m8	248	
m3	243	Depression	m9	249	
m4	244	Malignant disease	m0	250	
m5	245	Poor school performance	m-	251	
m6	246	Medical certificate	m+	252	
			m*	253	
Nervous system					
n1	261	Cerebral palsy	n7	267	Fits - epileptic
n2	262	Mental retardation	n8	268	Fits - febrile
n3	263	Vertigo	n9	269	Fits - other
n4	264	Migraine	n0	270	Other
n5	265	Cerebro-vascular accidents	n-	271	Non migraine headaches
n6	266	Brain damage other than CVA	n+	272	-
			n*	273	

Ophthalmic					
o1	281	PSR - no treatment	o7	287	
o2	282	PSR - Xenon photocoag	o8	288	
o3	283	PSR - Argon laser	o9	289	
o4	284	PSR	o0	290	Eye visit – No PSR
o5	285		o-	291	
o6	286		o+	292	
			o*	293	
Haematopoietic system					
p1	301	Presumed aplastic crisis	p7	307	Confirmed B19 infection
p2	302	Lymphadenopathy	p8	308	Haemorrhage
p3	303	Unexplained hypoplasia	p9	309	-
p4	304	Megaloblastic change	p0	310	-
p5	305	Iron deficiency	p-	311	-
p6	306	Combined folate and iron deficiency	p+	312	-
			p*	313	-
Infections / fever					
q1	321	Septicaemia – pneumococcal	q7	327	Meningitis – other bacterial
q2	322	Septicaemia – H.influenzae B	q8	328	Meningitis – viral
q3	323	Septicaemia –Salmonella	q9	329	Suspected meningitis
q4	324	Septicaemia –E Coli	q0	330	Non-specific viral illness
q5	325	Septicaemia –Other	q-	331	Blood culture sterile
q6	326	Meningitis - pneumococcal	q+	332	PUO (ill child, T 100.4 / 38.0 ? (cause)
			q*	333	Blood culture, pending result
Respiratory system					
r1	341	Wheezy bronchitis	r7	347	Asthma
r2	342	Bronchitis	r8	348	Chest signs (CXR nad, no CXR)
r3	343	Bronchiolitis	r9	349	-
r4	344	Croup	r0	350	Other respiratory problem
r5	345	Acute Chest Syndrome (abnormal CXR)	r-	351	-
r6	346	Unused	r+	352	-
			r*	353	Presumed ACS, no result
Skin					
s1	361	Abcess	s7	367	Scabies
s2	362	Cellulitis	s8	368	Acne
s3	363	Eczema	s9	369	Leg Ulceration > 3cm
s4	364	Impetigo / skin sepsis	s0	370	Other
s5	365	Dermatitis	s-	371	Skin trauma, cuts etc.
s6	366	Tinea	s+	372	-
			s*	373	-
Transfusion / treatment					
t1	381	Transfusion	t7	387	
t					
t2	382	Transfusion trial (stroke)	t8	388	
t					
t3	383	Painful crisis trial (pentoxyf.)	t9	389	
t4	384	Oral contraceptive trial	t0	390	
t5	385	Depoprovera trial	t-	391	
t6	386	Hydroxyurea	t+	392	
			t*	393	
Urogenital system: female					
u1	401	Menarche - (visit type V)	u7	407	Contraception - medroxyprogesterone
u2	402	Spontaneous abortion	u8	408	Contraception - IUD
u3	403		u9	409	Contraception - TL
u4	404	Stillbirth	u0	410	Hysterectomy
u5	405	Live delivery	u-	411	Vaginal discharge / PID

u6	406	Contraception - oral	u+	412	Other gynecological problems
			u*	413	Pregnancy
Surgery: general anaesthesia					
v1	421	Skin grafting	v7	427	Caesarean section
v2	422	Debridement of leg ulcers	v8	428	D and C
v3	423	Ocular Surgery	v9	429	Other gynaecological surgery
v4	424	Neurosurgery	v0	430	Drainage of osteomyelitis
v5	425	Penile surgery	v-	431	Hip replacement
v6	426	Breast surgery	v+	432	Other orthopaedic procedures
			v*	433	-
Surgery: local anaesthesia					
x1	461	Pinch grafting of leg-ulcers	x2	462	Other minor surgery
Routine clinic visit					
y1	481	Steady state			
y2	482				
Death					
z1	501	Death			
t Excluded from steady state for 90 days post transfusion.					

2.9 Reference List

(1) Serjeant GR, Hutson C. Patterns of attendance at Jamaican sickle cell clinics 1952 to 1981. Trans R Soc Trop Med Hyg 1984; 78(5):648-652.

(2) Fetter F, Schnabel TG. Sickle cell anemia in patients over 45: report of 2 cases. Geriatrics 1949; 4:309-314.

(3) Sydenstricker VP, Kemp JA, Metts JC. Prolonhed survival in sickle cell disease. Am Pract 1962; 13:584-590.

(4) Gause RC, Loomus GN, Nedelman A, Clifford GO. Atypical sickle cell anemia. J Am Med Ass 1963; 186:624-626.

(5) Charache S, Richardson SN. Prolonged survival of a patient with sickle cell anemia. Arch Intern Med 1964; 113:844-849.

(6) Serjeant GR, Richards R, Barbor PR, Milner PF. Relatively benign sickle-cell anaemia in 60 patients aged over 30 in the West Indies. Br Med J 1968; 3(610):86-91.

(7) Margolis K, Cohen IM, Rudman MS, Dawson RB. Long survival in sickle-cell disease. Lancet 1973; 1(7818):1510-1511.

(8) Sar AV, Huisman TH. Long survival in sickle cell anemia. Trop Geogr Med 1975; 27(1):95-98.

(9) Shurafa MS, Prasad AS, Rucknagel DL, Kan YW. Long survival in sickle cell anemia. Am J Hematol 1982; 12(4):357-365.

(10) Steinberg MH, Dreiling BJ, Morrison FS, Necheles TF. Mild sickle cell disease. Clinical and laboratory studies. JAMA 1973; 224(3):317-321.

(11) Millard D, Mason K, Serjeant BE, Serjeant GR. Comparison of the haematological features of the b^0 and b^+ thalassaemia traits in Jamaican Negroes. Br.J.Haematol. 36, 161-170. 1977.

(12) Beale RN, Bostrum JO, Taylor RF. Improved rapid methods for the determination of iron content and binding capacity of serum. Journal of Clinical Pathology 1962; 15:156-160.

(13) Lathe GH, Ruthven CRJ. Factors affecting the rate of coupling of bilirubin and conjugated bilirubin in the Van den Bergh reaction. Journal of Clinical Pathology 1958; 11:155-161.

(14) Rabb LM, Grandison Y, Mason K, Hayes RJ, Serjeant B, Serjeant GR. A trial of folate supplementation in children with homozygous sickle cell disease. Br J Haematol 1983; 54(4):589-594.

(15) ICD-10. The International Statistical Classification of Diseases and Related Health Problems, tenth revision. www.who.int/whosis/icd10/ . 2003. World Health Organisation.

(16) O'Neil MJ, Payne C, Read JD. READ codes version 3: A user led terminology. Meth Inform Med 1995; 34:187-192.

(17) Brillinger DR. The natural variability of vital rates and associated statistics. Biometrics 1986; 42(4):693-734.

(18) Emond AM, Collis R, Darvill D, Higgs DR, Maude GH, Serjeant GR. Acute splenic sequestration in homozygous sickle cell disease: natural history and management. J Pediatr 1985; 107(2):201-206.

(19) John AB, Ramlal A, Jackson H, Maude GH, Sharma AW, Serjeant GR. Prevention of pneumococcal infection in children with homozygous sickle cell disease. Br Med J (Clin Res Ed) 1984; 288(6430):1567-1570.

(20) Jolley D, Giles G. Visualising age-period-cohort trend surfaces: A synoptic approach. Int J Epidemiol 1992; 21(1):178-182.

(21) Redwood AM, Williams EM, Desal P, Serjeant GR. Climate and painful crisis of sickle-cell disease in Jamaica. Br Med J 1976; 1(6001):66-68.

(22) Hogg RV. Statistical robustness: one view of its use n applications today. American Statistician 1979; 33:108-116.

Book One

Study participants

Chapter 3

Recruiting participants

Background

Without early-life screening, patients are identified through siblings or family studies, or are clinically ascertained as they present to the healthcare system with clinical events. Reliance on clinical ascertainment impacts adversely on clinical practice, public health policymaking and research, yet it remains the only available method of patient identification for many SCD populations. Although the benefits of screening are well known, the extent of these benefits is less clear.

Methods

We conducted a retrospective clinic-based study of enrolment to outpatient clinics, using three outpatient facilities in Jamaica; the country's only specialist referral centres for sickle-cell disease since 1973. All patients enrolling to clinic for the first time between 01 January 1973 and 31 December 1999 and diagnosed with homozygous sickle-cell disease or sickle-cell (SC) disease were eligible for the study. In a setting without comprehensive neonatal screening, we predicted the percentage of people with sickle-cell disease that will enrol in a specialist clinic by 18-years of age, and the percentage of affected people with homozygous sickle-cell disease that will enrol early enough to benefit from penicillin prophylaxis (which is offered until five years of age). Among clinic enrollers we quantified the age at enrolment.

Findings

Between 1973 and 1981, 19% of Jamaica's newborns were screened. None were screened between 1982 and 1994, and 17% were screened between 1995 and 1999. Most patients (85% SS, 80% SC) are clinically well at first visit, suggesting that referral from elsewhere in the healthcare system is the primary mode of clinical ascertainment. Among unscreened homozygous sickle-cell disease patients, observed enrolment by five years of age was 10.1% (95% confidence interval 5.7 to 16.7) among 1974 births and is predicted to rise to 35.7% (35.0 to 36.4) among 1999 births. Observed enrolment by 18-years of age was 45.9% (35.7 to 58.2) among 1974 births, and is predicted to peak at 61.9% (60.5 to 63.2) among 1984 births, then fall to 48.9% (40.9 to 56.9) among 1999 births. Among unscreened enrollers, median age at enrolment was 10.5 years (9.9 to 11.2) in SS patients.

Interpretation

Among people born in Jamaica in 1999 with sickle-cell disease, almost 65% have not enrolled to our specialist clinics by five years of age and so will not benefit from important early-life clinical interventions. We predict that over half will not enrol for specialist clinical care during their childhood. Among SS disease patients that do enrol, over half do so in adolescence and adulthood when management is less focused on preventive care. Without a comprehensive screening programme the economic and social impact of the disease is likely to be underestimated. Programmes for systematic disease identification must be considered in countries with a substantial burden of this disease.

3.1 Introduction

The process of recruiting a patient to a sickle cell disease research programme has two complimentary features: disease ascertainment and patient enrolment. Disease ascertainment is the process of identifying SCD in an individual. Enrolment involves the subsequent identification of a sample of SCD participants. Because of age variation in disease ascertainment, participant enrolment is the single most important design consideration in SCD research. Differing enrolment criteria severely inhibit the ability to directly compare published research. Enrolment using early life screening is possible and neonatal screening is now universally considered the gold standard for patient care and enrolment to studies.

3.2 The importance of early disease ascertainment

Simple, reliable and inexpensive neonatal screening procedures to detect homozygous sickle-cell disease are available (1), and there is evidence from observational studies that newborn screening programmes can lead to substantial reductions in morbidity and mortality if linked to subsequent and appropriate patient-care and parental education. Mortality of 1.8% in the first 10 years of life among neonatally screened patients versus 8% among clinically ascertained controls has been reported (2).

Based on the proven efficacy of penicillin prophylaxis in the prevention of pneumococcal infections in the young child with homozygous sickle-cell disease (3), screening for all neonates in the US irrespective of ethnicity has been advocated by the National Institutes of Health since 1987 (4). In the United Kingdom, reports commissioned by the National Health Service advise universal neonatal screening in regions with more than 0.5-1.8 cases of sickle-cell disease per 1000 live births, with targeted screening elsewhere (5;6). The World Health Organisation working group on haemoglobinopathies recommended national sickle-cell programmes including neonatal screening in countries where the disease constitutes a 'common public-health problem' (defined as more than 0.5 affected patients per 1000 live births, in countries where the infant mortality rate has fallen to less than 40 per 1000 births), and where the country's infrastructure and health services allow such an approach (7).

Screening guidelines have been widely adopted in the US (8). In the absence of national guidelines, screening programmes exist in many countries, either targeting regions of special concern, or on a project basis (9-11). To our knowledge, many more countries in which sickle-cell disease constitutes 'a common health problem' have not introduced a neonatal screening programme for sickle-cell disease.

This reluctance to screen may be due to under-estimating the benefits of screening. We therefore estimate the proportion of unscreened patients that will eventually enrol in the sickle-cell clinics by selected ages, and we report the age at enrolment among unscreened

homozygous sickle-cell disease patients referred to three sickle-cell facilities in Jamaica. This baseline information is an important first step in quantifying the social and economic impact of screening versus not screening for homozygous sickle-cell disease at birth.

With an infant mortality of 24.5 per 1000 births (12) and approximately three cases of homozygous sickle-cell disease per 1000 live births, the disease is a common public health problem in Jamaica, a lower-middle income country (13). The burden of disease in Jamaica has shifted from paediatric and infectious disease to chronic illness (14). Given this epidemiological transition, our results are particularly relevant to many low and lower-middle income nations whose demographic pattern of disease is following a similar process (15).

3.3 Chapter plan

We report the proportion of islandwide sickle-cell disease births (SS and SC disease genotypes) that have enrolled in the Jamaican sickle-cell clinics – the notion of clinic coverage, then predict future enrolment among those people born recently with sickle-cell disease. In section 3.4 we examine the possible disease ascertainment strategies, and in sections 3.5 and 3.6 we describe screening policies for some SCD populations. In section 3.5 we include an analysis of the trait frequencies reported in the first nine years of a screening programme in Campinas, Brazil. In section 3.6 we include a case study examining factors affecting the probability of neonatal screening in the current Jamaican government screening programme. In sections 3.7 to 3.9 we analyse enrolment to the Jamaican sickle-cell clinics.

3.4 Disease ascertainment strategies

Two strategies exist to identify the sickle cell haemoglobin disorders: antenatal and neonatal screening (16).

3.4.1 Antenatal and neonatal screening

Antenatal haemoglobinopathy screening allows the identification of pregnancies at risk of an affected fetus. The diagnosis procedure is sequential. Mothers are carrier tested, and if positive for a haemoglobin disorder, partner testing is performed. For potentially affected foetuses ascertained through parental carrier testing, prenatal diagnosis is available. Termination of pregnancy is a final option available to parents of an affected foetus. The goal of antenatal screening should be to allow reproductive choice over affected pregnancies rather than a reduction in disease incidence. Despite this, affected births and number of terminations have been used as measures of antenatal screening program failure and success respectively (17).

Neonatal screening is the identification of newborns affected with a haemoglobin disorder, and not already diagnosed using pre-natal diagnosis. Enrolment into a comprehensive care facility with initiation of penicillin prophylaxis is the primary objective. In SCD, if diagnosis

is beyond the conventional neonatal period (4 weeks), it should ideally be before the onset of symptoms (generally between 3 and 6 months). Post-neonatal diagnoses within the first six months of life are often classified as neonatally screened for the purposes of research (18), although the validity of this classification will depend upon the reason for clinic enrolment.

3.4.2 Universal and selective screening

A universal antenatal screening programme offers antenatal screening to all pregnant women. A universal neonatal screening programme screens all newborns not diagnosed prenatally. A selective antenatal or neonatal programme identifies a subgroup of women at increased risk of a haemoglobin disorder (e.g. non North Europeans in the UK). For neonatal screening a third option exists - a targeted programme - which takes into account the parental carrier status in order to decrease the number of neonates requiring screening still further. Universal screening requires increased resources and, for antenatal screening, involves an increased risk of adverse screening outcomes. Selective screening can miss SCD cases, and the administration costs of selecting the population subgroup are expected to increase with increasing racial admixture (19).

3.5 Current guidelines and practice

Since the early 1970's neonatal diagnosis of the haemoglobinopathies has been available (20;21), and early screening programs were quickly initiated (22;23). The World Health Organisation summarised the programmes available in many countries by the mid-1980s (7)

3.5.1 United Kingdom

Antenatal and neonatal screening are regarded as a standard feature of healthcare delivery (24). Moreover, it has been established as legally unacceptable to have specific policies not to neonatally screen high-risk population subgroups (25). The primary policy decision for UK health authorities is therefore between universal and selective neonatal screening. The first guidelines were published in the late 1980's (26). In 1993, Standing Medical Advisory Committee (SMAC) guidelines suggested universal neonatal screening for authorities with greater than 15% of their antenatal population at risk from SCD (27). This incidence was based on a single locality and has been criticised (28). In 1999 and 2000, reports commissioned by the National Health Service Health Technology Assessment programme, developed decision models for all UK district health authorities for the comparison of the cost-effectiveness of universal and selective screening based on maternal ethnic status (5;6). In these models universal neonatal screening was advised in regions with more than 0.5 to 1.8 cases of sickle-cell disease per 1000 live births, with targeted screening elsewhere. With these reports still to be assessed and implemented, current practice is inconsistent (10).

3.5.2 North America

Guidelines from the USA, and the World Health Organisation (WHO) can be categorised into one of three types: (i) a decision on universal or selective neonatal screening should be

made at the local level, and should take into account disease prevalence, cost effectiveness and available resources (9;29), (ii) universal screening should be the preferred methodology due to the (increasing) difficulties of targeting high-risk groups by assigning ethnic origin (30;31), (iii) selective screening should be the preferred methodology, with universal screening reserved for areas with high-risk sub-populations (32). The first statewide screening program began in 1975 and was fully implemented in 1978 (33). In the light of overwhelming evidence for the benefits of early life screening, an NIH Consensus Development Conference concluded that every child should be screened early for sickle cell disease to prevent death during infancy (30). Program development was encouraged by direct funding (34). By 1994, 41 states, along with the territories of Puerto Rico and the US Virgin Islands had statewide programs. Thirty-six of these screen all infants (universal screening), and the remaining seven are geographically or demographically targeted programs.

3.5.3 Jamaica

There are no government guidelines on antenatal or neonatal screening. The primary practical source of screening is coordinated by the Sickle Cell Unit at the University Hospital of the West Indies in Kingston. Details are presented in section 3.6 and factors influencing the uptake of screening are presented in the accompanying case-study.

3.5.4 Africa

With the high incidence of SCD and the continued burden of malaria on SS patients, the provision of early life screening is a major public health necessity. A recent report describes the initiation of antenatal diagnosis in Nigeria (35) and highlights that this technique is still not affordable for the majority of at risk parents. The first large scale neonatal screening programme for SCD in tropical Africa began in Kumasi, Ghana, in February 1995 (36). Provision remains inadequate.

3.5.5 Brazil

In Brazil, the most comprehensive newborn screening programme started in Minas Gerais in 1998 (37), and a programme in Campinas, Sao Paulo State began in 1992, and has proceeded more slowly. In the following case-study we assess the HbS allele frequency recorded in the first 9 years of the Campinas programme.

3.5.6 ***Case Study 1:*** *Screening for sickle-cell disease in Brazil*

Data are available on AFS and AFC trait frequencies between 1992 and 2000 in Brazil, which we present in Table 3.1. There is evidence of a secular increase in trait rates, and we investigate possible reasons for this increase.

(a) Methods

We investigated the stability of trait frequencies during this 9-year period. We present annual trait incidence rates per 100 screened patients in Table 3.1, along with ninety-five percent jackknife confidence intervals, which are appropriate when the Poisson assumption (random occurrence of trait samples in time) is questionable. Any secular trend in trait frequency would violate this distributional assumption.

We described annual trait rates using a random-effects log-linear model, which allowed the longitudinal nature of the data and the differential effects of individual hospitals to be incorporated into the analysis. We examined two questions: (1) Is this change in secular trait frequency explained by enrolment of new hospitals during the screening period, which may have differential trait rates, and (b) do trait rates vary within the same hospital (perhaps due to increasing sensitivity in trait detection)?

The programme has identified participants as one of six possible genotypes: AA, AS, AC, SS, SC, and CC. The locus for sickle-cell disease has been examined for the three associated alleles: βA, βS, and βC. We tested whether the observed genotype frequencies are consistent with the Hardy-Weinberg equilibrium.

Table 3.1.

Frequency of AFS and AFC traits in Campinas, Brazil

Year	AFS	AFC	Population	AFS Incidence	AFS 95% ci	AFC incidence	AFC 95% ci
1992	8	3	379	2.11	(1.09-4.69)	0.79	(0.25-3.86)
1993	20	6	1110	1.80	(1.18-2.88)	0.54	(0.25-1.42)
1994	150	57	9702	1.55	(1.32-1.82)	0.59	(0.46-0.77)
1995	200	55	11713	1.71	(1.49-1.96)	0.47	(0.36-0.62)
1996	336	119	22563	1.49	(1.34-1.66)	0.53	(0.44-0.63)
1997	567	216	40838	1.39	(1.28-1.51)	0.53	(0.46-0.61)
1998	1126	367	62632	1.80	(1.7-1.91)	0.59	(0.53-0.65)
1999	1214	369	62995	1.93	(1.82-2.04)	0.59	(0.53-0.65)
2000	1576	423	69952	2.25	(2.15-2.37)	0.60	(0.55-0.67)

(b) Results

The small AFS and AFC trait frequencies in the first two years of screening are reflected in the wide confidence intervals. The log-linear test for trend performed independently for AFS and AFC trait rates suggests a linear increase in trait frequency between 1992 and 2000 for

both traits (AFS rate ratio 1.07, ci 1.05-1.09, χ^2=83.3 p<0.001. AFC rate ratio 1.07, ci 1.05-1.08 χ^2=80.2 p<0.001). There is approximately a 7% increase in both AFS and AFC trait frequency for every 1-year secular progression.

Table 3.2.

Years of screening data provided by 81 participating hospitals

Screening data provided (years)	Number of hospitals
Complete years	
1992-2000	1
1993-2000	0
1994-2000	1
1995-2000	1
1996-2000	12
1997-2000	47
1998-2000	1
1999-2000	1
2000	11
Partial years	
1997, 1998, 1999	1
1997, 1998, 2000	2
1998	1
2001 (no data yet)	2
	81

Hospitals joined the screening programme between 1992 and 2000, and provide screening information in subsequent years with frequencies shown in Table 3.2.

The majority of hospitals enrol in one of three years: 1996 (12 hospitals or 15%), 1997 (47 or 58%), or 2000 (11 or 14%). Secular investigations will be dominated by these three years. A single hospital that provided only partial information during one year (1998) and subsequently left the screening programme, and two hospitals who entered the programme in 2001 were not included in the analysis.

Using the Poisson model, the unadjusted secular increase in AFS trait frequency between successive years of screening was approximately 10% per year (rate ratio 1.10 95% ci 1.08-1.12 p<0.001). This secular increase remained important after adjusting for year of entry into the screening programme (rate ratio 1.16 95% ci 1.11-1.21 p<0.001). Year of entry to the screening programme had some effect on AFS trait frequency levels, but changes to the trait detection rate within hospitals must also be a factor.

In Figure 3.1 we present the estimated annual trait rates stratified by year of entry into the screening programme. In Table 3.3 we present the AFS frequency rate differences of hospitals recruited in each year, compared to hospitals recruited in 1997 (the largest group of hospitals). Only hospitals recruited in 2000 had a marginally significantly increased AFS trait frequency (AFS trait difference 0.34 95% ci 0.06 to 0.61 p=0.02).

Table 3.3.

Trait frequency for hospitals entering the screening programme in each year from 1992 to 2000, compared to hospitals entering the programme in 1997.

Year of entry to screening programme	Difference in AFS trait frequency in the year 2000 (95% ci)	Pr
1992	-0.12 (-0.77 to 0.53)	0.72
1993†	-	-
1994	0.13 (-0.46 to 0.72)	0.66
1995	0.39 (-0.21 to 0.99)	0.21
1996	-0.05 (-0.30 to 0.20)	0.68
1997‡	-	-
1998	-0.37 (-1.07 to 0.33)	0.30
1999	-0.76 (-2.03 to 0.51)	0.24
2000	0.34 (0.06 to 0.61)	0.02

† **No hospitals entered the screening programme in 1993**

‡ **Reference category**

Observed and expected frequencies (assuming Hardy-Weinberg equilibrium) are presented in Table 3.4.

Table 3.4.

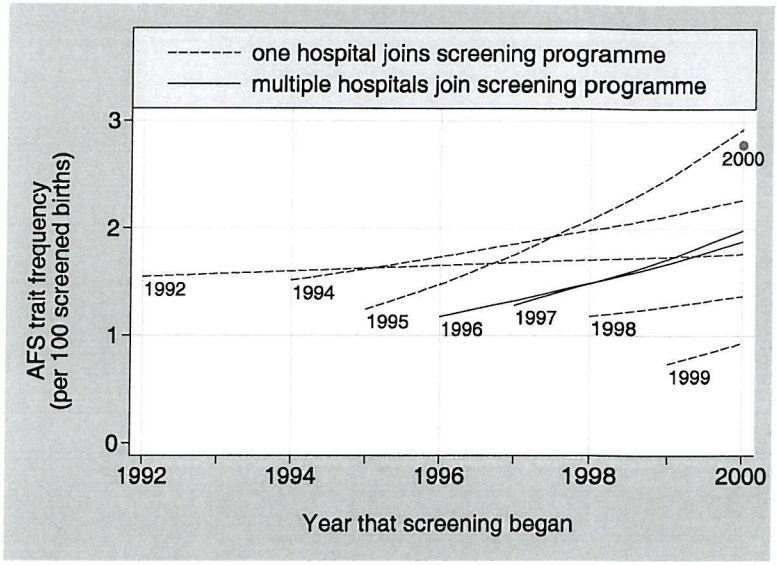
Observed genotype frequencies and expected genotype frequencies for the βA, βS and the βC alleles, assuming Hardy-Weinberg equilibrium.

	AA	AS	AC	SS	SC	CC	Total
Observed (O)	275 016	5197	1615	29	26	1	281 884
Expected (E)	275 002.5	5216.141	1622.821	24.734	15.391	2.394	281 884
$(O-E)^2/E$	0.0007	0.0702	0.0377	0.7360	7.3147	0.8118	8.97

The overall chi-squared statistic of 8.97 provides evidence for a departure from the Hardy-Weinberg equilibrium. Examining the individual chi-squared values, we note that most of the departure from Mendelian genetics comes from the SC genotype (its chi-squared value is 7.31 which represents 81.5% of the variation from H-W). In contrast, the SS genotype represents 0.74/8.97 or 8.20% of the variation from H-W. The Brazilian screening programme does not see an excess number of SS cases, but does see an excess of SC cases.

Figure 3.1

Predicted trait frequencies for the years 1992-2000 among 78 hospitals stratified by year of entry into the screening programme, allowing for different longitudinal trends.



3.6 Disease ascertainment at the Jamaican sickle-cell clinic

In Jamaica, the British Medical Research Council initiated geographically targeted neonatal screening in June 1973. The programme screened all non-operative live births from a single hospital in Kingston (Victoria Jubilee) for eight years (to December 1981) for recruitment to the JSSCD (see Chapter Two). From 1982 to 1994, there was no screening in Jamaica. In 1995 neonatal screening, funded by the Jamaican government and coordinated by the SCU, re-commenced at three hospital sites in Kingston, and is reviewed in the following case-study.

*3.6.1 **Case Study 2:** The uptake of neonatal screening for sickle-cell disease in Jamaica*

High rates of screening are needed for screening programmes to have a significant impact in reducing mortality and morbidity from inherited conditions. In this case-study we evaluated the uptake of the government neonatal screening programme in Jamaica. We determined the uptake of neonatal screening for sickle cell disease in 1999 at two Kingston hospitals, and investigated factors associated with increased screening.

(a) Material and methods

Infants born at two hospitals in Kingston (Victoria Jubilee and the University Hospital of the West Indies) between 01 January and 31 December 1999 were eligible for inclusion. Stillbirths were excluded. Details collected by both hospitals included date of birth, gender, the time of delivery, the type of delivery (vaginal or caesarean section), hospital personnel attending the delivery (doctor or midwife), whether the delivery was pre-booked, mother's age, birth weight (in kg), and the number of previous live-births, still-births and abortions the mother had experienced. UHWI additionally collected information on APGAR scores at

1 and 5 minutes post-delivery, location of the birth (before arrival at the hospital, in the labour-ward, in the labour-ward theatre, in the operating theatre), and whether the delivery was routine or an emergency. VJH additionally collected information on the mother's marital status, and the location of the birth (before arrival at the hospital, or in the hospital).

Statistical Methods: We tabulated all demographic variables by hospital, and by whether the birth was screened. Complete distributions of continuous variables were graphed by hospital and whether the birth was screened. We formally examined differences in mothers' ages and in birth weight for screened and unscreened babies in each hospital using Normal linear regression.

We present a profile of the weekly proportion of screened births for each hospital. We used a running mean, which averaged totals from every four consecutive week period. This technique smoothed the curve slightly, which improved its visual appeal, and highlighted any true trends above the 'noise' of weekly fluctuations. We used histograms to show the percentage of daily unscreened births in each hospital, which highlighted any days with particularly large levels of unscreened births.

We used logistic regression to examine the role of the various demographic characteristics on the odds of being screened. A preliminary model examined differential screening between the two hospitals. Separate models were then fitted for each hospital. The logistic models clustered births by date of birth to account for the possibility that two births on the same day are more likely to have a similar odds of screening than two births on different days.

(b) Results

Eligible sample: There were 13,791 births in the study period and 202 (1.46%) died at birth. At VJH there were 10,955 births and 165 (1.51%) died. At UHWI there were 2836 births and 37 (1.30%) died. These deaths were excluded from the current investigation, leaving a total of 13,589 eligible births (10,790 or 79.40% at VJH and 2799 or 20.60% at UHWI).

Characteristics: We present frequencies and summary statistics of all demographic variables in Table 3.5.

Table 3.5.

Characteristics of screened and unscreened births at two Kingston hospitals between January 01 and December 31 1999.

Characteristic	VJH		UHWI	
	Not-screened N (%)	Screened N (%)	Not-screened N (%)	Screened N (%)
Hospital	1405 (13.0)	9385 (87.0)	202 (7.2)	2597 (92.8)
Sex				
female	705 (13.2)	4626 (86.8)	99 (7.4)	1232 (92.6)
male	700 (12.8)	4757 (87.2)	101 (6.9)	1363 (93.1)
Time				
morning	334 (12.6)	2309 (87.4)	37 (5.7)	614 (94.3)
afternoon	370 (12.0)	2716 (88.0)	46 (5.4)	803 (94.6)
evening	297 (11.4)	2303 (88.6)	60 (8.3)	666 (91.7)
night	394 (16.2)	2045 (83.9)	54 (10.2)	477 (89.8)
Attending staff				
doctor	143 (10.8)	1181 (89.2)	92 (10.4)	790 (89.6)
midwife	1262 (13.3)	8204 (86.7)	108 (5.7)	1801 (94.3)
Delivery booked				
no	496 (17.5)	2332 (82.5)	5 (33.3)	10 (66.7)
yes	909 (11.4)	7053 (88.6)	197 (7.1)	2587 (92.9)
Location of birth				
outside	119 (56.7)	91 (43.3)	2 (20.0)	8 (80.0)
hospital	1286 (12.2)	9294 (87.4)	-	-
ward	-	-	126 (6.2)	1919 (93.8)
ward-theatre	-	-	72 (9.8)	666 (90.2)
Mode of delivery 1				
caesarian section	72 (6.5)	1045 (93.6)	74 (10.0)	670 (90.0)
nsvd	1333 (13.8)	8340 (86.2)	128 (6.2)	1927 (93.8)
Mode of delivery 2				
emergency	-	-	63 (11.3)	520 (88.7)
routine	-	-	139 (5.0)	2077 (95.0)
Married				
No	1267 (12.8)	8656 (87.2)	-	-
Yes	138 (15.9)	729 (84.1)	-	-
Neonatal death				
No	1385 (12.9)	9355 (87.2)	196 (7.0)	2589 (93.0)
Yes	20 (40.0)	30 (60.0)	6 (42.9)	8 (57.1)
	Mean (sd)	**Mean (sd)**	**Mean (sd)**	**Mean (sd)**
Age of mother (yrs)	25.5 (6.5)	25 (6.6)	28.3 (5.7)	28.1 (5.8)
birthweight (kg)	3 (0.7)	3.1 (0.6)	2.8 (1)	3.2 (0.6)
previous livebirths	1.66 (1.71)	1.47 (1.64)	0.8 (1.11)	0.78 (1.02)
previous stillbirths	0.01 (0.12)	0.01 (0.13)	0.01 (0.1)	0.01 (0.12)
previous abortions	0.19 (0.49)	0.2 (0.55)	0.5 (0.73)	0.42 (0.75)
apgar after 1 minute	-	-	7.5 (2.3)	8 (1.7)
apgar after 5 minutes	-	-	8.4 (2)	8.9 (1)

Figure 3.2

Distributions of age of mother for unscreened and screened births at VJH and UHWI

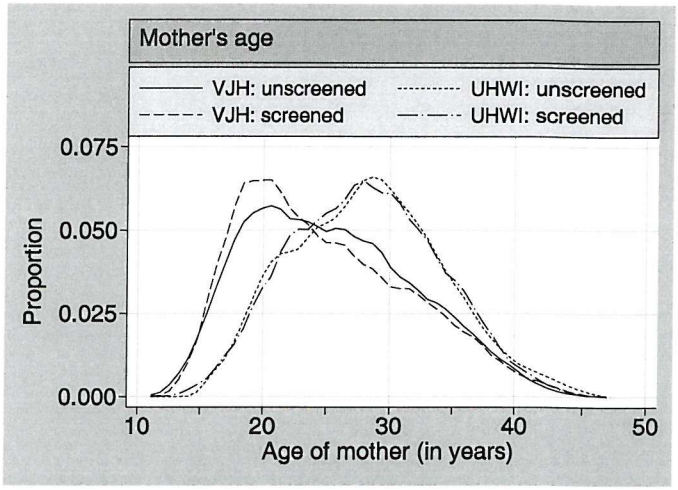


Figure 3.3

Distribution of birthweights for unscreened and screened births at VJH and UHWI

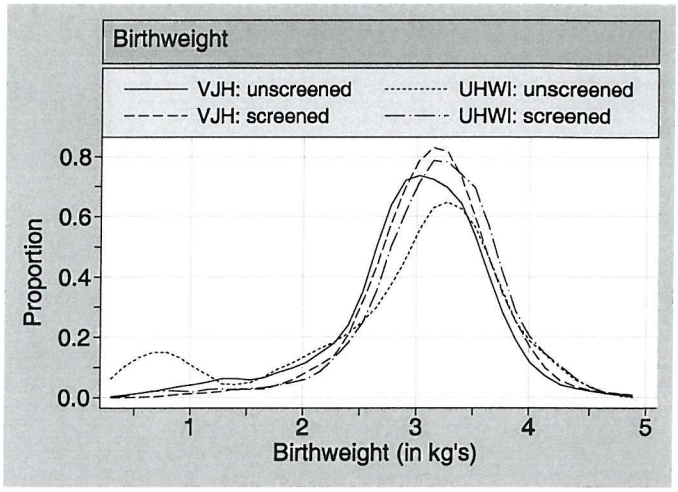
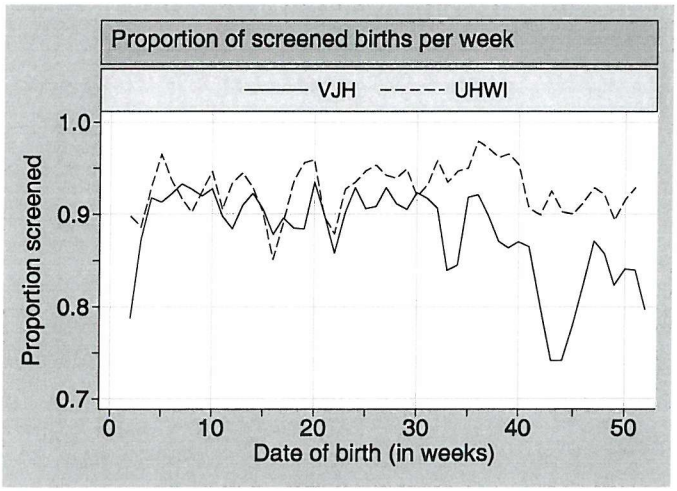


Figure 3.4

Proportion of weekly births that are screened at VJH and UHWI



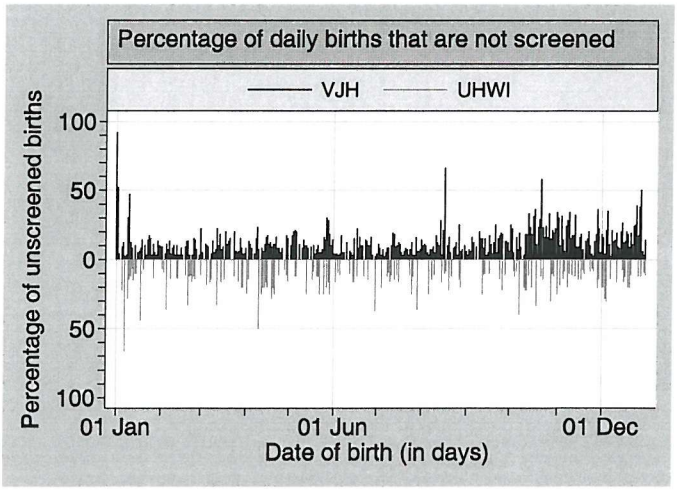
The distributions of the mothers' ages are presented in Figure 3.2. Mothers at the UHWI are significantly older than those at VJH (mean difference 2.85 years, 95% ci 1.90 to 3.81, t=5.9, Pr<0.001). The mothers of unscreened babies are slightly older at both hospitals, although this difference is not statistically strong (mean difference 0.72 years, 95% ci –0.44 to 1.90, t=1.2, Pr=0.22). The distributions of birthweights are presented in Figure 3.3. A significantly lower birthweight at the UWHI is primarily due to a cluster of low-birthweight, unscreened deliveries.

Secular trends: Secular trends in screening are presented in Figure 3.4 and Figure 3.5. After a poor start for VJH in early January, both hospitals maintain weekly screening proportions around of 0.9 until approximately week 30 (the beginning of August). Thereafter, the VJH screened proportions deteriorate towards 0.8, whilst the UHWI rate is maintained.

Predictors of screening: The odds of screening is higher at the UHWI compared to VJH, mainly due to a higher screening rate towards the end of 1999 (odds ratio 1.92, 95% ci 1.61 to 2.30). Because different information is collected by the two hospitals, and because a univariate examination of potential screening predictors (see Table 3) suggests a different spread of reasons for not-screening at each hospital, we fitted separate models for each hospital. Two main effects models are presented in Table 3.6. All terms are independently strong predictors of screening after accounting for the effects of other included predictors.

Predictors for screening at the UHWI: The odds of screening increased by 16% for every 1-unit increase in the 5-minute APGAR score, and by 44% for every 1 kg increase in birthweight. It was more than 1.5 times higher when a midwife attended the birth instead of a clinician, and in the morning compared to the evening, and almost 2.5 times higher compared to the night. It was more than 3 times higher among survivors compared to babies who died during the neonatal period.

Figure 3.5
Percentage of daily births that are not screened at VJH and UHWI



Predictors for screening at VJH: The odds of screening was 6% higher for every five-year decrease in the age of the mother, and 42% higher for every 1 kg increase in birthweight. It was 30% higher in the morning compared to the night. It was 3.5 times higher when a midwife attended the birth instead of a clinician. It was almost 7 times higher in caesarian section births versus normal vaginal deliveries, and almost 8 times higher if the patient delivered in the hospital rather than before arriving at the hospital. It was 39% higher among unmarried versus married mothers. It was over 3 times higher among survivors compared to babies who died during the neonatal period. Pre-booked births were 33% more likely to be screened.

Table 3.6.

Odds ratios, standard errors and significance of demographic determinants of screening at UHWI and VJH (using multiple logistic regression)

Characteristic	OR (95% CI)	z	Pr
UHWI			
APGAR score after 5 minutes	1.16 (1.05 to 1.29)	2.98	<0.001
Birthweight (in kg)	1.44 (1.16 to 1.79)	3.27	<0.001
evening vs. morning	0.62 (0.42 to 0.91)	-2.44	0.02
night vs. morning	0.42 (0.28 to 0.62)	-4.31	<0.001
midwife vs. doctor	1.87 (1.36 to 2.58)	3.82	<0.001
Survival vs. neonatal death	3.35 (1.13 to 9.91)	2.18	0.03
VJH			
Married (yes vs. no)	0.72 (0.58 to 0.89)	-3.08	<0.001
Age of mother (5-yr age increase)	0.94 (0.9 to 0.98)	-2.77	0.01
Birthweight (in kg)	1.42 (1.27 to 1.59)	6.24	<0.001
night vs. morning	0.77 (0.65 to 0.91)	-2.97	<0.001
midwife vs. doctor	3.49 (2.6 to 4.67)	8.35	<0.001
nsvd vs. caesarian section	0.15 (0.1 to 0.21)	-9.84	<0.001
hospital vs. outside	7.66 (5.68 to 10.34)	13.33	<0.001
Pre-booked (yes vs. no)	1.33 (1.17 to 1.52)	4.29	<0.001
Survival vs. neonatal death	3.46 (1.62 to 7.37)	3.21	<0.001

(c) Discussion

The dataset represents the majority of live deliveries in Kingston, and 25% of an anticipated 57,000 live deliveries island wide. Guidelines for improving screening must be hospital specific to accommodate alternative factors contributing to unscreened neonates

3.7 Materials and methods

In settings without universal neonatal screening, age at enrolment to a specialist sickle cell clinic infers the pre-enrolment period during which people with SCD are at an increased risk of undiagnosed outcome. We were interested in the proportion of babies with sickle-cell disease that have enrolled or will eventually enrol in the clinics of the Jamaican sickle-cell unit by 5-years of age (the end of the penicillin prophylaxis period in Jamaica), and by the end of childhood (which we defined as 18-years of age).

3.7.1 Participants

We enrolled participants diagnosed with homozygous sickle-cell disease defined by standard criteria (38), who were born between 01 January 1973 and 31 December 1999, and who attended one of three specialist clinics (Kingston, Montego Bay, or Black River) at least once in the first 18-years of life. A number of these participants were diagnosed from neonatal screening of 100 000 consecutive live births from a single Kingston hospital between 1973 and 1981 as part of the JSSCD (39). The Jamaican Ministry of Health diagnosed another subgroup of participants between 1995 and 1999 as part of an ongoing neonatal screening programme. The remaining unscreened participants were diagnosed on arrival to clinic.

3.7.2 Age at enrolment to clinic: the delay distribution

In Table 3.7 and Table 3.8 we present the year of birth and age at enrolment to clinic for all Jamaican SS and SC patients born and enrolling in the sickle cell clinic between 1973 and 1999. The age at enrolment is zero for patients diagnosed using neonatal screening, and otherwise is the year of life, so that category one includes unscreened infants less than 12 months old, category two includes unscreened infants from 12 months to just less than two years old, and so on. The data leave a triangle of empty cells in each table, reflecting the fact that the maximum possible age at enrolment decreases with the year of birth. There were 2517 presenting SS patients (2087 clinically ascertained), and 839 presenting SC patients (666 clinically ascertained). The time from birth to clinic enrolment is known as the delay.

The form of the delay distribution guided our choice of modelling technique; certain techniques required a delay distribution that did not change with time (40;41). We examined age at enrolment by five years of age among births from four clinic periods (1973-1977, 1978-1982, 1983-1987, and 1988-1992), and by ten years of age among births from three clinic periods (1973-1977, 1978-1982, and 1983-1987). These clinic period choices ensured equal follow-up among all participants. We present these age-at-enrolment distributions using kernel density estimation. We examined age at enrolment between the clinic periods, and between two major sickle-cell disease genotypes (SS disease and SC disease) graphically. We used a test of rank differences to formally compare these groups.

3.7.3 Reason for enrolment

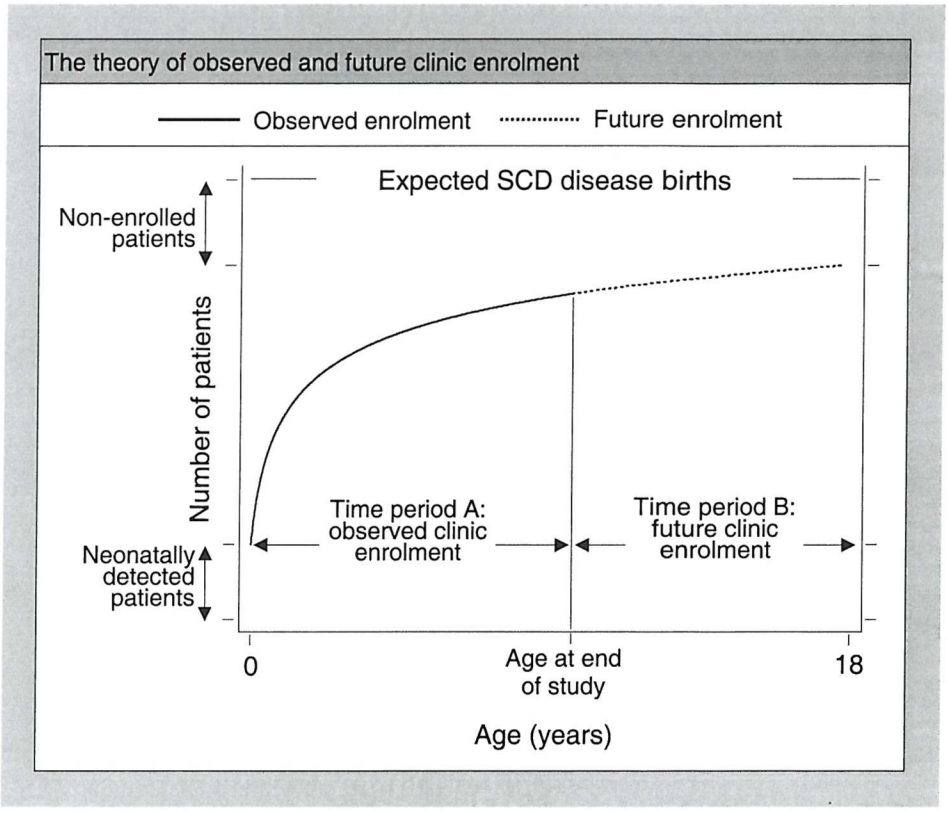
Among clinically ascertained patients, initial presentation may be during a symptomatic episode, or when clinically well. These alternatives suggest different clinic usage in the community. We report the proportions of symptomatic and asymptomatic first visits.

3.7.4 Clinic enrolment proportion

We represent the process of clinic enrolment for any single year of birth in Figure 3.6. Neonatally ascertained patients were invited to enrol in the clinics at birth. Many more unscreened patients enrolled in the clinics during time period A (before the end of the study window). Others, who were born during the study window, might enrol during time period B (after the end of our study window and before their 18th birthday). Younger patients have had less time to present during the study window, and this leads to negatively biased enrolment totals among infants born in recent years. Datasets of this type have been described previously, in relation to HIV/AIDS incidence (42), cystic fibrosis (41), and multiple sclerosis (40).

Figure 3.6

Clinic enrolment among neonatally-detected and unscreened patients with sickle-cell disease.



We identified the proportion of sickle-cell disease patients that will enrol to clinic in a three-stage process. First, we calculated the expected numbers of unscreened SCD-affected births in Jamaica. Second, we calculated the numbers of unscreened patients that have already enrolled in the clinics. Third, we estimated the number of unscreened patients that will eventually enrol in the clinics.

(a) ***Stage one:*** *Expected unscreened births*

The number of people born with homozygous sickle-cell disease (or SC disease) in Jamaica between 1973 and 1999 was the maximum number of patients that could join the clinic during the study window. Using the prevalence of homozygous sickle-cell disease (2.99 per 1000 live births) and sickle cell (SC) disease (2.13 per 1000 live births) (11), and the annual number of unscreened births (43), we calculated the expected numbers of annual unscreened births with homozygous sickle-cell disease in Jamaica.

(b) ***Stage two:*** *Observing patients that have already enrolled*

We present the number of unscreened births with SCD disease that have already enrolled to clinic, as a proportion of the islandwide unscreened births. We present this observed enrolment by 1-year, 5-years, 10-years, and 18-years of age. Our enrolment numbers are progressively under-represented with age: enrolment by 5-years of age is incomplete after 1995, and enrolment by 18-years of age is incomplete after 1982. In stage three, we use a log-linear modelling approach to predict these patients that will eventually enrol.

(c) ***Stage three:*** *Predicting patients that will eventually enrol*

The two dimensions of our data in Table 3.7 and Table 3.8 are year of birth and age at clinic enrolment. The age at clinic enrolment gives the delay over time. The row totals describe the numbers presenting at each age, with the most recent values too small because of the missing triangle of values not yet reported. Our data yield an 18×27 table with a triangle of 289 missing cells. Kalbfleisch and Lawless (44) suggested a likelihood modelling approach to such Poisson generated data, and several researchers (42;45;46) have noticed that a non-homogenous delay distribution can be incorporated using log-linear modelling. Our modelling approach therefore assumes random arrival to clinic, and estimates the number of expected unscreened births that will eventually enrol to clinic (Figure 3.8 section B) using a log-linear model.

Let $(birth_i, enrol_i)$ $(i = 1,\ldots,n)$ be the observed data, where for the ith individual $birth_i$ is the year of birth and $enrol_i$ is the date of clinic enrolment. Let $age_i = enrol_i - birth_i$ be the delay, which in our case is age at enrolment. We fitted Poisson regression models including $birth_i$ and age_i as categorical or continuous terms. Between 1973 and 1982, complete clinic enrolment data were available. As the year of birth approaches 1999, the time period A decreases and time period B increases (see Figure 3.6), and the estimation of clinic enrolment becomes less precise. The number of unscreened island-wide births in each year will affect the number of unscreened patients enrolling, and all models are adjusted to reflect the size of this unscreened population (see Table 3.9).

During the modelling procedure we paid close attention to two specific details: parametric versus non-parametric models, and a stationary versus a non-stationary delay distribution.

We investigated non-parametric versus parametric models. Although non-parametric models typically provide a better fit to data, this may simply reflect close modelling of random fluctuation, and this may hinder generalisations to other datasets. For this reason we used a penalized measure for comparing models, Akaike's information criteria (AIC), which adds a penalty to the maximum likelihood estimate for the number of terms in the model (47).

From our preliminary data exploration (see Figure 3.7) we expected a non-stationary delay distribution. We investigated the importance of a non-stationary delay by including interaction terms of $birth_i$ and age_i during the model development.

We report models using the widely accepted model notation of Wilkinson and Rogers (see for example S-Plus software documentation) (48).

(d) Presenting results as a clinic enrolment proportion

Unscreened clinic-coverage is defined as the number of unscreened homozygous sickle-cell disease births in a year that will subsequently enrol in the sickle-cell clinics, divided by all unscreened homozygous sickle-cell disease births in the same year. It describes the dynamics of patient presentation to clinic in the absence of a preferred clinical intervention strategy.

We present unscreened clinic-coverage for selected years between 1973 and 1999, and for enrolment by selected ages (ages 1, 5, 10, and 18 years). Enrolment by age five is of particular interest; penicillin prophylaxis is central to the preventive care regime for the young homozygous sickle-cell disease patient, and is offered by the sickle-cell clinics in Jamaica in the first four years of life, and in other settings in the first five years (49).

Table 3.7.

Age at initial clinic presentation by year of birth for SS disease patients, 1973-1999

Age	Year of birth (1973-1999)																												
	1973		**1975**					**1980**					**1985**					**1990**						**1995**				**1999**	
0	24	38	44	38	30	35	36	37	33	-	-	-	-	-	-	-	-	-	-	-	-	-	4	23	25	37	26	430
-1	0	4	4	3	1	7	11	10	7	16	13	8	14	21	6	8	22	11	14	11	16	21	19	18	17	17	3	302
-2	7	3	2	5	6	11	11	8	12	14	16	14	23	13	24	13	19	16	17	16	20	28	20	17	17	6		358
-3	4	2	6	7	3	7	4	6	7	9	10	9	11	14	8	12	11	17	9	17	22	17	8	9	3			232
-4	1	3	5	9	7	6	7	8	7	15	12	16	10	11	6	10	9	15	13	11	11	8	11	4				215
-5	4	3	8	6	6	5	7	3	8	5	7	12	13	8	10	5	5	7	13	5	11	10	4					165
-6	10	6	8	8	8	5	4	5	3	12	7	7	8	6	6	11	5	8	10	5	13	4						159
-7	7	4	6	5	5	1	3	3	4	8	4	3	6	4	5	7	9	4	5	8	4							105
-8	1	4	8	3	3	3	6	3	8	2	3	9	7	6	7	9	4	1	3	5								95
-9	6	5	4	3	4	4	1	4	0	4	3	2	4	3	6	2	6	6	1									68
-10	5	2	7	2	3	1	0	3	9	6	3	6	4	5	5	1	2	2										66
-11	4	3	4	4	4	6	9	6	6	8	8	4	5	1	3	2	3											80
-12	4	1	4	4	2	3	4	3	4	6	1	4	3	6	5	0												54
-13	2	4	5	3	4	2	1	2	3	3	3	4	3	1	2													42
-14	2	2	1	1	3	1	3	2	1	1	4	5	2	1														29
-15	4	3	3	4	3	5	2	0	2	3	2	2	0															33
-16	4	7	5	0	2	4	0	5	1	2	2	1																33
-17	2	4	3	2	0	2	3	3	3	8	1																	31
-18	0	8	2	3	2	2	1	1	1	0																		20
Total	91	106	129	110	96	110	113	112	119	122	99	106	113	100	93	80	95	87	85	78	97	88	66	76	62	60	29	2517

Table 3.8.

Age at initial clinic presentation by year of birth for SC disease patients, 1973-1999

Age	Year of birth (1973-1999)																												
	1973		**1975**					**1980**					**1985**					**1990**					**1995**				**1999**		
0	16	28	23	25	20	27	16	16	2	-	-	-	-	-	-	-	-	-	-	-	-	-	0	0	0	0	0	173
-1	0	1	2	0	1	0	1	3	3	4	2	2	2	1	2	0	3	4	3	2	3	4	3	4	2	4	5	61
-2	1	0	1	0	3	3	0	0	2	3	4	0	4	1	2	3	3	3	2	0	6	1	5	3	3	1		54
-3	0	0	1	0	1	0	3	2	0	4	4	1	0	0	4	1	3	3	1	2	3	3	2	1	0			39
-4	0	0	1	0	0	1	4	0	3	4	3	1	6	4	1	0	1	1	3	10	6	4	5	2				60
-5	1	2	3	1	0	1	3	3	1	4	2	3	3	1	1	2	4	3	6	6	5	4	4					63
-6	1	1	1	3	1	5	2	2	3	1	5	3	3	4	4	1	5	3	4	2	1	1						56
-7	0	2	1	1	2	2	2	2	2	0	4	2	2	4	0	5	5	4	0	3	2							45
-8	0	0	2	4	1	3	1	2	4	2	1	0	4	1	3	5	7	2	5	0								47
-9	2	4	1	0	3	0	2	1	4	1	7	3	3	3	4	2	4	1	2									47
-10	1	1	2	0	1	2	1	4	4	2	3	4	1	0	3	3	6	1										39
-11	0	3	2	0	2	0	4	3	6	1	2	6	6	2	4	3	0											44
-12	0	1	2	0	1	1	4	1	1	2	5	4	1	1	2	1												27
-13	0	3	0	1	1	0	5	1	1	5	1	3	2	1	1													25
-14	1	0	1	0	0	1	0	0	2	3	3	1	0	0														12
-15	1	0	4	0	3	0	2	1	2	1	1	0	0															15
-16	1	3	2	1	2	1	1	0	0	3	0	0																14
-17	2	0	1	0	0	1	1	0	1	0	2																	8
-18	0	1	3	0	0	2	0	0	4	0																		10
Total	27	50	53	36	42	50	52	41	45	40	49	33	37	23	31	26	41	25	26	25	26	17	19	10	5	5	5	839

Table 3.9.

Annual live births, and expected and observed sickle-cell disease births between 1973 and 1999 in Jamaica.

Year	Number of births in Jamaica		Expected SS births		Observed SS births		Expected SC births		Observed SC births	
	Screened	Unscreened	Screened	Unscreened	Screened	Unscreened	Screened	Unscreened	Screened	Unscreened
1973	6472	55 385	19	166	24	67	14	116	16	11
1974	12 208	49 298	37	148	38	68	26	105	28	22
1975	12 031	49 431	36	148	44	85	26	105	23	30
1976	12 179	48 479	36	145	38	72	26	103	25	11
1977	12 030	48 393	36	145	30	66	26	103	20	22
1978	11 580	46 609	35	140	35	75	25	99	27	23
1979	11 516	47 610	34	143	36	77	24	102	16	36
1980	11 003	47 586	33	142	37	75	23	102	16	25
1981	10 981	48 454	33	145	33	86	24	103	2	43
1982	0	61 477	0	184	0	122	0	131	0	40
1983	0	61 417	0	184	0	99	0	131	0	49
1984	0	57 533	0	172	0	106	0	123	0	33
1985	0	56 213	0	168	0	113	0	120	0	37
1986	0	54 067	0	162	0	100	0	115	0	23
1987	0	52 270	0	157	0	93	0	111	0	31
1988	0	53 623	0	161	0	80	0	114	0	26
1989	0	59 104	0	177	0	95	0	126	0	41
1990	0	59 606	0	178	0	87	0	127	0	25
1991	0	59 879	0	179	0	85	0	128	0	26
1992	0	58 627	0	176	0	78	0	125	0	25
1993	0	57 404	0	172	0	97	0	122	0	26
1994	0	59 235	0	177	0	88	0	126	0	17
1995	1333	62 154	4	186	4	62	2	133	0	19
1996	8581	50 613	26	152	23	48	18	108	0	10
1997	9728	49 657	29	149	25	37	21	106	0	5
1998	14 135	45 114	42	135	37	23	30	96	0	5
1999	17 220	39 691	52	119	26	3	36	85	0	5
Total	138 818	1 438 929	452	4310	430	2087	321	3065	173	666

3.8 Results

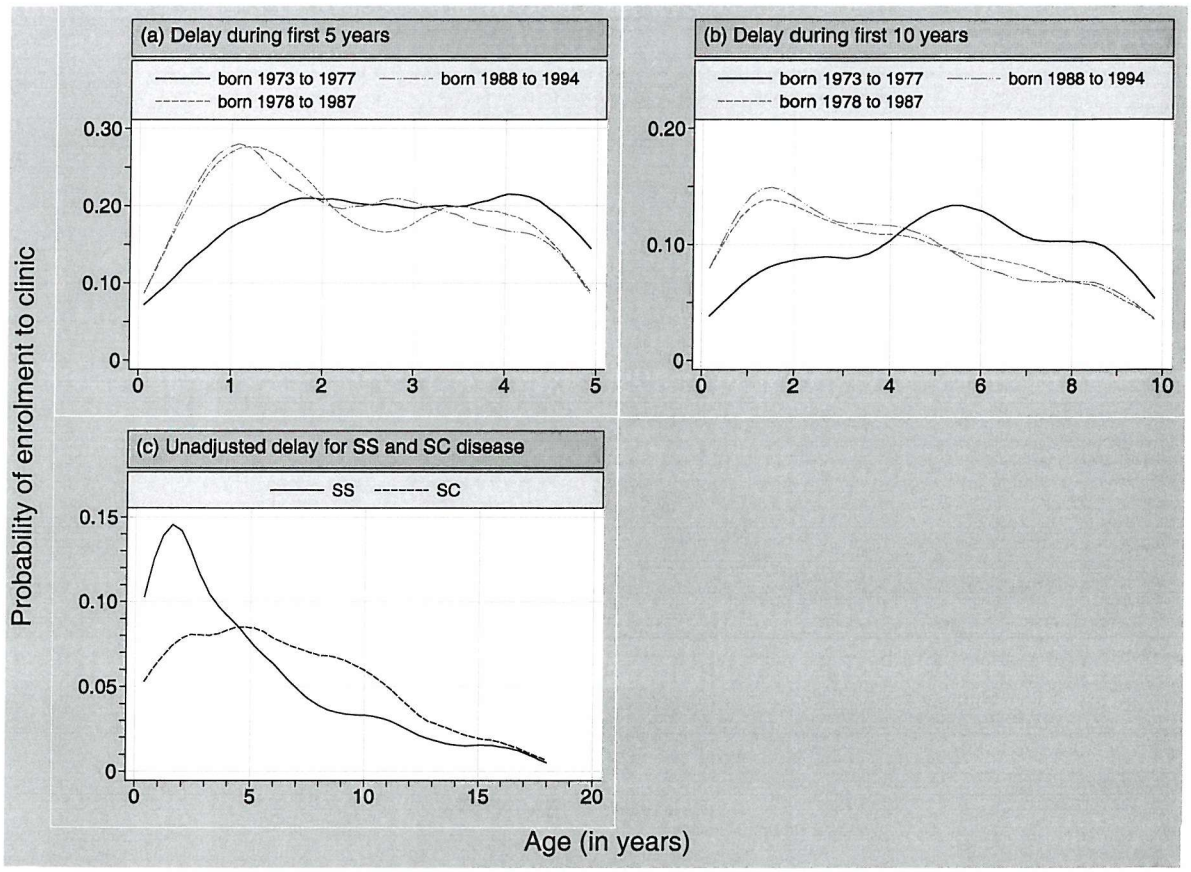
3.8.1 Patients

Between 1973 and 1981, 19% of Jamaica's newborns were screened for homozygous sickle-cell disease. None were screened between 1982 and 1994, and 17% were screened between 1995 and 1999. There were an expected 4762 homozygous sickle-cell disease births between 1973 and 1999 (4310 unscreened, 452 screened). There were 2517 paediatric homozygous sickle-cell disease patients enrolling in the clinics during the study period, and neonatal screening identified 430 of these (315 as part of the Jamaican Sickle-cell Cohort Study, and 115 as part of the government screening programme). There were an expected 3386 sickle-cell SC disease births between 1973 and 1999 (3065 unscreened, 321 screened). There were 839 paediatric sickle-cell disease SC patients enrolling in the clinics during the study period, and neonatal screening identified 173 of these (all as part of the Jamaican sickle-cell cohort study) (Table 3.9).

3.8.2 Age at enrolment to clinic: the delay distribution

Delay distributions are presented graphically in Figure 3.7 and summarized in Table 3.10.

Figure 3.7
Age at first presentation to clinic stratified by clinic period in 5 year bands (a-b) and by genotype (SS disease and SC disease) (c)



First visit to clinic is later among the 1973-1977 birth group, compared to all other birth groups whether looking at 5-year follow-up ($\chi^2_1 = 187.2$, $p < 0.001$), or 10-year follow-up ($\chi^2_1 = 68.4$, $p < 0.001$). It is possible that these early years of clinic operation represented a period of increasing community knowledge and acceptance of the sickle cell clinic. After this time, the delay distribution changed very little with time.

Table 3.10.
Median delay until first visit to clinic for 5-year and 10-year clinic follow-up using 5-year birth groups, and between SS and SC disease,

	5-year follow-up	10-year follow-up	18-year follow-up
	median (95% ci)	median (95% ci)	Median (95% ci)
Year of birth			
1973-1977	2.80 (2.38 to 3.14)	5.36 (5.03 to 5.61)	-
1978-1982	2.02 (1.92 to 2.35)	3.66 (3.36 to 4.02)	-
1983-1987	2.12 (1.97 to 2.35)	3.69 (3.47 to 3.87)	-
1988-1992	2.23 (2.05 to 2.41)	-	-
Genotype*			
SS	-	-	10.53 (9.93 to 11.24)
SC	-	-	12.10 (10.72 to 13.27)

***Adjusted for clinic period**

SS patients arrive earlier than SC patients ($\chi^2_1 = 51.0$ $p < 0.001$), which is likely to be a function of disease expression.

The delay between birth and presentation to clinic of unscreened patients is dependent on both clinic period and genotype. Subsequent estimation of the number of clinically ascertained patients and on clinic coverage are presented separately for each genotype, and accounts for the variation of clinic enrolment period (which we call non-stationarity).

3.8.3 Reason for enrolment

Among clinically ascertained patients, clinic presentations are grouped into routine and sick visits as described in chapter two. Of 2753 clinically ascertained SS and SC patients (SS 2087, SC 666), 2317 (SS 1783, SC 534) presented without clinically significant symptoms, representing 84.2% of all initial clinic visits (SS 85.4%, SC 80.2%). These large proportions of asymptomatic initial presentations suggest a defining method of clinic ascertainment. Patients will either: (i) use the clinic for an initial presentation to the healthcare system when well due to both prior knowledge of the clinic and a history of sickle-cell disease or trait in the family, or (ii) be referred to the clinic from elsewhere in the healthcare system as a result of a sickle-cell disease diagnosis and/or as a result of symptomatology consistent with the disease. When referral occurs as a result of morbidity, the patient is usually recovered before presentation at the sickle-cell clinic. It follows that there are likely to be

two forms of SCU non-attenders: (i) patients that die from acute SCD related complications prior to arrival to clinic, or (ii) a second subgroup that will not arrive due to absence of significant symptomatology or for other logistical reasons (e.g. distance to clinic). The features of non-attenders are considered further in Chapter Four.

3.8.4 Clinic enrolment proportion

(a) ***Stage one:*** *Expected unscreened births*

We present the expected numbers of islandwide unscreened SS and SC patients in Table 3.9 by year of birth.

(b) ***Stage two:*** *Observing patients that have already enrolled*

We present the proportion of expected unscreened deliveries that have enrolled in the clinic by selected ages (1-year, 5-years, 10-years, and 18-years) in Table 3.12 for people with SS disease, and in Table 3.13 for people with SC disease, with a visual display in Figure 3.9c (SS disease) and Figure 3.10c (SC disease). We show that enrolment proportions increase with age and with secular time, and note the incomplete information due to the younger age ranges in recent years (see Section 3.7.4 for an explanation of this bias). The most striking example of this bias is for enrolment by 18-years of age, where we have no information among people born after 1982. Without observed information, we use a prediction model to obtain estimates of enrolment.

(c) ***Stage three:*** *Predicting patients that will eventually enrol*

We present the fit of alternative models for predicting the expected numbers of patients enrolling to clinic by their 18th birthday in Table 3.11, and we graph these predicted numbers in Figure 3.8 (a and b).

For SS patients, the non-parametric stationary model has a deviance fit of 437 with 298 degrees of freedom, suggesting substantial non-stationarity. On fitting a reasonable non-parametric non-stationary model,

$$birth + age + \text{linear}(birth) + \text{linear}(age) + age \cdot \text{linear}(birth) + birth \cdot \text{linear}(age)$$

the deviance decreases by 125 on 22 degrees of freedom, which highlights the benefit of including interaction terms to account for the time variation of age at first clinic visit. Other non-parametric non-stationary models provide similar deviance reductions. Along with the delay distribution variation demonstrated in section 3.8.2, the evidence for non-stationarity is strong. This inclusion of interaction terms generally reduces the predicted level of patient enrolment (Figure 3.8).

Using deviance measures, the parametric models show systematic lack of fit compared to the non-parametric alternatives. However, the non-parametric models are fitting the random

fluctuations too closely for realistic modelling. Penalizing the models using the AIC measure highlights this overfitting and by this criterion, the parametric models improve upon their non-parametric alternatives.

Table 3.11.

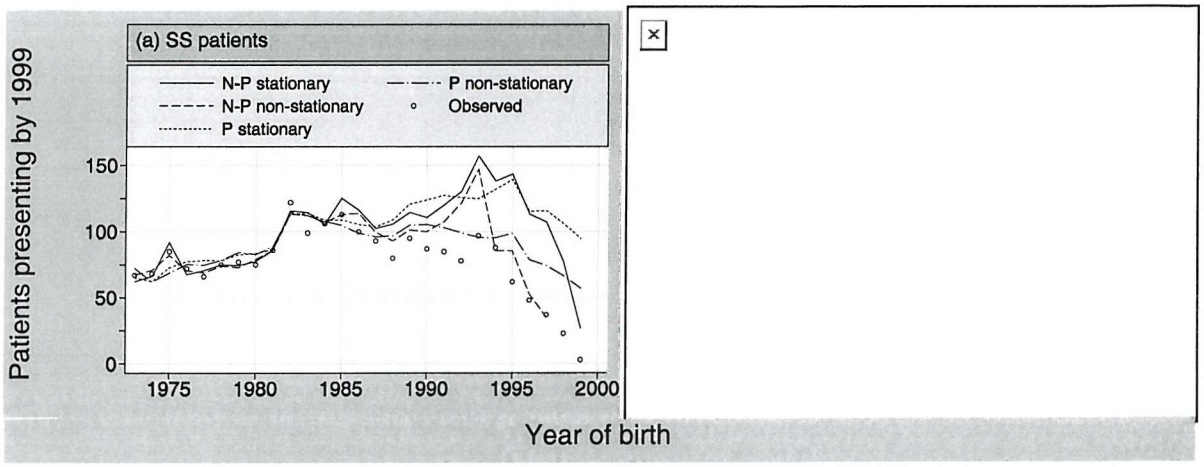
Deviance and AIC for a series of models fitted to SCU age at first presentation data for clinically ascertained patients.

Model	Stationary			Non-stationary		
	deviance	**df**	**AIC**	**deviance**	**df**	**AIC**
SS (n=2087)						
non-parametric	436.89	298	506.89	312.16	266	446.16
Parametric in age	465.75	312	507.75	328.70	278	438.70
Parametric in delay	459.27	312	501.27	321.57	280	427.57
full parametric	488.32	326	502.32	400.50	324	418.50
SC (n=666)						
non-parametric	401.23	298	471.23	354.93	266	488.93
parametric in age	424.93	312	466.93	396.27	295	472.27
parametric in delay	417.63	312	459.63	394.20	296	468.20
full parametric	440 49	326	454.49	428.94	325	444.95

Much of the statistical lack of fit of the chosen parametric models may be due to irregular delay and age distributions, and we demonstrate this by fitting semi-parametric models: parametric in age and non-parametric in delay, and vice versa. Among SS patients, approximately 29 (14 degrees of freedom) of the lack of fit of the stationary parametric model is due to the irregular form of the delay rate, and 22 (14 df) is due to the irregular age at presentation distribution. Among SC patients the lack of fit can be portioned into 24 (14 df) due to delay, and 16 (14 df) due to age at presentation.

Figure 3.8

Estimated clinic attendance among SS and SC patients, using four alternative models

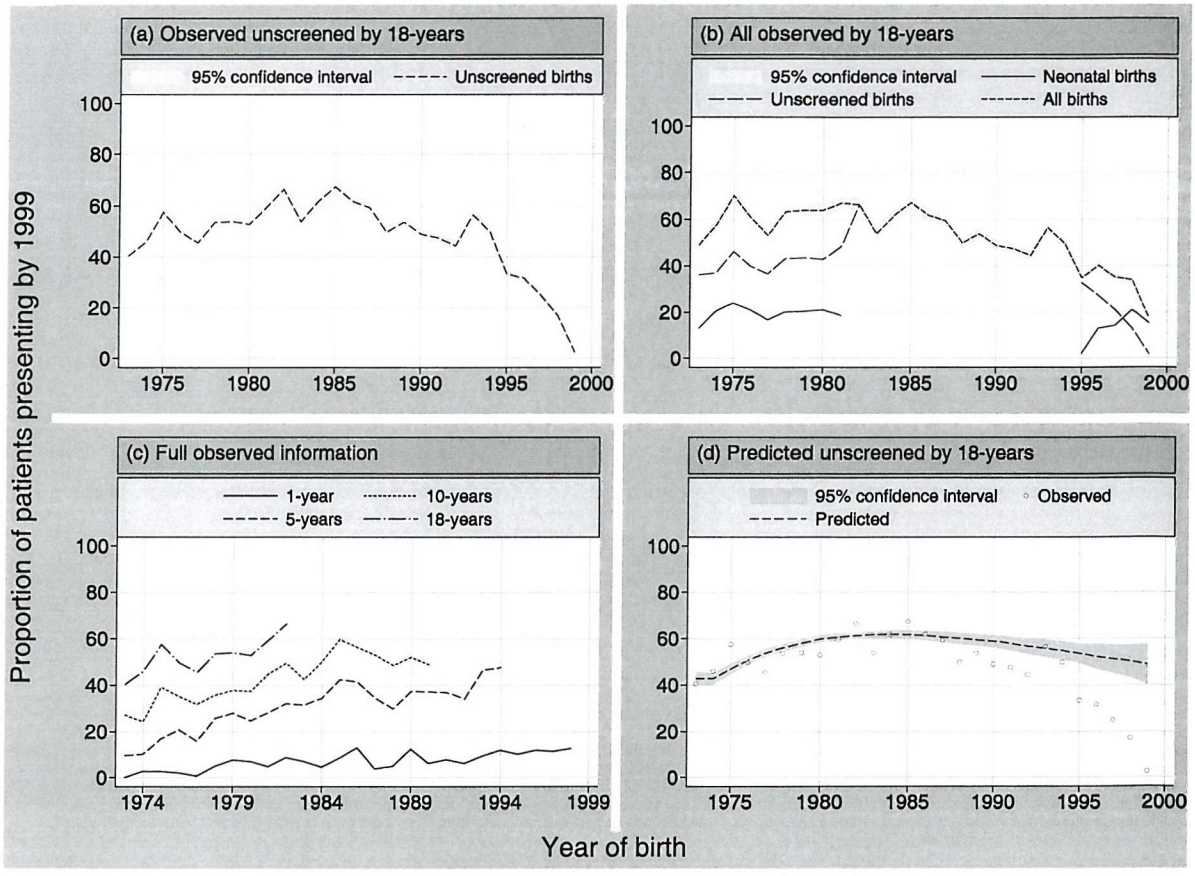


We present predicted unscreened clinic-coverage in SS disease by selected ages (1 year old, 5 years, 10 years, and 18 years) in Table 3.12 for selected years of birth between 1974 and 1999. We graph observed and predicted unscreened clinic-coverage by 18-years of age in Figure 3.9.

By December 1979 (when the patients born in 1974 were 5-years old), 10.1% (95% ci 5.7 to 16.7) of unscreened affected infants had enrolled in the clinics. This 5-year enrolment rose to levels around 40% through most of the 1980's and early 1990's, and is predicted to fall slightly to 35.7% (35.0 to 36.4) among 1999 births. By December 1992 (when the patients born in 1974 were 18-years old), 45.9% (35.7 to 58.2) of unscreened infants had enrolled at the clinics. This 18-year enrolment is predicted to rise to levels around 60% among patients born in the 1980's, before falling to 48.9% (40.9 to 56.9) among 1999 births. Uncertainty associated with the estimation of patients is summarised in the associated 95% confidence region, and this uncertainty is large among patients born in recent years.

Figure 3.9

Proportion of SS births presenting to the sickle-cell clinics by 18-years of age, presented by year of birth (a) unscreened observed (b) unscreened and screened observed (c) unscreened observed (full information) (d) unscreened predicted.



We present predicted unscreened clinic-coverage in SC disease by selected ages (1 year old, 5 years, 10 years, and 18 years) in Table 3.13 for selected years of birth between 1974 and 1999. We graph predicted unscreened clinic-coverage by 18-years of age in Figure 3.10.

By December 1979 (when the patients born in 1974 were 5-years old), 2.9% (95% ci 0.6 to 8.3) of unscreened affected infants had enrolled in the clinics. This 5-year enrolment rose to levels around 10% through most of the 1980's and early 1990's, and is predicted to increase slightly to 13.1% (11.2 to 15.1) among 1999 births. By December 1992 (when the patients born in 1974 were 18-years old), 21.0% (13.1 to 31.7) of unscreened infants had enrolled at the clinics. This 18-year enrolment is predicted to rise to levels around 30% among patients born in the 1980's, before falling to 25.5% (11.5 to 39.6) among 1999 births. Uncertainty associated with the estimation of patients is summarised in the associated 95% confidence region, and this uncertainty is large among patients born in recent years.

Figure 3.10

Proportion of SC births presenting to the sickle-cell clinics by 18-years of age, presented by year of birth (a) unscreened observed (b) unscreened and screened observed (c) unscreened observed (full information) (d) unscreened predicted.

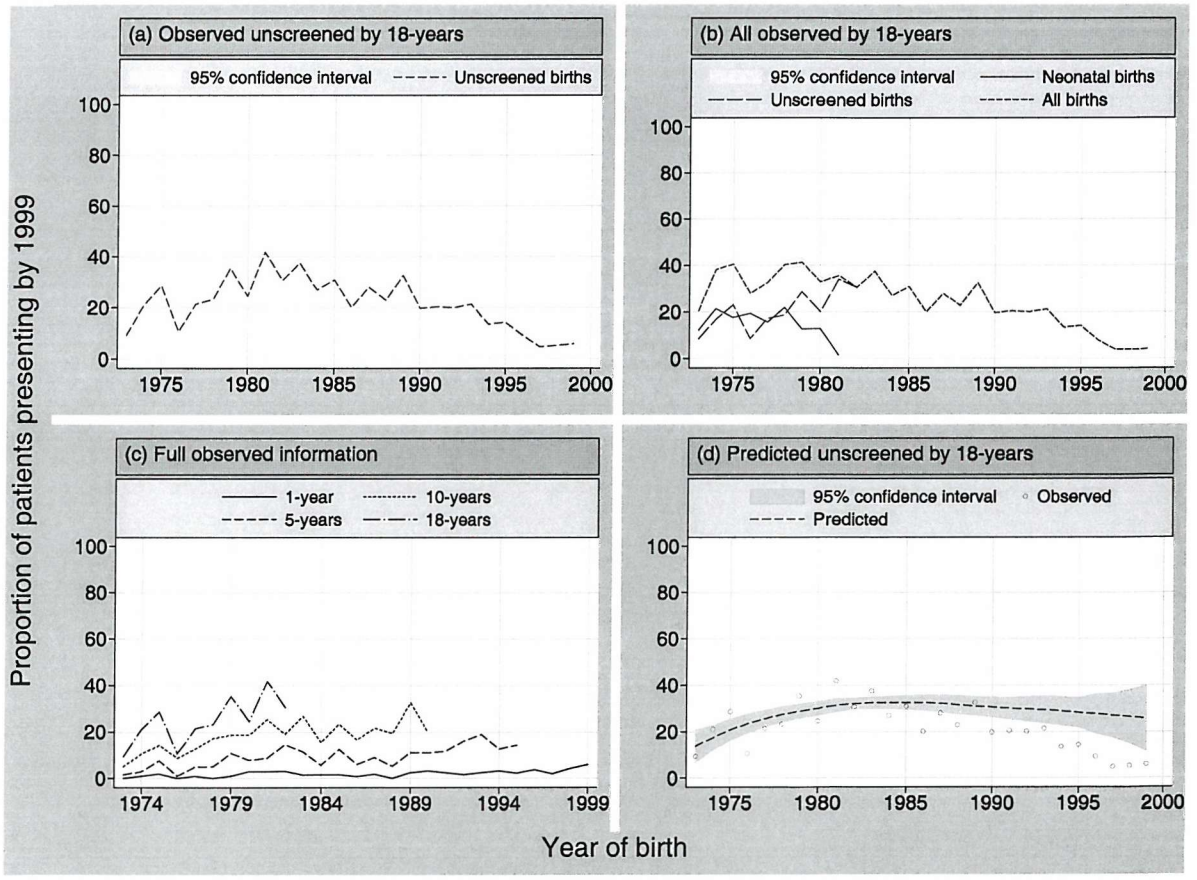


Table 3.12.

Observed and predicted clinic-coverage of unscreened homozygous sickle-cell disease patients at four ages (1-year, 5-years, 10-years, and 18-years) between 1974 and 1999 in Jamaica.

Year of birth	Age			
	1-year	5-years	10-years	18-years
Observed				
1974	2.7 (0.7 to 6.9)	10.1 (5.7 to 16.7)	24.3 (17.0 to 33.7)	45.9 (35.7 to 58.2)
1979	7.7 (3.8 to 13.8)	28.0 (20.0 to 38.1)	37.8 (28.4 to 49.3)	53.8 (42.5 to 67.3)
1984	4.7 (2.0 to 9.2)	34.3 (26.1 to 44.2)	50.0 (40.0 to 61.7)	-
1989	12.4 (7.8 to 18.8)	37.3 (28.8 to 47.4)	52.0 (41.9 to 63.7)	-
1994	11.9 (7.3 to 18.1)	47.5 (37.9 to 58.8)	-	-
1999	2.5 (0.5 to 7.4)	-	-	-
Predicted				
1974	1.4 (1.1 to 1.7)	13.4 (12.6 to 14.3)	26.8 (25.4 to 28.2)	42.5 (40.4 to 44.7)
1979	4.5 (4.4 to 4.6)	26.6 (26.2 to 27.0)	43.4 (42.7 to 44.1)	57.8 (56.6 to 59.1)
1984	7.1 (7.0 to 7.1)	34.1 (33.8 to 34.4)	50.5 (50.0 to 51.1)	61.9 (60.5 to 63.2)
1989	8.8 (8.8 to 8.9)	37.1 (36.8 to 37.3)	51.4 (50.8 to 51.9)	59.5 (57.3 to 61.7)
1994	9.9 (9.8 to 10.0)	37.3 (37.0 to 37.6)	49.2 (48.3 to 50.0)	54.8 (51.2 to 58.4)
1999	10.3 (10.2 to 10.5)	35.7 (35.0 to 36.4)	45.1 (43.0 to 47.1)	48.9 (40.9 to 56.9)

Table 3.13.

Observed and predicted clinic-coverage of unscreened sickle-cell haemoglobin-C disease patients at four ages (1-year, 5-years, 10-years, and 18-years) between 1974 and 1999 in Jamaica.

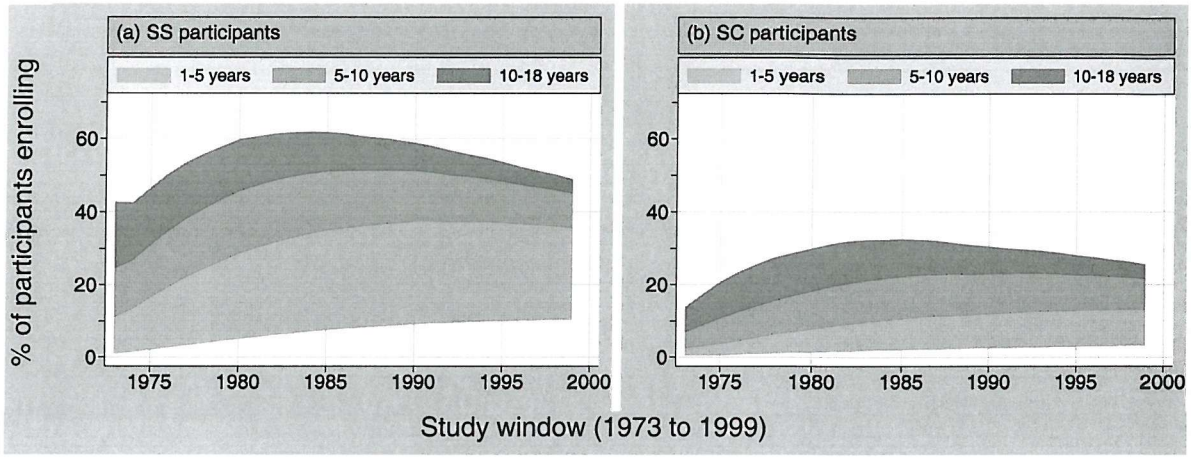
Year of birth	Age			
	1-year	5-years	10-years	18-years
Observed				
1974	1.0 (0.02 to 5.3)	2.9 (0.6 to 8.3)	10.5 (5.2 to 18.7)	21.0 (13.1 to 31.7)
1979	1.0 (0.02 to 5.5)	10.8 (5.4 to 19.3)	18.6 (11.2 to 29.1)	35.3 (24.7 to 48.9)
1984	1.6 (0.2 to 5.9)	5.7 (2.3 to 11.7)	15.4 (9.3 to 24.1)	-
1989	2.4 (0.5 to 7.0)	11.1 (6.1 to 18.6)	32.5 (23.4 to 44.1)	-
1994	3.2 (0.9 to 8.1)	12.7 (7.3 to 20.6)	-	-
1999	5.9 (1.9 to 13.7)	-	-	-
Predicted				
1974	0.4 (0 to 1.0)	3.2 (1 to 5.4)	8.9 (5.5 to 12.3)	17.3 (12 to 22.6)
1979	1.2 (0.9 to 1.6)	7.1 (5.9 to 8.2)	16.9 (15.1 to 18.8)	28.7 (25.6 to 31.7)
1984	1.9 (1.7 to 2.2)	10.2 (9.4 to 11)	21.7 (20.4 to 23)	32.4 (29.7 to 35.1)
1989	2.4 (2.2 to 2.6)	11.7 (11 to 12.4)	22.9 (21.6 to 24.2)	30.9 (27 to 34.9)
1994	2.9 (2.6 to 3.1)	12.8 (12 to 13.6)	23 (21.1 to 24.8)	28.8 (22.7 to 35)
1999	3.2 (2.8 to 3.6)	13.1 (11.2 to 15.1)	21.6 (16.8 to 26.4)	25.5 (11.5 to 39.6)

(d) Graphics of clinic enrolment

Clinic enrolment percentages at selected ages are presented graphically in Figure 3.11 by genotype. They provide no additional information but offer a useful visual interpretation of enrolment. Enrolment in SS disease is higher than SC disease enrolment at all ages, which is due to the increased clinical symptoms of the homozygous genotype.

Figure 3.11

The annual percentage of unscreened (a) homozygous sickle-cell disease and (b) sickle-cell SC disease patients that will enrol to clinic (by ages 1, 5, 10, and 18).



3.9 Discussion

Evidence on the benefits of early disease detection for the homozygous sickle-cell disease patient comes from a randomised clinical trial (3) supported by observational studies (2). This evidence is widely accepted (4;7), and neonatal screening is considered the gold-standard procedure for detecting the disease. The *extent* of the benefits stemming from neonatal screening is not well documented, and with the proven benefit of treatment, a study withholding intervention among a prospectively randomised subgroup to measure the size of these benefits would be unthinkable. Given this dilemma, we use the Jamaican reality of a largely unscreened population as an opportunity to document the effect of not screening for homozygous sickle-cell disease on the ability to identify people with the disease in the community. The corollary is the beneficial effect of neonatal screening for the disease.

Enrolment figures are important baseline information for the assessment of costs and benefits of neonatal screening. When they exist, data on observed enrolment provide the best available information for informing clinic managers and public health policymakers. However, in this analysis of clinic recruitment, observed enrolment is progressively underreported as enrolment age increases, and this is a common problem in cohorts with ongoing recruitment. To avoid the bias of underreporting, we must either restrict our dataset to age-at-recruitment/secular year combinations with complete follow-up, or attempt to predict future enrolment. We have presented both approaches in this chapter, and each has advantages and disadvantages.

We presented observed-enrolment results using complete-information in Tables 3.12 and 3.13 and in Figures 3.9c and 3.10c. Observed enrolment totals are progressively historical as age at enrolment increases: complete enrolment by 5-years of age is available among participants born before 1996, whereas enrolment by 18 years of age can only be reliably reported among participants born before 1982. The secular differences in observed totals complicates our interpretation of these results; we can only reliably compare enrolment at different ages among participants born before 1982.

We present predicted enrolment results in Tables 3.12 and 3.13 and in Figures 3.9d and 3.10d. Predicted enrolment is available for all births between 1973 and 1999, which allows us to compare enrolment at various ages for each study year. This removes the problem of secular changes affecting enrolment totals. Predicted precision decreases as the quantity of observed information decreases: we are far less certain about our predicted enrolment by 18-years of age. Although we have a model for clinic enrolment, this model is based on specific practices of a single clinic, and the generalisability of such a model to other sickle cell populations is likely to be highly dependent on variation in recruitment practices.

Without neonatal screening, patient presentation to a health-care provider can be delayed at each of three stages: the onset of clinical symptoms, disease diagnosis and clinic enrolment.

In an unscreened homozygous sickle-cell disease population, almost all patients have become symptomatic by their eighth birthday (50). Only two-thirds of these patients have been diagnosed (51), and we now show that less than one-third have enrolled in the clinics by that age, implying an equal and considerable delay at these two stages. Males enrol at a younger age than females; a feature that has been observed previously (52;53). Delayed diagnosis could be shortened with training programmes for health-care workers, and delayed arrival avoided by mandatory referral and a central patient registration facility. Inevitably however, in the absence of a universal neonatal screening programme, a proportion of the homozygous sickle-cell disease population will never present to the clinic, while the remainder will arrive with varying delay. It remains unknown, but possible, that the enrolled and non-enrolled patients have different morbidity and mortality risks stemming from either an inherent heterogeneity in disease expression, or the absence of comprehensive and prophylactic health-care, or both.

Unscreened clinic-coverage describes the likelihood of a person with unscreened homozygous sickle-cell disease to present to clinic. This unscreened coverage is below 50% among births in 1973, peaks at 62% in the early 1980's and decreases thereafter. Newborn screening has been performed exclusively in Kingston during two clinic periods (1973-1981 and 1995-present). Between 1973 and 1981 outreach clinics were initiated in western Jamaica, and these clinics probably fuelled the continued increase in enrolment of unscreened patients despite Kingston-based neonatal screening reducing the pool of unscreened individuals available in the island's capital. During the second and ongoing wave of neonatal screening (1995-present), there has been no new homozygous sickle-cell disease population tapped to offset the decreased pool of unscreened patients. The remaining pool of unscreened births is from outside of Kingston, and the increased distance from the main clinic facility in Kingston will be a defining factor in the decreased patient referral. Other possible causes of non-enrolment include good health, non-referral, death or migration.

Levels of clinic-coverage are generally lower in SC disease than in SS disease, which undoubtedly reflects a milder clinical course in SC patients. SC patients identified during the ongoing government neonatal screening programme have not been enrolled in the sickle-cell clinics, which explains the predicted drop-off in enrolled patients.

Delay distributions are encountered throughout epidemiology, although the recent development of statistical methodology to adjust for delay has been primarily motivated within HIV/AIDS research. Delay periods have generally been shorter than experienced in the current study, and the assumption of delay distribution invariance has often been approximately valid (41;54). This assumption is violated in the current study. Delay distribution variation is seen across genotype, and due to clinic period. Genotype variation causes little concern - combined SS and SC studies would be of little use due to marked heterogeneity between the diseases, and SCD research should always stratify by genotype. Clinic period is more problematic, and we adopt maximum-likelihood methodology that

extends to non-stationarity (42). This methodology loses efficiency over continuous time methods (55). Use of event times and the proportional retro-hazards model (56) might offer improved precision of recent birth years, but importantly, the proportional hazards assumption is violated.

The substantial levels of delayed and non-enrolment have important consequences for the clinical care of the homozygous sickle-cell disease patient, for public-health policymaking, and for clinical research. First, early life preventive management and emergency intervention are vital aspects of clinical care, and are only possible within a regime of early disease detection and comprehensive follow-up. We have shown that in the first few years of life, when penicillin prophylaxis plays a crucial role in this preventive management, between 50% and 90% of available homozygous sickle-cell disease patients will not have enrolled to a specialist clinic. Second, incomplete and delayed patient enrolment invalidates assessment of health-care infrastructure, by underestimating the size, morbidity and mortality of the patient population ('the burden of disease'). This results in a 'low visibility' among homozygous sickle-cell disease populations (7) that contributes to a failure to provide timely and adequate care, perpetuating inequality in health. Third, this artificially low burden of disease introduces an important bias in clinical research. Neonatal screening is the only method for achieving a representative patient sample. Despite this, observational research commonly employs cross-sectional clinic-based populations subject to delayed and non-enrolment bias. The failure to realise the limitations of studying these biased populations could present a significant problem in the advancement of knowledge concerning homozygous sickle-cell disease.

Improvements in hygiene, nutrition and control of infection are increasing the relative importance of homozygous sickle-cell disease (and other inherited haemoglobin disorders) as a global health problem (15). Our quantification of the 'low visibility' of homozygous sickle-cell disease, using unscreened patient coverage at various ages, and age at enrolment, has shown that without comprehensive and systematic identification of patients, the large burden of homozygous sickle-cell disease, suggested by the known prevalence of the disease in Jamaica, remains largely unrecognised. The true disease prevalence remains unknown in many countries, and national studies to obtain this information must be a priority. Agencies and governments of countries with a substantial burden of homozygous sickle-cell disease must then consider programmes for systematic disease identification, control, and management.

3.10 Early life screening vs. clinic ascertainment: the effect on research

Median age at first clinic visit among patients aged 18-years or younger is 10.5 years (9.9 to 11.2) years in SS disease and 12.1 years (10.7 to 13.3) in SC disease (Table 3.10), and we know from previous work that most SS patients will be symptomatic by eight years of age (50). This means that much early life sickle-cell disease morbidity will either go untreated, or

will be treated elsewhere in the healthcare system. There are two important consequences for research.

First, morbidity may have less favourable outcomes among untreated patients compared to those enrolled in a comprehensive sickle-cell disease clinic, creating patient subgroups with systematically different clinical outcomes. Second, there is no mandatory registration of sickle-cell patients, and so the incidence of clinical events is likely to be under-reported among patients not enrolled in the comprehensive care facility. An example of underreporting in infection rates among homozygous sickle-cell disease patients is presented in the following case-study. Further examples are presented in Chapter Eight.

3.10.1 ***Case study 3:*** *Differential incidence of bacteraemias*

People with homozygous sickle cell (SS) disease are at increased risk of infection with Streptococcus pneumoniae, Haemophilus influenzae type b, Salmonella spp, Escherichia coli and Klebsiella spp (57-59). Several mechanisms are believed to contribute to this susceptibility, a major factor being the early loss of splenic function, which may be abnormal as early as the first year of life (60). Development of clinical splenomegaly in the first 6 months of life has been shown to be significantly associated with greater risk of subsequent pneumococcal septicaemia (61).

(a) Patients and methods

The participants attended the sickle cell clinic of the University Hospital of the West Indies, Kingston, Jamaica. All had SS disease diagnosed by standard criteria and came from two clinic populations. The cohort group included all JSSCD participants. The clinic group included all other patients, most of whom had been symptomatically referred. To reduce the symptomatic bias in this second group, patients were required to have had at least two clinic visits and not to have been referred initially to the clinic with bacterial infection. Our study was confined to infections caused by S pneumoniae, H influenzae type b, Salmonella spp, E coli, or Klebsiella spp between 1 January 1974 and 31 December 1997.

There were 3820 participants (including 311 JSSCD participants) with 218 episodes of infection among 180 participants (90 episodes among 64 JSSCD participants). Four episodes identified on initial clinic referral in the clinic group were excluded, leaving 214 eligible episodes among 176 participants. Differences in recruitment of the JSSCD and clinic studies resulted in significantly different age structures. The median age at last clinic visit was 17.8 years (interquartile range, 11.2-21.2; range, 0.1-24.5) for the JSSCD and 20.7 years (10.7-31.4; 0.1-80.6) for the clinic group (Mann-Whitney U test, $z = 7.5$; $p < 0.001$).

(b) Definitions

Invasive bacterial infections were identified as the isolation of one of the five organisms from cultures of blood or cerebral spinal fluid and, in the case of Salmonella spp, from sinuses or

aspiration from bone sites. Patients with recurrent isolations of S pneumoniae were assumed to have separate infections if the serotype differed, or if the same serotype was isolated after an arbitrary interval of 14 days or more.

(c) Statistical methods

Age distributions at last visit for JSSCD and clinic participants exhibited non-normality and so were summarised by median, interquartile range, and range, and differences compared by the Mann-Whitney U test. Sex composition was assessed using the χ^2 test. Incidence rates for JSSCD and clinic groups by organism, age, and sex were estimated as the ratio of the number of events divided by the number of person-years of exposure. Confidence intervals (95% CI) for the incidence rates were calculated using jackknife methodology to compensate for multiple events within patients (62). Incidence rates were compared using rate ratios, controlling for confounding factors by stratification and subsequent pooling to give the Mantel-Haenszel estimate of the rate ratio. Standardised infection rates were calculated by comparing the infection rate of any subgroup (age, sex, organism) with the appropriate complete sample (JSSCD, clinic, or both) reference rate, a technique known as indirect standardisation. Analyses were performed using Stata statistical software (63).

(d) Results

There were 214 bacteraemias, *S pneumoniae* occurring in 81 (37.9%), *Salmonella* spp in 70 (32.7%), *H* influenzae in 30 (14.0%), E coli in 24 (11.2%), and Klebsiella spp in nine (4.2%). Of the 3820 patients (311 JSSCD), 3644 (247 JSSCD) had no bacteraemias, 151 patients (48 JSSCD) had one episode, 15 (nine JSSCD) had two, eight (five JSSCD) had three, and single cohort children had four and five episodes.

Most infections occurred in early-life: 68% occurred before the age of 10 years and 80% before 20 years (Table 3.14). There was no sex difference overall (53% males; $\chi^2 = 3.2$; $p = 0.07$), although males predominated among infections with haemophilus (risk ratio, 3.1; 95% CI, 1.4-7.0; $\chi^2 = 8.4$; $p<0.01$) and salmonella (risk ratio, 1.9; 95% CI, 1.2-3.1; $\chi^2 = 7.2$; $p = 0.01$), but not with S pneumonia (risk ratio, 1.0; 95% CI, 0.6-1.5; $\chi^2 = 0.1$; $p = 0.99$) or klebsiella (risk ratio, 4.0; 95% CI, 0.8-19.1; $\chi^2 = 3.5$; $p = 0.06$). Infections with E coli predominated among females (risk ratio, 20.3; 95% CI, 2.7-150.3; $\chi^2 = 17.6$; $p < 0.001$).

Crude incidence for all bacteraemias was 5.6 per 1000 patient-years (95% CI, 4.8-6.6), with JSSCD patients showing a five-fold greater frequency than patients in the main group (18.5 per 1000 patient-years (95% CI, 15.1-22.8) v. 3.7 per 1000 patient-years (95% CI, 3.1-4.5)). This difference will have been exaggerated by the predominance of older subjects in the clinic study who were less prone to bacteraemia. When this difference was allowed for by comparing relative incidence within age bands (Table 3.15), the risk ratio for bacteraemia among JSSCD relative to clinic group participants fell to 2.6 (95% CI, 1.9-3.5). In individual

age bands, the risk ratios for the JSSCD group relative to the clinic group were as follows: ages 0-2 years, 1.8 (95% CI, 1.0-3.1); ages 3-5 years, 2.5 (95% CI, 1.5-4.2); ages, 6-9 years, 2.8 (95% CI, 1.5-5.4); ages 10-19 years, 5.0 (95% CI, 2.3-10.8); and age 20 years and above, 7.2 (95% CI, 2.6-20.3). Incidence decreased linearly with age in the JSSCD group ($\chi^2 = 21.6$; $p < 0.001$) and the clinic group ($\chi^2 = 61.6$; $p < 0.001$). Incidence rates for the five bacteraemias were consistently higher in the JSSCD group than the clinic study group: pneumococcus, 7.8 (5.3 to 12.0) v 1.3 (0.9 to 1.8); salmonella, 5.6 (3.7 to 8.9) v 1.2 (0.9 to 1.7); haemophilus, 2.7 (1.5 to 5.2) v 0.5 (0.3 to 0.9); E coli, 1.2 (0.6 to 3.2) v 0.5 (0.3 to 0.9); and klebsiella, 1.0 (0.4 to 3.0) v 0.1 (0.05 to 0.4) respectively.

Table 3.14.

Distribution of infections by age, gender, and patient group (men / women)

Bacterial isolate	Age (in years)					
	0 to 2	3 to 6	7 to 9	10 to 19	20+	Total
Clinic						
S pneumoniae	7/4	5/10	2/6	2/2	1/3	17/25
Salmonella spp	6/1	1/2	10/2	1/7	10/3	28/15
H. Influenzae	3/2	7/1	1/0	1/0	1/1	13/4
Escherichia.coli	0/0	0/1	0/0	0/0	0/17	0/18
Klebsiella spp	1/0	0/0	0/0	1/0	2/0	4/0
Total (%)	24 (11)	27 (13)	21 (10)	14 (7)	38 (18)	124
JSSCD						
S pneumoniae	6/9	8/7	5/0	1/1	1/1	21/18
Salmonella spp	3/3	4/1	7/5	2/2	0/0	16/11
H. Influenzae	8/2	1/1	0/1	0/0	0/0	9/4
Escherichia.coli	1/0	0/0	0/0	0/3	0/2	1/5
Klebsiella spp	0/0	0/0	1/0	2/1	0/1	3/2
Total (%)	32 (15)	22 (10)	19 (9)	12 (6)	5 (2)	90

(e) Discussion

Presentation of infection data is complicated by the need to categorise by more than one criterion, which produces small or unreliable incidence data. A report of bacteraemias from the cooperative study in the USA stratified events into five age groups but not by sex or bacteraemia (64).

Substantial differences were apparent between the JSSCD and clinic participants. The age structure of these groups differed, the oldest subjects being 24.5 years in the cohort group compared with 20.6 in the main group. Although the interquartile ranges were less disparate (cohort group, 11.2-21.2; main group, 10.7-31.4), this difference in age distribution affected the pattern of infection, because 19 of 38 bacteraemias in patients in the clinic group aged 20 years and above were caused by E coli compared with two of six in the JSSCD. However, although it complicated assessment of the data, the inclusion of patients from the clinic group contributed most of the events, thereby increasing the sensitivity of analysis. The unadjusted fivefold increase in infections among participants in the JSSCD (18.5 per 1000 patient-years) compared with clinic study participants (3.7 per 1000 patient-years) was also a concern, raising the possibility of considerable underdiagnosis in the clinic group. Analysis of incidence within narrower age bands reduced this relative incidence to 2.6-fold. Factors

contributing to this difference included the more comprehensive and complete follow up of the JSSCD and the fact that patients in the clinic study are more likely than those in the JSSCD to attend other health care institutions, which might not have the same access to microbiological facilities. Under such circumstances, patients would be treated empirically, without culture confirmation of diagnosis. The JSSCD who have been monitored closely in this clinic since birth, would almost certainly attend for illness and be investigated aggressively. Because care of sickle cell patients worldwide more closely resembles that in our clinic study, the implications are that bacteraemia is underdiagnosed. A direct attempt to quantify the bias in reporting clinical events among clinic-ascertained study participants is presented in Chapter Six (Section 6.3.6).

Table 3.15.

Age related incidence of infections among 311 JCS and 3509 main study patients.

	Age group (years)				
	0 to 2	**3 to 5**	**6 to 9**	**10 to 19**	**20 +**
JSSCD					
Events	30	26	17	13	4
1000 person yrs	0.87	0.81	1.01	1.94	0.24
Rate (95% ci)	34.5 (23.1 - 53.9)	32.1 (20.9 - 51.8)	16.9 (10.5 - 29.0)	6.7 (3.7 - 13.5)	17.0 (6.6 - 57.8)
SIR (95% ci)	1.9 (1.3 - 2.9)	1.7 (1.1 - 2.8)	0.9 (0.6 - 1.6)	0.4 (0.2 - 0.7)	0.9 (0.4 - 3.1)
Clinic study					
Events	21	30	21	13	39
1000 person yrs	1.07	2.31	3.53	9.69	16.62
Rate (95% ci)	19.6 (11.9 - 34.7)	13.0 (8.8 - 20.0)	6.0 (3.9 - 9.6)	1.3 (0.8 - 2.5)	2.4 (1.7 - 3.3)
SIR (95% ci)	5.3 (3.2 - 9.4)	3.5 (2.4 - 5.4)	1.6 (1.1 - 2.6)	0.4 (0.02 - 0.7)	0.6 (0.5 - 0.9)

3.11 Reference List

(1) Henderson SJ, Fishlock K, Horn ME, Oni L, Bellingham AJ. Neonatal screening for haemoglobin variants using filter paper-dried blood specimens. Clin Lab Haematol 1991; 13(4):327-334.

(2) Vichinsky E, Hurst D, Earles A, Kleman K, Lubin B. Newborn screening for sickle cell disease: effect on mortality. Pediatrics 1988; 81(6):749-755.

(3) Gaston MH, Verter JI, Woods G, Pegelow C, Kelleher J, Presbury G et al. Prophylaxis with oral penicillin in children with sickle cell anemia. A randomized trial. N Engl J Med 1986; 314(25):1593-1599.

(4) Newborn screening for sickle cell disease and other hemoglobinopathies. NIH Consensus statement 1987; Apr 6-8(6 (9)):1-22.

(5) Zeuner D, Ades AE, Karnon J, Brown J, Dezateux C, Anionwu EN. Antenatal and neonatal haemoglobinopathy screening in the UK: review and economic analysis. Health Technol Assess 1999; 3(11).

(6) Davies SC, Cronin E, Gill M, Greengross P, Hickman M, Normand C. Screening for sickle cell disease and thalassaemia: a systematic review with supplementary research. Health Technol Assess 2000; 4(3):i-99.

(7) World Health Organisation. Guidelines for the control of haemoglobin disorders. Report of the VIth Annual Meeting of the WHO Working Group on Haemoglobinopathies, Caglieri, Sardinia, 8-9 April, 1989. (unpublished document WHO/HDP/WG/HA/89.2). 1989. Geneva, WHO.

(8) Ashley-Koch A, Yang Q, Olney RS. Sickle hemoglobin (HbS) allele and sickle cell disease: A HuGE review). Am J Epidemiol 2000; 151(9):839-845.

(9) World Health Organisation. Joint WHO/TIF Meeting on the Control of Haemoglobinopathies. Report of the VIIth Meeting of the WHO Working Group on the Control of Hereditary Anaemias, Nicosia, Cyprus, 3-4 April, 1994. (unpublished document WHO/HDP/TIF/HA/93.1). 1994. Geneva, WHO.

(10) Streetly A, Dick M, Layton M. Survey of the scope of neonatal screening in the United Kingdom. BMJ 1995; 311:726.

(11) Serjeant GR, Serjeant BE, Forbes M, Hayes RJ, Higgs DR, Lehmann H. Haemoglobin gene frequencies in the Jamaican population: a study in 100,000 newborns. Br J Haematol 1986; 64(2):253-262.

(12) UN-ONU. United Nations World Population Prospect; the 1996 revision: WHO/HST. 1997.

(13) World Bank. World Development Indicators, 2001.

(14) Handa S, Neitzert M. Chronic Illness and Retirement in Jamaica. World Bank LSMS Working Paper No 131 1998.

(15) Weatherall DJ, Clegg JB. Inherited haemoglobin disorders: an increasing global health problem. Bull World Health Organisation 2001; 79(8):704-712.

(16) Headings VE. Sickle cell disease in childhood. Strategies for early diagnosis. Am J Pediatr Hematol Oncol 1982; 4(1):67-71.

(17) Campbell H, Boyd K. Screening and the new genetics: a public health perspective on the ethical debate. J Public Health Med 1996; 18:485-488.

(18) Leikin SL, Gallagher D, Kinney TR, Sloane D, Klug P, Rida W. Mortality in children and adolescents with sickle cell disease. Cooperative Study of Sickle Cell Disease. Pediatrics 1989; 84(3):500-508.

(19) Lane PA, Eckman JR. Cost-effectiveness of neonatal screening for sickle cell disease. J Pediatr 1992; 120:162-163.

(20) Metters JS, Huntsman RG, Yawson GI. The use of the cord blood sample for the detection of sickle-cell anaemia in the newborn. J Obstet Gynaecol Br Commonw 1970; 77(10):935-938.

(21) Garrick MD, Dembure P, Guthrie R. Sickle-cell anemia and other hemoglobinopathies. Procedures and strategy for screening employing spots of blood on filter paper as specimens. N Engl J Med 1973; 288(24):1265-1268.

(22) Pearson HA, O'Brien RT, McIntosh S, Aspnes GT, Yang MM. Routine screening of umbilical cord blood for sickle cell diseases. JAMA 1974; 227(4):420-421.

(23) Serjeant BE, Forbes M, Williams LL, Serjeant GR. Screening cord bloods for detection of sickle cell disease in Jamaica. Clin Chem 1974; 20(6):666-669.

(24) King's Fund Forum consensus statement: screening for fetal and genetic abnormality. BMJ (Clin Res) 1987; 295:1551-1553.

(25) Jess M. Mum wins damages for sickle cell child. The Voice [Nov 28], 1-3. 1989.

(26) British Society for Haematology. Guidelines for haemoglobinopathy screening. Clin Lab Haematol 1988; 10:87-94.

(27) Report of a working party of the standing medical advisory committee on sickle cell, thalassaemia, and other haemoglobinopathies. 1993. London, HMSO.

(28) Davies S. Services for people with haemoglobinopathy. BMJ 1994; 308:87-94.

(29) US Preventive Task Force. Guide to clinical preventive services. DeGuiseppi C, Atkins D, Woolf ST, Kamarow DB, editors. 1996. Baltimore,MD., Williams and Wilkins.

(30) Consensus conference. Newborn screening for sickle cell disease and other hemoglobinopathies. JAMA 1987; 258(9):1205-1209.

(31) Moore SR. Sickle-cell disease - screening, diagnosis, management and counseling in newborns and infants. Journal Of The Royal Society Of Health 1993; 113:155.

(32) American College of Obstetricians and gynecologists committee opinion: Committee on genetics. Genetic screening for hemoglobinopathies. Int j Gynaecol Obstet 1996; 53:195-196.

(33) Grover R, Wethers D, Shahidi S, Grossi M, Goldberg D, Davidow B. Evaluation of the expanded newborn screening program in New York City. Pediatrics 1978; 61(5):740-749.

(34) Sundall DN. Availability of funds for maternal and child health projects. Fed Register 1987; 52:2072.

(35) Akinyanju OO, Disu RF, Akinde JA, Adewole TA, Otaigbe AI, Emuveyan EE. Initiation of prenatal diagnosis of sickle-cell disorders in Africa. Prenat Diagn 1999; 19(4):299-304.

(36) Ohene-Frempong K, Lamptey M, Hagan H, Essel-Ahun M, Bonney A, Nkrumah FK. Newborn screening for sickle cell disease in Ghana: follow-up of babies with SCD. 24th Annual Meeting of the National Sickle Cell Disease Program , 33a. 2000.

(37) Serjeant GR. Screening for sickle-cell disease in Brazil. Lancet 2000; 356(9224):168-169.

(38) Serjeant GR. Sickle Cell Disease. 2nd ed. Oxford: Oxford University Press, 1992.

(39) Serjeant GR, Grandison Y, Lowrie Y, Mason K, Phillips J, Serjeant BE et al. The development of haematological changes in homozygous sickle cell disease: a cohort study from birth to 6 years. Br J Haematol 1981; 48(4):533-543.

(40) Esbjerg S, Keiding N, Koch-Henriksen N. Reporting delay and corrected incidence of multiple sclerosis. Stat Med 1999; 18(13):1691-1706.

(41) Chong MY, Hamilton DC, Cole DEC. Retrospective estimation of the birth prevalence for delayed onset disorders: application to cystic fibrosis in Nova Scotia. Stat Med 2000; 19:743-751.

(42) Lindsey JK. Fitting bivariate intensity functions, with an application to modelling delays in reporting acquired immune deficiency syndrome. Journal Of The Royal Statistical Society Series A-Statistics In Society 1996; 159:125-131.

(43) STATIN. Statistical Institute of Jamaica: Demographic Statistics (Annual editions: 1973-1999). 2000.

(44) Kalbfleisch JD, Lawless JF. Inference based on retrospective ascertainment - an analysis of the data on transfusion-related aids. Journal Of The American Statistical Association 1989; 84:360-372.

(45) Brookmeyer R, Damiano A. Statistical methods for short-term projections of AIDS incidence. Stat Med 1989; 8(1):23-34.

(46) Zeger SL, See LC, Diggle PJ. Statistical methods for monitoring the AIDS epidemic. Stat Med 1989; 8(1):3-21.

(47) Akaike H. A new look at statistical model identification. IEEE Transactions on Automatic Control 1974; AC-19:716-723.

(48) Wilkinson GN, Rogers CE. Symbolic description of factorial models for analysis of variance. Applied Statistics 1973; 22:392-399.

(49) Falletta JM, Woods GM, Verter JI, Buchanan GR, Pegelow CH, Iyer RV et al. Discontinuing penicillin prophylaxis in children with sickle cell anemia. Prophylactic Penicillin Study II. J Pediatr 1995; 127(5):685-690.

(50) Bainbridge R, Higgs DR, Maude GH, Serjeant GR. Clinical presentation of homozygous sickle cell disease. J Pediatr 1985; 106(6):881-885.

(51) Singhal A, Jones R, David S, Serjeant G. Delayed diagnosis of homozygous sickle cell disease in Jamaica. In: Berchel C, Papiernik E, De Caunes F, editors. Perinatal problems of islands in relaton to the prevention of handicaps. 1992: 268-275.

(52) Platt OS, Brambilla DJ, Rosse WF, Milner PF, Castro O, Steinberg MH et al. Mortality in sickle cell disease. Life expectancy and risk factors for early death. N Engl J Med 1994; 330(23):1639-1644.

(53) Wierenga KJ, Hambleton IR, Lewis NA. Survival estimates for patients with homozygous sickle-cell disease in Jamaica: a clinic-based population study. Lancet 2001; 357(9257):680-683.

(54) Cui J. Estimating AIDS incidence and jack-knife variance from a continuous delay distribution and incomplete data. Stat Med 1999; 18(5):527-537.

(55) Dean CB, Balshaw R. Efficiency lost by analyzing counts rather than event times in Poisson and overdispersed Poisson regression models. Journal Of The American Statistical Association 1997; 92:1387-1398.

(56) Kalbfleisch JD, Lawless JF. Regression models for right truncated data with applications to AIDS incubation. Statist Sin 1991; 1:19-32.

(57) Barrett-Connor E. Bacterial infection and sickle cell anemia. An analysis of 250 infections in 166 patients and a review of the literature. Medicine (Baltimore) 1971; 50(2):97-112.

(58) Powars D, Overturf G, Weiss J, Lee S, Chan L. Pneumococcal septicemia in children with sickle cell anemia. Changing trend of survival. JAMA 1981; 245(18):1839-1842.

(59) Wright J, Thomas P, Serjeant GR. Septicemia caused by Salmonella infection: an overlooked complication of sickle cell disease [see comments]. J Pediatr 1997; 130(3):394-399.

(60) Pearson HA, McIntosh S, Ritchey AK, Lobel JS, Rooks Y, Johnston D. Developmental aspects of splenic function in sickle cell diseases. Blood 1979; 53(3):358-365.

(61) Rogers DW, Vaidya S, Serjeant GR. Early splenomegaly in homozygous sickle-cell disease: An indicator of susceptibility to infection. Lancet 1978; 2(8097):963-965.

(62) Efron B, Tibshirani RJ. An Introduction to the Bootstrap. New York: Chapman and Hall, 1993.

(63) StataCorp. Stata Statistical Software: Release 7. College Station, Texas: Stata Corporation, 2001.

(64) Zarkowsky HS, Gallagher D, Gill FM, Wang WC, Falletta JM, Lande WM et al. Bacteremia in sickle hemoglobinopathies. J Pediatr 1986; 109(4):579-585.

Chapter 4

Participant non-response

Background

Measurements are only possible if study members remain available and willing participants. Bias resulting from losing participants may invalidate subsequent findings, and the exploration of this assertion is a recent development in statistical research, which still often requires novel methodology. If non-response is dependent on current or previous levels of the outcome, the non-response should not be ignored, and the use of much standard statistical methodology may provide biased results.

Methods

We classify non-response as permanent non-response (or dropout) and temporary non-response (or default). We develop alternative definitions of default, and methods for quantifying default, and we introduce a simple summary measure of default (the default index). We describe default cross-sectionally and longitudinally in the JSSCD, and in the clinic population, which has less rigorous follow-up procedures. Using the JSSCD, we assess the influence of default on subsequent dropout using parametric survival modelling. We assess the dependence of selected haematological and clinical outcomes on the probability of default and dropout using recently developed pattern-mixture modelling.

Findings

Among homozygous sickle-cell disease JSSCD members, there has been 23% dropout due to death and 17% dropout due to migration from Jamaica between January 1973 and December 1999. Default from all pre-arranged appointments is 21.9% (95% confidence interval 20.1 to 24.0), default for an entire year is 2.7% (1.6 to 4.4), and default from providing asymptomatic haematology is 19.8% (17.8 to 22.0). Equivalent default from the main study is between 8 percentage points higher for steady-state visits and 57 percentage points higher for visits that collect haematology. Among JSSCD members, default is a strong predictor of subsequent death. Among members with 25% default 17% of males and 19% of females will die by 18 years of age. Among members with 75% default 59% of males and 63% of females will dropout by 18 years of age. Both default and death are shown to be non-ignorable when modelling haematological indices (total haemoglobin and fetal haemoglobin) and clinical outcome (pain crisis rate).

Interpretation

Dropout due to death in the JSSCD is high, and is an inevitable consequence of studying a life-threatening medical condition for a long period of time. Default is harder to quantify; it depends on the research question and on the method of measuring clinic absence. Although annual default is below 3%, for much sickle-cell epidemiology using steady-state haematology a default rate of 20% is a more appropriate summary. The prediction of subsequent death by levels of default provides a potential avenue for intervention. The non-ignorable nature of default and death in the JSSCD has consequences for the analysis of sickle-cell disease epidemiology. Further sensitivity studies are required to assess the size of the bias introduced by inappropriate analyses.

4.1 Introduction

The systematic collection of information is an integral feature of the research process. Its early position in this process means that inadequate data collection potentially invalidates subsequent research conclusions. Inadequate data collection encompasses failures to incorporate relevant information in the data collection design, inaccurate measurement of collected information, and the inability to collect information from some study participants. Here, we restrict our attention to the problems introduced by uncollected information, or non-response of study participants.

Data collection in medical research (and in epidemiology in particular) is a social science. It is reliant on the prevailing environmental conditions, and perfect (or complete) collection of required information is an artificial ideal. With the growth in longitudinal research to incorporate the influence of time in hypotheses, the changes in environmental conditions that are often of direct interest to researchers may also modify the likelihood of response.

The Jamaican Cohort Study of Sickle Cell Disease (JSSCD) was designed to implicitly incorporate the passage of time. Multiple observations are taken for each cohort member on a range of clinically relevant variables, collected according to a pre-defined regime (see Chapter Two, Section 2.2.3). This prospective design is necessary to capture the dynamic nature of participants' disease experiences.

Measurements can only be taken if cohort members remain available and willing participants, and the tracking and retention of cohort members is a central component of any ongoing cohort study. The financial costs associated with such endeavour are inevitably high. Implementing successful methods for retaining members is perhaps the greatest challenge of ongoing cohort studies. Bias resulting from loss of cohort members may invalidate subsequent findings and the exploration of this assertion is a recent methodological development in cohort research, which still often requires novel methodology.

In this chapter we provide the first description of non-attendance at the Jamaican Sickle cell clinic. We explore the role of non-attendance in biasing our attempts at describing clinical outcomes and modelling their potential risk factors. In section 4.2 we introduce the typology of non-response. In section 4.3 we detail the evidence on the consequences of non-response in aetiological studies. In section 4.4 we describe the methods used in the JSSCD to retain cohort members. In section 4.5 we provide a detailed description of the definitions of non-response for the JSSCD. In section 4.6 we provide a brief outline of the general method for modelling non-response. In sections 4.7 and 4.8 we present the methods and results for describing and measuring the effects of non-response in the JSSCD. We provide a discussion in section 4.9.

4.2 Types of non-response

4.2.1 definition

We anecdotally define non-response as measurements that were intended but not made. In longitudinal observational studies the distinction between missed measurements and measurements that are planned at irregular intervals can be difficult. Observational studies that include time as a design feature must provide a regime for data collection and clear definitions of non-response.

4.2.2 Non-response classifications

(a) JSSCD

An individual that declines to join a study is known as a *refusal.* A study member that misses one or more scheduled study appointments and subsequently attends is known as a *defaulter;* throughout this report we refer to this intermittent and temporary non-response as *default.* A study member that misses all appointments after a certain time is known as a *dropout.* In the JSSCD dropout is usually because of death or emigration. In this report we use the terms *death* and *migration* when referring to these specific causes of non-response. We use the term *dropout* when referring to all causes of permanent non-response. A study member that misses the latest study appointment is a *current defaulter.* Current default is a necessary temporary classification that will be re-classified as *default* or *dropout*, as more information becomes available. The JSSCD definitions of non-response are summarised in Table 4.1

Table 4.1.
Non-response typology adopted in the Jamaican Cohort Study of Sickle Cell Disease (JSSCD)

Term	Description
Refusal	An individual that declines to join a study.
Non-response	Measurements that were intended but not made.
Default	Temporary non-response when a study member misses 1 or more scheduled appointments, and subsequently returns.
Dropout*	A study member that misses all appointments after a certain time. In the JSSCD there are two main reasons for dropout: **death** and **emigration.**
Current default	A temporary classification that is updated to **default** or **dropout** as more information becomes available.

* **Dropout refers to all-causes of permanent non-response. Single causes (death and emigration) are stated explicitly.**

(b) Little and Rubin (1987)

Rubin (1) and later Little and Rubin (2) suggested three types of non-response that have an increasing impact on the results of a study. The definition has been widely adopted as the

basis for developing statistical methods to cope with non-response. The subsequent terminology of Diggle and Kenward (3) is less technical and is used here. If the reason for a study member to miss a particular visit is unrelated to the study outcome at that visit and at all previous visits the non-response is known as *completely random.* If the reason is unrelated to the outcome at that visit but depends on the outcome at previous visits the non-response is known as *random.* If the missed visit depends on the outcome at that visit the non-response is known as *informative.* This classification deals with the validity of applying research conclusions to the entire study population when a subgroup exhibits non-response. Lindsey (4) comments that the convention relates to whether a study outcome is independent of the reasons for non-response rather than randomness, and suggests a renaming of the three groups to *completely independent*, *independent*, and *dependent.*

(c) Lindsey (1999)

Crucially, the above classification assumes that any non-response is an available but missed measurement. In the important case of *dropout*, measurement is often no longer possible (in our study, dropout is generally due to death or migration overseas). Lindsey (4) offers a simpler alternative that examines the response profile over time. If there is no variation in dropout over time the process is known as *random.* If dropout varies with time in the same way for all patients the process is known as *ignorably non-random.* If dropout varies with time and differentially between patients the process is known as *non-ignorable.*

(d) Quantity missing

Data can be missing to different degrees, and a final classification might use the quantity of intended information that is missing. For a single patient, partial information (one or several variables) may be missing, all measurements may be missing for a particular time point, and these two possibilities may be missing systematically or erratically over several time points.

4.3 Consequences of non-response

Although a general maxim is to avoid non-response at all times, a policy of zero non-response is an artificial ideal. Some dropout (for us due to death, or migration from Jamaica) is an integral part of the research process.

4.3.1 Collecting reasons for default

The most important guideline must be to record the time and reason for the non-response. Potential cohort members that cannot be recruited (e.g. because of refusal, or non-ascertainment due to sampling methods) are the most problematic group of non-responders. Reasons for non-participation should be recorded in detail, although there are situations when little information will be available. For example, in a prevalent cohort, deaths in early-life are (a) informative with respect to disease outcome, and (b) occur before study recruitment. Information beyond date and cause of death are unlikely to be available. Study bias is inevitable.

4.3.2 Increased variability / Loss of power

A simple consequence of dropout or default is an overall reduction in power to answer any particular research question compared to a theoretical complete dataset. In a long running cohort study such as the JSSCD this is likely to be a minor concern compared to the potential bias introduced.

4.3.3 Bias

Much evidence suggests that dropouts and defaulters differ systematically from non-defaulters (5-8). The extent of this introduced bias and the methods for bias adjustment depend on which non-response mechanism is operating (*completely random*, *random*, or *informative*). Methods for describing and adjusting for bias have proliferated in recent years, and are described briefly in Section 4.6.

4.3.4 The 'healthy-person' effect

In the common situation of informative non-response, default and death often occur due to ill-health, which leaves a subset of responders that are the healthy remainder. This problem has been described previously, often in the context of occupational epidemiology, and is usually termed the 'healthy worker effect' (HWE) or 'healthy-person effect' (HPE) (9;10). The effect is particularly relevant to long-running studies such as the JSSCD where cumulative attrition may leave a mildly affected subgroup of participants. The opposite effect may also exist, may be termed the 'sick-person effect' (SPE), and would usually occur when a diseased patient group are compared with an inappropriate referent (11). In the JSSCD, an original hypothesis suggested that mild patients weren't represented in clinic-based study populations. Neonatal recruitment in the JSSCD was designed to examine this hypothesis.

4.4 Methods of retaining and tracking patients at the Jamaican sickle-cell unit

High retention rates in follow-up studies reduce the potential for biased data due to selective loss of study participants. Specific forms of dropout (e.g. death and migration) are integral and inevitable consequences of long-term follow-up, and cannot be influenced by efforts to retain study members. Other forms of dropout (e.g. participant refusal) and all forms of default are certainly influenced by study design, and are preventable. Literature on methods to enhance retention rates is recent and is growing (12-16). Common themes include the maintenance of regular contact with participants linked to regular encouragement to attend, and ensuring that the participants remain well informed of the study's progress. Special considerations are often necessary for 'hard-to-retain' members of a study (17). Methods to minimise default in the JSSCD use two broad techniques: encouraging retention of cohort members and tracking those cohort members that do default.

4.4.1 Encouraging retention in the JSSCD.

(a) Regular follow-up.

Regular follow-up of cohort members allows regular data collection during periods of steady-state. A continuing education programme details the benefits of preventive clinical management, and reminds participants that such management is only possible if they attend the clinic regularly when well.

(b) Appointment planning

At each appointment, the next clinic appointment is scheduled. Future appointments are stored in a dedicated clinical database, with letter reminders sent to members before the visit is due, and if necessary as soon as the appointment is missed. Annual 'birthday' appointments take a higher priority, and if this birthday appointment is missed, a telephone call reminds the study participant of the visit.

(c) Free clinical care and other 'rewards'

Clinical care is free to all cohort members. Jamaica offers means tested health-care, making free clinical care the overwhelming incentive among cohort members to attend the clinic for regular appointments, and also when sick. The cost of public transportation to and from the clinic is reimbursed for all *pre-arranged* appointments. All cohort members receive a T-shirt on their annual 'birthday' visit.

(d) 'Identifying' with the study

The continuity of long-serving staff has promoted a bond between staff and cohort members that helps to ensure ongoing identification with the study. A full time social worker and a patient-run support club help participants to cope with the social consequences of the disease, and promote a sense of community within the study.

4.4.2 Tracing default in the JSSCD

(a) Tracking system

A dedicated database maintains current contact details of all cohort members. Currently defaulted members are flagged and efforts to trace these members are centred around an annual cohort review.

(b) Annual review

In addition to the birthday visit, an annual review over a three-week period in late January allows the collection of specialised information (such as oximetry, and ocular, nutritional, and ultrasound information). An associated benefit of this effort is the opportunity to locate cohort members that are currently defaulted. Appointments are known one-year in advance, and reminders are mailed two-months before the appointment. If a cohort member misses the appointment, telephone reminders are made, and a new visit is re-scheduled within the three-week window. Personal collection is arranged for any cohort member that misses the

original and re-scheduled appointment. During this annual review, reasons for default are collected from members that have defaulted during the previous 12 months.

4.4.3 Tracking clinic patients

Clinic-study participants follow a six-month appointment regime. Because of resource limitations, no attempt is made to trace clinic-study members that miss pre-specified appointments.

4.5 Defining non-response

4.5.1 Defining dropout

Dropout is based on definitive endpoints (death, migration) and is irreversible. These endpoints, along with the date that the endpoint occurs define each participant dropout (see Table 4.1).

4.5.2 Defining default

Intermittent default is more difficult to define. Strictly, the period between a missed clinic appointment and a subsequent clinic visit defines an episode of intermittent default. In reality, very few cohort members present to clinic on the exact day of their pre-specified appointment, and a pragmatic definition must account for variation in appointment keeping. Moreover, the reported level of default should be tailored to the study outcome under investigation - for example, a patient can be sick at a pre-specified appointment, which leads to default from providing steady-state haematology but not default from the clinic. Algorithms are presented below that describe alternative approaches to understanding default in the JSSCD.

(a) Appointments and visits

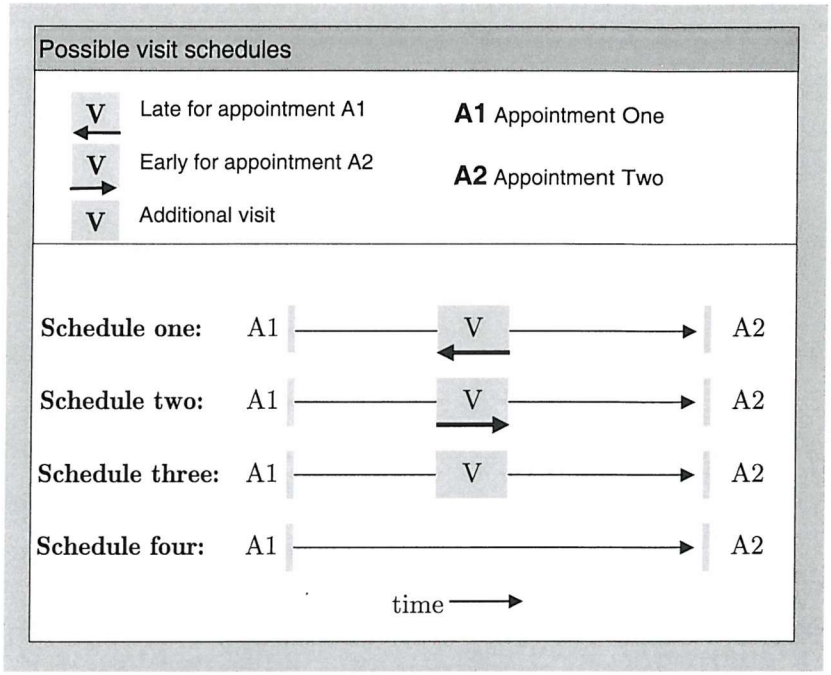
Default measurements are defined by the relationship between pre-defined appointments and actual patient visits. For two consecutive pre-defined appointments, four visit schedules are possible (Figure 4.1). When study participants present to clinic between consecutive appointments, they may be attending late for a previous appointment (schedule one), early for the next appointment (schedule two), or may be attending for other reasons (schedule three). A patient might not present to clinic at all between two consecutive appointments (schedule four). A combination of three definitions decide how we quantify default: the *appointment regime* of the cohort study, the *visit regime* of each study member, and how the discrepancy between appointments and visits is measured (the *default regime*).

(b) Appointment regime

The pre-defined appointment regime is presented in Section 2.2.3 (Tables 2.3 to 2.5). An important component of the JSSCD is the measurement of steady-state haematological indices, with collection between one and four times a year, depending on participant age and genotype. Two annual visits (a 'birthday' appointment and an annual January 'review') are the

cornerstone of the data collection regime and many more annual measurements are taken at these times. Collectively, the overall appointment regime is defined by any pre-arranged haematology or annual appointment. We can therefore define three alternative appointment regimes: *haematology appointments*, *annual appointments*, and *all appointments*.

Figure 4.1
Possible visit schedules



(c) Visit regime

A study member presents to the clinic when well, or because of clinical complications, and haematology may be taken at either type of visit. Haematology taken when a participant is without clinical symptoms is known as steady-state haematology. We can therefore define four alternative visit regimes: *all visits*, and *asymptomatic visits*, each with or without *haematology* measurements.

Table 4.2.
Five possible default regimes

Default regime	**Appointment regime**	**Visit regime**
All-default	All appointments	All visits
Annual-default	Annual appointments	All visits
Steady-state default	All appointments	Asymptomatic visits
All haematology default	Haematology appointments	All visits
Steady-state haematology default	Haematology appointments	Asymptomatic visits

(d) Default regime

Using combinations of appointment and visit regimes, five types of default regime are available to us (Table 4.2). All-default is considered the primary measure of interest for results in this chapter.

(e) Methods for measuring default

We define six and implement five ways of measuring each default regime. The five implemented methods are described with reference to Figure 4.2, a series of nine consecutive clinic appointments and seven actual visits between 1981 and 1983 for a male SS participant born in 1975 and six-years old at the first appointment in this series. Routine appointments were scheduled once every three months for an SS participant of this age. Appointment and visit dates in this two-year series are presented in Table 4.3. A visual description of the five default regime measurements is presented in Figure 4.2. For all methods, default is presented as the number of days of default (Table 4.5). There are three months between successive appointments and two years in the complete sample series.

Strict default (strict). Strict default requires the study participant to attend the clinic on the exact day of their appointment. Default is calculated as the number of days from the appointment to the subsequent visit. We considered this strict definition to be unrealistic in the Jamaican setting and have not implemented the measurement in this report.

Soft default (soft) *(Figure 4.2* ***A****).* If a participant does not present to clinic in the period between two consecutive appointments, the full three-month period is considered defaulted. This method is a relaxation of strict default, which requires presentation on the exact appointment date. In our sample series, the cohort member does not present between appointments two and three, appointments four and five, and appointments seven and eight. Three 3-month periods (91 days $\times$ 3 = 273 days) are defaulted.

Forward default (forward) *(Figure 4.2* ***B****)* The first visit after an appointment is considered an early visit for the next appointment. If an appointment has been attended, the next 3-month period is not considered defaulted. In our sample series, visit one fulfils appointment two, and the subsequent 3-month period (between appointments two and three) is not defaulted. There is no visit between appointments two and three, appointment three is not fulfilled, and the subsequent 3-month period (between appointments three and four) is considered defaulted *until another visit occurs.* Appointment three occurs on July 10, 1981 and the next visit (visit three) occurs on July 17, 1981, creating a defaulted period of 7 days. Visit three then fulfils appointment four and the subsequent 3-month period between appointments four and five is not defaulted, and so on.

Backward default (backward) *(Figure 4.2* ***C****).* The first visit after an appointment is considered a late visit for the previous appointment. If an appointment has been attended,

the next 3-month period is not considered defaulted. In our sample series, visit one fulfils appointment one, and the next 3-month period (between appointments one and two) is not defaulted. There is no visit between appointments two and three, appointment two is not fulfilled, and the subsequent 3-month period (between appointments two and three) is considered defaulted. Visit three is then considered a late visit for appointment three and the subsequent 3-month period between appointments three and four is not defaulted, and so on. This method produces equivalent results to *soft default.*

Table 4.3.

Appointment (A) and visit (V) dates for a male SS cohort member born in 1975 and aged six years at the initial appointment in this sample period.

1981 visits	**Date of visit**	**1982 visits**	**Date of visit**	**1983 visits**	**Date of visit**
A1	**10 Jan 1981**	A5	**10 Jan 1982**	A9	**10 Jan 1981**
V1	25 Jan 1981	V5	18 Mar 1982		
V2	19 Mar 1981	A6	**10 Apr 1982**		
A2	**10 Apr 1981**	V6	02 May 1982		
A3	**10 Jul 1981**	A7	**10 Jul 1982**		
V3	17 Jul 1981	A8	**10 Oct 1982**		
V4	29 Aug 1981	V7	30 Oct 1982		
A4	**10 Oct 1981**				

Nearest default (nearest) *(Figure 4.2* ***D****).* This practical default measurement method combines the features of the forward and backward measurement methods. It assigns each visit to its nearest appointment according to the algorithm presented in Table 4.4. The algorithm identifies the nearest visit to each appointment and the nearest appointment to each visit. A visit is assigned to an appointment if it is the nearest visit to that appointment, and if the visit is not nearer to another appointment. In our sample series, visit one is nearest to appointment one and appointment one is nearest to visit one. Visit one is assigned to appointment one and the next 3-month period (between appointments one and two) is not defaulted. In the same way, visit two is assigned to appointment two, visit three to appointment three, and visit four to appointment four. Visit five is the only possible assignment to appointment five. However, visit five is nearer to appointment six, and so no assignment to appointment five is possible. Appointment five has no assigned visit, and the period between appointment five and the next visit (visit five) is considered defaulted. Appointment five occurs on Jan 10, 1982 and visit five occurs on Mar 18, 1982, creating a defaulted period of 67 days. Appointment six is the nearest appointment to visits five and six. Visit six is the nearest visit to appointment six. Visit six is assigned to appointment six, and the next 3-month period (between appointments six and seven) is not defaulted, and so on.

Table 4.4.
Algorithm for nearest default

(1) For each appointment, select:
1A. The nearest visit from the previous time period
1B. The nearest visit from the subsequent time period
1C. The nearest visit from 1A and 1B.
(2) For each visit, select:
2A. The nearest appointment to the visit
(3) Assign visit to nearest appointment:
3A. Assign to previous appointment iff, the previous event is the appointment AND the nearest event to this visit is the previous appointment AND the nearest visit to the previous appointment is this visit.
3B. Assign visit to next appointment iff, the next event is the appointment AND the nearest event to this visit is the next appointment AND the nearest visit to the next appointment is this visit.

Appointment default (appointment) *(Figure 4.2* ***E****).* In practice, clinicians often (but not always) shift appointments forward if a patient presents to clinic between pre-defined appointments. The probability of appointment shifting increases if the patient is reasonably well at an intervening visit, and if the visit is very close to a subsequent appointment. This practice shifts the patient's entire future appointment regime forward in time. In our sample series, visit two is the last visit in the interval between appointments one and two. The patient presented on Mar 19, 1981 for visit two, and appointment two was originally scheduled for Apr 10, 1981, just 22 days later. Appointment two is shifted to occur 91 days after visit two (on Jun 18, 1981). Visits three and four occur less than 91 days apart, and so appointment three is shifted to occur 91 days after visit four (on Nov 28, 1981). In the same way, appointment four is shifted to occur 91 days after visit six (on Aug 01, 1982). No more appointments are scheduled in our two year sample series. The period between each shifted appointment and the subsequent visit is considered defaulted.

(f) Comparing regimes

An anecdotal comparison of default measurement regimes using our single appointment and visit sequence (Table 4.5), suggests a dichotomy into low-default regimes (forward shift and nearest shift) and high-default regimes (soft/backwards shift and appointment shift).

We note that our *nearest* default method is the only technique that is not a true Markov process; we require information on one future visit in order to assign each visit to an associated appointment. In practice, the process can be considered Markov as we do not require knowledge of the future visit in order to correctly count the number of defaulted days.

Figure 4.2

Five default measurement methods for nine consecutive appointments and seven consecutive clinic visits by a cohort participant aged six years at the initial appointment. The required interval between clinic appointments is three months. (- - - - - -) default (———) no default

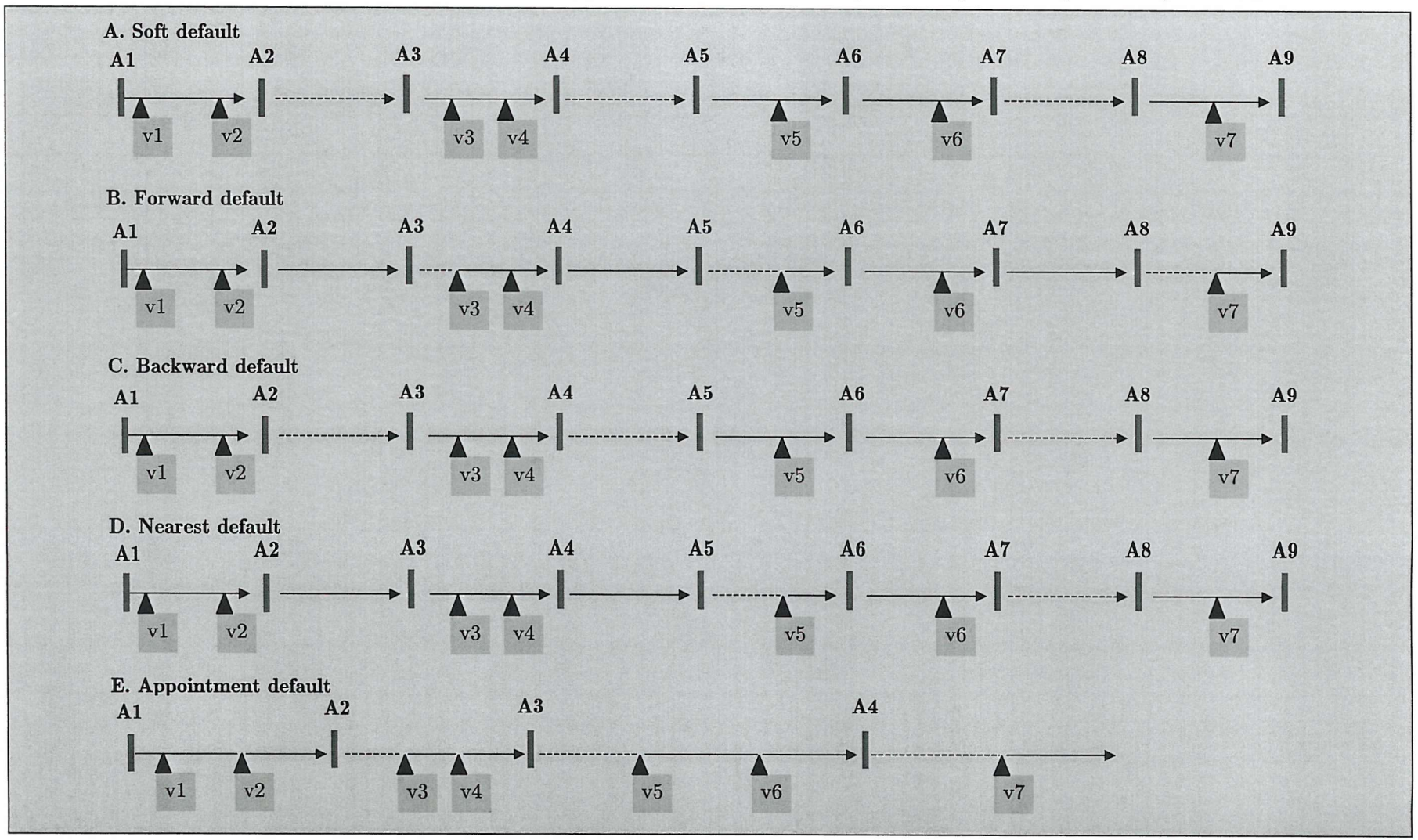


Table 4.5.

Number of days of default during a two year clinic appointment and clinic visit schedule for a male SS cohort member born in 1975 and aged six years at the initial appointment.

Appointments	Number of days defaulted				
	Soft	**Forward**	**Backward**	**Nearest**	**Appointment**
A1 to A2	0	0	0	0	0
A2 to A3	91	0	91	0	29
A3 to A4	0	7	0	0	110
A4 to A5	91	0	91	0	91
A5 to A6	0	67	0	67	-
A6 to A7	0	0	0	0	-
A7 to A8	91	0	91	91	-
A8 to A9	0	20	0	0	-
Total default	273	94	273	158	229
Total default (%)	37.5	12.9	37.5	21.6	31.3

4.6 Describing and analysing non-response: general methods

When describing and analysing non-response, the data-analyst should provide a level of detail that allows an audience to effectively assess the consequences of this default. A non-response report should include a quantification of the level of missing information, a description of the expected missing-data mechanism in operation, and an attempt to directly examine the impact of non-response on relevant research conclusions.

4.6.1 Describing the non-response

The CONSORT statement for clinical trials suggests a simple count of the number lost to follow-up (18). Observational studies have no equivalent guidelines, and non-response reporting (if it exists at all) rarely offers more than a cumulative count of participant dropouts. Such reporting ignores the quantity of time lost in longitudinal studies, and the form of the non-response mechanism. In this chapter we present a simple measure for quantifying the level of non-response in longitudinal studies, and apply it to the JSSCD and the clinic sample. The statistic, which we call the default index (D), is a ratio of the number of defaulted days to the number of potential days of study attendance, expressed as a percentage. This can equivalently be thought of as the number of defaulted days for every 100 days of potential follow-up:

$$D = 100 \sum_{i=1}^{n} t_i \Big/ \sum_{i=1}^{n} T_i \qquad (4.1)$$

for participant $i\,(i=1,\cdots,n)$ where T_i is the potential days of follow-up and t_i is the number of defaulted days. Dropout is considered an integral feature of this prospective study, and the post-dropout period does not contribute to potential follow-up time. A recent article offered an equivalent statistic, the completeness index (C), which is the ratio of the total observed person time of follow-up expressed as a percentage of potential time of follow-up in a study (19). Using the above notation, the completeness index numerator would be $\sum T - t$.

4.6.2 Describing the non-response mechanism

Faced with non-response, many studies adopt analysis techniques that require a *completely random* (MCAR) missing data structure for validity (see Chapter Five). This ignores a tenet of good research practice that requires us to assume a non-ignorable missing data mechanism and to disprove this assumption. Several studies have developed formal methodology to examine whether missing data are *completely random* (MCAR). Little offered a test for multivariate Normal data (20), and the test was extended by Park and Davis to cope with multivariate categorical data (21). These tests stratify a population according to its missing data pattern, and test the homogeneity of the parameter estimates across strata. If test statistics are significantly different across strata, then the missing data should not be ignored. Park and Lee, and Chen and Little independently utilised generalised estimating equations (22) to extend the approach (23;24). Within these GEE implementations continuous and discrete distributions can be handled, additional parameters can be included, and testing homogeneity is possible within a single model. These final approaches are related to Little's pattern-mixture model described in Chapter Five. Even using these techniques, extreme care must be taken when concluding that a missing data mechanism is MCAR, because the form of the dependence may not have been discovered. Applied evidence repeatedly confirms the presence of non-ignorable missing data (25-27).

4.7 Describing and analysing non-response in the JSSCD: methods

4.7.1 Describing dropout

We tabulated dropout, stratified by dropout reason (death or migration), by study group (JSSCD sample or clinic sample), and by genotype. We graphed dropout distributions by dropout reason (death or migration), by time scale (age at dropout or year of dropout) and by gender. Using just the JSSCD members, we further tabulated default, death, and migration by genotype (SS and AA), by sex, and by age (birth to 18 years).

Intermittent default predates death or migration by design, and a participant's tendency to default may be a predictor of subsequent death or migration. In this report we used a cross sectional summary of intermittent default for each participant (the default index averaged over time) to assess default as a predictor of time until death. We considered alternative semi-parametric and parametric models within a survival-model framework, and assessed competing models using Akaike's information criterion (AIC). The Cox model is the survival

model of choice for much epidemiology, and we considered it here along with a test of its assumption of proportional hazards of death. We also implemented a general parametric modelling framework using cubic splines that were linear between boundary points (or knots) using proportional hazards (PH) and proportional odds (PO) modelling (28). We chose the number of splines to incorporate in the model using AIC. With a single spline (i.e. no knots) the model reduces to the Weibull distribution under proportional hazards and the log-logistic distribution under proportional odds. We adjusted all models for differences across gender, and we used the final model to predict time until participant death for various levels of default. The JSSCD homozygous sickle-cell disease participants have the most accurate mortality information and we restricted modelling to this sample. Older JSSCD participants have been observed for longer, allowing a increased chance of observing deaths. We restricted our model to deaths by 18-years of age, which ensured an equivalent period of follow-up for all participants.

4.7.2 Describing intermittent default

We averaged the default index (D) over time for each participant, and we summarised the resulting average for JSSCD and clinic groups for each of the five default regimes (all default, annual default, steady-state default, all-haematology default, steady-state haematology default). To allow comparison with other work, we also present the completeness index (C). We constructed confidence limits for D and C from 1000 bootstrapped JSSCD and clinic study datasets. We plotted the observed follow-up time against potential follow-up time, following closely the graphical display of Clarke et al (19), and we call this display the completeness graph. Clarke measures potential follow-up days as the number of days from study enrolment to the end of the study for every study member. In our case, the end of the study would be December 31, 1999. Importantly, this makes no distinction between non-response due to default and due to dropout, and so confounds these distinct processes. In prospective cohort studies loss of information due to both these processes can be substantial, and is likely to have fundamentally different causes. In our presentation, we measured potential follow-up as the number of days from enrolment to either December 31, 1999 or the date of dropout, whichever occurred first. Our measures of D and C therefore describe study losses due to default only.

We also present intermittent default longitudinally by age (in years from birth to 27) and by time (from 1973 to 1999). We highlighted differences between the five default measurement regimes by plotting default against age for SS disease JSSCD members. We highlighted differences between JSSCD and clinic populations using the five default regimes, measured using the two practical default measurement methods – nearest default (*nearest*) and appointment default (*appointment*).

4.7.3 Describing the non-response mechanism

We examined the non-response mechanism using the GEE pattern-mixture modelling approach of Park and Lee (23). Tests for an MCAR missing data-mechanism were performed using three separate outcome measures: total haemoglobin (Hb), fetal haemoglobin (HbF), and total painful crisis events. Hb and HbF are important predictors for much clinical outcome (29;30), and the painful crisis is a widely used proxy for overall health-status in sickle-cell disease (31). If non-response affects these outcomes, there would be implications for much sickle-cell disease epidemiology. To ensure that all participants had the same length of time for default, death, and emigration, we performed our analysis on JSSCD members between birth and 18 years of age (the age of the youngest JSSCD member). To create the non-response patterns, we classified each participant as a defaulter (yes or no), and as either a dropout because of death (yes or no) or migration (yes or no). All models were adjusted for the potentially confounding effects of age and gender. The physiologic decrease in Hb and HbF immediately after birth is well recognized, and to capture this nonlinear trend we used fractional polynomials of age and a regression spline at age one (32;33). We describe these techniques for modelling non-linear trends in Chapter Five. For each outcome we fitted three models. In model one we fitted baseline covariates only (age and gender) and so assumed that the non-response mechanism is completely random (MCAR). In model two we additionally included the three non-response indicators, and because of the influence of default on subsequent death (see section 4.8.1), we also included two-way interactions between default and either death or migration (*default* × *death*, *default* × *migration*). In model three we used all terms in models one and two and additionally included two-way interactions between the non-response indicators and the baseline covariates (age and gender). For models two and three we explicitly examined the MCAR assumption for each of the non-response mechanisms (default, death, migration) using a generalized Wald test on all terms involving each indicator.

Table 4.6.

The number of study participants dropping out due to death and migration among the JSSCD and clinic populations between January 01, 1973 and December 31, 1999.

Dropout	JSSCD members		Clinic members	
	All genotypes	SS genotype	All genotypes	SS genotype
Non-dropout	561	190	5132	3256
Death	92	72	643	540
Migration	145	53	584	445
Total	798	315	6359	4241
Total Dropout	237	125	1227	985

4.8 Measuring non-response: results

4.8.1 Number of defaulters and dropouts

Numbers of participant dropouts between 1973 and 1999 are presented in Table 4.6, Table 4.7, and Table 4.8, and probability distributions of these deaths and migrations are presented in Figure 4.3. Among JSSCD members, there are more deaths than migrations in early-life, and an excess of migrations in the second decade of life produces a roughly equal contribution of death and migration by early adulthood (Figure 4.3a). Mortality is initially higher in females. Males have a higher mortality in the second five years of life, and by early adulthood the number of deaths are roughly equal across gender. This age-related mortality difference across gender is unexplained and is explored further in Chapter Six, section 6.3.8. The rates of migration, which began in volume in the mid-1980's, are equivalent across gender (Figure 4.3b). Among clinic members, death and migration are equivalent in the first few years of life, with more migration thereafter (Figure 4.3c). The lower mortality relative to the JSSCD is a feature of incomplete patient enrolment, which we discuss in Chapter Three. Mortality and migration seem to increase in the 1990's, and this is possibly an artefact of improved ascertainment (Figure 4.3d).

Around 9% of SS men and women had defaulted at some point during their 18th year, with lower levels among AA cohort members (5.7% for men and 6.5% for women). By 18 years of age dropout was primarily due to death among SS cohort members (male deaths 34 or 10.8%, female deaths 32 or 10.2%, male emigrations 20 or 6.3%, female emigrations 22 or 7%), and was primarily due to emigration among AA cohort members (male deaths 2 or 0.8%, female deaths 2 or 0.8%, male emigrations 14 or 5.7%, female emigrations 22 or 8.9%). We note the increased early-childhood deaths among SS women versus SS men

Table 4.7.

Numbers of childhood defaulters (using all-visit default) by age, genotype, and gender among 315 SS and 246 AA members of the Jamaican Study of Sickle-Cell Disease (JSSCD)

Age	All-visit default			
	SS		AA	
	Men	Women	Men	Women
1 day	1	0	0	0
1 week	1	1	2	1
2 weeks	4	2	3	2
1 month	7	3	4	5
2	8	9	6	8
3	11	11	5	7
4	11	13	5	8
6	15	16	5	9
8	14	15	3	12
10	16	14	6	12
1 year	18	13	8	10
2	20	20	12	20
3	27	23	11	19
4	26	23	12	22
5	23	25	12	20
6	25	26	14	21
7	24	28	14	18
8	22	23	15	16
9	19	25	12	17
10	26	34	13	18
11	23	30	11	17
12	23	28	9	15
13	27	29	12	17
14	25	29	9	16
15	30	30	11	19
16	30	28	14	20
17	30	29	14	21
	9.5%	**9.2%**	**5.7%**	**6.5%**

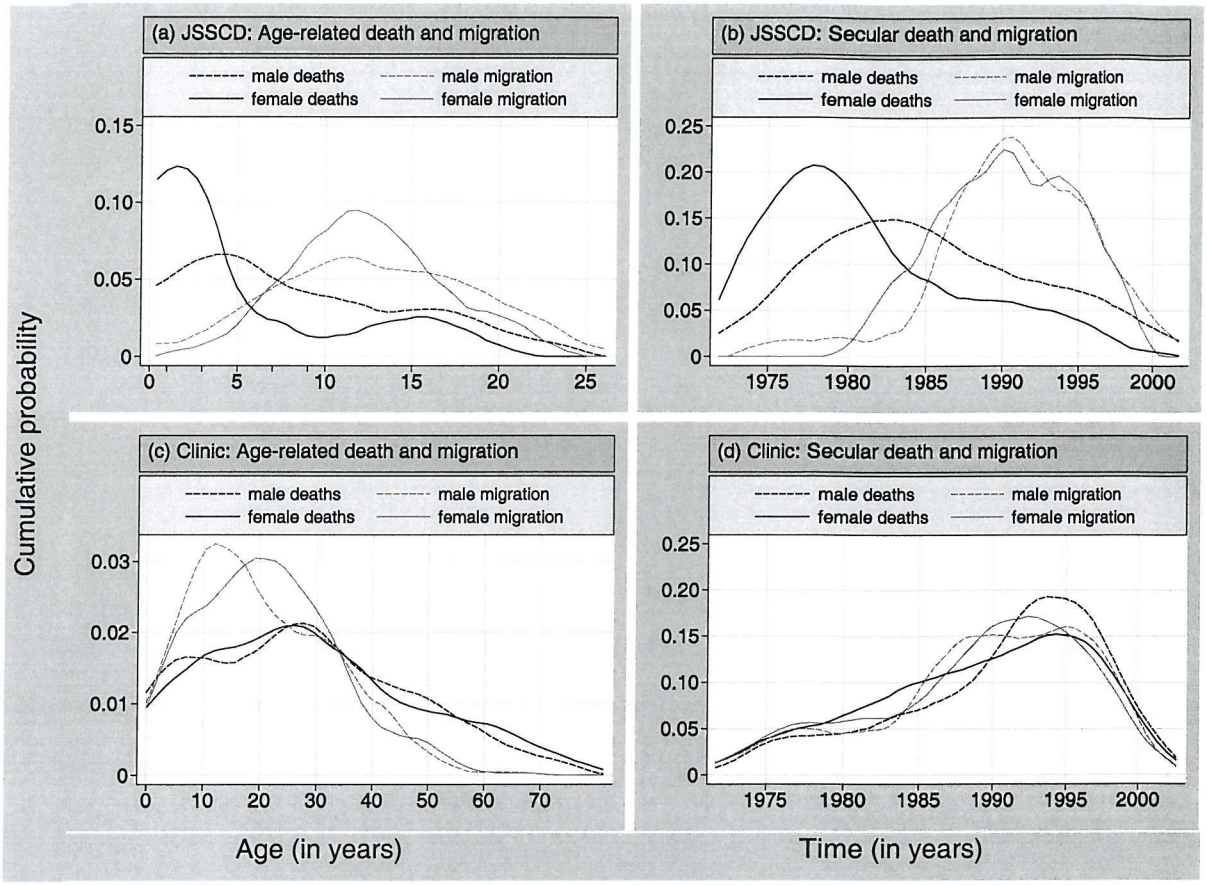
Table 4.8.

Numbers of childhood deaths and migrations by age, genotype, and gender among 315 SS and 246 AA members of the Jamaican Study of Sickle-Cell Disease (JSSCD)

Age	Death				Migration			
	SS		AA		SS		AA	
	Men	Women	Men	Women	Men	Women	Men	Women
1 day	0	0	0	0	0	0	0	0
1 week	0	0	1	1	0	0	0	0
2 weeks	0	0	1	1	0	0	0	0
1 month	0	0	1	1	0	0	0	0
2	0	0	1	1	0	0	0	0
3	0	0	1	1	0	0	0	0
4	1	0	1	1	0	0	0	0
6	1	3	1	1	0	0	0	0
8	4	6	2	1	1	0	0	0
10	5	10	2	1	1	0	1	0
1 year	5	13	2	1	1	0	1	0
2	8	18	2	1	1	0	1	0
3	11	22	2	2	1	0	1	2
4	13	22	2	2	2	0	1	2
5	15	24	2	2	2	1	1	3
6	18	25	2	2	2	1	1	3
7	19	26	2	2	2	2	2	3
8	24	27	2	2	6	3	3	4
9	25	27	2	2	7	6	3	5
10	26	27	2	2	9	8	3	5
11	26	28	2	2	12	9	5	8
12	26	28	2	2	12	13	8	10
13	27	29	2	2	14	15	9	11
14	30	30	2	2	15	17	10	15
15	31	30	2	2	18	21	12	18
16	34	32	2	2	19	21	14	18
17	34	32	2	2	20	22	14	22
	10.8%	**10.2%**	**0.8%**	**0.8%**	**6.3%**	**7.0%**	**5.7%**	**8.9%**

Figure 4.3

Age-related and secular probability distributions of JSSCD and clinic participants that leave the clinic because of death or migration between January 01, 1973 and December 31, 1999



Examining the effect of default on subsequent death among JSSCD participants, the excess early-life mortality among cohort females suggests a non-proportional risk of death across gender. Proportional-hazards is formally rejected (testing that the log-hazard ratio is constant over time, χ^2=6.6 p=0.01), and the Cox proportional-hazards model is therefore not appropriate. Alternative parametric survival models (with age at death as the outcome, percentage default as a covariate, and *gender* as a factor) are fitted and compared in Table 4.9. In all models, default is a highly significant predictor of subsequent death. The addition of a *ln(default)* term improves model fit substantially, and proportional-odds models produces marginally lower AIC values than proportional-hazards models. We opt for a two-knot PO cubic-spline model (AIC=454.4). Compared to our chosen model, the Weibull PH model (AIC=471.1) and the log-logistic PO model (AIC=466.7) are substantially worse.

Table 4.9.

Akaike's Information Criterion for competing parametric survival models

Model		Sex + Default		Sex + Default + ln(Default)	
		Proportional Hazard	Proportional Odds	Proportional Hazard	Proportional Odds
Spline	0 knots	497.9 (1)	494.3 (2)	471.1 (1)	466.7 (2)
	1 knot	485.0	482.7	459.7	456.4
	2 knots	481.2	479.2	457.4	454.4
	3 knots	481.7	480.0	459.0	456.4
	4 knots	483.6	481.9	463.4	460.6

(1) Weibull model with Proportional Hazards assumption

(2) Log-logistic model with Proportional Odds assumption

Comparing the Weibull hazard with the two-knot spline PH hazard (Figure 4.4a) only the spline model accounts for the increased early-life mortality among females and the subsequent fall to levels below that of males. We see the same pattern in PO models (Figure 4.4b), and note that PO models suggest first a slightly higher, then a slightly lower hazard than PH models (Figure 4.4c).

Predicted time until dropout is presented graphically in Figure 4.5 for five levels of patient default (10%, 25%, 50%, 75%, and 90%) and is tabulated in Table 4.10. Predicted deaths are directly related to the prior level of clinic default. The relationship is strongest in the first 5-years of life; maintaining clinic attendance in early-life is paramount.

Table 4.10.

Predicted percentage of deaths among JSSCD participants with homozygous sickle-cell disease by age, gender, and level of default, using a spline proportional-odds model.

Level of default (%)	Age (in years)			
	1	5	10	18
Men				
10	0.2	1.1	5.8	9.3
25	0.5	2.2	10.7	16.5
50	1.2	5.7	24.8	35.2
75	3.2	13.8	46.6	59.0
90	5.7	22.3	60.9	72.0
Women				
10	0.8	2.6	8.2	10.8
25	1.6	5.0	14.8	18.9
50	4.3	12.6	32.2	39
75	10.7	27.6	55.8	62.9
90	17.6	40.5	69.2	75.2

Figure 4.4

Hazard of dropout due to death in homozygous sickle-cell disease
using alternative parametric survival models

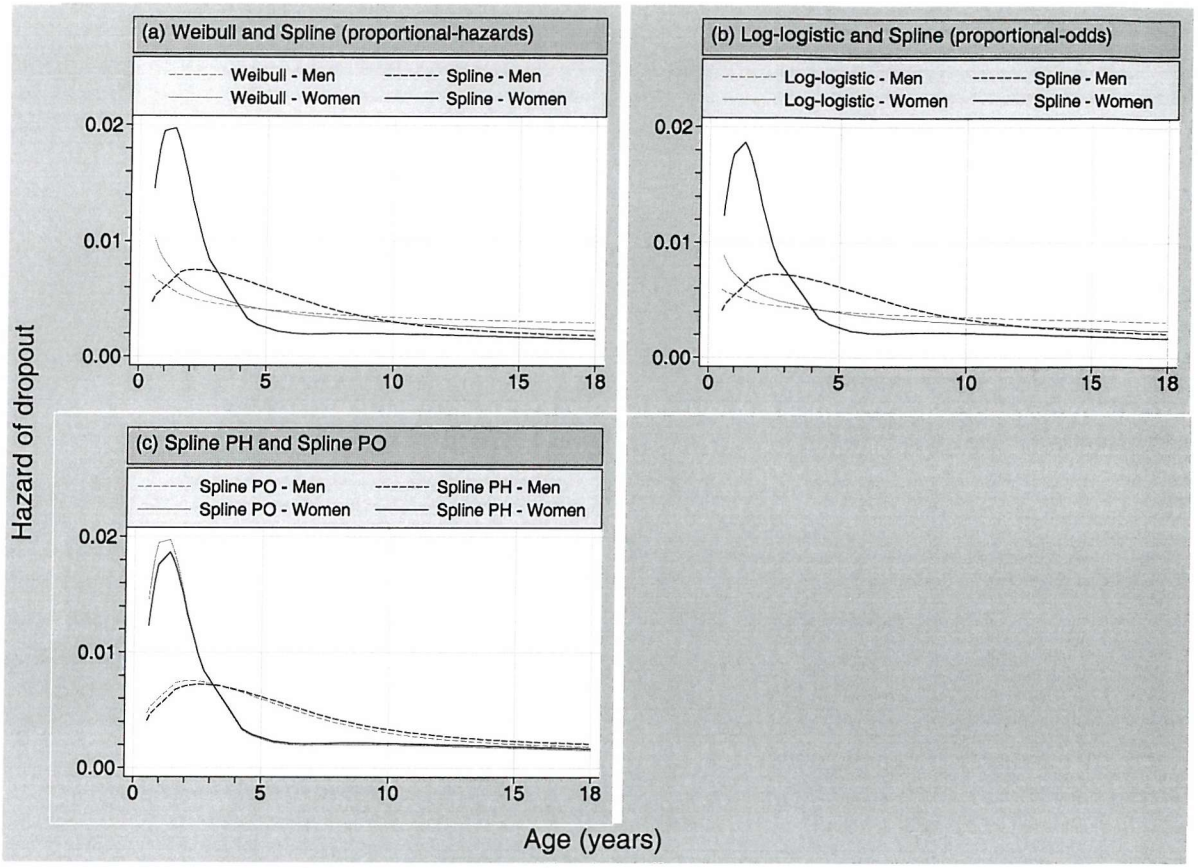
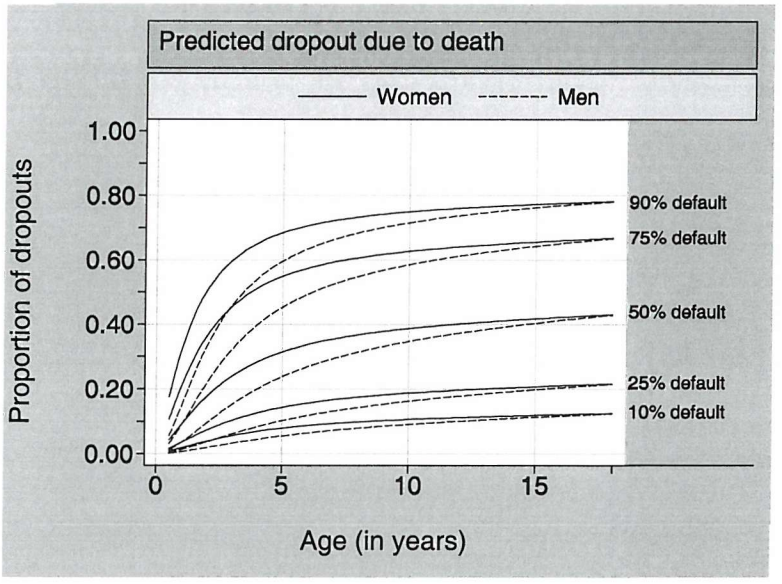


Figure 4.5

Predicted probability of death among JSSCD homozygous sickle-cell disease members
using a spline proportional-odds model



4.8.2 Describing intermittent default

Throughout this description of intermittent default, *all-default*, with default calculated using the *nearest* measurement regime is considered the primary result of interest. Default and completeness indices are presented in Table 4.11 for *all-default*, and for the four alternative default regimes (*annual-default*, *steady-state default*, *all-haematology default*, and *steady-state haematology default*, which are defined in Section 4.5.2) using the *nearest* measurement method. *All-default* is around 20% for JSSCD members and is roughly double for clinic members. Using the less stringent *annual-default* criterion, default is less than 3% in the JSSCD and is almost 40% among clinic members. *Annual-default* has been used regularly in descriptions of the JSSCD. *Steady-state default* is much higher (52% in the JSSCD, and 60% in the clinic). For many of these steady-state appointments patients do turn up to clinic, but have clinical symptoms that define the visit as 'sick' rather than 'steady-state'. JSSCD members default less than 5% from pre-defined haematology collection times and again, clinic default is substantially higher, at over 60%. This low JSSCD haematology default reflects the importance given to regular haematology collection in the cohort follow-up.

Table 4.11.

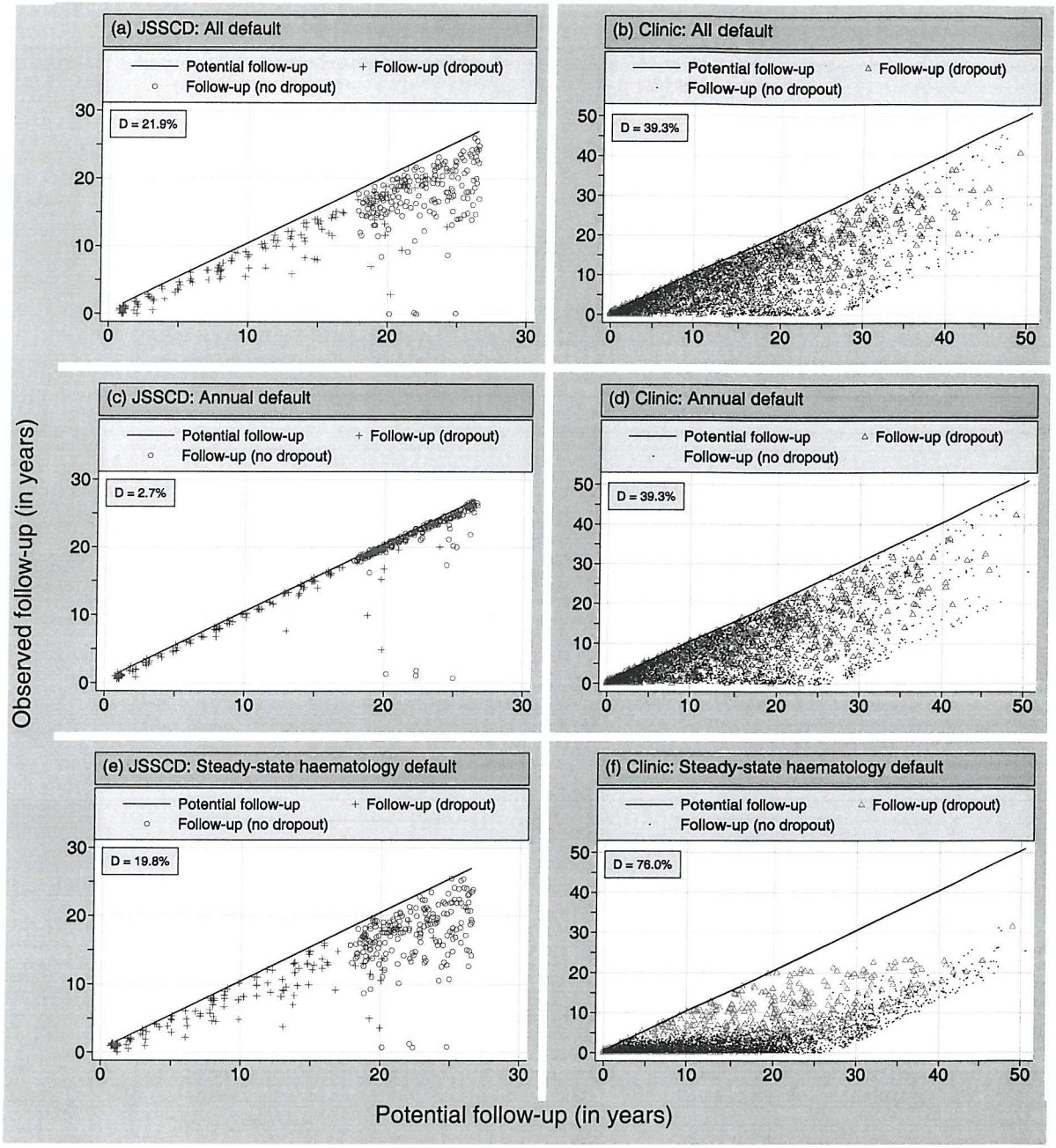
The default index and completeness index among JSSCD members and clinic members for the period from January 01 1973 to December 31, 1999, using nearest visit shift default.

	JSSCD	**Clinic**
Default index (D)		
All default	21.9 (20.1 - 24.0)	39.3 (38.4 - 40.2)
Annual default	2.7 (1.6 - 4.4)	39.3 (38.3 - 40.1)
Steady-state default	51.9 (50.1 - 53.8)	59.5 (58.7 - 60.3)
All haematology default	4.3 (2.9 - 6.0)	61.0 (60.2 - 61.9)
Steady-state haematology default	19.8 (17.8 - 22.0)	76.0 (75.4 - 76.8)
Completeness index (C)		
All default	78.1 (76.0 - 80.1)	60.7 (59.8 - 61.6)
Annual default	97.3 (95.6 - 98.4)	60.7 (59.8 - 61.6)
Steady-state default	48.1 (46.4 - 50.0)	40.5 (39.7 - 41.4)
All haematology default	95.7 (94.0 - 97.0)	39.0 (38.1 - 39.7)
Steady-state haematology default	80.2 (78.2 - 82.2)	24.0 (23.3 - 24.7)

Default from steady-state haematology is around 20% in the JSSCD and is 76% in the clinic, and this increase over general haematology collection again reflects the presentation of participants with clinical symptoms. Completeness graphs are presented for *all-default* (Figure 4.6 a and b), *annual default* (Figure 4.6 c and d), and *steady-state haematology default* (Figure 4.6 e and f). The solid diagonal line represents zero-default. The obvious visual contrast between the JSSCD and clinic populations are well summarised by our cross-sectional indices.

Figure 4.6

Completeness graphs for JSSCD members (a, c and e) and clinic members (b, d and f) for the period between January 01 1973 and December 31, 1999, using nearest default measurement.

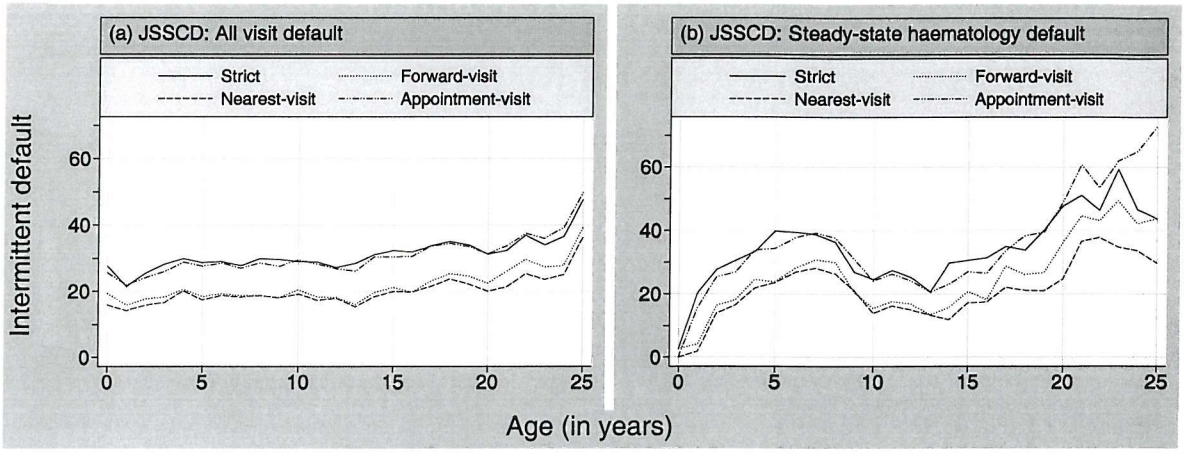


An anecdotal comparison of the five default measurement methods has been presented using a partial appointment and visit schedule for a single male patient (Table 4.5). These five default measurement methods are now compared using *all-default* and *steady-state haematology default* for all JSSCD homozygous sickle-cell disease patients (Figure 4.7). The measurement regimes produce similar default trends over time; only the levels of default vary. For *all-default*, *soft* results in average default of 31.7%, *forward* in default of 20.1%, *backward* in default of 31.7%, *nearest* in default of 21.9%, and *appointment* in default of 30.5%. For *steady-state haematology visit* default, the equivalent figures are: *soft* 29.3%, *forward* 16.2%. *backward* 29.3%, *nearest* 19.8%, and *appointment* 27.6%. The methods therefore stratify into two

groups based on level of default: soft, backward, and appointment (the high default methods), and forward, and nearest (the low default methods). Actual practice in quantifying default is likely to be a mixture of the *nearest* and *appointment* measurement regimes, and for the subsequent longitudinal comparisons of JSSCD and clinic default rates, we use these two measurement regimes as boundaries of the likely default rates.

Figure 4.7

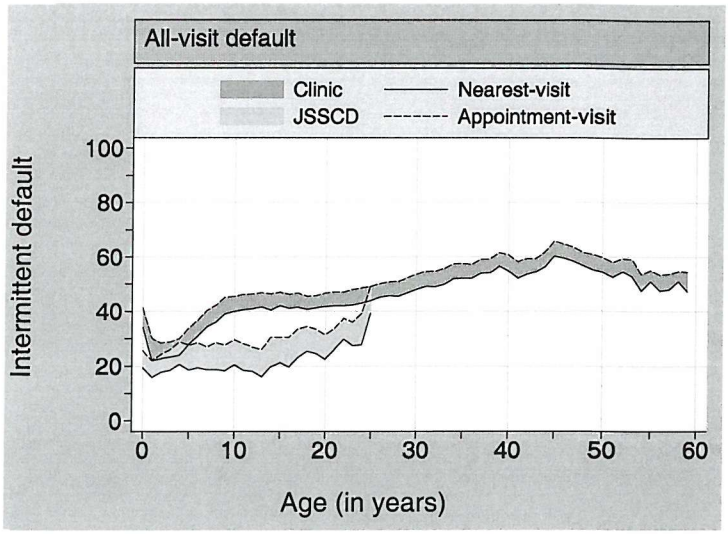
Comparing relative levels of default using five default regimes among JSSCD homozygous sickle-cell disease participants.



Default among JSSCD and among clinic members are compared graphically in Figure 4.8, Figure 4.9, and Figure 4.10, and are presented in 3-year age bands in Table 4.12. For *all-default*, JSSCD levels are initially around 20% (age 0-2 years: 17.6% to 23.9%), remain stable until puberty, and then climb gently to levels in excess of 30% (age 24-26 years: 33.5% to 44.5%). In contrast, the clinic levels climb rapidly to over 40% in childhood (age 9-11 years: 39.9% to 45.6%) and are over 50% by early adulthood (Figure 4.8). For *annual-default*, JSSCD levels are consistently below 5% until adulthood, when they climb to around 10%. Clinic levels are substantially higher, climbing from 30% in early childhood to over 50% in adulthood (Figure 4.9a). Patients can be unwell at a pre-specified appointment, and this is reflected in similar *steady-state* default levels in the JSSCD and the clinic, rising from around 50% in early childhood to over 80% in early adulthood (Figure 4.9b). The active follow-up in the JSSCD produces a marked age-related trend in this group, with default dropping in adolescence, which is a time with fewer clinical symptoms. For *haematology-default*, JSSCD levels are below 10% during childhood and adolescence and rise towards 30% in early adulthood. Clinic levels are once again substantially higher, reaching levels in excess of 70% after the few years of life (Figure 4.9c).

Figure 4.8

Comparing all-visit default among JSSCD and clinic homozygous sickle cell disease participants using *nearest* and *appointment* regimes.



Steady-state haematology default in the JSSCD follows the pattern of *steady-state default*, with increased default in childhood and again in early adulthood.

There are no important time-related default trends. *All-default* in the JSSCD is essentially constant at around 20% between 1973 and 1999. *All-default* in the clinic is raised during the period of JSSCD recruitment (1973 to 1981) and settles to around 50% thereafter (Figure 4.10). This is typical of all time-related default, and further graphs are not presented.

Figure 4.9

Comparing default between JSSCD and Clinic participants

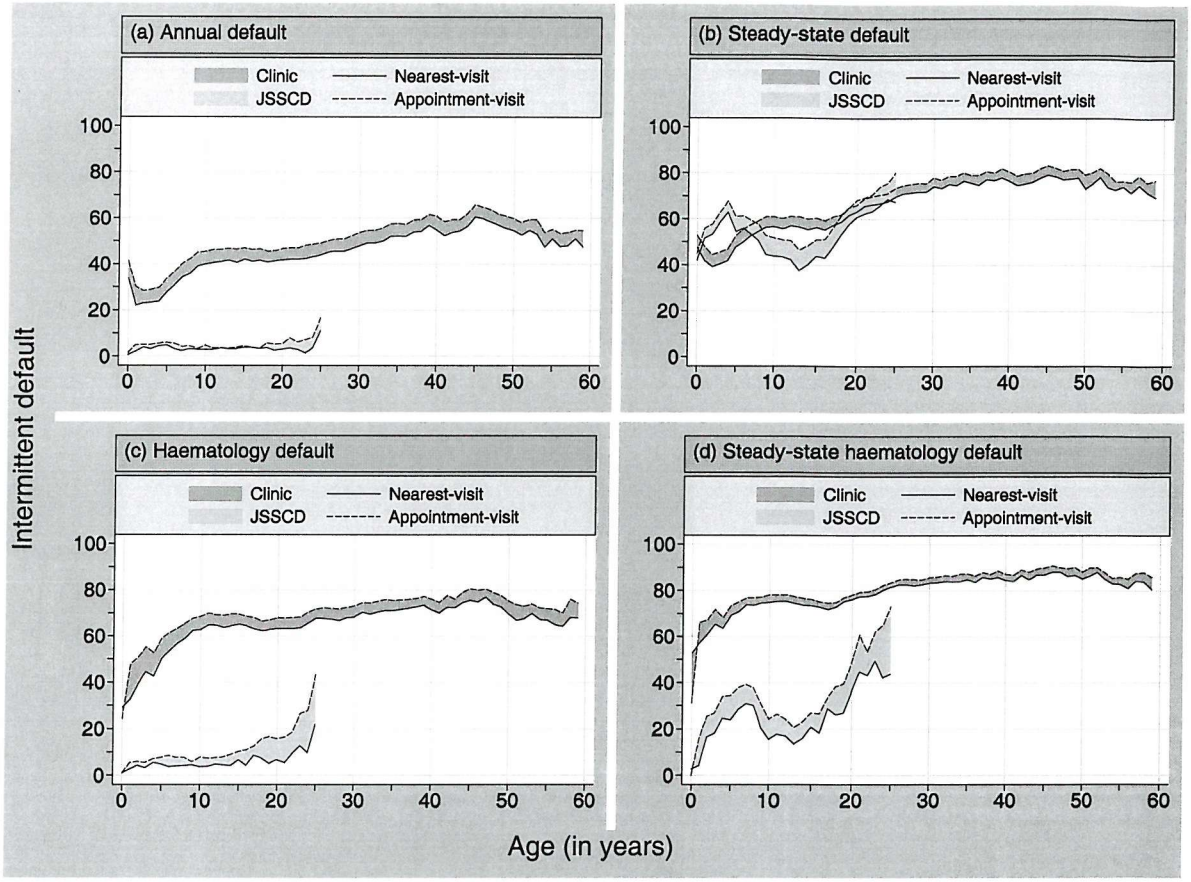


Figure 4.10

Comparing all-visit default among JSSCD and clinic homozygous sickle cell disease participants using *nearest* and *appointment* regimes.

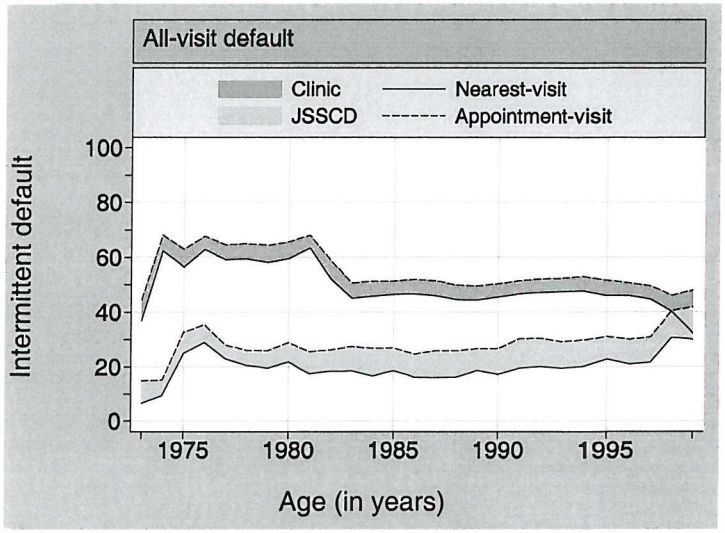


Table 4.12.

Age-related default among JSSCD members and clinic members using five default regimes (lower limit is nearest-shift measurement, upper limit is appointment-shift measurement).

Age	JSSCD					Clinic				
	all default	**annual default**	**steady-state default**	**haematology default**	**steady-state haematology default**	**all default**	**annual default**	**steady-state default**	**haematology default**	**steady-state haematology default**
0-2	(17.6 - 23.9)	(2.2 - 3.9)	(48.9 - 52.8)	(2.7 - 4.2)	(7.8 - 13.8)	(26.3 - 33.2)	(26.3 - 33.2)	(42.7 - 48.4)	(33.7 - 41.0)	(56.9 - 54.8)
3-5	(19.1 - 27.5)	(4.1 - 5.6)	(58.5 - 63.9)	(4.5 - 6.8)	(22.2 - 31.7)	(25.0 - 30.9)	(24.9 - 30.9)	(43.2 - 48.4)	(45.7 - 55.7)	(65.9 - 71.1)
6-8	(18.9 - 28.0)	(2.9 - 4.8)	(53.2 - 59.4)	(4.0 - 8.0)	(29.7 - 38.3)	(33.7 - 39.8)	(33.7 - 39.8)	(52.3 - 57.3)	(56.4 - 63.4)	(72.6 - 76.2)
9-11	(18.9 - 28.4)	(2.9 - 3.9)	(43.8 - 51.7)	(4.0 - 7.0)	(17.9 - 27.2)	(39.9 - 45.6)	(39.9 - 45.6)	(56.1 - 60.6)	(63.2 - 68.7)	(74.9 - 77.8)
12-14	(17.9 - 27.8)	(3.3 - 3.7)	(39.8 - 48.4)	(4.5 - 8.2)	(15.4 - 22.6)	(41.0 - 46.6)	(41.0 - 46.6)	(56.2 - 60.6)	(64.2 - 69.3)	(74.4 - 77.4)
15-17	(21.3 - 31.5)	(3.7 - 4.0)	(44.8 - 52.7)	(6.5 - 11.2)	(22.6 - 29.1)	(41.5 - 46.6)	(41.5 - 46.6)	(56.2 - 60.3)	(64.1 - 68.7)	(72.6 - 75.3)
18-20	(24.1 - 33.1)	(3.1 - 5.5)	(57.2 - 64.8)	(6.4 - 16.1)	(29.7 - 42.2)	(41.2 - 46.0)	(41.3 - 46.0)	(61.2 - 64.3)	(62.7 - 67.2)	(74.8 - 76.7)
21-23	(27.7 - 35.7)	(2.6 - 7.1)	(63.9 - 71.3)	(9.1 - 20.5)	(45.7 - 58.8)	(42.2 - 47.4)	(42.1 - 47.4)	(66.3 - 69.8)	(63.3 - 68.1)	(77.8 - 79.8)
24-26	(33.5 - 44.5)	(7.3 - 12.4)	(68.0 - 77.9)	(15.8 - 35.5)	(43.0 - 69.0)	(51.5 - 57.0)	(51.5 - 57.0)	(74.6 - 78.7)	(70.0 - 75.0)	(84.4 - 87.2)

4.8.3 Describing the non-response mechanism

(a) Haematology

The baseline model without conditioning on the non-response pattern assumes that non-response is MCAR. For haematology, this baseline model (model one - equation 4.2) is,

$$\mu\,(\text{Hb } or \text{ HbF})_{ij} = \gamma_0 + \gamma_1\,\text{sex}_i + \gamma_2\,\text{spline}_i + \gamma_3\,\text{age}_{ij} + \gamma_4\,\log(\text{age}_{ij}) \qquad (4.2)$$

Where *age* is the *j*th year of age for the *i*th SS patient (j=1,2,...,17), *spline*=1 if age is less than 2 years, and $sex_i = 1$ if the *i*th SS patient is female and $sex_i = 0$ otherwise. The marginal results confirm the well-known and rapid early-life decrease in total and fetal haemoglobin, with total haemoglobin levels decreasing faster and levelling off earlier than percentage fetal haemoglobin levels. Next, a pattern-mixture model (model two - equation 4.3) provides conditional haematology levels given the three non-response patterns without interaction between baseline covariates and the non-response parameters,

$$\begin{aligned}\mu\,(\text{Hb } or \text{ HbF})_{ij} = (\text{baseline model})_{ij} &+ \beta_1\,\text{default}_i + \beta_2\,\text{death}_i + \beta_3\,\text{migrate}_i + \\ &\beta_4\,\text{default}_i \times \text{death}_i + \beta_5\,\text{default}_i \times \text{migrate}_i\end{aligned} \qquad (4.3)$$

where $death_i = 1$ if the *i*th SS patient died at any time, $migrate_i = 1$ if the *i*th SS patient migrated at any time, and $default_i = 1$ if the *i*th SS patient defaulted temporarily at any time. All tests of MCAR are presented in Table 4.13. Using Hb, model estimates indicated that levels were increased among defaulters and among dropouts due to death. Levels among migrators were equivalent to non-migrators. For HbF, defaulters, deaths, and migrators were equivalent to non-defaulters, survivors, and non-migrators respectively (Table 4.13). Overall, the MCAR assumption is strongly rejected for Hb, and is not rejected for HbF ($H_0 : \beta_1 = \cdots = \beta_5 = 0$: Hb, $\chi^2 = 16.39$, $P = 0.006$ HbF, $\chi^2 = 3.72$, $P = 0.29$).

Table 4.13.

Tests of the MCAR assumption for total haemoglobin, fetal haemoglobin, and pain-crisis using three different methods of non-response (default, and dropout due to either death or migration).

Non-response mechanism	Model Two			Model Three		
	Null hypothesis	χ^2	P-value	Null hypothesis	χ^2	P-value
Hb						
Default	$H_0 : \beta_1 = \beta_4 = \beta_5 = 0$	12.54	0.006	$H_0 : \beta_1 = \beta_4 = \beta_5 = \beta_6 = \beta_7 = \beta_8 = 0$	62.65	0.001
Death	$H_0 : \beta_2 = \beta_4 = 0$	8.70	0.013	$H_0 : \beta_2 = \beta_4 = \beta_9 = \beta_{10} = \beta_{11} = 0$	33.03	0.001
Migration	$H_0 : \beta_3 = \beta_5 = 0$	0.49	0.78	$H_0 : \beta_3 = \beta_5 = \beta_{12} = \beta_{13} = \beta_{14} = 0$	2.74	0.60
HbF						
Default	$H_0 : \beta_1 = \beta_4 = \beta_5 = 0$	1.44	0.23	$H_0 : \beta_1 = \beta_4 = \beta_5 = \beta_6 = \beta_7 = \beta_8 = 0$	16.37	0.003
Death	$H_0 : \beta_2 = \beta_4 = 0$	1.67	0.20	$H_0 : \beta_2 = \beta_4 = \beta_9 = \beta_{10} = \beta_{11} = 0$	14.25	0.007
Migration	$H_0 : \beta_3 = \beta_5 = 0$	0.56	0.46	$H_0 : \beta_3 = \beta_5 = \beta_{12} = \beta_{13} = \beta_{14} = 0$	5.21	0.27
Pain crisis						
Default	$H_0 : \beta_1 = \beta_4 = \beta_5 = 0$	1.50	0.68	$H_0 : \beta_1 = \beta_4 = \beta_5 = \beta_6 = \beta_7 = \beta_8 = 0$	10.28	0.17
Death	$H_0 : \beta_2 = \beta_4 = 0$	13.24	0.013	$H_0 : \beta_2 = \beta_4 = \beta_9 = \beta_{10} = \beta_{11} = 0$	175.6	0.001
Migration	$H_0 : \beta_3 = \beta_5 = 0$	5.54	0.063	$H_0 : \beta_3 = \beta_5 = \beta_{12} = \beta_{13} = \beta_{14} = 0$	21.76	0.013

A more complicated pattern-mixture model includes all terms from models one and two, and additionally includes two-way interactions between non-response indicators and baseline covariates (model three - equation 4.4),

$$\begin{aligned}\mu\,(\text{Hb } or \text{ HbF})_{ij} = {} & (\text{baseline model})_{ij} + (\text{model two})_{ij} + \\ & \beta_6\ \text{default}_i \times \log(\text{age}_{ij}) + \beta_7\ \text{default}_i \times \text{sex}_i + \beta_8\ \text{default}_i \times \text{spline}_i + \\ & \beta_9\ \text{death}_i \times \log(\text{age}_{ij}) + \beta_{10}\ \text{death}_i \times \text{sex}_i + \beta_{11}\ \text{death}_i \times \text{spline}_i + \\ & \beta_{12}\ \text{migrate}_i \times \log(\text{age}_{ij}) + \beta_{13}\ \text{migrate}_i \times \text{sex}_i + \beta_{14}\ \text{migrate}_i \times \text{spline}_i\end{aligned} \tag{4.4}$$

Model three allows a more realistic situation with the three non-response mechanisms varying independently with age and gender. Using Hb, model estimates indicated that levels remained increased among defaulters. Levels among deaths were initially higher and then lower than survivors. Levels among migrators remained equivalent to non-migrators. Using HbF, defaulters had higher levels than non-defaulters, dropouts due to death had lower levels, and levels among migrators remained equivalent. Overall, the MCAR assumption is strongly rejected for both Hb and HbF ($H_0 : \beta_1 = \cdots = \beta_{14} = 0$: Hb, $\chi^2 = 91.10$, $P < 0.001$ HbF, $\chi^2 = 37.10$, $P < 0.001$).

(b) Pain crisis rate

For the pain crisis clinical outcome the baseline model assuming MCAR is,

$$\log(\text{pain rate}) = \gamma_0 + \gamma_1\ \text{sex} + \gamma_2\ \text{age} + \gamma_3\ \text{age}^2 \tag{4.5}$$

The pain crisis rate is initially low, climbs to a plateau that persists between 5 and 13 years, and then shows signs of further increase towards early adulthood. As with the models for Hb and HbF, models two and three for pain add non-response indicators, and 2-way interactions of these indicators with baseline covariates respectively, so for model three (equation 4.6),

$$\begin{aligned}\log(\text{pain rate}) = {} & \gamma_0 + \gamma_1\ \text{sex} + \gamma_2\ \text{age} + \gamma_3\ \text{age}^2 + \beta_1\ \text{default}_i + \beta_2\ \text{death}_i + \beta_3\ \text{migrate}_i + \\ & \beta_4\ \text{default}_i \times \text{death}_i + \beta_5\ \text{default}_i \times \text{migrate}_i + \\ & \beta_6\ \text{default}_i \times \text{age}^2_{ij} + \beta_7\ \text{default}_i \times \text{sex}_i + \\ & \beta_8\ \text{death}_i \times \text{age}^2_{ij} + \beta_9\ \text{death}_i \times \text{sex}_i + \\ & \beta_{10}\ \text{migrate}_i \times \text{age}^2_{ij} + \beta_{11}\ \text{migrate}_i \times \text{sex}_i\end{aligned} \tag{4.6}$$

Using either model two or three, rates of the pain-crisis were equivalent among defaulters and non-defaulters. Rates were increased in deaths and migrators (Table 4.13). Overall, the MCAR assumption is strongly rejected for the pain-crisis using either model two or model three (Model two, $H_0 : \beta_1 = \cdots = \beta_5 = 0$, $\chi^2 = 16.39$, $P = 0.006$ Model three, $H_0 : \beta_1 = \cdots = \beta_{11} = 0$, $\chi^2 = 193.11$, $P < 0.001$).

Table 4.14.

Marginal estimates of two haematological indices and a single clinical outcome under four different assumptions about non-response.

	1 year		2-5 yrs		6-9 yrs		10-13 yrs		14-17 yrs	
	Rate	**S.E.**	**Rate**	**S.E.**	**Rate**	**S.E.**	**Rate**	**S.E.**	**Rate**	**S.E.**
HbF. Model 1										
Ignore non-response	20.36	0.031	11.64	0.093	7.10	0.028	5.76	0.023	5.13	0.022
HbF. Model 2										
Default	21.44	0.117	12.87	0.338	8.23	0.110	6.86	0.093	6.29	0.082
Death	19.41	0.067	10.85	0.277	6.18	0.102	4.76	0.103	4.17	0.127
Migration	20.01	0.103	11.30	0.235	6.82	0.082	5.51	0.096	4.81	0.204
HbF. Model 3										
Default	17.87	0.182	13.19	0.423	8.23	0.091	6.91	0.058	6.23	0.044
Death	17.47	0.120	11.29	0.277	6.64	0.138	5.24	0.153	4.65	0.224
Migration	20.77	0.273	11.27	0.278	6.72	0.172	5.36	0.218	4.17	0.435
Hb. Model 1										
Ignores non-response	11.35	0.011	8.10	0.007	7.89	0.007	7.76	0.008	7.64	0.008
Hb. Model 2										
Default	11.73	0.083	8.43	0.064	8.35	0.060	8.15	0.061	8.10	0.040
Death	11.59	0.030	8.30	0.030	8.10	0.040	7.92	0.061	7.92	0.046
Migration	11.28	0.052	8.01	0.022	7.86	0.030	7.75	0.044	7.66	0.124
Hb. Model 3										
Default	13.03	0.031	8.26	0.061	8.11	0.048	7.95	0.060	7.92	0.009
Death	11.95	0.030	8.16	0.040	7.76	0.042	7.50	0.068	7.48	0.058
Migration	10.96	0.090	8.10	0.029	7.91	0.031	7.78	0.043	7.58	0.092
Pain Crisis. Model 1										
Ignore non-response	0.06	0.000	0.30	0.004	0.50	0.001	0.49	0.001	0.58	0.003
Pain Crisis. Model 2										
Default	0.05	0.003	0.28	0.023	0.47	0.019	0.47	0.017	0.55	0.016
Death	0.08	0.002	0.43	0.019	0.77	0.007	0.77	0.008	0.86	0.031
Migration	0.07	0.002	0.35	0.014	0.60	0.009	0.58	0.013	0.60	0.041
Pain Crisis. Model 3										
Default	0.01	0.001	0.20	0.025	0.38	0.015	0.39	0.015	0.62	0.032
Death	0.01	0.001	0.37	0.026	0.40	0.025	0.35	0.026	2.05	0.771
Migration	0.03	0.001	0.43	0.019	0.57	0.009	0.42	0.008	0.58	0.046

4.9 Discussion

Non-response is a pervasive feature in much observational and experimental medical research. The general advice to keep non-response to an absolute minimum is well known, with longitudinal studies (such as cohort and randomised trial designs) incorporating methods for retaining and tracking patients into their study protocols.

Descriptions of non-response remain sparse; most studies offer little more than the number of study members dropping out before a study ends. Those descriptions that do exist come from cohort and randomised controlled trial study designs, which are inherently longitudinal. The issue is also important in cross-sectional studies, where many potential study members dropout (they may die or migrate for example) before a cross-sectional study is initiated. This aspect is rarely considered.

It is now understood that non-response can be ignored if it is unrelated to the outcomes being studied. Analyses that assume complete information (which include most of the basic methodology available in off-the-shelf statistical software) will then be appropriate and will not bias results. If the reasons for non-response are related to outcomes then 'complete-case' analyses will lead to biased conclusions, although the extent of the bias will depend on these reasons and on other factors such as the level of non-response, and the chosen analysis technique, and will vary from study to study. Models to cope with such non-ignorable non-response are a recent and ongoing development in the statistical literature. Modelling solutions have been grouped into two models types: selection and pattern-mixture models, and sensitivity analyses are needed to better understand the consequences of choosing one technique over another. More generally, an increased awareness in the research community of the potential biases stemming from non-response has been called for, along with sensitivity analyses to assess the effect of non-response on inferences about target parameters of interest (34).

The distinction is made here between dropout (which is due to due deaths and migration in our study), which is an integral feature of the process under study, and temporary default, which is generally avoidable. Both aspects of non-response can bias research conclusions if ignored during analyses. It is important to understand the non-response process; to successfully adjust for non-response we need an understanding of why dropout or default occurred.

There are a lot of deaths in the JSSCD, and this is an inevitable consequence of studying a life-threatening medical condition for a long period of time. Migration is also relatively high; migration is primarily to North America and is a Caribbean-wide phenomenon. Various measures are available for us to gauge the level of default in the JSSCD. Cumulative levels range from 3% (annual default) to 52% (steady-state default) and the choice of an appropriate measure depends entirely on the research question and study design. Whilst an annual default of 3% is impressive for a 27-year cohort study, when studying disease aetiology using

steady-state haematological measurements for example, default from providing steady-state haematology is a more appropriate measure (which is 20%). The method of quantifying default is another variable feature of measurement, and the current presentation opts for a 'window' of percentage default based on two pragmatic methods: nearest default and appointment default. Clinic practice is likely to be a combination of these two methods.

We show that default is a strong predictor of subsequent death. Reasons for this are speculative. Defaulters may include patients with an increased underlying level of disease 'severity'. Alternatively, a poorer mortality experience may be directly related to defaulting from the prophylactic care offered by a comprehensive sickle-cell disease clinic.

The mechanism underlying non-response will vary from study to study. Using three important contributors to sickle-cell disease epidemiology (Hb, Hbf, and the painful crisis), we have shown the non-response process to be strongly non-ignorable. Levels of total and fetal haemoglobin are both affected by default and death. Dropout due to emigration has no effect. Rates of the pain crisis are affected by deaths and migrators, and not by default.

4.10 Reference List

(1) Rubin DB. Inference and missing data. Biometrika 1976; 63(3):581-592.

(2) Little RJ, Rubin DB. Statistical analysis with missing data. New York: Wiley, 1987.

(3) Diggle P, Kenward MG. Informative drop-out in longitudinal data-analysis. Applied Statistics-Journal Of The Royal Statistical Society Series C 1994; 43:49-93.

(4) Lindsey JK. Models for repeated measurements. Oxford: OUP, 1999.

(5) Criqui MH. Response bias and risk ratios in epidemiologic studies. Am J Epidemiol 1979; 109:394-399.

(6) Heilbrun LK, Nomura A, Stemmermann GN. The effects of non-response in a prospective study of cancer: 15-year follow-up. Int J Epidemiol 1991; 20:328-338.

(7) Britton A, Murray D, Bulstrode C, McPherson K, Denham R. Loss to follow-up: does it matter? Lancet 1995; 345:1511-1512.

(8) Lesaffre E, Molenberghs G, Dewulf L. Effect of dropout in a longitudinal study: an application of a repeated ordinal model. Stat Med 1996; 15:1123-1141.

(9) Zock JP, Heederik D, Doekes G. Evaluation of chronic respiratory effects in the potato processing industry: indications of a healthy worker effect? Occup Environ Med 1998; 55:823-827.

(10) Elders LAM, Burdorf A. Interrelations of risk factors and low back pain in scaffolders. Occup Environ Med 2001; 58:597-603.

(11) Sterling TD, Weinkam LL, Weinkam JL. The sick person effect. J Clin Epidemiol 1990; 43(2):141-151.

(12) Hunt JR, White E. Retaining and tracking cohort study members. Epidemiologic Reviews 1998; 20(1):57-70.

(13) Hahn LP, Sprafka JM, Burke GL, Jacobs DRJ. Comparison of two procedures for tracing participants in an epidemiologic cohort study. Epidemiology 1990; 1(2):157-160.

(14) Marmor JK, Oliveria SA, Donahue RP, Garrahie EJ, White MJ, Moore LL et al. Factors encouraging cohort maintenance in a longitudinal study. J Clin Epidemiol 1991; 44(6):531-535.

(15) Hellard ME, Sinclair MI, Forbes AB, Fairley CK. Methods used to maintain a high level of participant involvement in a clinical trial. J Epidemiol Community Health 2001; 55:348-351.

(16) Russell C, Palmer JR, Adams-Campbell LL, Rosenberg L. Follow-up of a large cohort of black women. Am J Epidemiol 2001; 154(9):845-853.

(17) Cottler LB, Compton WM, Ben-Abdullah A, Horne M, Claverie D. Achieving a 96.6 percent follow-up rate in a longitudinal study of drug abusers. Drug Alcohol Depend 1996; 41(3):209-217.

(18) Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. Lancet 2001; 357:1191-1194.

(19) Clarke TG, Altman DG, De Stavola BL. Quantification of the completeness of follow-up. Lancet 2002; 359:1309-1310.

(20) Little RJA. A test for missing completely at random for multivariate data with missing values. JASA 1988; 83:1198-1202.

(21) Park T, Davis CS. A test of the missing data mechanism for repeated categorical data. Biometrics 1993; 49:631-638.

(22) Liang KY, Zeger SL. Longitudinal data analysis using generalized linear models. Biometrika 1986; 73:13-22.

(23) Park T, Lee S-Y. A test for missing completely at random for longitudinal data with missing observations. Stat Med 1997; 16:1859-1871.

(24) Chen HY, Little RJ. A test of missing completely at random for generalised estimating equations with missing data. Biometrika 2001; 86:1-13.

(25) Cook NR. An imputation method for non-ignorable missing data in studies of blood pressure. Stat Med 1997; 16(23):2713-2728.

(26) Lipsitz SR, Ibrahim JG, Chen MH, Peterson H. Non-ignorable missing covariates in generalized linear models. Stat Med 1999; 18(17-18):2435-2448.

(27) Gao S, Hui SL. Estimating the incidence of dementia from two-phase sampling with non-ignorable missing data. Stat Med 2000; 19(11-12):1545-1554.

(28) Royston P. Flexible alternatives to the Cox model. The Stata Journal 2001; 1(1):1-28.

(29) Powars DR, Chan L, Schroeder WA. The influence of fetal hemoglobin on the clinical expression of sickle cell anemia. Ann N Y Acad Sci 1989; 565:262-78:262-278.

(30) Bordin JO, Kerbauy J, Lourenco DM, Sesso R. Level of fetal hemoglobin as an indicator of clinical complications in sickle cell anemia. Braz J Med Biol Res 1989; 22(11):1347-1353.

(31) Charache S, Terrin ML, Moore RD, Dover GJ, Barton FB, Eckert SV et al. Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. Investigators of the Multicenter Study of Hydroxyurea in Sickle Cell Anemia [see comments]. N Engl J Med 1995; 332(20):1317-1322.

(32) Royston P, Altman DG. Regression using fractional polynomials of continuous covariates - parsimonious parametric modeling. Applied Statistics-Journal Of The Royal Statistical Society Series C 1994; 43:429-467.

(33) McElroy PD, Lal AA, Hawley WA, Bloland PB, Ter Kuile FO, Oloo AJ et al. Analysis of repeated hemoglobin measures in full-term, normal birth weight Kenyan children between birth and four years of age III. The Asembo Bay cohort project. Am J Trop Med Hyg 1999; 61(6):932-940.

(34) Touloumi G, Babiker AG, Pocock SJ, Darbyshire JH. Impact of missing data due to dropouts on estimators for rates of change in longitudinal studies: a simulation study. Stat Med 2001; 20:3715-3728.

Book Two

Haematology

The haematological indices

Since its initial description in the US, sickle-cell disease has been recognised as a disorder of red blood cells (1). Diggs and Ching first linked polymerisation, vasoocclusion, and the clinical manifestations of the disease, which emphasised the role of irreversibly sickled cells (ISCs) (2). Although these ISCs are the trademark image of the disease, we now know that more normal-looking, reversibly sickled-cells are critical in initiating and maintaining vasoocclusion. This knowledge has lead researchers to consider a range of blood-cell measurements as risk factor markers for clinical events. We consider the following ten measurements in our investigations of the JSSCD.

Total haemoglobin (Hb)

The amount of haemoglobin in a volume of blood (measured in g/dl). The haemoglobin concentration reflects the balance between haemolysis and erythropoiesis, and is often considered the primary haematological measure of interest. People with SS disease have chronically lowered levels of *Hb*. High and low values, relative to a persons normal range (which is anecdotally known as their steady state range) appear to be risk factors for a range of clinical events. High values may promote avascular necrosis, painful crises, and proliferative sickle retinopathy. Low values are indicative of acute events such as acute splenic sequestration, and the aplastic crisis, and may impair exercise tolerance and cause congestive heart failure in older people. Normal ranges are between 13 and 18 g/dl in men and between 12 and 16 g/dl in women.

Red blood cell count (rbc)

The number of red blood cells in a volume of blood (measured in 10^{12} per litre). The anaemia of SS disease is also seen as a reduction in circulating red cells, and so the *rbc* changes follow those in *Hb*. Normal ranges are generally between 4.2 and 5.9×10^{12} cells per litre in men and women.

Packed cell volume (pcv)

Otherwise known as the haematocrit, the *pcv* is the ratio of the volume of red cells to the volume of whole blood (measured as a percentage). Usually, *pcv* changes follow those in *Hb*. The *pcv* values are less reliable because of the abnormal properties of sickled-cells; even when oxygenated, sickled-cells are stiff and do not pack normally during centrifugation (3). Normal ranges are generally between 45 and 52% for men and between 37 and 48% for women.

Mean corpuscular volume (mcv)

This calculated red blood cell index is the average volume of a red cell, obtained by dividing the haematocrit by the red blood cell count. It is measured in femtolitres (fl). Children with sickle-cell disease generally macrocytic (increased *mcv*) (4). Normal ranges are generally between 86 and 98 femtoliters in men and women.

Mean corpuscular haemoglobin (mch)

This calculated red blood cell index is the average amount of haemoglobin in the average red cell, obtained by dividing total haemoglobin by the red blood cell count. It is measured in picograms (pg).Children with sickle-cell disease are generally hypochromic (decreased *mch*) (4). Normal ranges are generally between 27 and 32 picograms in men and women.

Mean corpuscular haemoglobin concentration (mchc)

This calculated red blood cell index is the average concentration of haemoglobin in a given volume of red cells, obtained by dividing total haemoglobin by the haematocrit. It is measured as a percentage. Children with sickle-cell disease are generally hypochromic (decreased *mchc*) (4). Normal ranges are generally between 32 and 36% in men and women.

Nucleated blood cells (nbc)

The number of nucleated blood cells in a volume of blood (measured in 10^9 per litre), which approximates the number of white blood cells (or leukocytes). Leukocytes are the body's primary means of fighting infection. There are five types of white cells, each with different functions: neutrophils, lymphocytes, monocytes, eosinophils, and basophils, and a differential count (not available) is required to discriminate between these forms. Our simple count will identify leukocytosis (a high leukocyte count) or leukocytopenia (a low leukocyte count). Normal ranges are generally between 4.3 and 10.8×10^9 cells per litre.

Reticulocyte count (retics)

The number of immature red blood cells in a volume of blood (measured as a percentage). A reticulocyte count provides information about the rate at which the bone marrow is producing red cells. Reticulocytes continue to synthesize haemoglobin for a day after release into the bloodstream. A person under hematopoietic stress may contain stress reticulocytes, released prematurely from the bone marrow. Children with sickle-cell disease generally have an increased reticulocyte count (reticulocytosis) (4). Normal ranges are generally between 0.5 and 2.5%.

Platelet count (plat)

The number of platelets (or thrombocytes) in a volume of blood (measured in 10^3 per cubic mm). Platelets, the smallest of the cellular elements of blood, are involved in blood clotting. Because they can clump together, the automated counting method is subject to a certain level of error and may not be accurate enough for low platelet counts. Children with sickle-cell disease generally have an increased platelet count (thrombocytosis) (4). Normal ranges are generally between 150 and $400\times10^3/\text{mm}^3$).

Fetal haemoglobin (HbF)

The amount of fetal haemoglobin (haemoglobin F) in a volume of blood (measured as a percentage). *HbF* is the major haemoglobin component in the bloodstream of the fetus. At

birth, the newborn's blood is comprised of between 60% and 90% fetal haemoglobin. This fetal haemoglobin then rapidly decreases to 2% or less after the second to fourth years. By adulthood, only traces (0.5% or less) are found in the bloodstream. Elevated levels persist to varying degrees in people with sickle-cell disease. Red cells with high levels of *HbF* (F-cells) appear to have increased red-cell life-span, and improved morphology.

Reference List

(1) Herrick JB. Peculiar elongated and sickle-shaped red blood corpuscles in a case of severe anemia. Arch Intern Med 1910; 6:517-521.

(2) Diggs LW, Ching RE. Pathology of sickle cell anemia. Southern Med J 1934; 27:839-845.

(3) Kaul DK, Fabry ME, Windisch P, Baez S, Nagel RL. Erythrocytes in sickle cell anemia are heterogeneous in their rheological and hemodynamic characteristics. J Clin Invest 1983; 72(1):22-31.

(4) Serjeant GR, Grandison Y, Lowrie Y, Mason K, Phillips J, Serjeant BE et al. The development of haematological changes in homozygous sickle cell disease: a cohort study from birth to 6 years. Br J Haematol 1981; 48(4):533-543.

Chapter 5

Childhood haematology

Background

The JSSCD has reported previously on selected haematological indices between birth and six years of age. We now extend these descriptions through childhood and adolescence to 18 years of age.

Methods

We graphed the observed mean profile of ten haematological indices for SS and AA genotype participants of the JSSCD. We modelled these profiles using longitudinal models to incorporate correlation within individual participants, fractional polynomials and cubic splines to incorporate non-linear changes in haematology with age, and pattern-mixture models to assess the effect of participant non-response.

Findings

We present observed and predicted profiles graphically for each haematological index. We noted important gender differences for total haemoglobin (hb), haematocrit (pcv), and mean cell volume (mcv): hb was 0.3g/dl lower in boys, pcv was 0.9% lower and mcv was 1.6fl lower. Among surviving defaulters hb levels were 0.4g/dl higher, and pcv levels were 1.3% higher than surviving participants that had not defaulted. Among defaulters that had subsequently died, reticulocyte count was 4.5% higher.

Interpretation

These childhood and adolescent profiles represent the first longitudinal description of haematological change to adulthood. Further work will translate these descriptions to clinically useful reference intervals. A rapid decline in Hb associated with reticulocytosis indicated haemolysis at an early age in SS disease, and prior to the onset of clinical symptoms in analysable numbers, which suggests an avenue for exploring early-life indicators of later health-status. Our results also suggest that clinic default could serve as an early-warning system for adverse clinical outcome.

5.1 Introduction

Clinical complications of homozygous sickle-cell disease rarely occur before six-months of age (1;2), and the only report using early-life predictors to classify individuals into one of two disease states (described as 'severe' or 'mild' clinical-outcome) required follow-up until two years of age (3). Haematological abnormalities are apparent in the sickle-cell patient as early as the neonatal period (4) and may provide the earliest indication of the clinical-course that is to follow.

As a haematological disease, summaries of blood cell structure and activity have been a natural focus for research. Much early work developed the pathophysiology of the disease, and described the range of clinical complications as case-studies or as small cross-sectional epidemiological investigations (e.g. 5-9). More recently, haematological indices have been regularly included as potential risk factors for clinical complications (10-16) and see Chapters Seven and Eight. Most of these observational risk-factor studies are cross-sectional, and are possibly confounded by the profound effect of age on all aspects of the disease. Cross-sectional assessment of haematology is further complicated by factors such as the influence of acute or chronic complications, the biases inherent in clinic-based populations (see Chapters Three and Four), and the difficulties of comparing results from different laboratories.

Organised longitudinal follow-up of sickle-cell disease patients began in the 1970s and provided the first descriptions of haematological development with age. Early-life haematological change has been described in two disease cohorts: one from birth (17) and another from a maximum of six-months of age (18). The Jamaican birth cohort (The Jamaican Study of Sickle-Cell Disease or JSSCD) also recruited AA genotype controls, and so provided the only comparison of haematological development between people with and without the disease. The JSSCD has reported previously on levels of selected haematological indices between birth and six-years of age in SS patients relative to normal controls (4). They reported significantly lower levels of total haemoglobin from two weeks of age, and of red cell counts from one month, and significantly higher levels of mean cell haemoglobin concentration from 4 months, and mean cell volume from 8 months. Other major genotypes of sickle-cell disease (SC disease and the beta-thalassaemias) also show marked haematological differences from normal AA controls (19) and between themselves (20).

In this chapter, we provide the first longitudinal description of haematology from birth through childhood and adolescence. We develop longitudinal models for haematology that account for two features for the first time: the non-linear association of all haematological indices with age, and the possible biases introduced by cohort members that temporarily default or permanently dropout from haematology measurements.

Methods are described in section 5.2, descriptive and modelled results are presented in section 5.3, and these results are discussed in section 5.4.

5.2 Methods

We describe haematological parameters for homozygous sickle-cell (SS) disease and for normal genotype (AA) controls that participated in the JSSCD between birth and 18 years of age. We are interested in the average profile of each haematological index in each genotype group, and in haematological differences between defaulters, deaths, and those participants that remain in the study.

We describe ten parameters: total haemoglobin (Hb), red blood cell count (rbc), haematocrit or packed cell volume (pcv), mean cell volume (mcv), mean cell haemoglobin (mch), mean cell haemoglobin concentration (mchc), nucleated blood cell count (nbc), reticulocyte count (retics), platelet count (plate), and fetal haemoglobin (HbF) We have considered the clinical importance of each parameter in our introduction to Book Two. We have presented the measurement technique and measurement frequency for each parameter in Chapter Two, section 2.2.3(d).

We graph the observed mean profile for each parameter between birth and 18 years of age for SS and AA participants. We describe the variation about these group means using vertical bars signifying +/- one standard deviation. In the following sections we describe several important features of the data and the analysis techniques we have used to account for these features. We then describe our modelling strategy.

5.2.1 There are many measurements on each participant

With many measurements on each participant, we should expect correlation between different measurements on the same individual. To account for this feature, we developed our regression models using generalised estimating equations (or GEEs). These models (also known as marginal or population-averaged longitudinal models) are an extension of generalised linear models (21) and are used to estimate relationships in repeated measures data when within-subject correlation exists but is of secondary interest. The technique accounts for the correlation within an individual when generating regression coefficients and standard errors. Becaused predictions at each time point (or margin) are unconnected, the technique creates a predicted profile that may not summarise any individual (22). This important limitation should discourage the use of GEE modelling in causal experimental settings (23). However, in descriptive observational studies such as this the technique remains appropriate as the emphasis is on providing a group average and not a profile for a typical participant.

5.2.2 There are non-linear changes in haematology with age

The non-linear association of haematology with age (especially in the early years of life) is well known (24). Among sickle-cell disease risk factor studies that consider haematology, several methods to cope with this non-linearity are dominant. Early-life haematology is commonly excluded to simplify subsequent analyses (10). This loss of information reduces efficiency, and more importantly, the functional form of the resulting regression is almost

certainly incorrect. A linear relationship is often assumed, and this misspecification may lead to incorrectly included or excluded terms during subsequent model building. Grouping haematology into age bands is also popular (e.g. 25;26). Incorporating these 'cutpoints' into a model is an unrealistic way of modelling a smooth relationship, and introduces problems of defining arbitrary limits, overparameterisation, and loss of efficiency (27). In our modelling we keep each parameter continuous and model the non-linear association with age using two competing solutions: fractional polynomials and regression splines.

(a) Fractional polynomials

A polynomial is a simple way to introduce non-linearity, but the range of curve shapes offered by low-order polynomials is limited, and higher-order polynomials often predict clinically unrealistic trends. Fractional polynomials (28) allow terms of the form X^p, with the exponent, p, chosen from a pre-selected set of low-order integer and non-integer values. We use an iterative procedure for choosing optimal exponents (29).

(b) Regression splines

A regression spline is a smoothly joined piecewise polynomial for modelling non-linear relationships. The curve is divided into intervals defined at points (or knots) and the number and spacing of these knots accommodate any non-linear relationship. In each interval the regression fit is a kth degree polynomial – we use cubic polynomials.

5.2.3 Haematology may differ between responders and non-responders

We have shown (in Chapter Four) that both default and death are likely to be 'non-ignorable' when considering haematology or clinical events as outcomes. A simple average profile of haematology ignores these non-response processes and may present a biased description of haematological change. Models for incorporating a non-ignorable non-response process have been classified into two classes: selection models and mixture models (30). A selection model treats non-response as a nuisance and directly estimates the marginal distribution of the outcome. For us, the separate outcome distributions of each non-response type (default and death) are of interest, and we use a mixture technique, known as pattern-mixture modelling (31). Pattern-mixture modelling has recently been adapted for use with GEE modelling (32).

5.2.4 Regression strategy

We wanted to develop predictive models of haematological indices that were potentially applicable to similar populations in other settings. We were interested in models that required only basic predictive information: the age and gender of someone with sickle-cell disease. We fitted separate regression models for each of our ten haematological parameters and for SS and AA genotype participants, creating 20 final prediction models.

For each parameter/genotype combination we developed a model using the following strategy. We fitted six models of increasing complexity (see Table 5.1). In models 1 and 2 we fitted the baseline effects of age and gender: in model 1 we fitted main effects, and in model 2 we additionally included an age×gender interaction. In models 3 to 6 we investigated the additional effects of default, and death. We used a single indicator for default between birth and 18 years of age. We used a single indicator for death between birth and 18 years of age. Models were assessed using the quasi-likelihood information criterion (QIC), which has been recently developed as a penalised measure of model fit for use in GEE modelling (33).

Using fractional polynomials or cubic splines, it is easy to create overcomplex and medically inconsistent models. To reduce this possibility, we restricted our fractional polynomials to degree 2 (which restricted the age term to two polynomial transformations), and before examining our data we pre-selected our spline knots based on our initial JSSCD data collection design, with increasing time intervals to ensure adequate modelling of early-life changes (we chose knots at 1 month, 3 months, 6 months, 1 year, 5 years, 10 years, and 15 years).

Table 5.1.
Competing models fitted to 11 haematological parameters among 315 SS disease JSSCD participants and 246 AA controls.

Terms	Models					
	Baseline		Pattern Mixture			
	1	2	3	4	5	6
Age	•	•	•	•	•	•
Sex	•	•	•	•	•	•
Age×Sex		•	•	•	•	•
Default			•		•	•
Death				•	•	•
Default×Death						•

5.3 Results

5.3.1 Modelling haematology

We present the QIC for all fitted models in Table 5.2. Among SS disease we always chose model 6, fitted using cubic splines,

$$age + sex + age \times sex + default + death + default \times death \quad (5.1)$$

Using this model, we are able to stratify our SS participants into four groups based on non-response pattern, and we present these groups in Table 5.3.

Table 5.2.

Choosing preferred models using the Quasi-likelihood Information Criterion (QIC) for competing models using fourteen haematological indices among SS JSSCD participants.

Index	Fractional Polynomial models						Cubic Spline models					
	1	2	3	4	5	6	1	2	3	4	5	6
SS genotype												
Hb	9804	9737	9616	9735	9616	9600	9548	9551	9423	9546	9423	***9405***
rbc	1839	1828	1825	1831	1827	1829	1746	1747	1742	1748	1744	***1745***
pcv	77637	76644	75589	76590	75550	75320	72110	72125	70993	72098	70989	***70750***
mcv	43041	42351	42050	42366	42066	42074	37650	37601	37333	37668	37353	***37353***
Mch	68137	66862	66511	66857	66512	66531	61060	60980	60688	61030	60666	***60678***
mchc	29554	29531	28418	29476	29365	29331	29018	29016	28908	28944	28835	***28799***
Nbc	15510	15248	15207	15250	15209	15203	14655	14662	14616	14657	14619	***14611***
retics	12914	12857	12859	12837	12840	12797	12668	12664	12669	12645	12648	***12607***
plat	79184	79158	79100	78941	78871	78818	78835	78811	78759	78612	78523	***78468***
HbF	78985	78882	77356	78664	77170	76889	78820	78821	77317	78566	77100	***76823***
bilirubin	19734	19612	19498	19610	19497	19493	19521	19520	19403	19520	19402	***19401***
AA genotype												
Hb	2717	2500	2490	-	-	-	2431	2358	***2348***	-	-	-
Rbc	328	323	326	-	-	-	326	326	***329***	-	-	-
Pcv	15812	14528	14409	-	-	-	15020	14540	***14411***	-	-	-
Mcv	82474	81023	80359	-	-	-	74550	74097	***73401***	-	-	-
Mch	12826	12684	12594	-	-	-	11478	11422	***11332***	-	-	-
mchc	6099	6049	6043	-	-	-	6049	6043	***6042***	-	-	-
Nbc	10401	10304	10269	-	-	-	10290	10259	***10222***	-	-	-
retics	411	407	410	-	-	-	352	354	***356***	-	-	-
plat	103686	103667	103560	-	-	-	102814	102804	***102742***	-	-	-
HbF	538	539	***531***	-	-	-	550	552	544	-	-	-
bilirubin	25135	24884	24652	-	-	-	24026	24017	***23706***	-	-	-

Among AA controls death was negligible and models 4 to 6, which all included death, were not available. We chose model three, fitted using cubic splines in all indices except HbF, for which we used fractional polynomials,

$$age + sex + age \times sex + default \tag{5.2}$$

The method of cubic splines generally offered a better fit using our QIC statistic. We note, however, that in many cases the predicted curves using either cubic-splines or fractional-polynomials were comparable, and the final choice may ultimately have little effect on predicted parameters.

Table 5.3.

Non-response groups used for comparison of haematology indices.

	Default	Death	Description
1			Full attendance and is alive
2	•		Default and is alive
3		•	Full attendance and has died
4	•	•	Default and has died

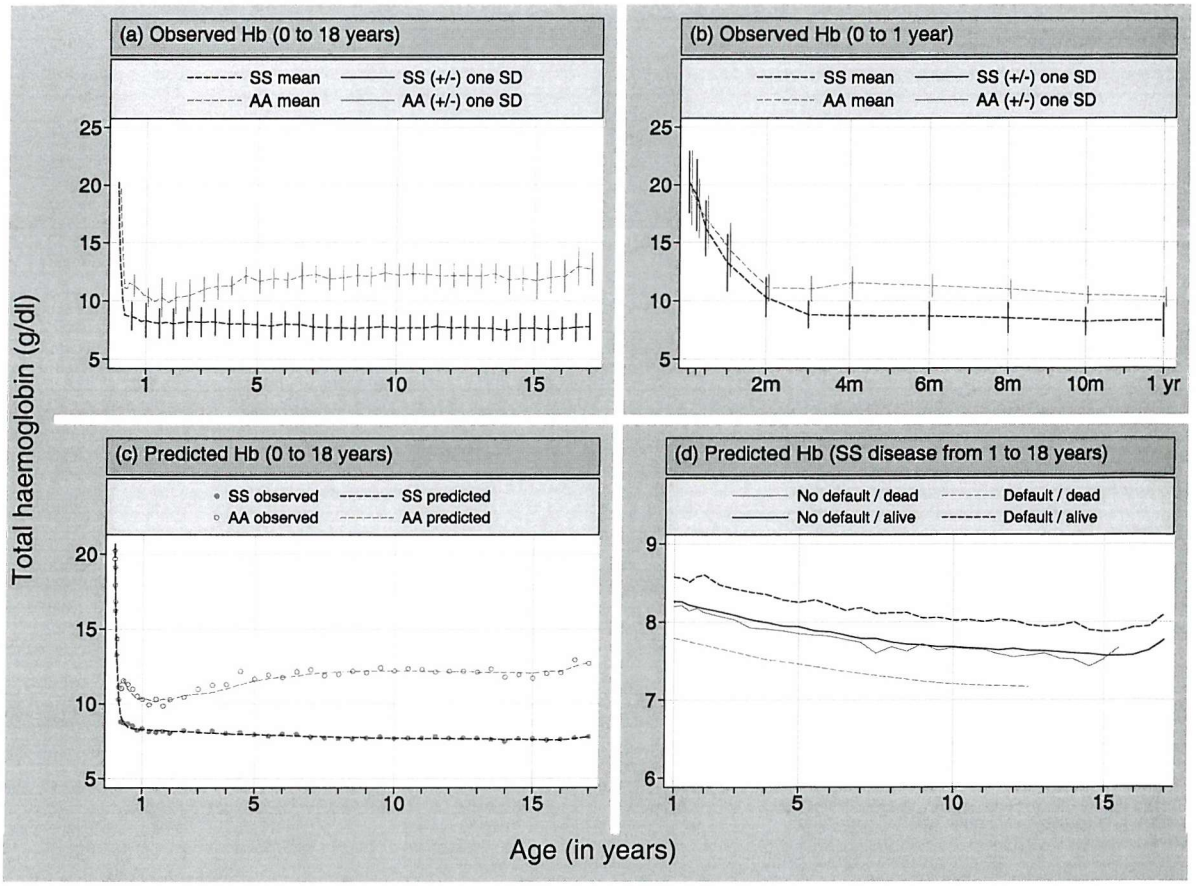
5.3.2 Total haemoglobin

Haemoglobin concentration at birth was similar in SS and AA babies (20.2g/dl in SS babies, 19.7g/dl in AA babies). Levels among SS infants fell rapidly in the first months of life, and by 3 months of age the average *Hb* in SS infants was 8.8g/dl, compared to 11.0g/dl in AA infants. Thereafter, changes were gradual (a gradual decrease among SS participants, and a gradual increase among AA participants). At 18 years of age SS participants had average levels of 7.8g/dl, compared to 12.7g/dl among AA controls (Figure 5.1a-c). Predicted haemoglobin concentration in SS boys remained lower than in girls throughout childhood (difference in *Hb* -0.27g/dl, 95% ci -0.47 to -0.08).

Surviving participants that defaulted from the JSSCD for at least one year had a higher average haemoglobin concentration than those who had never defaulted (difference in *Hb* 0.38g/dL, 95% ci 0.02 to 0.74). The picture was reversed in those that defaulted and who had subsequently died (difference in *Hb* -0.34g/dL, 95% ci -1.62 to 0.94) (Figure 5.1d).

Figure 5.1

Observed and predicted average profile of total haemoglobin (Hb) between birth and 18 years of age for 315 SS and 247 AA cohort members.



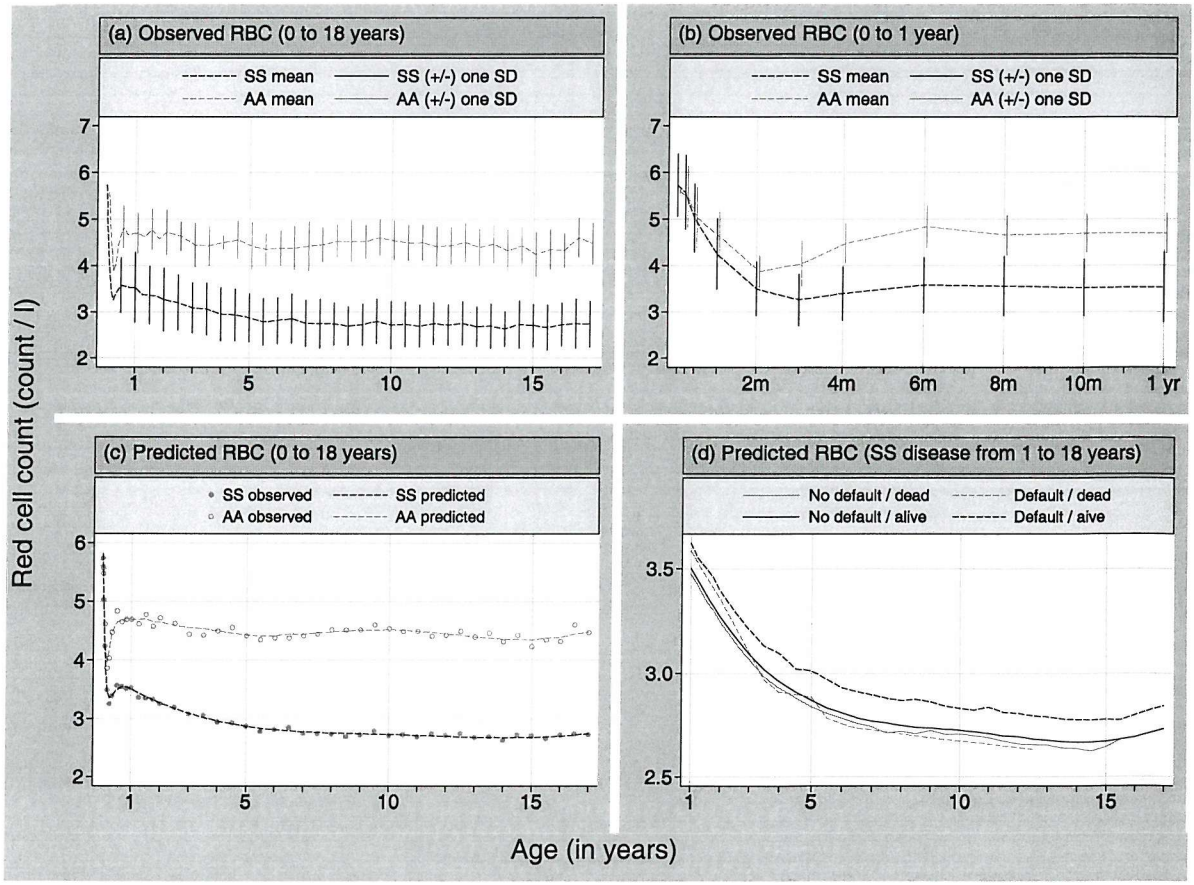
5.3.3 Red blood cells

The red blood cell count at birth was similar in SS and AA babies (5.8×10^{12} /litre in SS babies, 5.7×10^{12} /litre in AA babies). Levels fell rapidly in the first months of life, and by 3 months of age the average *rbc* in SS infants was 3.3×10^{12} /litre in SS infants, and was 4.0×10^{12} /litre in AA infants. The count quickly recovered in AA infants to remain steady at between 4.5 and 5.0 $\times10^{12}$ /litre until 18 years of age. In SS participants levels recovered marginally to 3.6 $\times10^{12}$ /litre by 1 year of age before declining once more to levels around 2.7×10^{12} /litre in adolescence (Figure 5.2a-c). Although predicted levels in SS boys remained marginally lower than in girls, this difference was not statistically important (difference in *rbc* -0.04×10^{12} /litre, 95% ci −0.14 to 0.05).

Non-response patterns were less pronounced than those for haemoglobin concentration. Surviving participants that defaulted from the JSSCD for at least one year had a higher average *rbc* count than those who have never defaulted but this difference was not statistically important (difference in *rbc* 0.09×10^{12} /litre, 95% ci -0.08 to 0.25) (Figure 5.2d).

Figure 5.2

Observed and predicted average profile of red blood cell count (RBC) between birth and 18 years of age for 315 SS and 247 AA cohort members.



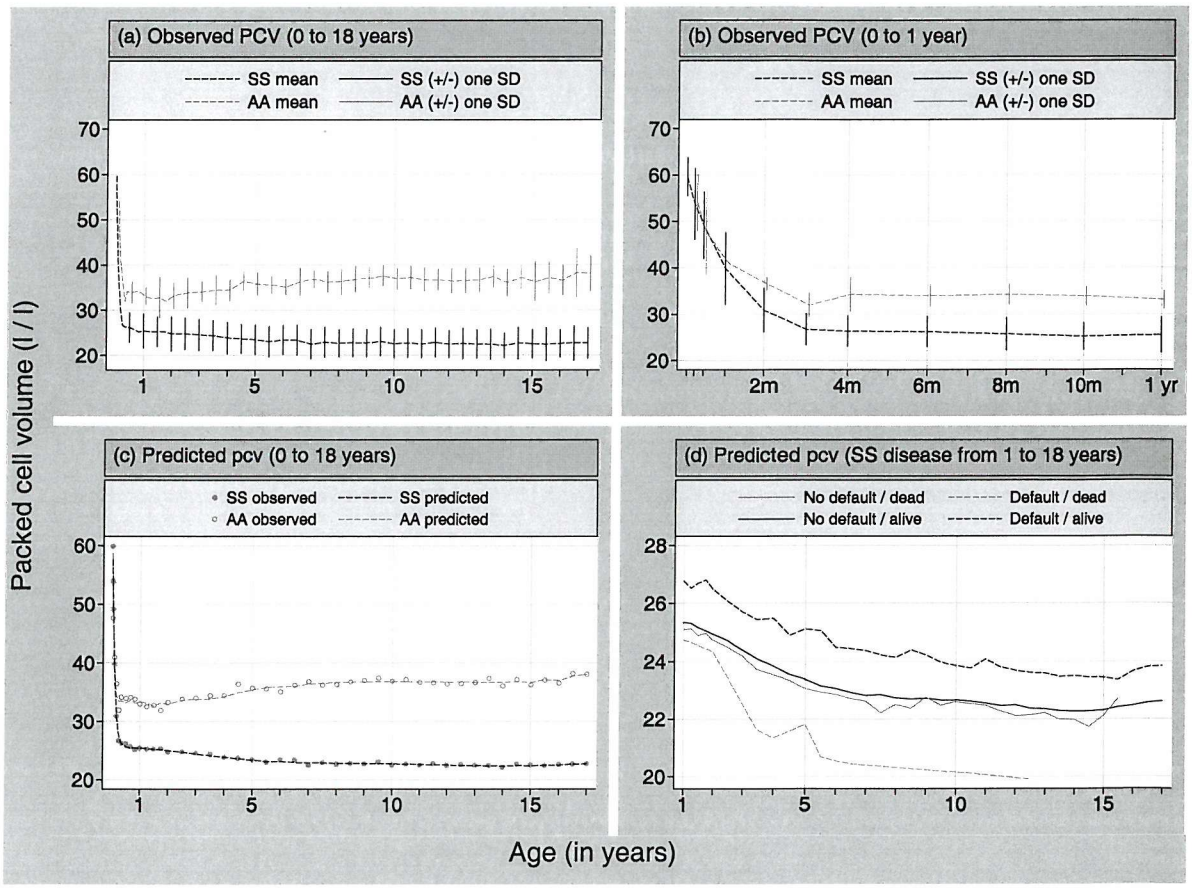
5.3.4 Packed cell volume

The haematocrit at birth was similar in SS and AA babies (59.9% in SS babies, 58.8% in AA babies), and the subsequent trend mirrored the age-related changes of haemoglobin concentration. By 3 months of age the average *pcv* in SS infants was 26.7% in SS babies, and was 32.0% in AA babies. The count recovered gently in AA participants to reach 38.1% by 18 years of age. In SS participants levels continued to fall gently to reach levels between 22% and 23% in adolescence (Figure 5.3a-c). Predicted levels in SS boys remained lower than in girls (difference in *pcv* -0.9%, 95% ci -1.5 to -0.3).

Non-response patterns were also similar to those for haemoglobin concentration. Surviving participants that defaulted from the JSSCD for at least one year had a higher average *pcv* count than those who have never defaulted (difference in *pcv* 1.3%, 95% ci 0.24 to 2.38). The picture was reversed in those that defaulted and who had subsequently died (difference in *pcv* –1.19%, 95% ci –4.93 to 2.55) (Figure 5.3d).

Figure 5.3

Observed and predicted average profile of packed cell volume (pcv) between birth and 18 years of age for 315 SS and 247 AA cohort members.



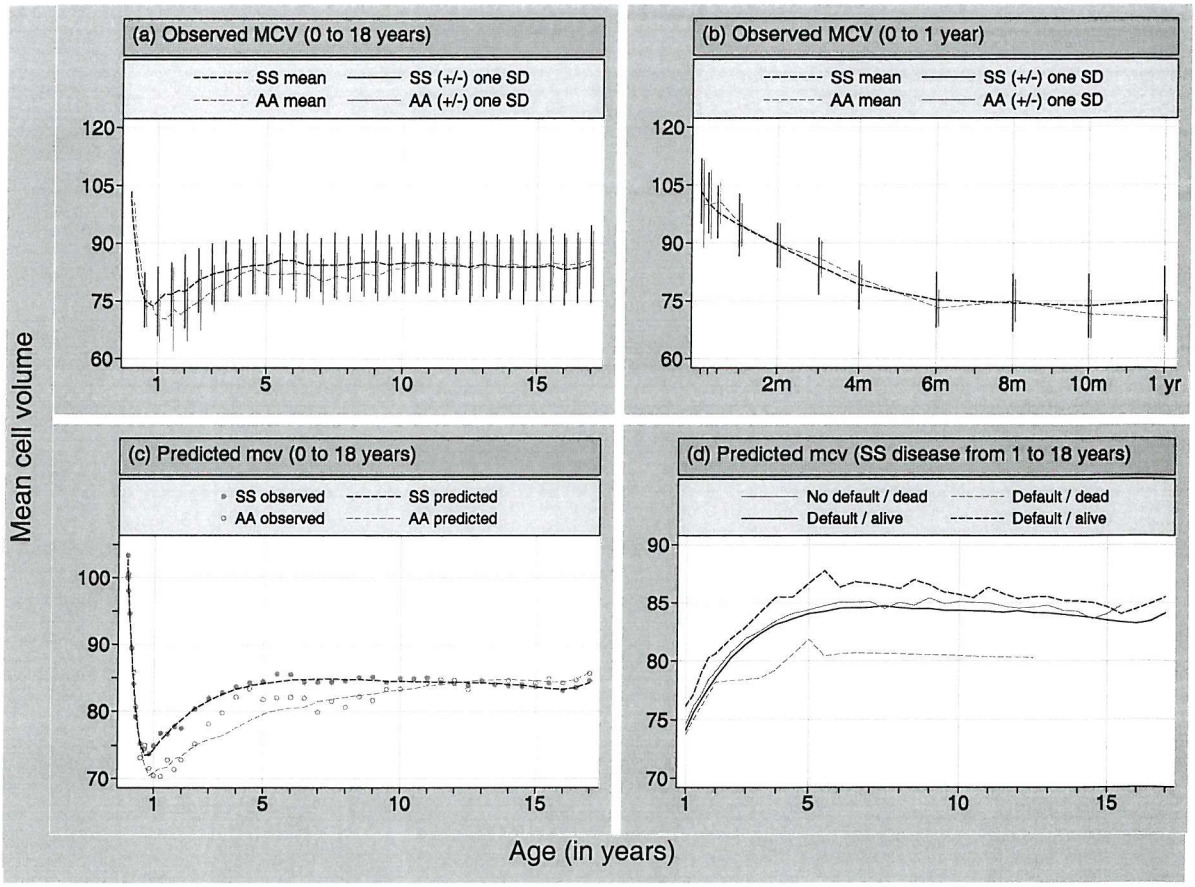
5.3.5 Mean cell volume

Mean corpuscular volume at birth was similar in SS and AA babies (103.4fl in SS babies, 100fl in AA babies). Levels dropped to a nadir of 73.7fl by 10 months of age in SS infants, and then recovered to levels between 83fl and 85fl by 4 years of age. The initial drop was larger and lasted longer in AA infants, who reached a minimum value of 70.3fl at 15 months of age. The subsequent recovery was slower, with levels between 83fl and 85fl not reached until 9 years of age (Figure 5.4a-c). Predicted *mcv* in SS boys remained lower than in girls throughout childhood (difference in *mcv* -1.6fl, 95% ci -2.9 to -0.2).

Surviving participants that defaulted from the JSSCD for at least one year had a higher average mean corpuscular volume than those who had never defaulted, but the effect was not statistically important (difference in *mcv* 2.3fl, 95% ci -0.3 to 4.8). The effect was reversed and was smaller in those that defaulted and who had subsequently died (difference in *mcv* – 1.4fl, 95% ci -10.2 to 7.4) (Figure 5.4d).

Figure 5.4

Observed and predicted average profile of mean cell volume (mcv) between birth and 18 years of age for 315 SS and 247 AA cohort members.



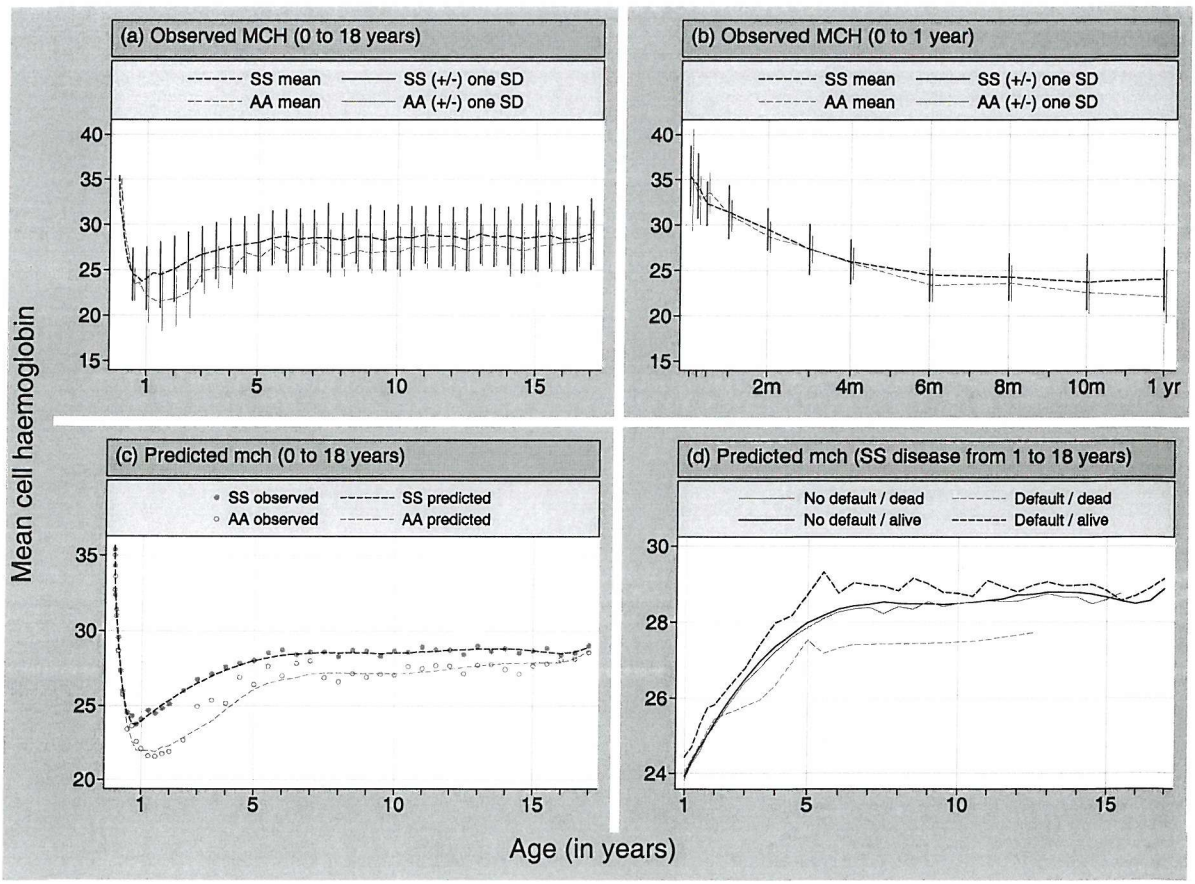
5.3.6 Mean cell haemoglobin

The age-related trend in mean corpuscular haemoglobin was very similar to *mcv*. Values at birth were similar in SS and AA babies (35.4pg in SS babies, 35.0pg in AA babies). Levels reached a nadir of 23.8pg by 10 months of age in SS infants, and then recovered to between 28.0pg and 29.0pg by 5 years of age. The initial drop was larger and lasted longer in AA infants, who reach a minimum value of 21.6pg at 15 months of age. Levels subsequently rose to 27.0g by 6 years of age, and then more slowly to 28.0g by 18 years of age (Figure 5.5a-c). Although the predicted mean cell volume in SS boys remained lower than in girls throughout childhood the difference was not statistically important (average difference in *mch* -0.5pg, 95% ci -1.0 to 0.1).

There was some suggestion of higher *mch* levels among surviving participants that defaulted from the JSSCD for at least one year (difference in *mch* 0.6pg, 95% ci -0.4 to 1.6) and lower levels among those that defaulted and who had subsequently died (difference in *mch* -0.2pg, 95% ci –3.8 to 3.3), but these effects were small and were not statistically important (Figure 5.5d).

Figure 5.5

Observed and predicted average profile of mean cell haemoglobin (mch) between birth and 18 years of age for 315 SS and 247 AA cohort members.

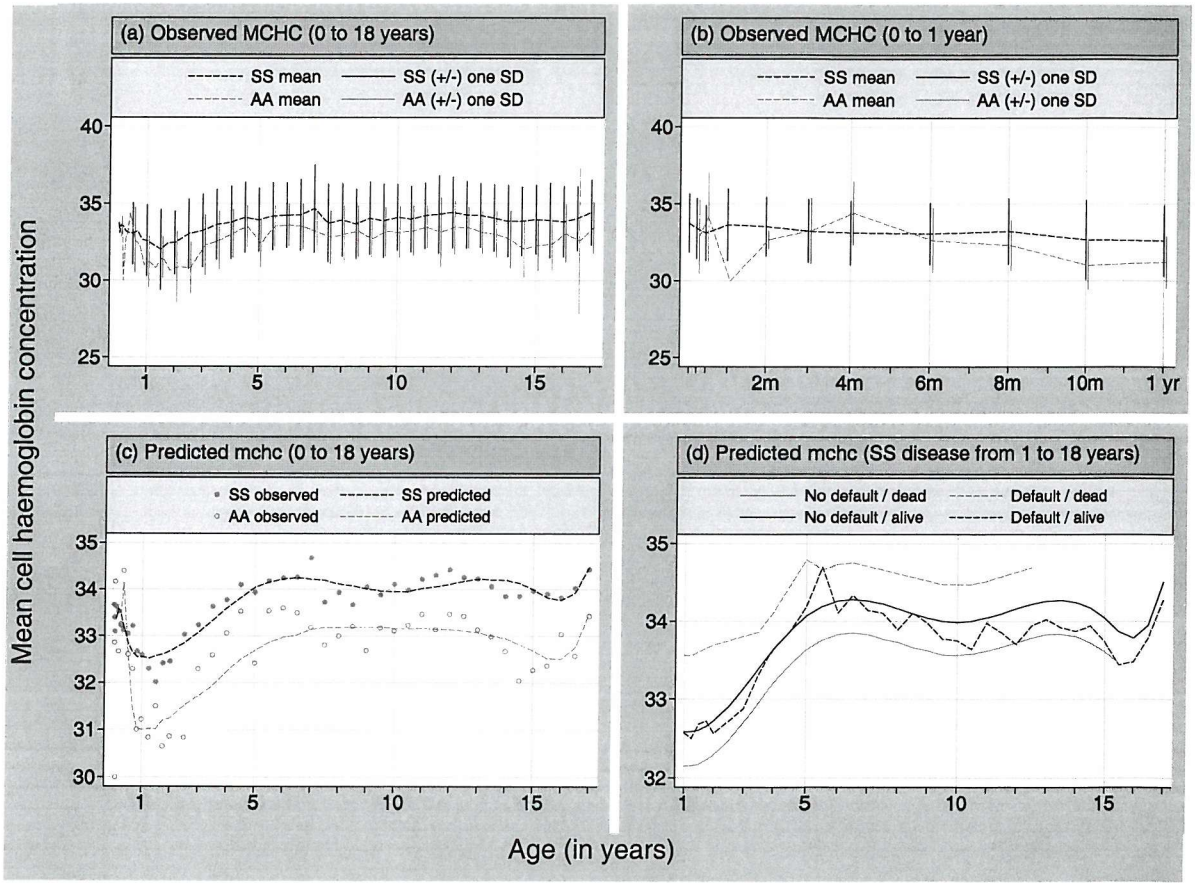


5.3.7 Mean cell haemoglobin concentration

Values at birth were similar in SS and AA babies (33.7% in SS babies, 32.9% in AA babies). Levels dropped to 32.0% by 15 months of age in SS infants, recovered to between 33.5% and 35% by 4 years of age, and remained t these levels throughout childhood. As with the other red cell indices, the initial fall was more pronounced in AA infants, who reach a minimum value of 30.7% at 21 months of age. Levels subsequently rose to around 33.0% by 4 years of age. In both genotypes there was a second minor dip in *mchc* in later adolescence (Figure 5.6a-c). Generally, variation in our steady-state *mchc* measurements was large, and this feature contributed to the mixed, and statistically unimportant differences due to gender and non-response patterns (Figure 5.6d).

Figure 5.6

Observed and predicted average profile of mean cell haemoglobin concentration (mchc) between birth and 18 years of age for 315 SS and 247 AA cohort members.



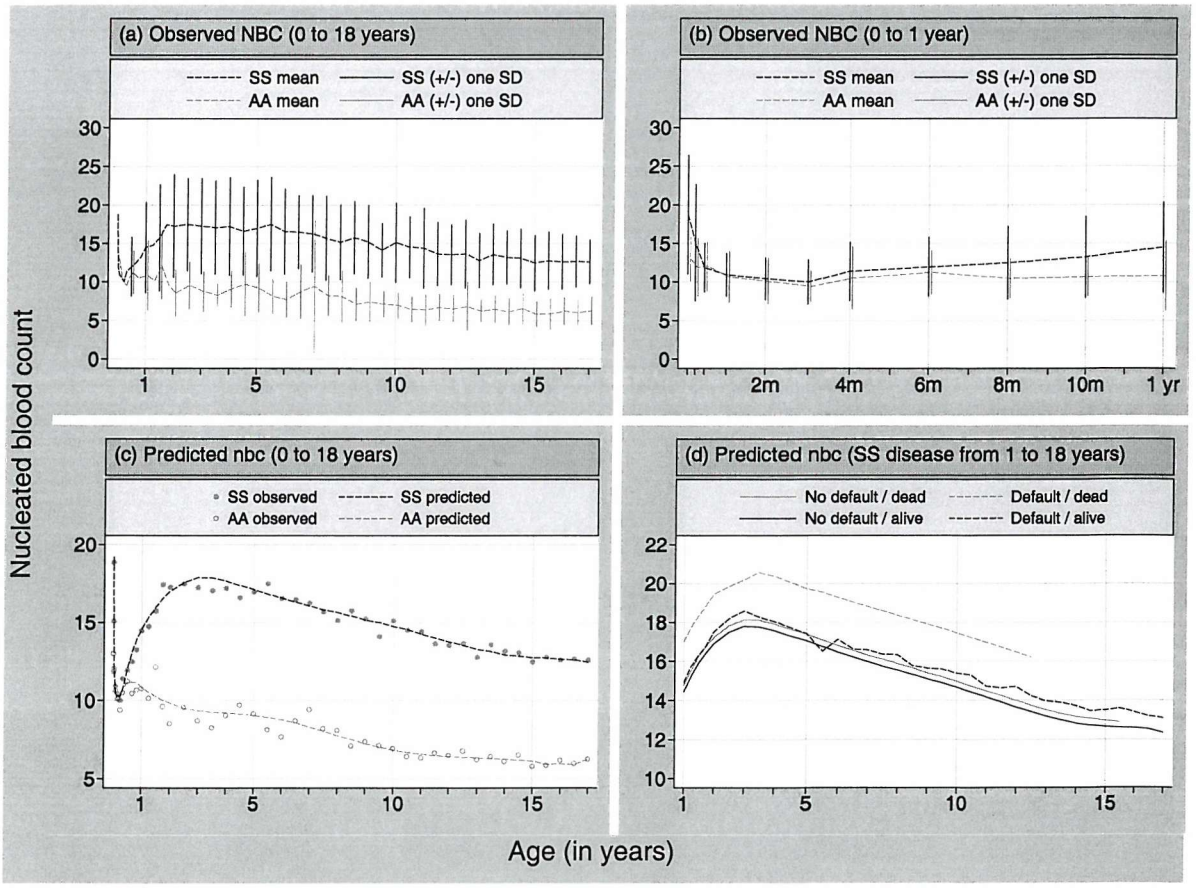
5.3.8 Nucleated blood cells

The nucleated blood cell count at birth was higher in SS babies (18.8×10^9 /litre in SS babies, 13.0×10^9 /litre in AA babies). Levels fell rapidly in the first months of life, and by 3 months of age the average *nbc* in SS infants was 10.0×10^9 /litre in SS infants and was 9.4×10^9 /litre in AA infants. In SS children the count increased in infancy to reach values in excess of 17×10^9 /litre between 2 and 4 years of age, before declining gently to values below 13×10^9 /litre by 18 years of age. In AA children a minor post neonatal increase was brief, with values climbing above 10×10^9 /litre between 6 and 15 months, before decreasing gently to around 6×10^9 /litre by 18 years of age. There was no gender difference in the nucleated blood count (Figure 5.7a-c).

Participants that defaulted for at least one year and who had subsequently died had higher average *nbc* levels than those who had never defaulted (difference in *nbc* 2.7×10^9 /litre, 95% ci –1.9 to 7.3) (Figure 5.7d). A pattern was less clear among surviving participants that defaulted.

Figure 5.7

Observed and predicted average profile of nucleated blood count (nbc) between birth and 18 years of age for 315 SS and 247 AA cohort members.



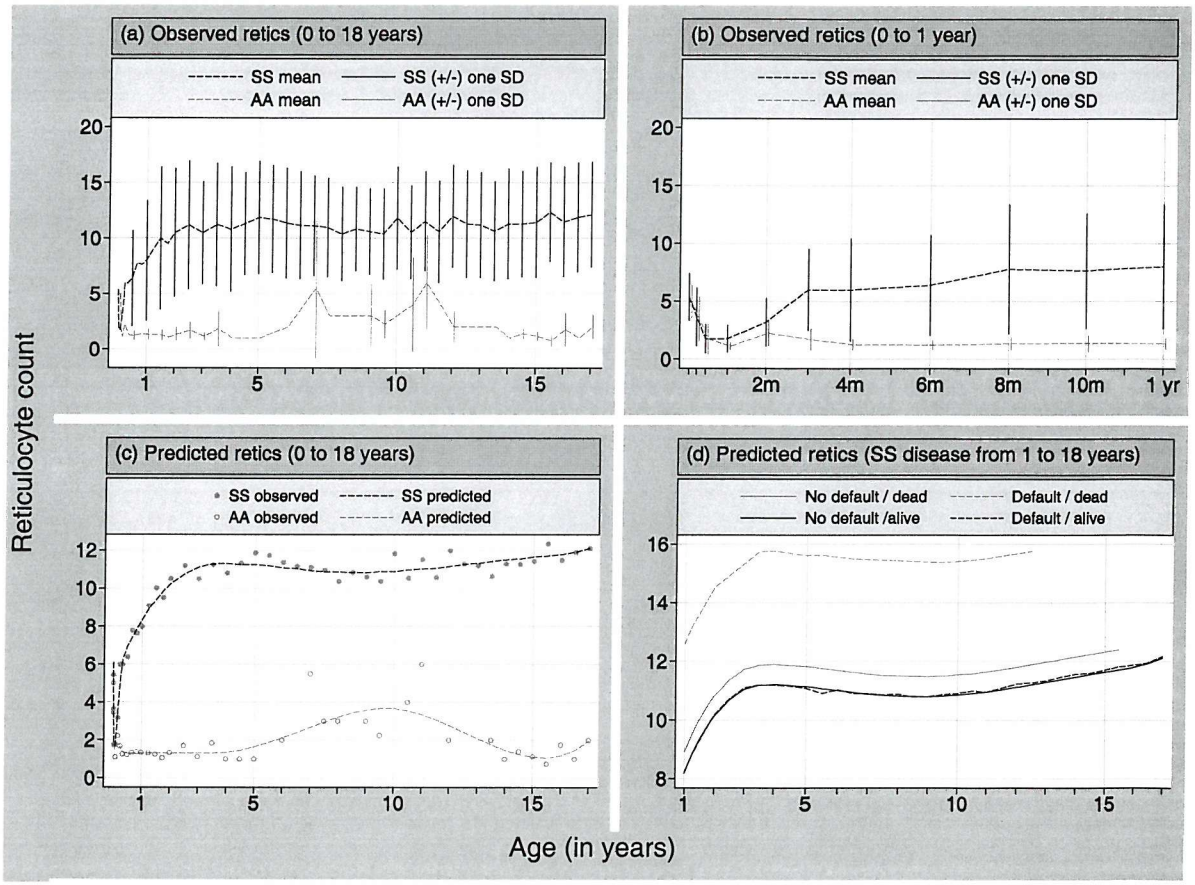
5.3.9 Reticulocyte count

Reticulocyte count at birth was similar in SS and AA babies (5.4% in SS babies, 5% in AA babies). Levels fell rapidly in the first weeks of life, and by 1 month of age the average reticulocyte count in SS infants was 1.8%, compared to 1.1% in AA infants. Thereafter, SS levels rose rapidly to above 10% by 18 months, and to above 12% by 18 years. Levels in AA participants remained low with a suggestion of a minor but inconsistent increase between 7 and 11 years of age (Figure 5.8a-c). There was no gender difference in reticulocyte count.

Participants that defaulted for at least one year and who had subsequently died had markedly higher average reticulocyte levels than those who had never defaulted (difference in *retics* 4.5%, 95% ci 0.6 to 8.4) (Figure 5.8d). There was no difference among surviving participants that defaulted.

Figure 5.8

Observed and predicted average profile of reticulocyte count (retics) between birth and 18 years of age for 315 SS and 247 AA cohort members.

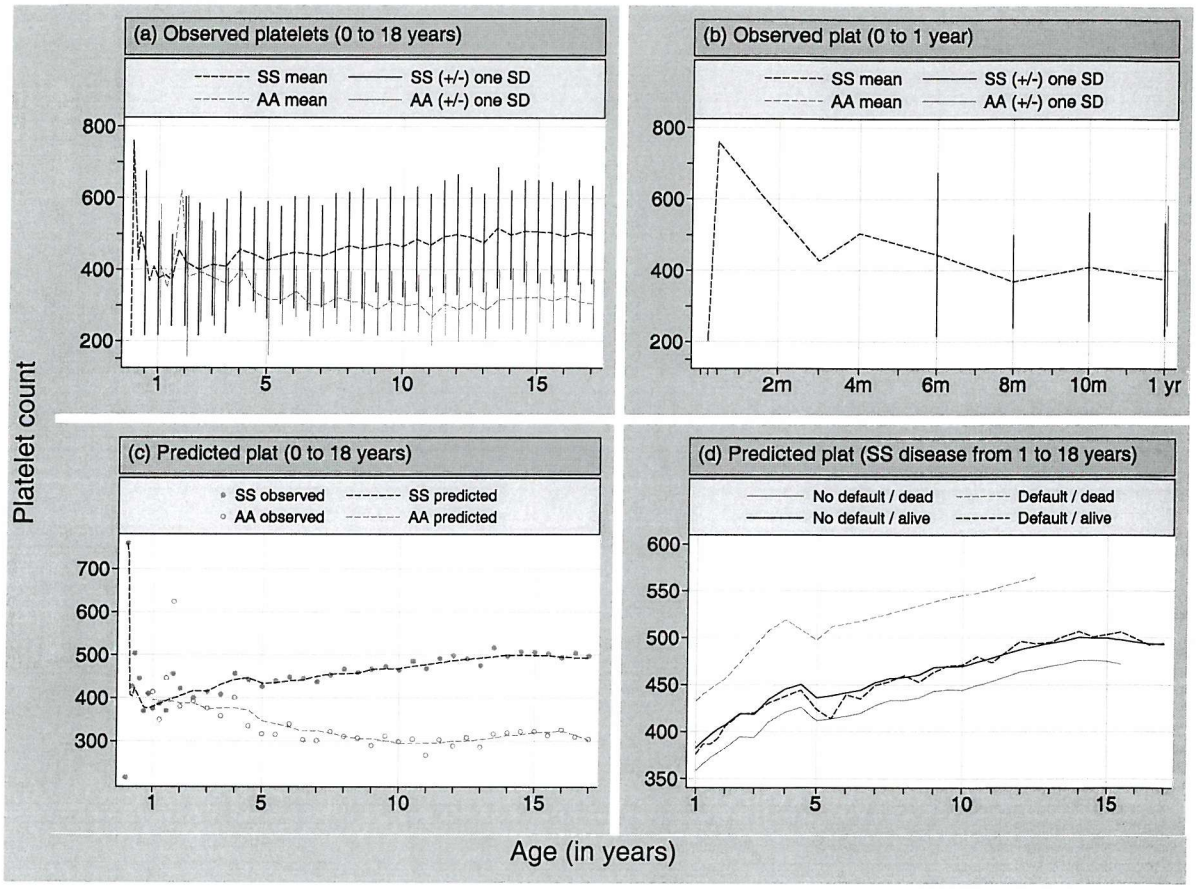


5.3.10 Platelet count

We have no reliable platelet counts before 3 months among SS participants and before 1 year among AA participants. Between 3 months and 1 year, SS levels varied around 400×10^3 /mm^3, then climbed steadily to 500×10^3 /mm^3 by 18 years of age. At 1 year of age AA levels were around 400×10^3 /mm^3, and decreased thereafter to around 300×10^3 /mm^3 by 18 years of age (Figure 5.9a-c). Generally, variation in our steady-state platelet measurements was large, and this feature contributed to the mixed, and statistically unimportant differences due to gender and non-response patterns (Figure 5.9d).

Figure 5.9

Observed and predicted average profile of platelet count (plat) between birth and 18 years of age for 315 SS and 247 AA cohort members.



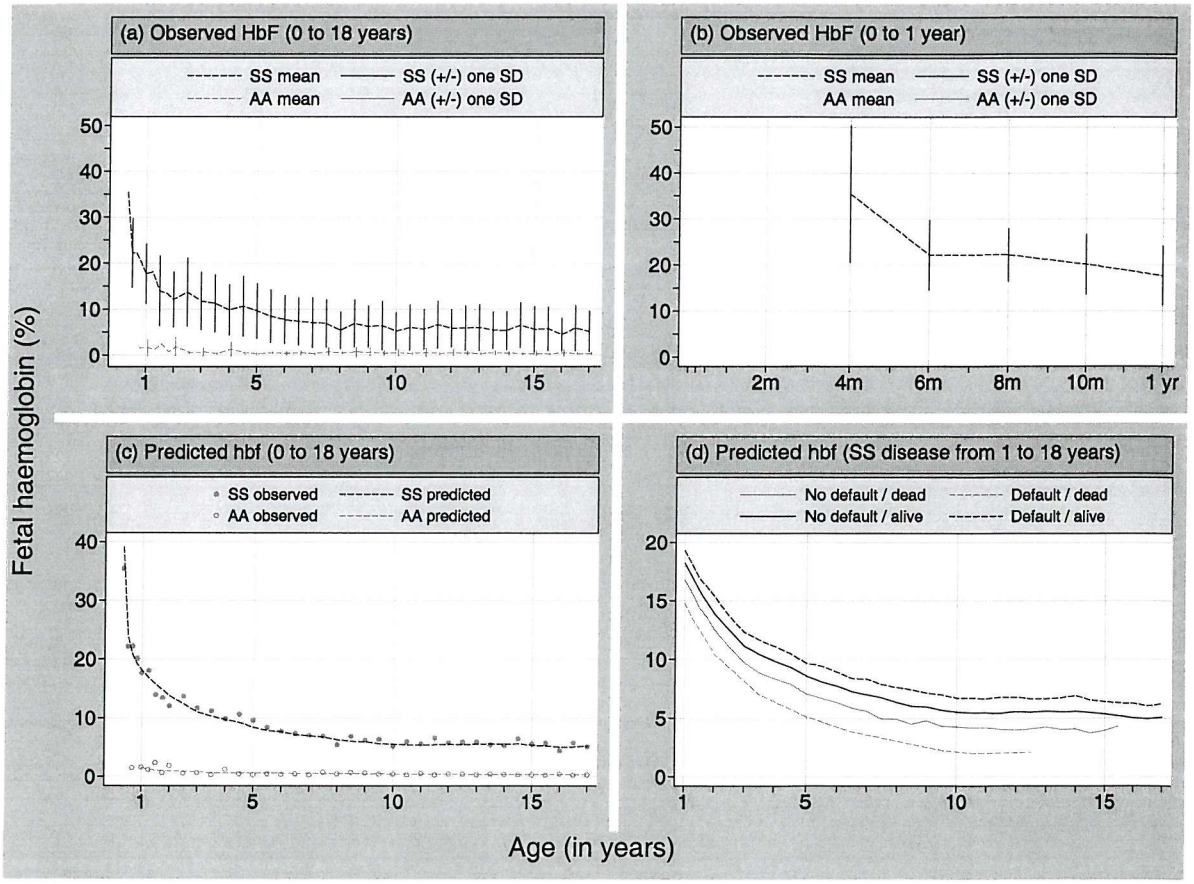
5.3.11 Fetal haemoglobin

We have no reliable HbF data before 4 months among SS participants and before 1 year among AA participants. At 4 months, SS infants had HbF levels of 35%. These levels declined rapidly to 17.7% by 1 year of age, 12.1% by 2 years of age, 9.6% by 5 years, and 5.2% by 10 years and older. Among AA participants HbF levels were 1.5% at 1 year of age, and quickly decreased to trace levels (<0.5%) by 2 years and older (Figure 5.10a-c).

Surviving participants that defaulted from the JSSCD for at least one year had a higher average HbF levels than those who had never defaulted (difference in *HbF* 1.3%, 95% ci -0.7 to 3.3), and the effect was more pronounced for those that defaulted in the second decade of life. The picture was reversed in those that defaulted and who had subsequently died (difference in *HbF* -3.0%, 95% ci -10.0 to 4.0) (Figure 5.10d).

Figure 5.10

Observed and predicted average profile of fetal haemoglobin (HbF) between birth and 18 years of age for 315 SS and 247 AA cohort members.



5.4 Discussion

Our results provide new baseline information of the haematological picture in an important sickle-cell disease cohort, extending earlier descriptions from six to 18 years of age (4). More work is needed to translate these information into practical tools. It is possible to extend the current analysis to a series of reference intervals for childhood haematology in SS disease, and we consider this future work in chapter nine. Our initial observations on differences between SS participants and AA controls could have implications for the use of haematology as biomarkers for the disease process, and we consider this future work in chapter nine.

We use certain analysis techniques for the first time in haematological analyses. Few attempts have been made to model the early-life haematological experience (34). In sickle-cell disease epidemiology, early-life changes in all haematological indices are non-linear, and analysts have historically chosen to ignore this important time of life. We now show that these changes can be successfully incorporated into a modelling framework. The procedures can be immediately utilised to examine the role of other factors on these haematological indices. Our modelling goals were to document the haematological profiles of our SS cohort, but in doing so we have obscured individual variability in haematological course. Important extensions will be to offer age-related reference intervals for each index, and to model our haematology using subject-specific (or random effects) models. These will allow us to evaluate the variability between individuals and to better understand the influence of specific interventions on individuals.

The rapid decline in haemoglobin concentration soon after birth, and its association with reticulocytosis and elevated bilirubin levels (not presented) indicates haemolysis at a very early age in SS disease, and prior to the onset of clinical symptoms in analysable numbers. These features suggest an important avenue for exploring early-life indicators of later health-status (see chapter nine). Leukocytosis ($\geq 15 \times 10^9$/litre) is apparent in early-life. Leukocytes have been linked recently to major health outcomes in sickle-cell disease (3;35), and the early recognition of an elevated white blood cell count may offer another avenue for early identification of people at risk of a problematic clinical course.

Our haematological profiles exclude haematology associated with acute clinical events (for example those associated with aplastic crisis, post-transfusion, acute splenic sequestration, acute chest syndrome, vasoocclusive episodes). Ultimately the interrelationship between our 'steady-state' haematology and the excluded 'non-steady state' may be valuable, and this discussed further in chapter nine.

Gender differences occurred in the haematological development. Females had higher haemoglobin concentration, haematocrit, and mean cell volume at the 5% level of statistical significance. Other indices had clinically interesting gender differences that did not achieve statis-

tical significance, primarily because of large measurement variation. Larger cohorts with greater statistical power would be required to examine these features.

We have shown (in chapter four) that non-response should not be ignored when modelling haematology or clinical events in sickle-cell disease, and that participant default influences subsequent mortality. We now show that surviving defaulters had significantly higher haemoglobin concentrations, and haematocrit than attending participants that have survived. Haemoglobin concentrations were on average 0.4g/dl higher, and haematocrit was 1.3% higher among surviving defaulters. Defaulting participants that died had significantly higher reticulocyte counts that attending participants that survived; the reticulocyte count was 4.5% higher among defaulters that subsequently died. Other relationships that were interesting, but not statistically significance (again possibly because of inadequate power) are detailed in graph (d) of each haematological index description. These differences suggest two mechanisms for default: those that are mildly affected by the disease and who do not need medical intervention, and those that are more severely affected, and for whom the act of defaulting may itself promote an unfavourable clinical outcome. Our results suggest that default itself can offer an early-warning system for adverse clinical outcome.

5.5 Reference List

(1) Powars DR. Natural history of sickle cell disease--the first ten years. Semin Hematol 1975; 12(3):267-285.

(2) Vichinsky E, Hurst D, Earles A, Kleman K, Lubin B. Newborn screening for sickle cell disease: effect on mortality. Pediatrics 1988; 81(6):749-755.

(3) Miller ST, Sleeper LA, Pegelow CH, Enos LE, Wang WC, Weiner SJ et al. Prediction of adverse outcomes in children with sickle cell disease [see comments]. N Engl J Med 2000; 342(2):83-89.

(4) Serjeant GR, Grandison Y, Lowrie Y, Mason K, Phillips J, Serjeant BE et al. The development of haematological changes in homozygous sickle cell disease: a cohort study from birth to 6 years. Br J Haematol 1981; 48(4):533-543.

(5) Sydenstricker VP. Further observations on sickle cell anemia. J Am Med Ass 1924; 83:12-15.

(6) Diggs LW. Siderofibrosis of the spleen in sickle cell anemia. J Am Med Ass 1935; 104:538-541.

(7) King AD. Sickle cell anemia. Arch Dermatol Syphilol 1936; 33:756.

(8) Winsor T, Burch GE. The habitus of patients with sickle cell anemia. Hum Biol 1944; 16:99-114.

(9) Pauling L, Itano HA, Singer SJ, Wells IC. Sickle cell anemia, a molecular disease. Science 1949; 110:543-548.

(10) Serjeant GR, Foster K, Serjeant BE. Red cell size and the clinical and haematological features of homozygous sickle cell disease. Br J Haematol 1981; 48(3):445-449.

(11) Hawker H, Neilson H, Hayes RJ, Serjeant GR. Haematological factors associated with avascular necrosis of the femoral head in homozygous sickle cell disease. Br J Haematol 1982; 50(1):29-34.

(12) Odenheimer DJ, Whitten CF, Rucknagel DL, Sarnaik SA, Sing CF. Heterogeneity of sickle-cell anemia based on a profile of hematological variables. Am J Hum Genet 1983; 35(6):1224-1240.

(13) Adedeji MO, Ukoli FA. Haematological factors associated with leg ulcer in sickle cell disease. Trop Geogr Med 1987; 39(4):354-356.

(14) Bailey K, Morris JS, Thomas P, Serjeant GR. Fetal haemoglobin and early manifestations of homozygous sickle cell disease. Arch Dis Child 1992; 67(4):517-520.

(15) Falusi AG, Olatunji PO. Effects of alpha thalassaemia and haemoglobin F (HbF) level on the clinical severity of sickle-cell anaemia. Eur J Haematol 1994; 52(1):13-15.

(16) Morris JS, Dunn DT, Poddar D, Serjeant GR. Haematological risk factors for pregnancy outcome in Jamaican women with homozygous sickle cell disease. Br J Obstet Gynaecol 1994; 101(9):770-773.

(17) Serjeant GR, Serjeant BE, Forbes M, Hayes RJ, Higgs DR, Lehmann H. Haemoglobin gene frequencies in the Jamaican population: a study in 100,000 newborns. Br J Haematol 1986; 64(2):253-262.

(18) Gaston M, Rosse WF. The cooperative study of sickle cell disease: review of study design and objectives. Am J Pediatr Hematol Oncol 1982; 4(2):197-201.

(19) Stevens MC, Maude GH, Beckford M, Grandison Y, Mason K, Serjeant BE et al. Haematological change in sickle cell-haemoglobin C disease and in sickle cell-beta thalassaemia: a cohort study from birth. Br J Haematol 1985; 60(2):279-292.

(20) Brown AK, Sleeper LA, Miller ST, Pegelow CH, Gill FM, Waclawiw MA. Reference values and hematologic changes from birth to 5 years in patients with sickle cell disease. Cooperative Study of Sickle Cell Disease. Arch Pediatr Adolesc Med 1994; 148(8):796-804.

(21) McCullagh P, Nelder JA. Generalized Linear Models. 2nd ed. London: Chapman and Hall, 1989.

(22) Lindsey JK, Lambert P. On the appropriateness of marginal models for repeated measurements in clinical trials. Stat Med 1998; 17(4):447-469.

(23) Touloumi G, Babiker AG, Pocock SJ, Darbyshire J. Impact of missing data due to drop-outs on estimators for rates of change in longitudinal studies: a simulation study. Stat Med 2001; 20:3715-3728.

(24) Hann IM, Lake BD, Lilleyman J, Pritchard J. Colour Atlas of Paediatric Haematology. Oxford: Oxford University Press, 1996.

(25) Hayes RJ, Beckford M, Grandison Y, Mason K, Serjeant BE, Serjeant GR. The haematology of steady state homozygous sickle cell disease: frequency distributions, variation with age and sex, longitudinal observations. Br J Haematol 1985; 59(2):369-382.

(26) Maude GH, Hayes RJ, Serjeant GR. The haematology of steady state homozygous sickle cell disease: interrelationships between haematological indices. Br J Haematol 1987; 66(4):549-558.

(27) Falusi AG, Kulozik AE. Relationship of foetal haemoglobin levels and beta s haplotypes in homozygous sickle cell disease. Eur J Haematol 1990; 45(1):1-4.

(28) Royston P, Altman DG. Regression using fractional polynomials of continuous covariates - parsimonious parametric modeling. Applied Statistics-Journal Of The Royal Statistical Society Series C 1994; 43:429-467.

(29) Sauerbrei W, Royston P. Building multivariable prognostic and diagnostic models: transformation of the predictors by using fractional polynomials Download Full Text of Article. Journal Of The Royal Statistical Society Series A-Statistics In Society 1999; 162:71-94.

(30) Little RJA. Modeling the drop-out mechanism in repeated-measures studies. Journal Of The American Statistical Association 1995; 90:1112-1121.

(31) Little RJA. Pattern-mixture models for multivariate incomplete data. Journal Of The American Statistical Association 1993; 88:125-134.

(32) Park T, Lee S-Y. Simple pattern-mixture models for longitudinal data with missing observations: analysis of urinary incontinence data. Stat Med 1999; 18:2933-2941.

(33) Pan W. Akaike's Information Criterion in Generalized Estimating Equations. Biometrics 2001; 57:120-125.

(34) McElroy PD, Lal AA, Hawley WA, Bloland PB, Ter Kuile FO, Oloo AJ et al. Analysis of repeated hemoglobin measures in full-term, normal birth weight Kenyan children between birth and four years of age III. The Asembo Bay cohort project. Am J Trop Med Hyg 1999; 61(6):932-940.

(35) Leikin SL, Gallagher D, Kinney TR, Sloane D, Klug P, Rida W. Mortality in children and adolescents with sickle cell disease. Cooperative Study of Sickle Cell Disease. Pediatrics 1989; 84(3):500-508.

Book Three
Clinical events

Chapter 6

Describing clinical events

Background

The clinical expression of sickle-cell disease is well documented, but published observations generally rely on clinically ascertained study participants with known biases (e.g. see Chapter Three). We describe clinical patterns of sickle-cell disease among the JSSCD birth cohort, which is free from ascertainment bias, and whose underreporting of clinical events is likely to be small.

Methods

For fourteen clinical complications we calculated incidence rates and the proportion of participants affected, by age, genotype (SS and SC disease), and gender. We quantified the bias introduced when using a clinically-ascertained study group by comparing the reported proportion of participants affected in the clinic study and in the JSSCD. We assessed two techniques to reduce this bias in the clinic study: an established technique reduces the at-risk population, and a new technique is based on a Monte-Carlo simulation. We summarised outcome as mortality-rates in the JSSCD, and as survival rates among clinic study participants who enrolled in our sickle-cell clinics during a 10-year window between 1987 and 1996, and who had their status (living, died, migrated) confirmed during the early stages of this doctoral work (in 1998 and 1999).

Findings

Among JSSCD participants with SS disease, the most common event in infancy was dactylitis, with 44 events per 100 years between 1 and 2 years of age. Although less common, acute splenic sequestration, the acute chest syndrome, and bacteraemias were also most likely to occur in infancy. From childhood to adulthood, the painful crisis was the most common clinical event, with incidence rates of 50 per 100 years until adolescence, rising to 190 events per 100 years in adults between 24 and 25 years of age. More men presented with dactylitis and hepatomegaly, and men had a higher frequency of dactylitis and the acute chest syndrome. The acute chest syndrome was the leading cause of death, and stroke carried the highest probability of death. Median survival using the Monte Carlo simulation was 53.0 (49.0 to 58.7) years for males and 58.5 (53.5 to 70.9) for females. Median survival using the 'population-at-risk' adjustment was 42.6 (40.0 to 49.1) years for males and 47.4 (37.8 to 55.1) for females. Using the clinical study, the proportion of participants affected by clinical endpoints was between 2 and 10 times lower than in the JSSCD. Using the 'population-at-risk' adjustment reduced this underreporting to (at most) 3 times lower.

Interpretation

Clinical events are strongly age-related, and an unselected birth cohort followed prospectively is required to accurately determine age-specific summary measures of event frequency. When the age-structure of a cohort does not allow adequate descriptions (e.g. our young Jamaican cohort cannot inform lifetime survival) methods of bias adjustment, if applied thoughtfully, can improve the accuracy of estimates applied to clinic ascertained participants.

6.1 Introduction

The clinical features of sickle-cell disease change with age (1). This well-known variation may be an expression of the pre-programmed progression of the disorder, it may reflect the changing interaction of the disorder with its host (changes as the body matures for example), and it may reflect the body's changing response to environmental challenges. Whatever the cause of these shifts in clinical expression, the existence of age-related trends highlights a pattern that can be exploited to help understand the reasons for differences in clinical expression between people with sickle-cell disease, and changes in the activity of clinical-expression within individuals. Ultimately we might be able to describe disease phenotypes that would benefit from invasive prophylactic clinical intervention, but this goal remains distant.

During the first decade of life the switch from fetal to adult haemoglobin underlies the changing clinical expression. This first decade is typified by acute problems: life-threatening infection, the acute-chest syndrome, acute splenic sequestration, and stroke. In the second decade of life the painful-crisis takes over as the dominant clinical event – rarely life threatening, but placing a physical and psychological burden on those that it affects. Late adolescence is a period of relative wellbeing for the sickle-cell patient. In the third decade and later chronic organ damage (such as renal failure or pulmonary deterioration) becomes an increasing burden.

Clinical heterogeneity is a key feature of the disease. Any single patient can have all complications. Some may have none but die with a single acute event. Some skip one or more 'phases'. A person with sickle-cell disease would be expected to survive into the fifth or sixth decade, although again there is wide variation in survival rates (2;3). There is much evidence that variation in the expression of the disease has a geographical dimension, although reports from different countries are complicated by marked differences in the characteristics of the populations studied (for example, many studies are cross sectional with different age structures).

How should we categorise these clinical features of sickle-cell disease? Sensible approaches have been adopted by others. Steinberg (1999) described those due to hemolysis of sickled cells and those due to vasoocclusion caused by sickled cells (4). Serjeant (1992) used a systemic approach, describing events by body systems (5). Others have grouped outcomes into distinct age-related phases (6;7). Given the longitudinal aspect of our investigations, we adopt an age-related description.

In this chapter we describe the annual incidence of common clinical events associated with sickle-cell disease, and describe the proportion of participants affected. Along with descriptions of mortality and survival, and in-depth case-studies of specific morbidity (in Sections 6.3.7, 6.3.9 and in Chapter Three), these clinical event descriptions fulfil the

original aim of the JSSCD and of this thesis – to document and summarise the aetiology and natural history of sickle-cell disease.

6.2 Methods

We describe fourteen common clinical events: eight acute events and six chronic events. The acute events are dactylitis, acute splenic sequestration, bacteraemia, aplastic crisis, stroke, acute chest syndrome, the painful crisis, and priapism. The chronic events are hypersplenism, gallstones, leg-ulceration, proliferative sickle retinopathy, osteonecrosis, and hepatomegaly.

6.2.1 Incidence rates

We examined the incidence rates of clinical events separately for homozygous sickle-cell (SS) disease and sickle-cell haemoglobin C (SC) disease using either the JSSCD or the clinic sample. Some clinical events are acute and potentially recurring, whilst others are chronic; sometimes irreversible and sometimes persisting for many years. For each acute clinical event we calculated incidence rates of all events in a study group and of individuals' first event. For chronic clinical events we calculated the incidence rate of individuals' first event. To calculate the first-event incidence rate, we removed participants from the calculations when their first event occurred. We can therefore interpret the first-event incidence rate as the incidence of a clinical event amongst those participants without a previous history of the event. We graphed incidence rates by year of age and tabulated selected incidence summaries: the 'all-event' and 'first-event' crude rates, the peak incidence rate and the age at which this peak rate occurs, and the clinical event age range.

6.2.2 Proportions affected

We calculated the proportions of participants affected by each clinical event (acute or chronic) by December 1999 (which was the end of our study window).

6.2.3 Gender differences

In chapters seven and eight we are interested in the contribution of patient characteristics and clinical events to an overall measure of health-status. Gender is a known contributor to variation in haematological expression (8), and we now examine whether it influences clinical outcomes.

We compare clinical events between male and female JSSCD participants with SS disease. For seven acute clinical events we calculated a relative-risk of all-event incidence rates for men compared to women (an eighth acute clinical event occurs only in males). We provided a formal test of these rates using a Mantel-Haenszel χ^2-statistic, adjusting for the potential effect of age as a continuous covariate. More events in men lead to a relative risk above one. For all events we calculated the proportion of each gender affected by December 1999. We

constructed a two-by-two table for each event (men and women, affected and not-affected) and compared these proportions using a χ^2-test.

6.2.4 Adjusting for multiple tests

The analysis of gender differences presents a number of independent univariate tests; we perform two tests on each acute event and a single test on each chronic event ($8\times2+6 = 22$ tests). False-positive conclusions are possible; the probability of a false positive conclusion at 5% significance is $1-(1-0.05)^{22} = 0.68$. We adjust these results using two techniques: control of the family-wise error rate (FWER), and control of the false discovery rate (FDR). FWER control protects against the probability of wrongly rejecting any null hypothesis (which is a false-positive result). These procedures give conservative protection, but are not powerful in the sense that the chance of rejecting null hypotheses that are truly false is also small. We implement a common FWER procedure known as Sidák's correction (9). At the other extreme is the common approach to ignore the multiplicity problem altogether, which is intuitively inappropriate. Using an FDR procedure we control the expected proportion of the rejected hypotheses that are falsely rejected; it provides a more powerful adjustment, whilst still offering a meaningful measure of error (10).

Additionally, a re-sampling technique was used to assess the robustness of all formal tests of significance. Using the original JSSCD sample (which has 315 patients), 315 patients were drawn randomly (and with replacement) to create a new sample in which each patient may appear once, more than once, or not at all. The same gender comparisons were performed on this 'bootstrap' dataset. The procedure was repeated many times (we choose 1000 repetitions) and a distribution of relative risks were formed for each clinical event. Several extra statistics were calculated:

(a) Bootstrap confidence intervals.

Bias-corrected and accelerated (BCa) confidence intervals (at the 95% level) were produced (11).

(b) Inference validity

We want to know whether any of our tests of inference could be falsely significant. Truly important differences should remain significant in most bootstrap samples. The number of bootstrap samples that record significant results was used as a measure of the robustness of our inference. We present (as percentages) the number of bootstrap samples for which p-values associated with gender comparisons of incidence rates or proportion of participants affected are less than three threshold levels of significance (the 5% level, and levels adjusted for multiple testing – see section 6.2.4, first paragraph).

6.2.5 Mortality

We present a description of mortality in the JSSCD. We grouped deaths by cause. We should interpret the frequency of these causes of death against the frequency of the event in the JSSCD population. To do this, we calculated the *case-fatality rate* as the number of deaths from each cause divided by the number of recorded clinical events. We assessed variation in the *case-fatality rate* using 95% bootstrapped confidence limits.

In 1995, Lee and colleagues reported that mortality in the JSSCD decreased among participants born later in the recruitment period. They explained this improvement as a combined reduction in mortality from acute splenic sequestration and pneumococcal septicaemia-meningitis, following introduction of specific interventions (12). We have updated this report to include mortality between 0 and 27 years of age. Following the original methods, we divided the JSSCD into tertiles based on date of birth (group one: June 1973 to Dec 1975, group two: Dec 1975 to Jan 1979, group three Jan 1979 to Dec 1981). We plotted Kaplan-Meier curves for each tertile, and assessed group differences formally using the log-rank test and the generalised Wilcoxon test (which accounts for possible deviations from the proportional-hazards assumption). We repeated this procedure for the original dataset (mortality by 1995), and for the updated dataset (mortality by 1999). When assessing formal group differences we ensured that each birth group was followed for an equal length of time; we restricted the original data to follow-up between 0 and 14 years of age, and the updated data to between 0 and 18 years. Deaths in the Government screening programme were included to further assess secular change in mortality.

6.2.6 Graphical displays

For acute clinical events, age-specific all-event incidence rates in the JSSCD are presented visually for each year of life between birth and 27 years of age (the maximum age of JSSCD members in 1999). Incidence rates can be quite variable for the less common clinical events. To highlight event trends above this variation we graphed two-year moving averages of incidence rates for events below a peak of 50 events per 100 patient years, and five-year moving averages for events below a peak of 20 events per 100 patient years. Jackknife 95% confidence intervals were calculated for all incidence rates. All-event incidence rates are also stratified by gender for acute clinical events.

The proportions of participants affected by each clinical event are plotted against time to first clinical event using the Kaplan-Meier function, which adjusts for censored participants; those that leave the study without experiencing the event. JSSCD participants are presented by genotype, and SS participants are also stratified by an adjustment to cope with late-entry bias (see section 6.2.8 for a description of this adjustment method).

6.2.7 Independent events

Repeat presentations to clinic may be due to the same underlying clinical event. Treating all participant presentations as independent clinical events is likely to overestimate clinical event frequency. If a participant presents more than once within a short period for the same clinical event, we treated these consecutive presentations as realisations of the same underlying clinical event: consecutive presentations for the ACS less than 15 days apart and consecutive presentations for any other acute event less than eight days apart.

6.2.8 Late entry bias

We have seen in Chapter Three that a clinic-based population will have a substantial late-entry bias, with up to 90% of people with sickle-cell disease not enrolled to a specialist clinic by their fifth birthday, and up to half not enrolled by 18 years of age. An unselected birth cohort with complete clinical event reporting is required to protect against late-entry bias. Although complete reporting is probably not possible, the JSSCD is a birth cohort that are encouraged to attend the free sickle-cell clinic whenever sick, and so most clinical events in this population are probably recorded (13).

In this chapter we quantify the effect of late-entry on clinical research, by comparing the cumulative proportions of clinical events in the clinic and JSSCD participants.

Methods to cope with late-entry bias in the clinic population are available at the analysis stage of any study. We implement two methods. The first is an accepted adjustment that examines morbidity and mortality incidence from birth with those at risk restricted to patients that have been recruited to clinic (Method One) (14). This technique requires that the risk of morbidity or mortality at any point is the same for those recruited and not recruited to the study, which may be unrealistic. The second method is a new simulation technique using the gold-standard JSSCD to inform the morbidity and mortality experience of the clinic population (Method Two). This technique is described in detail and is applied to survival in sickle-cell disease in case study 5.

6.2.9 Defining clinical events

Sickle-cell related events were defined at the initiation of the JSSCD. Only events that resulted in a clinic visit were recorded. Fourteen common clinical events associated with sickle-cell disease are described. *Dactylitis* (also called the hand-foot syndrome) was defined as pain with or without swelling and/or tenderness in the feet and/or hands. *Acute splenic sequestration* was defined as a decrease from steady-state total haemoglobin of at least 2g/dl, evidence of compensatory marrow response (measured by reticulocyte count) and an acutely enlarging spleen (15). *Hypersplenism* was arbitrarily defined as an enlarged spleen 4cm or more below the left-costal margin, a total haemoglobin level below 6.5g/dl, reticulocytes greater than 15 percent, and platelets below 200×10^9/l, observed on at least two occasions six months apart. *The acute chest syndrome* was defined as a patient presenting with either

chest pain, a temperature above 38.5°C, tachypnea, wheezing or cough, with confirmation of a new pulmonary infiltrate involving at least one complete segment that was consistent with the presence of alveolar consolidation. A *bone pain crisis* was defined as bone pain (not affecting ribs or sternum) or chest pain confined to the sternum and/or ribs, of sufficient severity to require clinic attendance and analgesia (a severe crisis requiring narcotic analgesia, a mild crisis requiring non-narcotic analgesia), and for which no other explanation could be found. *Osteonecrosis* (also called avascular necrosis) was defined if a bone pain crisis was associated with swelling of the affected areas. Osteonecrosis of the hip can be graded as stages I to IV of increasing severity using the system of Ficat, which classifies using radiograph and MRI (16). *Aplastic crisis* was defined as a fall in haemoglobin concentration to below steady-state levels (this fall is usually greater than 3g/dl) associated with zero reticulocytes or, if present, a daily increase consistent with the recovery stage. *Stroke* (also called a cerebrovascular accident or CVA) was defined as an acute neurological syndrome secondary to the occlusion of an artery or to hemorrhage with resultant neurological signs and symptoms. The presence of *gallstones* (also called cholilithiasis) was confirmed by ultrasound examination performed by a single observer using a 3.0-MHz or 5.0-MHz sector probe and an ATL Ultramark 4 instrument (Advanced Technology Laboratories, Tempe, Arizona). Gallstones were defined as discrete echogenic objects that maintained their shape and moved with rotation of the gallbladder. Sludge was defined as echogenic material within the gallbladder lumen that layered and changed shape and position on moving the patient. *Priapism* was defined as a prolonged, undesirable, and painful erection lasting beyond any period of sexual stimulation. *Stuttering priapism* was defined as short (typically less than three hours duration), self-limiting attacks that were recurrent with normal intervening sexual function. *Major priapism* was defined as an attack lasting over 24 hours. *A leg-ulcer* was defined as a local excavation of the skin surface of the lower leg, with or without a history of local trauma, which had persisted for a minimum of two weeks. *Proliferative sickle retinopathy* was defined as the presence of proliferative lesions in the peripheral retinal vasculature secondary to peripheral retinal ischaemia. Lesions were identified by fluorescein angioscopy and angiography following intravenous injection of 3-4ml of 20% sodium flourescein. This diagnostic technique obtained permanent photographs through the dilated pupil with a retinal camera once the dye appeared in the retinal vasculature, and allowed subtle, progressive changes in retinal vasoperfusion to be detected. *Invasive bacterial infection* (also called bacteraemia) was defined as the isolation of one of five organisms (*S pneumoniae*, *H influenzae* type b, *Salmonella spp*, *E coli*, or *Klebsiella spp*) from cultures of blood of cerebral spinal fluid and, in the case of *Salmonella spp*, from sinuses or aspiration from bone sites. *Hepatomegaly* was defined as enlargement of the liver compared to age-dependent reference values. In adults, hepatomegaly was established by clinical examination, if the liver was palpable below the left costal margin or had a span of 14cm or greater.

6.2.10 Defining the periods of life

For JSSCD participants we roughly categorise clinical events into either the first, second, or third decade of life. The first decade includes the neonatal period, infancy and childhood. The neonatal period is the first four weeks of extra-uterine life. We define infancy as the period between neonatal life and two-years of age. We define childhood as the period between infancy and puberty. The second decade is adolescence, which we define as the period between puberty and maturity. We assume maturity at 20 years of age. The third decade is the 10-year period beyond maturity.

6.3 Results

We tabulate summaries of incidence rates for study participants with SS disease (JSSCD participants in Table 6.1, clinic sample participants in Table 6.2), and with SC disease (JSSCD participants in Table 6.3, clinic sample participants in Table 6.4). We present age-related incidence rates for high incidence acute events (dactylitis, and the painful crisis) in Figure 6.1a, for medium incidence acute events (ACS, ASS, and priapism) in Figure 6.1b, and for low incidence clinical events (bacteraemia, stroke, and the aplastic crisis) in Figure 6.1c. We present age-related incidence rates for acute clinical events by gender in Figure 6.5. We present the cumulative proportion of participants affected by each clinical event at various ages for each genotype in Table 6.5 to Table 6.7 (JSSCD participants in Table 6.5, acute events among clinic participants in Table 6.6, chronic events among clinic participants in Table 6.7). We present these cumulative proportions graphically in Figure 6.2 to Figure 6.4 (high incidence events in Figure 6.2, moderate incidence events in Figure 6.3, and low incidence events in Figure 6.4). We present gender differences in incidence rates and in cumulative involvement for JSSCD participants in Table 6.8 and for clinic study participants in Table 6.9. We present the clinic study bias in unadjusted and adjusted age-specific proportions for each clinical event in Table 6.10.

6.3.1 The first decade

(a) The neonatal period

At birth, and for the first few weeks of life, children with sickle-cell disease have no typical symptoms. Haematologic differences between SS and AA controls were apparent from as early as the second week of life (13) and these early life differences have been described in Chapter Five.

(b) Infants

The earliest recorded clinical complication in the JSSCD was an episode of acute chest syndrome in a two-week old neonate, and seven ACS events occurred in children less than three months old. Other known early-life events began around the third month of life (e.g. the first case of dactylitis was seen in an 89-day old child and the first case of ASS in an 85-day old child). By one year of age typical clinical event patterns are evident. Dactylitis and splenic dysfunction are the most common early-life events.

Dactylitis in SS disease

The crude all-event incidence rate of dactylitis among JSSCD participants with SS disease was 8.6 per 100 patient years (95% confidence interval 7.1 to 10.4), with a peak incidence of 44.2 per 100 patient years (34.9 to 56.9) in infants between one and two years old (Table 6.1 and Figure 6.1a). Over half of all SS participants had experienced a dactylitis event by 10 years of age. Compared to SC disease, the event rate was 12 times higher in SS disease (Table 6.5 and Figure 6.2aI).

Acute Splenic Sequestration in SS disease

The crude all-event incidence rate of ASS among JSSCD participants with SS disease was 3.8 per 100 patient years (3.1 to 4.6), with a peak incidence of 25.3 per 100 patient years (18.8 to 34.8) in infants between one and two years old (Table 6.1 and Figure 6.1b). Over one-third of all SS participants had experienced an ASS event by 10 years of age. The event was rarely seen in SC disease (Table 6.5 and Figure 6.3aI).

(c) Childhood

Early splenic dysfunction leads to infant susceptibility to opportunistic infection (17); common infective agents are *Streptococcus pneumoniae* and b19 infection (18). Splenomegaly becomes common and is often related to a haematological picture of hypersplenism; lowered total haemoglobin and platelet count, and an increased reticulocyte count. Beyond infancy, the pattern of recurrent pain usually becomes established, with early-life dactylitis replaced by the well known episodic pain of limbs, back, and abdomen. These painful crises, along with episodes of the acute chest syndrome, become the top two causes of hospitalisation. Stroke, caused by cerebrovascular damage from occlusion of the major vessels emerges as an infrequent but often fatal complication.

Hypersplenism in SS disease

The crude first-event incidence rate of hypersplenism among JSSCD participants with SS disease was 1.3 per 100 patient years (1.0 to 1.7), with a peak incidence of 6.4 per 100 patient years (4.1 to 10.8) in infants between one and two years old (Table 6.1). One-fifth of all SS participants had experienced hypersplenism by 25 years of age. The event was rarely seen in SC disease (Table 6.5 and Figure 6.4cI).

Table 6.1.

The incidence of common clinical events among 315 JSSCD participants with homozygous sickle-cell disease.

	Follow-up / # events			Incidence						
Clinical event	**All Events**	**First event**	**Peak event**	**All-events (95% CI)**	**First-event (95% CI)**	**Peak (95% CI)**	**Age at peak**	**median age**	**age IQR**	**age range**
Acute events										
Dactylitis	5154.4 443	2838.9 155	285.0 126	8.6 (7.1 - 10.4)	5.46 (4.40 – 6.8)	44.2 (34.9 – 56.9)	1 - 2	1.75	1.0 – 3.2	0.4 – 8.6
Acute splenic sequestration	5154.4 195	3427.8 109	285.0 72	3.8 (3.1 – 4.6)	3.18 (2.53 – 4.0)	25.3 (18.8 – 34.8)	1 - 2	1.29	0.8 – 2.2	0.2 – 9.2
Bacteraemia	5154.4 72	4541.1 54	285.0 10	1.4 (1.1 – 1.9)	1.19 (0.90 – 1.6)	3.5 (2.0 – 7.0)	1 - 2	4.06	1.7 – 7.5	0.1 – 24.1
Aplastic crisis / b19 infection	--	4021.2 101	221.4 11	--	2.51 (2.06 – 3.1)	5.0 (2.8 – 9.6)	6 - 7	7.86	4.7 – 11.3	0.5 – 19.5
Stroke	5154.4 36	4983.7 26	274.4 6	0.7 (0.5 – 1.1)	0.52 (0.36 – 0.8)	2.2 (0.8 – 8.8)	3 - 4	8.47	5.1 – 13.8	1.3 – 22.2
Acute chest syndrome	5154.4 509	2463.8 189	285.0 77	9.9 (8.6 – 11.46)	7.67 (6.39 – 9.2)	27.0 (21.0 – 35.3)	1 - 2	5.25	2.4 – 8.6	0.4 – 20.9
Painful Crisis (mild and severe)	5154.4 2628	1821.7 255	38.4 72	52.0 (44.2 – 61.7)	14.0 (12.55 – 15.6)	187.7 (116.9 – 321.5)	24 - 25	14.00	7.6 – 19.5	1.4 – 25.4
Painful Crisis (severe only)	5154.4 854	3510.5 172	38.4 35	16.6 (13.2 – 21.1)	4.9 (4.26 – 5.6)	91.3 (46.2 – 207.3)	24 - 25	17.08	8.8 – 20.7	1.3 – 25.6
Priapism	2738.9 68	2595.6 31	64.7 12	2.5 (1.6 – 4.2)	1.19 (0.87 – 1.7)	18.6 (6.4 – 75.7)	20 - 21	18.58	15.8 – 20.4	2.1 – 24.5
Chronic events										
Hypersplenism	--	4334.8 56	264.6 17	--	1.29 (0.98 – 1.7)	6.4 (4.1 – 10.8)	1 - 2	3.56	1.7 – 5.8	0.4 – 14.5
Gallstones	--	1980 96	169.3 15	--	4.85 (3.98 – 5.9)	8.9 (5.4 – 15.5)	13-14	13.37	11.0 – 17.8	5.1 – 23.8
Leg-ulceration	--	3207.2 122	121.8 16	--	3.8 (2.1 – 7.5)	13.1 (5.6 – 38.3)	18 - 19	16.05	13.8 – 18.1	6.0 – 22.8
Proliferative sickle retinopathy	--	3120 14	77.4 4	--	0.45 (0.28 – 0.8)	5.2 (2.0 – 17.8)	22 – 23	21.6	19.0 – 22.7	16.4 – 26.2
Osteonecrosis	--	3436.6 139	247.5 23	--	4.04 (3.38 – 4.9)	9.3 (6.3 – 14.4)	2 - 3	7.29	3.5 – 12.9	0.7 – 22.3
Hepatomegaly	--	4516.1 67	220.4 8	--	1.5 (1.2 – 1.9)	3.6 (1.9 – 8.1)	8 - 9	9.52	7.4 – 12.7	2.0 – 23.5

Table 6.2.

The incidence of common clinical events among 4207 clinic participants with homozygous sickle-cell disease.

	Follow-up / # events			Incidence						
Clinical event	**All Events**	**First event**	**Peak event**	**All-events (95% CI)**	**First-event (95% CI)**	**Peak (95% CI)**	**Age at peak**	**median age**	**age IQR**	**age range**
Acute events										
Dactylitis	46034 567	43593.3 337	802 297	1.2 (1.1 – 1.4)	0.8 (0.7 – 0.9)	37.0 (32.0 – 43.1)	0 - 2	1.91	1.3 – 3.1	0.4 – 28.5
Acute splenic sequestration	46034 222	45037.9 150	1769.1 49	0.5 (0.4 – 0.6)	0.3 (0.3 – 0.4)	11.6 (8.9 – 15.5)	0 - 2	2.42	1.4 – 5.9	0.6 – 25.2
Bacteraemia	46034 89	45574.3 81	802 13	0.2 (0.2 – 0.3)	0.2 (0.1 – 0.2)	1.6 (0.9 – 3.5)	0 - 2	9.23	3.0 – 22.8	0.6 – 56.8
Aplastic crisis / b19 infection	--	44282.4 234	2129.5 43	--	0.5 (0.5 – 0.6)	2.0 (1.5 – 2.8)	4 - 6	8.62	5.3 – 14.6	1.3 – 32.5
Stroke	46034 144	45457.9 112	2620.2 20	0.3 (0.3 – 0.4)	0.3 (0.2 – 0.3)	0.8 (0.46 – 1.4)	10 - 12	11.16	7.3 – 22.2	1.4 – 64.7
Acute chest syndrome	46034 1698	38418.6 878	1769.1 225	3.7 (3.4 – 4.0)	2.3 (2.1 – 2.5)	12.7 (10.8 – 15.1)	2 - 4	9.41	5.0 – 22.6	1.0 – 53.1
Painful Crisis (mild and severe)	46034 16112	26058.4 2418	2218.2 1183	35.0 (32.8 – 37.5)	9.3 (8.9 – 9.7)	53.3 (46.7 – 61.2)	26 - 28	23.18	13.7 – 30.7	2.0 – 57.6
Painful Crisis (severe only)	46034 7795	32376 1565	2218.2 618	16.9 (15.4 – 18.7)	4.8 (4.6 – 5.1)	27.9 (23.1 – 33.9)	26 - 28	23.29	13.9 – 30.3	2.0 – 54.5
Priapism	20615.5 918	19042.8 212	973.4 158	4.5 (3.6 – 5.6)	1.1 (1.0 – 1.3)	16.2 (11.5 – 23.7)	26 - 28	25.70	21.8 – 29.0	8.0 – 47.3
Chronic events										
Hypersplenism	--	44536 198	782.1 36	--	0.4 (0.4 – 0.5)	4.6 (3.3 – 6.5)	0 - 2	6.03	3.6 – 9.8	0.9 – 33.8
Gallstones	--	46033 251	1276.7 16	--	0.5 (0.5 – 0.6)	1.3 (0.8 – 2.1)	34 - 36	26.35	19.8 – 34.3	7.0 – 60.9
Leg-ulceration	--	34555.9 1226	2167.9 164	--	3.6 (3.4 – 3.8)	7.6 (6.5 – 8.9)	18 - 20	28.20	22.1 – 36.7	11.7 – 60.2
Proliferative sickle retinopathy	--	44787.2 128	201.1 6	--	0.3 (0.2 – 0.3)	3.0 (1.4 – 7.8)	52 - 54	36.63	31.9 – 44.4	7.9 – 67.6
Osteonecrosis	--	40242.3 741	1668 79	--	1.8 (1.7 – 2.0)	4.7 (3.8 – 6.0)	2 - 4	20.76	10.0 – 28.8	1.5 – 54.7
Hepatomegaly	--	40958 542	1698.4 51	--	1.3 (1.2 – 1.4)	3.0 (2.3 – 4.0)	2 - 4	15.07	7.4 – 30.8	1.6 – 63.5

Table 6.3.

The incidence of common clinical events among 167 JSSCD participants with sickle-cell (SC) disease.

	Follow-up / # events			Incidence						
Clinical event	**All Events**	**First event**	**Peak event**	**All-events (95% CI)**	**First-event (95% CI)**	**Peak (95% CI)**	**Age at peak**	**median age**	**age IQR**	**age range**
Acute events										
Dactylitis	3207.22	2933.115	159.29	0.7 (0.4 – 1.4)	0.5 (0.3 – 0.9)	5.7 (2.8 – 13.1)	1 - 2	1.57	1.2 – 2.5	0.6 – 5.3
Acute splenic sequestration	3207.21	--	--	--	--	--	--	--	--	4 – 5
Bacteraemia	3207.29	3100.68	--	0.3 (0.1 – 0.7)	0.3 (0.1 – 0.6)	--	0 - 3	5.42	1.2 – 8.3	0.8 – 23.8
Aplastic crisis / b19 infection	--	3090.412	--	--	0.4 (0.2 – 0.7)	--	--	13.34	9.5 – 16.7	5.5 – 18.0
Stroke	3207.20	--	--	--	--	--	--	--	--	--
Acute chest syndrome	3207.2102	2380.755	153.916	3.2 (2.4 – 4.2)	2.3 (1.7 – 3.1)	10.4 (5.9 – 20.2)	0 - 1	4.73	1.5 – 10.1	0.1 – 21.2
Painful Crisis (mild and severe)	3207.21308	1324.6143	43.341	40.8 (34.6 – 48.4)	10.8 (9.4 – 12.4)	94.7 (69.5 – 132.3)	23 - 24	13.58	8.2 – 18.4	2.3 – 24.8
Painful Crisis (severe only)	3207.2246	2350.582	24.18	7.7 (6.0 – 9.9)	3.5 (2.9 – 4.3)	33.2 (16.8 – 75.1)	24 - 25	14.11	9.0 – 19.4	2.5 – 25.2
Priapism	1647.19	1639.85	--	0.6 (0.1 – 3.6)	0.3 (0.1 – 0.9)	--	19 - 24	21.11	20.1 – 21.6	19.2 – 23.2
Chronic events										
Hypersplenism	3207.21	--	--	--	--	--	--	--	--	24 – 25
Gallstones	--	1359.118	89.84	--	1.3 (0.8 – 2.2)	4.5 (1.7 – 15.9)	18 - 19	15.14	12.7 – 18.2	10.6 – 20.0
Leg-ulceration	--	4582.389	157.514	--	1.94 (1.63 – 2.3)	8.9 (5.4 – 15.8)	16 - 17	18.66	16.4 – 20.8	10.8 – 24.8
Proliferative sickle retinopathy	--	1936.845	57.54	--	2.3 (1.8 – 3.0)	7.0 (2.7 – 24.0)	22 - 23	17.2	14.4 – 20.3	8.1 – 26.3
Osteonecrosis	--	2363.462	144.410	--	2.6 (2.0 – 3.4)	6.9 (3.8 – 14.1)	3 - 4	8.41	5.1 – 12.3	1.2 – 22.8
Hepatomegaly	--	3124.46	--	--	0.2 (0.1 – 0.5)	--	--	6.28	4.7 – 17.7	2.9 – 17.7

Table 6.4.

The incidence of common clinical events among 1567 clinic participants with sickle-cell (SC) disease.

	Follow-up / # events			Incidence						
Clinical event	**All Events**	**First event**	**Peak event**	**All-events (95% CI)**	**First-event (95% CI)**	**Peak (95% CI)**	**Age at peak**	**median age**	**age IQR**	**age range**
Acute events										
Dactylitis	11730 11	11632.3 11	--	0.1 (0.05 – 0.18)	0.09 (0.05 – 0.18)	--	--	6.02	1.6 – 19.8	1.0 – 32.4
Acute splenic sequestration	11730 17	11666.9 14	249.9 5	0.1 (0.08 – 0.28)	0.12 (0.07 – 0.21)	2.0 (0.4 – 18.8)	2 - 4	5.21	3.9 – 12.5	2.4 – 40.7
Bacteraemia	11730 3	11717.8 3	--	0.03 (0.01 – 0.13)	0.03 (0.01 – 0.13)	--	--	9.43	--	3.6 – 21.8
Aplastic crisis / b19 infection	--	11689.4 13	--	--	0.11 (0.07 – 0.20)	--	--	14.85	4.2 – 13.4	3.4 – 28.8
Stroke	11730 7	11725.6 6	--	0.1 (0.03 – 0.17)	0.05 (0.02 – 0.13)	--	--	42.76	20.7 – 54.0	7.6 – 62.9
Acute chest syndrome	11730 169	10806.6 125	93 13	1.4 (1.2 – 1.8)	1.2 (1.0 – 1.4)	14.0 (8.1 – 26.1)	0 - 1	11.15	5.2 – 22.7	1.1 – 69.9
Painful Crisis (mild and severe)	11730 3403	7038.6 790	402 176	29.0 (26.5 – 31.8)	11.2 (10.3 – 12.2)	43.8 (35.2 – 55.2)	4 - 6	18.84	11.4 – 27.8	3.2 – 60.2
Painful Crisis (severe only)	11730 1243	8951.7 451	532 91	10.6 (9.4 – 12.0)	5.0 (4.6 – 5.6)	17.9 (13.6 – 23.9)	6 - 8	18.33	10.7 – 27.2	3.2 – 56.9
Priapism	5504.8 45	5448.5 17	--	0.8 (0.4 – 2.16)	0.3 (0.2 – 0.5)	--	--	30.4	23.4 – 36.9	12.4 – 54.4
Chronic events										
Hypersplenism	--	11651.8 20	--	--	0.2 (0.1 – 0.3)	--	--	14.85	10.6 – 21.6	2.9 – 49.0
Gallstones	--	11730 14	370.4 4	--	0.12 (0.06 – 0.26)	1.1 (0.4 – 3.8)	34 - 36	34.91	31.5 – 37.6	28.8 – 59.0
Leg-ulceration	--	11264.4 81	685.3 12	--	0.7 (0.6 – 0.9)	1.8 (1.0 – 3.3)	18 - 20	31.00	19.8 – 51.3	8.6 – 61.7
Proliferative sickle retinopathy	--	9222.2 297	35.1 7	--	3.2 (2.9 – 3.6)	19.9 (8.8 – 50.2)	50 - 52	31.06	24.8 – 38.8	15.4 – 66.0
Osteonecrosis	--	10668.2 163	489.3 19	--	1.5 (1.3 – 1.8)	3.9 (2.5 – 6.3)	6 - 8	18.23	9.8 – 27.2	3.4 – 58.2
Hepatomegaly	--	11730 16	--	--	0.14 (0.09 – 0.23)	--	--	19.36	15.3 – 34.6	5.5 – 72.0

Bacteraemia in SS disease

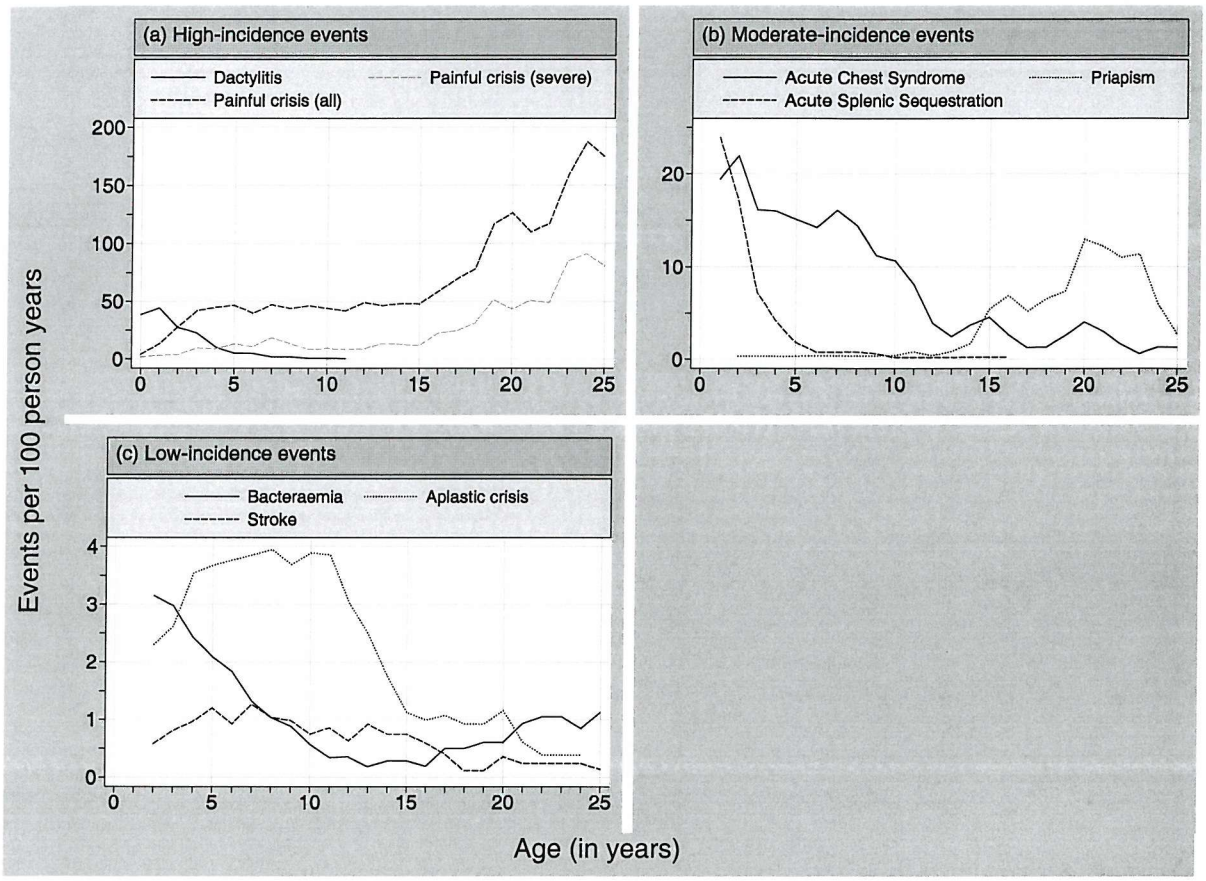
The crude all-event incidence rate of bacteraemia among JSSCD participants with SS disease was 1.4 per 100 patient years (1.1 to 1.9), with a peak incidence of 3.5 per 100 patient years (2.0 to 7.0) in infants between one and two years old Table 6.1 and Figure 6.1c). Approximately one-fifth of all SS participants had experienced one or more bacteraemias by 25 years of age. Compared to SC disease, the crude event rate was 5 times higher in SS disease (Table 6.5 and Figure 6.4bI).

Acute Chest Syndrome in SS disease

The crude all-event incidence rate of ACS among JSSCD participants with SS disease was 9.9 per 100 patient years (8.6 to 11.5), with a peak incidence of 27.0 per 100 patient years (21.0 to 35.3) in infants between one and two years old (Table 6.1 and Figure 6.1b). Almost three quarters of all SS participants had experienced one or more ACS episode by 25 years of age. Compared to SC disease, the crude event rate was 3 times higher in SS disease (Table 6.5 and Figure 6.2dI).

Figure 6.1

Incidence of acute clinical events among 315 JSSCD members with SS disease.



Osteonecrosis in SS disease

The crude first-event incidence rate of osteonecrosis among JSSCD participants with SS disease was 4.0 per 100 patient years (3.4 to 4.9), with a peak incidence of 9.3 per 100 patient years (6.3 to 14.4) in children between three and four years old (Table 6.1). Approximately half of all SS participants had experienced osteonecrosis by 25 years of age. Compared to SC disease, the proportion affected was 30% higher in SS disease (Table 6.5 and Figure 6.2fI).

Aplastic crisis in SS disease

The crude first-event incidence rate of aplastic crisis among JSSCD participants with SS disease was 2.5 per 100 patient years (2.1 to 3.1), with a peak incidence of 5.0 per 100 patient years (2.8 to 9.6) in children between six and seven years old (Table 6.1 and Figure 6.1c). Approximately two-fifths of all SS participants had experienced an aplastic crisis by 25 years of age. Compared to SC disease, the event rate was 6 times higher in SS disease (Table 6.5 and Figure 6.3cI).

Stroke in SS disease

The crude all-event incidence rate of stroke among JSSCD participants with SS disease was 0.7 per 100 patient years (0.5 to 1.1), with a peak incidence of 2.2 per 100 patient years (0.8 to 8.8) in children between three and four years old (Table 6.1 and Figure 6.1c). Approximately 10% of all SS participants had experienced one or more strokes by 25 years of age. The event was not seen in SC disease (Table 6.5 and Figure 6.4aI).

Hepatomegaly in SS disease

The crude first-event incidence rate of hepatomegaly among JSSCD participants with SS disease was 1.5 per 100 patient years (1.2 to 1.9), with a peak incidence of 3.6 per 100 patient years (1.9 to 8.1) in children between eight and nine years old (Table 6.1). Over one-quarter of all SS participants had experienced hepatomegaly by 25 years of age. Compared to SC disease, the proportion affected was 8 times higher in SS disease (Table 6.5 and Figure 6.3eI).

6.3.2 ***The second decade: Adolescence***

Adolescents with SS disease face the physical limitations of the disease and the psychological impact of a serious chronic condition. The expression of sickle cell disease in older children and adolescents is not fundamentally different from childhood, but certain clinical events become less or more common. Bacteraemias, dactylitis, ASS, ACS, and stroke decrease in frequency, and gallstones, episodes of severe pain, and leg ulceration increase in frequency. A large literature investigates the psychosocial issues of coping with the disease (19-21).

Gallstones in SS disease

The crude first-event incidence rate of gallstones among JSSCD participants with SS disease was 4.9 per 100 patient years (5.4 to 15.5), with a peak incidence of 8.9 per 100 patient years (5.4 to 15.5) in adolescents between 13 and 14 years old (Table 6.1). Approximately half of all SS participants had gallstones by 25 years of age. Compared to SC disease, the proportion affected was 4 times higher in SS disease (Table 6.5 and Figure 6.2gI).

Painful crisis (all events) in SS disease

The crude all-event incidence rate of all painful crises among JSSCD participants with SS disease was 52.0 per 100 patient years (44.2 to 61.7), with a peak incidence of 187.7 per 100 patient years (116.9 to 321.5) in adults between 24 and 25 years old (Table 6.1 and Figure 6.1a). Almost all SS participants had experienced one or more painful crisis by 25 years of age. Compared to SC disease, the crude event rate was 1.3 times (or 30%) higher in SS disease (Table 6.5 and Figure 6.2bI).

Painful crisis (severe events) in SS disease

The crude all-event incidence rate of severe painful crises among JSSCD participants with SS disease was 16.6 per 100 patient years (13.2 to 21.1), with a peak incidence of 91.3 per 100 patient years (46.2 to 207.3) in adults between 24 and 25 years old (Table 6.1 and Figure 6.1c). Approximately three-quarters of all SS participants had experienced one or more severe painful crisis by 25 years of age. Compared to SC disease, the crude event rate was 2 times higher in SS disease (Table 6.5 and Figure 6.2cI).

Priapism in SS disease

The crude all-event incidence rate of priapism among JSSCD male participants with SS disease was 2.5 per 100 patient years (1.6 to 4.2), with a peak incidence of 18.6 per 100 patient years (6.4 to 75.7) in men between 20 and 21 years old (Table 6.1 and Figure 6.1b). Approximately two-fifths of all SS participants had experienced one or more episodes of priapism by 25 years of age. Compared to SC disease, the crude event rate was 4 times higher in SS disease (Table 6.5 and Figure 6.3bI).

Table 6.5.

Cumulative proportion of JSSCD members with each clinical event by genotype (315 members with SS disease and 167 members with SC disease) and by age in years.

		Age (in years)								
Event	**Genotype**	**1**	**2**	**3**	**4**	**5**	**10**	**15**	**20**	**25**
Acute events										
Dactylitis	SS	21.7	39.4	46.5	48.6	50.4	53.6	53.6	53.6	53.6
	SC	1.9	6.3	7.5	8.2	8.8	9.5	9.5	9.5	9.5
Acute splenic sequestration	SS	15.5	29.1	33.4	34.9	35.6	37.5	37.5	38.0	38.0
	SC	0.0	0.0	0.0	0.0	0.7	0.7	0.7	0.7	0.7
Bacteraemia	SS	3.1	6.2	8.7	10.8	13.4	17.5	18.0	19.7	21.6
	SC	0.6	1.9	2.5	2.5	2.5	3.8	4.5	4.5	7.1
Aplastic crisis / b19 infection	SS	1.3	1.7	3.9	6.8	10.9	26.5	36.7	40.1	41.3
	SC	0.0	0.0	0.0	0.0	0.0	2.0	5.4	8.4	8.4
Stroke	SS	0.0	0.4	0.4	1.8	2.2	6.1	8.4	10.3	11.3
	SC	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Acute chest syndrome	SS	9.9	28.6	34.5	41.6	48.4	61.8	65.7	68.7	68.7
	SC	8.3	13.9	15.1	17.7	20.3	26.8	35.1	35.1	36.1
Painful Crisis (mild and severe)	SS	4.1	11.5	26.3	41.7	53.6	75.7	88.0	96.3	
	SC	0.6	3.1	15.1	24.7	36.3	67.6	84.1	91.1	93.7
Painful Crisis (severe only)	SS	1.7	3.8	6.7	14.0	19.1	38.1	47.1	65.5	76.6
	SC	0.0	0.6	1.9	3.2	8.3	27.5	42.6	48.7	68.7
Priapism	SS	0.0	0.0	0.7	0.7	1.3	2.1	6.3	19.6	38.3
	SC	0.0	0.0	0.0	0.0	0.0	0.0	0.0	3.3	11.7
Chronic events										
Hypersplenism	SS	4.1	10.0	12.8	14.3	16.1	18.8	19.7	20.2	20.2
	SC	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	2.9
Gallstones	SS	0.0	0.0	0.0	0.0	0.0	18.7	36.0	49.7	--
	SC	0.0	0.0	0.0	0.0	0.0	0.0	6.1	13.7	--
Leg-ulceration	SS	0.0	0.0	0.0	0.0	0.0	1.6	14.9	38.8	51.2
	SC	0.0	0.0	0.0	0.7	0.7	3.3	12.9	21.8	32.8
Proliferative Sickle retinopathy	SS	--	--	--	--	0.0	0.0	0.0	2.8	10.6
	SC	--	--	--	--	0.0	1.5	10.7	24.9	40.5
Osteonecrosis	SS	3.4	8.0	16.2	20.5	26.4	39.5	46.7	52.3	55.4
	SC	0.0	1.3	2.5	8.9	13.5	27.4	37.9	40.4	43.6
Hepatomegaly	SS	0.0	0.4	1.1	2.2	2.9	16.2	23.2	26.1	30.8
	SC	0.0	0.0	0.6	0.6	1.3	2.6	3.3	4.0	4.0

Table 6.6.

Cumulative proportion of clinic members with each acute clinical event (unadjusted and with an adjustment for late-entry bias) by genotype (4207 members with SS disease and 1567 members with SC disease) and by age in years.

			Age (in years)													
Event		**Genotype**	**1**	**2**	**3**	**4**	**5**	**10**	**15**	**20**	**25**	**30**	**35**	**40**	**50**	**70**
Acute events																
Dactylitis	Adjusted	SS	23.3	42.4	47.8	49.4	51.0	51.8	52.0	52.1	52.2	52.3	52.3	52.3	52.5	53.1
		SC	2.1	4.8	6.7	6.7	6.7	7.8	7.8	8.1	8.1	8.4	8.8	8.8	8.8	8.8
	Unadjusted	SS	1.6	4.9	6.4	7.0	7.7	8.2	8.4	8.5	8.6	8.8	8.8	8.8	9.1	10.1
		SC	0.1	0.2	0.4	0.4	0.4	0.6	0.6	0.8	0.8	0.9	1.2	1.2	1.2	1.2
Acute splenic sequestration	Adjusted	SS	6.2	14.4	17.1	18.3	19.3	20.8	21.3	21.5	21.7	21.8	21.9	21.9	21.9	21.9
		SC	0.0	0.0	2.8	2.8	4.0	5.2	5.7	6.0	6.3	6.3	6.7	6.7	7.4	7.4
	Unadjusted	SS	0.5	1.6	2.2	2.5	2.9	3.5	3.7	3.9	4.1	4.2	4.3	4.3	4.3	4.3
		SC	0.0	0.0	0.2	0.2	0.4	0.6	0.8	0.9	1.1	1.1	1.3	1.3	1.8	1.8
Bacteraemia	Adjusted	SS	0.8	2.4	3.4	3.8	4.3	5.4	5.9	6.3	6.9	7.7	8.0	8.3	9.0	11.1
		SC	0.0	0.0	0.0	0.7	0.7	1.0	1.0	1.0	1.3	1.3	1.3	1.3	1.3	1.3
	Unadjusted	SS	0.1	0.3	0.5	0.6	0.7	1.2	1.4	1.7	2.1	2.8	3.0	3.3	4.0	5.8
		SC	0.0	0.0	0.0	0.1	0.1	0.2	0.2	0.2	0.3	0.3	0.3	0.3	0.3	0.3
Aplastic crisis / b19 infection	Adjusted	SS	0.0	1.6	3.3	4.9	6.6	12.9	16.2	17.7	18.5	19.3	19.6	19.7	19.7	19.7
		SC	0.0	0.0	0.0	1.4	2.6	3.6	4.4	4.9	4.9	5.3	5.3	5.3	5.3	5.3
	Unadjusted	SS	0.0	0.2	0.6	1.0	1.5	3.8	5.5	6.5	7.2	7.8	8.1	8.2	8.2	8.2
		SC	0.0	0.0	0.0	0.2	0.3	0.6	0.9	1.1	1.1	1.3	1.3	1.3	1.3	1.3
Stroke	Adjusted	SS	0.0	0.6	0.7	1.3	1.7	4.3	6.3	6.8	7.5	7.8	8.4	8.6	9.7	21.0
		SC	0.0	0.0	0.0	0.0	0.0	0.4	0.4	0.4	0.7	0.7	1.1	1.1	2.0	10.2
	Unadjusted	SS	0.0	0.1	0.1	0.3	0.4	1.3	2.2	2.5	3.1	3.4	3.9	4.0	5.0	15.0
		SC	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.1	0.2	0.2	0.5	0.5	1.1	6.5
Acute chest syndrome	Adjusted	SS	4.8	12.5	21.9	28.5	33.8	45.5	50.0	53.1	56.7	59.5	61.8	63.9	67.5	72.9
		SC	4.8	19.6	22.9	28.2	30.0	38.6	41.9	44.0	45.4	46.6	47.9	48.5	53.2	63.3
	Unadjusted	SS	0.3	1.5	3.5	5.6	7.4	14.7	21.2	29.0	40.7	50.4	56.6	61.4	67.2	75.2
		SC	0.2	0.3	0.8	1.6	3.5	11.4	18.8	25.1	32.2	38.1	42.9	45.2	52.8	65.8
Painful Crisis (mild and severe)	Adjusted	SS	9.0	25.5	37.8	47.6	55.3	72.1	81.5	87.6	92.3	95.1	96.7	97.5	98.7	99.6
		SC	24.3	28.4	36.4	50.4	63.6	86.4	92.5	95.5	97.3	98.2	98.8	99.1	99.6	99.9
	Unadjusted	SS	0.6	3.2	6.2	9.3	12.4	22.7	33.1	45.2	58.3	68.0	75.1	79.5	86.9	94.6
		SC	0.3	0.6	1.5	3.7	6.5	18.8	29.5	39.3	48.7	56.7	63.9	68.9	78.3	91.3
Painful Crisis (severe only)	Adjusted	SS	3.4	11.8	20.9	28.3	33.9	49.6	58.6	65.9	74.3	80.3	83.8	86.2	88.9	92.2
		SC	11.7	13.2	17.9	24.4	36.2	60.4	70.9	76.9	82.1	85.3	87.4	88.3	91.0	94.5
	Unadjusted	SS	0.3	1.5	3.5	5.6	7.4	14.7	21.2	29.0	40.7	50.4	56.6	61.4	67.2	75.2
		SC	0.2	0.3	0.8	1.6	3.5	11.4	18.8	25.1	32.2	38.1	42.9	45.2	52.8	65.8
Priapism	Adjusted	SS	0.0	0.0	0.0	0.0	0.2	2.7	6.6	11.2	20.9	30.0	33.6	36.4	40.3	42.3
		SC	0.0	0.0	0.0	0.0	0.0	0.0	1.1	1.7	5.2	8.5	10.4	11.7	14.5	20.2
	Unadjusted	SS	0.0	0.0	0.0	0.0	0.1	1.0	3.0	5.6	12.6	19.9	23.1	25.7	29.3	31.2
		SC	0.0	0.0	0.0	0.0	0.0	0.0	0.4	0.7	2.3	4.0	5.2	6.0	7.8	11.2

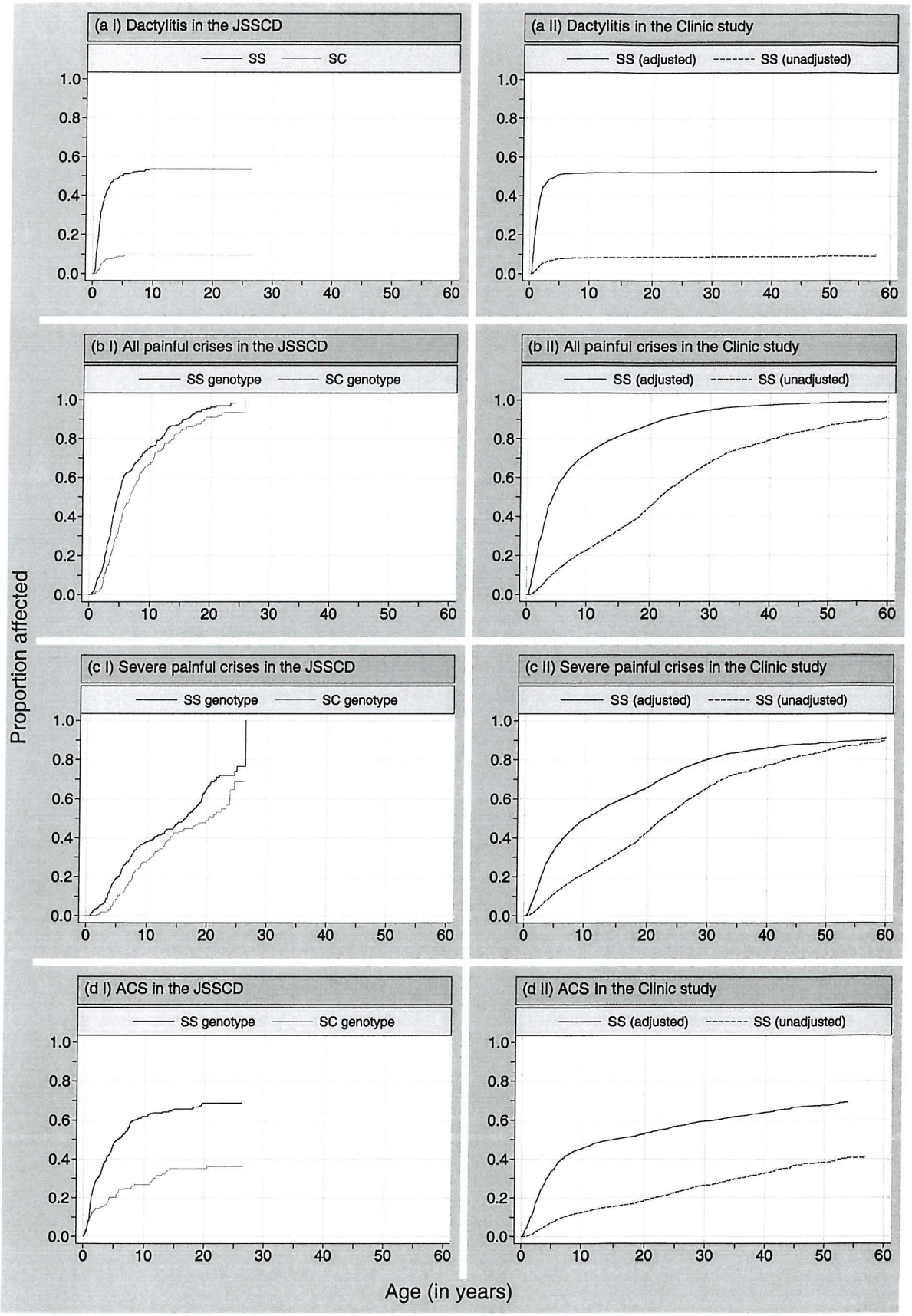
Table 6.7.

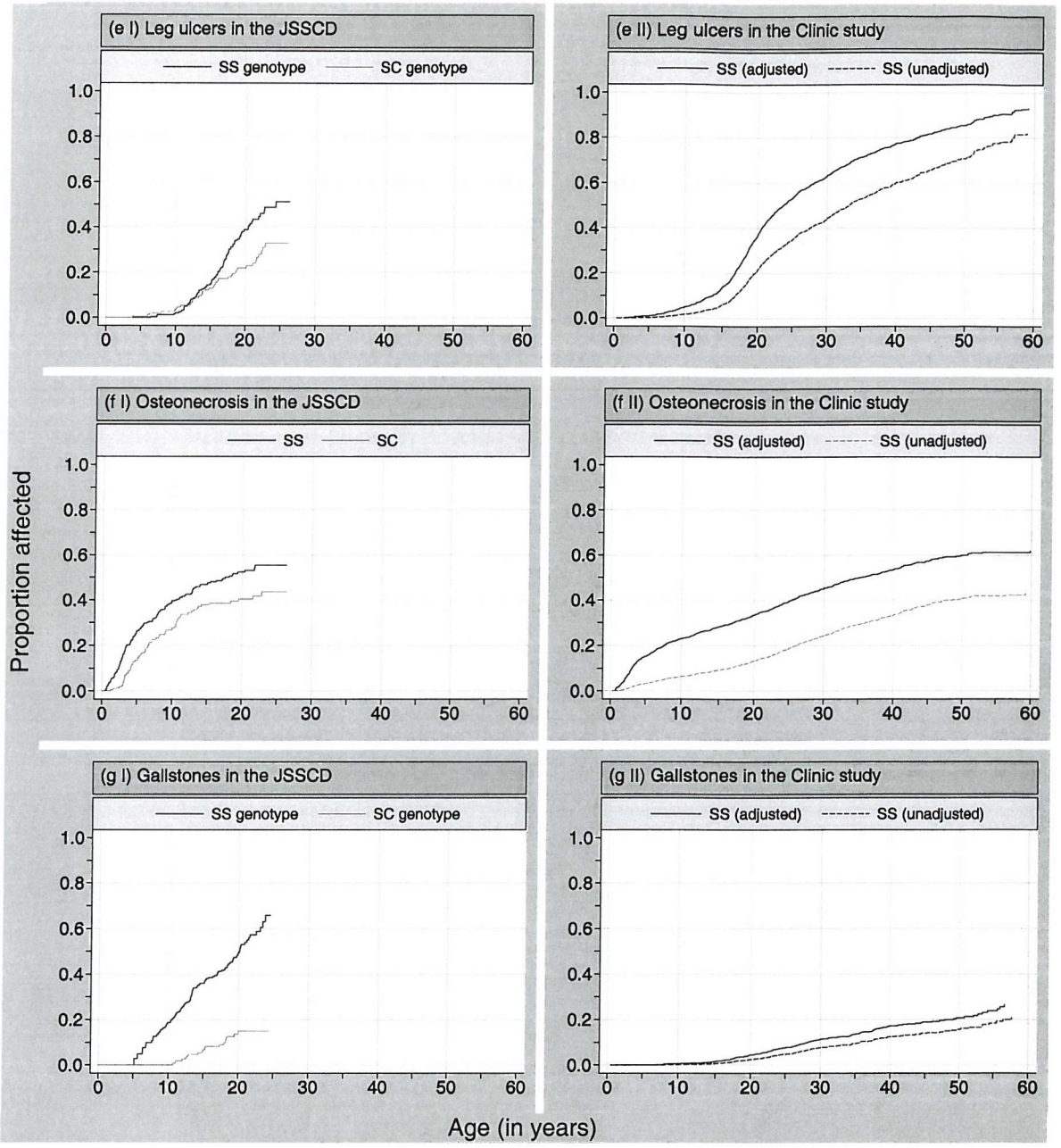
Cumulative proportion of clinic members with each chronic clinical event (unadjusted and with an adjustment for late-entry bias) by genotype (4207 members with SS disease and 1567 members with SC disease) and by age in years.

			Age (in years)													
Event		**Genotype**	**1**	**2**	**3**	**4**	**5**	**10**	**15**	**20**	**25**	**30**	**35**	**40**	**50**	**70**
Chronic events																
Hypersplenism	Adjusted	SS	2.4	7.3	10.5	13.0	14.7	18.0	19.7	20.1	20.3	20.5	21.0	21.0	21.2	22.1
		SC	0.0	0.0	0.8	0.8	0.8	1.9	3.5	4.4	4.9	5.6	6.0	6.6	8.4	8.4
	Unadjusted	SS	0.2	0.9	1.6	2.3	2.8	4.1	5.0	5.3	5.4	5.7	6.1	6.1	6.3	7.2
		SC	0.0	0.0	0.1	0.1	0.1	0.3	0.9	1.2	1.5	1.9	2.1	2.5	3.6	3.6
Gallstones	Adjusted	SS	0.0	0.0	0.0	0.0	0.0	0.7	1.7	4.5	7.7	11.3	13.5	17.1	21.2	31.9
		SC	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.8	2.7	3.9	5.5	10.8
	Unadjusted	SS	0.0	0.0	0.0	0.0	0.0	0.2	0.8	2.5	4.8	7.7	9.5	12.5	16.1	25.7
		SC	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.4	1.6	2.4	3.3	7.0
Leg-ulceration	Adjusted	SS	0.0	0.2	0.6	0.9	1.0	5.0	13.7	36.8	53.3	63.2	71.4	77.4	85.4	95.5
		SC	0.0	0.0	0.0	0.7	0.7	1.7	3.6	8.8	12.9	15.3	17.6	20.9	32.6	47.2
	Unadjusted	SS	0.0	0.0	0.1	0.2	0.2	1.7	6.0	21.4	34.8	44.2	53.0	60.0	70.7	87.2
		SC	0.0	0.0	0.0	0.1	0.1	0.3	1.0	3.3	5.3	6.7	8.2	10.5	18.5	30.5
Proliferative sickle retinopathy	Adjusted	SS	0.0	0.0	0.0	0.0	0.0	0.6	1.6	4.4	7.6	11.0	13.1	16.0	20.1	29.4
		SC	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.8	2.3	3.5	5.1	10.4
	Unadjusted	SS	0.0	0.0	0.0	0.0	0.0	0.2	0.7	2.5	4.8	7.5	9.2	11.6	15.2	23.6
		SC	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.4	1.4	2.1	3.0	6.7
Osteonecrosis	Adjusted	SS	1.7	4.6	9.8	13.4	15.3	23.0	28.4	33.5	39.5	45.3	49.7	53.4	60.0	64.6
		SC	0.0	0.0	0.9	3.7	5.8	18.0	25.4	30.1	34.4	40.6	43.3	46.1	49.4	54.1
	Unadjusted	SS	0.1	0.6	1.7	2.6	3.2	6.3	9.3	13.2	18.7	24.5	29.2	33.2	40.8	46.5
		SC	0.0	0.0	0.1	0.4	0.7	3.5	6.4	8.8	11.4	15.7	18.0	20.5	23.5	28.2
Hepatomegaly	Adjusted	SS	0.8	2.9	6.4	8.6	11.1	19.9	24.7	27.8	30.7	34.4	37.2	39.6	47.4	72.7
		SC	0.0	0.0	0.0	0.0	0.0	0.8	1.4	2.5	2.8	3.4	3.9	4.5	6.3	9.0
	Unadjusted	SS	0.1	0.4	1.1	1.7	2.4	5.8	8.3	10.5	13.0	16.5	19.3	21.6	29.9	58.6
		SC	0.0	0.0	0.0	0.0	0.0	0.2	0.4	0.8	1.0	1.3	1.6	2.0	3.1	5.0

Figure 6.2

Time until first instance of seven high incidence clinical events (figures A – G) among (I) JSSCD members and (II) clinic members.



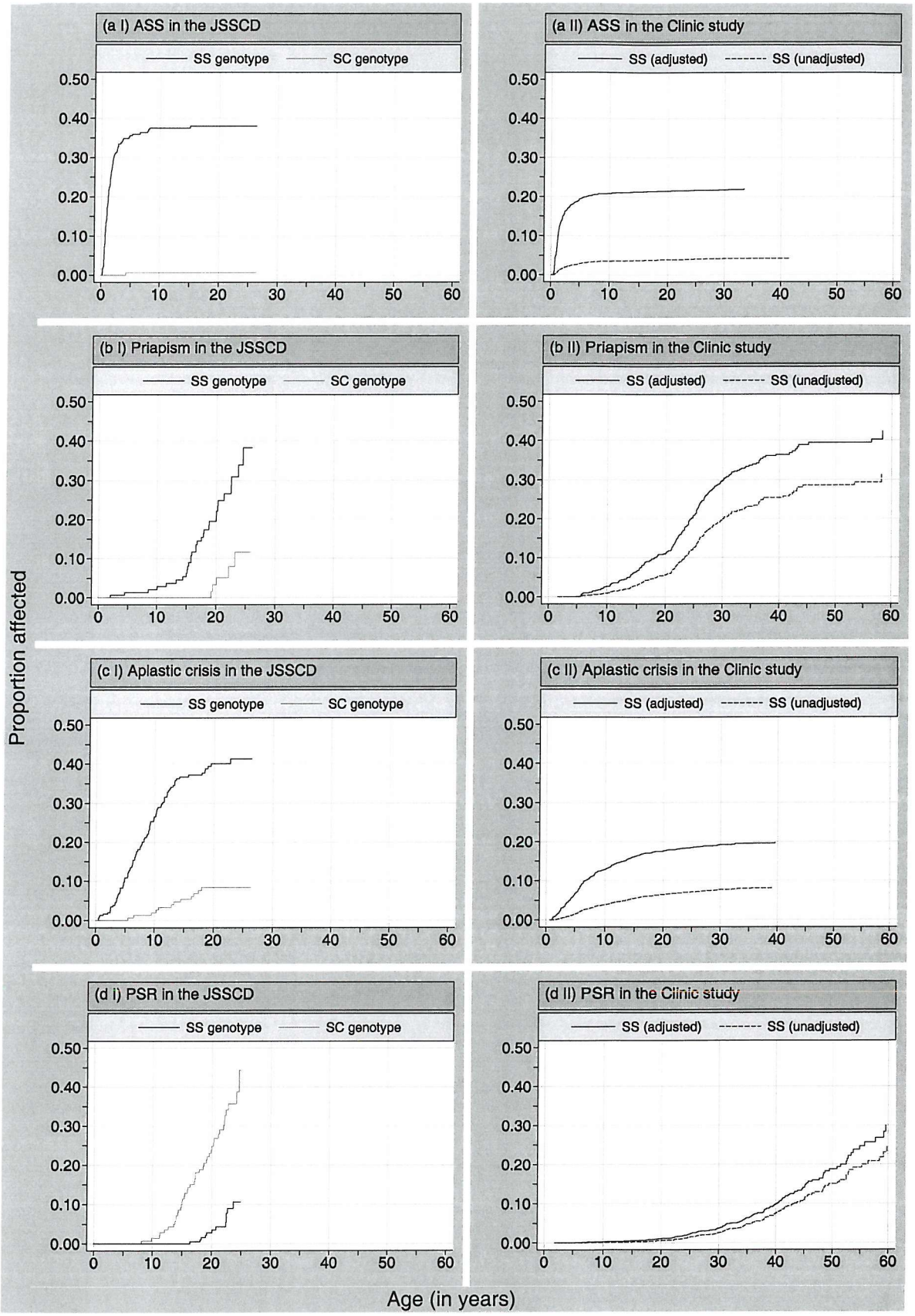


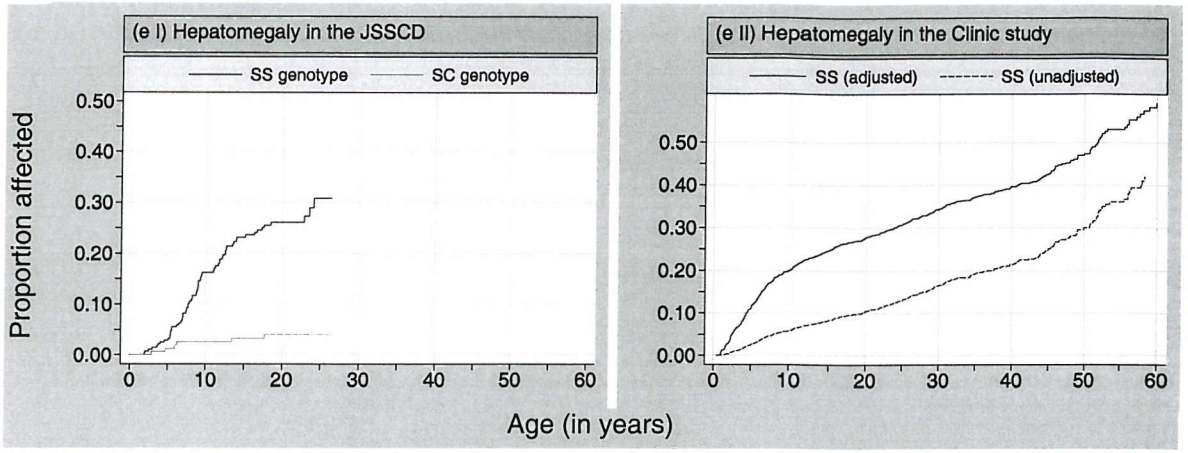
Leg Ulceration in SS disease

The crude first-event incidence rate of leg ulceration among JSSCD participants with SS disease was 3.8 per 100 patient years (2.1 to 7.5), with a peak incidence of 13.1 per 100 patient years (5.4 to 15.8) in adolescents between 18 and 19 years old (Table 6.1). Approximately half of all SS participants had experienced one or more leg ulcers by 25 years of age. Compared to SC disease, the proportion affected was 1.5 times (or 50%) higher in SS disease (Table 6.5 and Figure 6.2eI).

Figure 6.3

Time until first instance of five medium incidence clinical events (figures A – E) among (I) JSSCD members and (II) clinic members.





6.3.3 ***The third decade: Early Adulthood***

The manifestations of adolescence continue into early adulthood, generally becoming more frequent into the middle of the third decade. Additionally, complications surrounding pregnancy becomes an issue for the female with sickle-cell disease (see Chapter Nine, case study 18). The cumulative effect of bone infarction can lead to loss of joint function. The affected joint (usually the hip) may need replacement (22). Proliferative sickle retinopathy, another complication that is infrequently encountered in adolescence increases in incidence during early adulthood.

Proliferative Sickle Retinopathy in SS disease

The crude first-event incidence rate of PSR among JSSCD participants with SS disease was 0.5 per 100 patient years (0.3 to 0.8), with a peak incidence of 5.2 per 100 patient years (2.0 to 17.8) in adults between 22 and 23 years old (Table 6.1). Approximately 10% of all SS participants had experienced PSR by 25 years of age. Compared to SC disease, the crude event rate was 4 times *lower* in SS disease (Table 6.5 and Figure 6.3dI).

6.3.4 ***Older adults***

No data are available from the JSSCD beyond the third decade of life. Studies involving clinic populations in Jamaica and elsewhere suggest that painful crises and leg ulceration become less frequent and less severe with advancing age, and are uncommon over the age of 40 years (23-25). Cerebrovascular disease re-emerges in later life (26), and chronic renal failure and congestive heart failure are likely to increase with age (27;28).

Figure 6.4

Time until first instance of three low incidence clinical events (figures A – C) among (I) JSSCD members and (II) clinic members.

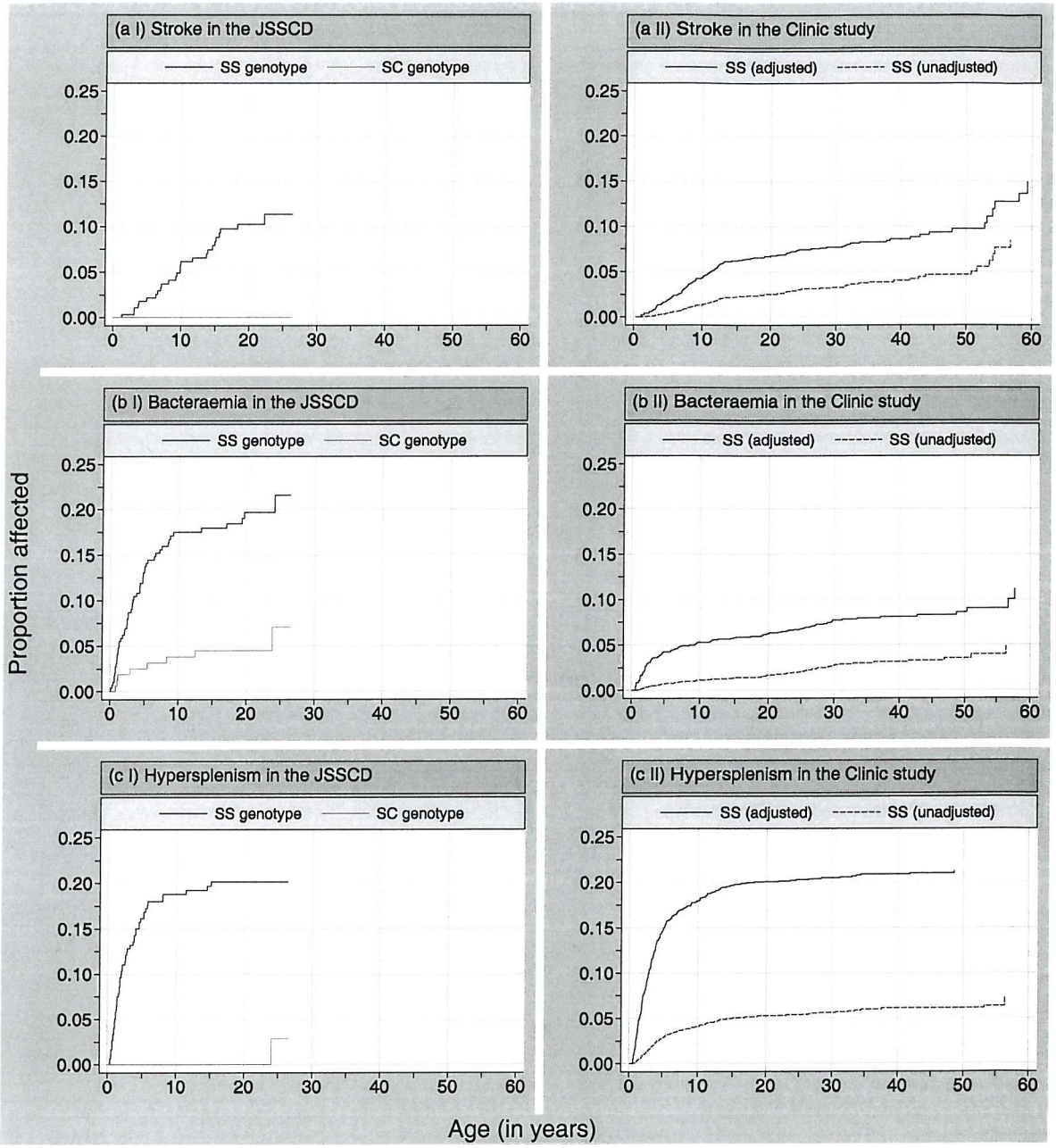


Table 6.8.

Gender difference in the incidence of seven acute clinical events among 315 JSSCD participants with homozygous sickle-cell disease.

	Observed			FDR critical p-value	Resampling (1000 bootstrapped samples)			
Event	**RR**	**Chi 2**	**Pr**		**95% CI**	**% Pr(0.05)***	**% Pr(FWER)****	**% Pr(FDR)**
Acute events								
Dactylitis	1.56	20.42	<0.001	0.002	(1.3 - 1.9)	99.5	93.7	93.7
Acute splenic Sequestration	1.04	0.07	0.80	0.045	(0.79 - 1.42)	6.3	0.3	5.5
Bacteraemia	0.78	1.09	0.30	0.03	(0.48 - 1.23)	16.5	2.1	11.6
Aplastic crisis / b19 infection	1.09	0.32	0.57	0.039	(0.79 - 1.47)	8.8	0.6	7.3
Stroke	1.79	2.75	0.10	0.016	(0.84 - 3.84)	38.9	6.4	23.1
Acute chest syndrome	1.33	9.80	<0.001	0.005	(1.11 - 1.6)	87.7	52.5	62.6
Painful Crisis (all)	0.98	0.37	0.54	0.034	(0.91 - 1.06)	8.8	0.8	6.8
Painful Crisis (severe)	1.17	5.21	0.02	0.011	(1.03 - 1.35)	62.6	19.9	39.2

*** Uncorrected critical P-value = 0.05**

**** FWER = 0.002**

Table 6.9.

Gender difference in the proportion of study participants who have one of seven acute or six chronic clinical events among 315 JSSCD participants with homozygous sickle-cell disease.

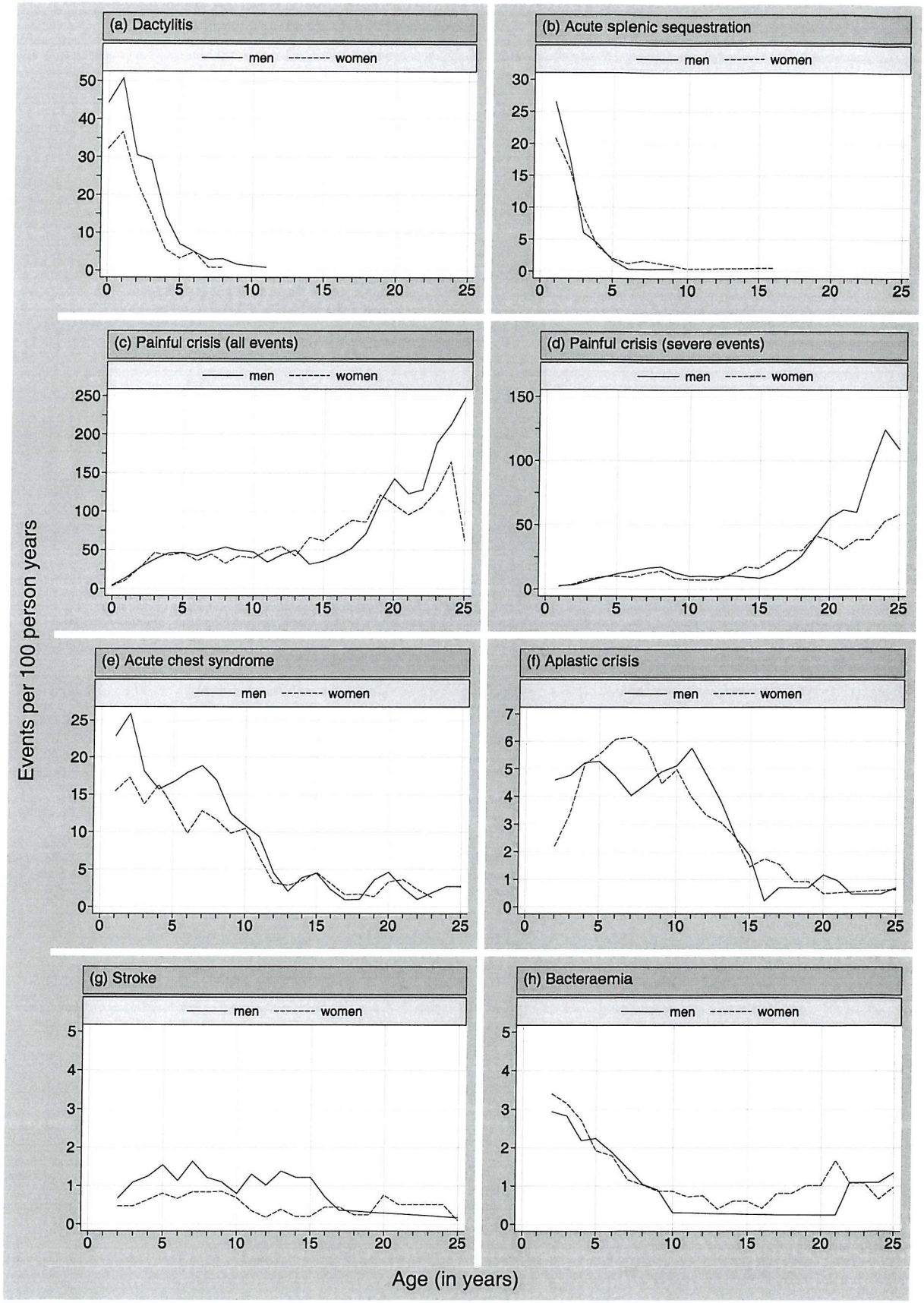
	Observed				FDR critical P-value	Resampling (1000 bootstrapped samples)			
Event	**M**	**F**	**Chi 2**	**Pr**		**95% CI**	**% Pr(0.05)***	**% Pr(FWER)****	**% Pr(FDR)**
Acute events									
Dactylitis	0.58	0.42	8.42	0.004	0.007	(1.07 - 1.81)	83.5	43.8	59.8
Acute splenic sequestration	0.36	0.35	0.02	0.90	0.05	(0.74 - 1.37)	4.5	0.2	4.5
Bacteraemia	0.18	0.17	0.10	0.76	0.043	(0.69 - 1.86)	6.5	0.2	5.7
Aplastic crisis / b19 infection	0.36	0.29	1.92	0.17	0.023	(0.9 - 1.77)	27.2	4.9	18.4
Stroke	0.10	0.07	1.08	0.30	0.032	(0.65 - 3.36)	16.7	1.2	12.9
Acute chest syndrome	0.65	0.57	2.05	0.15	0.02	(0.96 - 1.36)	32.5	5.1	21.8
Painful Crisis (all)	0.85	0.80	1.41	0.24	0.027	(0.96 - 1.18)	22.2	2.5	15.3
Painful Crisis (severe)	0.54	0.57	0.22	0.64	0.041	(0.78 - 1.17)	9.4	0.6	7.6
Chronic events									
Hypersplenism	0.19	0.17	0.35	0.55	0.036	(0.68 - 1.89)	9.5	0.7	7.0
Gallstones	0.28	0.29	0.04	0.85	0.048	(0.7 - 1.32)	5.9	0.2	5.3
Leg-ulceration	0.32	0.26	1.53	0.22	0.025	(0.88 - 1.81)	22.9	3.6	15.0
PSR	0.17	0.12	2.21	0.14	0.018	(0.86 - 2.45)	31.2	5.0	17.2
Osteonecrosis	0.51	0.38	5.26	0.02	0.014	(1.05 - 1.78)	63.4	20.9	41.8
Hepatomegaly	0.28	0.15	8.11	0.004	0.009	(1.21 - 3.09)	87.7	39.8	60.6

*** Uncorrected critical P-value = 0.05**

**** FWER = 0.002**

Figure 6.5

Gender-specific incidence of eight acute clinical events among 315 JSSCD members with homozygous sickle-cell disease.



6.3.5 *Gender differences*

Generally, gender differences were minor; most events had similar gender-specific incidence rates and similar proportions of affected men and women. Dactylitis emerged as the single consistent gender–specific clinical complication: there was a greater incidence of dactylitis events among men (relative risk=1.6, χ^2=20.4, Pr<0.001), and a greater proportion of men were diagnosed with the complication (men=58% women=42%, χ^2=8.4, Pr=0.004). Similar proportions of men and women were diagnosed with the acute chest syndrome (men=65% women=57%, χ^2=2.1, Pr=0.15), but men presented with more events (relative risk=1.3, χ^2=9.8, Pr<0.001). A greater proportion of men presented with hepatomengaly (men=28% women=15%, χ^2=8.1, Pr=0.004). Although there was a greater incidence of severe painful crisis in men, this effect was not statistically significant after adjustment for multiple testing (relative risk=1.2, χ^2=5.2, Pr=0.02).

Inclusion proportions suggested that dactylitis incidence was the single robust gender difference (significant in 93.7% of 1000 bootstrapped datasets). ACS incidence, and the proportion of participants affected by dactylitis and hepatomegaly were all significant in about 60% of the bootstrapped datasets (ACS incidence 62.6%, dactylitis proportion 59.8%, hepatomegaly proportion 60.6%). All other clinical events were statistically significant in 40% or fewer of the bootstrapped datasets.

Table 6.10.

Bias by clinical event among 315 JSSCD members with SS disease followed until 25-years of age

Event	Unadjusted			Adjusted		
	5 years	10 years	25 years	5 years	10 years	25 years
Acute events						
Dactylitis	6.49	6.49	6.25	0.99	1.03	1.03
Acute splenic sequestration	12.06	10.61	9.28	1.83	1.79	1.74
Bacteraemia	19.22	15.22	9.97	3.32	3.25	3.11
Aplastic crisis / b19 infection	7.60	7.27	5.75	1.81	2.18	2.22
Stroke	4.68	4.19	3.62	1.08	1.32	1.50
Acute chest syndrome	6.25	4.92	2.96	1.38	1.36	1.20
Painful crisis (mild and severe)	4.29	3.27	1.73	1.01	1.06	1.07
Painful crisis (severe only)	2.68	2.56	1.83	0.61	0.77	1.02
Priapism	14.34	2.79	3.32	4.49	1.03	2.04
Chronic events						
Hypersplenism	5.89	4.44	3.72	1.17	1.03	0.99
Gallstones	-	33.64	4.88	-	12.73	3.08
Leg-ulceration	-	1.71	1.41	-	0.60	0.93
Proliferative sickle retinopathy	25.65	16.32	5.23	7.08	5.51	3.33
Osteonecrosis	7.99	6.17	2.86	1.74	1.72	1.38
Hepatomegaly	1.54	2.64	2.29	0.36	0.79	0.99

6.3.6 Late-entry Bias

At any age, the clinic study group has a lower cumulative proportion of each clinical event compared to the JSSCD (see Figure 6.6 a-o). By 25 years of age the unadjusted cumulative proportions were 1.5-times lower or 67% of the JSSCD proportion for leg ulcers, one-half or 50% of the JSSCD rate for all-painful crises, severe painful crises and hepatomegaly, one-third or 33% of the JSSCD rate for ACS, stroke, priapism, hypersplenism, and osteonecrosis, one-fifth or 20% of the JSSCD rate for gallstones and proliferative sickle retinopathy, one-sixth or 17% of the JSSCD rate for dactylitis and the aplastic crisis, one-ninth or 11% of the JSSCD rate for acute splenic sequestration, and one-tenth or 10% of the JSSCD rate for bacteraemias (Table 6.10).

The accepted statistical adjustment (Method One) generally reduced these levels of bias. It rarely eliminated bias throughout the age-range, although its performance improved with age. By 25-years of age cumulative proportions of selected clinical events were almost bias free for dactylitis, the painful crisis, hypersplenism, leg ulcers, and hepatomegaly. Cumulative proportions were 1.2 times lower or 83% of the JSSCD rate for ACS, 1.4 times lower or 71% of the JSSCD rate for osteonecrosis, 1.5 times lower or 67% of the JSSCD rate for stroke, 1.8 times lower or 56% of the JSSCD rate for acute splenic sequestration, one-half or 50% of the JSSCD rate for priapism and the aplastic crisis, one-third or 33% of the JSSCD rate for bacteraemias, gallstones, and proliferative sickle retinopathy.

Based on these adjustments we anecdotally classify the clinical event adjustments into four groups. Groups one and two are overestimated by Method One in early life, and converge towards a bias-free adjustment with increasing age. By adulthood, Method One is an acceptable adjustment for these two groups. Groups three and four remain underestimated by this adjustment procedure throughout the age range of this review. The adjustment is adequate for clinical events that are common acute events or chronic events, that are not life threatening and that can be diagnosed without referral to a specialist.

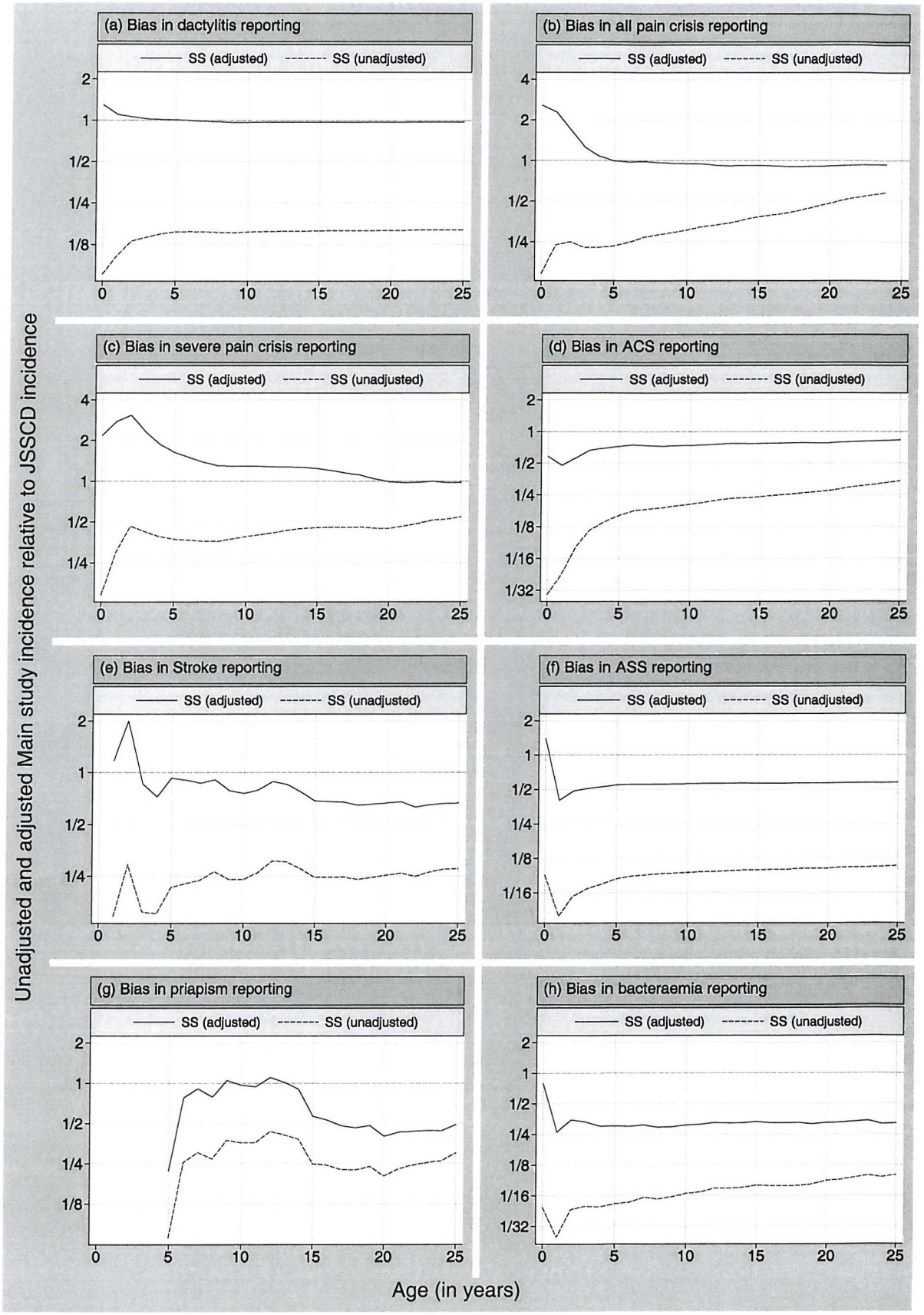
Table 6.11.

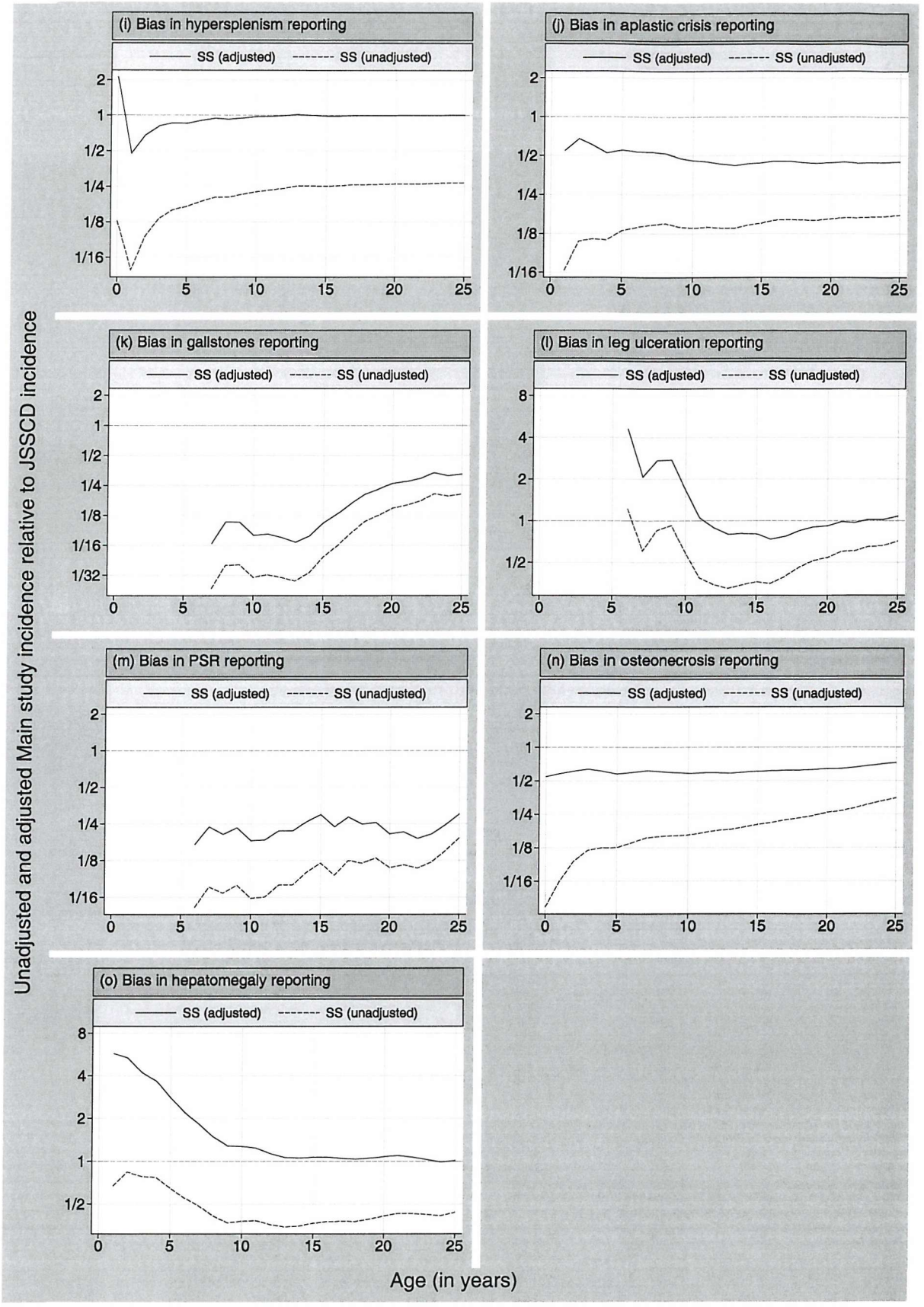
Four groups of clinical events according to the success of adjusting for late-entry bias

Group One	Common acute event / not life threatening / diagnosis by clinician	dactylitis painful crisis
Group Two	Chronic event / not life threatening / diagnosis by clinician	hypersplenism hepatomegaly leg ulceration
Group Three	Chronic event / not life threatening / diagnosis by specialist	gallstones proliferative sickle retinopathy osteonecrosis
Group Four	Acute event / life-threatening	acute chest syndrome stroke acute splenic sequestration priapism the aplastic crisis

Figure 6.6

Bias introduced by clinical event and age among 315 JSSCD members with SS disease.




(i) Bias in hypersplenism reporting
(j) Bias in aplastic crisis reporting
(k) Bias in gallstones reporting
(l) Bias in leg ulceration reporting
(m) Bias in PSR reporting
(n) Bias in osteonecrosis reporting
(o) Bias in hepatomegaly reporting
SS (adjusted)
SS (unadjusted)
Unadjusted and adjusted Main study incidence relative to JSSCD incidence
Age (in years)

6.3.7 Life-course epidemiology in homozygous sickle-cell disease

Clinical outcomes in sickle-cell disease are characterised by strong age-related influences. Despite this fundamental feature, studies involving people with SS-disease are rarely longitudinal. Studies that do incorporate time invariably focus on one particular clinical outcome, or specific predictors, and so compartmentalise the disease process. Birth cohorts allow us to take a more holistic approach to clinical outcomes, and the methodologies that promote this approach have become known as life-course epidemiology.

Life-course epidemiology attempts to integrate clinical, biological and social risk processes rather than draw false dichotomies between them. It studies how prior exposures influence later disease risk, and hence may account for inequalities in adult health and mortality.

The purpose of life-course epidemiology is to build and test theoretical models that postulate pathways linking exposures across the life course to later life health outcomes (29). These models explicitly require the temporal ordering of exposures and their inter-relationships.

The development of these models in life course epidemiology provides a persuasive rationale for time related study designs. It has led to a growing interest in existing and new longitudinal studies that capture certain time windows or other potentially significant features of the life course (30;31) They include new birth cohorts (32;33) and the revitalisation of old historical cohorts (34).

In the following section we offer a clinical case-study of early-life growth and its relationship with later clinical morbidity. It provides an early example of life-course epidemiology in sickle-cell disease.

(a) Case study 4: Growth in homozygous sickle-cell disease

Pathology in SS disease emerges after birth; symptoms rarely occur before six-months of age (see Section 6.3.1(b)). Birth-weight in babies with SS disease is normal (35), and birth-weight and length at one month of age are similar in SS disease and AA controls in the JSSCD. The average weight in SS disease is reduced in adults (36), and a weight deficit has been documented in the second year of life (37). Height is reduced in childhood in SS children (38), but early information from Jamaica suggests that adult height in SS disease may reach that of normal controls (39). More retardation in weight means a thinner body build, which we generally measure using body mass index.

We are interested in the association between growth and disease expression, although the direction of any anticipated effect is unclear (is growth retardation a feature of pre-programmed disease severity that also manifests as greater levels of disease morbidity, or does morbidity cause wasting – if a child eats less during periods of morbidity then more morbid periods mean a lower energy intake).

Growth retardation in infancy means that if a search for predictors of this delay is sensible, the potential predictors must also be available in infancy or earlier. This creates difficulties for the analyst. Additionally, there is currently no procedure for assessing what we might anecdotally call 'health status' in sickle-cell disease (see Chapters 7 and 8). Common clinical proxies (such as painful crisis frequency) for health-status are rarely apparent in analysable numbers before the second year of life (dactylitis frequency is a possible exception). More importantly, most clinical events are acute and strongly age-dependent, which complicates their use as predictors of a continuous phenomenon such as growth.

We examine the size of SS participants relative to AA controls from the same study, and to a reference population from the United States. We examine the length of time that SS participants remain 'wasted'. We present the predictive effect of a genetically determined haematological index on wasting, and the effect of wasting on two proxy measures of health-status (the painful crisis and all vaso-occlusive events), and on a measure of inflammatory response (white blood cell count).

Patients and methods

Patients

From the JSSCD, four AA classifications were subsequently found to be AS trait, and four SS participants defaulted without a single clinic attendance, leaving 311 SS and 246 AA controls (40). Reference population information is available from two-years of age. Twenty-six SS cohort members died and one emigrated before two years of age, and five defaulted without presenting to clinic, leaving 283 SS participants available for this review. Twenty AA controls died or emigrated before two years of age, and a further 5 provided inadequate height or weight information, leaving 221 participants available for this review.

Measures of wasting

BMI is a recognised measure of adiposity in adults. Because BMI in children changes as they age, the equivalent measure in childhood is BMI-for-age. We calculated BMI-for-age at six-month intervals between two and 18 years of age, and calculated weight-for-age and height-for-age in the same way. We standardized our age-stratified BMI values on a reference population using the LMS method (41). An adult with a BMI below 18.5 is classified as underweight by the Center for Disease Control (CDC). This roughly equates to the 3rd BMI-for-age centile in males and the 10th BMI-for-age centile in females. An alternative underweight classification from the WHO suggests the 5th BMI-for-age centile in males and females.

External reference population

We adopted the Center for Disease Control childhood growth reference charts for BMI-for-age, which were constructed using a US population (NHANES). This standard may not be

appropriate for the general Jamaican population, and we included AA controls from the JSSCD to assess this potential bias.

Statistical methods

We standardized three common measures of childhood growth (Weight-for-age, Height-for-age, and BMI-for-age) using a reference population, to give standardized scores (SD-scores). As an initial summary, we calculated average SD-scores between two and 18 years of age for participants with homozygous sickle-cell (SS) disease, and for normal (AA) controls. We plotted the distribution of these summary scores by genotype, and we tested for genotype differences using a t-test. We converted these SD-scores to centiles and graphed average growth for each genotype, including the 5th, 25th, 50th, and 75th reference centiles from the US population.

We used the 5th BMI-for-age centile as the definition of underweight, and compared JSSCD participants who had ever been below that centile to those who had not. We used logistic regression to examine the potential effect of genotype, gender, and a single (possibly genetically determined) measure of haematology – fetal haemoglobin.

Among SS participants, we used BMI-for-age (as an SD-score) to model the effects of growth on three outcome measures, two clinical and one haematological. Painful crisis is the most common acute expression of morbidity in sickle-cell disease, and we used the cumulative count of painful crisis events by 10-years of age as a proxy for health-status in pre-pubertal children with sickle-cell disease. We used the combined number of vaso-occlusive events as a second marker of general 'health-status'. We included painful crises, dactylitis events, abdominal crises, acute chest syndrome events, and strokes in this summary measure. Clinic presentations less than 14 days apart were arbitrarily considered realizations of the same underlying pathology. We used the average of steady-state white blood cell counts measured between 10 and 18 years of age as a measure of inflammatory response in childhood and adolescence. We used log-linear regression to model the painful crisis and vaso-occlusive event rates, and linear regression to model the white blood cell count.

We used BMI SD-scores in early childhood (at two-years of age) and later childhood (at eight-years of age) as model predictors, and fitted four models, following recent guidelines (42). Model one (early model) used BMI in early childhood and assessed the effect of early size on later outcome. Model two (combined model) included early and later size and assessed the effect of age-related changes in body size on outcome (in other words it assessed centile crossing). Model three (interaction model) added the interaction of early and later size to the model and assessed whether centile crossing varied according to early size (for example, were extreme sizes in early life more likely to cross centiles). Model four (late model) used BMI in later childhood and assessed the effect of later size on outcome.

Results

Average growth

Average growth measures (BMI-for-age, weight-for-age, height-for-age) between two and 18 years of age are presented in Table 6.12 and in Figure 6.7.

Table 6.12.
Summary measures of childhood growth between 2 and 18 years of age in 283 JSSCD participants with SS disease, and in 221 AA controls.

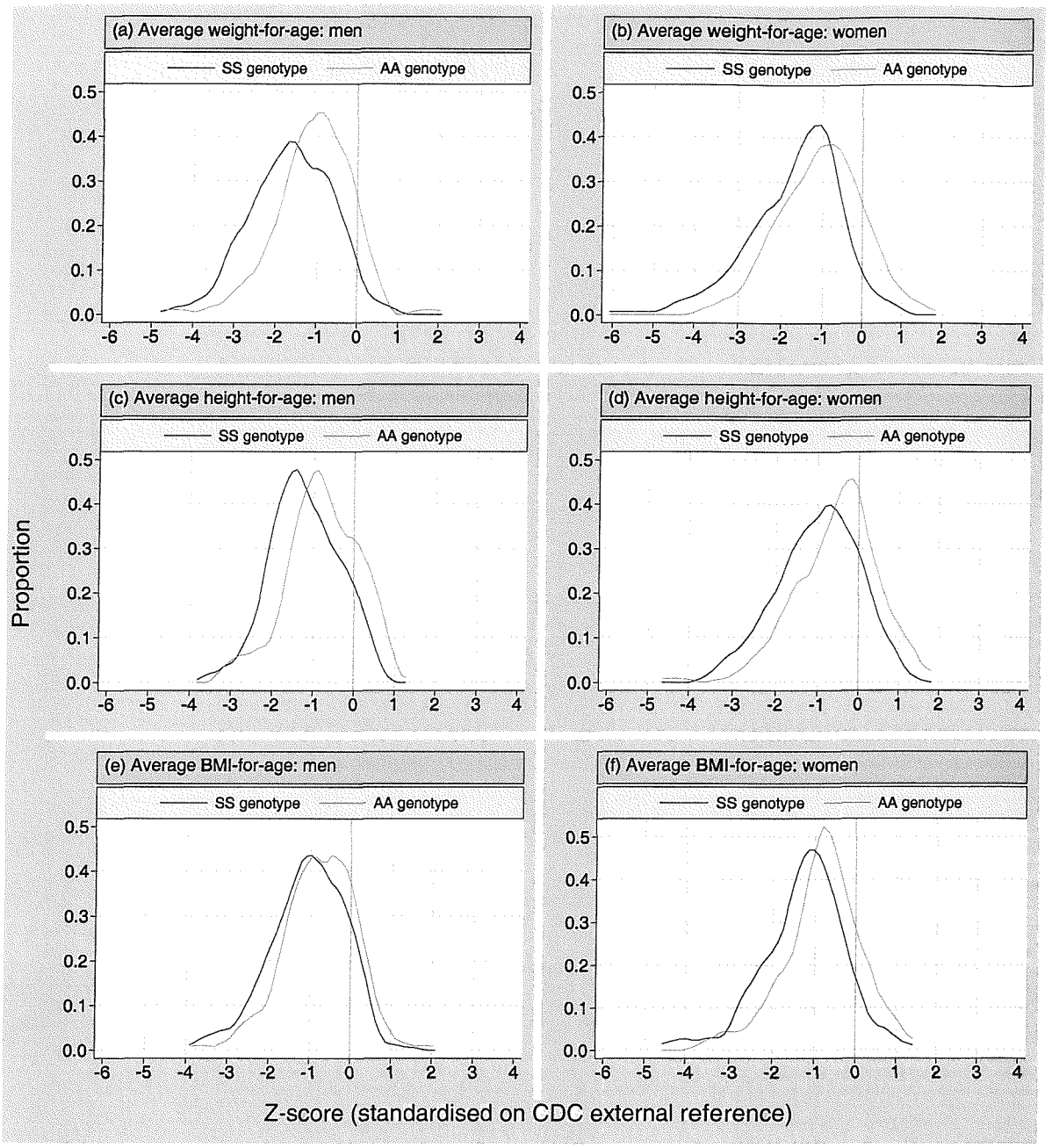
	SS		AA	
	Mean z-score (95% CI)	**Mean centile (95% CI)**	**Mean z-score (95% CI)**	**Mean centile (95% CI)**
Men (SS n=149, AA n=101)				
Weight-for-age	-1.52 (-1.68 to -1.36)	13.7 (11.1 to 16.2)	-0.95 (-1.13 to -0.76)	24.1 (20.0 to 28.2)
Height-for-age	-1.12 (-1.26 to -0.98)	15.8 (12.6 to 19.1)	-0.61 (-0.79 to -0.44)	27.7 (22.8 to 32.6)
BMI-for-age	-1.13 (-1.27 to -0.98)	18.9 (14.9 to 22.8)	-0.83 (-1.00 to -0.67)	25.2 (20.8 to 29.5)
Women (SS n=128, AA n=114)				
Weight-for-age	-1.52 (-1.70 to -1.34)	13.4 (10.5 to 16.2)	-0.84 (-1.02 to -0.66)	27.4 (22.7 to 32.0)
Height-for-age	-0.84 (-1.01 to -0.67)	20.3 (15.6 to 25.0)	-0.33 (-0.52 to -0.15)	34.8 (29.2 to 40.4)
BMI-for-age	-1.41 (-1.60 to -1.23)	15.5 (11.9 to 19.0)	-0.87 (-1.05 to -0.69)	27.1 (22.5 to 31.7)

Between two and 18 years of age SS and AA participants have lower average levels of weight, height, and BMI than the US reference population. Within the JSSCD, genotype differences are important for both males and females. SS participants had significantly lower height-for-age, weight-for-age, and BMI-for-age than AA controls [Males: weight difference -0.6 (95% CI -0.8 to -0.3), height difference -0.4 (-0.7 to -0.2), BMI difference -0.3 (-0.5 to -0.1). Females: weight difference -0.6 (-0.9 to -0.4), height difference -0.5 (-0.7 to -0.2), BMI difference -0.4 (-0.7 to -0.2)]. Associated P-values were significant at levels below 0.001.

Centile distributions of weight-for-age, height-for-age, and BMI-for-age are presented in Figure 6.8. When interpreting these charts we should be aware that average curves may not reflect the growth profile of any given individual. SS and AA members of the JSSCD were small in early-life compared to their US counterparts. AA females crossed centiles towards the median centile in adolescence, and AA males cross centiles towards the 25th centile. SS males remained wasted using any size measure in relation to the AA controls and the US population. SS females remained wasted using weight and BMI compared to AA controls and the US population, and reached the median height centile in later adolescence.

Figure 6.7

Distribution of childhood growth between 2 and 18 years of age in 280 JSSCD participants with SS disease, and in 221 AA controls.



Percentage of wasted cohort members

Using the CDC definition of underweight in adults, there were 109 (72%) SS males, and 110 (85%) SS females who were underweight at some point, with significantly more underweight females than males ($\chi 2$=10.6 p=0.001). Using the alternative WHO definition there were similar numbers of underweight males and females: 120 (79%) SS males and 100 (78%) SS females ($\chi 2$=1.0 p=0.33). The numbers of cohort members below the 3rd, 5th, and 10th centiles, and the proportion of their measurements that are classified as wasted are presented separately for males and females in Table 6.13.

Genotype, gender and haematology as descriptors of wasting

The odds of being wasted was three times greater in SS compared to AA individuals (odds ratio=3.1, p<0.001), with no gender difference (OR=1.2 p=0.33). The odds of being underweight decreased as fetal haemoglobin increased (OR=0.9 p<0.001 for every 1% increase in HbF).

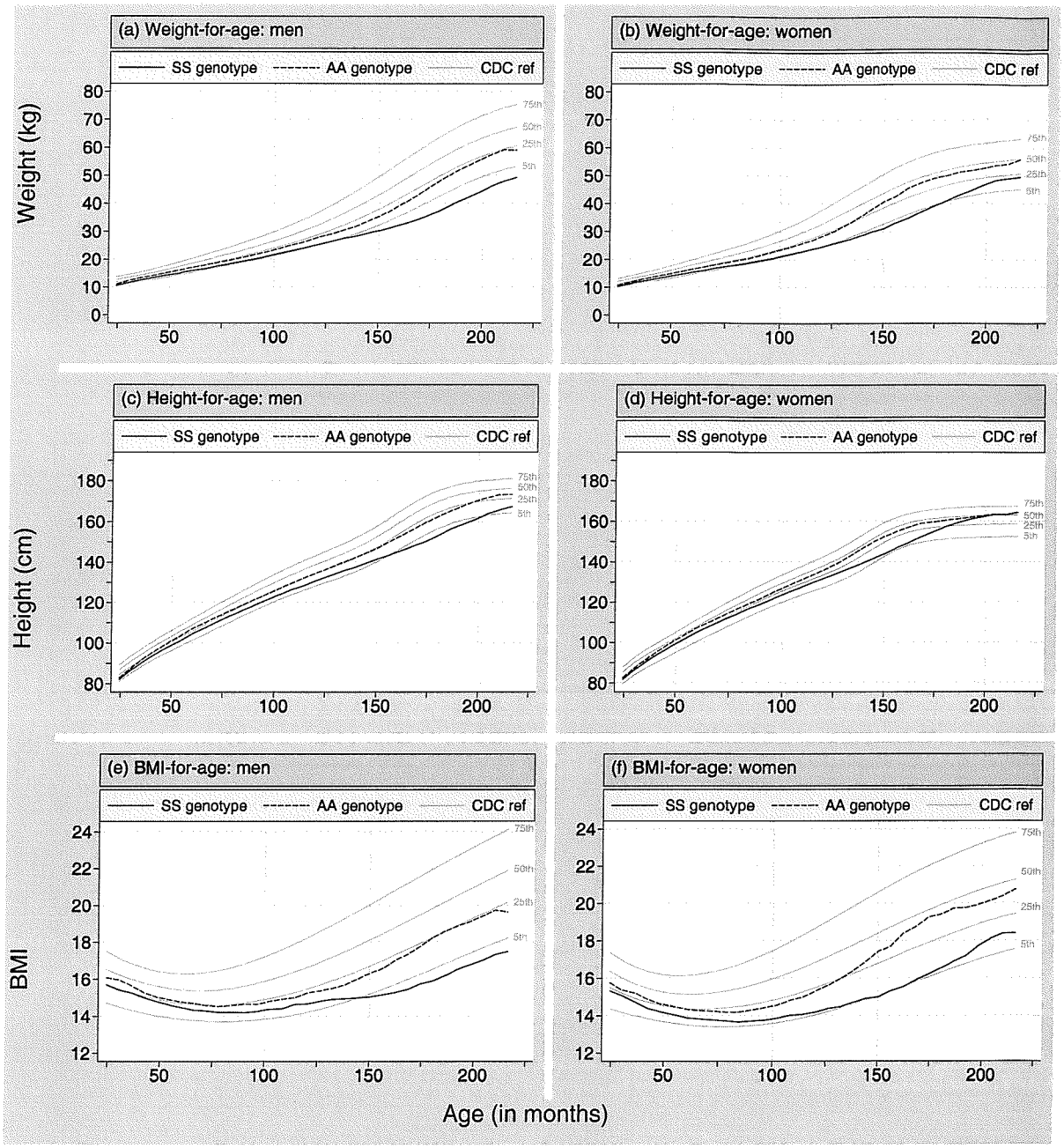
Table 6.13.

Number of JSSCD participants below the 3rd, 5th amd 10th CDC BMI-for-age reference centiles between the ages of two and 18, by genotype and gender.

Centile	Number below centile (%)	Number (%) with proportion of time below centile			
		0.1 to 0.24	0.25 to 0.49	0.50 to 0.74	0.75 to 1
SS Men (n=151)					
3rd	109 (72)	29 (19)	33 (22)	27 (18)	20 (13)
5th	120 (79)	29 (19)	32 (21)	31 (21)	28 (19)
10th	128 (85)	21 (14)	17 (11)	34 (23)	56 (37)
AA Men (n=103)					
3rd	48 (47)	30 (29)	6 (6)	7 (7)	5 (5)
5th	57 (55)	28 (27)	8 (8)	11 (11)	10 (10)
10th	75 (73)	25 (24)	18 (17)	14 (14)	18 (17)
SS Women (n=129)					
3rd	95 (74)	32 (25)	21 (16)	22 (17)	20 (16)
5th	100 (78)	27 (21)	13 (10)	33 (26)	27 (21)
10th	110 (85)	17 (13)	15 (12)	23 (18)	55 (43)
AA Women (n=118)					
3rd	49 (42)	28 (24)	7 (6)	9 (8)	5 (4)
5th	62 (53)	33 (28)	11 (9)	8 (7)	10 (8)
10th	76 (64)	31 (26)	18 (15)	12 (10)	15 (13)

Figure 6.8

Age-specific childhood growth between 2 and 18 years of age in 280 JSSCD participants with SS disease, and in 221 AA controls, with added CDC reference centiles



Regression on painful crisis outcome

The number of painful crisis events were negatively related to size in early childhood – a unit increase in the BMI SD-score at two-years of age was associated with a 13% decrease in the number of painful crises over the 10-year period. There was a similar negative effect later in childhood - a unit increase in the BMI SD-score at eight-years of age was associated with a 21% decrease in the number of painful crises over the 10-year period. The number of painful crisis events were unrelated to BMI centile crossing (combined model), and there was

little difference in the amount of BMI centile crossing based on early size (interaction model).

Regression on vaso-occlusive events

There were 1729 vaso-occlusive events among the SS participants by 10-years of age. This total comprised 391 (23%) dactylitis events, 672 (39%) mild painful crises, 196 (11%) severe painful crises, 76 (4%) abdominal painful crises, 21 (1%) strokes, and 373 (22%) ACS events. The effect of BMI-for-age on this summary measure of vaso-occlusive events was similar to results for our painful crisis outcome. Percentage decreases in outcome for unit BMI increases were marginally smaller, but these changes remained strongly statistically significant.

Regression on white blood cell count outcome

Although increasing size in children tended to be associated with reduced white cell count in later life, these effects were not statistically important.

Table 6.14.

Regression models investigating the effects of size in childhood on clinical and haematological outcomes among JSSCD participants with homozygous sickle-cell disease*

Outcome	**BMI (SD-score)**		**2 years × 8 years**
	2 years	**8 years**	
Painful crisis			
Early	-0.13 (-0.20 to -0.06)	-	-
Later	-0.21 (-0.27 to –0.14)	-	-
Combined	0.01 (-0.08 to 0.10)	-0.21 (-0.29 to –0.12)	-
Interaction	0.01 (-0.14 to 0.16)	-0.21 (-0.31 to –0.10)	0.002 (-0.056 to 0.062)
Vaso-occlusive events			
Early	-0.10 (-0.15 to –0.04)	-	-
Later	-0.17 (-0.22 to –0.12)	-	-
Combined	0.02 (-0.05 to 0.08)	-0.18 (-0.24 to –0.11)	-
Interaction	0.04 (-0.07 to 0.15)	-0.17 (-0.24 to –0. 09)	0.01 (-0.03 to 0.05)
White blood cell			
Early	-0.29 (-0.71 to 0.13)	-	-
Later	-0.32 (-0.72 to 0.08)	-	-
Combined	-0.14 (-0.67 to 0.38)	-0.24 (-0.73 to 0.26)	-
Interaction	-0.59 (-1.42 to 0.25)	-0.46 (-1.06 to 0.13)	-0.25 (-0.61 to 0.11)

***All models adjusted for gender and for early dropout**

6.3.8 Mortality

(a) Cause of death

In the 27-year period to 31 December 1999 there were 84 deaths among JSSCD participants with SS or SC disease (75 with SS disease, 9 with SC disease). Principle causes of death were restricted to the acute chest syndrome (21% of all deaths), septicaemia/meningitis (20%), acute splenic sequestration (14%), stroke (12%), gastroenteritis (8%), and the aplastic crisis (2%), (Table 6.15). Other causes of death (11% of all deaths) included 1 from chronic renal failure, 1 portal vein thrombosis, 2 motor vehicle accidents, 1 death from substance abuse, 2 from pregnancy-related complications, and 2 from stab wounds. Septicaemia / meningitis deaths are categorised by organism (pneumococcus, salmonella, *H.influenzae*, and unknown). The cause of nine deaths (11%) was unknown.

Table 6.15.
Number of deaths among JSSCD participants with SS or SC disease, by cause of death, gender, genotype, and gender.

Cause of death	SS disease		SC disease	
	Men	Women	Men	Women
Septicaemia / meningitis	8	9	0	0
Pneumococcal	4	2		
Salmonella	2	2		
Haemophilus influenzae	0	1		
Unknown organism	2	4		
Acute chest syndrome	5	11	1	1
Acute splenic sequestration	3	8	1	0
Stroke	9	1	0	0
Gastroeneritis	3	1	0	3
Aplastic crisis	1	1	0	0
Other	6	2	1	0
Unknown	5	2	2	0
Total	**40**	**35**	**5**	**4**

Using the case-fatality rate to incorporate the underlying event rate, stroke carries the highest risk of death; around one-in-four of all JSSCD cases were fatal. One-in-five of all septicaemia / bacteraemia events were fatal, 6-in-100 ASS events were fatal, 3-in-100 ACS events, 2-in-100 aplastic crisis events, and 1-in-1000 gastroeneritis events (Table 6.16).

Table 6.16.
Case-fatality rate among JSSCD participants with SS disease, by cause of death, and gender.

Cause of death	Case-fatality rate per 100 events (95% bootstrapped confidence interval)		
	Men	Women	All
Septicaemia / meningitis	23.53 (11.76 – 35.29)	23.68 (13.16 - 34.21)	23.61 (15.28 - 31.94)
Acute chest syndrome	1.63 (0.65 - 2.94)	5.42 (2.96 - 7.88)	3.14 (1.96 - 4.51)
Acute splenic sequestration	2.86 (0.05 - 5.71)	8.89 (4.44 - 14.44)	5.64 (3.08 - 8.21)
Stroke	37.50 (20.83 - 54.17)	8.33 (0 - 25)	27.78 (16.68 - 38.89)
Gastroeneritis	0.14 (0.05 - 0.28)	0.05 (0 - 0.1)	0.10 (0.02 - 0.17)
Aplastic crisis	1.72 (0 - 5.17)	2.33 (0 - 6.98)	1.98 (0 - 4.95)

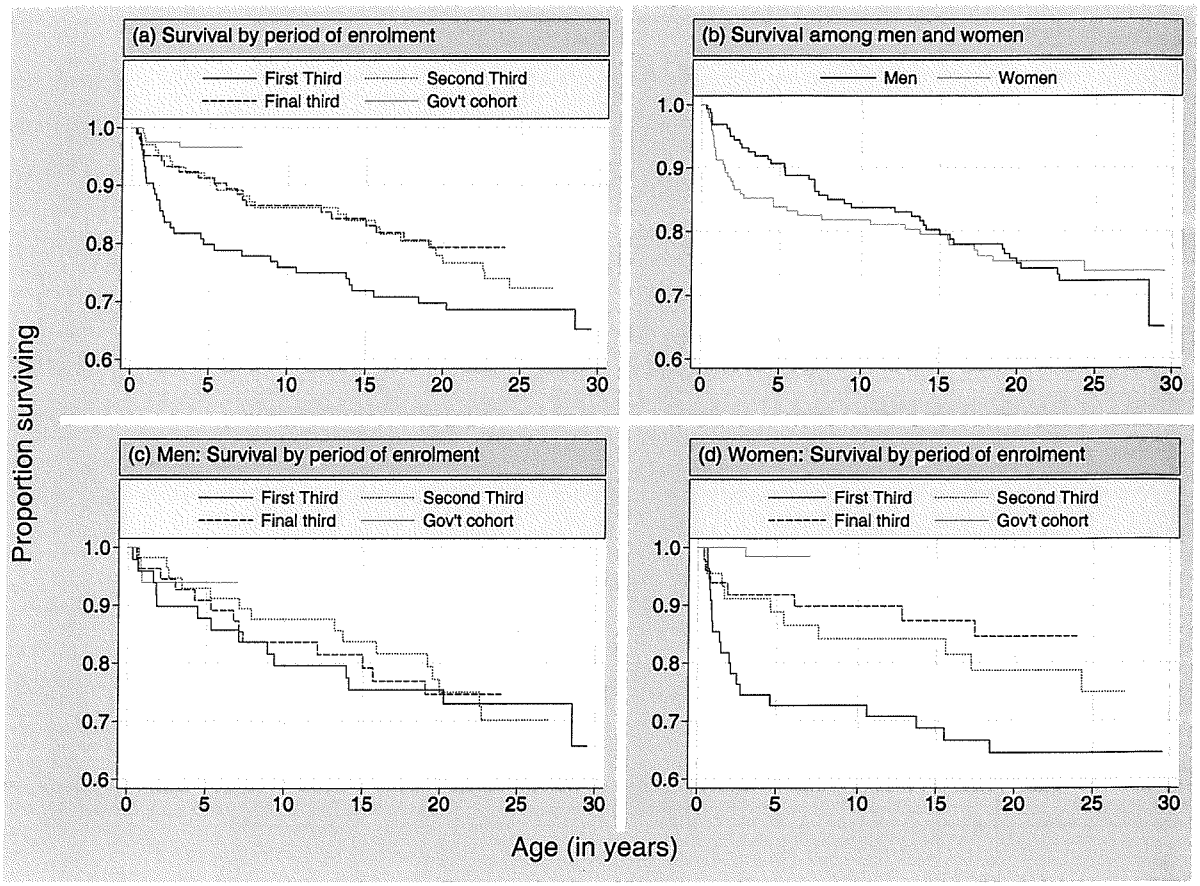
(b) Mortality by period of enrolment

Survival was increased in JSSCD participants born in the second and third tertiles relative to the first tertile (Log-rank test=7.05 Pr=0.03). This difference was due entirely to many early-life deaths in the first tertile; the mortality trend among participants aged five-years and older was roughly equivalent in all tertiles (**Figure 6.9**a). This difference was also due entirely to females, and the reason for this is unknown (**Figure 6.9**b). Although there were excess females deaths in early life, higher male mortality in adolescence means that by the middle of the third decade survival rates in male and female participants were equivalent.

The Government screening programme began in 1995 and by December 1999 115 participants had been recruited). The oldest participants were four years old at the time of this investigation. There have been three deaths in this Government cohort to date. At this early stage, the survival rate was improved compared to all tertiles of the JSSCD (Log-rank test=7.78 Pr=0.005) (**Figure 6.9**a).

Figure 6.9

Survival of JSSCD participants with homozygous sickle-cell disease followed to 31st December 1999 by period of enrolment and by gender



The log-rank test was used for all survival group comparisons. This test requires the proportional-hazards assumption, which we examined in Figure 6.10. We plotted the observed

Kaplan-Meier curves for each survival group and the Cox predicted curves for the same group. The closer the observed values were to the predicted, the less likely it was that the proportional hazards assumption had been violated. There was some mild deviation of predicted from observed in groups one and two, and for formal comparisons of survival across groups we presented an alternative to the log-rank test which is appropriate when hazard functions may be non-proportional Table 6.17. The log-rank and generalised Wilcoxon tests provide very close agreement, suggesting that the deviation from proportional hazards assumption was mild.

Figure 6.10
Survival of JSSCD participants with homozygous sickle-cell disease followed to 31st December 1999 by period of enrolment and by gender

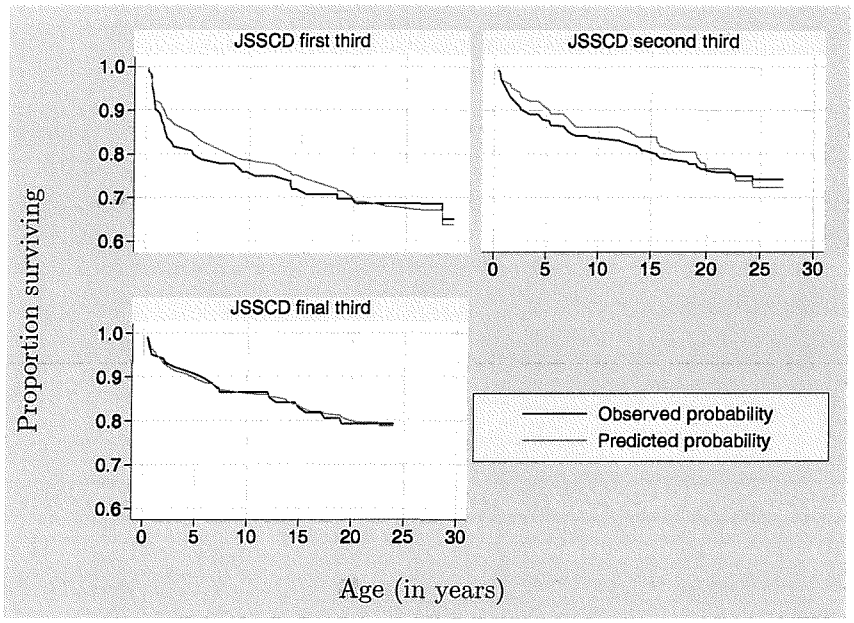


Table 6.17.
Test of the equality of the survivor function of three birth groups from the JSSCD.

	Mortality by 14-years of age Test statistic (P-value)		**Mortality by 18-years of age Test statistic (P-value)**	
	Log-Rank	**Wilcoxon**	**Log-Rank**	**Wilcoxon**
Men	1.40 (0.50)	1.42 (0.49)	0.92 (0.63)	1.05 (0.59)
Women	6.46 (0.04)	6.31 (0.04)	5.35 (0.07)	5.66 (0.06)
All	7.05 (0.03)	7.18 (0.03)	4.79 (0.09)	5.53 (0.06)

6.3.9 Case study 5: Survival in homozygous sickle cell disease

Information on survival in homozygous sickle cell (SS) disease is important in patient counselling, assessing adequacy of medical management, targeting clinical research, and in shaping the concept of clinical severity in SS disease.

An investigation from the Cooperative Study for Sickle Cell Disease (CSSCD) among 2,412 patients between 1978 and 1988 provided the first insight into life expectancy from birth, quoting median survival for this US-based population of 42 years for SS males and 48 years for SS females (2). With over 177 citations to date (Science Citation Index, March 01, 2000), these statistics have been embraced by the research community as a contemporary summary of clinical expression.

Unbiased estimation of lifetime survival requires patient identification at birth, with prospective follow-up thereafter. Reliable neo-natal screening has only been available since the early 1970's however (43;44) and newborn cohorts can currently only provide survival experience to early adulthood (6;45). Clinically referred patients offer an alternative population, but have widely documented biases (46). If using such a population, careful consideration of data quality, and appropriate statistical analyses are required to increase the chance of valid and generalizable results.

In a clinic-based SS population, a patient arrives to clinic after disease onset. This phenomenon is known as 'late-entry', and is quantified by the period between birth and clinic arrival (47;48). Alternatively, an SS patient may die before recruitment to study. Mortality in SS disease is increased in early life (12;49), with greatest mortality experienced between the ages of 6 months and 3 years (6;45;50) and the possibility of missing mortality, especially in early childhood, must be considered (51). Late-entry will impact on survival estimates if mortality rates for patients in and out of a study are different. Techniques to compensate for late-entry are applied during data analysis.

Additionally, patients that have presented to clinic may subsequently stop attending before the end of a study. If the reasons for this default are related to the disease being studied, survival estimates are likely to be affected. Attempts to minimise default were made during data collection, with further consideration during data analysis.

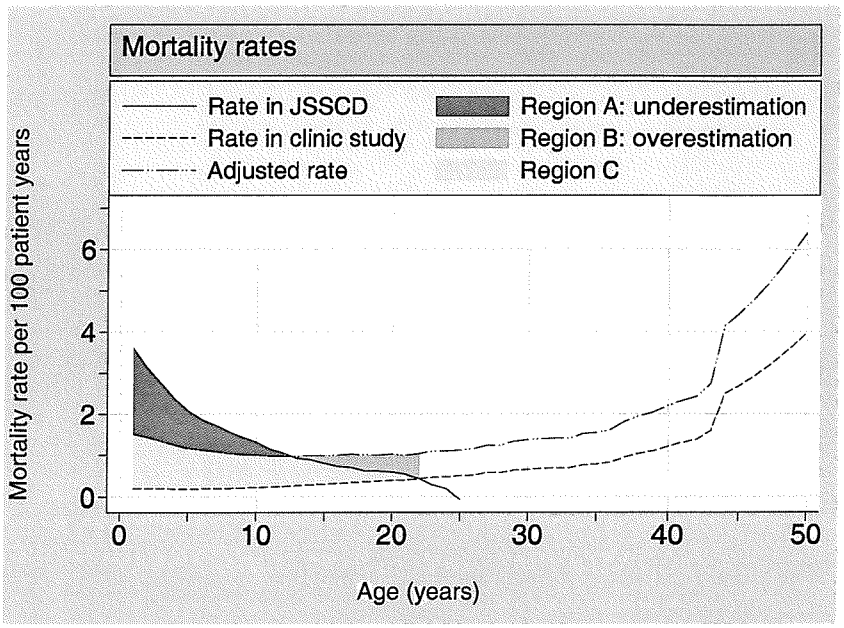
A formal study of life expectancy of Jamaican SS patients has not been done, although it has been known for many years that despite the burden of high early childhood mortality, survival beyond age 30 (52) or even 40 (28;53) was not uncommon. Data from a clinic-based patient population, and from a birth cohort are available in Jamaica, and lifetime survival is investigated using both these populations.

(a) Methods

Patients diagnosed with SS disease defined by standard criteria (5), resident in Jamaica, who had attended one of the three study centres (Kingston, Montego Bay and Black River) (54) at least once between January 1, 1987 and December 31, 1996, were eligible for inclusion. A total of 3,301 patients were enrolled in study, of which 3,035 (91.9%) were enrolled in clinic following referral by hospitals, health centers or private physicians (97 before 6 months of age). The remaining 266 (8.1%) were diagnosed from neonatal screening between 1973 and 1981 as part of the JSSCD, the details of which have been described in Chapter Two.

Figure 6.11

Age-specific mortality rates among clinic and JSSCD study participants.



(b) Default

Within the study window, entry to study was defined as the first clinic attendance, and the endpoint was death. Patients alive and resident in Jamaica at their last visit to clinic within the study window and with no clinic visit on or after January 1, 1997 were initially considered defaulted. The post-study status of defaulted patients was investigated. Tracing strategies included questioning relatives, review of hospital dockets, letters, telephone calls, and home visits by staff members or local health workers. The status of traced patients was converted to alive, dead, or migrated. Deaths were actively traced through hospital and civil death registries to obtain an exact date of death where possible. Dates of death or migration were recorded as the date of last clinic visit when unknown. Tracing of 1,007 defaulted patients proved successful in all but 32, confirming the status of 3,269 / 3,301 (99.0%) of the initial sample. Of the 975 traced patients 130 had emigrated within the study window, 85 had died, and 760 were alive at the end of the study window. The exact date of death of 16 / 290 (5.5%) patients could not be established.

(c) Late entry

The JSSCD represents a birth cohort of 315 patients currently aged between 18 and 26 years. Among non-emigrated SS patients (representing 84.4% of the original sample on January 1, 1997) complete mortality data are available. Annual mortality rates among the clinic-based patient population and among the JSSCD are presented in Figure 6.11. The JSSCD population confirms the period of increased mortality in early childhood and highlights an excess mortality rate compared to the clinic-based patients, which persists until early adulthood (figure one, regions A + C). This difference in mortality is likely to be the result of follow-up from birth among JSSCD participants and has been previously highlighted when examining the incidence of clinical events (see Section 6.3.6). An accepted statistical procedure attempts to adjust for this difference (14) but underestimates mortality in the first 10 years (Figure 6.11, region A), and overestimates mortality thereafter (Figure 6.11, region B). Incorporation of the excess cohort mortality into the clinic-based population creates a new analysis dataset for which the assumption of comprehensive mortality information is appropriate. No statistical adjustment for late-entry bias is therefore necessary.

(d) Statistical methods

Gender compositions for the complete sample, and for subgroups (alive, dead, migrated, and defaulted patients) are compared using an exact binomial test. Distributions of patient age at entry and length of follow-up are positively skewed and are summarized using robust measures: median, median absolute deviation (55), interquartile range, and range. Although less appropriate given this skewed characteristic, mean and standard deviation are also presented to allow comparison with published work (2). The excess cohort mortality rate in each year of life is converted to the expected number of unrecorded deaths in the clinic-based patient population in each year from birth to 25 years (total simulated deaths=684), and each death is randomly assigned a date of birth within the year. These extra simulated deaths are appended to the clinic-based patient dataset, and time from birth to death is presented by gender using standard Kaplan-Meier methodology. Results are compared to a standard statistical adjustment (14). Bootstrapping (56) is a technique in wide use in epidemiology (57;58), and is used in this study to examine the precision of simulated Kaplan-Meier statistics. Two sets of bootstrapped confidence intervals were produced: one set assuming independence of all simulated deaths, and a second set to account for the fact that each single excess death in the JSSCD was used to simulate multiple deaths in the clinic-based patient population, creating dependence between simulated deaths. This second measure of precision that accounts for clustering is more appropriate.

(e) Ethical considerations

All SS patients routinely attend the sickle cell clinic every 3 or 6 months, depending on age. Default is common, and is frequently due to distance from domicile to clinic. An outreach

program ensures better access for all, and includes domiciliary visits (8). Care was taken to remain within this tradition during the tracing of defaulted patients.

Table 6.18.
Numbers of homozygous SS patients by gender and status on January 01, 1997.

status	Patient gender		
	Male (%)	**Female (%)**	**Total**
Alive	1281 (38.81)	1401 (42.44)	2682 (81.25)
Dead	150 (4.54)	140 (4.24)	290 (8.79)
Migrated	121 (3.67)	176 (5.33)	297 (9.00)
Default	18 (0.55)	14 (0.42)	32 (0.97)
Total	1570 (47.56)	1731 (52.44)	3301 (100.00)

(f) Results

Patient numbers by gender and final status (on January 1, 1997) are presented in Table 6.18. There were more female patients than males (p=0.01). At the close of the study, the proportions of dead and defaulted patients did not vary across gender (dead: p=0.60, defaulted: p=0.60). There was a greater proportion of emigrated female patients (p=0.002), and a greater proportion of females alive and available for continuing follow-up (p=0.02).

Table 6.19.
Age at entry to study duration of follow-up, and age at death by gender
for 3301 homozygous SS patients.

Gender	median (mad*)	iqr	range	mean (sd)
Age at entry (n=3301)				
Male (n=1570)	11.71 (12.34)	4.76 - 22.42	0 - 69.36	15.07 (12.82)
Female (n=1731)	13.96 (13.40)	5.70 - 24.43	0 - 72.37	16.65 (13.37)
Follow-up (n=3301)				
Male (n=1570)	7.22 (3.93)	2.89 - 9.61	0 – 10	6.24 (3.34)
Female (n=1731)	7.15 (4.02)	2.65 - 9.68	0 – 10	6.26 (3.46)
Age at death (n=290)				
Male (n=150)	24.91 (15.14)	10.20 - 40.62	0.70 – 72.39	26.90 (18.19)
Female (n=140)	25.65 (12.54)	13.30 - 38.19	0.28 – 77.45	27.90 (18.31)

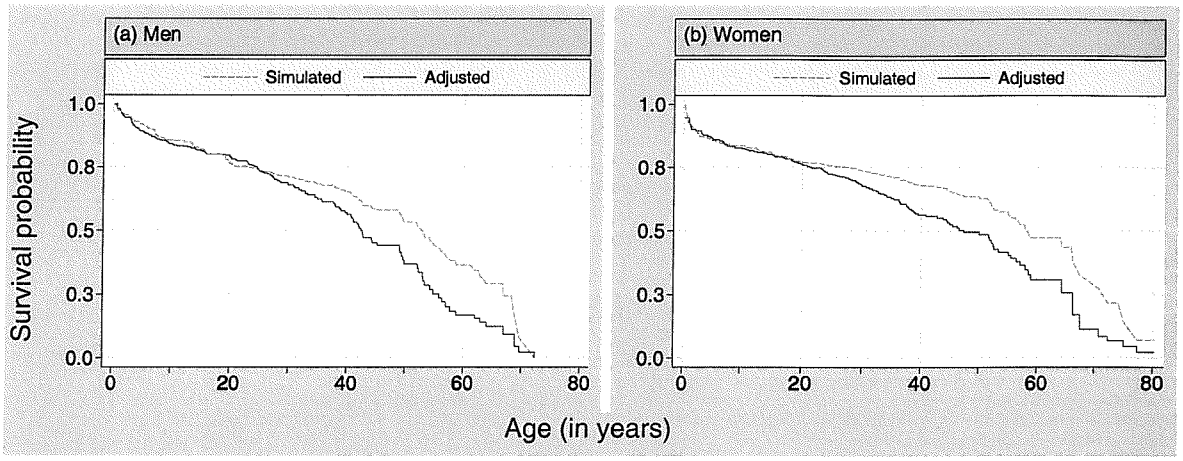
*** mad = median absolute deviation**

Females were significantly older than males on entry to study (logrank test $\chi 2$=10.5, p=0.001). Duration of follow-up was similar across gender ($\chi 2$=1.4, p=0.24). Among the 290 deaths there was no age difference across gender ($\chi 2$=0.4, p=0.54) (Table 6.19). There was a

potential of 22,357 years of follow-up, of which 1,720 (7.7%) years were lost (1,529 years due to migration, 191 years due to default). Survival estimates using the standard statistical adjustment and the 'excess mortality rate' simulation are graphed for men in Figure 6.12(a), and for women in Figure 6.12(b). Compared to men, women have a poorer survival experience in early childhood. Adult survival is generally improved in women. Median survival using the 'excess mortality rate' simulation is 53.0 (clustered 95% CI 49.0, 58.7) years for men and 58.5 (clustered 95% CI 53.5, 70.9) for women. Median survival using the standard statistical adjustment is 42.6 (40.0, 49.1) years for men and 47.4 (37.8, 55.1) for women (Table 6.20).

Figure 6.12

Kaplan-Meier survival estimates from birth for 3301 SS patients by gender using two competing methodologies



(g) Discussion

This study provides the first insight into the lifetime survival experience of SS patients in Jamaica between 1987 and 1996 . It further represents the largest investigation of survival among an SS population. Patient age at entry and duration of follow-up describe a similar population to that available in the Cooperative Study of Sickle Cell Disease (CSSCD), and using the same survival analysis technique (14), gender-specific median survival estimates are almost identical (2). These striking demographic and lifetime survival similarities offer a persuasive argument that the Jamaican and US SS populations are homogenous.

Late-entry bias poses the most serious challenge to the study of lifetime survival estimates in clinic-based SS populations. An accepted statistical adjustment used previously (14) to account for unseen deaths assumes an equal risk of death at any time for patients in and out of the study, and this critical assumption is shown to be inappropriate for the current patient population. Using a technique that has alternative and potentially more realistic assumptions supported by empirical evidence, the current study offers an new, milder description of median lifetime survival in SS disease.

The study offers the first presentation of precision for a survival analysis of sickle cell disease. It highlights the marked uncertainty of the standard statistical adjustment in early and late life, and is an important reminder that median survival estimates should be quoted as intervals for which one is 95% confident.

In the next two to three decades more accurate information on median survival in SS disease will become available from patient groups like the JSSCD, ascertained at birth and prospectively followed. Until then, survival summaries in homozygous sickle cell disease will continue to depend on the appropriateness of the techniques used and on the assumptions made.

Table 6.20.

Kaplan-Meier survival estimates (with 95% confidence intervals)

for 3301 SS patients by gender using two competing methodologies

S(t)	Adjustment				Simulation					
	Men		Women		Men			Women		
	Age	95% CI	Age	95% CI	Age	95% CI	95% CI clustered	Age	95% CI	95% CI clustered
0.95	2.0	(0.7,3.8)	0.3	(0.0,3.4)	2.6	(1.4,4.0)	(0.8 to 6)	0.7	(0.4, 1.0)	(0.4 to 2)
0.90	4.4	(0.7,9.1)	2.2	(0.0,11.0)	6.6	(4.7,7.9)	(2.8 to 12.6)	1.9	(1.1,2.9)	(0.8 to 7.2)
0.85	9.3	(3.4,18.7)	7.0	(0.0,19.4)	12.9	(7.7,15.3)	(6.1 to 19.3)	6.4	(2.9,12.8)	(2 to 17.6)
0.80	18.7	(7.4,24.6)	15.3	(0.0,25.8)	19.0	(13.8,20.1)	(12.2 to 25.5)	15.7	(12.2,21.2)	(5.7 to 29.8)
0.75	24.6	(15.3,28.2)	21.6	(0.0,31.1)	23.0	(19.4,29.9)	(15.9 to 35.6)	28.6	(18.6,36.0)	(15.2 to 40.5)
0.70	28.0	(23.1,33.2)	28.7	(8.0,36.3)	32.3	(24.7,40.6)	(20.2 to 42)	37.6	(31.6,47.2)	(25.1 to 51.8)
0.65	32.9	(27.2,38.7)	33.1	(20.1,39.5)	40.6	(34.8,45.6)	(29.2 to 49.2)	46.2	(37.9,53.1)	(36 to 55.9)
0.60	37.9	(31.8,41.6)	37.6	(28.2,45.4)	42.8	(40.6,52.1)	(38.7 to 53)	52.5	(46.2,58.2)	(44.4 to 58.5)
0.55	40.7	(35.7,42.7)	43.8	(33.8,51.9)	49.6	(44.2,54.6)	(42.3 to 54.9)	56.5	(53.1,66.0)	(51.7 to 66.2)
0.50	42.6	(40.0,49.1)	47.4	(37.8,55.1)	53.0	(49.3,57.0)	(49 to 58.7)	58.5	(55.1,67.5)	(53.5 to 70.9)

6.4 Reference List

(1) Ohene-Frempong K, Steinberg MH. Clinical aspects of sickle cell anaemia in adults and children. In: Steinberg MH, Forget BG, Higgs DR, Nagel RL, editors. Disorders of haemoglobin: genetics, pathophysiology, and clinical management. Cambridge: Cambridge University Press, 2001: 611-669.

(2) Platt OS, Brambilla DJ, Rosse WF, Milner PF, Castro O, Steinberg MH et al. Mortality in sickle cell disease. Life expectancy and risk factors for early death. N Engl J Med 1994; 330(23):1639-1644.

(3) Wierenga KJ, Hambleton IR, Lewis NA. Survival estimates for patients with homozygous sickle-cell disease in Jamaica: a clinic-based population study. Lancet 2001; 357(9257):680-683.

(4) Steinberg MH. Management of sickle cell disease. N Engl J Med 1999; 340(13):1021-1030.

(5) Serjeant GR. Sickle Cell Disease. 2nd ed. Oxford: Oxford University Press, 1992.

(6) Gill FM, Sleeper LA, Weiner SJ, Brown AK, Bellevue R, Grover R et al. Clinical events in the first decade in a cohort of infants with sickle cell disease. Cooperative Study of Sickle Cell Disease [see comments]. Blood 1995; 86(2):776-783.

(7) Powars D. Natural history of disease: the first two decades. In: Embury SH, Hebbel RP, Mohandas N, Steinberg MH, editors. Sickle cell disease: basic principles and clinical practice. New York: Raven Press, 1994: 395-412.

(8) Hayes RJ, Beckford M, Grandison Y, Mason K, Serjeant BE, Serjeant GR. The haematology of steady state homozygous sickle cell disease: frequency distributions, variation with age and sex, longitudinal observations. Br J Haematol 1985; 59(2):369-382.

(9) Sidak Z. Rectangular confidence regions for the means of multivariate normal distributions. Journal of the American Statistical Association 1967; 62:626-633.

(10) Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. Journal of The Royal Statistical Society, Series B 1995; 57:289-300.

(11) Efron B, Tibshirani RJ. Better bootstrap confidence intervals. An Introduction to the Bootstrap. New York: Chapman and Hall, 1993: 178-201.

(12) Lee A, Thomas P, Cupidore L, Serjeant B, Serjeant G. Improved survival in homozygous sickle cell disease: lessons from a cohort study. BMJ 1995; 311(7020):1600-1602.

(13) Serjeant GR, Grandison Y, Lowrie Y, Mason K, Phillips J, Serjeant BE et al. The development of haematological changes in homozygous sickle cell disease: a cohort study from birth to 6 years. Br J Haematol 1981; 48(4):533-543.

(14) Cnaan A, Ryan L. Survival analysis in natural history studies of disease. Stat Med 1989; 8(10):1255-1268.

(15) Topley JM, Rogers DW, Stevens MC, Serjeant GR. Acute splenic sequestration and hypersplenism in the first five years in homozygous sickle cell disease. Arch Dis Child 1981; 56(10):765-769.

(16) Ficat RP. Idiopathic bone necrosis of the femoral head. Early diagnosis and treatment. J Bone Joint Surg Br 1985; 67(1):3-9.

(17) Stevens MC, Hayes RJ, Vaidya S, Serjeant GR. Fetal hemoglobin and clinical severity of homozygous sickle cell disease in early childhood. J Pediatr 1981; 98(1):37-41.

(18) Rogers DW, Vaidya S, Serjeant GR. Early splenomegaly in homozygous sickle-cell disease: An indicator of susceptibility to infection. Lancet 1978; 2(8097):963-965.

(19) Morgan SA, Jackson J. Psychological and social concomitants of sickle cell anemia in adolescents. J Pediatr Psychol 1986; 11(3):429-440.

(20) Hurtig AL, White LS. Psychosocial adjustment in children and adolescents with sickle cell disease. J Pediatr Psychol 1986; 11(3):411-427.

(21) Hurtig AL, Koepke D, Park KB. Relation between severity of chronic illness and adjustment in children and adolescents with sickle cell disease. J Pediatr Psychol 1989; 14(1):117-132.

(22) Milner PF, Kraus AP, Sebes JI, Sleeper LA, Dukes KA, Embury SH et al. Sickle cell disease as a cause of osteonecrosis of the femoral head. N Engl J Med 1991; 325(21):1476-1481.

(23) Koshy M, Entsuah R, Koranda A, Kraus AP, Johnson R, Bellvue R et al. Leg ulcers in patients with sickle cell disease [see comments]. Blood 1989; 74(4):1403-1408.

(24) Platt OS, Thorington BD, Brambilla DJ, Milner PF, Rosse WF, Vichinsky E et al. Pain in sickle cell disease. Rates and risk factors [see comments]. N Engl J Med 1991; 325(1):11-16.

(25) Baum KF, Dunn DT, Maude GH, Serjeant GR. The painful crisis of homozygous sickle cell disease. A study of the risk factors. Arch Intern Med 1987; 147(7):1231-1234.

(26) Ohene-Frempong K, Weiner SJ, Sleeper LA, Miller ST, Embury S, Moohr JW et al. Cerebrovascular accidents in sickle cell disease: rates and risk factors. Blood 1998; 91(1):288-294.

(27) Wong WY, Elliott-Mills D, Powars D. Renal failure in sickle cell anemia. Hematol Oncol Clin North Am 1996; 10(6):1321-1331.

(28) Morgan AG, Serjeant GR. Renal function in patients over 40 with homozygous sickle-cell disease. Br Med J (Clin Res Ed) 1981; 282(6271):1181-1183.

(29) Ben-Shlomo Y, Kuh D. A life course approach to chronic disease epidemiology: conceptual models, empirical challenges and interdisciplinary perspectives. Int J Epidemiol 2002; 31(2):285-293.

(30) Eaton WW. The logic for a conception-to-death cohort study. Ann Epidemiol 2002; 12:445-451.

(31) Susser E, Terry MB, Matte T. The birth cohorts grow up: new opportunities for epidemiology. Paediat Pernat Epidemiol 2000; 14:98-100.

(32) Golding J, Pembrey M, Jones R. ALSPAC--the Avon Longitudinal Study of Parents and Children. I. Study methodology. Paediatr Perinat Epidemiol 2001; 15:74-87.

(33) Smith K, Joshi H. The millenium cohort study. Pop Trends 2002; 107:30-34.

(34) Leon DA, Lithell HO, Vagero D, Koupilova I, Mohsen R, Berglund L et al. Reduced fetal growth rate and increased risk of death from ischaemic heart disease: cohort study of 15 000 Swedish men and women born 1915-29. BMJ 1998; 317:241-245.

(35) Kramer MS, Rooks Y, Washington LA, Pearson HA. Pre- and postnatal growth and development in sickle cell anemia. J Pediatr 1980; 96(5):857-860.

(36) Platt OS, Rosenstock W, Espeland MA. Influence of sickle hemoglobinopathies on growth and development. N Engl J Med 1984; 311(1):7-12.

(37) Stevens MC, Maude GH, Cupidore L, Jackson H, Hayes RJ, Serjeant GR. Prepubertal growth and skeletal maturation in children with sickle cell disease. Pediatrics 1986; 78(1):124-132.

(38) Luban NL, Leikin SL, August GA. Growth and development in sickle cell anemia. Preliminary report. Am J Pediatr Hematol Oncol 1982; 4(1):61-65.

(39) Ashcroft MT, Serjeant GR, Desai P. Heights, weights, and skeletal age of Jamaican adolescents with sickle cell anaemia. Arch Dis Child 1972; 47(254):519-524.

(40) Serjeant GR, Serjeant BE, Forbes M, Hayes RJ, Higgs DR, Lehmann H. Haemoglobin gene frequencies in the Jamaican population: a study in 100,000 newborns. Br J Haematol 1986; 64(2):253-262.

(41) Cole TJ, Green PJ. Smoothing reference centile curves: the LMS method and penalized likelihood. Stat Med 1992; 11(10):1305-1319.

(42) Lucas A, Fewtrell MS, Cole TJ. Fetal origins of adult disease-the hypothesis revisited. BMJ 1999; 319(7204):245-249.

(43) Metters JS, Huntsman RG, Yawson GI. The use of the cord blood sample for the detection of sickle-cell anaemia in the newborn. J Obstet Gynaecol Br Commonw 1970; 77(10):935-938.

(44) Serjeant BE, Forbes M, Williams LL, Serjeant GR. Screening cord bloods for detection of sickle cell disease in Jamaica. Clin Chem 1974; 20(6):666-669.

(45) Serjeant GR, Serjeant BE. Management of sickle cell disease; lessons from the Jamaican Cohort Study. Blood Rev 1993; 7(3):137-145.

(46) Hoover DR, Munoz A, Carey V, Odaka N, Taylor JM, Chmiel JS et al. The unseen sample in cohort studies: estimation of its size and effect. Multicenter AIDS Cohort Study. Stat Med 1991; 10(12):1993-2003.

(47) Brookmeyer R, Gail MH. Biases in prevalent cohorts. Biometrics 1987; 43(4):739-749.

(48) Simon R. Length biased sampling in etiologic studies. American Journal of Epidemiology 1980; 111(4):444-452.

(49) Rogers DW, Clarke JM, Cupidore L, Ramlal AM, Sparke BR, Serjeant GR. Early deaths in Jamaican children with sickle cell disease. Br Med J 1978; 1(6126):1515-1516.

(50) Leikin SL, Gallagher D, Kinney TR, Sloane D, Klug P, Rida W. Mortality in children and adolescents with sickle cell disease. Cooperative Study of Sickle Cell Disease. Pediatrics 1989; 84(3):500-508.

(51) Corey M. Survival estimates in cyctic fibrosis: snapshots of a moving target. Pediatric Pulmonology 1996; 21:149-150.

(52) Serjeant GR, Richards R, Barbor PR, Milner PF. Relatively benign sickle-cell anaemia in 60 patients aged over 30 in the West Indies. Br Med J 1968; 3(610):86-91.

(53) Morris J, Dunn D, Beckford M, Grandison Y, Mason K, Higgs D et al. The haematology of homozygous sickle cell disease after the age of 40 years. Br J Haematol 1991; 77(3):382-385.

(54) Serjeant GR, Hutson C. Patterns of attendance at Jamaican sickle cell clinics 1952 to 1981. Trans R Soc Trop Med Hyg 1984; 78(5):648-652.

(55) Bowman AW, Azzalini A. Applied smoothing techniques for data analysis. Oxford: OUP, 1997.

(56) Efron B, Tibshirani RJ. An Introduction to the Bootstrap. New York: Chapman and Hall, 1993.

(57) Hendriks JC, Satten GA, van Ameijden EJ, van Druten HA, Coutinho RA, van Griensven GJ. The incubation period to AIDS in injecting drug users estimated from prevalent cohort data, accounting for death prior to an AIDS diagnosis. AIDS 1998; %20;12(12):1537-1544.

(58) Tsodikov A, Hasenclever D, Loeffler M. Regression with bounded outcome score: evaluation of power by bootstrap and simulation in a chronic myelogenous leukaemia clinical trial. Stat Med 1998; 17(17):1909-1922.

Book Four

Health status

Chapter 7
Measuring health status

Background

Methods for summarising the health status of people living with homozygous sickle cell (SS) disease are not well developed. Evidence is available, but has not received widespread clinical acceptance. The evidence of methodological quality (internal validity) and of the generalisability of results, which is important to the promotion of such evidence, is not convincing.

Methods

We conducted a systematic review to identify prognostic factor studies of SS disease populations which used an outcome measure considered by the contributors of each article to be a summary of health status in sickle-cell disease. For each article, we examined the methodological quality according to predefined criteria. We summarised article quality based on the use of aspects of study design and analysis that are important to sickle-cell disease epidemiology.

Findings

We identified 77 severity prediction articles, with 66 (87%) of these classified as exploratory. Minimal standards of methodological quality were achieved in 3 (4%) of articles.

Interpretation

The complex aetiology of SS disease has kept the research focus on the identification of prognostic factors. Methodological quality has been lacking in a majority of articles.

7.1 Introduction

Homozygous sickle cell (SS) disease has diverse clinical symptoms, with variability between individuals and within individuals as they age (see chapter six). A large body of literature has explored possible risk factors for disease outcome, offering genetic (1;2), haematological (3-5), rheological (6), metabolic, and socioeconomic (7) factors as plausible independent determinants.

7.2 Measuring health

In its simplest form, 'health' means the absence of disease. In 1940, the World Health Organization (WHO) described health as the *'state of complete physical, mental, and social well-being, and not merely the absence of disease or infirmity'* (8). This widely accepted definition was expanded in the 1970's and 1980's as other components were included: intellectual, environmental, and spiritual health. In 1986, the World Health Organization further refined the definition of health within the framework of health promotion: *'Health is seen as a resource for everyday life, not the objective of living; it is a positive concept emphasizing social and personal resources, as well as physical capacity'* (9).

Although the theoretical basis of measuring health is well established in the field of psychometrics (10), there is little agreement on the naming conventions of health-specific outcomes (11). In health research generally, measurement instruments are variously called 'Quality of Life' (QoL), 'health-related QoL', 'heath status', 'functional status', 'disability', 'functional well-being'. In SCD research in particular, health outcome has been referred to as 'disease severity', 'clinical outcome', 'clinical expression', 'disease expression', 'clinical course', and 'natural history'. To some extent, this diversity reflects real differences in measurement focus. In many situations, though, these terms are used interchangeably to refer to a more general and abstract notion of health.

Strategies for conceptualising the measurement of SS disease health have emerged. Articles have identified frequent or life-threatening clinical events for use as markers of health status, either for use on their own (12-14), or using methodology for summarising more than one clinical event (15;16). The abstraction has been taken a step further with the use of proxy markers for frequent clinical events such as the number of hospitalisations or transfusions (17-20). Articles have further attempted to classify individual patients (19) or groups of patients (15) according to their health status (21;22). These approaches follow a 'disease model' concept of health (23), with the signs and symptoms of disease considered adequate for the description of health status. For the current study, we offer definitions for common terminology (Table 7.1).

Health-status is the most generic health-measurement term, and refers to any attempt to summarise the health of individuals or populations qualitatively or (more usually) quantitatively. *Clinical outcome* involves one or more measures of mortality and morbidity.

Disease outcome allows the inclusion of other biological indicators such as haematology in the definition of health. *Disease severity* additionally emphasises the perception of the patient, which is widely recognised as a central features of successful health status measurement (24-26). Currently, SCD literature offers little consideration of patient-based health outcome. We recognise that *disease severity* must form a central component of future measures of SCD health. Currently, we are constrained by the availability of information and in this review chapter we investigate the measurement and prediction of *disease outcome.*

Table 7.1.

Definitions of common terminology for health in SCD research

Term	Definition
Health-status	A description and/or measurement of the *health* of an individual or population at a particular point in time against identifiable standards, usually by reference to *health* indicators (27).
Clinical outcome	The clinical expression of sickle-cell disease
Disease outcome	The effect of sickle-cell disease and resulting therapy upon a person, as defined by clinical measures*
Disease severity	The effect of sickle-cell disease and resulting therapy upon a person, as defined by clinical measures *and* as perceived by the person*

*** Adapted from Schipper H, Clinch J, Olweny C. Quality of life studies: definitions and conceptual issues pp 11-23. In: Quality of life and pharmacoeconomics in clinical trials Ed: Spiker B. Philadelphia, Lippincott-Raven.**

7.2.1 Measuring clinical outcome

Descriptive summaries of clinical symptoms have allowed anecdotal descriptions of *clinical outcome.* The process of synthesising these individual and heterogeneous complications into a simple, objective and accepted summary is currently unclear. Obstacles to such a summary are formidable and include the time related variability of expression within an individual, and the economic costs of identifying and following an unselected population sample. Moreover, measurement of certain clinical symptoms (such as those involving a measurement of pain) are complicated by potentially subjective determination.

7.2.2 Measuring disease outcome or disease severity

Disease outcome and *disease severity* are not directly measurable, and proxy markers are necessary. The use of proxy measures means that any classification scheme will have a subjective component, making clinical acceptance difficult. Following some basic guidelines should help to increase the acceptability of any *disease outcome* or *disease severity* scheme: the proxy should be clinically important and defined in detail adequate for replication; it must have a direct relationship with some aspect of health, and be acceptable to the clinical community. If the outcome status of patients is assessed subjectively, it should be done so

without recourse to the values of clinical predictors - a process known as blind assessment (28). Measures should be easy to obtain, accurate, and reliable.

7.3 Predicting disease outcome or disease severity

An extensive literature has investigated the contribution of individual disease characteristics to *disease outcome*, and the methodological features of these articles are summarized in section 7.6. This body of work has contributed to important scientific advances (29;30), with direct translation to practical clinical management (31). In addition, the clinical community have promoted a justifiable call for the classification of SCD individuals according to an objective and quantitative *disease outcome* scheme (32;33).

Clinical interventions known to cure the disease or ameliorate symptoms are generally expensive, can be invasive, and carry associated risks. Bone marrow transplantation (34-36), although curative, has associated risks of mortality and failure (34), with potential infertility and carcinogenic complications. Hydroxyurea therapy (37) is currently the most widely studied of several therapeutic agents aimed at pharmacologic modulation of fetal haemoglobin. It has potential teratogenic effects, with the major side effect expected to be myelosuppression (12;38). Chronic transfusion therapy (39) is regularly indicated for neurovascular events (40). Complications are common (41;42), and longer term problems of iron overload exist (43). An ability to predict *disease outcome* might allow selection of adversely affected patient subgroups for prospective trials, and for proven clinical intervention.

The role of predictive schemes is well established, for identifying individuals to benefit from scarce resources or groups of patients for clinical trials, or for conducting comparative audits of medical facilities. The Glasgow coma scale (44), APACHE III (45), and the PRISM score of paediatric ICU mortality (46) are three examples of prognostic models widely used to inform difficult medical decisions. Many more schemes are published each year, and few of these achieve popular acceptance (47). Ultimately, schemes are judged on their clinical credibility - evidence that a clinically useful prognostic model can accurately generalise to new patient populations. Additionally, proof of substantially better prognostic ability than currently available schemes and independent confirmation of results should be required before a new scheme is considered for clinical use (48). Without evidence of such practical significance, acceptance is unwise and unlikely.

7.4 Evaluating disease outcome or disease severity predictions

Guidelines to aid both developers and users of prognostic schemes exist (49;50). In particular, the assessment of such schemes should be based on the general principles of *internal validity*, *accuracy*, and *generalisability*, which together constitute a formalisation of clinical credibility (51). An investigation of internal validity examines the methodological quality of a prognostic scheme. Assessment of accuracy and generalisability examine the

capacity of the scheme to preserve its prognostic ability in applications to new patient populations. *Accuracy* in this context has two dimensions: *calibration*, which examines whether predictions are too high or low, and *discrimination*, which examines the ability of a scheme to correctly classify patients into pre-defined groups. Generalisability also has two dimensions: *reproducibility*, which examines the prognostic ability of a scheme in patients who did not contribute to the development of the scheme but who are from the same underlying population. and *transportability*, which examines the prognostic ability of a scheme in patients from a different underlying population. The failure to examine or failure of, aspects of *internal validity*, *accuracy* or *generalisability* will undermine clinical credibility, and this invariably leads to rejection by the clinical community (52).

7.5 Chapter plan

A systematic review of articles predicting or using the concepts of *disease outcome* or *disease severity* in SS disease is described in sections 7.6 and 7.7. Results of the systematic review are presented in section 7.8, with a description of included studies (section 7.8.1), a description of study participants (section 7.8.2), and an examination of article quality (section 7.8.3).

7.6 Reviewing the evidence: a systematic review of disease outcome in SS disease

7.6.1 Objectives

We performed the systematic review to summarise the evidence on the risk factors for *disease outcome* in homozygous sickle cell disease and to assess the methodological quality of this evidence. Specific objectives were as follows:

(a) To identify articles that involve the prediction of disease outcome or disease severity,

(b) To describe articles according to the prognostic factor study classification of Simon and Altman (48),

(c) To explore the internal validity of articles, by defining how many articles apply appropriate statistical techniques, and how many articles meet pre-defined minimal criteria for acceptable methodology,

(d) To explore possible secular change in objectives (b), and (c).

7.6.2 Criteria for considering studies

We considered an article for inclusion in the systematic review if it was a prognostic factor study using an SS patient population and an outcome measure considered by the contributors of each article to be a summary of *disease outcome* or *disease severity.*

7.6.3 Search strategy

We decribe the search for acceptable articles as a three-stage process, and summarise this process in Figure 7.1.

In stage one, we searched the Medline and Embase online databases for all English language articles published between database inception and March 2000, using the algorithm presented in Table 7.2. We designed this algorithm to capture SS *disease outcome* or *disease severity* through common synonyms, using the NIH Medical Subject Headings (MeSH) classification of an article, or the actual use of these terms in the text of the article itself.

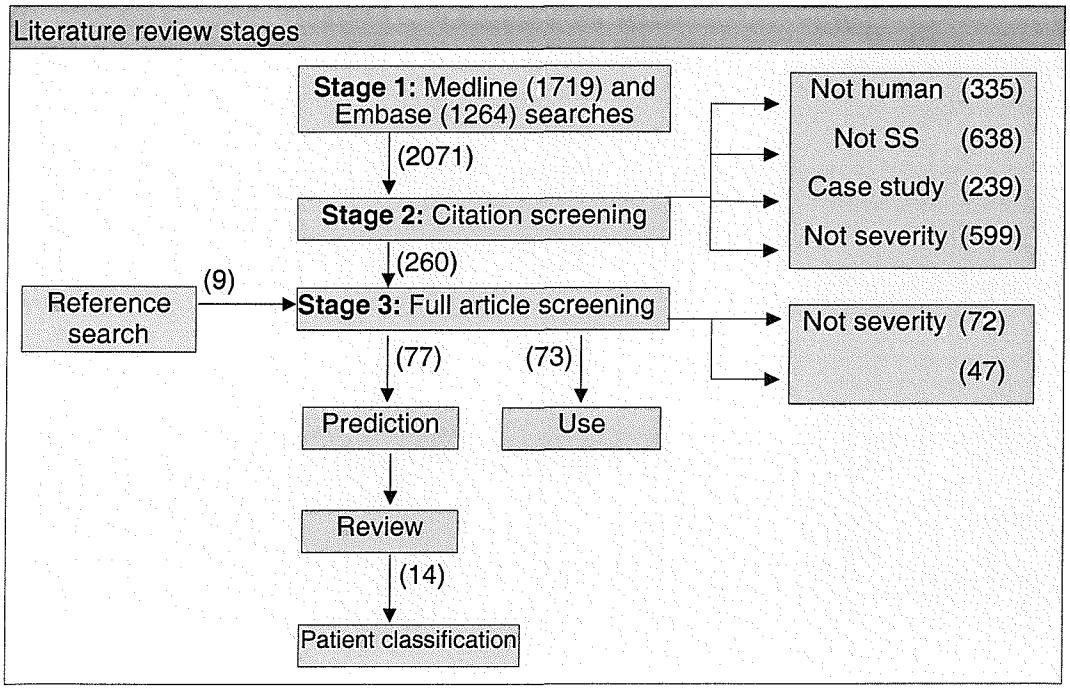
In stage two, two contributors (IH, LL) independently examined articles identified during the Medline search, using citation information, which usually included the abstract. In this citation screening we considered each potential article for inclusion in the review based on four criteria: three objective criteria,

(a) An article must involve a human population sample,
An article must include an SS disease patient sample,
An article must not be a case study,

and a fourth criterion based on the definitions of disease outcome or disease severity:

(b) An article must contain written confirmation that the outcome measures it uses are considered to be proxy markers of disease outcome or disease severity.

Figure 7.1
Literature review stages, and summary of candidate article adjudications (with the number of included and excluded articles in parentheses).



We classified each article as 'included', excluded', or 'unsure'. Failure to meet any one of the criteria resulted in exclusion from the final literature review. If we disagreed over an article it was classified as 'unsure'. Most 'unsure' classifications were due to a lack of information in the citation - usually the absence of an abstract.

Table 7.2.
Search algorithm applied to the Medline and Embase online database.

	Search Strategy
1	Sickle
SCD specific *disease severity* terminology	
2	(severe) or (severity) or (mild) or (clinical expression) or (disease expression)
3	(clinical course) or (progress) or (natural history) or (manifestation)
4	(heterogeneity) or (homogeneity) or (stability) or (adverse)
Generic *disease severity* terminology	
5	(quality of life) or (quality-of-life) or (life quality) or (life-quality)
6	(health status) or (health-status) or (well being) or (well-being) or (wellbeing)
7	(functional status) or (functional-status)
8	(disability scale) or (disability-scale)
9	(performance status) or (performance-status)
10	(1) AND (2 or 3 or 4 or 5 or 6 or 7 or 8 or 9)

In stage three, we located the full text of all articles classified as 'include' or 'unsure'. Two contributorrs (IH, KW), or all 3 contributors independently determined final eligibility. Whenever we disagreed over eligibility, all contributors reviewed the article and a consensus was achieved by group discussion. Articles were classified as follows:

Table 7.3.
Article classification during stage three of the literature review process

Article classification	Decision	Description
Prediction	Include	Investigation of prognostic factors for a patient characteristic that the article contributors considered a proxy for *disease outcome* or *disease severity*
Use	Exclude	A proxy marker for *disease outcome* or *disease severity* was used as a descriptor of, or prognostic factor for a secondary patient characteristic.
Review	Exclude	Contained information on *disease outcome* or *disease severity*, but offered no new data or results
Non-disease severity	Exclude	Did not contain information on *disease outcome* or *disease severity*

During this third stage a single contributor (IH) examined the reference lists of all

'prediction' articles to identify further relevant publications not referenced in Medline or Embase.

7.6.4 Methods of review

We developed a standard datasheet for data collection (see appendix one) and pre-tested the datasheet using a random 10% sample of articles. All contributors (IH, LL, KW) collected data on all prediction articles, and discrepancies were resolved in regular consensus meetings.

We present results of included studies. We present the patient populations by age, gender, and geographical region. We classified articles by year of publication and journal speciality. We grouped endpoints for *disease outcome* into pre-defined systemic categories. We used a descriptive clustering procedure to highlight categories with similar patterns of usage.

We classified each article according to the criteria of Simon and Altman (48), as a phase I, II or III prognostic study. A phase I study involved early exploration, investigating associations between a risk factor and an outcome. A phase II or III study classified individuals or groups according to risk of *disease outcome*. A phase II study was exploratory and a phase III study was confirmatory.

Table 7.4.
Sources of systematic bias, and the method of estimating these biases in observational studies of SS disease outcome

Type of bias	Description	Associated design feature	Reason for associating design feature with type of bias
Detection	The method of assembling participants.	(1) Neonatal ascertainment	(1) Neonatal ascertainment protects against patient attrition due to unrecruited SS patients (53-56)
Attrition	The method of maintaining participation in a study	(2) Follow-up reporting	(2) Follow-up reporting allows the potential for attrition bias due to missing data and patient dropout to be estimated.
Performance	The method of measuring disease outcome.	(3) Longitudinal study design	(3) Longitudinal study design allows changes in disease outcome due to patient age and due to secular time to be explicitly estimated.
Selection	The method of accounting for potential confounders.	(4) Appropriate statistical methods	(4) Appropriate statistical methodology allows adjustment for the effect of suspected confounders.

We assessed statistical aspects of study design and analysis using published standards (57-59) along with specific recommendations for modelling potential predictors (60). Techniques for the control of potential confounders were of particular interest. We assessed overall article quality using categories of systematic bias identified by the Cochrane Collaboration for use in reviews of randomised controlled trials (61), and adapted here for SCD observational studies (Table 7.4).

(a) Detection and attrition bias

We have described how using a systematically selected group of participants and how participant non-response can bias results (see chapters three and four respectively). We define the ideal identification of participants for sickle-cell disease research as neonatal screening, and define the ideal follow-up reporting as descriptive summaries of participant non-response.

(b) Performance bias

We require unbiased measures of disease outcomes. Because the expression of sickle-cell disease is age-related (see chapter six) we require that study participants are followed through time, with repeated measurement collection. We assessed departure from this ideal as a measure of performance bias.

(c) Selection bias

Because our review includes observational studies we must assess how articles have identified and accounted for potential confounders. In each article we identified the number of outcomes and the number of potential predictors and confounders. We assessed if the chosen statistical analysis controlled adequately for identified confounders, and for correlation between confounders (if necessary). We assessed departure from appropriate statistical methodology as a measure of selection bias.

This bias checklist is not comprehensive, but represents design considerations expected to be major influences on the level of systematic bias in SCD *disease outcome* or *disease severity* research. We then classified each article as having a low, moderate, or high risk of bias, according to the number of design features it met (Table 7.5).

Table 7.5.
Classification of overall article quality according to risk of bias.

Bias Risk	Relationship to design features	Interpretation
Low	All criteria met.	Bias unlikely to seriously affect results.
Moderate	One criteria not met	Level of bias raises doubt about results
High	More than one criteria not met.	Little confidence in results.

7.7 Description of systematic review

7.7.1 Article eligibility

We identified 2071 candidate papers. Of these, 335 articles did not employ a human sample, 638 did not include an SS patient sample, 239 were case studies, and 599 did not involve a consideration of *disease outcome* or *disease severity*, leaving 260 fulfilling the stage-two baseline inclusion criteria. During stage three we identified a further nine articles from reference lists of included articles. We excluded a further 72 articles as not considering

disease outcome or *disease severity* articles, 47 as *review* articles, and 73 as *use* articles, leaving 77 articles predicting the concept of SS *disease outcome* or *disease severity.*

7.7.2 Reviewer agreement

In Table 7.6 we present the agreement achieved by two reviewers during stage three of article identification. We agreed on 224 articles. The crude classification agreement was 83% and the kappa weighted measure of agreement, κ, was 0.78, representing substantial agreement according to published guidelines for interpretation (62). We mainly disagreed on the classification of an article as predicting or using *disease outcome* or *disease severity* (15 articles) or whether an article had confirmed its outcome measure to be summarising *disease outcome* or *disease severity* (28 articles).

Table 7.6.
Agreement between reviewers during Stage 3 of classification of 269 articles.

		Reviewer 1 (IH)			
		Prediction	Use	Review	Exclude
Reviewer 2 (KW)	Prediction	63	10	0	3
	Use	5	57	0	6
	Review	0	0	47	2
	Exclude	8	11	0	57

Crude agreement = 83.3%; κ=0.78

7.8 Description of included articles

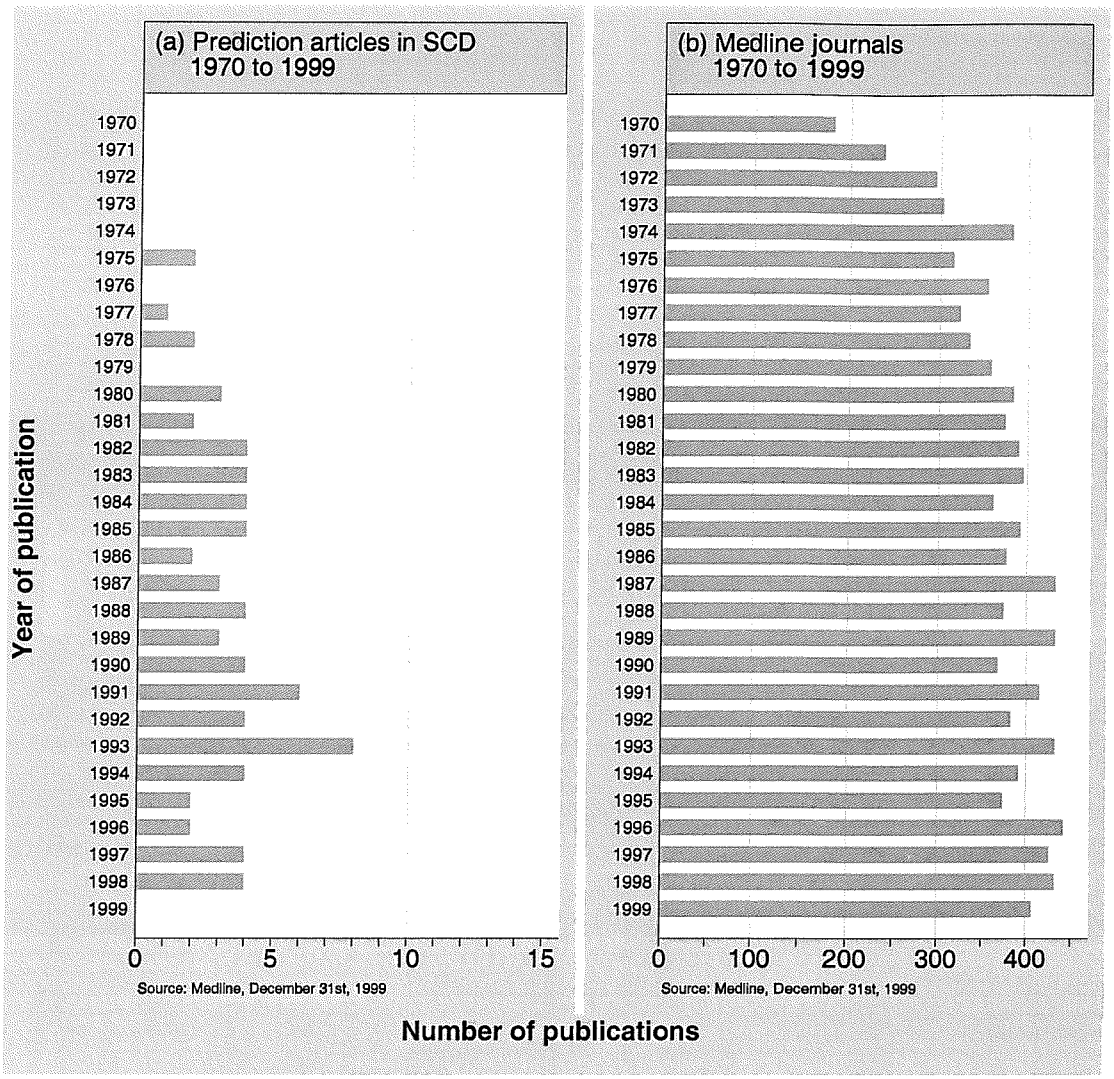
7.8.1 Characteristics of included studies

Articles were published in 31 unique journals, with almost half the publications in five journals (Blood 13 articles, American Journal of Hematology 10 articles, New England Journal of Medicine 5 articles, Journal of Tropical Paediatrics 5 articles, British Journal of Haematology 4 articles). The number of articles in each of eight publication categories is presented in Table 7.7. Haematological journals published the majority of the articles, reflecting the popular understanding that haematological indices are predictive of *disease outcome* or *disease severity.*

The distribution of the year of publication from 1966 to 1999 is presented in Figure 7.2 for (a) 77 severity prediction articles, and (b) 11,772 'sickle' articles. Data were incomplete for 2000, the year in which the review was carried out, and are not presented. The rate of prediction article publications per year has remained steady since the early 1980's. The overall numbers of 'sickle' articles increased steadily in the 1970's, with numbers levelling at around 400 per year from the early 1980's.

Figure 7.2

Number of sickle-cell disease publications predicting health-status, and all sickle-cell disease publications listed in Medline between 1970 and 1999



Study populations originated from various locations: 29 (38%) articles considered populations resident in the USA, 15 (19%) in the Middle East (Saudi Arabia 14, UAE 1), 10 (13%) in Nigeria, 9 (12%) in the Caribbean (Jamaica 8, Cuba 1), 6 (8%) in Europe (France 3, UK 2, The Netherlands 1), 3 (4%) in India, 3 (4%) in Brazil, and 2 articles considering a mixed US and African population. In addition to SS patients the following SCD genotypes were considered: S-beta^0 thalassaemia (17 articles, 22%), S-beta$^+$ thalassaemia (12, 16%), SC disease (9, 12%), SO^{Arab} (2 articles), SD Punjab (2 articles), and S-hereditary persistence of fetal haemoglobin (1 article).

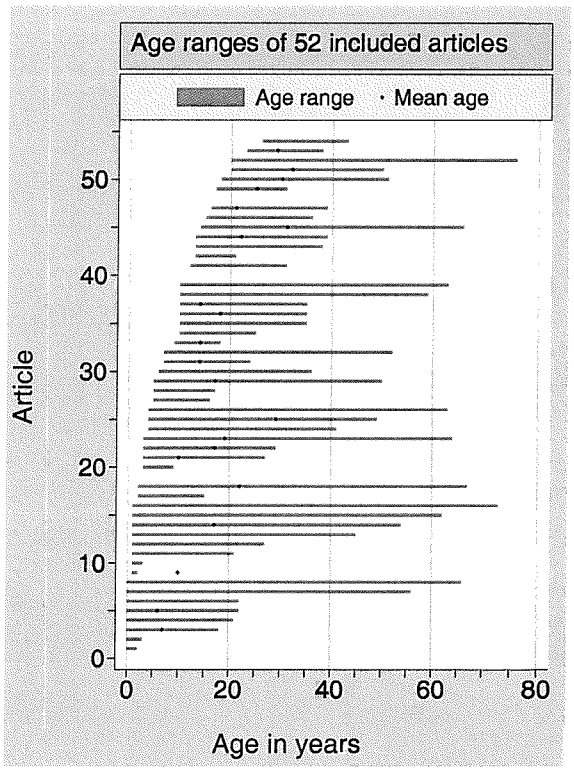
Table 7.7.
Number of prediction and use articles by journal group.

Journal type	Number of articles (%)
Haematology	41 (53)
General Medicine	20 (26)
Paediatrics	7 (9)
Genetics	4 (5)
Biochemistry	3 (4)
Epidemiology	1 (1)
Book chapter	1 (1)
Total	**77 (100)**

7.8.2 Characteristics of participants

Age at entry to study was reported in 64 (83%) articles. Age range was the most common summary (52 articles), followed by mean age (26 articles), standard deviation of age (19 articles), an age distribution (11 articles) and median age (2 articles). We present age ranges from the 52 reporting articles (Figure 7.3). Most articles recruited adolescent and early adult patient groups. The median mean age was 17 years (mad 6.5). Excluding articles investigating G6PD deficiency (which occurs almost exclusively in males) the proportion of males in studies was 0.52 (sd 0.08, range 0.31-0.79).

Figure 7.3
Age ranges of patients populations from 52 *disease outcome* or *disease severity* articles.



7.8.3 Methodological features of included studies

(a) Study classification

Most articles were classified as phase I exploratory studies (66 or 86%), with the remaining 11 (14%) articles classified as phase II studies. There were no phase III studies. The proportion of Phase I and phase II articles grew in each decade (Cochran-Armitage exact test for trend: phase I $p<0.001$, phase II $p=0.15$), with no suggestion of the two phases increasing at differential rates (Exact test for homogeneity of proportions, $p=0.78$). Clear hypotheses were available in 11 (14%) articles: 10 phase I studies and a single phase II study.

(b) Endpoints and predictors

Most studies offered a multivariate description of *disease outcome* or *disease severity*, with a median of 8 endpoints per article (median absolute deviation: 5, iqr: 4 to 15, range: 1 to 36). Ten (13%) articles used a single endpoint. Overall, there were 821 endpoint uses among 154 unique endpoints. The 5 most common endpoints were painful crisis (49, 6.0%), total haemoglobin (Hb) (43, 5.2%), hospitalisation (30, 3.7%), fetal haemoglobin (HbF) (27, 3.3%), and blood transfusion (26, 3.2%), which together accounted for 21.3% of all usage. The same studies used a median of 3 predictor variables per article (mad: 2, iqr: 1 to 6, range: 1 to 23). Overall, there were 320 predictor uses among 126 unique predictors. The 5 most common predictors were HbF (28, 8.8%), alpha thalassaemia status (26, 8.1%), age (22, 6.9%), gender (16, 5.0%), and Hb (15, 4.7%), which together accounted for 33.4% of all usage. There were significantly more endpoints than explanatory variables per article (median difference 4, mad: 5, iqr: 0 to 13, range: -21 to 35) (matched test of median difference, $p<0.001$).

Individual endpoints and predictors were grouped according to whether the participants were sick or well at measurement, and into 15 systemic categories, and the frequency of endpoint and predictor usage is presented in Table 7.8. Overall, blood related measurements form the most popular category, with 33% of all endpoint usage and 35% of all predictor usage.

Among endpoint measurements, the clustering algorithm suggested a division into two well-separated clusters (Figure 7.4a). One cluster contained the four most common categories (blood, GI system, musculoskeletal, and clinical intervention). Papers offering large multivariate descriptions of severity tend to consider these groups of variables as the core of their description. The second major cluster contains the remaining systemic categories, all of which have lower levels of usage. A single variable (general illness) is alone as a third minor cluster. This variable represents a conglomerate of one-off variables that defied classification, and might anecdotally be considered proxy measures for general ill-health.

Table 7.8.

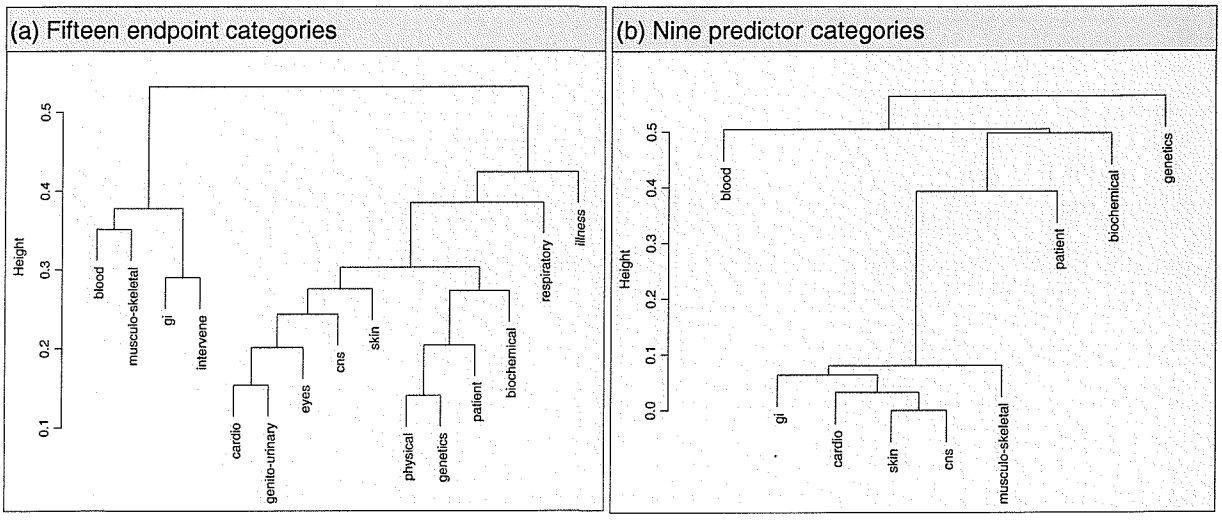
Endpoint usage among 77 articles categorised by systemic group and whether measurement was taken during symptomatic clinic visit

Systemic category	Endpoint measurements (%)			Predictor measurements		
	well	sick	total	well	sick	total (%)
Blood / immune	225 (63.0)	45 (9.7)	270 (32.9)	111	-	111 (34.7)
Musculoskeletal	3 (0.8)	136 (29.3)	139 (16.9)	-	6	6 (1.9)
GI system	50 (14.0)	35 (7.5)	85 (10.4)	2	1	3 (0.9)
Clinical intervention	-	68 (14.7)	68 (8.3)	-	-	-
Biochemical	24 (6.7)	40 (8.6)	64 (7.8)	104	-	104 (32.5)
Miscellaneous	2 (0.6)	28 (6.0)	30 (3.7)	-	-	-
Patient characteristics	29 (8.1)	-	29 (3.5)	44	-	44 (13.8)
Respiratory system	-	28 (6.0)	28 (3.4)	-	-	-
Skin	-	25 (5.4)	25 (3.1)	-	1	1 (0.3)
Central nervous system	-	23 (5.0)	23 (2.8)	-	1	1 (0.3)
Genito-urinary system	1 (0.3)	22 (4.7)	23 (2.8)	-	-	-
Cardiovascular system	8 (2.2)	5 (1.1)	13 (1.6)	1	-	1 (0.3)
Eyes	-	9 (2)	9 (1.1)	-	-	-
Genetics	8 (2.2)	-	8 (1.0)	49	-	49 (15.3)
Physical/sexual/nutrition	7 (2)	-	7 (0.9)	-	-	-
Total	357 (100)	464 (100)	821 (100)	311	9	320

Among predictor measurements five primary clusters were identified (Figure 7.4b). Articles either focussed on 1 of 4 specific predictor groups: static patient measures (genetic or basic features such as age and gender), or measures taken while the patient was without clinical symptoms (haematological or biochemical), or otherwise used a range of clinical symptoms recorded during symptomatic episodes.

Figure 7.4

Clustering dendrograms for (a) 15 endpoint categories and (b) 9 predictor categories.



(c) Statistical methodology

Table 7.9 presents the types of statistical analysis employed, with articles classified according to the numbers of endpoints and predictors. Seventy-one articles gave information on statistical techniques. The largest group of articles used univariate inference (33 or 47%), and in 30 of these articles the presence of multiple endpoints or predictors suggested the need for methodology to account for potentially confounding correlations. Two articles provided explicit adjustment for potentially confounding associations (using partial correlations) (63;64), and two more provided Bonferronni adjusted significance (1;65). Twenty-seven (38%) articles used regression techniques to accommodate multiple predictors. Three further articles accounted for multiple endpoints (2 using MANOVA, 1 using principal components analysis).

Table 7.9.

Type of statistical analysis used by 71 severity prediction articles

statistical analysis	one endpoint		More than one endpoint		Total (%)
	one predictor	Multiple predictors	One predictor	Multiple predictors	
univariate descriptive	1	3	1	3	8 (11)
univariate inferential	3	1	11	18	33 (47)
multiple regression	0	3	3	21	27 (38)
multivariate regression	0	0	0	3	3 (4)
all	4	7	15	45	71

(d) Methodological quality of articles

Table 7.10 presents the frequency of three methodologically desirable features among 77 *disease outcome* prediction articles, along with the references of articles meeting each criterion.

Table 7.10.
Percentage of prediction articles meeting methodologically desirable features.

Criterion	Articles meeting criterion	Article References
Detection bias: neonatal ascertainment	12 (16%)	(a8;a10;a27;a29;a41;a43;a45; a46;a61;a69;a71;a77)
Attrition bias: participant follow-up	22 (29%)	(a3;a7;a9;a10;a12;a14;a15;a21;a31; a33;a35;a36;a44;a45;a47;a48;a61;a64; a65;a69;a74;a77)
Performance bias: longitudinal study design	11 (14%)	(a5;a8;a10;a13;a29;a32;a45; a46;a50;a61;a77)
Selection bias: statistical methodology	39 (51%)	(a2;a5;a6;a8;a11;a12;a15;a18;a19; a21-a23;a26-a35;a37;a41;a43;a45-a47; a57;a59;a60;a65;a66;a68;a69;a71;a73;a74; a77)
Bias Risk		
Low	3 (4%)	(a45;a61;a77)
Moderate	5 (6%)	(a8;a10;a29;a46;a69)
High	69 (90%)	

No more than half of all prediction articles met any single design feature. Only eight articles met all design criteria, for a low bias risk, or any three design criteria, for a moderate bias risk. The remaining 69 articles had levels of bias that left little confidence in their results.

7.9 Appendix One

Data collection forms:

Internal validation of 77 articles predicting *disease outcome* or *disease severity* in homozygous sickle cell disease.

(A) Standardizing the Definition and Prediction of Clinical Outcome in Homozygous Sickle Cell Disease.

- Article Checklist -

reviewer _____

Section One: General description of study

Article ref _____
name of article _____

journal _____
volume, page _____
number _____
primary author _____
year of publication _____

Article Classification — Severity Prediction ☐ Severity Use ☐ Severity Review ☐

Prediction (all):	Complete sections Two -> Six
Prediction (predictive index):	Also complete section Seven
Use:	Complete sections 4 and 8
Review:	Complete sections 4 and 5

Section Two: Study design criteria

Study type (check one)
descriptive ☐
inferential / model-based ☐

Study design (check one)
experimental
randomised trial ☐
observational trial ☐
non-experimental
prospective ☐
retrospective ☐
cross-sectional ☐

Study aim (1) (check one)
Severity prediction (no hypothesis) ☐
Severity prediction (hypothesis) ☐

Study aim (2) (check one)
risk factor ☐
prognostic index ☐

Study aim (3) (check one)
Exploratory: Early exploration: Type I ☐
Exploratory: hypothesis generation: Type II ☐
Confirmatory: Pre-stated hypthesis: Type III ☐

Section Three: Patient sample criteria (1)

Nature of study population
(check all that apply)
- Community ☐
- Hospital ☐
- SCD centre / outpatient clinic ☐
- multiple centres ☐
- more than one type (please state) ☐
- Other _____

Location of population
(check al that apply and describe)
- North America ☐
- Caribbean ☐
- Europe ☐
- Africa ☐
- Middle East ☐
- Asia ☐
- state country _____

Patient acquisition
(check all that apply)
- Ante- / neo- natal ascertainment ☐
- hospital / clinic ascertainment ☐
- Other _____

Patient selection/eligibity
(check all that apply)
- Randomization ☐
- patient characteristics ☐
- patient disease status ☐
- study window ☐
- Other _____

Genotypes studied (check all that apply)
- SS ☐
- S beta 0 ☐
- S-beta + ☐
- SC ☐
- AA ☐
- which others _____

Section Three: Patient sample criteria (2)

Exclusion criteria
(of eligible patients only)
- not stated ☐
- transfusion ☐
- hydroxyurea ☐
- age-related ☐
- no consent ☐
- other _____

patient numbers
- number of patients ☐
- number of females ☐
- Proportion of females _____

Lost to follow-up
- not stated ☐
- stated: none lost ☐
- stated: with comparison (lost v not lost) ☐
- stated: without comparison ☐
- irrelevant (cross sectional / retrospective) ☐

Missing data
- not stated ☐
- stated: no missing data ☐
- stated: number of exclusions ☐

Sample size
- not stated ☐
- stated: no methods ☐
- stated: incorrect method ☐
- stated: correct method ☐

Section Four: endpoints for severity (1) : Listing
List ALL endpoints used by the study.

Number of endpoints ☐

List of endpoints

Section Four: Endpoints for severity (2):
If painful crisis is an endpoint

Likely to be the most common endpoint. Details of ascertainment.

location of crisis
- not stated ☐
- all crises ☐
- home-based ☐
- outpatient clinic ☐
- hospital-based ☐

Summary measure of crisis
- not stated ☐
- count ☐
- count / year ☐
- irrelevant (qualitative) ☐
- other _____

interval for same crisis
- not stated ☐
- none ☐
- 7 days ☐
- 14 days ☐
- irrelevant (qualitative) ☐
- other _____

pain site
- not stated ☐
- arms and legs ☐
- back ☐
- abdomen ☐
- chest ☐
- head ☐
- irrelevant (qualitative) ☐
- other _____

Section Five: Explanatory variables (1)

Number of predictors ☐

Patient characteristics
age ☐
gender ☐
other 1 _____
other 2 _____
confounders used _____

Haematology
haematology used _____

Genetic
genotype ☐
beta-globin haplotype ☐
alpha thalassaemia ☐
other _____

Biochemistry
biochemistry used _____

Section Five: Explanatory variables (2)

Clinical events
clinical events used _____

Anthropometry
height ☐
weight ☐
bmi ☐
other _____

Environmental
temperature ☐
location ☐
socio-economic rating ☐
other _____

Psycho-social
psycho-social indicators used _____

Section Six: Statistical methodology criteria

Type of model
Normal regression ☐
logistic regression ☐
Cox survival model ☐
Recursive partitioning ☐
No model ☐
other model type _____

Variable selecton
not stated ☐
univariate ☐
all included ☐
stepwise procedure ☐
best subset analysis ☐
other _____

Model assumptions
checked _____
not stated _____
partly checked _____

Model fit
checked _____
not stated _____

Section Seven: Validation

Statistical validation

validation type
internal ☐
temporal ☐
external ☐
not performed ☐
other _____

Internal validation
goodness-of-fit ☐
cross validation ☐
data-splitting ☐
bootstrap ☐
not performed ☐
other _____

Clinical validation

(a) Instructions for practical use	**Yes**	**No**	
(b) Data required usually collected ?	**Yes**	**No**	
(c) Simple to interpret all definitions ?			
endpoints for severity	**Yes**	**No**	
explanatory/predictor variables	**Yes**	**No**	
(d) Can model be applied?	**No**	**group**	**individual**
(e) Use of arbitrary thresholds ?	**Yes**	**No**	
(f) Are definitions generally accepted ?	**Yes**	**No**	**n/a**
(g) number of explanatory categories covered	**out of 7**		
(h) Rationale for endpoint inclusions	**Yes**	**No**	
(i) Rationale for predictor inclusions	**Yes**	**No**	

Section Eight: Use of Severity Index

Type of study

clinical trial ☐
risk factor analysis ☐
descriptive (1 population) ☐
comparison of >1 population ☐
other _____

Use of severity

group definition ☐
therapy assessment ☐
other _____

** Complete below if **severity prediction** or **severity use** **

Does this paper contain a prognostic model or index

no ☐
yes ☐

references another article (give article reference number) _____

7.10 Appendix Two

Articles included in the final literature review - *disease outcome* prediction articles (n=77), disease outcome use articles (n=75), and disease outcome review articles (n=48)

7.10.1 Disease outcome prediction articles

(A.1) Bienzle U, Sodeinde O, Effiong CE, Luzzatto L. Glucose 6-phosphate dehydrogenase deficiency and sickle cell anemia: frequency and features of the association in an African community. Blood 1975; 46(4):591-597.

(A.2) Gaston MH, Fobi MAL. Sickle cell disease in children, a spectrum of illness. In: Cabannes R, editor. La Drepanocytose - Sickle Cell Anemia. Paris: INSERM, 1975: 19-32.

(A.3) Steinberg MH, Dreiling BJ, Lovell WJ. Sickle cell anemia: erythrokinetics, blood volumes, and a study of possible determinants of severity. Am J Hematol 1977; 2(1):17-23.

(A.4) Steinberg MH, Eaton JW, Berger E, Coleman MB, Oelshlegel FJ. Erythrocyte calcium abnormalities and the clinical severity of sickling disorders. Br J Haematol 1978; 40(4):533-539.

(A.5) White JM, Billimoria F, Muller MA, Davis LR, Stroud CE. Serum-alpha-hydroxybutyrate dehydrogenase levels in sickle-cell disease and sickle-cell crisis. Lancet 1978; 1(8063):532-533.

(A.6) Hebbel RP, Boogaerts MA, Eaton JW, Steinberg MH. Erythrocyte adherence to endothelium in sickle-cell anemia. A possible determinant of disease severity. N Engl J Med 1980; 302(18):992-995.

(A.7) Gibbs WN, Wardle J, Serjeant GR. Glucose-6-phosphate dehydrogenase deficiency and homozygous sickle cell disease in Jamaica. Br J Haematol 1980; 45(1):73-80.

(A.8) Powars DR, Schroeder WA, Weiss JN, Chan LS, Azen SP. Lack of influence of fetal hemoglobin levels or erythrocyte indices on the severity of sickle cell anemia. J Clin Invest 1980; 65(3):732-740.

(A.9) Serjeant GR, Foster K, Serjeant BE. Red cell size and the clinical and haematological features of homozygous sickle cell disease. Br J Haematol 1981; 48(3):445-449.

(A.10) Stevens MC, Hayes RJ, Vaidya S, Serjeant GR. Fetal hemoglobin and clinical severity of homozygous sickle cell disease in early childhood. J Pediatr 1981; 98(1):37-41.

(A.11) Ogunye OO, Ejiogu BU. Red cell antigens in Nigerian paediatric sickle cell anaemics. Acta Haematol 1982; 68(4):325-328.

(A.12) Embury SH, Dozy AM, Miller J, Davis JR, Jr., Kleman KM, Preisler H et al. Concurrent sickle-cell anemia and alpha-thalassemia: effect on severity of anemia. N Engl J Med 1982; 306(5):270-274.

(A.13) Shurafa MS, Prasad AS, Rucknagel DL, Kan YW. Long survival in sickle cell anemia. Am J Hematol 1982; 12(4):357-365.

(A.14) Higgs DR, Aldridge BE, Lamb J, Clegg JB, Weatherall DJ, Hayes RJ et al. The interaction of alpha-thalassemia and homozygous sickle-cell disease. N Engl J Med 1982; 306(24):1441-1446.

(A.15) Odenheimer DJ, Whitten CF, Rucknagel DL, Sarnaik SA, Sing CF. Heterogeneity of sickle-cell anemia based on a profile of hematological variables. Am J Hum Genet 1983; 35(6):1224-1240.

(A.16) Hutz MH, Salzano FM, Adams J. Hb F levels, longevity of homozygotes and clinical course of sickle cell anemia in Brazil. Am J Med Genet 1983; 14(4):669-676.

(A.17) Cameron BF, Christian E, Lobel JS, Gaston MH. Evaluation of clinical severity in sickle cell disease. J Natl Med Assoc 1983; 75(5):483-487.

(A.18) Mears JG, Lachman HM, Labie D, Nagel RL. Alpha-thalassemia is related to prolonged survival in sickle cell anemia. Blood 1983; 62(2):286-290.

(A.19) Steinberg MH, Rosenstock W, Coleman MB, Adams JG, Platica O, Cedeno M et al. Effects of thalassemia and microcytosis on the hematologic and vasoocclusive severity of sickle cell anemia. Blood 1984; 63(6):1353-1360.

(A.20) Embury SH, Clark MR, Monroy G, Mohandas N. Concurrent sickle cell anemia and alpha-thalassemia. Effect on pathological properties of sickle erythrocytes. J Clin Invest 1984; 73(1):116-123.

(A.21) Fabry ME, Mears JG, Patel P, Schaefer-Rego K, Carmichael LD, Martinez G et al. Dense cells in sickle cell anemia: the effects of gene interaction. Blood 1984; 64(5):1042-1046.

(A.22) Powars DR, Weiss JN, Chan LS, Schroeder WA. Is there a threshold level of fetal hemoglobin that ameliorates morbidity in sickle cell anemia? Blood 1984; 63(4):921-926.

(A.23) Babiker MA, El Hazmi MA, Al Jobori AM, Obeid H, Bahakim HM. Splenic function in children with sickle cell disease: two different patterns in Saudi Arabia. Scand J Haematol 1985; 35(2):191-193.

(A.24) El Hazmi MA. Clinical manifestation and laboratory findings of sickle cell anaemia in association with alpha-thalassaemia in Saudi Arabia. Acta Haematol 1985; 74(3):155-160.

(A.25) Brittenham GM, Schechter AN, Noguchi CT. Hemoglobin S polymerization: primary determinant of the hemolytic and clinical severity of the sickling syndromes. Blood 1985; 65(1):183-189.

(A.26) Schacter LP, DelVillano BC, Gordon EM, Klein BL. Red cell superoxide dismutase and sickle cell anemia symptom severity. Am J Hematol 1985; 19(2):137-144.

(A.27) Al Awamy BH, Niazi GA, el Mouzan MI, Altorki MT, Naeem MA. Relationship of haemoglobin F and alpha thalassaemia to severity of sickle-cell anaemia in the Eastern Province of Saudi Arabia. Ann Trop Paediatr 1986; 6(4):261-265.

(A.28) Baudin V, Pagnier J, Labie D, Girot R, Wajcman H. Heterogeneity of sickle cell disease as shown by density profiles: effects of fetal hemoglobin and alpha thalassemia. Haematologia (Budap) 1986; 19(3):177-184.

(A.29) Powars DR, Chan LS. Is sickle cell crisis a valid measure of clinical severity in sickle cell anemia? Prog Clin Biol Res 1987; 240:393-402:393-402.

(A.30) Aluoch JR. Possible determinants of the clinical course of sickle cell anaemia. East Afr Med J 1987; 64(5):327-332.

(A.31) Odenheimer DJ, Sarnaik SA, Whitten CF, Rucknagel DL, Sing CF. The relationship between fetal hemoglobin and disease severity in children with sickle cell anemia. Am J Med Genet 1987; 27(3):525-535.

(A.32) Steinberg MH, West MS, Gallagher D, Mentzer W. Effects of glucose-6-phosphate dehydrogenase deficiency upon sickle cell anemia. Blood 1988; 71(3):748-752.

(A.33) Pajot N, Maier-Redelsperger M, Dode C, Labie D, Girot R. Density distribution of red cells and prognostic significance in 50 patients with homozygous sickle-cell disease. Haematologia (Budap) 1988; 21(4):189-197.

(A.34) Lande WM, Andrews DL, Clark MR, Braham NV, Black DM, Embury SH et al. The incidence of painful crisis in homozygous sickle cell disease: correlation with red cell deformability. Blood 1988; 72(6):2056-2059.

(A.35) Ballas SK, Larner J, Smith ED, Surrey S, Schwartz E, Rappaport EF. Rheologic predictors of the severity of the painful sickle cell crisis. Blood 1988; 72(4):1216-1223.

(A.36) Bordin JO, Kerbauy J, Lourenco DM, Sesso R. Level of fetal hemoglobin as an indicator of clinical complications in sickle cell anemia. Braz J Med Biol Res 1989; 22(11):1347-1353.

(A.37) Keidan AJ, Sowter MC, Johnson CS, Noguchi CT, Girling AJ, Stevens SM et al. Effect of polymerization tendency on haematological, rheological and clinical parameters in sickle cell anaemia. Br J Haematol 1989; 71(4):551-557.

(A.38) El Hazmi MA, Warsy AS. The effects of glucose-6-phosphate dehydrogenase deficiency on the haematological parameters and clinical manifestations in patients with sickle cell anaemia. Trop Geogr Med 1989; 41(1):52-56.

(A.39) El Hazmi MA, Al Swailem AR, Bahakim HM, Al Faleh FZ, Warsy AS. Effect of alpha thalassaemia, G-6-PD deficiency and Hb F on the nature of sickle cell anaemia in south-western Saudi Arabia. Trop Geogr Med 1990; 42(3):241-247.

(A.40) El Hazmi MA. Beta-globin gene haplotypes in the Saudi sickle cell anaemia patients. Hum Hered 1990; 40(3):177-186.

(A.41) el Mouzan MI, Al Awamy BH, al Torki MT. Clinical features of sickle cell disease in eastern Saudi Arab children. Am J Pediatr Hematol Oncol 1990; 12(1):51-55.

(A.42) Addae S, Adzaku F, Mohammed S, Annobil S. Sickle cell disease in permanent residents of mountain and low altitudes in Saudi Arabia. Trop Geogr Med 1990; 42(4):342-348.

(A.43) Thame M, Grandison Y, Mason K, Thompson M, Higgs D, Morris J et al. The red cell distribution width in sickle cell disease--is it of clinical value? [see comments]. Clin Lab Haematol 1991; 13(3):229-237.

(A.44) Rieder RF, Safaya S, Gillette P, Fryd S, Hsu H, Adams JG, III et al. Effect of beta-globin gene cluster haplotype on the hematological and clinical features of sickle cell anemia [see comments]. Am J Hematol 1991; 36(3):184-189.

(A.45) Platt OS, Thorington BD, Brambilla DJ, Milner PF, Rosse WF, Vichinsky E et al. Pain in sickle cell disease. Rates and risk factors [see comments]. N Engl J Med 1991; 325(1):11-16.

(A.46) Bailey K, Morris JS, Thomas P, Serjeant GR. Fetal haemoglobin and early manifestations of homozygous sickle cell disease. Arch Dis Child 1992; 67(4):517-520.

(A.47) Phillips G, Jr., Coffey B, Tran-Son-Tay R, Kinney TR, Orringer EP, Hochmuth RM. Relationship of clinical severity to packed cell rheology in sickle cell anemia. Blood 1991; 78(10):2735-2739.

(A.48) Ballas SK. Sickle cell anemia with few painful crises is characterized by decreased red cell deformability and increased number of dense cells. Am J Hematol 1991; 36(2):122-130.

(A.49) El Hazmi MA, Bahakim HM, al Fawaz I. Endocrine functions in sickle cell anaemia patients. J Trop Pediatr 1991; 38(6):307-313.

(A.50) Phillips G, Tangney CC. Relationship of plasma alpha tocopherol to index of clinical severity in individuals with sickle cell anemia. Am J Hematol 1992; 41(4):227-231.

(A.51) Fatunde OJ, Scott-Emuakpor AB. Foetal haemoglobin in Nigerian children with sickle cell anaemia. Effect on haematological parameters and clinical severity. Trop Geogr Med 1992; 44(3):264-266.

(A.52) El Hazmi MA, Bahakim HM, Warsy AS. DNA polymorphism in the beta-globin gene cluster in Saudi Arabs: relation to severity of sickle cell anaemia. Acta Haematol 1992; 88(2-3):61-66.

(A.53) El Hazmi MA, Bahakim HM, Warsy AS, al Momen A, al Wazzan A, al Fawwaz I et al. Does G gamma/A gamma ratio and Hb F level influence the severity of sickle cell anaemia. Mol Cell Biochem 1993; 124(1):17-22.

(A.54) Okany CC, Akinyanju OO. The influence of socio-economic status on the severity of sickle cell disease. Afr J Med Med Sci 1993; 22(2):57-60.

(A.55) de Montalembert M, Maier-Redelsperger M, Girot R, Belloy M, Vilmer E, Ducrocq R et al. Beta-globin gene cluster haplotype and alpha-thalassemia do not correlate with the acute clinical manifestations of sickle cell disease in children [letter]. Blood 1993; 82(8):2595-2596.

(A.56) Hedo CC, Okpala IE, Aken'ova YA. Foetal haemoglobin levels in Nigerians with sickle cell anaemia. A revisitation. Trop Geogr Med 1993; 45(4):162-164.

(A.57) Hedo C, Aken'Ova Y, Okpala I, Salimonu L. Serum immunoglobulin (G, A and M) classes and IgG subclasses in sickle cell anaemia. APMIS 1993; 101(5):353-357.

(A.58) El Hazmi MA. The relationship of the genetic heterogeneity of sickle cell gene to clinical manifestations. J Trop Pediatr 1993; 39(1):23-29.

(A.59) Hedo CC, Aken'ova YA, Okpala IE, Durojaiye AO, Salimonu LS. Acute phase reactants and severity of homozygous sickle cell disease. J Intern Med 1993; 233(6):467-470.

(A.60) El Hazmi MA, Warsy AS. On the molecular interactions between alpha-thalassaemia and sickle cell gene. J Trop Pediatr 1993; 39(4):209-213.

(A.61) Bray GL, Muenz L, Makris N, Lessin LS. Assessing clinical severity in children with sickle cell disease. Preliminary results from a cooperative study. Am J Pediatr Hematol Oncol 1994; 16(1):50-54.

(A.62) Olatunji PO, Falusi AG. Persistent hepatomegaly: an index of severity in sickle cell anaemia. East Afr Med J 1994; 71(11):742-744.

(A.63) El Hazmi MA, Warsy AS, Al Swailem AR, Al Faleh FZ, al Jabbar FA. Genetic compounds--Hb S, thalassaemias and enzymopathies: spectrum of interactions. J Trop Pediatr 1994; 40(3):149-156.

(A.64) Falusi AG, Olatunji PO. Effects of alpha thalassaemia and haemoglobin F (HbF) level on the clinical severity of sickle-cell anaemia. Eur J Haematol 1994; 52(1):13-15.

(A.65) Steinberg MH, Hsu H, Nagel RL, Milner PF, Adams JG, Benjamin L et al. Gender and haplotype effects upon hematological manifestations of adult sickle cell anemia. Am J Hematol 1995; 48(3):175-181.

(A.66) Muniz A, Corral L, Alaez C, Svarch E, Espinosa E, Carbonell N et al. Sickle cell anemia and beta-gene cluster haplotypes in Cuba. Am J Hematol 1995; 49(2):163-164.

(A.67) Figueiredo MS, Kerbauy J, Goncalves MS, Arruda VR, Saad ST, Sonati MF et al. Effect of alpha-thalassemia and beta-globin gene cluster haplotypes on the hematological and clinical features of sickle-cell anemia in Brazil. Am J Hematol 1996; 53(2):72-76.

(A.68) Brooks LJ, Koziol SM, Chiarucci KM, Berman BW. Does sleep-disordered breathing contribute to the clinical severity of sickle cell anemia? [see comments]. J Pediatr Hematol Oncol 1996; 18(2):135-139.

(A.69) Thomas PW, Higgs DR, Serjeant GR. Benign clinical course in homozygous sickle cell disease: a search for predictors. J Clin Epidemiol 1997; 50(2):121-126.

(A.70) Mukherjee MB, Lu CY, Ducrocq R, Gangakhedkar RR, Colah RB, Kadam MD et al. Effect of alpha-thalassemia on sickle-cell anemia linked to the Arab-Indian haplotype in India. Am J Hematol 1997; 55(2):104-109.

(A.71) Homi J, Levee L, Higgs D, Thomas P, Serjeant G. Pulse oximetry in a cohort study of sickle cell disease. Clin Lab Haematol 1997; 19(1):17-22.

(A.72) Mukherjee MB, Colah RB, Ghosh K, Mohanty D, Krishnamoorthy R. Milder clinical course of sickle cell disease in patients with alpha thalassemia in the Indian subcontinent [letter]. Blood 1997; 89(2):732.

(A.73) Anyaegbu CC, Okpala IE, Akren'Ova YA, Salimonu LS. Peripheral blood neutrophil count and candidacidal activity correlate with the clinical severity of sickle cell anaemia (SCA) [letter]. Eur J Haematol 1998; 60(4):267-268.

(A.74) Poillon WN, Kim BC, Castro O. Intracellular hemoglobin S polymerization and the clinical severity of sickle cell anemia. Blood 1998; 91(5):1777-1783.

(A.75) Mukherjee MB, Surve R, Tamankar A, Gangakhedkar RR, Ghosh K, Lu CY et al. The influence of alpha-thalassaemia on the haematological & clinical expression of sickle cell disease in western India. Indian J Med Res 1998; 107:178-81:178-181.

(A.76) el Kalla S, Baysal E. Genotype-phenotype correlation of sickle cell disease in the United Arab Emirates. Pediatr Hematol Oncol 1998; 15(3):237-242.

(A.77) Miller ST, Sleeper LA, Pegelow CH, Enos LE, Wang WC, Weiner SJ et al. Prediction of adverse outcomes in children with sickle cell disease. N Engl J Med 2000; 342(2):83-89.

7.10.2 Disease outcome use articles

(B.1) Perrine RP, Brown MJ, Clegg JB, Weatherall DJ, May A. Benign sickle-cell anaemia. Lancet 1972; 2(7788):1163-1167.

(B.2) Steinberg MH, Dreiling BJ, Morrison FS, Necheles TF. Mild sickle cell disease. Clinical and laboratory studies. JAMA 1973; 224(3):317-321.

(B.3) Alexanian R, Nadell J. Oxymetholone treatment for sickle cell anemia. Blood 1975; 45(6):769-777.

(B.4) Deiderich DA, Trueworthy RC, Gill P, Cader AM, Larsen WE. Hematologic and clinical responses in patients with sickle cell anemia after chronic extracorporeal red cell carbamylation. J Clin Invest 1976; 58(3):642-653.

(B.5) Haghshenass M, Ismail-Beigi F, Clegg JB, Weatherall DJ. Mild sickle-cell anaemia in Iran associated with high levels of fetal haemoglobin. J Med Genet 1977; 14(3):168-171.

(B.6) Brittenham G, Lozoff B, Harris JW, Sharma VS, Narasimhan S. Sickle cell anemia and trait in a population of southern India. Am J Hematol 1977; 2(1):25-32.

(B.7) Perrine RP, Pembrey ME, John P, Perrine S, Shoup F. Natural history of sickle cell anemia in Saudi Arabs. A study of 270 subjects. Ann Intern Med 1978; 88(1):1-6.

(B.8) Kamel K. Heterogeneity of sickle cell anaemia in Arabs: review of cases with various amounts of fetal haemoglobin. J Med Genet 1979; 16(6):428-430.

(B.9) Roth EF, Jr., Schiliro G, Russo A, Musumeci S, Rachmilewitz E, Neske V et al. Sickle cell disease in Sicily. J Med Genet 1980; 17(1):34-38.

(B.10) Perrine RP, John P, Pembrey M, Perrine S. Sickle cell disease in Saudi Arabs in early childhood. Arch Dis Child 1981; 56(3):187-192.

(B.11) Al Awamy B, Wilson WA, Pearson HA. Splenic function in sickle cell disease in the Eastern Province of Saudi Arabia. J Pediatr 1984; 104(5):714-717.

(B.12) Acquaye JK, Omer A, Ganeshaguru K, Sejeny SA, Hoffbrand AV. Non-benign sickle cell anaemia in western Saudi Arabia. Br J Haematol 1985; 60(1):99-108.

(B.13) El Hazmi MA, Warsy AS. On the nature of sickle cell disease in the south-western province of Saudi Arabia. Acta Haematol 1986; 76(4):212-216.

(B.14) Eluwa EO, Obidoa O, Obi GO, Onwubiko HA. Variations in the relative activities of erythrocyte membrane ATPase with changes in severity of sickle cell anemia. Biochem Med Metab Biol 1987; 38(2):142-148.

(B.15) El Hazmi MA, Jabbar FA, Al Faleh FZ, Al Swailem AR, Warsy AS. The haematological, biochemical and clinical--presentation of haemoglobin S in Saudi Arabia (i). Haematological & clinical expression. Trop Geogr Med 1987; 39(2):157-162.

(B.16) el Mouzan MI, Al Awamy BH, al Torki MT, Niazi GA. Variability of sickle cell disease in the Eastern Province of Saudi Arabia. J Pediatr 1989; 114(6):973-976.

(B.17) Hurtig AL, Koepke D, Park KB. Relation between severity of chronic illness and adjustment in children and adolescents with sickle cell disease. J Pediatr Psychol 1989; 14(1):117-132.

(B.18) Gil KM, Abrams MR, Phillips G, Keefe FJ. Sickle cell disease pain: relation of coping strategies to adjustment. J Consult Clin Psychol 1989; 57(6):725-731.

(B.19) Chaplin H, Monroe MC, Malecek AC, Morgan LK, Michael J, Murphy WA. Preliminary trial of minidose heparin prophylaxis for painful sickle cell crisis. East Afr Med J 1989; 66:574-584.

(B.20) Cetiner S, Akoglu TF, Kilinc Y, Akoglu E, Kumi M. Immunological studies in sickle cell disease: comparison of homozygote mild and severe variants [published erratum appears in Clin Immunol Immunopathol 1990 Jun;55(3):492]. Clin Immunol Immunopathol 1989; 53(1):32-39.

(B.21) Christakis J, Vavatsi N, Hassapopoulou H, Papadopoulou M, Mandraveli K, Loukopoulos D et al. Comparison of homozygous sickle cell disease in northern Greece and Jamaica [see comments]. Lancet 1990; 335(8690):637-640.

(B.22) El Hazmi MA, Bahakim HM, Babikar MA, al Swailem AM, Warsy AS. Symptom-free intervals in sicklers: does pneumococcal vaccination and penicillin prophylaxis have a role? J Trop Pediatr 1990; 36(2):56-62.

(B.23) El-Hazmi MA, Bahakim HM, al-Swailem AM, Warsy AS. The features of sickle cell disease in Saudi children. J Trop Pediatr 1990; 36(4):148-155.

(B.24) Mulik R, Butikofer A, Aramouni G, Munshi N, Iliff P. A clinico-epidemiological study of sickle cell anaemia in Saudi Arabia. J Trop Pediatr 1991; 37(3):100-105.

(B.25) El Hazmi MA, Jabbar FA, Al Faleh FZ, Al Swailem AR, Warsy AS. Patterns of sickle cell, thalassaemia and glucose-6-phosphate dehydrogenase deficiency genes in north-western Saudi Arabia. Hum Hered 1991; 41(1):26-34.

(B.26) Padmos MA, Roberts GT, Sackey K, Kulozik A, Bail S, Morris JS et al. Two different forms of homozygous sickle cell disease occur in Saudi Arabia. Br J Haematol 1991; 79(1):93-98.

(B.27) Kodish E, Lantos J, Stocking C, Singer PA, Siegler M, Johnson FL. Bone marrow transplantation for sickle cell disease. A study of parents' decisions. N Engl J Med 1991; 325(19):1349-1353.

(B.28) El Hazmi MA, Warsy AS, al Momen A, Harakati M. Hydroxyurea for the treatment of sickle cell disease. Acta Haematol 1992; 88(4):170-174.

(B.29) El Hazmi MA. Heterogeneity and variation of clinical and haematological expression of haemoglobin S in Saudi Arabs. Acta Haematol 1992; 88(2-3):67-71.

(B.30) El Hazmi MA. Clinical and haematological diversity of sickle cell disease in Saudi children. J Trop Pediatr 1992; 38(3):106-112.

(B.31) Schiliro G, Samperi P, Consalvo C, Gangarossa S, Testa R, Miraglia V et al. Clinical, hematological, and molecular features in Sicilians with sickle cell disease. Hemoglobin 1992; 16(6):469-480.

(B.32) Ferster A, De Valck C, Azzi N, Fondu P, Toppet M, Sariban E. Bone marrow transplantation for severe sickle cell anaemia. Br J Haematol 1992; 80(1):102-105.

(B.33) Bernaudin F, Souillet G, Vannier JP, Plouvier E, Lemerle S, Michel G et al. Bone marrow transplantation (BMT) in 14 children with severe sickle cell disease (SCD): the French experience. GEGMO. Bone Marrow Transplant 1993; 12 Suppl 1:118-21:118-121.

(B.34) Brown RT, Kaslow NJ, Doepke K, Buchanan I, Eckman J, Baldwin K et al. Psychosocial and family functioning in children with sickle cell syndrome and their mothers. J Am Acad Child Adolesc Psychiatry 1993; 32(3):545-553.

(B.35) Chavis WM, Norman GS. Sexuality and sickle cell disease. J Natl Med Assoc 1993; 85(2):113-116.

(B.36) El Hazmi MA, Warsy AS, Bahakim H. Blood proteins C and S in sickle cell disease. Acta Haematol 1993; 90(3):114-119.

(B.37) Kilinc Y, Acarturk E, Kumi M. Echocardiographic findings in mild and severe forms of sickle cell anemia. Acta Paediatr Jpn 1993; 35(3):243-246.

(B.38) Ladipo OA, Falusi AG, Feldblum PJ, Osotimehin BO, Otolorin EO, Ojengbede OA. Norplant use by women with sickle cell disease. Int J Gynaecol Obstet 1993; 41(1):85-87.

(B.39) Nduka N, Owhochuku SM, Odike P. Current observations on sickle cell genotype in Nigeria. East Afr Med J 1993; 70(10):646-649.

(B.40) Hurtig AL. Relationships in families of children and adolescents with sickle cell disease. J Health Soc Policy 1994; 5(3-4):161-183.

(B.41) Thompson RJ, Jr., Gil KM, Keith BR, Gustafson KE, George LK, Kinney TR. Psychological adjustment of children with sickle cell disease: stability and change over a 10-month period. J Consult Clin Psychol 1994; 62(4):856.

(B.42) Yang YM, Cepeda M, Price C, Shah A, Mankad V. Depression in children and adolescents with sickle-cell disease. Arch Pediatr Adolesc Med 1994; 148(5):457-460.

(B.43) al Momen AK. Diminished vitamin B12 levels in patients with severe sickle cell disease. J Intern Med 1995; 237(6):551-555.

(B.44) Charache S, Terrin ML, Moore RD, Dover GJ, Barton FB, Eckert SV et al. Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. Investigators of the Multicenter Study of Hydroxyurea in Sickle Cell Anemia [see comments]. N Engl J Med 1995; 332(20):1317-1322.

(B.45) El Hazmi MA, al Momen A, Warsy AS, Kandaswamy S, Huraib S, Harakati M et al. The pharmacological manipulation of fetal haemoglobin: trials using hydroxyurea and recombinant human erythropoietin. Acta Haematol 1995; 93(2-4):57-61.

(B.46) El Hazmi MA, al Momen A, Kandaswamy S, Huraib S, Harakati M, al Mohareb F et al. On the use of hydroxyurea/erythropoietin combination therapy for sickle cell disease. Acta Haematol 1995; 94(3):128-134.

(B.47) Ferster A, Corazza F, Vertongen F, Bujan W, Devalck C, Fondu P et al. Transplanted sickle-cell disease patients with autologous bone marrow recovery after graft failure develop increased levels of fetal haemoglobin which corrects disease severity. Br J Haematol 1995; 90(4):804-808.

(B.48) Knight S, Singhal A, Thomas P, Serjeant G. Factors associated with lowered intelligence in homozygous sickle cell disease. Arch Dis Child 1995; 73(4):316-320.

(B.49) Vichinsky EP, Haberkern CM, Neumayr L, Earles AN, Black D, Koshy M et al. A comparison of conservative and aggressive transfusion regimens in the perioperative management of sickle cell disease. The Preoperative Transfusion in Sickle Cell Disease Study Group [see comments]. N Engl J Med 1995; 333(4):206-213.

(B.50) Thompson RJ, Jr., Gil KM, Abrams MR, Phillips G. Psychological adjustment of adults with sickle cell anemia: stability over 20 months, correlates, and predictors. J Clin Psychol 1996; 52(3):253-261.

(B.51) Adekile AD, Haider MZ. Morbidity, beta S haplotype and alpha-globin gene patterns among sickle cell anemia patients in Kuwait. Acta Haematol 1996; 96(3):150-154.

(B.52) Aikimbaev KS, Oguz M, Guvenc B, Baslamisli F, Kocak R. Spectral pulsed Doppler sonography of renal vascular resistance in sickle cell disease: clinical implications. Br J Radiol 1996; 69(828):1125-1129.

(B.53) al Sheyyab M, Rimawi H, Izzat M, Batieha A, el Bashir N, Almasri N et al. Sickle cell anaemia in Jordan and its clinical patterns. Ann Trop Paediatr 1996; 16(3):249-253.

(B.54) El Hazmi MA, Warsy AS, al Fawaz I, Opawoye AO, Taleb HA, Howsawi Z et al. Piracetam is useful in the treatment of children with sickle cell disease. Acta Haematol 1996; 96(4):221-226.

(B.55) Evliyaoglu N, Kilinc Y, Sargin O. Thyroid functions in mild and severe forms of sickle cell anemia. Acta Paediatr Jpn 1996; 38(5):460-463.

(B.56) Ferster A, Vermylen C, Cornu G, Buyse M, Corazza F, Devalck C et al. Hydroxyurea for treatment of severe sickle cell anemia: a pediatric clinical trial. Blood 1996; 88(6):1960-1964.

(B.57) Jayabose S, Tugal O, Sandoval C, Patel P, Puder D, Lin T et al. Clinical and hematologic effects of hydroxyurea in children with sickle cell anemia. J Pediatr 1996; 129(4):559-565.

(B.58) Rodrigue JR, Streisand R, Banko C, Kedar A, Pitel PA. Social functioning, peer relations, and internalizing and externalizing problems among youths with sickle-cell disease. Childrens Health Care 1996; 25:37-52.

(B.59) Scott JP, Hillery CA, Brown ER, Misiewicz V, Labotka RJ. Hydroxyurea therapy in children severely affected with sickle cell disease. J Pediatr 1996; 128(6):820-828.

(B.60) de Montalembert M, Belloy M, Bernaudin F, Gouraud F, Capdeville R, Mardini R et al. Three-year follow-up of hydroxyurea treatment in severely ill children with sickle cell disease. The French Study Group on Sickle Cell Disease. J Pediatr Hematol Oncol 1997; 19(4):313-318.

(B.61) Hilton C, Osborn M, Knight S, Singhal A, Serjeant G. Psychiatric complications of homozygous sickle cell disease among young adults in the Jamaican Cohort Study. Br J Psychiatry 1997; 170:69-76:69-76.

(B.62) Houston PE, Rana S, Sekhsaria S, Perlin E, Kim KS, Castro OL. Homocysteine in sickle cell disease: relationship to stroke. Am J Med 1997; 103(3):192-196.

(B.63) Lima CS, Arruda VR, Costa FF, Saad ST. Minimal doses of hydroxyurea for sickle cell disease. Braz J Med Biol Res 1997; 30(8):933-940.

(B.64) Ievers CE, Brown RT, Lambert RG, Hsu L, Eckman JR. Family functioning and social support in the adaptation of caregivers of children with sickle cell syndromes. J Pediatr Psychol 1998; 23(6):377-388.

(B.65) Kell RS, Kliewer W, Erickson MT, Ohene-Frempong K. Psychological adjustment of adolescents with sickle cell disease: relations with demographic, medical, and family competence variables. J Pediatr Psychol 1998; 23(5):301-312.

(B.66) McCrae JD, Lumley MA. Health status in sickle cell disease: examining the roles of pain coping strategies, somatic awareness, and negative affectivity. J Behav Med 1998; 21(1):35-55.

(B.67) Russo-Mancuso G, Romeo MA, Guardabasso V, Schiliro G. Survey of sickle cell disease in Italy. Haematologica 1998; 83(10):875-881.

(B.68) Diop S, Thiam D, Cisse M, Toure-Fall AO, Fall K, Diakhate L. New results in clinical severity of homozygous sickle cell anemia, in Dakar, Senegal. Hematol Cell Ther 1999; 41(5):217-221.

(B.69) Koren A, Segal-Kupershmit D, Zalman L, Levin C, Abu HM, Palmor H et al. Effect of hydroxyurea in sickle cell anemia: a clinical trial in children and teenagers with severe sickle cell anemia and sickle cell beta-thalassemia. Pediatr Hematol Oncol 1999; 16(3):221-232.

(B.70) Mouele R, Boukila V, Fourcade V, Feingold J, Galacteros F. Sickle-cell disease in Brazzaville, Congo: genetical, hematological, biochemical and clinical aspects [see comments]. Acta Haematol 1999; 101(4):178-184.

(B.71) Wison Schaeffer JJ, Gil KM, Burchinal M, Kramer KD, Nash KB, Orringer E et al. Depression, disease severity, and sickle cell disease. J Behav Med 1999; 22(2):115-126.

(B.72) Grant MM, Gil KM, Floyd MY, Abrams M. Depression and functioning in relation to health care use in sickle cell disease [In Process Citation]. Ann Behav Med 2000; 22(2):149-157.

(B.73) Walters MC, Storb R, Patience M, Leisenring W, Taylor T, Sanders JE et al. Impact of bone marrow transplantation for symptomatic sickle cell disease: an interim report. Blood 2000; 95(6):1918-1924.

7.10.3 Disease outcome review articles

(C.1) Powars DR. Natural history of sickle cell disease--the first ten years. Semin Hematol 1975; 12(3):267-285.

(C.2) Serjeant GR. Fetal haemoglobin in homozygous sickle cell disease. Clin Haematol 1975; 4(1):109-122.

(C.3) Eaton WA, Hofrichter J, Ross PD. Editorial: Delay time of gelation: a possible determinant of clinical severity in sickle cell disease. Blood 1976; 47(4):621-627.

(C.4) Bannerman RM. Pathophysiology and management of the severe sickling syndromes. Prog Clin Biol Res 1979; 34:369-79:369-379.

(C.5) Harkness DR. Hematological and clinical features of sickle cell diseases: a review. Hemoglobin 1980; 4(3-4):313-334.

(C.6) Hebbel RP, Eaton JW, Steinberg MH, White JG. Erythrocyte/endothelial interactions and the vasocclusive severity of sickle cell disease. Prog Clin Biol Res 1981; 55:145-62:145-162.

(C.7) Serjeant GR. Observations on the epidemiology of sickle cell disease. Trans R Soc Trop Med Hyg 1981; 75(2):228-233.

(C.8) Hebbel RP, Eaton JW, Steinberg MH, White JG. Erythrocyte/endothelial interactions in the pathogenesis of sickle-cell disease: a "real logical" assessment. Blood Cells 1982; 8(1):163-173.

(C.9) Wethers DL. Problems and complications in the adolescent with sickle cell disease. Am J Pediatr Hematol Oncol 1982; 4(1):47-53.

(C.10) Smith JA. Management of sickle cell disease: progress during the past 10 years. Am J Pediatr Hematol Oncol 1983; 5(4):360-366.

(C.11) Steinberg MH, Hebbel RP. Clinical diversity of sickle cell anemia: genetic and cellular modulation of disease severity. Am J Hematol 1983; 14(4):405-416.

(C.12) Embury SH. The interaction of coexistent alpha-thalassemia and sickle cell anemia: a model for the clinical and cellular results of diminished polymerization? Ann N Y Acad Sci 1985; 445:37-44:37-44.

(C.13) Lubin B. Evaluation of clinical severity and prognostic factors in patients with sickle cell disease. In: Beuzard Y, Charache S, Galacteros F, editors. Approaches to the therapy of sickle cell anaemia. Paris: INSERM, 1986: 521-531.

(C.14) Steinberg MH. The difficulty and paradox of assessing clinical severity of sickle cell anaemia. In: Beuzard Y, Charache S, Galacteros F, editors. Approaches to the therapy of sickle cell anaemia. Paris: INSERM, 1986: 457-470.

(C.15) Dover GJ, Charache S. Increasing fetal hemoglobin production in sickle cell disease: results of clinical trials. Prog Clin Biol Res 1987; 251:455-66:455-466.

(C.16) Rucknagel DL, Sarniak SA, Whitten CF, Odenheimer DA. Fetal hemoglobin concentration predicts disease severity in children with sickle cell anemia. Prog Clin Biol Res 1987; 251:487-96:487-496.

(C.17) Steinberg MH. Determinants of vaso-occlusive severity in sickle cell disease. Prog Clin Biol Res 1987; 240:413-28:413-428.

(C.18) Yardumian A, Davies SC. Clinical management of severe sickle cell disease. Acta Haematol 1987; 78(2-3):193-197.

(C.19) Embury SH. The interaction of alpha-thalassemia with sickle cell anemia. Hemoglobin 1988; 12(5-6):509-517.

(C.20) Akinyanju OO. A profile of sickle cell disease in Nigeria. Ann N Y Acad Sci 1989; 565:126-36:126-136.

(C.21) Noguchi CT, Rodgers GP, Schechter AN. Intracellular polymerization. Disease severity and therapeutic predictions. Ann N Y Acad Sci 1989; 565:75-82:75-82.

(C.22) Piomelli S. The possible role of genetic modifiers in the clinical severity of sickle cell syndromes. Ann N Y Acad Sci 1989; 565:207-10:207-210.

(C.23) Powars DR, Chan L, Schroeder WA. The influence of fetal hemoglobin on the clinical expression of sickle cell anemia. Ann N Y Acad Sci 1989; 565:262-78:262-278.

(C.24) Smith JA. The natural history of sickle cell disease. Ann N Y Acad Sci 1989; 565:104-8:104-108.

(C.25) Powars D, Chan LS, Schroeder WA. The variable expression of sickle cell disease is genetically determined. Semin Hematol 1990; 27(4):360-376.

(C.26) Powars DR, Chan L, Schroeder WA. Beta S-gene-cluster haplotypes in sickle cell anemia: clinical implications. Am J Pediatr Hematol Oncol 1990; 12(3):367-374.

(C.27) Nagel RL. Severity, pathobiology, epistatic effects, and genetic markers in sickle cell anemia. Semin Hematol 1991; 28(3):180-201.

(C.28) Powars DR. Sickle cell anemia: beta s-gene-cluster haplotypes as prognostic indicators of vital organ failure. Semin Hematol 1991; 28(3):202-208.

(C.29) Powars DR. Beta s-gene-cluster haplotypes in sickle cell anemia. Clinical and hematologic features. Hematol Oncol Clin North Am 1991; 5(3):475-493.

(C.30) Smith JA. What do we know about the clinical course of sickle cell disease? Semin Hematol 1991; 28(3):209-212.

(C.31) Apperley JF. Bone marrow transplant for the haemoglobinopathies: past, present and future. Baillieres Clin Haematol 1993; 6(1):299-325.

(C.32) Davies SC. Bone marrow transplant for sickle cell disease--the dilemma. Blood Rev 1993; 7(1):4-9.

(C.33) Powars D, Hiti A. Sickle cell anemia. Beta s gene cluster haplotypes as genetic markers for severe disease expression. Am J Dis Child 1993; 147(11):1197-1202.

(C.34) Serjeant GR. The clinical features of sickle cell disease. Baillieres Clin Haematol 1993; 6(1):93-115.

(C.35) Powars DR, Meiselman HJ, Fisher TC, Hiti A, Johnson C. Beta-S gene cluster haplotypes modulate hematologic and hemorheologic expression in sickle cell anemia. Use in predicting clinical severity. Am J Pediatr Hematol Oncol 1994; 16(1):55-61.

(C.36) Radel E. Advances in the Treatment of Adolescents with Sickle Hemoglobinopathies. Adolesc Med 1994; 5(2):271-292.

(C.37) Serjeant GR. Natural history and determinants of clinical severity of sickle cell disease. Curr Opin Hematol 1995; 2(2):103-108.

(C.38) Steinberg MH. Genetic modulation of sickle cell anemia. Proc Soc Exp Biol Med 1995; 209(1):1-13.

(C.39) Koshy M, Dorn L. Continuing care for adult patients with sickle cell disease. Hematol Oncol Clin North Am 1996; 10(6):1265-1273.

(C.40) Charache S. Mechanism of action of hydroxyurea in the management of sickle cell anemia in adults. Semin Hematol 1997; 34(3 Suppl 3):15-21.

(C.41) Rodgers GP. Overview of pathophysiology and rationale for treatment of sickle cell anemia. Semin Hematol 1997; 34(3 Suppl 3):2-7.

(C.42) Serjeant GR. Sickle-cell disease [see comments]. Lancet 1997; 350(9079):725-730.

(C.43) Ballas SK. Sickle cell disease: clinical management. Baillieres Clin Haematol 1998; 11(1):185-214.

(C.44) Hoppe C, Styles L, Vichinsky E. The natural history of sickle cell disease. Curr Opin Pediatr 1998; 10(1):49-52.

(C.45) Schnog JJ, Lard LR, Rojer RA, van der Dijs FP, Muskiet FA, Duits AJ. New concepts in assessing sickle cell disease severity. Am J Hematol 1998; 58(1):61-66.

(C.46) Anie KA, Green J. Psychological therapies for sickle cell disease and pain (Cochrane review) [In Process Citation]. Cochrane Database Syst Rev 2000;(3):CD001916.

(C.47) Hagar RW, Vichinsky EP. Major changes in sickle cell disease [In Process Citation]. Adv Pediatr 2000; 47:249-72:249-272.

7.11 Reference List

(1) Embury SH, Dozy AM, Miller J, Davis JR, Jr., Kleman KM, Preisler H et al. Concurrent sickle-cell anemia and alpha-thalassemia: effect on severity of anemia. N Engl J Med 1982; 306(5):270-274.

(2) Steinberg MH, Hsu H, Nagel RL, Milner PF, Adams JG, Benjamin L et al. Gender and haplotype effects upon hematological manifestations of adult sickle cell anemia. Am J Hematol 1995; 48(3):175-181.

(3) Odenheimer DJ, Whitten CF, Rucknagel DL, Sarnaik SA, Sing CF. Heterogeneity of sickle-cell anemia based on a profile of hematological variables. Am J Hum Genet 1983; 35(6):1224-1240.

(4) Rucknagel DL, Sarniak SA, Whitten CF, Odenheimer DA. Fetal hemoglobin concentration predicts disease severity in children with sickle cell anemia. Prog Clin Biol Res 1987; 251:487-96:487-496.

(5) Powars DR, Chan L, Schroeder WA. The influence of fetal hemoglobin on the clinical expression of sickle cell anemia. Ann N Y Acad Sci 1989; 565:262-78:262-278.

(6) Ballas SK, Larner J, Smith ED, Surrey S, Schwartz E, Rappaport EF. Rheologic predictors of the severity of the painful sickle cell crisis. Blood 1988; 72(4):1216-1223.

(7) Okany CC, Akinyanju OO. The influence of socio-economic status on the severity of sickle cell disease. Afr J Med Med Sci 1993; 22(2):57-60.

(8) WHO. Preamble to the Constitution of the World Health Organization as adopted by the International Health Conference, New York, 19-22 June, 1946; signed on 22 July 1946 by the representatives of 61 States and entered into force on 7 April 1948. Official Records of the World Health Organization 1946; 2:100.

(9) Ottawa Charter on Health Promotion. Copenhagen: World Health Organization Regional Office for Europe, 1986.

(10) Nunnally J, Bernstein JC. Psychometric theory. 3rd ed. New York: McGraw-Hill, 1994.

(11) McDaniel RW, Bach CA. Quality of life: a concept analysis. Rehabilitation. Nursing Research 1994; 3:18-22.

(12) Charache S, Terrin ML, Moore RD, Dover GJ, Barton FB, Eckert SV et al. Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. Investigators of the Multicenter Study of Hydroxyurea in Sickle Cell Anemia [see comments]. N Engl J Med 1995; 332(20):1317-1322.

(13) Powars DR, Chan LS. Is sickle cell crisis a valid measure of clinical severity in sickle cell anemia? Prog Clin Biol Res 1987; 240:393-402:393-402.

(14) Shurafa MS, Prasad AS, Rucknagel DL, Kan YW. Long survival in sickle cell anemia. Am J Hematol 1982; 12(4):357-365.

(15) Steinberg MH, Dreiling BJ, Morrison FS, Necheles TF. Mild sickle cell disease. Clinical and laboratory studies. JAMA 1973; 224(3):317-321.

(16) El-Hazmi MA, Bahakim HM, al-Swailem AM, Warsy AS. The features of sickle cell disease in Saudi children. J Trop Pediatr 1990; 36(4):148-155.

(17) Vichinsky EP, Haberkern CM, Neumayr L, Earles AN, Black D, Koshy M et al. A comparison of conservative and aggressive transfusion regimens in the perioperative management of sickle cell disease. The Preoperative Transfusion in Sickle Cell Disease Study Group [see comments]. N Engl J Med 1995; 333(4):206-213.

(18) Ferster A, Vermylen C, Cornu G, Buyse M, Corazza F, Devalck C et al. Hydroxyurea for treatment of severe sickle cell anemia: a pediatric clinical trial. Blood 1996; 88(6):1960-1964.

(19) Cameron BF, Christian E, Lobel JS, Gaston MH. Evaluation of clinical severity in sickle cell disease. J Natl Med Assoc 1983; 75(5):483-487.

(20) Mukherjee MB, Surve R, Tamankar A, Gangakhedkar RR, Ghosh K, Lu CY et al. The influence of alpha-thalassaemia on the haematological & clinical expression of sickle cell disease in western India. Indian J Med Res 1998; 107:178-81:178-181.

(21) Bordin JO, Kerbauy J, Lourenco DM, Sesso R. Level of fetal hemoglobin as an indicator of clinical complications in sickle cell anemia. Braz J Med Biol Res 1989; 22(11):1347-1353.

(22) Miller ST, Sleeper LA, Pegelow CH, Enos LE, Wang WC, Weiner SJ et al. Prediction of adverse outcomes in children with sickle cell disease. N Engl J Med 2000; 342(2):83-89.

(23) Bowling A. Meauring health: A review of quality of life measurement scales. 2nd ed. Buckingham: Open University Press, 1997.

(24) WHOQOL Group. Study protocol for the World Health Organisation project to develop a quality of life assessment instrument (WHOQOL). Qual Life Res 1993; 2:153-159.

(25) Calman KC. Quality of life in cancer patients - an hypothesis. J Medical Ethics 1984; 10:124-127.

(26) Lovatt B. An overview of quality of life measures and outcome measures. Br J Med Econ 1992; 4:1-7.

(27) World Health Organisation. Health Promotion Glossary. Division of Health Promotion, Education and Communications (HPR). Health Education and Health Promotion Unit (HEP). WHO/HPR/HEP/98.1. 1998.

(28) Wasson JH, Sox HC, Neff RK, Goldman L. Clinnical prediction rules: application and methodological standards. N Engl J Med 1985; 313:793-799.

(29) Emond AM, Collis R, Darvill D, Higgs DR, Maude GH, Serjeant GR. Acute splenic sequestration in homozygous sickle cell disease: natural history and management. J Pediatr 1985; 107(2):201-206.

(30) Gaston MH, Verter JI, Woods G, Pegelow C, Kelleher J, Presbury G et al. Prophylaxis with oral penicillin in children with sickle cell anemia. A randomized trial. N Engl J Med 1986; 314(25):1593-1599.

(31) National Heart LaBI. Managaement and therapy of sickle cell disease (NIH No: 96-2117). 3rd ed. National Institutes of Health, 1995.

(32) Smith KD. Assessment of clinical severity of sickle cell disease. In: Knakoo Y, Davis H, editors. Academic Press, New York, 1978: 77-91.

(33) Powars DR. Progress in the natural history studies of the clinical severity of sickle cell disease. Academic Press, New York, 1978: 151-164.

(34) Walters MC, Patience M, Leisenring W, Eckman JR, Scott JP, Mentzer WC et al. Bone marrow transplantation for sickle cell disease [see comments]. N Engl J Med 1996; 335(6):369-376.

(35) Platt OS, Guinan EC. Bone marrow transplantation in sickle cell anemia--the dilemma of choice [editorial; comment]. N Engl J Med 1996; 335(6):426-428.

(36) Rehman KL. Bone marrow transplantation for sickle cell disease [letter; comment]. N Engl J Med 1996; 335(24):1845-1846.

(37) Scott JP, Hillery CA, Brown ER, Misiewicz V, Labotka RJ. Hydroxyurea therapy in children severely affected with sickle cell disease. J Pediatr 1996; 128(6):820-828.

(38) de Montalembert M, Begue P, Bernaudin F, Thuret I, Bachir D, Micheau M. Preliminary report of a toxicity study of hydroxyurea in sickle cell disease. French Study Group on Sickle Cell Disease. Arch Dis Child 1999; 81(5):437-439.

(39) Reed WF, Vichinsky EP. Transfusion practice for patients with sickle cell disease. Curr Opin Hematol 1999; 6(6):432-436.

(40) Ohene-Frempong K. Stroke in sickle cell disease: demographic, clinical, and therapeutic considerations. Semin Hematol 1991; 28(3):213-219.

(41) Vichinsky EP, Earles A, Johnson RA, Hoag MS, Williams A, Lubin B. Alloimmunization in sickle cell anemia and transfusion of racially unmatched blood [see comments]. N Engl J Med 1990; 322(23):1617-1621.

(42) Orlina AR, Sosler SD, Koshy M. Problems of chronic transfusion in sickle cell disease. J Clin Apheresis 1991; 6(4):234-240.

(43) Pippard MJ. Iron overload and iron chelation therapy in thalassaemia and sickle cell haemoglobinopathies. Acta Haematol 1987; 78(2-3):206-211.

(44) Teasdale C, Jennett B. Assessment of coma and impaired consciousness: a practical scale. Lancet [2], 81-84. 1974.

(45) Knaus WA, Wagner DP, Lynn J. Short term mortality predictions of critically ill hospitalised adults: science and ethics. Science 254, 389-393. 1991.

(46) Pollack MM, Ruttimann UE, Getson PR. Pediatric risk of mortality (PRISM) score. Crit Care Med 1988; 16(11):1110-1116.

(47) Concato J, Feinstein AR, Holford TR. The risk of determining risk with multivariable models. Annals of Internal Medicine 1993; 118:201-210.

(48) Simon R, Altman DG. Statistical aspects of prognostic factor studies in oncology. Br J Cancer 1994; 69:979-985.

(49) Levine MN, Browman GP, Gent M, Roberts R, Goodyear M. When is a prognostic factor useful? A guide for the perplexed. J Clin Oncol 1991; 9:348-356.

(50) McGuire WL. Breast cancer prognostic factors: evaluation guidelines. J Natl Cancer Inst 1991; 83:154-155.

(51) Justice AC, Covinsky KE, Berlin JA. assessing the generalizability of prognostic information. Annals of Internal Medicine 1999; 130:515-524.

(52) Wyatt JC, Altman DG. Commentary: Prognostic models: clinically useful or quickly forgotten? Br Med J 1995; 311:1539-1541.

(53) Rogers DW, Clarke JM, Cupidore L, Ramlal AM, Sparke BR, Serjeant GR. Early deaths in Jamaican children with sickle cell disease. Br Med J 1978; 1(6126):1515-1516.

(54) Leikin SL, Gallagher D, Kinney TR, Sloane D, Klug P, Rida W. Mortality in children and adolescents with sickle cell disease. Cooperative Study of Sickle Cell Disease. Pediatrics 1989; 84(3):500-508.

(55) Gill FM, Sleeper LA, Weiner SJ, Brown AK, Bellevue R, Grover R et al. Clinical events in the first decade in a cohort of infants with sickle cell disease. Cooperative Study of Sickle Cell Disease [see comments]. Blood 1995; 86(2):776-783.

(56) Wierenga KJ, Hambleton IR, Lewis NA. Survival estimates for patients with homozygous sickle-cell disease in Jamaica: a clinic-based population study. Lancet 2001; 357(9257):680-683.

(57) Marks RG, Dawson-Saunders EK, Bailar JC, Dan BB, Verran JA. Interactions between statisticians and biomedical journal editors. Stat Med 1988; 7(10):1003-1011.

(58) Checklist for statisticians. British Medical Journal 1993; 306:2-3.

(59) Altman DG, Gore SM, Gardner MJ, Pocock SJ. Statistical guidelines for contributors to medical journals. Br Med J (Clin Res Ed) 1983; 286(6376):1489-1493.

(60) Harrell FE, Jr., Lee KL, Califf RM, Pryor DB, Rosati RA. Regression modelling strategies for improved prognostic prediction. Stat Med 1984; 3(2):143-152.

(61) Clarke M, Oxman A. Assessment of study quality. Cochrane Reviewers' Handbook 4.1 [updated June 2000]. Review Manager (RevMan) [Computer Program]. Version 4.1. Oxford, England: The Cochrane Collaboration, 2000.

(62) Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics 1977; 33(1):159-174.

(63) Keidan AJ, Sowter MC, Johnson CS, Noguchi CT, Girling AJ, Stevens SM et al. Effect of polymerization tendency on haematological, rheological and clinical parameters in sickle cell anaemia. Br J Haematol 1989; 71(4):551-557.

(64) Thame M, Grandison Y, Mason K, Thompson M, Higgs D, Morris J et al. The red cell distribution width in sickle cell disease--is it of clinical value? [see comments]. Clin Lab Haematol 1991; 13(3):229-237.

(65) Anyaegbu CC, Okpala IE, Akren'Ova YA, Salimonu LS. Peripheral blood neutrophil count and candidacidal activity correlate with the clinical severity of sickle cell anaemia (SCA) [letter]. Eur J Haematol 1998; 60(4):267-268.

Chapter 8

Measuring health status in the JSSCD

Background

Methods for summarising the health status of people living with homozygous sickle cell (SS) disease are not well developed. Evidence is available, but has not received widespread clinical acceptance. The evidence of methodological quality (internal validity) and of the generalisability of results, which is important to the promotion of such evidence, is not convincing (see chapter seven), and we now examine the generalisability of results.

Methods

From a systematic review of health status in SCD (see Chapter seven), we identified a subset of articles offering a quantitative index for the classification or prediction of disease outcome or disease severity. We assessed these for their ability to maintain prognostic accuracy when applied to an alternative population - the JSSCD. We assessed accuracy using measures of calibration and discrimination, and interpreted results in the context of study differences that could influence this external validation.

Findings

Sixteen articles offered original systems for defining disease outcome or disease severity: 13 articles classified current severity and 3 articles predicted future severity. Four of these met criteria for application to the JSSCD (2 classification articles, 2 prediction articles). A single prediction scheme performed well in its primary aim of minimising the false positive identification of adversely affected patients (original specificity, 99%, JSSCD specificity, 85%). More generally, its ability to correctly identify adversely affected patients degraded substantially (original predictive ability 78.5% [70.6% to 86.4%], JSSCD predictive ability 5.6% [0 to 20.8%]). A second prediction article did less well in its stated aim of maximising positive predictive value (original positive predictive value 59%, JSSCD positive predictive value 39%), and could not effectively identify predefined disease severity (original predictive ability 5.5% [0 to 27%], JSSCD predictive ability 0% [0 to 12.3%]). Two articles classified current disease outcome or disease severity, and informal comparisons of generalisability are presented.

Interpretation

There have been several attempts to classify disease outcome or disease severity, but without external validation of results, the clinical credibility of these indices remains an obstacle to popular acceptance. The current external validation can verify the prognostic ability of a single index if subsequent application matches the primary goal of that index.

8.1 Classifying SS disease outcome: internal validity, accuracy, and generalisability

Quantitative indices for the classification of study participants according to aspects of *disease outcome* or *disease severity* can be divided into prediction-schemes and classification-schemes (1). A prediction scheme is a statistical model that predicts whether a predefined aspect of *disease outcome* or *disease severity* will occur in a patient. A classification scheme classifies a patient's current *disease outcome* or *disease severity* status according to a single summary measure, constructed from combining at least two individual items.

8.2 Chapter Plan

Methodology for the assessment of published indices for the quantification of *disease outcome* or *disease severity* is described in section 8.3. Results are presented in section 8.4.

8.3 Methods

8.3.1 Objectives

We performed the systematic review to summarise the evidence on quantitative methods for the classification of homozygous sickle cell patients according to *disease outcome* or *disease severity* status. Specific objectives were as follows:

- To identify articles offering a new quantitative summary of *disease outcome* or *disease severity.*
- To examine the internal validity of these articles using pre-defined minimal criteria for acceptable methodology.
- To examine the accuracy and generalisability of these articles.

8.3.2 Criteria for considering studies

We included an article in the assessment of internal validity if it was a prognostic factor study using an SS disease population and constructed an original index (prediction or classification scheme) considered by the contributors of each article to be a summary of *disease outcome* or *disease severity.* Some published indices were developed for use only in the original article. We included an article in the assessment of accuracy and generalisability if the published index was explicitly offered for clinical application, or had been used in a subsequent article by independent authors.

8.3.3 Search strategy

The search strategy for acceptable articles is described as a four-stage process. Stages one to three are described in Chapter seven (section 7.6.3). In stage four, we reviewed all *prediction* and *use articles* identified in stage three to identify prognostic indices of *disease outcome* or *disease severity.* An article contained an index if it presented either a model-based prognostic index (a prediction scheme) or a composite measurement scale (a classification scheme).

8.3.4 Methods of review

We developed a standard datasheet for data collection (see section 8.6) and pre-tested this tool in a sample of non-eligible articles (each contained a non-original prognostic index). We collected data on all eligible articles. Two statisticians collected all data independently, and discrepancies were resolved in a single consensus meeting.

(a) Characteristics and internal validity of included studies

We described patient characteristics using sample size, age range, genotypes studied, and geographical region. We described article characteristics by the study period. We grouped variables included in a prognostic index into pre-defined systemic categories (patient characteristics, haematology, clinical signs and symptoms, anthropometry, and composite) and tabulated the numbers of variables in each group. We assessed internal validity using the sources of systematic bias identified by the Cochrane Collaboration for use in reviews of randomised controlled trials (2), and adapted here for SCD observational studies (See Chapter seven, Table 7.4). This bias checklist is not comprehensive, but represents design features expected to be major influences on the level of systematic bias in SCD *disease outcome* or *disease severity* research. Each article was then classified as having a low, moderate, or high risk of bias, according to the number of design features it met (Chapter seven, Table 7.5).

(b) Accuracy of Prediction Schemes

For each article, we applied definitions for predictor variables and for *disease outcome* or *disease severity* variables to data from the external population (the JSSCD). We have summarised methods for investigating aspects of accuracy and generalizability in Table 8.1, separately for prediction schemes and classification schemes.

We applied each 'frozen' prediction scheme (3) to the JSSCD population. Comparison of the predicted outcome with the actual *disease outcome* in the JSSCD provides a route for assessing the accuracy of each prediction scheme. We assessed calibration using a calibration curve – plotting observed against predicted *disease outcome.* We assessed discrimination using receiver-operating characteristics – sensitivity, specificity, and predictive values. Definitions of sensitivity and specificity differed between articles. Here, we followed the convention of Miller (2000) and adapted other articles to this convention (4). Sensitivity is the proportion of clinically severe patients correctly identified by the model and specificity is the proportion of clinically mild patients correctly identified by the model. The point of a prognostic model is to 'diagnose' severity; we want to know the probability that the model will give the correct diagnosis, and sensitivity and specificity do not give us this information. Instead, we use predictive values. The positive predictive value (ppv) is the proportion of patients predicted to be clinically severe who are diagnosed as clinically severe. The negative predictive value (npv) is the proportion of patients predicted to be clinically mild who are diagnosed as clinically mild. A general measure of discrimination is known as the concordance index (c) and is the proportion of all pairs of patients, one with adverse disease outcome, one without, in

which the patient with adverse outcome has been correctly predicted. We present this proportion as a rank correlation coefficient (Somers-D) by calculating 2(c-0.5). We produce confidence intervals for this correlation using jackknife variances.

(c) Accuracy of Classification Schemes

We applied each classification scheme to the JSSCD population. A classification scheme has no pre-defined 'reference' measure of disease outcome and so measurement of absolute accuracy is not possible. Instead, we informally examined relative accuracy by comparing classification schemes with each other. We assessed calibration by comparing summary score distributions for all classification schemes. We calculated classification scheme scores for each year of patient follow-up, and summarised these as a single mean score.

Table 8.1.

Analyses used to investigate components of external validity.

Component of accuracy and generalisability		**Method of investigation**	
	Description	**Prediction Scheme (absolute accuracy) ***	**Classification Scheme (relative accuracy) ****
Accuracy			
Calibration	Are prognostic index predictions too high or too low?	Calibration curve. Plot predicted versus observed outcome	Compare summary score distributions.
Discrimination	The ability of a prognostic index to correctly rank patients.	Sensitivity, specificity, predictive values, Somers D statistic.	Relative ranking analysis using modified Kappa statistic
Generalisability			
Reproducible	Maintains accuracy in sample from the same population as model development	Examine potential for over- or under-fitting	-
Historical	Maintain accuracy in sample from different secular period	Compare study period and age range of participants.	Compare study-period and age range of participants.
Geographic	Maintain accuracy in sample from different location	Compare study location.	Compare study location.
Methodological	Maintain accuracy in data collected using alternative methods	Examine internal validity of prognostic model	Examine internal validity of prognostic model
Spectrum	Maintain accuracy in sample with different disease features	Incidence of outcome measures	Incidence of outcome measures.
Follow-up	Maintain accuracy over longer than intended time period	JSSCD validation restricted to equivalent time period	Profile plot. Summary score/year are plotted against age

*** compare each application with the JSSCD**
**** compare all JSSCD applications with each other**

We compared distributions of classification scheme scores after standardising each score as z-scores and alternatively as a proportion of the maximum score possible for the classification scheme. We assessed discrimination by comparing the relative order of the JSSCD patients using each of the classification schemes. For each classification scheme, patients were ordered according to their summary z-score and assigned a rank. The agreement between classification schemes was assessed by comparing their performance to randomly generated index z-scores (see section 8.8 for details of this methodology).

The painful crisis has often been used as a proxy for sickle cell disease outcome (5-7) and we include this measure in all classification scheme comparisons. We have defined the painful crisis in section 8.2.9.

(d) Generalisability

Components of generalisability have been identified as historical, geographic, methodological, spectrum, and follow-up (8), and are described in Table 8.1. For each included article, we interpreted accuracy with reference to each component of generalisability, by comparing the JSSCD population to the population in the original article. All classification schemes were originally developed using cross-sectional data. We applied each classification scheme to the 27-years of JSSCD follow-up to provide an informal examination of follow-up generalisability. We calculated classification scheme summary scores for each year of patient follow-up, and plotted profiles for each classification scheme, along with 95% bootstrapped confidence intervals. Here we were interested in differences between classification schemes.

8.4 Results

8.4.1 Study inclusion

From 150 prediction and use articles, there were 3 original prediction schemes (4;9;10) and 14 original classification schemes from 11 articles (11-23). There were 24 subsequent uses of an original prognostic index (24-47).

From the 17 original prognostic indices, 2 prediction schemes were offered for general use (4;10), and 2 classification schemes were subsequently used by independent authors (11;17). We assessed internal validity in the 17 original prognostic indices. We assessed accuracy and generalisability in the subset of 4 prognostic indices offered for external use or used externally.

8.4.2 Characteristics of included studies

We present characteristics of the 3 prediction schemes and 14 classification schemes in Table 8.2. The number of items in a prognostic index tended to be higher in a classification scheme than in a prediction scheme. The nature of these items differed fundamentally, with classification schemes focussing on clinical signs and symptoms and prediction schemes using haematological indices. Most of the items were available from retrospective information at the

Jamaican sickle cell clinic (117 out of 124 items). Two items were unavailable for the El Hazmi classification scheme (history of polyurea, history of deep vein thrombosis). A single item was unavailable in longitudinal format for the Steinberg classification scheme ('active life' measured by being at school, a homemaker, or in employment), and 'active life' at the end of 1999 was used. Only 38 (31%) items had clear and reproducible definitions (32/112 or 29% classification scheme items, 6/12 or 50% prediction scheme items) and no classification scheme provided a complete set of definitions. When item definitions were unavailable, definitions from the JSSCD were used. Two prediction schemes provided a biological rationale for item inclusion (9;10). All prognostic indices used arbitrary cutpoints, with no classification schemes and all prediction schemes providing a rationale for their choices.

Four *levels of measurement* (nominal, ordinal, interval, ratio) represent number usage with implications for the legitimacy of applying statistical techniques; parametric techniques are not strictly applicable to nominal or ordinal outcomes (48). Among classification schemes, two articles contained interval items (14) (20). The remaining classification schemes treated nominal or ordinal items as interval or ratio scales, either when constructing interval or ratio outcome measurements given ordinal items (11-13;15;16;18;22;23;49), or when analysing ordinal outcomes using parametric techniques (17;19). Among prediction schemes, all articles used nominal or ordinal items appropriately to stratify disease outcomes.

Most classification scheme outcomes were based on weighted sums of the item scores (11-16;18-20;22;23;49). Weighting systems were chosen arbitrarily and without explanation. All classification schemes were constructed in studies not specifically aimed at validating the final prognostic index. Psychometric properties were addressed in 2 out of 10 classification schemes (14;16), and no article provided a comprehensive assessment of reliability, and sensitivity.

Table 8.2.

Characteristics of three articles containing prediction schemes and 14 articles containing classification schemes.

Article	Sample size	Study location	Study period	Age range	Genotypes	Number of items in PI					
						A	B	C	D	E**	All
Prediction schemes											
Odenheimer et al (1983)	360	USA, Detroit	1973-1980	0-18	SS	1	6	0	0	0	7
Bordin et al (1989) *	89	Brazil, São Paulo	?-1989	3-64	SS	0	1	0	0	0	1
Miller et al (2000) *	392	USA	1978-1998	0-10	SS, $S\beta^0$	1	2	1	0	0	3
Classification schemes											
Steinberg et al (1973) *	33	USA, Mississippi	1971-1972	18-56	SS	1	0	5	0	2	8
Gaston MH (1975)	95	USA, Cincinnati	?-1975	0-22	SS, SC, $S\beta^0$, $S\beta^+$, SD	1	0	6	0	1	8
Bienzle et al (1975)	30	Nigeria, Ibadan	?-1975	10-25	SS	0	1	2	0	3	6
Cameron et al (1983) (1)†	24	USA, Cincinnati	?-1983	1-21	SS, SC, $S\beta^+$	1	0	5	1	1	8
Cameron et al (1983) (2)†	24	USA, Cincinnati	?-1983	1-21	SS, SC, $S\beta^+$	0	0	0	0	3	3
Pajot et al (1988)	50	France, Paris	?-1988	1-27	SS	2	0	5	0	1	8
Keidan et al (1989)	30	UK, Birmingham	?-1989	17-49	SS	0	0	17	1	2	20
El Hazmi et al (1990) *	137	Saudi Arabia, Riyadh	?-1990	1-12	SS, $S\beta^0$	0	1	13	0	2	16
Olatunji and Falusi (1994)	80	Nigeria, Ibadan	?-1994	15-36	SS	0	1	1	0	1	3
Houston et al (1997)	100	USA, Washington D.C.	?-1997	1-58	SS, $S\beta^0$	0	0	6	0	0	6
Thomas et al (1997)	280	Kingston, Jamaica	1973-1994	0-13	SS	0	0	14	0	0	14
Anyaegbu et al (1998)	64	Nigeria, Ibadan	?-1998	16-33	SS	0	1	1	0	1	3
Ievers et al (1998)	67	USA, Charleston	1997-1998	5-17	SS, SC, Sβ, Other	0	1	1	0	2	4
Diop et al (1999)	60	Senegal, Dakar	1996-1998	2-49	SS	1	0	2	0	3	6

***** **Offered for external use or used in a subsequent article by independent authors.**

****** **A composite item is defined as a clinical event serving as a proxy for other SCD related complications (e.g. hospital admission, blood transfusion).**

† **Article contains two classification schemes**

A Patient characteristics. B Haematology. C Clinical. D Anthropometry. E Composite.**

8.4.3 Methodological quality of included studies

In Table 8.3 we present the frequency of four methodologically desirable features among 13 articles containing original disease outcome classification tools.

Table 8.3.
Percentage of prognostic index articles meeting methodologically desirable features.

Criterion	Articles meeting criterion	Article References
Neonatal ascertainment	2 (13%)	(11;16)
Patient follow-up	6 (38%)	(1;4;8;11;13;16)
Longitudinal study design	1 (6%)	(16)
Appropriate statistical methodology	8 (50%)	(1;4;7;11-14;16)
Bias Risk		
Low	1 (6%)	(16)
Moderate	1 (6%)	(11)
High	14 (88%)	(1-10;12-15)

A maximum of 8 (50%) articles met any individual design feature. Only 2 articles met all design features, for a low bias risk, or any 3 design features, for a moderate bias risk. The remaining 14 articles had levels of bias that left little confidence in their results.

Neonatal patient ascertainment, and longitudinal patient follow-up, which require substantial resource commitment, were design features of only 2 articles. A low level of bias, which would not be expected to seriously affect results, was a feature of a single article.

8.4.4 Eligibility for assessment accuracy and generalisability

We present summary descriptions of the four prognostic indices eligible for assessment of accuracy and generalisability in Table 8.4.

Table 8.4.

Description of four articles offered for external application or used subsequently by independent authors.

Article	Description
Steinberg et al (1973)	An early classification scheme using 8 clinical and lifestyle items developed in the context of identifying patients with mild disease expression. It was designed to describe the 'degree of interference with normal life produced by the disease'. A weighted item summation for each patient was produced. The criteria for group classification (mild or severe disease) were unclear.
El Hazmi et al (1990)	A classification scheme developed using 16 clinical events as a descriptive tool in the context of documenting the clinical features of a geographically distinct group of SCD patients. The classification scheme was defined as the 'total number of attacks, hospitalisations, crises, transfusions, symptoms and signs per year'. A weighted item summation for each patient was divided by the number of years of patient follow-up. The classification scheme summary measure was used as a continuous variable, and in subsequent uses by the same authors (46) and by others (36), ≥6 or ≥7 has been arbitrarily considered prescriptive of severe disease.
Bordin et al (1989)	A simple prediction scheme using a single item (HbF) selected on the basis of previous research. Alternative HbF cutpoints (8%, 10%, 12%) classified patients into 1 of 2 groups defined as benign and severe disease. Selected clinical events pre-defined a reference for severe disease, and the classification ability of HbF was assessed using sensitivity and specificity.
Miller et al (2000)	A prediction scheme developed to determine whether features of SCD in early life could be used to predict adverse outcome later in life. Selected clinical events defined disease outcome, and prediction scheme items were identified from clinical events and haematological indices collected in the first two years of life. A two-stage Cox regression of 'time to adverse event' identified significant predictors at the 20% level, which were entered into a second multivariate phase requiring 5% significance. The final prediction scheme was applied to an internal validation sample using logistic regression, and the predictive ability of the prediction scheme assessed using sensitivity and specificity.

8.4.5 Accuracy of the Bordin prediction scheme

Bordin sensitivity and specificity equate to Miller specificity and sensitivity respectively. Bordin ppv and npv equate to Miller npv and ppv respectively. Three clinical events define adverse outcome (leg ulceration, aseptic necrosis, stroke). We present the classification ability of the model for the original Bordin validation, and after application to the JSSCD in Table 8.5.

For the JSSCD validation, HbF predictor information was unavailable in 43 (13.8%) patients, either due to early death (41 cases) or emigration (2 cases) before 3 years of age, reducing the available sample to 268 patients (86.2% of the original sample). The aim of the original study was to 'determine whether HbF level could be a useful test for indicating the possible development of severe complications', suggesting that a high ppv is the primary goal of the model. In the original validation it was predicted that 64 patients would have a severe course, and 24 actually did (ppv=59%), from a total severe sample of 32 (sensitivity 76%).

In the JSSCD validation, it was predicted that 188 would have a severe course, and 72 of these actually did (ppv=38%), from a total severe sample of 103 (sensitivity 70%) (Table 8.5).

Table 8.5.
Patients predicted and observed with mild or severe disease
using two validations of the Bordin prediction scheme.

Predicted outcome	**Pre-defined outcome**			
Bordin (1989)	Mild	Severe		
Mild (HbF > 8%)	17	8	25	npv 68%
Severe (HbF ⩽ 8%)	40	24	64	ppv 59%
Total	57	32	89	
	specificity 30%	sensitivity 76%		
JSSCD validation				
Mild (HbF > 8%)	49	31	80	npv 61.3%
Severe (HbF ⩽ 8%)	116	72	188	ppv 38.3%
Total	165	103	268	
	specificity 29.7%	sensitivity 69.9%		

The model offers a similar performance in the 2 validations for correctly identifying mild patients (Bordin specificity=30%, JSSCD specificity=29.7%) or accurately predicting mild patients (Bordin npv=68%, JSSCD npv=61.3%). The model's ability to discriminate between mild and severe patient groups is very limited in the original development (Somers D=5.5% [0,27%]), and in the JSSCD application (Somers D=0% [0, 12.3%]). The model is better at predicting who will not have a severe course than identifying who will.

Calibration of the Bordin system is presented in Figure 8.1. The percentages of observed severe disease in each of the predicted categories (mild and severe) is similar between the 2 validations, indicating that calibration is maintained in the subsequent application to the JSSCD.

8.4.6 Accuracy of the Miller prediction scheme

Early life predictor information were unavailable in 83 (26%) patients, often due to early death (40 cases) or emigration (9 cases), reducing the available sample to 239 patients (74% of the original sample). The difficulty in obtaining early-life information, even in a cohort regime, is apparent.

The classification ability of the model for the original Miller validation, and after application to the JSSCD is presented in Table 8.6. The prediction model was developed with the aim of maximising specificity (minimizing the false positive rate of classification). Using the predefined predicted probability of 36% that a child would have a severe disease course,

specificity in the JSSCD was 85%, which is high but shows some degradation compared to the almost perfect original specificity of 99%.

Table 8.6.
Patients predicted and observed with mild or severe disease
using two validations of the Miller prediction scheme.

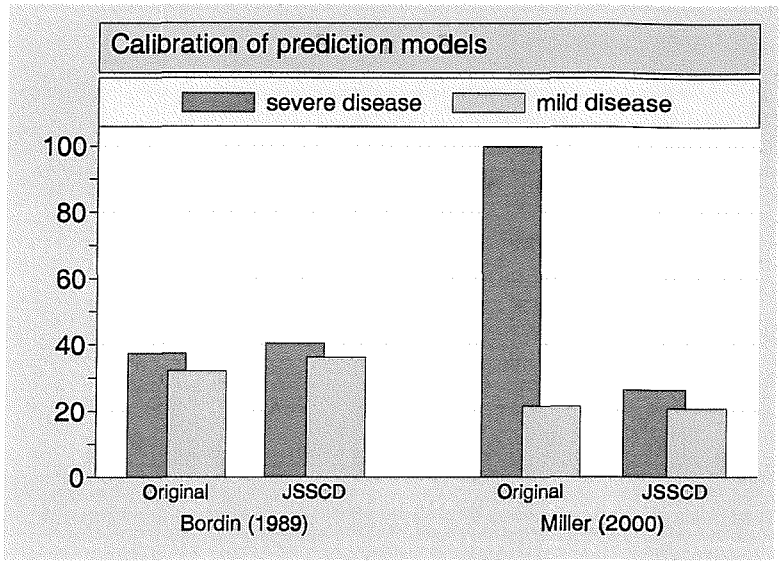
Predicted outcome	**Pre-defined outcome**			
Miller (2000)	Mild	Severe	total	
Mild (prob < 36%)	95	12	107	npv 89%
Severe (prob ⩾ 36%)	1	3	4	ppv 75%
Total	96	15	111	
	specificity 99%	sensitivity 20%		
JSSCD validation				
Mild (prob < 36%)	160	41	201	npv 79.6%
Severe (prob ⩾ 36%)	28	10	38	ppv 26.3%
Total	188	51	239	
	specificity 85.1%	sensitivity 19.6%		

In the original validation it was predicted that 4 patients would have a severe course, and 3 actually did (ppv=75%), from a total severe sample of 15 (sensitivity 20%). In the JSSCD validation, it was predicted that 38 would have a severe course, and 10 of these actually did (ppv=26%), from a total severe sample of 51 (sensitivity 20%). The model transports reasonably well to the JSSCD in its stated aim of minimising the number of mild patients that are wrongly classified as severe. The model performs poorly in the more general aim of accurately identifying truly severe patients. In particular, the model's ability to discriminate between mild and severe patients has degraded substantially between the Cooperative Study of Sickle Cell Disease (CSSCD) validation (Somers D=78.5% [70.6% to 86.4%]) and the JSSCD validation (Somers D=5.6% [0 to 20.8%]). The model is better at predicting who will not have a severe course than identifying who will.

Calibration of the Miller system is presented in Figure 8.1. The percentages of observed adverse outcome in patients predicted as severe varied between the 2 validations, indicating that calibration is not maintained in the subsequent application to the JSSCD.

Figure 8.1

Percentage of predicted patients with observed adverse outcome for Bordin and Miller systems



8.4.7 Generalisability of the Bordin system

(a) Reproducibility

The Bordin prediction scheme used a single predictor and is possibly underfit, which could limit its accuracy if applied to alternative populations. Reproducibility was not examined.

(b) Historical

Patients aged between 3 and 64 years were recruited in 1989 for development of the Bordin system. This sample spans a far wider birth period than the JSSCD validation sample, which were born and recruited between 1973 and 1981.

(c) Geographical

The Bordin sample is a Brazilian population. The beta-globin haplotype is predominantly Bantu in Brazil, and Benin in Jamaica (50), which may influence variation in disease expression between the two populations. No other systematic differences have been documented.

(d) Methodological

The Bordin prediction scheme publication is classified as having a 'high' bias risk (Table 8.3), because of a clinically ascertained patient sample, a cross-sectional analysis, and potentially inappropriate statistical analyses.

(e) Spectrum

Three clinical events define adverse outcome in the Bordin system and are presented in Table 8.7 in the Brazilian and Jamaican population samples.

Table 8.7.

Incidence of adverse events in the original Bordin system, and in the JSSCD.

Any adverse event	Number of patients (%)	Age	Number of patients (%)	Age
	Bordin (1989)		JSSCD (n=311)	
Leg ulceration	17 (19)	32.9±9.5	89 (29)	15.2±3.3
Aseptic necrosis	13 (15)	27.7±14.9	8 (3)	17.3±3.1
Stroke	8 (9)	10.8±4.0	19 (6)	12.6±4.6

There is a striking difference in leg ulceration and aseptic necrosis prevalence. This increased leg ulceration prevalence in Jamaica has been noted in comparisons with many other sickle cell disease populations (51).

(f) Follow-up

The JSSCD validation followed the cross sectional design of the original Bordin validation.

8.4.8 Generalisability of the Miller system

(a) Reproducibility

The Miller prediction scheme used many of the important early-life indicators of health-status in sickle cell disease and incorporated resampling techniques to adjust for potential overfitting. Validation in a new sample from the same underlying population examined its reproducibility.

(b) Historical

Patients were neonatally ascertained in both studies. The Miller development sample was born between 1978 and 1988, and the JSSCD sample was recruited up to 5 years earlier. This was a period of rapid development in the management of the disease, and although a 5-year recruitment difference seems minimal, the calibration of the system may be sensitive to secular variation.

(c) Geographical

The Miller prediction scheme was developed in patients from multiple sites in the US, and the JSSCD validation based on a Jamaican population. Although anecdotal comparisons highlight differences in the incidence of clinical outcomes, there is little evidence to suggest a fundamental difference in disease expression. Recent estimates from the US and Jamaica describe a similar survival experience when applying the same analysis methods: 42 and 48 years for US men and women, and 43 and 47 for Jamaican men and women (52;53).

(d) Methodological

The Miller system publication is classified as having a 'low' bias risk (Table 8.3) – it uses a neonatally ascertained patient sample, longitudinal data collection, and applies appropriate statistical analyses.

Table 8.8.

Incidence of adverse events in the original Miller system, and in the JSSCD.

First adverse event	Number of patients (%)	Age	Number of patients (%)	Age
	Miller (n=392)		JSSCD (n=322)*	
Painful events	17 (4.3)	7.9±3.7	10 (3.1)	7.6±5.9
ACS	10 (2.6)	3.5±1.0	1 (0.3)	3.4
Stroke	25 (6.4)	6.1±3.4	17 (5.3)	8.3±3.9
Death	18 (5.6)	5.1±3.7	63 (19.6)	5.8±6.4
Total	70 (17.9)	5.9±3.6	91 (28.3)	6.4±6.0

*** Miller (2000) additionally included 11 S-beta 0 patients in the initial patient sample**

(e) Spectrum

Four clinical events define adverse outcome in the Miller system and are presented in Table 8.8. Ninety-one (28%) JSSCD patients had adverse outcomes compared with 70 (18%) from Miller's CSSCD population. The striking mortality difference is due primarily to increased levels of early life mortality in the first tercile of JSSCD recruitment (54). From the available sample, 51 (21%) were classified as severe (9 pain crises, 1 ACS, 12 strokes, 29 deaths). Considering the predictor information, there were 48 (20.1%) cases of dactylitis in the JSSCD, representing a significantly greater first year incidence than that seen in the CSSCD original cohort (incidence rate ratio 1.7, 95% ci 1.1-2.7). Levels of steady state haemoglobin and steady state leucocyte count were anecdotally lower in the JSSCD compared to the CSSCD (Hb: 8.1 vs. 9.0 g per decilitre, leucocyte count: 16.3 vs. 16.9 x 103 per cubic millimetre).

(f) Follow-up

Age ranges were restricted to 0-10 years for model application in both studies.

8.4.9 Accuracy of the El-Hazmi and Steinberg Composite Measurement Scales, and the pain index

The 2 classification schemes (11;17) and the pain crisis index were applied to 292 JSSCD SS patients who had at least one complete year of follow-up. Discrimination between the three systems is presented in Table 8.9. The pain index is defined in Section 8.3.4(c), and a description of the methods used to define the discrimination in Table 8.9 is provided in Section 8.8.

Table 8.9.

Pairwise agreement between 2 classification schemes systems and the Pain Index

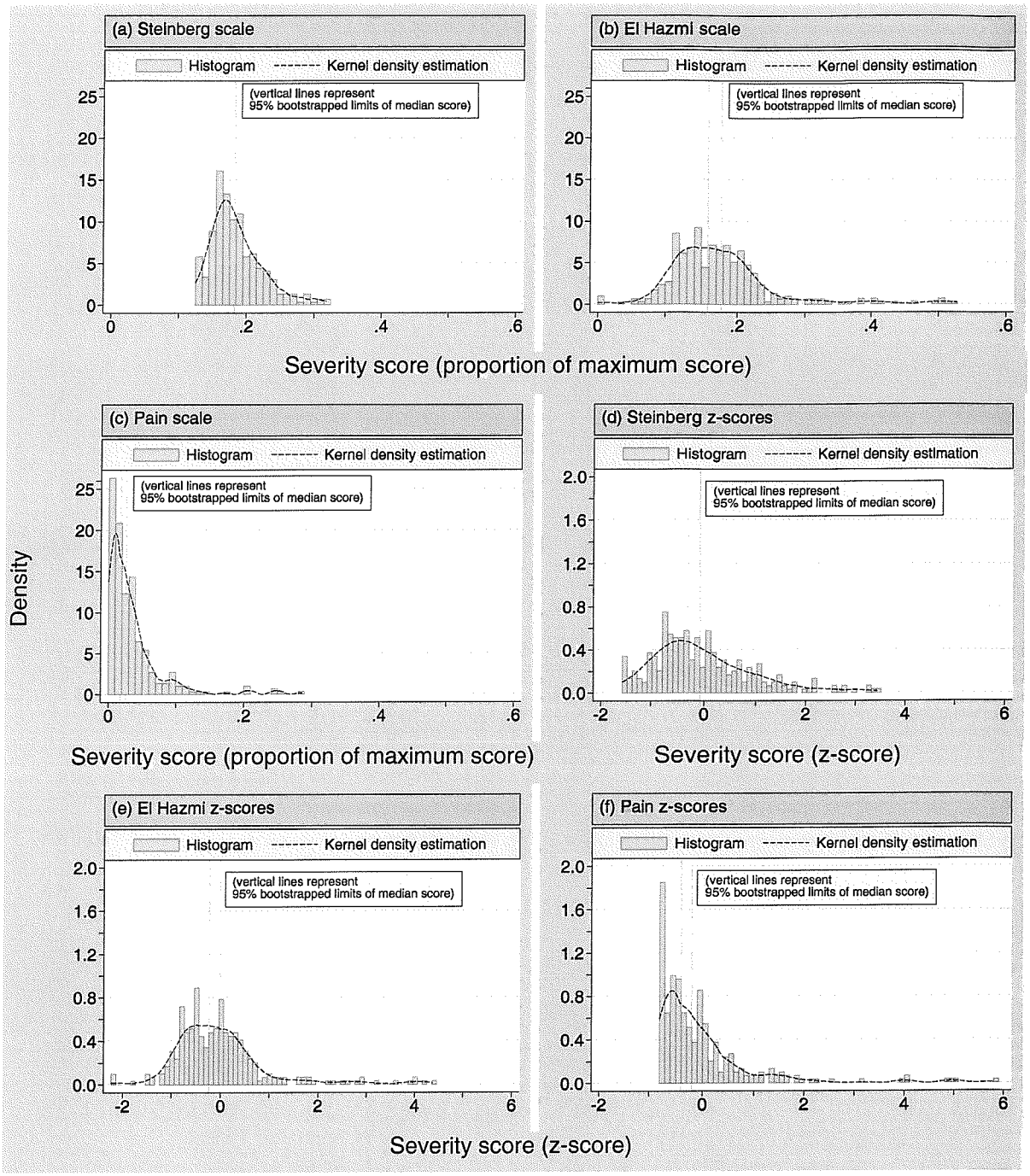
Comparison	Agreement	Interpretation % of patients (difference between indices)
Steinberg vs. El Hazmi	0.41 (0.37 - 0.45)	50% of patients (differed by 117 and 161 places)
		75% of patients (differed by 73 and 88 places)
		95% of patients (differed by 58 and 73 places)
Steinberg vs. Pain Index	0.34 (0.29 - 0.37)	50% of patients (differed by 161 and 204 places)
		75% of patients (differed by 88 and 102 places)
		95% of patients (differed by 73 and 88 places)
El Hazmi vs. Pain Index	0.34 (0.30 - 0.38)	50% of patients (differed by 161 and 204 places)
		75% of patients (differed by 88 and 102 places)
		95% of patients (differed by 73 and 88 places)

Comparing z-scores, all indices had better than random agreement with each other (Steinberg vs. El-Hazmi: observed difference, 169.9 expected difference 304.3 (95% ci 288.9 to 319.4) $p<0.001$. Steinberg vs. Pain Index: observed, 197.5 expected 292.5 (277.7 to 306.7) $p<0.001$. El-Hazmi vs. Pain Index: observed, 171.0 expected 276.0 (262.0 to 288.8) $p<0.001$). Rank agreement is presented in Table 8.9. Pairwise rank agreement ranged from 0.34 to 0.41 and was highest for the Steinberg – El Hazmi comparison. Using the simulation study described in Section 8.8, an agreement of between 0.3 and 0.4 translates to 50% of a sample differing by between 50% and 75% (out by between 146 and 219 places in a sample of 292 people).

Calibration is informally assessed using summary score distributions and are presented in Figure 8.2 as z-scores, and as a proportion of the theoretical maximum score for each classification scheme (16 for Steinberg, 14 for El Hazmi) or the practical maximum score of 13 for the pain crisis index. The two classification scheme measures indicate similar levels of median disease severity among the JSSCD patients (17.7%, 95% confidence interval 17.4 to 18.4 for the Steinberg index; 16.8%, 95% ci 15.8 to 17.8 for the El Hazmi index). The greater variability of the El-Hazmi index is partly a consequence of more index items (16 compared to 8 for Steinberg). The pain crisis index provided a narrower and more stringent measure of disease severity, with a median score of 2.1% (95% ci 1.7 to 2.6). There were no gender differences among the three indices (Steinberg: $\chi^2=1.67$ $p=0.20$, El-Hazmi: $\chi^2=1.67$ $p=0.20$, Pain crisis: $\chi^2=0.67$ $p=0.41$).

Figure 8.2

Summary distributions for Steinberg and El Hazmi classification schemes, and the pain crisis index among 292 JSSCD patients, with associated bootstrapped 95% confidence limits for the median score.



8.4.10 Generalisability of the El-Hazmi and Steinberg Composite Measurement Scales, and the pain index

All indices were applied to the same external population.

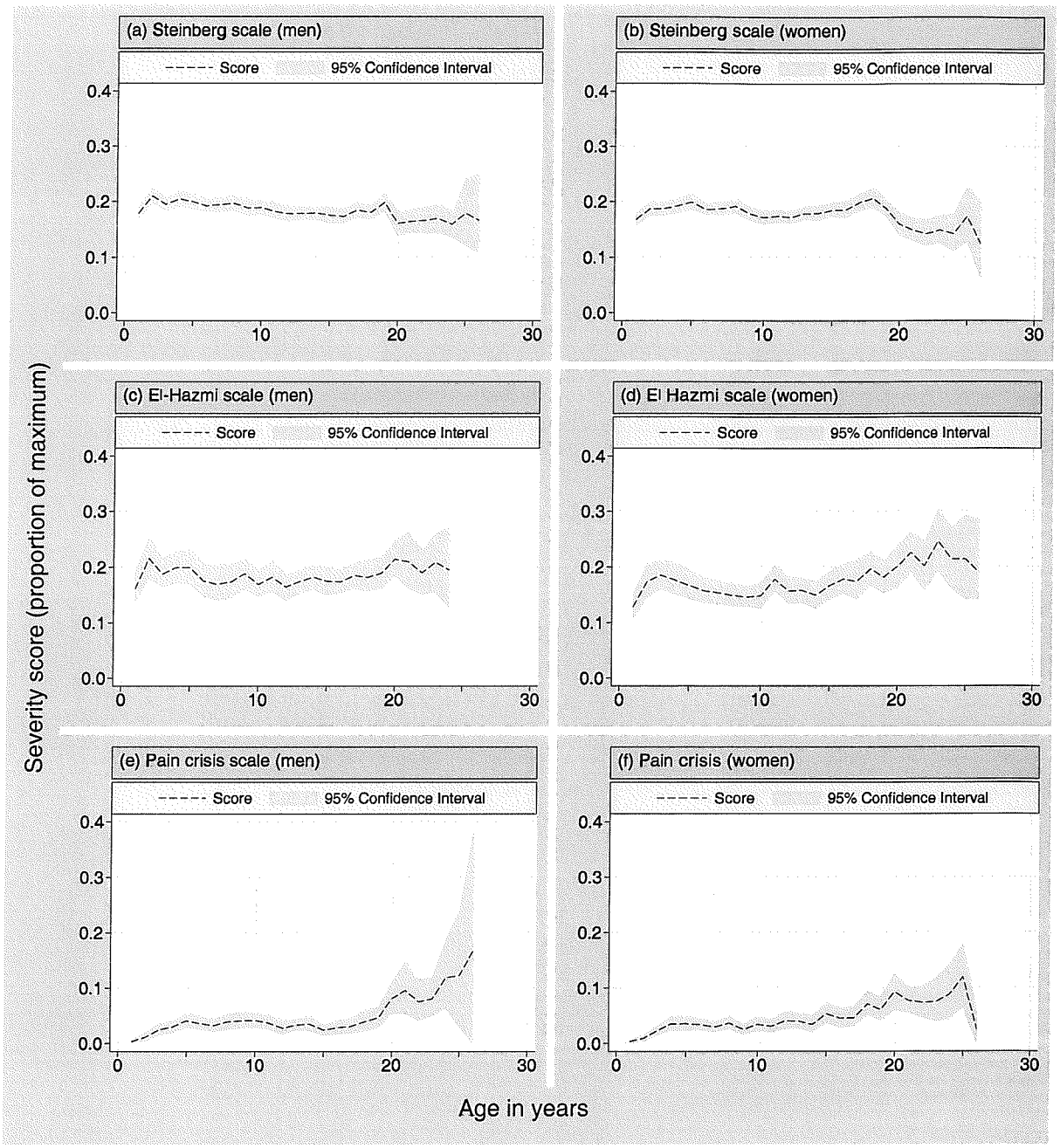
(a) Follow-up

All classification schemes were originally intended for cross-sectional use, and follow-up generalisability among the 2 schemes and the pain crisis index is presented in Figure 8.3. There

is little variation in scoring with age. The Steinberg classification scheme suggests a decreasing severity, and this is due in part to the lower severity score allocated to patients over 20 years of age. The El Hazmi classification scheme and pain crisis indices suggest a mild severity increase in early adulthood. Both the Steinberg and El-Hazmi indices include painful crisis as an item. The precision of all indices decreased beyond 18 years, as JSSCD members are currently aged between 18 and 26.

Figure 8.3

Annual severity scores by gender for 292 JSSCD patients using the Steinberg(1973), El Hazmi(1990) and pain crisis classification schemes.



8.5 Discussion

Preventive clinical procedures for the management of homozygous sickle cell disease remain invasive and costly, and carry associated risks (55-57). The possibility of identifying those most affected by the disease as primary candidates for intervention has encouraged a vocal and persistent call for methods to inform the classification of people with SS disease according to some notion of health-status (58;59). At the same time, the barriers to such a classification are widely understood (60). For a quantitative scheme to be of practical benefit, it should be capable of identifying 'severe disease' from early-life information, as the chance of success for much intervention is improved when irreversible organ damage is minimal.

The systematic review identified 17 original quantitative summaries of SS disease health-status: 14 classification schemes and 3 prediction schemes. A classification scheme quantifies a patient's health-status at a moment in time – it is a snapshot of a moving target, and as such can be of little use in the central question of whether the SS child will subsequently develop severe symptoms. Moreover, all classification schemes were constructed with little consideration for the basic tenets of good prognostic-index development (1). In particular, the psychometric properties of the schemes were not presented. The classification schemes included arbitrary features, such as item inclusion without quantitative evidence, and use of cutpoints, and there is a burden of proof on the scheme developers to substantiate these arbitrary decisions and validate the final scheme. A prediction scheme examines the predictive ability of prior events on subsequent outcome, and is likely to be a more fruitful framework for quantitative health-status assessment.

A single scheme met the minimal 'low-bias' criteria for internal validity (4). The remaining schemes had methodological problems that reduced the chance of valid and generalisable results. In particular, only 2 articles used unselected patient populations, identified by neonatal screening. The remaining articles use clinic-based patient samples, which underestimate morbidity (61) and mortality (53), and so create a biased picture of health-status.

Five schemes were examined for accuracy and generalisability: 2 prediction schemes and 3 classification schemes. The well-constructed 'low-bias' Miller prediction scheme transported reasonably well to the JSSCD in its stated aim of minimising the number of mild patients that were wrongly classfied as severe. Generally, however, accuracy of both prediction schemes was poor, and general discrimination ability was minimal. Both schemes were better at predicting who would not have a severe course than identifying who would. The three classification schemes offered alternative descriptions of severity with substantial disagreement in discrimination and calibration between schemes. With no absolute measure of accuracy possible for classification schemes the choice of scheme is important but intractable.

The ability of any scheme to successfully transport to new populations will be dependent on the relative differences in patient demographics and environmental conditions between the

original and new application environments. Specific differences between Jamaica and the original populations have been discussed. Generally, there is a trade-off between the complexity of a scheme and its ability to successfully transport, which must be guided by the specific goals of the research (62).

The failure to examine or failure of aspects of internal validity or accuracy will undermine clinical credibility, which invariably leads to rejection by the clinical community. A five-level hierarchy for examining the transportability of a scheme has recently been suggested, from prospective validation by the same authors (stage one), through a single independent validation (stage two), to multiple independent validations (stages three to five) (8). This report represents the first stage two validation for prognostic schemes in homozygous sickle cell disease. Whilst subsequent applications are crucial, good internal validity and accuracy will not guarantee the eventual acceptance of results. The likelihood that prediction rules will be accepted, and be used is increased if results make clinical sense, and are easy to interpret and use. If aspects of the study design and implementation are contentious the probability of acceptance is decreased.

8.6 Appendix One

Data collection form

Internal validation of 13 articles presenting a new prognostic index for the classification of patients according to *disease outcome* or *disease severity* in homozygous sickle cell disease.

(B) ASSESSMENT OF SEVERITY INDICES/PROGNOSTIC MODELS USED IN HOMOZYGOUS SICKLE CELL DISEASE.

- ARTICLE CHECKLIST -

Reviewer _____

Section One: Basic details of article

Article ref _____
Name of article _____
_____
Journal _____
Volume, page number _____
Primary author _____
Year of publication _____

Article Classification — **Composite Index** ☐ **Prognostic Model** ☐

Aim of Study — **Complete validation** ☐ **Partial validation** ☐ **Other objective** ☐

State other:

Composite Index: All sections except 4
Prognostic Model: All sections except 5

Section Two: Variables included in index/final model : Listing

List under following categories:
1. Patient characteristics, 2. Hematology, 3. Genetic, 4. Biochemical,
5. Clinical, 6. Anthropometry, 7. Environmental, 8. Psychosocial,
9. Confounder, 10. Composite, 11. Other

Section Three: General characteristics of measurement scales

Variables included in final model/index
Total number
Number of categories covered
Number of composite variables used

Type of scales of variables in final model/index (enter the number of variables with that scale)
Nominal
Ordinal
Interval
Ratio
Not stated

Type of measurement scale of the outcome variable
Nominal
Ordinal
Interval
Ratio
Not stated

Subscales/Subgroupings
None
≤ 3 groups
> 3 groups

Section four: Statistical methods for construction and validation of prognostic models

Type of model used to select candidate predictor variables
Normal regression
Logistic regression
Cox survival model
Recursive partitioning
Other model type _____

Method of variable selection
Not stated
Univariate
All included
Stepwise procedure
Best subset analysis
Other _____

Selection model assumptions
Checked
Not stated
Partly checked

Selection model fit
Checked
Not stated

Type of final prediction model
- Coefficients for a normal regression ☐
- Coefficients for a logistic regression ☐
- Coefficients for a cox regression ☐
- Prognostic tree ☐
- Graphical ☐
- Other _____

Final model assumptions
- Checked ☐
- Not stated ☐
- Partly checked ☐

Evaluation of final model (predicted vs observed)
- Performed ☐
- Not performed ☐
- State method if performed _____

Validation of final model
- Not performed ☐
- Internal ☐
- Temporal ☐
- External ☐
- Other _____

Internal validation (if yes)
- Cross validation ☐
- Data-splitting ☐
- Bootstrap ☐
- Other _____

Adjustment for overoptimism
- Performed ☐
- Not performed ☐
- State method if performed _____

Section Five: Statistical methods for construction, analysis and validity of composite indices

Scoring System
- No details ☐
- Boolean ☐
- Simple sum ☐
- Normalized (0 to 100) sum ☐
- Weighted sum ☐
- Other _____

Summary measures of index
- None ☐
- Mean ☐
- Median ☐
- Variance or confidence interval ☐
- Range or IQR ☐
- Frequency distribution of scores ☐
- Number or % of patients in subgroup ☐
- Other _____

Type of analysis used with index
- None ☐
- Parametric ☐
- Nonparametric ☐
- State methods used _____

Content validity (any aspect)
- Not considered ☐
- Considered ☐
- Details if considered _____

Construct validity (any aspect)
- Not considered ☐
- Considered ☐
- Details if considered _____

Reliability (any aspect)
- Not considered ☐
- Considered ☐
- Details if considered _____

Sensitivity to change (in time)
- Not considered ☐
- Considered ☐
- Details if considered _____

Section Six: Clinical validation of Final Model/Index

Instructions for practical use
Provided and clear ☐
Provided but unclear ☐
Not given ☐

Data required usually collected (enter number of variables)
Yes ☐
No ☐

Clear definitions of variables (enter number of variables)
No definitions provided ☐
Yes ☐
No ☐

Definitions generally accepted if yes to above (enter number of variables)
Yes ☐
No ☐

Use of arbitrary thresholds
Yes ☐
No ☐

Biological Rationale for predictors (enter no. of variables or 999 for n/a)
Yes ☐
No ☐

Biological Rationale for endpoints (enter number of variables)
Yes ☐
No ☐

Comprehensibility (i.e.clinical coverage of index/predicor variables)
Not considered ☐
Considered ☐
Details if considered _____

Can model/index be applied
Yes, to individuals ☐
Yes, to a group ☐
No, not enough information ☐

Section Seven: Utilization of the index

Has the model index been used in other severity studies
Yes, exactly (state number) ☐ of which creator of index is an author ☐
Yes, modified (state number) ☐ of which creator of index is an author ☐
No ☐

List of references that have used the index/model exactly (state if author of index)	*List of references that have modified index/model (state if author of index)*

8.7 Appendix Two

Articles containing prognostic indices of disease outcome

(D.1) Steinberg MH, Dreiling BJ, Morrison FS, Necheles TF. Mild sickle cell disease. Clinical and laboratory studies. JAMA 1973; 224(3):317-321.

(D.2) Gaston MH, Fobi MAL. Sickle cell disease in children, a spectrum of illness. In: Cabannes R, editor. La Drepanocytose - Sickle Cell Anemia. Paris: INSERM, 1975: 19-32.

(D.3) Bienzle U, Sodeinde O, Effiong CE, Luzzatto L. Glucose 6-phosphate dehydrogenase deficiency and sickle cell anemia: frequency and features of the association in an African community. Blood 1975; 46(4):591-597.

(D.4) Odenheimer DJ, Whitten CF, Rucknagel DL, Sarnaik SA, Sing CF. Heterogeneity of sickle-cell anemia based on a profile of hematological variables. Am J Hum Genet 1983; 35(6):1224-1240.

(D.5) Cameron BF, Christian E, Lobel JS, Gaston MH. Evaluation of clinical severity in sickle cell disease. J Natl Med Assoc 1983; 75(5):483-487.

(D.6) Pajot N, Maier-Redelsperger M, Dode C, Labie D, Girot R. Density distribution of red cells and prognostic significance in 50 patients with homozygous sickle-cell disease. Haematologia (Budap) 1988; 21(4):189-197.

(D.7) Keidan AJ, Sowter MC, Johnson CS, Noguchi CT, Girling AJ, Stevens SM et al. Effect of polymerization tendency on haematological, rheological and clinical parameters in sickle cell anaemia. Br J Haematol 1989; 71(4):551-557.

(D.8) Bordin JO, Kerbauy J, Lourenco DM, Sesso R. Level of fetal hemoglobin as an indicator of clinical complications in sickle cell anemia. Braz J Med Biol Res 1989; 22(11):1347-1353.

(D.9) El-Hazmi MA, Bahakim HM, al-Swailem AM, Warsy AS. The features of sickle cell disease in Saudi children. J Trop Pediatr 1990; 36(4):148-155.

(D.10) Olatunji PO, Falusi AG. Persistent hepatomegaly: an index of severity in sickle cell anaemia. East Afr Med J 1994; 71(11):742-744.

(D.11) Thomas PW, Higgs DR, Serjeant GR. Benign clinical course in homozygous sickle cell disease: a search for predictors. J Clin Epidemiol 1997; 50(2):121-126.

(D.12) Houston PE, Rana S, Sekhsaria S, Perlin E, Kim KS, Castro OL. Homocysteine in sickle cell disease: relationship to stroke. Am J Med 1997; 103(3):192-196.

(D.13) Ievers CE, Brown RT, Lambert RG, Hsu L, Eckman JR. Family functioning and social support in the adaptation of caregivers of children with sickle cell syndromes. J Pediatr Psychol 1998; 23(6):377-388.

(D.14) Anyaegbu CC, Okpala IE, Akren'Ova YA, Salimonu LS. Peripheral blood neutrophil count and candidacidal activity correlate with the clinical severity of sickle cell anaemia (SCA) [letter]. Eur J Haematol 1998; 60(4):267-268.

(D.15) Diop S, Thiam D, Cisse M, Toure-Fall AO, Fall K, Diakhate L. New results in clinical severity of homozygous sickle cell anemia, in Dakar, Senegal. Hematol Cell Ther 1999; 41(5):217-221.

(D.16) Miller ST, Sleeper LA, Pegelow CH, Enos LE, Wang WC, Weiner SJ et al. Prediction of adverse outcomes in children with sickle cell disease. N Engl J Med 2000; 342(2):83-89.

8.8 Appendix Three

We explored the level of discrimination between the composite measurement scales using two Monte Carlo simulations: one to examine the level of agreement between competing indices, and a second to interpret the observed agreement in terms of the relative ordering of patients under competing classification schemes.

(a) Observed agreement

We applied two composite measurement scales (11;17) and the Pain Index to a single population (the JSSCD) and standardised scores as z-scores, so that each person has three scores, 1 from each index. Pairwise differences between z-scores were computed for each person and these differences summarised as a total difference for the whole sample (*observed difference*).

A set of two random vectors of z-scores was simulated and differences between z-scores computed as before. This simulation was repeated 5000 times to produce a distribution of random z-score differences (*expected difference*). Observed and expected differences were compared to obtain an exact p-value that describes the probability of obtaining an expected difference as or more extreme than the observed difference.

Observed agreement was calculated as (observed – expected / expected) and can be any value between 0 and 1, where 1 is perfect agreement and 0 is random agreement. The interpretation of the levels of observed agreement, described in terms of the relative ordering of patients under competing classification schemes, was provided by a second simulation study.

(b) Interpretation of observed agreement

Two vectors of ranks were simulated to create a pre-defined percentage of the sample (5%, 10% and so on) with a rank order differing by 5%, 10% and so on (in the current sample of 292 patients, 5%=15 places, 10%=29 places and so on). Pairwise differences between ranks were computed for each person and these differences summarised as a total difference for the whole sample (*observed difference*). A set of two random vectors was simulated as before, and a total expected difference calculated using ranks instead of z-scores.

Table 8.10.

Simulated agreement for different percentages of a sample varying by differing numbers of places

Sample	Discrepancy (%)						
(%)	5	10	25	50	75	90	95
5	0.992	0.985	0.962	0.928	0.894	0.885	0.878
10	0.985	0.970	0.928	0.861	0.815	0.788	0.782
25	0.961	0.926	0.824	0.695	0.617	0.590	0.562
50	0.922	0.854	0.663	0.418	0.275	0.273	0.256
75	0.884	0.778	0.472	0.098	0	0	0
90	0.861	0.732	0.344	0	0	0	0
95	0.854	0.719	0.303	0	0	0	0

Agreement was calculated under the various levels of simulated difference, and these levels of agreement are presented in Table 8.10, which can be used for interpretation of agreement. For example an agreement of 0.5 relates to 25% of the sample out by over 95% (277 places), or 50% of the sample out by between 25 and 50% (73 to 146 places), or 75% of the sample out by approximately 25% (73 places) and so on.

8.9 Reference List

(1) Coste J, Fermanian J, Venot A. Methodological and statistical problems in the construction of composite measurement scales: a survey of six medical and epidemiological journals. Stat Med 1995; 14(4):331-345.

(2) Clarke M, Oxman A. Assessment of study quality. Cochrane Reviewers' Handbook 4.1 [updated June 2000]. Review Manager (RevMan) [Computer Program]. Version 4.1. Oxford, England: The Cochrane Collaboration, 2000.

(3) Harrell FE, Jr., Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med 1996; 15(4):361-387.

(4) Miller ST, Sleeper LA, Pegelow CH, Enos LE, Wang WC, Weiner SJ et al. Prediction of adverse outcomes in children with sickle cell disease. N Engl J Med 2000; 342(2):83-89.

(5) Ferster A, Vermylen C, Cornu G, Buyse M, Corazza F, Devalck C et al. Hydroxyurea for treatment of severe sickle cell anemia: a pediatric clinical trial. Blood 1996; 88(6):1960-1964.

(6) de Montalembert M, Belloy M, Bernaudin F, Gouraud F, Capdeville R, Mardini R et al. Three-year follow-up of hydroxyurea treatment in severely ill children with sickle cell disease. The French Study Group on Sickle Cell Disease. J Pediatr Hematol Oncol 1997; 19(4):313-318.

(7) Charache S, Terrin ML, Moore RD, Dover GJ, Barton FB, Eckert SV et al. Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. Investigators of the Multicenter

Study of Hydroxyurea in Sickle Cell Anemia [see comments]. N Engl J Med 1995; 332(20):1317-1322.

(8) Justice AC, Covinsky KE, Berlin JA. assessing the generalizability of prognostic information. Annals of Internal Medicine 1999; 130:515-524.

(9) Odenheimer DJ, Whitten CF, Rucknagel DL, Sarnaik SA, Sing CF. Heterogeneity of sickle-cell anemia based on a profile of hematological variables. Am J Hum Genet 1983; 35(6):1224-1240.

(10) Bordin JO, Kerbauy J, Lourenco DM, Sesso R. Level of fetal hemoglobin as an indicator of clinical complications in sickle cell anemia. Braz J Med Biol Res 1989; 22(11):1347-1353.

(11) Steinberg MH, Dreiling BJ, Morrison FS, Necheles TF. Mild sickle cell disease. Clinical and laboratory studies. JAMA 1973; 224(3):317-321.

(12) Gaston MH, Fobi MAL. Sickle cell disease in children, a spectrum of illness. In: Cabannes R, editor. La Drepanocytose - Sickle Cell Anemia. Paris: INSERM, 1975: 19-32.

(13) Bienzle U, Sodeinde O, Effiong CE, Luzzatto L. Glucose 6-phosphate dehydrogenase deficiency and sickle cell anemia: frequency and features of the association in an African community. Blood 1975; 46(4):591-597.

(14) Cameron BF, Christian E, Lobel JS, Gaston MH. Evaluation of clinical severity in sickle cell disease. J Natl Med Assoc 1983; 75 (5):483-487.

(15) Pajot N, Maier-Redelsperger M, Dode C, Labie D, Girot R. Density distribution of red cells and prognostic significance in 50 patients with homozygous sickle-cell disease. Haematologia (Budap) 1988; 21(4):189-197.

(16) Keidan AJ, Sowter MC, Johnson CS, Noguchi CT, Girling AJ, Stevens SM et al. Effect of polymerization tendency on haematological, rheological and clinical parameters in sickle cell anaemia. Br J Haematol 1989; 71(4):551-557.

(17) El-Hazmi MA, Bahakim HM, al-Swailem AM, Warsy AS. The features of sickle cell disease in Saudi children. J Trop Pediatr 1990; 36(4):148-155.

(18) Olatunji PO, Falusi AG. Persistent hepatomegaly: an index of severity in sickle cell anaemia. East Afr Med J 1994; 71(11):742-744.

(19) Thomas PW, Higgs DR, Serjeant GR. Benign clinical course in homozygous sickle cell disease: a search for predictors. J Clin Epidemiol 1997; 50(2):121-126.

(20) Houston PE, Rana S, Sekhsaria S, Perlin E, Kim KS, Castro OL. Homocysteine in sickle cell disease: relationship to stroke . Am J Med 1997; 103(3):192-196.

(21) Anyaegbu CC, Okpala IE, Akren'Ova YA, Salimonu LS. Peripheral blood neutrophil count and candidacidal activity correlate with the clinical severity of sickle cell anaemia (SCA) [letter]. Eur J Haematol 1998; 60(4):267-268.

(22) Ievers CE, Brown RT, Lambert RG, Hsu L, Eckman JR. Family functioning and social support in the adaptation of caregivers of children with sickle cell syndromes. J Pediatr Psychol 1998; 23(6):377-388.

(23) Diop S, Thiam D, Cisse M, Toure-Fall AO, Fall K, Diakhate L. New results in clinical severity of homozygous sickle cell anemia, in Dakar, Senegal. Hematol Cell Ther 1999; 41(5):217-221.

(24) Steinberg MH, Dreiling BJ, Lovell WJ. Sickle cell anemia: erythrokinetics, blood volumes, and a study of possible determinants of severity. Am J Hematol 1977; 2(1):17-23.

(25) El Hazmi MA, Warsy AS. On the molecular interactions between alpha-thalassaemia and sickle cell gene. J Trop Pediatr 1993; 39(4):209-213.

(26) Steinberg MH, Eaton JW, Berger E, Coleman MB, Oelshlegel FJ. Erythrocyte calcium abnormalities and the clinical severity of sickling disorders. Br J Haematol 1978; 40(4):533-539.

(27) Hebbel RP, Boogaerts MA, Eaton JW, Steinberg MH. Erythrocyte adherence to endothelium in sickle-cell anemia. A possible determinant of disease severity. N Engl J Med 1980; 302(18):992-995.

(28) Schacter LP, DelVillano BC, Gordon EM, Klein BL. Red cell superoxide dismutase and sickle cell anemia symptom severity. Am J Hematol 1985; 19(2):137-144.

(29) Eluwa EO, Obidoa O, Obi GO, Onwubiko HA . Variations in the relative activities of erythrocyte membrane ATPase with changes in severity of sickle cell anemia. Biochem Med Metab Biol 1987; 38(2):142-148.

(30) El Hazmi MA, Bahakim HM, Babikar MA, al Swailem AM, Warsy AS. Symptom-free intervals in sicklers: does pneumococcal vaccination and penicillin prophylaxis have a role? J Trop Pediatr 1990; 36(2):56-62.

(31) El Hazmi MA, Bahakim HM, al Fawaz I. Endocrine functions in sickle cell anaemia patients. J Trop Pediatr 1991; 38(6):307-313.

(32) El Hazmi MA. Clinical and haematological diversity of sickle cell disease in Saudi children. J Trop Pediatr 1992; 38(3):106-112.

(33) Keidan AJ, Sowter MC, Johnson CS, Noguchi CT, Girling AJ, Stevens SM et al. Effect of polymerization tendency on haematological, rheological and clinical parameters in sickle cell anaemia. Br J Haematol 1989; 71(4):551-557.

(34) El Hazmi MA, Warsy AS, al Momen A, Harakati M. Hydroxyurea for the treatment of sickle cell disease. Acta Haematol 1992; 88(4):170-174.

(35) Phillips G, Tangney CC. Relationship of plasma alpha tocopherol to index of clinical severity in individuals with sickle cell anemia. Am J Hematol 1992; 41(4):227-231.

(36) Hedo CC, Aken'ova YA, Okpala IE, Durojaiye AO, Salimonu LS. Acute phase reactants and severity of homozygous sickle cell disease. J Intern Med 1993; 233(6):467-470.

(37) Poillon WN, Kim BC, Castro O. Intracellular hemoglobin S polymerization and the clinical severity of sickle cell anemia . Blood 1998; 91(5):1777-1783.

(38) Hedo C, Aken'Ova Y, Okpala I, Salimonu L. Serum immunoglobulin (G, A and M) classes and IgG subclasses in sickle cell anaemia. APMIS 1993; 101(5):353-357.

(39) El Hazmi MA. The relationship of the genetic heterogeneity of sickle cell gene to clinical manifestations. J Trop Pediatr 1993; 39(1):23-29.

(40) El Hazmi MA, Warsy AS, Bahakim H. Blood proteins C and S in sickle cell disease. Acta Haematol 1993; 90(3):114-119.

(41) Hedo CC, Okpala IE, Aken'ova YA. Foetal haemoglobin levels in Nigerians with sickle cell anaemia. A revisitation. Trop Geogr Med 1993; 45(4):162-164.

(42) El Hazmi MA, Warsy AS, Al Swailem AR, Al Faleh FZ, al Jabbar FA. Genetic compounds--Hb S, thalassaemias and enzymopathies: spectrum of interactions. J Trop Pediatr 1994; 40(3):149-156.

(43) al Momen AK. Diminished vitamin B12 levels in patients with severe sickle cell disease. J Intern Med 1995; 237(6):551-555.

(44) El Hazmi MA, Bahakim HM, Warsy AS, al Momen A, al Wazzan A, al Fawwaz I et al. Does G gamma/A gamma ratio and Hb F level influence the severity of sickle cell anaemia. Mol Cell Biochem 1993; 124(1):17-22.

(45) El Hazmi MA. Heterogeneity and variation of clinical and haematological expression of haemoglobin S in Saudi Arabs. Acta Haematol 1992; 88(2-3):67-71.

(46) El Hazmi MA, Bahakim HM, Warsy AS. DNA polymorphism in the beta-globin gene cluster in Saudi Arabs: relation to severity of sickle cell anaemia. Acta Haematol 1992; 88(2-3):61-66.

(47) El Hazmi MA, al Momen A, Kandaswamy S, Huraib S, Harakati M, al Mohareb F et al. On the use of hydroxyurea/erythropoietin combination therapy for sickle cell disease. Acta Haematol 1995; 94(3):128-134.

(48) Armitage P, Berry G. Statistical Methods in Medical Research. Oxford: Blackwell, 1994.

(49) Anyaegbu CC, Okpala IE, Akren'Ova YA, Salimonu LS. Peripheral blood neutrophil count and candidacidal activity correlate with the clinical severity of sickle cell anaemia (SCA) [letter]. Eur J Haematol 1998; 60(4):267-268.

(50) Costa FF, Arruda VR, Goncalves MG, Miranda SR, Carvalho MH, Sonati MF et al. Beta S-gene-cluster haplotypes in sickle cell anemia patients from two regions of Brazil [letter]. Am J Hematol 1994; 45(1):96-97.

(51) Eckman JR. Leg ulcers in sickle cell disease. Hematol Oncol Clin North Am 1996; 10(6):1333-1344.

(52) Platt OS, Brambilla DJ, Rosse WF, Milner PF, Castro O, Steinberg MH et al. Mortality in sickle cell disease. Life expectancy and risk factors for early death [see comments]. N Engl J Med 1994; 330(23):1639-1644.

(53) Wierenga KJ, Hambleton IR, Lewis NA. Survival estimates for patients with homozygous sickle-cell disease in Jamaica: a clinic-based population study. Lancet 2001; 357(9257):680-683.

(54) Lee A, Thomas P, Cupidore L, Serjeant B, Serjeant G. Improved survival in homozygous sickle cell disease: lessons from a cohort study. BMJ 1995; 311(7020):1600-1602.

(55) Walters MC, Patience M, Leisenring W, Eckman JR, Scott JP, Mentzer WC et al. Bone marrow transplantation for sickle cell disease [see comments]. N Engl J Med 1996; 335(6):369-376.

(56) Scott JP, Hillery CA, Brown ER, Misiewicz V, Labotka RJ. Hydroxyurea therapy in children severely affected with sickle cell disease. J Pediatr 1996; 128(6):820-828.

(57) Reed WF, Vichinsky EP. Transfusion practice for patients with sickle cell disease. Curr Opin Hematol 1999; 6(6):432-436.

(58) Smith KD. Assessment of clinical severity of sickle cell disease. In: Knakoo Y, Davis H, editors. Academic Press, New York, 1978: 77-91.

(59) Powars DR. Progress in the natural history studies of the clinical severity of sickle cell disease. Academic Press, New York, 1978: 151-164.

(60) Steinberg MH. The difficulty and paradox of assessing clinical severity of sickle cell anaemia. In: Beuzard Y, Charache S, Galacteros F, editors. Approaches to the therapy of sickle cell anaemia. Paris: INSERM, 1986: 457-470.

(61) Magnus SA, Hambleton IR, Moosdeen F, Serjeant GR. Recurrent infections in homozygous sickle cell disease. Arch Dis Child 1999; 80(6):537-541.

(62) Kirshner B, Guyatt G. A methodological framework for assessing health indices. J Chron Dis 1985; 38(1):27-36.

Chapter 9

Summary

9.1 The Jamaican Study of Sickle Cell Disease in 2003

Last year, the JSSCD celebrated its 30th anniversary. Since its inception in 1973, the many hundreds of researchers involved with the study have produced a prodigious literature on many aspects of the disease, from basic epidemiology to successful clinical interventions to genetic advances. The continual (and continuing) clinical epidemiology that has been a hallmark of the study has ensured an enviable international research reputation for the Jamaican sickle-cell unit. For most of these 30 years Graham Serjeant (now Emeritus Professor at the University of the West Indies) guided the fortunes of the Unit. The success and longevity of the Unit and of the JSSCD are due largely to his considerable efforts, and also to the dedication of the clinic staff, and the willingness and cooperation of the study participants.

But the study has grown beyond the research. It has become a way of life for over 700 participants, and for over 300 members with SS disease it has provided the security of specialist clinical care in a familiar environment.

The JSSCD today remains an active and important resource. It is the longest running cohort study on sickle-cell disease and is the only ongoing birth cohort studying adults with the disease. Its longevity has allowed researchers to amass an unrivalled data resource on the life-course of people with the disease, and we are only now beginning to tap the enormous potential of this longitudinal databank.

9.2 The challenges facing SCD epidemiology

In chapter one we identified three major challenges facing SCD epidemiology: an incomplete natural history of the disease, how to recruit study participants and define haematology and clinical endpoints in ways that minimise study bias, and how to predict SCD health-status. Through most of the thesis we have investigated aspects of these challenges.

9.2.1 Incomplete natural history of SCD

Researchers have been describing the clinical expression of SCD for over 60 years, but many of these published observations rely on clinically ascertained study participants with known biases. Many more aspects of the disease remain poorly defined, often because study populations (such as the very young or the old) are not readily available.

The JSSCD participants were recruited at birth and followed regularly thereafter and so represent a remarkably detailed account of the first 30 years of life. We have used this strength in our descriptions of haematology (chapter 5) and clinical outcomes (chapter 6), and in our series of clinical case studies. We planned these descriptions as the backbone of this thesis, and we have also expanded the thesis to consider the more general notion of how research methodology in SCD affects conclusions concerning the clinical course and health-status of people with the disease.

9.2.2 Minimising study bias 1: Participant recruitment

In chapters 3 and 4 we have described how methods of identifying, recruiting, and following-up people with SCD can influence clinical care, public health policymaking, and clinical research. In chapter 3 we have shown that without a national neonatal screening programme, then in the first few years of life (when penicillin prophylaxis plays a crucial role in preventive management) up to 90% of all SS children will not have enrolled to a specialist clinic. Moreover, we suggest that up to 50% of people with the disease may not receive specialist care in childhood. Comprehensive neonatal screening does not exist in many of the resource-poor countries where SCD is a significant problem (using WHO criteria), and programmes for systematic disease identification, with regular follow-up thereafter must be a funding priority in these settings.

This incomplete and delayed patient enrolment leads us to underestimate the size, morbidity, and mortality of the patient population (the burden of disease); we are effectively pushing the disease underground. We might expect this low disease-visibility to translate into inadequate resources allocated to cope with the true disease burden.

Also, because most SCD researchers still choose cross-sectional clinic-based populations their studies present biased descriptions of disease morbidity. Moreover, many studies are contradictory, and often disagree partly due to different study methods or participants with different disease characteristics (age for example will dramatically alter the incidence of most clinical sequelae of the disease). If we continue to ignore the limitations of studying these biased populations we will continue in our circular epidemiology of contradiction without progress. In chapter six (section 6.3.6) we have estimated the bias inherent in clinical event reporting, and have shown how statistical methods can be used to reduce these biases. We have offered guidelines for when an accepted statistical adjustment can work well, but it will not always be appropriate. In case study 5 we have presented a new adjustment method, which has allowed us to report new and encouraging figures on lifetime survival in SS disease; between 54 and 71 for women and between 49 and 59 for men. We were also able to show that the marked difference between our results and those from the US was entirely due to the method used to adjust for bias in the study population.

9.2.3 Minimising study bias 2: Participant follow-up

In chapter 4 we have reported that dropout due to death in the JSSCD is high, and is an inevitable consequence of studying a life-threatening condition for a long period of time. Death of a cohort member was always a cause for sadness, but was always important information in our attempts to understand and minimise future mortality. Even default, which we attempted to minimise with active and persistent methods of follow-up, has provided us with information: we now know that the percentage of missed appointments is a strong predictor for subsequent death, and this provides us with a potential avenue for clinical intervention. Most importantly, we have shown that participants that default or dropout have different levels of haematology and different clinical expressions, which has consequences for how we analyse observational studies in sickle-cell disease.

In chapter 5 we reported important differences in haematology among SS disease defaulters that survived and SS disease defaulters that died. In those that have survived we report increased levels of haemoglobin concentration, haematocrit, and fetal haemoglobin which together suggest a milder haematological expression. In those that have died we report increased reticulocytosis. These results support (for the first time) the original theory of biased clinic populations suggested by the Jamaican SCU in the 1970s - that people with SCD do not attend clinics for two competing reasons: they have severe expression of the disease and possibly die before presenting to clinic, or they have mild disease expression and rarely need to present to clinic.

9.2.4 Minimising study bias 3: Steady-state haematology

Methods to describe and to model haematological indices must be sensitive to their non-linear associations with age. In chapter 5 we have described and implemented several useful strategies for modelling haematology, and have used these procedures to model 10 haematological indices from birth to 18 years of age, which extends an original description from birth to 6 years of age (1).

Steady-state haematology is a fundamental exclusion criterion in SCD risk-factor epidemiology. Haematology in the young child (less than 5 years old) is regularly discarded as an unrepresentative period, but in chapter 5 we have shown that the period between birth and 5 years of age can be modelled successfully.

9.2.5 Health-status

Health status in SCD has received many journal column inches in recent years. The possibility of identifying those most affected by the disease as candidates for clinical intervention has encouraged a vocal and persistent call for methods to inform the classification of SS disease according to some notion of health.

However, we have shown using a systematic literature review in chapter seven that our desire for a clinically meaningful classification of SCD is not yet matched by published work. The literature is currently confused and contradictory, and few articles meet minimal criteria for acceptable design. In chapter eight we have provided the first external validation of several promising articles offering health status prediction schemes. We can verify the prognostic ability of a single article if subsequent application matches the goal of that index (2). Generally, however, the models do not transport well to our Jamaican population.

9.3 The future

9.3.1 Consensus on definitions and best-practice

Definitions and best-practice in SCD research are urgently needed. Definitions and standards are available at the many SCD research centres around the world; the standards of each centre are usually developed by clinicians and are sensible. But without an evidence-base or a general consensus, 'standard' practice will continue to vary between the centres and their publications, making the comparison of articles difficult. International action is required to develop best-practice, and should begin with a consensus meeting to identify the issues and the path forward.

9.3.2 Larger international studies

The descriptions of disease aetiology have been led by two SCD cohorts: the JSSCD in Jamaica, and the Cooperative Study of Sickle-Cell Disease (CSSCD) in the US. These cohorts were each developed in the 1970s to describe the natural history of the disease in children, and they were suitably powered to meet their goals. Publications continue from both studies, and commonly the questions asked of these cohorts go beyond the original aims; complex statistical models and genetic studies will often be insufficiently powered using these cohorts.

If new observational work is to continue in SCD, we must consider a new paradigm for our study populations. It is not unrealistic to consider a multi-centre cohort design with participating centres collecting information using a standardized patient entry system. Such a design will allow a study with considerably greater power than has been available. Additionally, it will pave the way for international comparisons of the disease, which will become increasingly important as the search for environmental causes of variation in disease expression gathers pace.

9.3.3 The prediction of health status

The prediction of health status is perhaps the greatest research challenge facing the disease. We have described our initial efforts in this thesis to document the state of play in SCD health status research. We have concluded that Miller and colleagues have provided the best health status prediction model to date, using early-life events and sound statistical procedures to predict future adverse clinical outcomes (2). Despite this, the model does not transport well to other SCD populations, and it is unlikely to receive the clinical credibility it

needs for general acceptance. An important question now faces us. Can any single research centre improve upon this well-constructed model? Indeed, can SCD health-status ever be predicted? To make further progress we certainly need to consider major shifts in the methods we use to develop our models.

Firstly, we must draw on international groups of participants, and create models that include international validation as part of their development process. An early example of such modelling is described in our ongoing study below (section 9.3.5(c)). Secondly, we must reconsider the 'classical' risk factors for adverse outcome: early-life events and 'steady-state' haematology. Early-life events are not easily analyzable using current cohorts – the events are not available in large numbers, and so the power to detect meaningful differences in multiple regression models is probably inadequate. More fundamentally, many of the clinical events that might define 'adverse health outcome' (such as stroke, ACS, or the painful crisis) are acute and short lived, and we should question the ability of underlying, chronic (or steady-state) measures of haematology to accurately predict these outcomes. By definition, non-steady-state haematology are currently discarded as unrepresentative periods in a patient's life. Yet paradoxically, it is these acute phases that define the disease. Perhaps the use of non-steady-state haematology as alternative or supplementary risk factors may ultimately allow an improved prediction of health outcome.

9.3.4 Updating our description of the disease

Our ability to manage the disease contributes to the definition of the disease at any point in time. As our management techniques improve we hope to reduce the clinical impact of the disease, and so bring about a corresponding improvement in quality of life. This process has consequences for SCD research. Clinical epidemiology reports a snapshot in time, and we must be vigilant and sensitive to secular changes in clinical outcomes. Regular updates to our clinical descriptions are required to monitor our changing ability to cope with the clinical sequelae of the disease. Health-status will be affected by these secular changes, and we should be careful to define health-status in ways that are not overly sensitive to secular variation.

9.3.5 Ongoing studies and other work

There are currently three major ongoing studies, which we describe below. These three studies were originally integral aspects of this doctoral thesis. We soon realized that the prerequisite information for these studies was itself a major undertaking, and the original studies were downgraded to descriptions of future work.

(a) The hematological steady-state

The haematological steady-state is a fundamental inclusion criterion in sickle-cell disease risk factor epidemiology. An accepted steady-state definition is not available. Definitions are generally based on clinical expertise, and substantial variation between study centres is appar-

ent. In this ongoing study we will highlight and quantify the level of variability in the haematological steady-state definition. We will quantify the practical effects of this variability on risk factor conclusions. We will develop a new steady-state definition using an unselected neonatal cohort and Bayesian statistical principles, and we will compare this new definition with currently available steady-state criteria. By definition, non-steady-state haematology are currently discarded as unrepresentative periods in a patient's life. Yet paradoxically, it is these acute phases that define the disease. For the first time we will use non-steady-state haematology as alternative or supplementary risk factors for predicting clinical outcome.

(b) Haematological reference intervals

For the physician, an important tool in the clinical management of the sickle-cell patient is the comparison of pertinent haematology collected during a clinical event with known steady-state levels for the patient. The size of the departure can inform the physician about the progression and severity of the event. Such comparisons are only possible if the patient has a recorded steady-state history, collected during asymptomatic visits to their healthcare provider. Moreover, steady-state levels of much haematology change as the patient ages, and without ongoing attendance during asymptomatic periods, a patient's known steady-state levels soon become obsolete. Our proposed study will develop age-related reference intervals (RIs) for ten haematological indices that have a practical clinical application, which we have described in our introduction to Book Two. The study will have two components:

Development. We will construct *size* RIs that are appropriate for comparing single values from an individual with an appropriate reference population. We will construct *growth* RIs that are appropriate for tracking an individual's changing haematological picture against the reference population. Our reference population will be the 315 SS participants from the JSSCD (165 men and 150 women).

Publication. We will initially publish our findings in peer reviewed journals. We will disseminate our findings to practising clinics in practical formats, using a dedicated website, and specially developed software.

(c) Predicting health-status in the JSSCD

Sickle-cell disease is characterised by a variable clinical course between individuals, and within individuals as they age. This variability poses a challenge to clinical trials of interventions for sickle-cell disease, which aim to reduce clinical complications. Power calculations often require many hundreds of patients followed over several years, making the development of new therapies a long-term process.

Biomarkers are measurable biological features that predict a clinical outcome, and which can be measured (with greater accuracy) earlier in the disease process. Their use as primary outcomes can reduce the required sample size and trial length. A previous systematic review of

trials in sickle-cell disease found that, although use of biomarkers was widespread, insufficient data were available to show that they reliably and accurately predicted the clinical event.

In this proposed study we will use data from the Jamaican Cohort Study of Sickle-Cell Disease to develop prognostic models for biomarkers of painful crises and acute chest syndrome. We will validate our models for accuracy and generalisability using an external population from a London sickle-cell disease register. We aim to identify which biomarkers could be confidently used in future clinical trials in place of common clinical outcomes, and will offer guidelines for their use.

The project will be an international collaboration between the Tropical Medicine Research Institute, Kingston, Jamaica, the Institute of Child Health, Liverpool, UK and the Brent Sickle-cell and Thalassaemia Unit, London, UK.

(d) Other studies

Several other studies will develop from this thesis. Following from our description of the sickle-cell unit workload in chapter 2, we plan to convert this analysis to an economic assessment of the cost of treating SCD in Jamaica. This will offer the first insight into the financial burden of this disease in the Caribbean. Allied to this study will be a cost / benefit projection for the introduction of neonatal screening across the island. We also hope to pursue a more formal international comparison of SS disease between Jamaica and the US by comparing the two major cohort studies to emerge so far – the JSSCD and the CSSCD. We will begin by comparing study methodologies and participant demographics, with a view to using each cohort as a validation sample for models developed in the other.

9.3.6 Targeting resources and research

In the US in 1970, Colbert King, now an editor at the Washington Post, conducted research for Elliott Richardson, then the Secretary of the Department of Health, Education and Welfare. They reported that the total historical federal funding for SCD was US$150,000, while that for cystic fibrosis (a similarly inherited and burdensome disorder but a disease for which the clinical consequences are perhaps more identifiable) was US$11.8m between 1967 and 1971. In 2001, NIH funding for SCD research was US$59.8m compared with a US$85m research budget for cystic fibrosis. This 42% lag in SCD funding is a glaring disparity considering that an estimated 30,000 Americans have CF compared to the estimated 80,000 Americans with SCD.

The situation may be even worse in the UK. On March 6th 2000, Jane Griffiths, Member of Parliament for Reading East introduced a debate on sickle-cell disease in the House of Commons. She noted a similar UK discrepancy in funding between SCD and CF, and also

commented on anecdotal evidence of fundamental gaps in general practitioner knowledge about the disease,

> "Evidence also shows that, in recent years, when people have visited their doctor or gone to hospital suffering from symptoms relating to sickle cell anaemia, they have been asked, "How long have you had the sickle cell condition?" That indicates that not all doctors even know that it is an inherited condition that cannot be contracted".
>
> **House of Commons Hansard Debates. March 06, 2000.**
> **www.publications.parliament.uk**

These disparities in resource allocation and knowledge have been ascribed to ethnic differences in the disease populations, and this is a legitimate concern. It is also quite possible that the low-visibility of SCD will contribute to the reduced drive of institutional measures to effect change. Add to these problems the social stigma of the disease, and we have a widespread medical and social problem to which the response of governments is often inadequate.

Despite an estimated 230,000 new cases per year, and approximately 70% of all cases living in sub-Saharan Africa (3), this is where the response to the disease is least adequate. The recognition of SCD as a social and medical problem in Africa will increase as the burden of infectious disease is reduced. More people with SCD will survive childhood, to place an even greater burden on healthcare infrastructures. It is imperative that we plan for this eventuality, and focus our planning on solutions that can have a real impact in resource-poor environments. And this is where the JSSCD can continue to impact on SCD research.

9.4 Reference List

(1) Serjeant GR, Grandison Y, Lowrie Y, Mason K, Phillips J, Serjeant BE et al. The development of haematological changes in homozygous sickle cell disease: a cohort study from birth to 6 years. Br J Haematol 1981; 48(4):533-543.

(2) Miller ST, Sleeper LA, Pegelow CH, Enos LE, Wang WC, Weiner SJ et al. Prediction of adverse outcomes in children with sickle cell disease. N Engl J Med 2000; 342(2):83-89.

(3) Weatherall DJ, Clegg JB. Inherited haemoglobin disorders: an increasing global health problem. Bull World Health Organisation 2001; 79(8):704-712.