Cancer incidence in young people in Saudi Arabia: relation to socioeconomic status and population mixing

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The candidate confirms that the work submitted is her own and that appropriate credit has been given where reference has been made to the work of others.

To Mummy and Daddy

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Abstract

This study describes cancer incidence in under 24 year olds, particularly leukaemias, lymphomas and central nervous system tumours. It also describes the socioeconomic status (SES) of the geographically delimited Governorates in Saudi Arabia, by deriving two indices – the first time this has been done in the country. It also sought to determine whether SES and Hajj (occurring in Makkah) as a measure of population mixing has an association with the incidence of these cancers.

During 1994 to 2008, 17,150 cases were identified from the Saudi Cancer Registry. Census data were accessed for 2004 and included 29 indicators. A continuous SES index was constructed using exploratory factor analysis (EFA) and a categorical index using latent class analysis (LCA). Incidence rate ratios (IRRs) were calculated for cancers in Makkah compared to other Governorates by year to assess the effect of Hajj, and for all Governorates to assess the effect of SES.

The Hajj had no significant effect on the incidence for all cancer groups. The continuous index produced by EFA consisted of scores ranging from 100 to 0, for affluent to deprived Governorates. The LCA found a four-class model as the best model fit. Class 1 was termed ‘affluent’, Class 2 ‘upper-middle’, Class 3 ‘lower-middle’ and Class 4 ‘deprived’. The urbanised Governorates were affluent, whereas the rural Governorates were on average more deprived. For SES, an elevated risk was found for acute lymphoblastic leukaemia in the affluent class (IRR=1.38, 95%CI=1.23-1.54), and was reduced in the deprived class (IRR=0.17, 95%CI=0.10-0.29). Similar associations were observed for all cancer groups.

The findings are not supportive of the PM hypothesis, but give support to the delayed infection hypothesis, suggesting that delayed exposure to infections may prevent immune system modulation, although results may be exacerbated by poor case-ascertainment/under-diagnosis in deprived areas. Similarities between the two indices suggest validity.

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List of Abbreviations

ABIC	Adjusted Bayes information criterion
AIC	Akaike information criterion
ASR	Age-standardised rate
ALL	Acute lymphoblastic leukaemia
AML	Acute myeloid leukaemia
BCG	Bacillus Calmette-Guérin
BIC	Bayes information criterion
BL	Burkitt's lymphoma
BLRT	Bootstrap likelihood ratio test
CDSI	Central Department of Statistics and Information
CFA	Confirmatory factor analysis
CI	Confidence interval
COMARE	Committee on Medical Aspects of Radiation in the Environment
CML	Chronic myeloid leukaemia
CNS	Central nervous system
CTHMIHR	Custodian of the Two Holy Mosques Institute for Hajj Research
DAG	Directed Acyclic Graph
DNA	Deoxyribonucleic acid
DM	Diabetes Mellitus
E	Expected
EBV	Epstein-Barr virus
EFA	Exploratory factor analysis
GIS	Geographical information systems
GLM	Generalised linear model
GP	General Practitioner
GRO	General Register Office

HBV	Hepatitis B virus
HIB	Haemophilus influenza B virus
HIV	Human immunodeficiency virus
HL	Hodgkin's lymphoma
HPV	Human Papillomavirus
HSC	Haematopoietic stem cell
HTLV-1	Human T-cell leukaemia/lymphoma virus type 1
ICCC	International Classification of Childhood Cancers
ICD-10	International Classification of Disease 10th edition
ICD-O-3	International Classification of Diseases for Oncology 3rd edition
ILC	Index of Local Conditions
ILD	Index of Local Deprivation
IMD	Indices of Multiple Deprivation
JC virus	John Cunningham virus
LADs	Local authority districts
LCA	Latent class analysis
LMR-LRT	Lo-Mendell-Rubin likelihood ratio test
KMO	Kaiser-Meyer-Olkin
MoH	Ministry of Health
NB	Negative binomial
NCCLS	North California Childhood Leukaemia Study
NHL	Non-Hodgkin's lymphoma
NRCP	National Council on Radiation Protection and Measurements
O	Observed
ONS	Office for National Statistics
OR	Odds ratio
PCMR	Proportional cancer mortality ratio
PM	Population mixing
RNA	Ribonucleic acid

RR	Relative risk
RTI	Respiratory tract infections
SCR	Saudi Cancer Registry
SD	Standard deviation
SIR	Standardised incidence ratio
SMR	Standardised mortality ratio
SES	Socioeconomic status
UAE	United Arab Emirates
UKCCS	United Kingdom Childhood Cancer Study
US	United States of America
WHO	World Health Organisation
ZIP	Zero-inflated Poisson
ZINB	Zero-inflated negative binomial model

List of Equations

$$SIR = \frac{Observed}{Expected} \times 100$$ **Equation 3.1**

Posterior = *Prior* x *Likelihood* **Equation 3.2**

$$E(\theta_i \mid O_i; \alpha, \nu) = \frac{O_i + \nu}{E_i + \alpha}$$ **Equation 3.3**

$$Z_x = \frac{x - \mu}{\sigma}$$ **Equation 3.4**

$$z_j = a_{j1}F_1 + a_{j2}F_2 + \cdots + a_{jm}F_m + a_{ju}U_j$$ **Equation3.5**

$$\begin{cases} z_1 = a_{11}F_1 + a_{12}F_2 + \cdots + a_{1m}F_m + a_{1u}U_1 \\ z_2 = a_{21}F_1 + a_{22}F_2 + \cdots + a_{2m}F_m + a_{2u}U_2 \\ \cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots \\ z_n = a_{n1}F_1 + a_{n2}F_2 + \cdots + a_{nm}F_m + a_{nu}U_n \end{cases}$$ **Equation 3.6**

$$h_j^2 = a_{j1}^2 + a_{j2}^2 + \cdots + a_{jm}^2$$ **Equation 3.7**

$$V_p = \sum_{j=1}^{n} a_{jp}^2$$ **Equation 3.8**

$$II = \sum F_n W_n$$ **Equation 3.9**

$$SI_i = \frac{II_i - II_{min}}{II_{max} - II_{min}} x100$$ **Equation 3.10**

$$p(X_{vi} = 1) = \sum_{g=1}^{G} \pi_g \pi_{ig}$$ **Equation 3.11**

$$\sum_{g=1}^{G} \pi_g = 1$$ **Equation 3.12**

$$\pi_{ig} = p(X_{vi=1} \mid G = g)$$ **Equation 3.13**

$$AIC = -2 ln L_{max} + 2k$$ **Equation 3.14**

$$BIC = -2 L_{max} + k lnN$$ **Equation 3.15**

$$ABIC = -2 L_{max} + k ln\left(\frac{n+2}{24}\right)$$ **Equation 3.16**

$$ln(r) = a + b_1 x_1 + b_2 x_2 + ... + b_j x_j$$ **Equation 3.17**

1 Introduction

1.1 Study rationale

The global burden of cancer continues to increase as a result of a growing and aging population, as well as adoption of behaviours believed to cause cancers, such as tobacco smoking. It is the leading cause of death in developed countries, and the second leading cause of death in developing countries. Worldwide, an estimated 12.7 million people with cancer were identified and 7.6 million died of cancer in 2008 (Jemal et al., 2011, WHO, 2008). In Saudi Arabia, a steady increase in incidence was observed from the start of reporting to the Saudi Cancer Registry (SCR) in 1994, and reached a total of 11,946 cases in 2008 (Adler et al., 1994). The most common causes of death in Saudi relate to heart problems and road traffic accidents, and although the causes of death are not broken down by age, congenital anomalies have been reported (Memish et al., 2014). Although cancers are not within the 10 most commonly occurring diseases causing deaths within the country, the rapidly changing profile of diseases, as well as the constant growth of the Saudi population, suggests that cancer may become a major health issue. Hence, cancer will pose a challenge to the Saudi health care system (Memish et al., 2014).

Cancer usually takes many years to develop, which is why it predominantly occurs in adults (Bleyer et al., 2006). However, cancer does develop in children below 14 years of age, and in young adults aged between 15 and 24 years of age. There is a strong reason to look at cancers within these age groups in Saudi due to the age structure of the population, where more than 52% of the population is under the age of 25 (CDSI, 2004a). Furthermore, although incidence in these age groups is considerably lower than in adults, the level of incidence is disproportionately low when compared to the net years of disability due to disease occurrence and treatment, as well as the years of life lost (Yeates et al., 2009, NICE, 2011). Hence, these age groups are given considerable care and attention and are targeted in several epidemiological studies worldwide, but not in Saudi Arabia.

Cancer epidemiology remains in its infancy in Saudi Arabia where very few studies exist, none of which have focused on cancer incidence in children and young people aged less than 25 years and none have attempted to describe incidence geographically through mapping within these age groups. This gap in the knowledge is reflected in the SCR annual reports, where only childhood cases are reported as a separate age group, and young adults are included with adults cases

(Al-Eid et al., 2008). This is not the best practice, as treatments for cancers occurring in the young adult age group do not follow adult protocols, but usually follow paediatric protocols (Boissel et al., 2003). Also, geographical epidemiology assists in discovering disease patterns that may have otherwise been unknown. The application of disease mapping in Saudi Arabia is very recent, and has only been aimed at the common types of cancers occurring in the population of all ages, not at the 0-24 year old age group. Therefore, exploring incidence rates and geographical distributions of cancers occurring in these age groups helps in understanding its aetiology.

In childhood, acute lymphoblastic leukaemia (ALL) is the most common cancer with incidence peaking between two and five years. In young adults the most common types of cancers are lymphomas (Bleyer et al., 2008). Over the past 30 years, many research papers have examined the epidemiology of childhood cancers, especially childhood and young adult leukaemias and lymphomas (Law et al., 2003, Feltbower et al., 2009, Doll, 1989, Stiller, 2004). In an attempt to understand their aetiology, three infectious hypotheses have been formulated, namely, the population mixing (PM) hypothesis, the delayed infection hypothesis and the in utero infection hypothesis.

1.1.1 Infectious hypotheses

The population mixing (PM) hypothesis suggests that leukaemia is a rare response to a common infection, and that this infection occurs as a result of PM whereby a relatively isolated community, which has not yet been exposed to this infection, receives an influx of people coming mostly from urban backgrounds (Kinlen, 1996). It has been suggested that the infection, which may be bacterial or viral, may lead directly to leukaemia. The delayed infection hypothesis, which suggests that the common childhood ALL occurs as a result of two mutations, the first happens in utero and the second happens after birth, once the child has been exposed to several types of infections (Greaves, 1988). The hypothesis has been supported by both biological and epidemiological studies. The third is the in utero infection hypothesis which states that childhood ALL may be due to an infection that occurs in utero during pregnancy (Smith, 1997).

However, it has proven difficult to test these hypotheses directly as there are many factors to consider, such as the timing of exposure to infections and the subsequent response to them, as well as assessing exposure to infection in early life (Law et al., 2008). This is exacerbated by the lack of discovery of the infectious agent in

question. Several studies have also examined the incidence of CNS tumours in light of these hypotheses after emerging evidence of the involvement of infections in their aetiology.

1.1.1.1 Relevance of the Hajj

Saudi Arabia is home to the holy city of Makkah, as a result it experiences the Hajj pilgrimage, which is one of the five pillars of Islam. It is an event that has been going on for more than 1000 years. It is obligatory upon every able Muslim to perform it at least once in their lifetime, '*Announce Hajj to mankind. They will come to you on foot and on every sort of lean animal, coming by every distant road so that they can be present at what will profit them*' (The Holy Qur'an, 22.27). Annually, more than two million Muslim pilgrims from over 140 countries gather in Makkah. The Hajj takes five days to perform, though pilgrims may start to arrive weeks before the event, and stay several weeks after. During this season, crowd density can increase to up to seven individuals per square metre (Memish et al., 2009).

Mass migration of this kind increases the risk of contracting communicable diseases. For example, respiratory tract infections (RTIs) are very common among pilgrims. In a study during the 1991 and 1992 Hajj seasons, the syncytial virus, influenza virus A, parainfluenza virus and adenovirus were the more dominant viruses causing RTIs (El-Sheikh et al., 1998). Also, viruses causing pneumonia such as mycobacterium tuberculosis, gram-negative bacilli and streptococcus pneumonia are easily spread during the Hajj (Alzeer et al., 1998). The biggest outbreak of the W135 serogroup of meningitidis in the world was reported in 2002 (Memish et al., 2003).

The Saudi Ministry of Health (MoH) every year puts forward plans to facilitate the Hajj, and safeguard pilgrims from such risks. Vaccinations against meningitis are now obligatory for every pilgrim, and pilgrims coming from countries where yellow fever is known to be common should present a yellow fever vaccination certificate upon arrival. However, with such a massive gathering, disease outbreaks still occur. Although some diseases may be mild in nature, they do however prime the immune system, thereby increasing protection against potential infections.

The influx of people into Makkah, and its associated infections are similar to that suggested by Kinlen (1988). Therefore, the Hajj presents itself as an opportunity to test the PM hypothesis in Saudi in relation to childhood cancers. Although, it should be stressed that Hajj is an annual event, not a one-off event.

1.1.1.2 Relevance of socioeconomic status

Several factors are potentially related to the aetiology of these cancers such as diet and breastfeeding, but most importantly is socioeconomic status (SES) which is also related to the first two hypotheses, i.e. the PM and the delayed infection hypotheses. High affluence is often associated with lower levels of mixing, hence less exposure to infectious agents. However, none of the Arabian Gulf countries have an established area-based SES measure that can be used in epidemiological studies. Such a huge gap in health and social research is frequently reported (AlGhamdi et al., 2014), and prevents the understanding and examination of any possible associations. Therefore, utilisation of national Saudi census data has provided an excellent opportunity to derive two area-based measures that could be used both in this research and in other future health and social research dealing with data on a national level.

1.2 Aims and structure of the thesis

This thesis focuses on childhood and young adult cancers aged less than 24 years reported in Saudi Arabia between 1994 and 2008. The aims of this thesis are to:

- Describe the pattern of incidence of childhood and young adult cancers particularly leukaemias, lymphomas and central nervous system (CNS) tumours across Saudi Arabia, as well as produce international comparisons with other countries.
- Describe the geographical variation in incidence of these cancers.
- Construct indices of SES for use in the subsequent analysis, as well as for use in future research in Saudi.
- Examine the effect of SES and Hajj on the incidence of childhood and young adult cancers in Saudi and interpret the findings in relationship to the PM hypothesis.

Chapter 2 reviews the literature on cancer and cancer incidence both internationally and in Saudi Arabia. It focuses on haematopoietic cancers as well as their incidence in the childhood and young adult population. Furthermore, an overview of the potential aetiological factors relating to cancers is presented, focusing on SES and the three infectious hypotheses postulated to play a role in childhood leukaemia and lymphoma.

Chapter 3 provides an overview of the methods used for handling and analysing both the cancer data and the census data. The results of these analyses are presented in Chapters 4, 5 and 6. Chapter 4 presents the results of the descriptive analyses including direct and indirect standardisations of incidence rates overall and by geographical region. Chapter 5 presents the results of the two area-based indices of SES, and Chapter 6 presents the results of the regression analyses of PM and SES, including sensitivity analysis and an assessment of case-ascertainment of cancer data.

Chapter 7 discusses in detail the methods used as well as the results of these analyses, pointing out limitations encountered during the work and putting forward recommendations for future work.

2 Literature review

2.1 Cancer

The word cancer was derived by the father of medicine, Hippocrates, from the Greek word *karkinos;* a word used to describe a crab, which Hippocrates (460-370 BC) thought a tumour looked like (Schwab, 2008). It is a group of diseases and over 100 types have been identified; they differ in their age of onset and rate of growth. All cancers can be called tumours; however, not all tumours can be called cancers. Tumours refer to swelling, which may be caused by several other factors apart from cancer, e.g. inflammation or haemorrhage, or from a growth which is then classified into either benign or malignant (Renneker, 1988). Unlike malignant tumours which are cancerous, benign tumours are mainly characterised by their inability to spread or metastasize to other areas (Knowles and Selby, 2005).

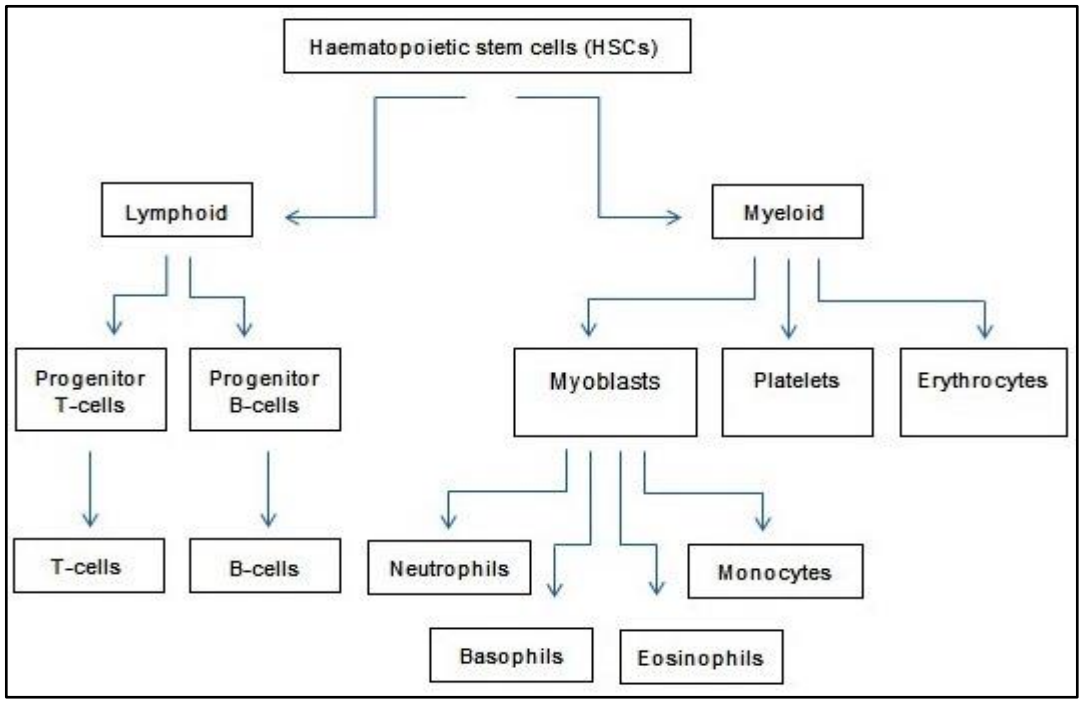
The human body has four groups of tissues: the mesenchyme tissues, the epithelium tissue, the nervous system and the haematolymphoid tissue. Each has its own particular types of cells that sustain its structure and functions. In the case of injury, other surviving cells start to divide to substitute the injured cells and then stop. This process is known as cell proliferation and is distinguished from cell growth where the cell increases in size (Knowles and Selby, 2005).

The way in which the numbers of cells increase is known as the cell cycle. The cycle briefly involves the growth or maturation of all cell components, and then division to produce two new descendant cells. Almost all cancers are characterised by dysregulation or disruption of the cell cycle (Weber, 2007, Ruddon, 2007). Thus, cancer may be defined as an abnormal growth of cells which subsequently leads to a dysregulated balance of cell proliferation and death of cells, these develop into a population of cells that may penetrate normal tissues and further metastasize to other sites (Ruddon, 2007).

2.1.1 Haematopoietic cancers

All cells in the body arise from pluripotent stem cells. These cells differentiate into any of the main germ layers, i.e. the endoderm, the mesoderm or the ectoderm, and the pluripotent stem cells become multipotent stem cells (Figure 2.1). If they arise in the blood, then they are known as haematopoietic stem cells (HSCs). HSCs are one type of multipotent stem cell. HSCs are further classified into either lymphoid stem cells or myeloid stem cells, depending on the type of targeted cells

(lymphoid or myeloid). Lymphoid stem cells differentiate into progenitor T-cells and progenitor B-cells, which then mature into T-cells and B-cells. Myeloid stem cells differentiate into platelets, erythrocytes, leukocytes and myeloid progenitor cells. Blood cancers are classified according to the type of cell involved (Reaman and Smith, 2011, Crowley, 2011).



Adapted from Reaman and Smith (2011)

Figure 2.1: Diagram of basic haematopoietic stem cell differentiation

2.1.1.1 Leukaemias

Leukaemia is a group of diseases originating from the haematolymphoid tissue. It is a disease mainly characterised by an excessive proliferation of leukocytes. Unlike solid tumours, leukaemic cells penetrate the lymphoid and myeloid tissues, leaking into the bloodstream and infiltrating other body organs (Crowley, 2011). In leukaemia, the bone marrow produces abnormal or immature white cells that overcrowd the normal cells. The inability of the abnormal cells to mature makes it difficult for the body to fight infections, and the overcrowding of the abnormal cells reduces the production of red blood cells leading to anaemia, which is why most leukaemic patients die from either infections or haemorrhage if left untreated, or if treatment is unsuccessful (Reaman and Smith, 2011, Schade, 2006).

Leukaemia is classified into several subtypes based on the types of cells and the level of maturity of the proliferating cells. The main two subtypes are lymphocytic leukaemia and myelocytic leukaemia. Lymphocytic leukaemia is further characterised as T lymphocytic leukaemia if it occurs in T cells and B lymphocytic leukaemia if it occurs in B cells. The maturity of the proliferating cells further identifies the status of the disease, i.e. if the cells are mature the disease is chronic, if the cells are primitive then the disease is classified as acute. Acute leukaemia is a rapid progressive disease, in contrast to chronic leukaemia where the disease progresses relatively slowly, leading to longer survival rates (Crowley, 2011, Reaman and Smith, 2011).

Over recent years, it has been possible to understand what occurs at a cellular level to patients diagnosed with childhood ALL by genetic epidemiological studies and molecular scrutiny. In childhood leukaemia, chromosomal rearrangements disrupt the genes that regulate the blood cell formulation (Inaba et al., 2013). Such rearrangements include chromosomal hyperdiploidy/hypodiploidy and chromosomal translocations, such as the MLL gene translocation forming the MLL fusion gene in infant leukaemia with incidence peaks in children younger than one year old, and the TEL and AML1 translocations to form the TEL-AML1 fusion genes in common childhood ALL, with incidence peaks between two and five years of age (Inaba et al., 2013, Greaves, 2002, Lightfoot and Roman, 2004).

2.1.1.2 Lymphomas

Lymphoma is another type of haematopoietic cancer which differs from leukaemia mainly by the site of origin. In lymphoma the disease develops from lymphocytes within the lymphatic system, and causes a malignant neoplasm or tumour. The disease is divided into two major categories: Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma (NHL). The main difference between the two is the involvement of Reed-Sternberg cells, which originate from B-cells. In a patient with HL, the disease develops in an orderly manner, i.e. once one lymph node is affected then adjacent lymph nodes are expected to be affected as well (Crowley, 2011). In NHL, many subtypes have been identified, and although identification of these subtypes is complex, the details are crucial to determine the most favourable therapy. In contrast to HL, NHL may develop from either B-cells or T-cells. The incidence of HL peaks in childhood in many developing countries, followed by a steady decline in young adults. However, Burkitt's lymphoma (BL) is a very common form of lymphoma in Africa and is linked to Epstein Barr-virus (EBV).

During the period between 1968 and 1982, it accounted for almost 68% of all childhood cancers in Uganda, though it is rare in young adults (Stiller and Parkin, 1996, Stiller, 2007).

2.2 International variations in cancer incidence

The World Health Organization (WHO) identified cancer as the leading cause of death in economically developed countries, and the second leading cause of death in economically developing countries (WHO, 2008). Worldwide, an estimated 12.7 million cancer cases occurred and 7.6 million people died of cancer in 2008 (Jemal et al., 2011). However, cancer incidence varies greatly between the different regions in the world, as well as by age and sex (Table 2.1).

Table 2.1: Age standardised rates of cancer incidence worldwide in 2008

WHO regions [a]	Males [b]	Females [b]	Total [b]
Africa	115.2	123.7	118.7
Americas	253.3	211.7	229.1
Eastern Mediterranean	109.1	104.6	106.3
Europe	281.6	207.3	236.7
Southeast Asia	106.9	119.9	112.7
Western Pacific	219.9	157.9	187.0

Source: http://globocan.iarc.fr

[a] Rates are standardised to the world population and are per 100,000 person years

[b] Includes all cancers excluding non-melanoma skin cancers for 2008.

Globally, lung cancer is the most common cancer for both genders combined, followed by breast cancer, colorectal cancer, stomach cancer and prostate cancer (Ferlay et al., 2010). In males, lung cancer is the most occurring cancer with an age-standardised rate (ASR) of 33.8 per 100,000 person years followed by prostate cancer (27.3 per 100,000 person years). In females, breast cancer is the most commonly occurring cancer with an ASR of 38.9 per 100,000 person years followed by colorectal cancer with an ASR of 14.6 per 100,000 person years (Ferlay et al., 2010).

Incidence of cancer varies greatly between different regions of the world by sex. In males, lung cancer is most common in areas of Eastern Europe and Asia, while prostate cancer is most common in North America, Western and Northern Europe, South America and Australia. Kaposi Sarcoma is common in Central Africa, liver

cancer in Western Europe and oesophageal cancer in Eastern Africa. In females, breast cancer is the most commonly occurring cancer almost everywhere in the world. Cervical cancer is common in Central America, and in certain parts of South America (Jemal et al., 2010). Geographical variations in cancer incidence assist in illustrating aetiological inferences about the different types of cancers (Horner and Chirikos, 1987). Nonetheless, differences in ASRs between the different regions of the world may partially be an artefact attributed to the difference in the quality and nature of the data collection process. Indeed, data from these countries range from actual numbers of cases and deaths to only estimates derived from samples (Jemal et al., 2011).

2.2.1 Childhood and young adult cancers

2.2.1.1 Childhood cancers

Childhood cancers are very rare when compared to adult cancers, where the total incidence rate usually lies between 70-160 per million (Stiller, 2004). They have been and still are of great interest to scientists, not only because of their target population, but also because the types of cancers occurring in this age group are unique in comparison with cancers occurring in older age groups. The carcinomas mostly occurring in adults, such as lung, colon and breast carcinomas are extremely rare in children. In the past, childhood cancers have almost always led to death (Chan and Raney, 2010). In recent years, survival rates have improved greatly, for example according to the Surveillance, Epidemiology and End Results (SEER) data, for childhood ALL survival rates increased to 88.5% in the decade between 2000 and 2010. This is due to the excellent progress in cancer treatment (Ma et al., 2014, Voute et al., 2005).

Among children aged less than 15 years, the annual ASR of cancer typically lies between 75 and 40 per million in different parts of the world. Childhood leukaemia is the most common cancer in children in almost all parts of the world, except in Africa, where Kaposi Sarcoma and Burkitt's lymphoma are more common. Variations are seen within the specific types of cancers (Table 2.2) (Stiller and Parkin, 1996, Stiller, 2004).

Table 2.2: Age standardised rates of childhood cancers aged 0-14 between 1960-1984

Diagnostic group[a]	Zimbabwe (Harare)	UK (England and Wales)	Australia	Japan (Osaka)
ALL	11.6	32.8	39.9	28.4
AML	11.0	6.3	8.0	8.0
HL	3.2	4.6	4.2	0.7
CNS	12.0	27.0	29.6	26.5

Source: (Parkin et al., 1988)

[a] Rates are standardised to the world population and are per million person years

2.2.1.2 Young adult cancers

Adolescents and young adults are defined by age, and different age ranges exist. The WHO considers individuals aged between 15 and 19 years of age to be adolescents, and those between 15 and 24 years of age as young adults (WHO, 2009).

The malignancies found largely within children under five years of age, such as retinoblastomas and neuroblastomas are very rare in young adults (Eden et al., 2008). Also, young adults very rarely develop the cancers found in older adults such as the aerodigestive and genitourinary carcinomas (Bleyer and Barr, 2007, Stiller, 2007). Among adolescents aged 15 to 19 years, the most common types of cancers worldwide are leukaemias, lymphomas, CNS tumours, gonadal tumours, thyroid carcinomas and malignant melanomas (Stiller, 2007).

According to a study by Stiller et al. (2007), cancer incidence in adolescents was higher in males than in females, where incidence in males ranged from 105 to 264 per million in males, compared to 85 to 228 per million in females. The incidence also varies by geographical region (Table 2.3).

Table 2.3: Age standardised rates of adolescent cancers aged 15-19 between 1980 and 1994

Country [a]	Zimbabwe		Canada		Australia		Japan	
Years	1990-1997		1993-1997					
Gender	M	F	M	F	M	F	M	F
ALL	11.9	1.6	18.2	10.0	21.7	9.0	11.5	5.9
AML	15.9	3.1	6.9	6.4	8.9	7.7	12.3	6.4
HL	6.0	1.6	34.9	47.9	25.6	25.3	3.3	2.1
CNS tumours	11.9	3.1	20.6	15.4	18.9	17.6	11.9	6.8
Melanoma	4.0	0	8.0	10.2	69.9	77.9	0.4	0.4

Source: (Stiller, 2007)

[a] Rates are standardised to the world population and are per million person years

2.2.1.3 Classification and coding of childhood, adolescent and young adult cancers

The standard classification system used to code diseases is the International Classification of Diseases – 10th edition (ICD-10), which for cancer only focuses on the anatomical site, i.e. topography. Therefore, the International Classification of Diseases for Oncology, now in its third edition (ICD-O-3), is more appropriate for coding detailed diagnoses of cancers including the various morphological (histology) and topographical (site) types of the disease in adults, which are usually derived from a pathology report (Voute et al., 2005). The ICD-O-3 was introduced in 2000, and it classifies cancers by topography, morphology, behaviour and grading of neoplasms. The update and shift from the first edition, which was first introduced in 1976 and the second edition in 1992, was prompted by improvements in diagnostic medicine, genetics and pathology (WHO, 1976, WHO, 1992). The third edition of the ICD-O includes new morphology codes especially for leukaemias and lymphomas. However, childhood cancers usually present with special morphological characteristics that are very rarely seen within adults. Therefore, the International Classification of Childhood Cancers (ICCC) which is based on the ICD-O-3 is now used to account for these special characteristics (Voute et al., 2005, Steliarova-Foucher et al., 2005b). The codes of the combinations of histology and topography from the ICD-O-3 are assigned to the main diagnostic groups (12 in

total), which are further subdivided into 47 subgroups (see Appendix A and B) (Steliarova-Foucher et al., 2005b).

For young adults aged between 15 and 24 years, the Birch et al. (2002) classification was designed to specifically report the most frequent cancers occurring within this age group. It is similar to the ICCC classification in that it is primarily based on morphology. The motivation behind this classification was that the carcinomas specified in the ICCC are not adequately subdivided to properly describe the pattern observed in this age group. In addition, the ICD classification – if used – cannot distinguish carcinomas from non-epithelial tissues. For example, carcinomas and soft tissue sarcomas occurring in the liver will all be assigned the code for malignant neoplasm of the liver (Birch et al., 2002). Hence, for studies that are concerned with cancers occurring in this age group, the Birch et al. classification is more appropriate. However, in studies that include children and young adults, the classification used should represent the numerically important age group in the study (Birch et al., 2002).

2.3 The Saudi Arabian context

Officially known as the Kingdom of Saudi Arabia, it is the second largest Arab country in the Middle East. It is bordered by Iraq, Jordan and Syria in the north, Kuwait, Bahrain, Qatar and United Arab Emirates (UAE) to the east, Oman and Yemen to the south and the Red Sea to the west. According to the latest census in 2011, the total population was 28,376,355, with a population density of 14 persons/square km. The capital city is Riyadh and it is also the largest city in the country. Saudi Arabia a country known for its production of oil and gas from its natural reserves, but is more prominent in the Muslim world for hosting the two holy mosques in Makkah and Medinah (CDSI, 2011).

The country is divided into 13 administrative areas, also known as provinces. The provinces are further divided into 118 Governorates, which are also divided into sub-Governorates. Each of these divisions differs in terms of the total population, and population density (CDSI, 2004a). Cancer reporting is relatively new to the country as it only started in 1994 through the SCR.

2.3.1 Cancer incidence in Saudi Arabia

In Saudi, 11,659 cancer cases were reported to the SCR between the 1st of January 2007 and the 31st of December 2007 with an incidence rate of 82.1 per 100,000 person years. Females had an ASR of 84.2 per 100,000 person years, and males had an ASR of 80 per 100,000 person years. Rates were highest in females aged between 45 and 59 years of age, and occurred mostly within males aged between 60 and 74 years (Al-Eid et al., 2008). Table 2.4 gives ASRs for Saudi as well as other countries. The incidence is higher in the US and the UK where cancer registration has a long history, however for Saudi Arabia and the UAE, the relatively low numbers may suggest under-reporting of cases in both countries, in which cancer registries are relatively new especially for the UAE which commenced reporting in 1998 (NCR, 2014).

Table 2.4: Comparisons of age standardised incidence rates of all cancers including Saudi Arabia for 2008

Country [b]	Males [a]	Females [a]	Total [a]
Saudi Arabia	85.9	102.8	91.1
United Arab Emirates	83.8	127.1	92.5
UK	284.0	267.3	272.9
US	347.0	297.4	318.0

Source: (http://globocan.iarc.fr/)

[a] Rates are standardised to the world population and are per 100,000 person years

[b] Includes all cancers excluding non-melanoma skin cancers for 2008.

The most common cancer in males for all ages was colorectal cancer, followed by NHL, leukaemia, lung cancer and liver cancer. In females, the most common cancer was breast cancer, followed by thyroid cancer, colorectal cancer, NHL and leukaemia. A possible reason for differences in disease occurrence worldwide and in Saudi may be a reflection of environmental and lifestyle factors that play an aetiological role in occurrence. A gradual increase in cancer incidence is found in Saudi from 1994 to 2008. This may partly be the result of improvement in reporting of cancer cases, as well as raised public awareness of early screening programmes (Al-Eid et al., 2008).

2.3.2 Childhood cancer incidence in Saudi Arabia

For children in Saudi, and since the start of reporting of cancer in 1994, incidence has been steadily increasing. This may partly be a result of the improvement in reporting of cases through time, which is typical of a newly established cancer registry (Al-Eid et al., 2008); it may also reflect the increase in the total population within the country.

According to the SCR report in 2008, the number of cancer cases reported in children was 770. This was equal to 6.5% of all cancers in all ages. Males had a higher incidence than females, and the most frequent cancers in this age group were leukaemia, NHL and HL, which accounted for 34.8%, 12.7% and 10.4% of all childhood cancers respectively (Al-Eid et al., 2007a). Unfortunately, the SCR does not report incidence rates of childhood cancers for international comparison, neither does it report incidence in young adults.

2.4 Cancer aetiology in children and young adults

Cancers in young children are thought to be influenced by pre-natal factors, and cancers in older adults are thought to be influenced by prolonged exposure to environmental factors. In young adults however, it is thought that cancer is influenced by a mixture of both factors (Bleyer and Barr, 2007). Causal factors for cancers fall into two major categories, environmental and lifestyle factors and genetic predisposition.

2.4.1 Genetic predisposition and susceptibility

Predisposing genes are the genes that can cause a high relative risk of developing some malignancies within a family, but with low attributable risk to the general population (Eden, 2010). For example, neurofibromatosis type 1 – a genetic disorder – is found to be linked to both ALL, chronic myeloid leukaemia (CML) and lymphoma in families carrying that disorder. Also, children with Down syndrome are more likely to develop leukaemias especially ALL and AML. In young adults, leukaemias (including ALL) were found to develop in families with germ-line TP53 mutations (Eden, 2010). On the other hand, the susceptible genes are the genes that affect how each person responds to the surrounding environmental exposures. In other words, the risk of acquiring cancer through environmental factors is modulated by these genes. The types of cancers developed are more common sporadic cancers and, unlike predisposing genes, individuals carrying these genes rarely have a family history of cancer (Eden, 2010, Kelloff et al., 2008). An example is the CHEK2 gene, involved in the DNA damage-repair response pathway which was identified in non-familial breast cancer patients (Meijers-Heijboer et al., 2002). However, the underlying mechanisms have only recently started to unfold.

2.4.2 Environmental and lifestyle factors

2.4.2.1 Ionising radiation

People are exposed to ionising radiation on a daily basis, either from natural sources such as radon gas through inhalation, or from artificial man-made sources such as x-rays and CT scans. The National Council on Radiation Protection and Measurements (NRCP) has set an average safe limit of 15 mSv for exposure to ionising radiation. Exceeding this limit subsequently increases the risk of developing cancer in both children and adolescents. Evidence is available from the atomic bomb survivors who were exposed to up to 200 mSv and foetuses that have been

exposed to much lower dosages in utero (Doll and Wakeford, 1997). Moreover, prenatal exposure to ionising radiation through diagnostic radiography was associated with childhood leukaemia as well as other cancers (Stewart et al., 1958). It has been generally accepted that children and adolescents are vulnerable to the effects of ionising radiation with special emphasis on the dose and gestational age during the time of exposure (Wakeford, 1995). Fortunately, ultrasound has largely replaced obstetric X-ray in pregnancy, and there is no evidence to date that connects obstetric ultrasound with any childhood cancer (Wilson and Waterhouse, 1984).

Parental occupational exposure to ionising radiation has also been examined. Gardner and colleagues (1990) examined the incidence of leukaemia and NHL in the offspring of workers based in a nuclear plant and reported that exposure of fathers to radiation was associated with incidence of both diseases in their offspring, with a dose response effect with the highest relative risk (RR) found for those exposed to higher cumulative doses of radiation. The estimates for leukaemia were high with a RR = 8.4 and a confidence interval (CI) of 1.40 - 52.00 and for NHL the association was very high too (RR = 8.2, 95%CI = 1.36 - 50.56). Both leukaemia and NHL were found within those with the highest accumulated exposure of 100 mSv or more before conception (Gardner, 1990). The study only included 52 cases of leukaemia and 23 cases of HL, hence the wide CIs. It is unlikely that these findings will ever be corroborated as the radiation doses that the fathers were exposed to were unusually high. It has been argued however, that if these cancers occurred as a result of sperm stem cells being exposed to radiation, then cancer should have been only one of many consequences, such as spontaneous abortion or other birth defects, as was seen with the victims of the atomic bomb in Japan and these should have been also examined (Coulter, 1990). Other case-controls were carried out in other nuclear plants whose workers were exposed to lower doses than that at Sellafield, but these studies reported contradictory results (McLaughlin et al., 1993, Draper, 1997). Only one other study reported a significant increase in risk of childhood leukaemia (RR = 8.0, 95%CI = 1.40 - 54.60) amongst children whose fathers had been exposed to ionising radiation (Roman et al., 1993a). The study reported that neither the cases nor the controls were exposed to more than 5 mSv of radiation before child conception, which is below the safe limit set by the NRCP. Similarly, this study also had a wide CI and a small sample size of only 54 children suggesting that the findings may be attributed to chance.

In terms of maternal exposure, a case-control study from West Germany examined the association between maternal exposure to ionising radiation from West German nuclear plants and childhood leukaemia, lymphoma and solid tumours. The study reported that maternal exposure significantly increased the odds ratio (OR) for childhood lymphoma (OR = 3.87, 95%CI = 1.54 - 9.75), but no association was found for either childhood leukaemia or solid tumours. A non-significant increase in risk for children of fathers working at nuclear plants was also reported (OR = 1.80, 95%CI = 0.71 - 4.58) (Meinert et al., 1999).

The United Kingdom Childhood Cancer Study (UKCCS) looked into the effects of household radon, in which the concentrations of radon were measured throughout a period of six months in the houses of children with leukaemias. The levels of radon in these houses were compared with those of the controls, and no evidence for higher levels of radon in houses of cases were found (UKCCS, 2002). Furthermore, a meta-analysis of five studies found that there was no evidence of association between childhood leukaemia and radon (Yoshinaga et al., 2005). The same was found for adults also (Law et al., 2000).

Ionising radiation at high levels can be lethal and long-term effects have been seen in unusual situations such as that in Japan. However, doses at lower levels, such as those observed in normal living conditions have not been shown to increase risk. The preconception paternal irradiation theory proposed by Gardner (1990) is difficult to substantiate, since there is a lack of comparable data.

2.4.2.2 Non-ionising radiation

Non-ionising radiation from natural sources such as sunlight has been known to cause melanoma and other skin cancers (Voûte, 2005). Also, electromagnetic radiation such as that emitted from electrical appliances and high voltage electricity lines has been extensively examined, but has delivered inconsistent results. For example, a meta-analysis of a group of nine case control studies found no evidence of an increase in leukaemia when exposure was below 0.4 μT (Microtesla is the measurement unit of field intensity for magnetic fields), but exposure higher than these levels was found to double the risk (Ahlbom et al., 2000). It is thought however, that some of the observed risk was related to the bias in the selection of controls, in which most of the controls who volunteer for case-control studies have a higher SES, this is because 0.4 μT is considered a very weak magnetic field.

The UKCCS also examined the association between childhood cancers and power lines by measuring the distance between a home and a particular power line in a

case-control study, but no association between cancers and field exposures and between cases and controls was found (Skinner et al., 2002). No underlying biological mechanism has been agreed upon as to how this might trigger carcinogenesis (Eden, 2010).

2.4.2.3 Alcohol consumption and cigarette smoking

Information on the relationship between parental alcohol consumption and childhood cancers, leukaemia in particular, has mainly focused on maternal consumption throughout pregnancy. For leukaemias, Severson et al. (1993) found a positive association between maternal alcohol consumption and AML in children diagnosed before their second birthday (OR = 3.00, 95%CI = 1.23 - 8.35). Although, the sample size in this study was relatively small, this is reflected in the wide CIs. (Severson et al., 1993). A second study found a similar association was reported for AML (OR = 2.64, 95%CI = 1.36 - 5.06), but not for ALL. With regards to paternal alcohol consumption, no association was found with childhood leukaemias (Severson et al., 1993, Shu et al., 1996).

Cigarette smoking is one of the most well documented carcinogens. Studies that examined parental alcohol consumption also examined parental smoking either independently or together, since both are highly correlated (Eden, 2010). One study found that paternal smoking was associated with lymphomas and neuroblastomas (RR = 1.37, 95%CI = 1.02 - 1.83 and RR = 1.48, 95%CI = 1.09 - 2.02, respectively). The same study also looked at maternal smoking during pregnancy and found that it had a positive association with childhood ALL (RR = 1.24, 95%CI = 1.01 - 1.52) (Sorahan, 1997).

The UKCCS case-control study examined the association for smoking by both parents and found no statistically significant association. Since the study depended entirely on self-reported behaviour, then any under-reporting within parents of cases could have revealed significant associations (Pang et al., 2003). It is believed that germ cell mutations and/or damage occur during spermatogenesis. This belief is supported by research that has shown a significant increase in oxidative damage of smokers' sperm DNA, and that this damage may be linked to childhood cancers and birth defects in their offspring (Fraga et al., 1996). In order to better understand any association, examination of biomarkers for genotypes and phenotypes relevant to tobacco products is essential.

2.4.3 Infections

One of the earliest suggestions of infections relating to leukaemia incidence was made in the late 1930s, in which a cluster of cases of childhood leukaemia was found in Ashington, Northumberland (Kellet, 1937). It was suggested that the cause may be due to 'some unknown specific external infection' (Kellet, 1937, p.245). After recognising that leukaemia in itself was not contagious, the idea of an infectious aetiology somewhat subsided. However, the discovery of the role of the Human T-cell leukaemia/lymphoma virus (HTLV-I) in causing adult T-cell leukaemia/lymphoma (Gallo et al., 1984), as well as findings on animal studies in which it was found that leukaemia in cats, chicken and cattle was viral in origin, sustained the idea of an infectious aetiology (Schulz, 2002).

Indeed, there is no doubt that specific infections/parasitic agents have been implicated in cancers. For example, Human Papillomavirus (HPV) infection is associated with cervical cancer (Schiffman et al., 1993). In Africa, EBV antibodies were present in most cases of BL, although not all individuals with the virus developed BL (Brady et al., 2007). Furthermore, the Hepatitis B virus (HBV) is associated with liver cancer, but patients usually are only diagnosed with acute hepatitis. Therefore, the development of hepatic cancer may be triggered by environmental factors after the infection, but HBV increases the risk nonetheless (Mera, 1997). In addition, viruses that contain reverse transcriptase – an enzyme that shifts the viral ribonucleic acid (RNA) to deoxyribonucleic acid (DNA) – have been found to have a role in some cases, whereby the viral DNA is merged with the host cell, hence causing cell disruption (Mera, 1997). Examples of RNA viruses include the Human Immunodeficiency virus (HIV), which is an established risk factor for Kaposi Sarcoma, and NHL as well as the HTLV-I and HTLV-II which causes hairy cell leukaemia (Engels, 2001, Mera, 1997).

The pathological findings coupled with epidemiological studies are in favour of an infectious aetiology of childhood leukaemia/lymphoma. The way in which infections spread is governed by two important concepts in the study of infections: herd immunity and hygiene hypothesis.

2.4.3.1 Herd immunity

The first concept related to infectious disease transmission is known as herd immunity, which is based on the theory that the extent of spread of an infectious disease in a particular community is based on a balance between the number of susceptibles to that infection and the number of non-susceptibles, i.e. those who

are immune either due to a prior exposure, vaccination or who are genetically immune. Resistance of the susceptibles to that infection occurs when a sufficient proportion of the community are immune, i.e. herd immunity. The herd effect occurs for the reason that a high enough proportion of the community is immune, which makes it less likely that a susceptible individual will acquire that infection (John and Samuel, 2000, Gordis, 2013).

In order for herd immunity to occur, certain conditions should be met. First, random mixing, so that the probability that an infected individual is mixing with all other individuals is the same. Where the infected individual only interacts with the susceptibles, then it is likely that the infection will spread to them (Gordis, 2013). By analogy, communities in isolated rural areas are in effect susceptible to new infections that may be brought in by infected individuals, because they have little or no herd immunity against this new infection. An example is that of the measles infection which produced an epidemic in the Faroe Islands when infected individuals entered the isolated population (Panum, 1847). A good determining factor of the amount of mixing within populations is population density – the higher the population density the better the chance for mixing, which in turn increases the likelihood of producing at least one secondary case of infection from a primary case (Anderson and May, 1990). The second condition is that the infectious agent should be restricted to a single host species. Hence, if this condition is not met in that the infectious agent could be transmitted from outside the human host, then herd immunity will be compromised as there are other means for transmission (Gordis, 2013).

Herd immunity is very important because it may not be possible to vaccinate 100% of the population to achieve immunity. However, if a large proportion of the population is vaccinated, for example by governmental vaccination programmes, then the rest that are unvaccinated or susceptible to the infection, such as those who refuse vaccinations due to religious beliefs, or individuals with compromised immune systems, will be protected as a result of herd immunity. The proportion needed to achieve herd immunity differs from one infection to another, for example for measles it is thought that 92% to 95% coverage is sufficient to achieve herd immunity, whilst for the polio virus 80% to 85% coverage is required (Anderson and May, 1990). This concept of herd immunity is postulated to play a role in the aetiology of childhood leukaemia where low herd immunity is assumed to increase the risk of the disease.

2.4.3.2 Hygiene hypothesis

The immune system is programmed to anticipate exposure to infections in utero and postnatally in early life. Such exposures are necessary to be able to modulate, and prime its immunological network of interconnected cells for future efficient responses. Therefore, it is assumed that the absence of such infections in early life may cause a dysregulated immune response to any later infections. Delayed exposure to infections may be due to a lack of exposure as a result of social or geographical isolation, such as that associated with higher socioeconomic positions (Greaves, 1988).This is related to the second concept which was proposed by Strachan (1989) and is known as the 'hygiene hypothesis'. It was initially suggested in relation to hay fever, but has also been suggested to play a role in the aetiology of autoimmune diseases such as type 1 diabetes and multiple sclerosis (Bach, 2005, Fleming and Fabry, 2007). It sought to explain the increase in hay fever and suggested that it was due to the improved hygiene in western industrialised countries, which decreases exposure to infections in early life due to better hygienic living conditions, reduced social contact and reduced family size – all characteristics of higher affluence.

Therefore, close examination of the socioeconomic position of cases is vital in the understanding of diseases hypothesised to have an infectious aetiology, such as childhood leukaemia/lymphoma and type 1 diabetes. The behaviours and lifestyle factors linked to SES matter, such as breastfeeding, overcrowding and hygienic conditions. Indeed, higher incidence of childhood leukaemia was reported in populations with higher socioeconomic positions (Doll, 1989). Furthermore, SES plays a role in the delayed infection hypothesis, which postulates that common childhood ALL is initiated by a genetic mutational event in utero, and that for overt leukaemia to occur a second mutation is required. A detailed discussion of SES and the delayed infection hypothesis is discussed in sections 2.5.

2.4.3.3 Epidemiological evidence for the role of infections in childhood cancers

Channels for infectious exposure related to herd immunity and the hygiene hypothesis have been examined in relation to childhood leukaemia in several studies. For example, breastfeeding is thought to be beneficial as it exposes infants to foreign antigens and infections through close maternal contact, and hence results in immunity against these infections. The UKCCS reported a non-significant OR of 0.89 (95%CI = 0.80 - 1.00) if the child has ever been breastfed. The same study

reviewed 15 case-control studies and reported a statistically significant reduction of risk with children who were ever breastfed (OR = 0.86, 95%CI = 0.81 - 0.92) and the reduction was more pronounced for children who were breastfed for a period of six months or more. Similar significant reductions were found for HL and all childhood cancers combined (Beral, 2001). If this association is real, case-control studies may not be the best method to measure it, since the controls tend to be from higher socioeconomic groups, whilst breastfeeding is usually higher in these groups. This serves as an obstacle towards unbiased evidence of any true effect.

It is important to understand the role that PM plays in epidemiological studies that deal with the spread and distribution of diseases, especially with communicable infectious diseases which may increase with the increased contact made between susceptible and infected individuals through migration (Carver, 2003). The PM hypothesis was suggested by Kinlen (1988) in relation to childhood cancers in an attempt to explain the higher incidence of childhood leukaemia near the British nuclear power stations at Sellafield and Dounreay. The 1988 study proposed that leukaemia may be a rare response to a common infection, and that occurrence of this infection is facilitated by PM, which occurs when a relatively isolated community which has not yet been exposed to the infection (susceptibles) receives a rapid influx of newcomers mostly from urban backgrounds (infecteds) (Kinlen, 1988, Kinlen et al., 1995). A plethora of research studies exist in the literature using different proxy measures for PM, these are discussed in more detail in section 2.4.3.4.

The evidence for the association between vaccinations and childhood leukaemia has been inconsistent. Four studies reported a protective effect for the haemophilus influenza B (HIB) vaccine, measles and the Bacillus Calmette-Guérin (BCG) virus which protects against tuberculosis with RR/OR ranging from 0.1 to 0.57 (Groves et al., 1999, Schuz et al., 1999, Nishi and Miyake, 1989, Hartley et al., 1988). On the other hand, a border line significant increased risk with the measles vaccine was reported in another study (OR = 1.9, 95%CI = 1.00 - 3.50), although it may be due to chance since the ORs for the other vaccines within the study were below 1.00 (Dockerty et al., 1999).

It is important to understand that the idea of mixing in the PM hypothesis is rapid and sudden, whereas the mixing necessary to maintain herd immunity which exists prior to any exposure to infection is protective against leukaemia. The most compelling evidence of a protective effect of PM against cancers with a potential infectious aetiology was found in studies that examined attendance of children at

day care centres. A review of 14 case-control studies showed that almost all showed a protective effect against childhood leukaemia. The two largest studies which were the UKCCS and the North California Childhood Leukaemia Study (NCCLS) both reported similar associations (OR = 0.66, 95%CI = 0.56 - 0.77 and OR = 0.60, 95%CI = 0.28 - 1.27, respectively) (Gilham et al., 2005, Ma et al., 2005). The UKCCS reported that a dose-response effect was seen in which the reduction was substantially pronounced with formal day care attendance with at least four other children, and the NCCLS found a significant dose-response relationship between child-hours of exposure and a reduction in risk of childhood ALL for non-Hispanic white children.

On the other hand, other studies found a link between infections and increased risk of childhood leukaemia. One such study of maternal infections during pregnancy occurred in a case-control study based in Finland. It found a significantly increased risk of EBV infection and ALL, where the odds ratio was 2.9 (Lehtinen et al., 2003). Also, lower genital tract infection was found to have an elevated OR of 1.8, and repeated exposure to the infection was associated with a non-significant increase in risk (Naumburg et al., 2002).

The three hypotheses that attempt to explain the aetiology of childhood leukaemia are discussed in further detail below.

2.4.3.4 Population mixing and childhood leukaemia

A substantial amount of literature has emerged to try to explain the possible mechanism behind the clustering of childhood leukaemia and lymphoma during the last 30 years (Gatrell, 2011). To date, the definition of PM remains elusive, as researchers disagree on what this term represents (Law et al., 2008). Generally, it may be described as the ‘movement and interaction of people over time and space’ (Miller et al, 2007, p. 626). There are several ways in which populations do mix, whether partaking in leisure activities, moving to areas or commuting to work. Children mix by attending day care centres, schools and playgroups. However, the concept remains complex, no right or wrong answer exists on how to measure PM, although certainly some measurements are more robust than others (Law et al., 2008). These are discussed further below.

A series of studies by Kinlen and others, both within the UK and other countries, have used different definitions and proxy measures for PM, which partly explains why they have come up with such equivocal results. The differences have been mainly due to data availability issues or simply because of prior beliefs of the

author, such as occupation as a measure for PM. The studies may be grouped into several categories based on the level of study, i.e. area or individual level and type of measurement used in each study. A summary of all studies and their types are presented in Tables 2.5 and 2.6 for childhood leukaemias, and in Table 2.5 for childhood diabetes.

2.4.3.4.1 Area based studies

The majority of studies on PM and childhood cancer were carried out at the population level, i.e. were ecological in nature. These came up with measures of PM as proxies for the number of circulating infections within a community (Law et al., 2008). Although ecological studies are often appropriate to use in rare diseases, such as childhood leukaemias, by increasing the power of the statistical analyses through aggregating the number of cases, they do suffer from a few disadvantages. First, ecological study designs suffer from the ecological fallacy, whereby associations observed on the area level may not hold on the individual level. Second, they are susceptible to confounding factors that are thought to influence the outcome, so in the case of childhood leukaemia/lymphoma some confounders include breastfeeding, vaccinations and attending day care centres. This is mainly because confounders are extremely difficult to collect and measure on the community level. Also, ecological studies typically rely on routinely collected data that tend to provide a crude measure of the exposure of interest at one point in time (Ebrahim and Bowling, 2005). Several types of PM measures were used in these studies, as summarised in Table 2.7.

The majority of area-based measures used population growth (Kinlen, 1988, Kinlen et al., 1990, Dockerty et al., 1996, Alexander et al., 1997) and population change (Wartenberg et al., 2004, Langford, 1991, Koushik et al., 2001, Clark et al., 2007). Although all, except for the study in New Zealand (Dockerty et al., 1996), concluded support for the PM hypothesis, as suggested by Kinlen (1988), there are issues with the design and methodology of these studies. First, these studies were retrospective in nature, which poses an important issue in that the areas chosen by the researcher were only chosen due to an observed excess of cases. This is related to a methodological term known as boundary shrinkage in the investigations of possible clusters, such as in the case of the Sellafield childhood leukaemia cluster (Olsen et al., 1996). Boundary shrinkage can be described as limiting the investigation to the population from which the cases were identified geographically, as well as the time period of the suspected cluster. This may be described as the

‘Texas sharpshooter who first fires his gun and then draws the target around the bullet hole’ (Olsen et al., 1996, p. 864). Since the population is involved in the calculation of the expected number of cases by multiplying the incidence/death rates in age/sex strata by that population, then limiting that population to a set of boundaries both in space and time will greatly affect the resulting ratio. Hence, it is expected to find an excess in such areas, the narrower the area is, the higher the excess in cases (Olsen et al., 1996). A better practice is to generalise the study to cover a wider area, so that for example instead of only examining Sellafield, it may have been better to look at England as a whole. Furthermore, the sole use of crude measures of incomers has not made it possible to assess the place of origin of incomers.

Other studies examined PM through occupational moves, i.e. any migration whether temporary or permanent for occupational reasons (Kinlen et al., 1991, Kinlen and Stiller, 1993, Kinlen, 1995, Kinlen, 1997, Boutou et al., 2002, Kinlen, 2006, Fear et al., 1999b). All were supportive of the Kinlen’s hypothesis except for the study by Fear et al. (1999b), which is also the only study that did not suffer from boundary shrinkage. Fear et al. (1999b) did not limit the study to specific areas, on the contrary, they utilised routinely collected mortality data from leukaemia from across England and Wales between the years 1959 to 1963 and 1970 to 1990, and found a non-significant inverse association with high social contact for overall leukaemia, and leukaemia in the 0-4 age group and ALL. They concluded that high social contact is in fact protective against leukaemia. The results are unlikely to be due to chance since for the low social contact group almost all of the risk estimates were not significant.

Commuting and residential migration have been used as proxy measures for PM in the UK (Kinlen et al., 1990), France (Rudant et al., 2006) and Hungary (Nyári et al., 2006), all of which concluded their support for the PM hypothesis. None of these studies however, adjusted for SES and all had the same boundary shrinkage problem. On the other hand, a few studies used a reproducible measure of PM from routinely collected data as opposed to crude numbers using the Shannon index of diversity (Shannon, 1948), which takes into account both the volume and diversity of incomers (Stiller and Boyle, 1996, Dickinson et al., 2002, Dickinson and Parker, 1999, Parslow et al., 2002, Stiller et al., 2008). Some found a significant positive association between childhood leukaemia/NHL and migration (Dickinson et al., 2002, Stiller and Boyle, 1996, Dickinson and Parker, 1999, Stiller et al., 2008). Although results of these studies arrived at the same conclusion, they should be compared with care as they analysed data on different geographical levels and

covered different years. However, one study found contrasting results (Parslow et al., 2002), noting that incidence of ALL and all leukaemia groups was significantly low in areas of high childhood PM in terms of migration diversity (IRR = 0.67, 95%CI = 0.47 - 0.94 and IRR = 0.72, 95%CI = 0.54 - 0.97 respectively). Another found no association between population volume and incidence of ALL, although a non-statistically significant positive association was found for incidence in rural areas (IRR = 1.26) and incidence in the 0-4 age group was higher in wards where incomers were more diverse (Stiller et al., 2008). The study does not exclusively support the PM hypothesis, but does support an infectious aetiology for ALL in that immune responses to ordinary infections play a major role in its aetiology.

These groups of studies should not be compared to the earlier studies by Kinlen mainly because the areas he chose witnessed sudden and rapid population growth and were examined retrospectively, unlike these studies that examined the effects of PM in areas that did not necessarily experience rapid influxes of populations (Parslow et al., 2002). A possible explanation of the findings of Parslow et al. (2002) and Stiller et al. (2008) is the protection conferred upon those living in areas with high levels of PM, since these high levels increase the chance of exposure to a wide range of infections, thereby improving the immune system. This suggestion is related to the alternative hypothesis suggested by Greaves (1988). The findings from the study by Parslow et al. (2002) support this hypothesis since areas witnessing low PM have a higher incidence of ALL.

A few studies on PM have examined the effects of large one-off events, mostly focusing around war evacuations and refugees. These studies, along with some of the earlier work on PM, were concerned with threshold effects, i.e. where considerable movement or migration occurred, such as in war time related migration studies (Kinlen and John, 1994, Kinlen and Balkwill, 2001), all of these studies supported the PM hypothesis.

One study examined incidence of leukaemia across 34 countries by gathering mortality information from the WHO mortality database. It was found that leukaemia mortality was high in Greece, Denmark, Sweden and Italy. Kinlen offered explanations for the high incidence in Greece and Italy as being the countries characterised as being rural, and having experienced significant population movement and rural-urban movement. However, no explanation was given for increases in Denmark or Sweden which were, as Kinlen noted himself, urban. A possible explanation for the high increases in Denmark and Sweden may be the high SES of these countries. These two countries have been categorised as being

within the highest-income by The World Bank (TWB, 2014). Under the hygiene hypothesis, communities with a high SES have fewer infections in early life as a result of better hygienic conditions (Strachan, 1989). This is further linked to the delayed infection hypothesis (Greaves, 1988).

2.4.3.4.2 Individual based studies

The majority of individual-based studies on PM relate to paternally mediated transmission of infections, due to the availability of paternal occupation information relating to each case of leukaemia (Roman et al., 1993b, Kinlen and Bramald, 2001, Pearce et al., 2004, Keegan et al., 2012, Law et al., 2003). Some have supported the PM hypothesis (Kinlen and Bramald, 2001, Pearce et al., 2004, Kinlen et al., 2002). One found that parents of children with leukaemia did not seem to have more or less social contact (Roman et al., 1993b). On the other hand, a recent study found that higher paternal occupational social class was associated with an increased risk for lymphoid leukaemia (OR = 1.42, 95%CI = 1.03 to 1.94), with a significant declining trend with lower paternal social class (Keegan et al., 2012). Although this study did not examine the association with regard to the urban/rural status of cases, and the resulting reduction in risk with the lower social class does not support the PM hypothesis per se, it does give credible evidence to the infectious aetiology of childhood leukaemia, even in urban areas where higher social class does include some type of social isolation.

Only one case-control study examined the effect of residential mobility – as a proxy for PM – on childhood leukaemia and NHL in the UK (Law et al., 2003). Again, the study assessed PM using census-based data to derive both population volume and population diversity, which was calculated using the Shannon index of diversity (Shannon, 1948). The population volume for all ages and for children was not associated with ALL. There was a significant increase in risk of ALL for the lowest percentile of mixing diversity for all age populations (OR = 1.37, 95%CI = 1.00 to 1.86), However, the study was not supportive of the PM hypothesis, similar to that of Parslow et al. (2001).

These studies looked into paternal occupational/social contact only, without looking into maternal contact. The examination of maternal occupational and social contact especially throughout pregnancy and around the time of diagnosis should be examined, since usually mothers are closer to their children than fathers, thus it is more likely that mothers could transmit infections to their children. Also, if mothers

have more social contact then they may confer immune protection to the child through pregnancy and/or breastfeeding.

2.4.3.4.3 Population mixing and childhood diabetes

Research shows that childhood leukaemia particularly ALL, and childhood type 1 diabetes mellitus (DM) share similar geographical characteristics. For example, Staines (1996) showed that both diseases are more common in affluent areas, in areas of low population density and within rural areas. Also, countries with high or low incidence of either disease are likely to have a corresponding rate for the other disease (Feltbower et al., 2004). Although the two diseases do not seem to be biologically similar, evidence suggests that environmental exposures probably influence occurrence of both diseases (Parslow et al., 2005, Staines, 1996).

Several studies on PM and parental occupational contact with childhood type 1 diabetes have been carried out. For example, the case-control study by Fear et al. (1999) found no association between childhood type 1 DM and high maternal or paternal contact occupations in Yorkshire and Northern Ireland (Fear et al., 1999a). Unlike previous studies on PM and childhood leukaemia which mainly focused on fathers' occupational contact retrospectively, this study investigated both maternal and paternal occupational contacts prospectively, thus a more realistic measure of parental social contact was captured. Also, McKinney et al. (2000) examined social mixing of children through attendance at day care centres as a proxy for exposure to infections. The study found that there was a borderline significant negative association between day care attendance for children under one year of age and incidence of childhood type 1 DM (OR = 0.71, 95%CI = 0.51 – 1.00). The same association was found for exclusively breastfeeding for three months and atopy (OR = 0.63, 95%CI = 0.39 – 1.01 and 0.41, 95%CI = 0.41 – 0.81). Furthermore, the study results show a significant trend of decreasing risk with increasing numbers of childhood contacts reflecting a dose-response relationship that strengthens the association as a causal one (McKinney et al., 2000). Attendance to pre-school day care centres and breastfeeding are good proxy measures for measuring exposure to infections in early life, especially as they also cause exposure to sub-clinical or asymptomatic infections. A similar effect was seen for childhood type 1 DM when PM was measured using the Shannon Index of Diversity (Parslow et al., 2001). More recently, the same association was found in New Zealand (Miller et al., 2007). The study, however, was severely affected by mathematical coupling in the multivariate model, which occurs if two variables share a common component.

Mathematical coupling causes bias to parameter estimates due to violation of the assumption of lack of collinearity between the variables, thereby giving misleading results (Tu and Gilthorpe, 2011). In this study, the multivariate model included PM as an overall measure against individual components of that measure.

These studies on PM and childhood type 1 DM are very relevant to childhood leukaemia. Firstly, both diseases share common epidemiological and possible aetiological features (Feltbower et al., 2004). It is now accepted that environmental triggers, such as delayed exposure to infections play a role in children who are already genetically susceptible to DM (Miller et al., 2007, Daneman, 2006). This scenario is closely linked to the 'delayed infection hypothesis', although for this hypothesis to play a role in the aetiology of childhood leukaemia, a pre-malignant clone developed in utero should occur, as well as some degree of genetic susceptibility that may be imposed by an inherited allelic variation in the immune response genes of the offspring (Greaves, 2009). The previous studies, although relating to a biologically different disease and not in support of the PM hypothesis, add evidence to support the delayed infection hypothesis where immunological isolation due to social isolation (whether that be in rural areas that allow for only a limited scope of infections, or communities in urban areas that are affluent and thus live a more isolated lifestyle), may lead to childhood type 1 DM and childhood leukaemia (Parslow et al., 2002, Law et al., 2003).

Table 2.5: Area-based studies on population mixing and childhood leukaemia

Pop. Mix. type	Author (Year)	Areas & Years covered	Study pop.	Methods	Results	Limitations	Conclusion
Population growth	Kinlen (1988)	Glenrothes Scotland 1951 - 1967	0 – 24	Observed and expected measure of childhood leukaemia mortality in Glenrothes	In the period of great growth between 1951 and 1967, an excess of cases was found in <25 year olds	Ecological study2. Use of mortality rather than incidence data. 3. Assumes a threshold effect 3. Subgroups were not chosen a priori 4. Boundary shrinkage 5. No account of confounders e.g. SES	Supportive of PM hypothesis
	Kinlen (1990)	British New Towns UK 1946 - 1975	0 – 24	Observed and expected measure of childhood leukaemia compared between overspill and rural new towns	In the period between the years of designation of the towns to 1965, an excess of deaths in the 0–4 age groups was found in rural towns. No excess was found in overspill towns.		
	Dockerty et al. (1996)	Rural New Towns New Zealand 1949 - 1983	0 – 14	Age adjusted rate ratios of leukaemia cases were derived for the three rural new towns combined and then compared to the rest of the areas in the country	No significant increase in age adjusted rate ratios in the rural areas.	Ecological study2. Subgroups were not chosen a priori 3.Boundary shrinkage 4. No account of confounders e.g. SES	Not supportive of PM hypothesis
	Alexander et al. (1997)	Aggregated areas Hong Kong 1984 - 1990	0 – 4	Standardised morbidity ratios of leukaemia cases were derived for TPUs. Also, spatial clustering was checked for association with leukaemia.	Evidence of clustering of ALL cases in the TPU found within the highest population growth category (p = 0.005).		Supportive of infectious aetiology

Pop. Mix. type	Author (Year)	Areas & Years covered	Study pop.	Methods	Results	Limitations	Conclusion
Population change (Increase or decrease in populations)	Langford (1991)	England and Wales 1969-1973	0 – 14	IRRs calculated for each local authority area compared to the national average. Then aggregated to 8 categories based on 10% increments of pop. change	A statistically significant increase of leukaemia cases found in rural areas close by large urban areas (RR = 1.41, 95% CI = 1.26 – 1.76).	1. Ecological study2. Use of mortality rather than incidence data 3. No account of confounders e.g. SES	Supportive of PM and Greaves hypotheses
	Koushik et al. (2001)	Ontario Canada 1978 - 1992	0 – 14	Leukaemia incidence rate ratios were estimated by Poisson regression in relation to 10% increments of pop. change and urban/rural status	Leukaemia incidence increased in children 0–4 years residing in rural areas that witnessed population increase of > 20% (RR = 1.8, 95% CI = 1.1 – 2.8).	1. Ecological study 2. No account of confounders e.g. SES 3. Did not study mixing diversity	Supportive of PM hypothesis
	Wartenberg et al. (2004)	US SEER data 1973 - 1999	0 – 19	Study period was divided to three 10-year periods, and pop. change was categorised to three groups, >0 to 10%, >10% to 20% change, and >20% population change. Then both logistic regression and Poisson regressions were conducted.	Analysis of base case data shows an OR of 1.9 (95% CI = 1.0 – 3.6), which steadily increases to 2.6 (95% CI = 1.5 - 4.6. CNS tumours also showed an increase, however the wide CIs pose questions to the validity of the ORs.	1. Ecological study. 2. Low sample size in subgroups 3. Very broad geographical resolution 4. No account of confounders e.g. SES	
	Clark, et al. (2007)	US Ohio 1996 - 2000	0 – 19	Ohio county divided to quartiles of median income, % urban vs. rural and pop. density. Indirect standardisation to US pop. used to obtain rates, and used Poisson regression.	High rate of ALL in 1–4 groups in counties >10% - 64.3% pop. growth (R = 7.1, 95%CI = 5.3 – 8.9). No excess found in nine counties with little pop. growth or a decreasing pop (-0.8%).	1. Ecological study 2. No account of confounders, e.g. SES	

Pop. Mix. type	Author (Year)	Areas & Years covered	Study pop.	Methods	Results	Limitations	Conclusion
Occupational moves and paternal occupational contact	Kinlen, and Hudson (1991)	England and Wales rural districts 1950 - 1953	0 – 15	Rural and urban LADs grouped by counties and ranked by proportion of servicemen. Five groups created. LADs grouped to 10ths. Leukaemia mortality was examined in these groups.	Significant excess of leukaemia in children <15 years in the highest combined fifth group of servicemen (O/E=1.21, trend P<0.01), due to excess in >1 year age (O/E=4.13, trend p<0.01).	1. Ecological study 2. Retrospectively examining unusual events 3. Subgroups were not chosen a priori 4. Boundary shrinkage 5. No account of confounders e.g. SES	Supportive of PM hypothesis
	Kinlen et al. (1993)	Scotland 1974-1988	0 – 25	Rural areas of Scotland divided to three groups with similar numbers of children. Groups ranked by prop. oil workers. Leukaemias and NHL examined in these groups for three five-year periods.	Early post-mixing period (1979 – 1983) excess in leukaemia/NHL for 0–4 years found (RR = 2.67, 95%CI = 1.30 – 5.88), in rural high oil workers group. No excess in other periods.		
	Kinlen et al. (1995)	Scotland	0 – 15	Observed/expected leukaemia and NHL mortality and incidence examined in areas close to construction sites, located more than 20 km from a population centre, they were also examined in terms of social class.	Excess of leukaemia and NHL in 0–14 and 0–4, (O/E = 1.37, 95%CI = 1.10 – 1.73) and (O/E = 1.51, 95%CI = 1.15 – 1.63). Excess in cases pronounced in high social class in 0–4 age group (O/E = 2.16, 95%CI = 1.39 – 3.22).	1. Ecological study 2. Retrospectively examine unusual events 3. Subgroups were not chosen a priori 4. Boundary shrinkage	
	Boutou et al. (2002)	La Manche France 1979 - 1998	0 – 24	PM index created by dividing the number of workers born outside La Manche by number of men aged 20 to 59. Rural communes were ranked by prop. of workers with similar expected. Statistical methods included indirect standardisation, Poisson and extra-Poisson variation used.	High risk of ALL in the rural communes with high population mixing (IRR = 2.721, 95%CI = 1.10 – 6.35) and effect was most shown in the 1–6 age group (IRR = 5.46, 95%CI = 1.43 – 19.84)	1. Ecological study 2. Retrospectively examine unusual events 3. Subgroups were not chosen a priori 4. Boundary shrinkage 5. No account of confounders e.g. SES	Supportive of an infectious aetiology

Pop. Mix. type	Author (Year)	Areas & Years covered	Study pop.	Methods	Results	Limitations	Conclusion
Occupational moves and paternal occupational contact	Kinlen L.J. (2006)	West Cumbria England 1941 – 1943	1 – 14	Observed/expected mortality of leukaemia compared between Ennerdale, Millon, Whitehaven, and across West Cumbria, where PM occurred as a result of the construction of the Royal Ordinance Factories .	Excess of leukaemia in 1–14 year olds in West Cumbria (O/E = 4.48, 95%CI = 1.14 – 12.19) due to excesses in Whitehaven (O/E = 7.69, 95%CI = 1.29 – 25.41).	1. Ecological study 2. CIs reflect the very low sample size 3. No account of confounders e.g. SES	Supportive of PM hypothesis
	Kinlen (1997)	Five previous PM studies	0 – 14	Occupations of five PM studies grouped to low, medium, high and indeterminate according contact. Cases extracted and assigned to each group. Controls obtained from the same studies where possible.	The high contact occupational group was related to excess in leukaemia in previous studies of PM combined (O/E=2.00, P < 0.001). No association was found for the general population	1. Ecological study 2. Subgroups were not chosen a priori 3. No account of maternal or social contacts	
	Fear et al. (1999)	England and Wales 1959 – 1963 1970 – 1990	0 – 14	Leukaemia and paternal occupational social contact was analysed using proportional mortality ratio. The 95%CI and two-sided tests of significance estimated from chi-square or Poisson distribution.	Negative association of lymphoid leukaemia and high contact (PCMR = 92, 95%CI = 83 - 103). Age 0–4, negative association for all leukaemia and high contact (PCMR = 94, 95%CI = 83 - 108).	1. Ecological study 2. Use of mortality rather than incidence data 3. No account of confounders e.g. SES	Not supportive of PM
	Kinlen et al. (1991)	28 county boroughs UK 1971 - 1981	0 – 24	Change in commuting studied as level of 1981 minus level in 1971 against baseline pop. of 1971. Observed/expected numbers calculated for three five-year periods.	Excess in leukaemia found in the decile that had the highest increase in commuting in both 0–4 and 0–14 age groups (O/E=1.76, P<0.001 and O/E=1.5, P<0.001)	1. Ecological study 2. Boundary shrinkage 3. No account of confounders e.g. SES	Supportive of PM hypothesis

Pop. Mix. type	Author (Year)	Areas & Years covered	Study pop.	Methods	Results	Limitations	Conclusion
Commuting and residential mobility	Stiller and Boyle (1996)	403 districts in England and Wales 1979 - 1985	0 – 14	Proportion of migrants and commuters from 1981 census used. A value of diversity given to districts based on Shannon Index. SES based on three measures. Poisson regression used to examine associations.	For 0–4 age group, a significant increase in trend with the prop. of all migrants and child migrants. For 5–9 a significant increasing trend was found for only child migrants.	1. Ecological study 2. Broad geographical resolution, thus not sufficiently sensitive 3. Migration data from decennial census	Supportive of PM hypothesis
	Dickinson et al. (2002)	Census wards in England and Wales 1966 - 1987	0 – 14	Poisson regression included Townsend scores. Migration from 1981 census, as those who were resident outside the ward a year previously for six levels. Diversity of migrants examined by Shannon Index.	PM was associated with leukaemia and NHL (RR = 1.9, 95%CI = 1.2 – 2.9). A non-significant increase was found in affluent rural areas (RR = 14.0, 95%CI = 0.3 – 26.6).	1. Ecological study 2. Long period under study does not capture subtle shifts in the population	
	Parslow et al. (2002)	532 wards in Yorkshire 1981 - 1996	0 – 14	Pop. migration and PM examined for any age, ≥1 and children (1–15 years). Pop diversity calculated using Shannon Index. Poisson regression for analysis.	Decrease in IRR for ALL in high decile of PM (IRR = 0.67, 95%CI = 0.47 – 0.94) also all leukaemias (IRR = 0.72, 95%CI = 0.54 – 0.97). Reduced IRR for ALL in high decile of any age PM (IRR = 0.68, 95%CI = 0.47– 0.99).	1. Ecological study 2. Migration data from decennial census	Supportive of Greaves
	Rudant et al. (2006)	French communes 1990 - 1998	0 – 6	Yearly SIRs of all leukaemias and its specific subtypes were calculated. SIRR was calculated as the ratio of the SIR relative to the SIR of the lowest incoming rates.	ALL increase with migration in rural areas, and was marked when migration was from another region (SIRR = 2.59, 95%CI = 1.48 – 4.49). Weaker trend found in non-rural areas.	1. Ecological study 2. No account of confounders e.g. SES	Supportive of an infectious aetiology

Pop. Mix. type	Author (Year)	Areas & Years covered	Study pop.	Methods	Results	Limitations	Conclusion
Commuting and residential mobility	Nyari et al. (2006)	South Hungary 1981 - 1997	0 – 5	PM analysed as prop. of all incomers, and prop. of child incomers >5 years, and were standardised. Poisson regression used to assess possible relations.	ALL increased with increasing PM (RR = 2.13, 95%CI = 1.02 – 4.44). The increase was most marked in boys (RR = 3.1, 95%CI = 1.1 – 8.5).	1. Ecological study 2. No account for confounders e.g. SES	Supportive of PM
	Bellec et al. (2008)	French communes 1990- 2003	0 – 14	PM computed as incomers from outside the department, region or commune.. Poisson regression to assess associations between PM measures and CL.	A prop of >13% of migrants from regions to isolated commune associated with CL (SIRR = 1.18, 95%CI = 1.01 – 1.39). In 0–4 group, migration distance >185km associated with CL in isolated communes (SIRR = 1.41, 95%CI = 1.09 – 1.83).		Supportive of an infectious aetiology
	Stiller et al. (2008)	England and Wales 1986 - 1995	0 – 14	Counts of children in wards from 1991 census to provide estimates of person –years at risk. PM measured by Shannon Index. Poisson regression used to examine any associations.	incidence was higher in rural wards, and increased with the diversity of incomers and was lower in deprived wards.	1. Ecological study 2. Migration data from decennial census	
	Van Lar et al. (2014)	Census wards England	15 – 24	Leukaemia, lymphoma and CNS data obtained by ward. PM index measured by Shannon index from 1991 census. Negative binomial regression used.	High PM associated with low incidence of CNS (IRR = 0.83, 95%CI = 0.75-0.91). No association found for leukaemias and lymphomas. Lower incidence of CNS and lymphomas in deprived wards.	1. Ecological study 2. Migration data from decennial census	

Pop. Mix. type	Author (Year)	Areas & Years covered	Study pop.	Methods	Results	Limitations	Conclusion
One-off events	Kinlen and John (1994)	LADs in England and Wales 1945 - 1949	0 – 14	The rural LADs ranked by ratio of war evacuees. Districts divided to three groups with similar numbers of children, but having different ratios of evacuees to local children.	A significant excess of leukaemia was found in the 0–14 age group for the rural high category of evacuee index relative to the low category (RR = 1.47, 95%CI = 1.07 – 2.06).	1. Ecological study 2. Subgroups not selected a priori 3. Crude measure of PM 4. No account of confounders e.g. SES	Supportive of PM hypothesis
	Kinlen and Petridou (1995)	34 European countries 1950 - 1987	0 – 14	SMRs were compared across countries.	Rates were highest in Greece, Italy, Sweden and Denmark.		
	Kinlen, L.J. & Balkwill, A (2001)	Scotland 1941 – 1970	0 – 14	Observed and expected deaths from leukaemia were compared between war time cohort and post war cohort.	Significant excess of deaths from leukaemia in war time cohort (O/E = 3.64, 95%CI = 1.67 – 6.92), no excess in post war cohort.	1. Ecological study 2. Examination of a threshold effect (war) retrospectively 3. Crude measure of PM 4. No account of confounders e.g. SES	
	Labar et al. (2004)	Croatia 1991 - 1995	0 – 14	Incidence rates were calculated for each county in pre-war period, war period, post-war period.	Rates of ALL increased in the war period in the four counties that were mostly affected by PM (IR = 3.74, P<0.05).		

Table 2.6: Individual-based studies on population mixing and childhood leukaemia

Pop. Mix. type	Author (Year)	Areas & Years covered	Study pop.	Methods	Results	Limitations	Conclusion
	Kinlen and Bramald (2001)	Scotland 1950 - 1989	0 – 14	Cases matched to three controls by age and sex. Paternal occupations grouped according to level of social contact. Conditional logistic regression used and analysis adjust for social class.	A significant positive trend for children aged 0 to 4 years with increasing paternal contact level in rural areas (P=0.02) adjusted for social class, but not in urban areas (P=0.26).	1. Crude approach in grouping occupational contact categories 2. No account of maternal or opportunities for social contacts 3. The occupations may have changed during the long study period leading to exposure misclassification	Supportive of PM hypothesis
	Kinlen et al. (2002)	Sweden 1958 - 1998	0 – 14	Cases matched to four controls by age, sex and district. Grouping of paternal contact was similar to previous studies. Conditional logistic regression and test for trend used.	In rural areas, high paternal contact had OR of (3.47, 95% CI= 1.54 – 7.85) for age 0–4. Increase in positive trend for three contact categories (P for trend 0.02).		
	Pearce et al. (2004)	England 1968 - 1997	0 – 14	Cases matched to two controls by age and sex. Classification of occupational contact category based on number of daily contacts. OR and 95% CI by conditional logistic regression.	Increased risk of leukaemia/NHL found with the increase in paternal occupational contacts. Also, there was an increased risk for both diseases with fathers who were teachers around the time of birth.		Supportive of an infectious aetiology

Pop. Mix. type	Author (Year)	Areas & Years covered	Study pop.	Methods	Results	Limitations	Conclusion
Parental occupational contact	Roman et al. (1994)	West Berkshire and North Hampshire England 1972 - 1989	0 – 4	For 54 leukaemia/NHL cases, four controls were matched by sex, birth date, mother's age, residence at birth and diagnosis date. 95%CI computed using conditional exact methods on the binomial distribution	No association was found between incidence of leukaemia and/or NHL and the family's estimated social contact.	1. Crude approach in grouping occupational contact categories 2. No account of maternal or opportunities for social contacts 3. Boundary shrinkage 4. No account of confounders e.g. SES	Not supportive of PM hypothesis
Residential mobility	Law et al. (2003)	Britain 1991 - 1996	0 – 14	A matched case-control study, two controls per case matched by age and sex. Townsend score was used for deprivation. PM defined as volume and diversity for child and any age measured by Shannon Index and. Urban/rural status calculated by population density.	Increased risk of ALL in lowest category of mixing diversity for all ages (OR = 1.37, 95%CI = 1.00 – 1.86) Also for NHL but for child PM (OR = 2.83, 95%CI = 1.15 – 7.00). Volume of PM not associated with ALL. Increased risk of ALL in rural areas (OR = 1.35, 95%CI = 1.02 – 1.80).	None	Not supportive of PM hypothesis

Table 2.7: Studies on population mixing and childhood diabetes

Pop. Mix. type	Author (Year)	Areas & Years covered	Study pop.	Methods	Results	Limitations	Conclusion
Parental occupational contact	Fear et al. (1999)	Yorkshire N. Ireland 1993 - 1994	0 – 14	Each case was matched to two controls by age and sex. Conditional logistic regression used to assess associations.	No association was observed between high level of paternal occupational contact and childhood type 1 DM.	Prone to recall bias although very limited	Supports the hygiene hypothesis by analogy the Greaves hypothesis
	McKinney et al. (2000)	Yorkshire 1993 - 1994	0 – 14	Cases matched to two controls by age/sex. Townsend score for SES. PM derived with equal weightings given to infections >1 year olds, attendance to day care at >1 and other children living in house at birth. Used conditional logistic regression.	Day care attendance in <1 year olds negatively associated with diabetes (OR = 0.71, 95%CI = 0.51 – 1.00). Also breastfeeding and atopy (OR = 0.63, 95%CI = 0.39 – 1.01 and 0.41, 95%CI = 0.41 – 0.81).		
	Parslow et al. (2001)	Yorkshire 1986 - 1994	0 – 14	Ethnicity, unemployment, crowding, housing tenure and car ownership data from 1991 census. Pop. density measured as persons per hectare. Shannon Index for PM. Negative binomial model used.	Bottom decile for pop. density associated with an increase in childhood type 1 diabetes (IRR = 1.46, 95%CI = 1.01 – 2.11). Same association found with higher population density (0.68, 95%CI = 0.52 – 0.87).	1. Ecological study 2. Migration data from decennial census	
	Feltbower et al. (2005)			Data on both childhood leukaemia and type 1 DM were collected and a multivariate spatial model was implemented. For each disease, a Poisson regression was used. PM by Shannon Index.	High rates of both childhood leukaemia and diabetes were present in areas of low PM, although not statistically significant after adjustment (IRR = 1.29, 95%CI = 0.94 – 1.78) and 1.27, 95%CI = 0.59 – 2.75).		

Pop. Mix. type	Author (Year)	Areas & Years covered	Study pop.	Methods	Results	Limitations	Conclusion
Parental occupational contact	Miller et al. (2009)	Canterbury New Zealand 1999- 2004	0 – 14	PM measure from census data, which included migration diversity and migration distance. Adjusted for pop. density and SES. Poisson regression used to examine any associations.	Incidence of childhood diabetes was increased in areas of high PM.	Mathematical coupling	Supportive of PM hypothesis
	Hall et al. (2014)	Colorado USA 1993-2014	0 – 14	Cox proportional hazards regression used to examine associations between incidence of diabetes, day care attendance and breastfeeding.	No associations observed between diabetes and daycare attendance (HR: 0.89; CI: 0.54–1.47). Adjusting for breastfeeding modified the associations and diabetes was increased in non-breastfed children although non-significant (HR: 1.56; CI: 0.77–3.16).	1. Small number of cases 2. No account of confounders e.g. SES	Supportive of an infectious aetiology

2.4.3.4.4 Summary of studies on population mixing

Estimation of the level of infection for each individual is fraught with difficulty. The indicators for infection rely on biological markers and/or clinically diagnosed symptoms, and the majority of infections experienced in early life do not require medical consultation (Law et al., 2008). The measures of PM used in these studies are merely proxies, and they are not expected to capture an individual's exposure to infections completely. Nonetheless, the series of studies on PM and childhood leukaemia and NHL have generated much controversy and confusion for several reasons. The first of which is the gradual change of the hypothesis that can be seen under close examination of these studies. The original hypothesis suggested by Kinlen in 1988 was based on the idea that PM leads to the mixing of susceptible and infected children, which subsequently results in an epidemic of a yet unidentified infection, and that this infection leads to leukaemia (Kinlen, 1988, Kinlen, 1995). Kinlen further explains in his 1990 study, that the mixing of children subsequently leads to a child-child transmission of the unknown infective agent, and draws attention to the high density of children in the British New Towns as a result of the high proportion of young adults within those towns (Kinlen et al., 1990). Although the excess was limited to pre-school children, he explained that 'infected older siblings and parents are well placed to infect young children, moreover with large doses of the agent' (Kinlen et al., 1990, p. 581). The hypothesis then included an adult-child transmission of the infection by adults commuting to work. Thereby, it was no longer exclusive to influxes of people to a relatively rural area (Kinlen et al., 1991). The hypothesis was then further extended to examine whether an excess of childhood leukaemia was linked to paternal occupational contact only in areas that had witnessed an excess of the disease (Kinlen, 1997, Kinlen and Bramald, 2001, Kinlen et al., 2002). Therefore, a close examination of the studies published on PM (Tables 2.4 and 2.5) shows how the original hypothesis published in the late 1980s has been refined to only include areas in which an excess of cases was found.

Such an approach is not ideal because limiting the boundaries of an area under study will almost always result in an excess of the outcome – a problem commonly referred to as boundary shrinkage. A further problem with such an approach is that it will also result in a small sample size, especially if the disease in question is rare. Consequently, a better method is to generalise the study area to cover large parts chosen a priori, not only to specific areas, such as those adopted in more recent studies (Fear et al., 1999b, Roman et al., 1994, Parslow et al., 2002, Law et al.,

2003). These studies produced different results that were unsupportive of the hypothesis and some concluded that PM may actually be protective.

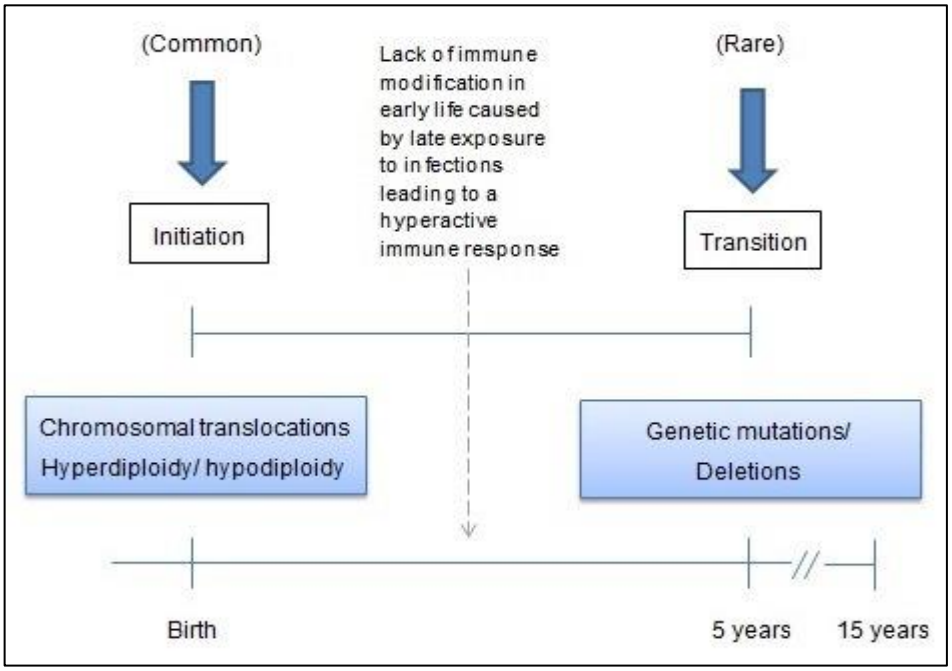
Also, PM has been defined in a different way to that seen in most of the traditional studies. Within these studies, a reproducible measure of PM was used which included both the volume of the people and their places of origin. The data used in this measure was collected independently of the study itself, i.e. census data, ensuring its accuracy and consistency in contrast to crude numbers used in the majority of the other studies. Further, several traditional studies used leukaemia mortality instead of leukaemia incidence, which is understandable in the earlier years where no data on incidence was available. However, in the past few decades, survival from childhood cancers, particularly lymphoblastic leukaemia has improved (Ma et al., 2014). The type of the study, i.e. area-based or individual-based plays an important role in the variation between these studies. The use of individual-based studies improves the accuracy in the measurement of confounding variables.

Studies on PM carried out in countries other than the UK have tried to use similar measures of PM. However, the limited availability of the data limits the efforts in creating a unified definition of PM. The seriousness of childhood cancers should increase international efforts to construct studies similar to the UKCCS in other countries, so as to come up with conclusions on the aetiology of not only childhood leukaemia, but also childhood cancers in general. This will allow for comparison between these studies and a better understanding of the underlying risk factors will emerge. Furthermore, it would be useful to test the validity of the different measures of PM in these studies by assessing the type of infection, incubation period and reproductive rate (Law et al., 2008)

In conclusion, Kinlen (1988) sought to refine the PM hypothesis, but failed to provide a biological mechanism for all situations. Furthermore, in almost all studies, all subtypes of ALL were assumed to have the main underlying cause whether infant ALL or common childhood ALL. In contrast, Wiemles et al. (1999) provided evidence of a genetic mutational event occurring neonatally, from blood spots obtained from 12 children aged between two and five years in Italy and the UK who had been recently diagnosed with ALL. This finding, along with those from the studies on PM and diabetes, and some of those on leukaemia are in support of the alternative hypothesis put forward by Greaves (1988) (Wiemels et al., 1999a).

2.4.3.5 Greaves' hypothesis

Greaves (1988) put forward the 'two-hit hypothesis' also known as the 'delayed infection hypothesis' in which he proposed that common childhood ALL, which has a peak in incidence between two and five years, results from two spontaneous mutations (Figure 2.2). The first mutation occurs in utero during the rapid multiplication of the lymphoid B-cell precursor cells, especially since these cells have a high proliferative rate, which makes them susceptible to spontaneous mutations. The second mutation is suggested to occur after birth once an infant is exposed to diverse infections (Greaves, 1988, Lightfoot and Roman, 2004).



Adapted from Greaves (2006)

Figure 2.2: The minimal two-hit model illustrating the natural history for childhood ALL/AML

Clinical symptoms of ALL are usually present for only a few weeks, and rarely for a few months, before a sound clinical diagnosis is made (Saha et al., 1993, Breatnach et al., 1981). Therefore, it is evident that a silent phase between initiation and onset of symptoms exists, and given the relatively young age at diagnosis, it is possible to assume that initiation occurs in utero (Wiemels et al., 1999a). This assumption holds for the common childhood ALL and AML, since an opportunity for exposure exists between the in utero mutation and the second genetic change that presents with clinically diagnosed overt leukaemia. For infant ALL however, it is assumed that genetic susceptibility and exposure to infections in utero play a significant role (Greaves, 2006, Greaves et al., 2003).

2.4.3.5.1 Biological evidence

At the time when the hypothesis was first suggested in 1988, it was merely speculative, however by the end of the 1990s and with advances in molecular biology the hypothesis has become substantiated (Greaves, 2006). Evidence for the first hit came from molecular inspection of several pairs of identical twins (i.e. monozygotic twins formed from a single fertilised egg and split into two embryos), aged between 2 and 14 years when diagnosed with ALL or infant ALL. These studies provided evidence that the TEL-AML1 breakpoints for childhood ALL, as well as the MLL gene breakpoints in infant ALL, are exactly the same. This means that such mutations occur in one cell in one foetus in utero, and then passed to the second twin via the shared placental circulation (Ford et al., 1997, Ford et al., 1998, Wiemels et al., 1999b). Furthermore, with several pairs of twins, asynchronous diagnosis was made in where there was a gap of a few years between the diagnoses of each twin, indicating the need for a second postnatal event whether genetic or involving infectious exposure (Greaves et al., 2003). Studies on twins also revealed that in one set of twins, one twin was diagnosed with T-cell ALL and the other with T-cell NHL, which supports the idea that these two diseases are biologically similar (Ford et al., 1997, Greaves et al., 2003).

Furthermore, Guthrie cards, which contain neonatal blood spots that are typically retained for several years, have been retrospectively examined in several studies (Wiemels et al., 1999a, Gale et al., 1997). These cards are a good source of intact DNA that can be easily amplified by the polymerase chain reaction (PCR) technology to look for any genetic mutations (Jinks et al., 1989). These studies showed that the TEL-AML1 fusion genes that are frequently seen in the common form of ALL were present in these blood spots, providing strong unequivocal support for the first mutation originating in utero.

2.4.3.5.2 Epidemiological evidence

A substantial body of epidemiological studies have sought to address the infectious aetiology of childhood ALL (Table 2.7). Although they mainly addressed the PM hypothesis, several of these studies also supported the delayed infection hypothesis. For example, an assumption may be made that the cases within the studies dealing with clusters of leukaemia had the common prenatal genetic mutation, i.e. the first hit. Consequently, delayed exposure to infection through isolation or high socioeconomic conditions may have initiated the second postnatal promotional event (Greaves, 2006). It is necessary to point out that these studies

did not examine both infant and common childhood ALL, and did not look at these subtypes separately.

In addition, the likelihood of acquiring infections is highly dependent on social contact as well as the frequency of such contact. In children, attendance to day care centres or playgroups may be used as a proxy measure for social contact. It was found that such attendance increases the chances of acquiring viruses such as the HIB and common upper respiratory tract infections (Istre et al., 1985, Greaves, 2006). Also, the frequency of attendance, as well as the number of children within a social group, increases the chances of acquiring infections even further (Greaves, 2006). Studies on attendance to day care centres have shown that attendance confers protection against autoimmune diseases (Krämer et al., 1999, McKinney et al., 2000). Similar associations have been reported for common childhood ALL from the UKCCS and the NCCLS (estimates previously reported) (Gilham et al., 2005, Ma et al., 2005). These studies are supportive of the delayed infection hypothesis.

The UKCCS further investigated clinically diagnosed infections in the first year of life, abstracted from general practitioner (GP) records for both cases and controls. According to the delayed infection hypothesis, the cases would have a deficit of infections compared to the controls (Roman et al., 2007). However, the results showed that only 18% of controls compared to 24% of cases were diagnosed with at least one infection in the first month of life (OR = 1.4, 95%CI = 1.1 – 1.9), and by the end of the first year of life the numbers increased to 85% in controls and 88% in cases (OR = 1.3 – 1.8) (Roman et al., 2007). A similar association was reported in another study (Cardwell et al., 2008). Although the results were contrary to the original hypothesis, they do not refute it for two reasons. The first is that the hypothesis does not specify that the underlying infection is overt and clear in a way that necessitates a visit to the GP. It may be an innocuous infection with minimal symptoms, hence these studies do mask such infections. The second is that assuming all cases had the first mutation in utero, then an abnormal response to infections may precipitate the second mutation that develops the leukaemic cells into full blown leukaemia. Such an abnormal response may be reflected in the high level of reported infections within GP records.

2.4.3.5.3 Contrasts with PM

It is important to note that the PM hypothesis and the delayed infection hypothesis are not mutually exclusive. The two hypotheses share common grounds in that they postulate that childhood leukaemia is a rare response to a common infection that

may be acquired by a delayed exposure to that infection, whether due to isolation or modern living conditions. High levels of mixing to a previously isolated area introduce novel infections to the host community, thereby providing an opportunity for the second hit necessary to develop overt leukaemia (Greaves, 2006). Furthermore, unlike the PM hypothesis which depends solely on epidemiological theories, the delayed infection hypothesis considers the natural history of ALL in terms of the actual biological and immunological nature of the disease. Also, although the epidemiological studies concerned with PM are based on data of patients who mostly had the common form of ALL, the interpretation of the data indicated that all subtypes of ALL as well as NHL shared a common aetiology. However, the delayed infection hypothesis was only concerned with common types of ALL in children with incidence peaking between two and five years of age.

2.4.3.6 Smith's hypothesis

Smith (1997) proposed an alternative model to explain the peak in common childhood ALL, that aetiological agents causing an infection during pregnancy are transmitted to the foetus, thereby resulting in an in utero infection, consequently increasing the risk of ALL. This hypothesis attributes the latency period between the in utero infection and the clinical presentation of ALL to a second post-natal event or to a true latency period related to the growth rate of leukaemia cells. Certain characteristics of the aetiological agent have been identified to allow for the broad range of suspected agents to be narrowed. First, since hyperdiploidy is the most common cytogenetic abnormality in ALL, and since the median age at diagnosis of ALL with hyperdiploidy coincides with the peak in ALL incidence found in epidemiological studies, the aetiological agent should therefore be able to cause genomic instability. Secondly, since hyperdiploidy is mostly associated with B-cell ALL, and rarely with T-cell ALL, and since the elevated risk of ALL related to socioeconomic status is specific to B-cell ALL, the agent should consequently affect B lymphocytes. Also, the agent should have minimal symptoms otherwise any obvious symptoms caused by the infectious agent would have been reported. Additionally, the agent must be capable of passing to the foetus through the placenta without causing any foetal abnormalities otherwise these abnormalities would have been seen among ALL cases. Equally important is that this agent should have a limited cancer causing potential. One potential candidate suggested was the John Cunningham (JC) virus from the polymavirus family, which meets most of these conditions (Smith, 1997).

Some studies attempted to detect the JC virus as well as the polymavirus hominis 1, also known as the BK virus, from the polymavirus family using specimens from children diagnosed with common childhood ALL (Smith et al., 1999, MacKenzie et al., 1999). However, not one was able to detect these viruses, concluding that these were unlikely to be implicated in the aetiology of the disease.

2.5 Socioeconomic status

Throughout the years, studies of populations have documented an association between SES and health. Since the 19th century, the link between SES and ill health has been extensively examined, from the time when researchers examined the health outcome differences between the working class in Europe, the royalty and the elite (Antonovsky, 1967). Ever since, the examination of the relationship between SES and health has been of much interest. The relationship is better described as a gradient, because the differences in incidence and mortality in health are found at every level of the hierarchy of SES regardless of a cut-off point (Adler et al., 1994).

It is very important to understand that SES does not refer to a single measure – it is in fact multi-dimensional. Measures typically include social status which may be measured by education, economic status which may be measured by income and/or ownership of several other items such as a home or a car, and also work status which may be measured by occupation (Dutton and Levine, 1989). Confusion may arise as a result of the different terms used to name this field of research. Such terms may include SES, deprivation or poverty, all of which are sometimes mistakenly used interchangeably, despite the fact that different concepts lie beneath these terms.

Poverty refers to living below a certain threshold of income, this term must not be mistaken with relative poverty, as relative poverty refers to the lack of resources regarded as necessary in a community (Shaw et al., 2007). Several definitions of poverty exist, Townsend (1979) defined it as 'the absence or inadequacy of those diets, amenities, standards, services and activities which are common or customary in society', the European Union (1985) defines it as 'persons whose resources (material, cultural and social) are so limited as to exclude them from the minimum acceptable way of life in the Member State to which they belong'. It is the socially defined concept of relative poverty, i.e. of what others regard as necessary for an acceptable standard of living, which differs from poverty alone, i.e. income.

On the other hand, deprivation is a concept that overlaps, but is not equal to the meaning of poverty. Deprivation is a wider concept, which includes material deprivation, social deprivation and multiple deprivation (Shaw et al., 2007). Material deprivation reflects access to the different resources and goods which allow individuals 'to play the roles, participate in relationships and follow the customary behaviour which is expected of them by virtue of their membership in society' (Townsend, 1993). Social deprivation, however, relates to the social contacts, roles

and membership of people within their community. Multiple deprivation, which is widely used within health research, reflects the deprivation of several factors at the same time, these factors may include income, employment and housing environment, for example availability of televisions, phones or even cars (CLIP, 2002). The main difference between the concepts of deprivation and SES is that the former examines the unavailability of living conditions whereas the latter examines the status of people within an area. However, indices measuring deprivation such as the IMD are able to identify both the disadvantaged and the affluent. In this body of work, the term SES will be used.

2.5.1 Socioeconomic status and health

For all people, the opportunity to live a healthy long life is unequal. It has been found that those who are more deprived have a higher risk of disease, disability and death (Graham, 2009). This association is part of the socioeconomic gradient, where people in the middle levels of the social hierarchy tend to enjoy a healthier longer life. Indeed, it is evident that in low income societies infections spread and morality rates are high, and in rich societies where death rates are low, chronic disease rates are high (Graham, 2009, Adler et al., 1994). Acknowledging that an association exists between SES and health is not the same as explaining how it operates. The general consensus is that such a health gradient persists because a person's access to health resources is determined by his/her socioeconomic position, regardless of the changes in causes of death over time. Consequently, the more advantaged people have better access to health resources and thereby have a better chance in health enhancement, whereby the most disadvantaged have limited access to health resources and thus may be more exposed to health risks (Power and Matthews, 1997, Graham, 2009). A further explanation is that the lifestyle behaviours associated with the socioeconomic position of individuals may be considered risk factors for specific diseases such as smoking and physical inactivity. Therefore, epidemiological research investigating possible risk factors associated with a disease are considered suspect unless SES is controlled for, i.e. SES must almost always be included in the analyses of health research as a potential confounding factor (Liberatos et al., 1988, Adler et al., 1994).

Similarly, children living in poor conditions are more likely to be exposed to health-related risks. For example, cerebral palsy is more common in families with a low SES (Dolk et al., 2001), a similar association is found for emotional and behavioural problems (Meltzer et al., 2003), as well as obesity (Shrewsbury and Wardle, 2008).

Even as early as infancy, such an association is found, for example poorer mothers are more likely to deliver pre-term or give birth to smaller babies (Spencer, 2003).

2.5.2 Socioeconomic status and childhood cancers

The notion that SES is in some way related to the development of childhood ALL is not new. The National Cancer Institute published a report in 1999 which included high SES as a 'known risk factor' for ALL (Ries, 1999, p. 29). Although others may correctly argue that high SES in itself is not the cause, behaviours and lifestyles associated with high SES are. Such behaviours include better hygienic living conditions, more breastfeeding and reduced family size (Eden, 2010). Measures of SES are of particular interest to the PM and delayed infection hypothesis suggested for the aetiology of ALL (Greaves, 2006). It is hypothesised that the second hit that leads to full blown leukaemia is mediated by delayed exposure to infections, seen in circumstances such as those found in affluent societies.

A systematic review identified 47 studies that examined SES and childhood leukaemia between 1945 and 2002, and reported that the association was heterogeneous (Poole et al., 2006). Possible explanations for the inconsistent results may be due to the different study designs, which included ecological and case-controls. With individual based case-control studies, a methodological issue is often encountered in the selection of the controls which affects the resulting outcome. Usually, the controls come from individuals with high SES, which creates participation bias (Law et al., 2002). A further review found that incidence of childhood ALL was persistently higher in affluent societies (Kroll et al., 2011b), and although this finding is in support of the delayed infection hypothesis, another possible explanation reported in the review was the potential under-reporting/under-diagnosis of cases. Although, under-diagnosis may be more likely, since it would be expected that there would be some improvement, hence attenuation of the association in recent years, which is not the case (Kroll et al., 2011b).

2.5.3 Socioeconomic trends and patterns

The distribution of people who are in poor health is not random in the population. Instead, they are more likely to concentrate amongst those with fewer resources that enable them to live an economically secure and prosperous life (Graham, 2009). Differences persist between countries as they do within countries. Globally, a 20-year difference in life expectancy was found between the 60% of the world's population living in low income countries and the one-sixth of people living in high-income countries (UNDP, 2007). Furthermore, socioeconomic inequalities continue

to persist across time, a prominent example was in 19th century Britain where infectious diseases were associated with overcrowding and poor sanitation. Then, mortality from infectious diseases dropped and by the 20th century, chronic diseases such as heart disease and cancer were high (Graham, 2009). The socioeconomic conditions of overcrowding and poor sanitation play an insignificant role in these chronic conditions, instead a constellation of behaviours such as physical inactivity, smoking and high fat diets are the major risk factors (Graham, 2009, Lopez, 2006).

2.5.4 Measures of socioeconomic status

The UK has given careful attention to the measurement of SES. The creation of a measure of deprivation has been one of the governments' priorities, to help identify people who are in more need (Smith, 2002). Indeed, it has been a function of the General Register Office (GRO) to measure the differences in mortality and other health inequalities since 1837 and now the tradition is carried out by the Office for National Statistics (ONS). The main focus of the literature is aimed at measurement of SES in the UK, as it has a long experience in this particular area. The indices of SES developed in the UK do not only include income as an indicator, but rather a variety of indicators (Table 2.8). Different methods of obtaining measures or scores of deprivation exist and may be generally categorised as either weighted or un-weighted depending on the method used.

Measures of SES include individual characteristics that may be collected from actual patients, such as measures used in case-control studies of ALL, or ecological measures using routinely collected census data. These typically include matching individuals' residential information, such as postcodes, to a spatial location, thus creating area-profiles that are easy to use in research (Denny and Davidson, 2012).

A variety of area-based indices have been developed in the UK since the 1981 census. The function of an index is to come up with one single value that would represent the different measures of deprivation. It may be that the value is meaningful, for example the proportion of households in an area that are considered deprived, or that the number in itself is meaningless, but provides an abstract measure of deprivation, i.e. the figure may be used to rank areas. These indices include the Indices of Local Conditions (ILCs) and Local Deprivation, the Carstairs index, the Townsend index and the Indices of Multiple Deprivation (IMD). The indices were developed to aid in the identification of highly deprived areas,

which in turn supports proper resource allocation (Shaw et al., 2007, CLIP, 2002). The majority of these measures are frequently updated to take into account changes in the census data and community characteristics.

2.5.4.1 The Townsend index

The Townsend index, developed by Peter Townsend in the late 1980s aimed to explain the inequalities between the populations of the 678 wards in the northern region of England (Townsend et al., 1988). The measure makes use of indicators of deprivation derived from the 1981 census data, but which can also be derived using subsequent census data from 1991 and 2001 (Table 2.8). The indicators used are unemployment, car ownership, home ownership and overcrowding. Unemployment and overcrowding are log transformed to normalise their distributions. The final score for a specific area is the sum of the z scores for all indicators. The resulting score provides a convenient method of ranking areas according to the SES. Therefore, areas that are more deprived have high positive scores and areas that are less deprived have high negative scores (Townsend et al., 1988).

2.5.4.2 The Carstairs index

The Carstairs index is another type of area based deprivation index developed by Vera Carstairs and Russell Morris in 1991. It was aimed at measuring the level of deprivation using data derived from decennial censuses in Scotland. It was designed to measure access 'to those goods and services, resources and amenities and characteristics of a physical environment which are customary to a society' (Carstairs and Morris, 1991). The index is made up of four indicators, two of these indicators are the same as those used in the Townsend index, namely, overcrowding and car ownership. However, the other two indicators include low social class and unemployment in the male population only (Table 2.8). Given that the index focuses on material resources, it emphasises wealth and income as important determinants of deprivation. Therefore, the use of the car ownership indicator was intended as a surrogate for income, since no information on income is included in census data. The method of calculation is similar to the Townsend index. Equal weights are given to all indicators, and the final score is the sum of the standardised indicators which are divided into seven categories ranging from very high to very low deprivation (Carstairs and Morris, 1991).

2.5.4.3 Strengths and limitations of the Carstairs and Townsend indices

Given that both of these indices are area based, this has the advantage of assigning individuals to an area by means of a postcode. This allows for linking of other SES characteristics from that area to individuals whose records do not contain individual level socioeconomic data. Also, these indices have the advantage of simplicity in the method of construction; the indices can be easily constructed consistently over time using the same indicators from decennial census data. Furthermore, researchers are able to construct these indices across the UK for comparison, whereas a different IMD was constructed for each of the four countries.

Nonetheless, the two indices suffer from a few limitations. First, because the indices employ indicators derived from the UK census data, they can only be produced every 10 years and are restricted by any policy changes made to the way the data are collected. Secondly, changes in the scores from the 1981 census and the 1991 census for a given ward or area do not necessarily reflect changes in that area's level of SES, any changes may well be a reflection of the social characteristics in home and car ownership, e.g. car ownership once was an indication of affluence, but is now the norm. Furthermore, the fact that the Carstairs index measures unemployment in men alone is a strong drawback, given the currently high participation of women in the labour force. The fact that the indices are area-based puts them at risk for the ecological fallacy. Also, there are vast urban and rural differences where the rural wards are usually much larger then urban wards, and the populations are much smaller. Therefore, it has been argued that deprivation in rural wards is almost invisible, where high and low deprivation scores are likely to be in wards which are internally similar (Morgan and Baker, 2006).

2.5.4.4 The Indices of Local Conditions and Local Deprivation

The ILC is an area-based measure of deprivation, developed around the mid-1990s by the then Department of the Environment. The index included 12 indicators taken from census and non-census variables (Table 2.8). Therefore, it was intended for use on the local authority level, but it may be used on the electoral ward level if only census indicators are included (Shaw et al., 2007). An update to this index is known as the Index of Local Deprivation (ILD) produced in 1998 by the then Department for the Environment, Transport and the Regions. There are two main differences between both indices. First, when calculating the ILD only positive values of the log

transformed signed chi-square values are summed, whereas for the ILC all the transformed values are summed to come up with the overall score. The use of the signed chi-square method aimed to reduce the problem of the small denominators found in some areas (DoE, 1995). Secondly, two of the ILD indicators are multiplied by two, namely, the SMR and the home insurance premium. However, no weights are given to the ILC indicators (Shaw et al., 2007, Simpson, 1995).

The main purpose of the indices was to assist the government in targeting resources to local organisations. They are not appropriate for health research because they include SMR within their calculations, especially when examining mortality, as mathematical coupling may be introduced. Furthermore, since the ILC uses raw numbers as opposed to percentages, lower weights are given to areas that have a lower count, e.g. an area with 3 out of 10 people unemployed will therefore have a lower score than an area that has 30 out of 100 people unemployed, hence producing spurious results (Simpson, 1995, CLIP, 2002).

2.5.4.5 The indices of multiple deprivation

The IMD is another type of area-based measure of deprivation. The first version was produced in 2000 after a review of the ILC by the University of Oxford. The idea of the index of multiple deprivation is that the term ‘deprivation’ is multi-dimensional, therefore, a number of indicators were chosen to represent a separate dimension, where multiple deprivation is the combination of these domains or dimensions. Indicators within the domains were carefully selected so as to comprehensively represent the deprivation within those domains using the available data. The IMD produced for England is discussed as an example below.

The construction of the IMD 2000 was innovative in the selection of indicators and the underlying methodology. As opposed to the 12 indicators used in the ILD, 33 separate indicators were chosen to describe the six domains of the index (Table 2.8). Furthermore, shrunken estimates of the ward to the local authority district mean were adopted to account for the small number problems that may arise from rural or small areas. The method through which indicators were summed to form domains involved factor analysis for those domains that included indicators measured on different scales. These domains allowed ranking the wards according to deprivation relative to all other wards for each domain. However, to obtain an overall index for deprivation, the domains were first transformed to an exponential distribution, and after giving higher weights to the income and employment domains they were then summed (SDRG, 2000).

The major advantage of this index is the inclusion of the six domains of deprivation, which means that each ward in England can be ranked relative to other wards for each separate domain. Also, when including the index in research, an author has the choice of including the overall IMD score for all domains, or conducting research with the domains themselves. Furthermore, the IMD 2000 demonstrates an evolution in the measures of SES, where methods used are continuously refined, an example is the use of factor analysis rather than the signed chi-square method which was used in the previous index. Nonetheless, the overall IMD 2000 score has two main drawbacks. First, since the IMD 2000 includes a domain for health deprivation and disability, it is not suitable for inclusion in health related research, an alternative is to use other domains of the IMD as opposed to the overall score. Secondly, an issue with the 'geographical access to services' arises because this domain was found to behave in a different way to other domains, in the sense that all other domains are positively associated with each other, i.e. if one area is housing deprived then it is mostly like to be employment deprived. However, for this particular domain this is not the case. This is understandable considering that the areas that are income deprived are usually in the highly populated areas where GP surgeries and hospitals are a short distance away, whilst the rural areas are relatively more affluent, but are found to be far from such health facilities. This issue should be considered in certain health applications where distance to health facilities is considered important (Shaw et al., 2007). Furthermore, the IMD discussed here is for England alone. Other IMDs have been constructed for Scotland, Northern Ireland and Wales, but are not comparable. Discussions on the feasibility of producing an IMD for the UK are now in the process (UKSA, 2011).

The development of the IMD 2000 served as a basis for more up-to-date versions. The IMD 2004, 2007 and 2010 followed, all of which were very similar to each other, although there are two key differences between them and the IMD 2000. First, the later indices included a seventh domain defined as 'crime', and secondly, they measured each of these domains on the Lower Super Output Area (LSOA) which allows for examining deprivation on a finer geographical spatial scale (DCLG, 2011). Since the methodology and the measured domains are similar in these subsequent indices, they are comparable. These indices suffer from the same drawbacks as the IMD 2000 (Shaw et al., 2007). Furthermore, the use of these indices in health research can cause mathematical coupling as health and disability are one of the indicators used (Table 2.8), unless the researcher chooses to select individual domains rather than the overall score.

2.5.5 Socioeconomic status in Saudi Arabia

Measures of SES in the Gulf countries and particularly in Saudi Arabia have not been developed. The typical measures of SES used in health research in these countries rely solely on individuals, such as income or educational status of the individual or the individual's parents, and these measures fail to account for the social and health context (Al-Baghli et al., 2010, Shah et al., 1999). To our knowledge, no study has yet examined the relationship between any health outcome and SES on an area-based level in the Gulf region, because no area-based measure exists for any of these countries. In Saudi, the problem is more pronounced, because it is the largest country in the Gulf (WHO, 2011). Unlike the UK and other developed countries, it is a common perception that rural areas are more deprived than urban areas, particularly in education, income and health outcomes. Inequalities in health outcomes are inevitable due to the larger transport distances to specialised health institutions for those living within the highly isolated and rural areas.

Saudi researchers and planners who seek to describe and take action on health disparities caused by SES face a major challenge in the lack of any measure of SES within the country. Such a gap prevents researchers from accounting for socioeconomic inequalities that inevitably influence any health outcome, especially in studies utilising data from national disease registries (AlGhamdi et al., 2014). The examination of area-based SES will encourage the study of health inequalities in Saudi Arabia, and provide a valid measure to be used in future research, as well as provide disease registries in Saudi Arabia with the opportunity of including these measures within the patient information to facilitate their use among researchers.

Table 2.8: Indicators of the main socioeconomic indices in the UK

	ILC[a]	ILD[b]	IMD[c] 2000	IMD[c] 2004	IMD[c] 2007/ 2010	Townsend	Carstairs
Long-term unemployment	✓	✓					
Income support recipients	✓	✓			✓		
Low educational attainment	✓	✓					
Standardised mortality ratios	✓	✓					
Derelict land	✓	✓					
Insurance premium	✓	✓					
Unemployment	✓		✓	✓	✓	✓	✓ (male)
Children in low households	✓	✓					
Overcrowding	✓	✓				✓	✓
Car/home ownership	✓					✓	✓
Children in unfit housing	✓						
Educational input at 17	✓	✓					
In receipt of Council Tax		✓					
Health dep. and disability			✓	✓	✓		
No/low level of amenities	✓	✓	✓	✓			
No access to services			✓		✓		
Education skills and training			✓	✓	✓		
Barriers to housing/service				✓	✓		
Crime				✓	✓		
Low social class							✓

[a] Index of Local Conditions.

[b] ILD: Index of Local Deprivation.

[c] IMD: Index of Multiple Deprivations.

2.6 Research to be conducted

Based on the evidence reviewed in this chapter, the following research areas have been identified:

- There is a paucity of research on childhood cancers in Saudi Arabia, and none for young adult cancers, although data on cancer cases have been reported since 1994. Therefore, there is no understanding of the pattern of incidence in these age groups.
- There is a lack of an established area-based SES measure for Saudi Arabia, which poses a challenge for health researchers dealing with Saudi data. Several studies on Saudi Arabia have mentioned this as a limitation.
- Saudi Arabia provides an excellent opportunity to examine how PM in terms of the Hajj affects the incidence of childhood and young adult cancers, particularly leukaemia and lymphoma.

3 Materials and analytical methods

3.1 Administrative geography

The study area was geographically defined by the boundaries set by royal decree of King Fahd Al-Saud in 1992. The country consists of 13 Provinces, and nested within them are Governorates. The number of Governorates differs from one Province to the other, but range from 19 in the Riyadh Province, to three in both the Jouf and the Northern Border Province. The total population of the country as reported by the 2004 census was 22,678,262, which is mainly centralised in urban Governorates with modern health and educational facilities and services. The average population within the Governorates is 192,189, and the median is 57,792. The population numbers range from 4,138,329 in the capital Riyadh to 3,785 in Kharkheer (CDSI, 2004a), and the outer boundaries of these provinces are Iraq, Jordan and Syria to the north, the Arabian Gulf Sea, Kuwait, Bahrain, Qatar and United Arab Emirates to the east, Yemen and Oman to the south and the Red Sea to the west (CDSI, 2004b). Figure 3.1 shows the 13 provinces and Figure 3.2 shows the 118 Governorates defined within the provinces.

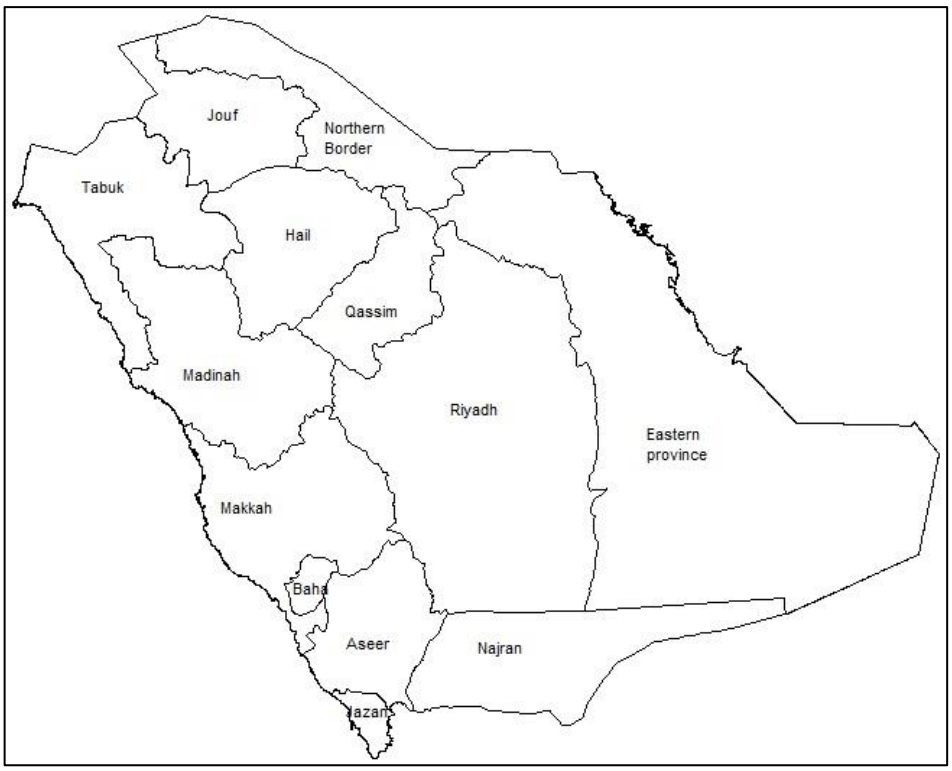
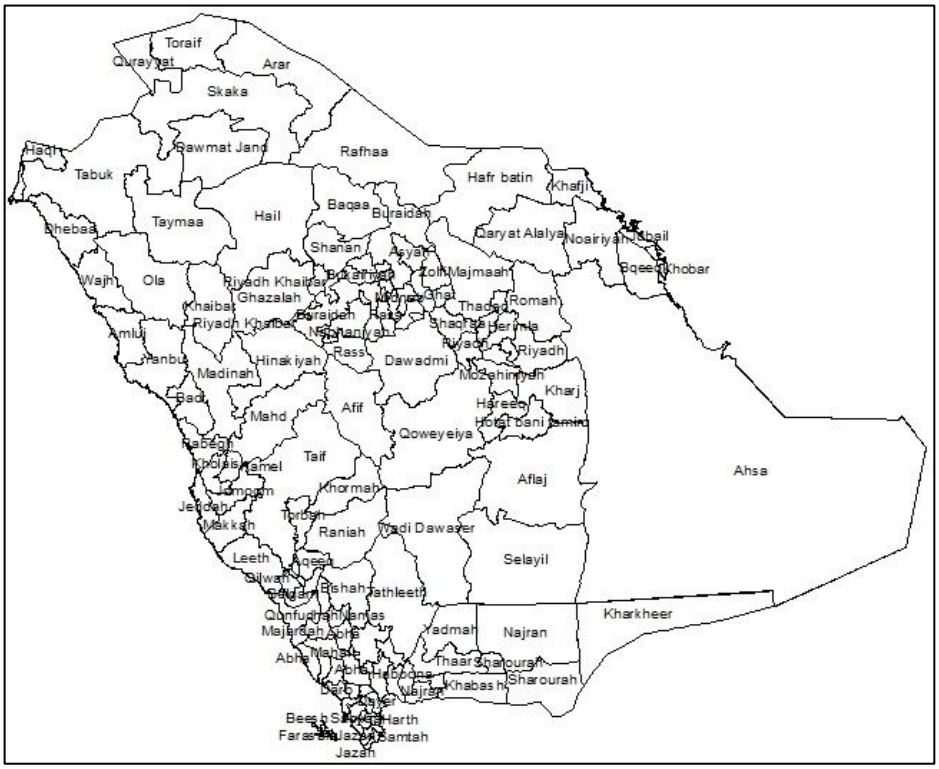


Figure 3.1: The Provinces of Saudi Arabia



*The Empty Quarter desert is included in the border of the Ahsa Governorate, only 18% of this Governorate is inhabited.

Figure 3.2: The Governorates of Saudi Arabia

3.2 Data sources, collection and manipulation

3.2.1 Cancer data

3.2.1.1 The Saudi Cancer Registry

The Saudi Cancer Registry (SCR) was established in 1992, under the authority of the MoH and began reporting cases of cancers in Saudi Arabia from the 1st of January 1994 (Al-Eid et al., 2007b). The objective of the SCR was to describe the incidence of cancer in the population of Saudi, as well as to provide valid data for medical research. The SCR is based in the capital city of Riyadh, and has set up five regional branches as well as four offices based at different hospitals to ensure the ongoing reporting of cases. Data abstraction is performed by SCR trained cancer registrars, who use medical records as the main source of information, as well as histopathological reports and death certificates. The data abstraction form includes personal and demographic information as well as cancer morphology and topography (Appendix C) (Al-Eid et al., 2007b). The SCR uses the International Classification of Diseases for Oncology – 3rd edition (ICD-O-3) to code cancers. Although the exact procedure is not known, quality assurance of all collected data is done by verification of topography, morphology and staging information, as well as data consolidation from multiple sources. It is not made clear whether there is a standard for the SCR for cross-checking the quality of the acquired data, and the level of case ascertainment (Al-Eid et al., 2007b).

Patients suspected of cancer of all ages are referred from primary health care centres to secondary hospitals for further care, and if required are further referred to specialist hospitals.

3.2.1.2 Data collection

The request for cancer data was facilitated by on-site visits to the cancer registry, and the data were finally received on 27/07/2012. For this research, the target population consisted of young people in Saudi Arabia (0 to 24 years). This population was the focal point to enable comparison with other studies from different countries, as well as to be able to study the effect of population mixing (PM) on this specific age group based on the discussed hypotheses. Hence, the obtained data included all Saudis and non-Saudis aged between 0 and 24 years with a newly diagnosed malignancy. The addresses of patients were not given, although in any case, the P.O. box traditionally identified a central post office for mail collection and not a residential address. However, the province and Governorate of each individual patient was provided. The data also included the topography and morphology of each patient.

3.2.1.3 Data manipulation

As the target population involved patients aged <24 years, the malignancies had to be coded using the International Classification of Childhood Cancers (ICCC-3) to identify disease patterns. The conversion was performed using statistical coding in Stata Software version 12 (StataCorp, 2011a), using the extended classification table (Appendix A), then the main classification table (Appendix B), to enable arrangement of diseases into main diagnostic groups (Steliarova-Foucher et al., 2005a). The procedure was performed in 2 phases:

- Phase 1: This phase involved combining the morphology and topography of each patient from the cancer data to assign a diagnosis to each patient, with guidance from the extended classification table (example given in Appendix D).
- Phase 2: This phase involved summarising the extended classification table of disease groups to the main classification table, and labelling each cancer type for use in subsequent analyses (example given in Appendix E).

The location of each patient was not logged in the same geographical manner, as some patients recorded Governorates and some recorded neighbourhoods or districts. For the purpose of unifying the geographical level of patient allocation, and for linkage with census data, each location was cross-referenced to ensure accuracy of patient address. In the case where neighbourhoods or districts were recorded instead of Governorates, these were substituted by the Governorate to which that centre or district belonged. From the total number of patients, 4.36% (782) had unknown locations. This group had to be excluded from some of the analyses concerned with patient location.

3.2.2 Census data

3.2.2.1 The Central Department of Statistics and Information

The Central Department of Statistics and Information (CDSI) is the organisation responsible for organising, monitoring and producing reliable population data. The first census was carried out in 1974, followed by other censuses in the years 1992, 2004 and results are yet to be published for the 2010 census. Prior to the 2004 census, fieldwork preparation started in September 2001 and continued until October 2003. This preparation included producing a directory to clarify the names

of all areas such as cities, villages, farms and Bedouin gatherings and how they relate to the main administrative area. It also included estimating the number of households in each of these areas, so as to be able to divide them into small census units and assign a worker to each unit. The data collection method of the census consisted of a questionnaire that included 62 questions covering geographic, educational, economic and migration information of each member within a household (CDSI, 2004b).

3.2.2.2 Data collection

Population data used to calculate standardised incidence rates were obtained from the CDSI using the 2004 national census on 04/09/2012. The CDSI webpage (www.cdsi.gov.sa) only publishes data per province. Therefore, population data containing counts for five-year age groups for males and females per Governorate, as well as socioeconomic indicators collected from the census questionnaire per Governorate were requested. The data on socioeconomic indicators were received as whole numbers for each Governorate, for use in constructing the measures of socioeconomic status (SES). The indicators included educational status, employment status, type of housing, housing tenure and the availability of several household items (Table 3.1).

Table 3.1: The socioeconomic indicators obtained from the 2004 national census of Saudi Arabia

Socioeconomic categories	Variables within each category	Denominator
Educational status	Illiterate / read and write / school degree / diploma / university / masters / PhD	Population aged >10 years
Variables after grouping[a]	Illiterate and read and write / school degree / diploma and university / higher education (masters and PhD)	
Employment status	In the labour force / students / housewives / retired / other employment	Population aged >15 years
Variables after grouping[a]	In the labour force / not in the labour force	
Type of housing	Traditional house / villa / a floor in a traditional house or villa / apartment / other type of housing	Households
Tenure of housing	Owned, rented, provided, other tenure	Households
Car ownership	No car available / one car / two cars / three cars / four cars / five cars / six cars / seven cars / eight cars / nine cars / ten or more cars	Households
Variables after grouping[a]	No car / one car / two or more cars	
Availability of household items	Phone, TV, PC, internet, library, satellite, videos, video games	Households

[a] These variables were grouped prior to analysis to facilitate their inclusion in the multivariate analyses.

3.2.2.3 Data manipulation

The data on socioeconomic indicators were given as whole numbers. The total number of people within each Governorate, as provided within the socioeconomic indicator dataset, was cross-checked with the number of populations provided within the population age-sex dataset, to ensure accuracy. Further, the total counts of people/households within each indicator group were checked with the total given for each Governorate. Discrepancies were found within the household level indicators only, where the totals for each indicator group were higher than the total number of households for each Governorate. Therefore, the total of each indicator group was chosen as the denominator (Appendix F). Prior to analysis, some

variables had to be aggregated for example, the illiterate and the read and write variables were aggregated into one variable. The aggregation allowed the variables to be more normally distributed, as well as being easier to include in the analysis.

Then, all indicators were expressed as proportions to be able to measure the actual effect of each indicator. Proportions were calculated using indicator specific denominators for both the education and employment indicators. The counts of people regarding the educational indicators only included those above 10 years of age, and within the employment status indicators included those above 15 years of age (CDSI, 2004b). Therefore, the population denominator only included the number of people aged above 10 years and 15 years, respectively (Table 3.1).

Since the age and sex data for each Governorate was only available for 2004, populations for the years from 1994 to 2008 were estimated based on the 2.5% annual increase reported by the annual census reports available online (www.cdsi.gov.sa). The estimated population of 1994 was divided by the actual population reported from the 1992 census which produced a value to be used as a multiplier. This value was then multiplied by the actual population of 2004 in each stratum to produce an estimated value of the population for 1994. The same process was done for all years except 2004, since the actual number was available.

3.2.3 Hajj data

3.2.3.1 Custodian of the Two Holy Mosques Institute for Hajj Research

The Custodian of the Two Holy Mosques Institute for Hajj Research (CTHMIHR), formerly known as the Hajj Research Centre, was established in 1975, as a group of researchers based at King Abdulaziz University in Jeddah, with the aim of establishing an information bank about the Hajj. CTHMIHR has now moved to Um-AlQuraa University in Makkah and currently aims to become the primary source of Hajj-related scientific information, where relevant statistics may be provided for research and policy making services (UQU, 2014).

3.2.3.2 Data collection

A data request was made, and the data were received on 21/11/2011. The data included the number of pilgrims arriving into Makkah by the Islamic calendar (also known as the Um-AlQuraa calendar) year. The original data requested included a

request for all pilgrims by nationality, age and sex. However, that information was only available from the Ministry of Interior and was not accessible.

3.2.3.3 Data manipulation

The data provided was in total counts by Islamic calendar year. Therefore, the dates had to be converted to the Gregorian calendar for data linkage purposes. The Um-AlQuraa official calendar website (http://www.ummulqura.org.sa/Index.aspx) was used for date conversion. The act of Hajj starts between the 8th day and the 13th day of the last month (Thu-alhujja) of each Islamic calendar year, therefore the mid-point (the 10th day) was chosen for conversion (Table 3.2).

Table 3.2: Conversion of dates from the Islamic calendar to the Gregorian calendar

Islamic calendar date	Gregorian calendar date	Year assigned
10 Thu-alhujja 1414	21 May 1994	1994
10 Thu-alhujja 1415	10 May 1995	1995
10 Thu-alhujja 1416	28 April 1996	1996
10 Thu-alhujja 1417	18 April 1997	1997
10 Thu-alhujja 1418	7 April 1998	1998
10 Thu-alhujja 1419	28 March 1999	1999
10 Thu-alhujja 1420	16 March 2000	2000
10 Thu-alhujja 1421	5 March 2001	2001
10 Thu-alhujja 1422	22 February 2002	2002
10 Thu-alhujja 1423	11 February 2003	2003
10 Thu-alhujja 1424	1 February 2004	2004
10 Thu-alhujja 1425	21 January 2005	2005
10 Thu-alhujja 1426	10 January 2006	2006
10 Thu-alhujja 1427	31 December 2006	2007*
10 Thu-alhujja 1428	20 December 2007	2008*

* Any effect would happen after the event, therefore the next year was chosen

3.2.4 Geographical information systems

3.2.4.1 Data collection

Geographical information systems (GIS) boundary data of the Saudi Arabian Governorates were requested and received from the Farsi GeoTech Company on 05/05/2012. This company is renowned for its work and has an index of governmental services (Appendix G).

3.2.4.2 Data manipulation

The GIS data included digital boundaries of provinces and Governorates, each on a separate layer, accessible through ArcMap software version 10 (ESRI, 2010). The Governorate level layer included 142 polygons rather than 118 (each polygon should represent a Governorate). This was due to the fact that some Governorates were divided into smaller districts. Therefore, the dissolve tool within the ArcMap software was used to re-group and merge divided Governorates. This tool then generated a new layer that contained 118 polygons. This layer was used for the cartography.

3.3 Descriptive analytical methods

3.3.1 Descriptive statistics

Summary descriptive statistics were used to examine the census data. Statistics included the mean, so as to provide a number to represent the centre or average of the data, as well as the standard deviation (SD) to measure the spread of the data from the mean. Also, skewness and kurtosis were inspected – these are measures to check for the normality of the data, where skewness indicates whether the data are asymmetrical or positively/negatively skewed, and the kurtosis checks the peakedness of the data.

3.3.2 Standardised incidence rates

Incident cases were defined as the occurrence of new cases over a specific time period within a specific population. An incidence rate is defined as the number of new cases of a disease divided by the population at risk within a specified time period. Direct standardisation was used to account for the different population structures upon comparing the incidence in Saudi with other countries and indirect standardisation was used to account for the different population structure between the different Governorates, thereby facilitating internal comparisons, as opposed to

crude rates that do not (Dos Santos Silva, 1999). The analyses in this thesis concentrate on haematological cancers and CNS tumours.

3.3.2.1 Directly standardised rates

The most widely used approach for international comparison is direct standardisation. This method utilises an independent standard population, such as the World standard, or the European standard population to enable direct comparisons between countries. The direct standardisation can be thought of as a weighted average of the age/sex-specific rates, where the weights are acquired from the standard population (Dos Santos Silva, 1999).

The direct standardisation has been carried out using the `dstdize` command in Stata (StataCorp, 2011a). The weights used for this command were based on the populations in each age-sex strata. The external reference population chosen is the new World Standard Population for 2000 to 2025 (Table 3) (O. Ahmed et al., 2002). The dstdize command returns 95% exact Poisson confidence intervals. The resulting age-adjusted rates are expressed per 100, 000,00 person years.

Table 3.3: The new World Standard Population for the years 2000-2025

Age (years)	WHO World (2000-2025)
0-4	8860
5-9	8690
10-14	8600
15-19	8470
20-24	8220

3.3.2.2 Indirectly standardised rates

Indirect standardisation may be used when comparing regions within a country, for example comparing the different Governorates of Saudi Arabia. It is used when the population in each of the age-sex strata for the whole country is known. Indirect standardisation uses the population for the whole country to calculate the age/sex adjusted rates (Dos Santos Silva, 1999). The resulting age-sex adjusted rates are expressed per 100,000 person years.

The `istdize` command in Stata (StataCorp, 2011b) has been used to derive the indirect standardised rates for each Governorate, using the population in each age-sex strata for Saudi Arabia as the standard population. The command also produces 95% exact Poisson confidence intervals.

3.3.2.3 Standardised incidence ratios

A common method of presenting internal comparisons within an area, for example, the Governorates of Saudi Arabia, is to calculate the standardised incidence ratios (SIRs). These rates were originally designed for mortality, therefore they are more often known as standardised mortality ratios (SMRs). However, they can also be calculated for incidence. The SIR is:

$$SIR = \frac{Observed}{Expected} \times 100$$

Equation 3.1

The expected numbers of cases are calculated by multiplying the age and sex specific rates by the population corresponding to each stratum. The `istdize` command in Stata (StataCorp, 2011b), that was used to produce the indirectly adjusted rates also produces the SIRs, along with the exact Poisson 95% confidence intervals. The SIRs are expressed as percentages, if the resulting SIR in a Governorate is 100%, then that indicates that the risk for that Governorate is equal to the average for Saudi Arabia. A Governorate with an SIR lower than 100% indicates that the Governorate has a lower risk, and a Governorate with an SIR higher than 100% indicates a higher risk than the average for the country.

3.3.3 Cartography

The GIS maps served as a tool to present the calculated SIRs and SES indices for each of the Governorates. Disease mapping provides a spatial perspective when studying disease aetiology, highlighting areas with potentially elevated risk.

3.3.3.1 Data linkage and mapping

The calculated SIRs were linked to the GIS boundary data by the use of a unique variable. This variable facilitated data linkage and checks were made to ensure that each SIR corresponded to the correct Governorate. The SIRs were then divided into fifths and presented within the map by shading each Governorate with a colour

corresponding to the SIR: Governorates with the lowest quintile of SIRs are coloured white, and Governorates with the highest quintile are coloured a darker shade of blue.

3.3.3.1.1 Smoothing the standardised incidence ratios

The raw SIRs calculated for each Governorate may misrepresent the geographical distribution of the disease risk, since it does not take into account the differing population sizes of the Governorates. Clayton and Kaldor (1987) proposed Empirical Bayes smoothing to account for the small population sizes, and stabilise rates. The basic underlying theory is to compute the posterior distribution where:

Posterior* = *Prior* x *Likelihood **Equation 3.2**

The likelihood relates to the Poisson distributed observed cases, and the prior is based on prior belief from the distribution of cases, for example, the rates are more likely to be reliable in areas with large population sizes than those with smaller population sizes.

From a Gamma distribution, where ν is the shape parameter, α is the scale parameter and $\frac{\nu}{\alpha}$ is the mean, then the posterior expectation conditional on O_i $E(\theta_i \mid O_i;\alpha,\nu)$ of the *i*th area is:

$$= \frac{O_i + \nu}{E_i + \alpha}$$ **Equation 3.3**

O_i is the observed number of cases in area *i*

E_i is the expected number of cases in area *i*

Equation 3.3 shows how the SIR is smoothed or shrunk towards the overall mean (Clayton and Kaldor, 1987). Therefore, if the *i*th area has a small population, the values of O_i and E_i will be small compared to the mean, thus the empirical Bayes estimate will shrink towards the mean. Conversely, if the *i*th area has a large population size, the values of O_i and E_i will be large compared to the mean, and the empirical Bayes estimate will be very close to the actual SIR.

Spatial empirical Bayes (SEB) however, defines a neighbourhood around which each area is smoothed. A neighbourhood may be defined as all the contiguous

areas plus the *i*th area itself. Contiguity may be defined as ‘a measure to check for continuity between areas’ (Lai et al. 2008, p. 79). There are two types of contiguity: the queen and the rook contiguity. The queen contiguity accepts an adjacent area that has a meeting point with the *i*th area, whilst the rook contiguity only accepts the neighbourhoods with a considerable amount of adjacency (Lai et al., 2008). First order contiguity is chosen if it is only desired to include the adjacent areas to the centre cell, and higher orders may be chosen if areas that share a border with the adjacent areas are included. For this study, the queen contiguity with first and second order was mapped, because disease risk is not restricted to one direction, and also because some Governorates have very low population sizes. It has also been noted that patients travel across Governorate borders for further diagnostic and treatment purposes. The SEB smoothing was performed in GeoDa software (Anselin et al., 2006).

3.3.4 Funnel plots

Originally, funnel plots were used in meta-analysis to examine any possible bias. They are also used to make institutional comparisons on the basis of outcome measures, so whether these institutions were hospitals, hospital departments, or in this case, Governorates. The plots get the name from the funnel shape formed by upper and lower 95% and 99.8% control limits around the central line that is equal to an incidence ratio of 1, the limits become narrower when the sample size becomes larger. The observed indicator variable is plotted against a measure of its precision (Spiegelhalter, 2005, Spiegelhalter, 2002).The plots show the SIRs for each Governorate before and after empirical Bayes smoothing against the expected number of cases. Funnel plots have been constructed in Stata (StataCorp, 2011b) using the `funnelcompar` command.

3.3.5 Case ascertainment

Since the data were acquired from a relatively new cancer registry, it is reasonable to check for case ascertainment of the data. The usual method of capture-recapture could not be used in this data since this method requires examining records from the different sources of data, and this is not feasible for reasons of confidentiality and time limitations. Therefore, age-sex standardised incidence rates between the US and Saudi Arabia were examined and compared by the year of diagnosis for all disease categories. Also, incidence rates in both countries were compared by the method of direct standardisation to the US standard population. This made it

possible to look for any signs of under ascertainment of cases by identifying unusually low rates, although, rates may well be different between the US and Saudi Arabia.

3.4 Derivation of area-based measures of socioeconomic status

Two measures of SES were derived for the 118 Governorates of Saudi using the 2004 census data (CDSI, 2004b). The first measure was constructed using exploratory factor analysis (EFA) resulting in a continuous latent measure, and the second measure was constructed using latent class analysis (LCA) resulting in a categorical latent measure.

3.4.1 Standardised index of socioeconomic status

The standardised index of SES was constructed using EFA. Figure 3.3 provides a very brief description of the steps undertaken to produce the standardised index of SES.

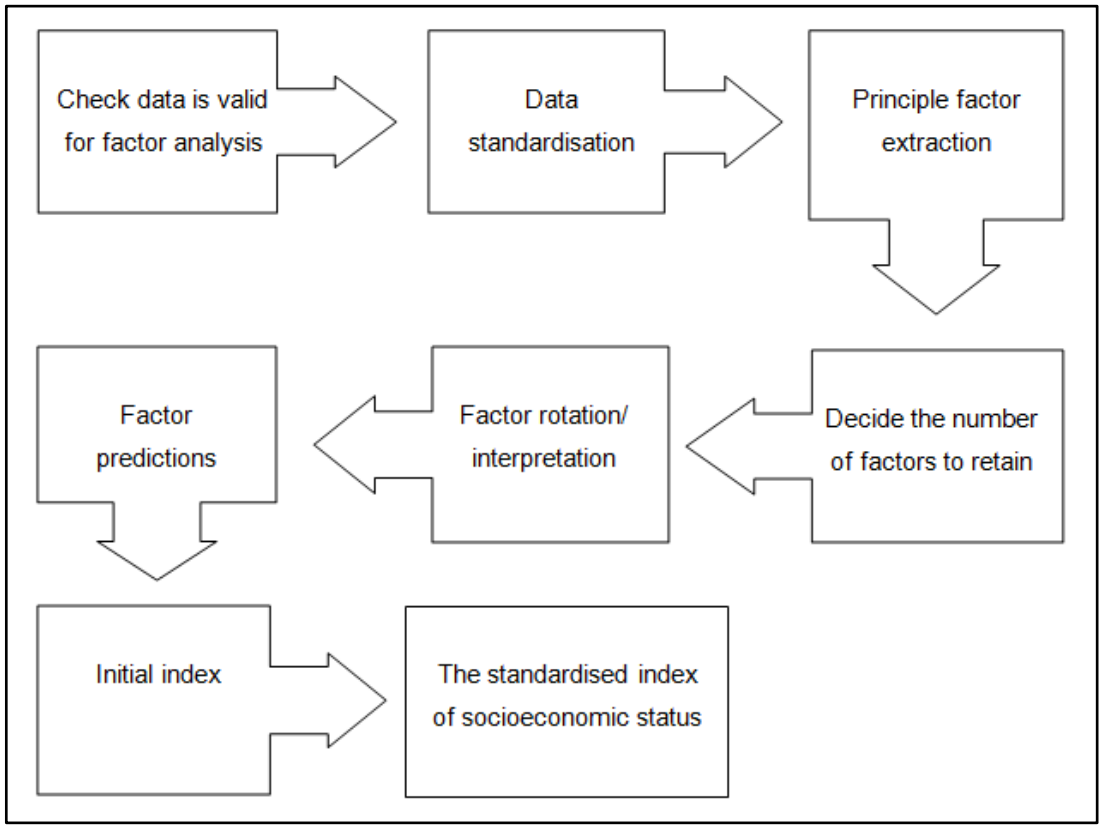


Figure 3.3: Steps taken to derive the standardised index of socioeconomic status

Exploratory factor analysis (EFA) is a multivariate technique that is used to identify the latent structures or factors from a set of indicator variables. The starting point for the EFA is a correlation matrix between the indicator variables. The diagonal component of the matrix is 1, since each variable correlates perfectly with itself. The

off-diagonal components are the correlation coefficients between each pair of variables. In the event that there are clusters of high correlation coefficients, then this may mean that a number of latent structures or factors exist. EFA is a multivariate analysis that uncovers these latent structures by explaining the maximum amount of common variance within the interrelated factors (Field, 2000).

3.4.1.1 Data checks

The data within the analysis included the grouped variables from Table 3.1, except for the 'employment category' variable, where the ungrouped original variables were used. The first step was to check whether the data were appropriate for an EFA by conducting two tests. The first is the Bartlett's test of sphericity, which is a statistic that tests whether the correlation matrix is an identity matrix, i.e., that the diagonal components are equal to one, and the off-diagonal components are equal to zero, which means the variables are not correlated (Bartlett, 1951). The statistic produces a P-value, if the value is significant ($P < 0.05$) then the null hypothesis is rejected, and it is concluded that the variables are highly correlated suggesting factorability. The second test is the Kaiser-Meyer-Olkin (KMO) test, which is a measure of sampling adequacy. It is a test that compares the observed correlation coefficient to the partial correlation coefficient (Kaiser and Rice, 1974). The partial correlation coefficients are the correlations between a pair of variables after the common variance has been removed. If the ratio is close to one, then this indicates that the partial correlations are small and therefore the variables are highly correlated, but if the ratio is small then this indicates that the partial correlation is high and the variables are not sufficiently correlated for an EFA. Kaiser and Rice (1974) labelled the possible outcomes as 'marvellous' if the value is in the 0.90s, 'meritorious' in the 0.80s, 'middling' in the 0.70s, 'mediocre' in the 0.60s, 'miserable' in the 0.50s and unacceptable <0.50. The command `factortest` in Stata (StataCorp, 2011b) was used to compute both test statistics.

3.4.1.2 Factor extraction method

Prior to factor extraction, the indicator variables were standardised to have a mean of zero and a standard deviation of one, so that the standardised Z score for an observation x (Z_x) is given by

$$Z_x = \frac{x - \mu}{\sigma} \qquad \textbf{Equation 3.4}$$

Where, μ is the mean of the variable x and σ is the standard deviation. This step is crucial before an aggregation process, not only to account for the different scales of the indicator variables, but also to prevent variables with disproportionate ranges unnecessary prominence at the expense of others (Gilthorpe, 1995).

The basic factor analysis formula for a variable j (Z_j) is given by:

$$z_j = a_{j1}F_1 + a_{j2}F_2 + \cdots + a_{jm}F_m + a_{ju}U_j \qquad \textbf{Equation 3.5}$$

(j = 1, 2, …, *n)*

Where each of the *n* observed variables are linearly described in terms of *m* common factors that are usually much smaller than *n*. The a_j are the factor loadings, for example a_{j1} is the loading of variable z_1 on factor F_1. The $a_{ju}U_j$ is the unique factor that accounts for the remaining variance (including residual error) for the observed variable Z_j (Harman, 1967).

The procedure starts with estimating the first principal factor that explains the maximum amount of common variance possible, then the second principal factor is estimated that accounts for the maximum amount of common variance from the remaining residual space after the first factor is removed, until the *nth* factor has been extracted, so that the factor analysis models for variable 1 to n are given by

$$\begin{cases} z_1 = a_{11}F_1 + a_{12}F_2 + \cdots + a_{1m}F_m + a_{1u}U_1 \\ z_2 = a_{21}F_1 + a_{22}F_2 + \cdots + a_{2m}F_m + a_{2u}U_2 \\ \cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots \\ z_n = a_{n1}F_1 + a_{n2}F_2 + \cdots + a_{nm}F_m + a_{nu}U_n \end{cases} \qquad \textbf{Equation 3.6}$$

The principal factor was chosen as the factor extraction method. Although previous papers have chosen principal-component factoring, this method has an assumption that the communality is equal to one for all variables (StataCorp, 2012). The communality is the variance of the variable accounted for by the factors. It is calculated by taking the squared sum of a variable's loadings across the extracted factors (Harman, 1967).

From the basic factor analysis formula in Equation 3.5, the communality (h_j^2) may be expressed as:

$$h_j^2 = a_{j1}^2 + a_{j2}^2 + \ldots + a_{jm}^2$$ **Equation 3.7**

Stata does not report the communality, but it reports the uniqueness. The uniqueness is the variance that is unique to each variable, so it is simply one minus the communality. Therefore, since the principal-component factor extraction method assumes that the communalities are equal to one, the uniqueness should then be equal to zero. This method was first used, and the uniquenesses were examined and were found to be more than zero. Therefore, the data violates this assumption, and the principal factoring extraction method was used.

The `factor` command in Stata (StataCorp, 2011b) performs the factor analysis with the principal factoring extraction method as the default.

3.4.1.3 Factor retention

The EFA produces the same amount of factors as there are variables. Each factor is assigned an eigenvalue (V_m) which is a value that describes the contribution of each factor to the overall factor solution. It is calculated as the sum of the loadings for a factor across all observations (Harman, 1967). The eigenvalue of a factor may also be expressed in terms of its proportion in explaining the overall common variance, and so the higher the proportion the more important that factor is. Eigenvalues are mathematically represented as:

$$V_m = \sum_{j=1}^{n} a_{jm}^2$$ **Equation 3.8**

Where n are the observed variables and a_{jm} are the factor loadings for a variable j on factor m.

The decision on the number of factors to retain was based upon three criteria. First, the Guttman-Kaiser rule, which describes the truly existing factors as the factors with eigenvalues above one (Kaiser, 1960, Guttman, 1954). The second criterion is the scree-plot, which is a plot of the eigenvalues and the factors and is determined by the point at which the plotted values start to level off (Cattell, 1966). The third and final criterion is the ability to interpret all potentially retained factors (Bandalos, 2009).

Less common methods are used for factor retention and include parallel analysis and minimum average partial procedures. The parallel analysis includes simulation

of a random data matrix, whilst the minimum average partial procedures include computing the average squared off-diagonal component of the matrix, and is in any case only applicable to the principal component analysis, not to the common factor analysis used here (Bandalos, 2009). Furthermore, reviewers have stressed on the interpretability of the extracted factors and consider it the ultimate criteria (Cortina, 2002, Worthington and Whittaker, 2006).

3.4.1.4 Factor rotation and interpretation

The initial factor extraction tends to yield factors that are difficult to interpret. A very common procedure is to rotate the factor axes to achieve a simple structure, whereby the factor loadings become either higher or lower than the loadings obtained from the initial extraction, hence the factors are easier to interpret. Two types of rotations are available, orthogonal and oblique. The main difference between the two methods is that the orthogonal rotation considers the extracted factors as being completely independent of each other (Bandalos, 2009). In the SES developed for Saudi Arabia, the factors are assumed to be correlated since the indicator variables are proportions of the population, whereby each factor may include a proportion of all indicator variables. Therefore, an oblique rotation was used.

3.4.1.5 Factor predictions

Subsequent to the rotation, the scores of all the observations (Governorates) on a factor based on their loadings for the indicator variables were computed. These are linear composites that are formed by standardising all variables by zero mean and unit variance, then weighting with factor loadings and finally summing for each factor (Hamilton, 2012). The `predict` command in Stata (StataCorp, 2011b), produces these scores and automatically includes them as separate variables within the dataset, so as to be able to use them in subsequent analyses.

3.4.1.6 Initial index

Once the factors were extracted and rotated, the proportion of each factor in explaining the overall common variance was used as a weight within the initial index. The reason for using weights was to avoid giving each factor equal

importance, and to account for factors that could be more important in explaining the SES than others within the population (Kishnan, 2010). The formula for the initial index II is straightforward and is given by:

$$II = \sum F_n W_n \qquad \textbf{Equation 3.9}$$

Where F_n is the score for each factor and W_n is the weight of each factor or the proportion of common variance explained for that factor.

This initial index then produced a score for each of the 118 Governorates of Saudi Arabia, and the values ranged from positive to negative numbers, where the highest positive number indicated the corresponding Governorate to be the most affluent and the lowest negative number indicated the corresponding Governorate to be the most deprived.

3.4.1.7 Final standardised index

The initial index produces values that are both positive and negative. For easier interpretation, the index is calibrated on a scale from 100 to 0, whereby 100 corresponds to the affluent Governorate and 0 to the most deprived. The formula for the i th Governorate is given as follows:

$$SI_i = \frac{II_i - II_{min}}{II_{max} - II_{min}} x100 \qquad \textbf{Equation 3.10}$$

Where II_i is the initial index for i th Governorate, and II_{min} is the lowest value of any Governorate from the initial index, and II_{max} is the highest value of any Governorate from the initial index.

This formula enables the measuring of SES of a Governorate relative to the difference between the best and the worst Governorate. It also provides a clearer means of comparison compared to the initial index. This method has been used in previous measures of SES in other countries (Hightower, 1978, Kishnan, 2010, Sekhar et al., 1991, Fukuda et al., 2007).

3.4.2 Classes of socioeconomic status

The first index produces a continuous measure of SES for Saudi Arabia. Latent class analysis (LCA) was used to produce a categorical measure of SES. LCA is a model-based approach to the clustering of individuals, in this case Governorates, into a small set of homogeneous groups or latent classes (Wang and Wang, 2012). The increase in availability and access to specialised computer software has led to a wider application of this method which was first developed in 1950 (Lazardsfeld, 1950).

The objective of LCA is to identify clusters of unobserved latent subgroups (or Classes) that contain similar observations based on the pattern of each Governorate's response to the observed indicator variables. The method of identification of these unobserved latent subgroups is based on posterior membership probabilities (Wang and Wang, 2012). The classical LCA model only applies to categorical variables. However, the Mplus software (Muthen and Muthen, 2012) allows the use of continuous variables such as those available from the Saudi census data. In this instance, the analysis is usually referred to as latent profile analysis, however, the term LCA will be used for uniformity with resulting classes of SES. Figure 3.4 provides a very brief description of the steps undertaken to produce the classes of SES.

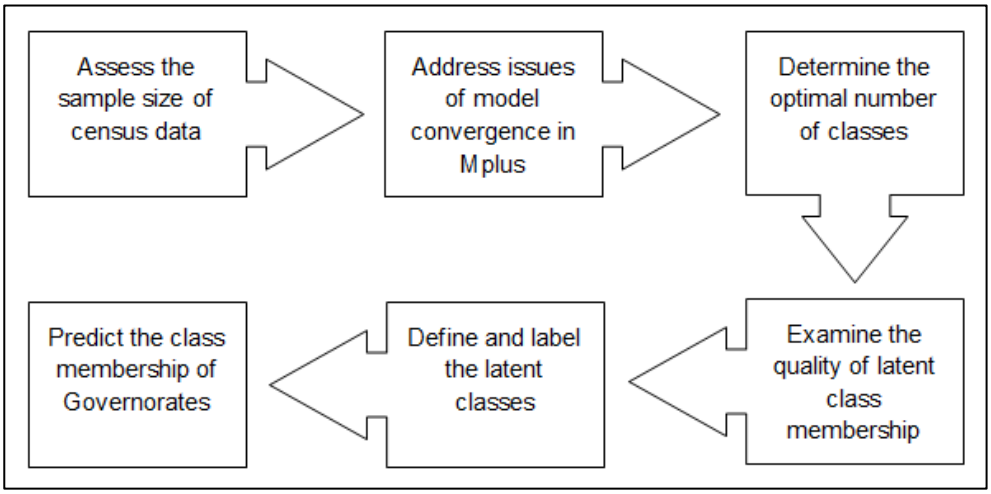


Figure 3.4: Steps taken to derive the socioeconomic classes of Saudi Arabia using latent class analysis

In its simplest form, for a dichotomous variable, the LCA model for a single item is given by the following:

$$p(X_{vi}=1)=\sum_{g=1}^{G}\pi_g\pi_{ig}$$ **Equation 3.11**

Where, $p(X_{vi}=1)$ indicates the unconditional probability that a random individual v achieves a score of $X=1$ (which is the highest score possible) on the item i, where $i=1,2..,I$. The π_g is the class size parameter that indicates the unconditional probability of the observation v belonging to the latent class g, where $g=1,2..,G$ (Geiser, 2010). One important assumption is that each observation v belongs to only one latent class, in other words the latent classes are independent of each other. Therefore, the summation of probabilities of all the classes is equal to one:

$$\sum_{g=1}^{G}\pi_g=1$$ **Equation 3.12**

The conditional probability of a score of one on item i given membership in class g is given by the following:

$$\pi_{ig}=p(X_{vi=1}\,|\,G=g)$$ **Equation 3.13**

Similar to EFA, the decision on the optimal number of classes is made by the researcher by means of certain criteria. The parameter estimates and model fit statistics such as the Akaike Information Criterion (AIC) and the Bayes Information Criterion (BIC) are determined by an iterative estimation procedure based on the maximum likelihood estimation, which is the default in Mplus (Geiser, 2010, Muthen and Muthen, 2012). The objective is to maximise the likelihood function in order to find the model with the largest possible log likelihood value. This log likelihood is a measure of the probability of the observed indicator variables given the model, and is the measure used as the basis for the calculation of the model fit statistics (Geiser, 2010).

3.4.2.1 Overcoming issues with sample size

The analysis was started in Mplus and included the same variables used within the EFA. However, the model would not converge. It was then found that the problem persisted because of the small sample size relative to the number of indicator variables used. Wang and Wang (2012) noted, 'It is widely recognized that small sample size could cause a series of problems, including, but not limited to, failure of estimation convergence, improper solutions ...' (p.391). There is no consensus in the literature with regards to the sample size required for LCA and structural equation modelling (SEM) in general. For example, some find that N=100-150 is the minimum sample required (Tabachnick and Fidell, 2001, Ding et al., 1995), while some researchers consider that N=200 is the minimum required (Boomsma and Hoogland, 2001, Kline, 2005).

It is often necessary to consider the sample size in relation to the number of indicator variables used. One accepted rule of thumb is to have ten observations for every one indicator variable (Nunnally, 1967). A much lower ratio was suggested that allows for five observations per indicator variable (Bentler and Chou, 1987). Considering the 29 variables available after the necessary grouping from Table 3.1, this would mean that for the first rule of thumb, at least 290 observations would be required, and with the second at least 145. However, since the observations are Governorates and they are only 118, it is impossible to increase the sample size. Therefore, a decision was made to reduce the number of indicator variables to achieve the widely accepted ratio of 10:1. The variables chosen include only the disadvantage indicators: not in the labour force, illiterate or can read and write, no car, living in a traditional house, living in a floor of a villa or a traditional house, house not owned, no phone, no television, no internet, no library and no satellite. Consequently, there are 11 variables for 118 Governorates, thereby achieving the 10:1 accepted ratio.

3.4.2.2 Issues of model convergence

A common problem with iterative estimation procedures, such as those underlying LCA, is that the default set of starting values (e.g. in Mplus the default is 10) for the parameter does not allow the model to converge with the best possible log likelihood value. Because the estimation method is iterative, many solutions are obtained for these iterations. The solution with the highest log likelihood value indicates that the model converged on what is known as the global maximum. Consequently, if the model does not find the global maximum, it then terminates on

the local maximum, which is associated with inaccurate parameter estimates (Geiser, 2010, Wang and Wang, 2012).

In the event that only a few starting values are used in Mplus (or in any other structural equation modelling software), then it is likely that the estimation will terminate on a local maximum. Therefore, in order to increase the chances of obtaining the global maximum solution, a sufficient number of starting values should be used. A set of different numbers of starting values were tried, and a global maximum was obtained when the number of starts was increased to 1000.

3.4.2.3 Deciding the number of classes

The number of latent classes is unobserved, and therefore it cannot be directly estimated from the dataset. To determine the optimal number of classes in LCA, a series of LCA models were run starting with a one-class model and increasing the number of classes with each run. Then, the optimal number of classes was chosen based on a comparison of the model fit indices of the k-class model and the (k-1)-class model. The (k-1)-class model is the same as the k-class model, but with one latent class set to zero (Wang and Wang, 2012, Geiser, 2010).

The first model fit index to examine is the AIC (Akaike, 1987). The idea underlying the AIC is to select the best model that minimises the difference between the unknown true data and the estimated model. This difference is known as the Kullback-Leibler difference. It is widely used for its simplicity, as it only requires the maximum likelihood achieved by the model, and is calculated by:

$$AIC = -2 \ln L_{max} + 2k$$ **Equation 3.14**

Where L_{max} is the maximum likelihood value from the model, and k is the number of parameters reported for the model, and is the penalty term that is used to combine absolute model fit and model parsimony. The lower the AIC the better the model fit (Wang and Wang, 2012). The second model fit index is the BIC (Schwarz, 1978). Similar to the AIC, the BIC adds a stronger penalty term by adding more parameters to the model and is estimated by:

$$BIC = -2 L_{max} + k \ln N$$ **Equation 3.15**

Where N is the sample size used for the model. The lower the value of the BIC the better the model fit. A further model fit index reported by Mplus is the Adjusted

Bayes Information Criterion (ABIC) (Wang and Wang, 2012), which reduces the penalty of the BIC for smaller sample sizes by:

$$ABIC = -2\boldsymbol{L}_{max} + k\,ln\left(\frac{n+2}{24}\right) \qquad \textbf{Equation 3.16}$$

Other model fit indices reported in Mplus include the Lo-Mendell-Rubin likelihood ratio test (LMR-LRT), this examines the model fit and looks for any improvement between a k-class and a (k-1)-class model. A significant P-value (P<0.05) indicates that the k-class model fit is significantly better than a (k-1)-class model. If however, the P-value is non-significant (P≥0.05), then the (k-1)-class model is preferred (Lo et al., 2001). The final model fit index is the Bootstrap Likelihood Difference test (BLRT), which also compares a k-class model with a (k-1)-class model. Using a parametric bootstrapping procedure, P-values for the likelihood difference are estimated by fitting the k-class and (k-1)-class model to every bootstrap sample and calculating the likelihood ratio for each bootstrap sample. A significant P-value (P<0.05) indicates that the k-class model is a better fit than the (k-1)-class model (Geiser, 2010, Wang and Wang, 2012).

All these model fit indices were taken into account during the model fit selection process, and they all usually led to the same conclusion, although, some discrepancies were found. The evidence suggests that the BIC along with the BLRT fit indices are the most reliable (Nylund et al., 2007).

3.4.2.4 Examining the quality of latent class membership

Upon deciding on the optimal number of classes for the model, the observations or Governorates were then classified into the latent classes. The way in which each Governorate was assigned to a class was through the conditional probability from Equation 3.13. The latent class membership of the Governorates was identified based on the estimated probability. The sum of the probabilities is equal to one (Equation 3.12). Therefore, the closer the value is to one the more likely it belongs to that latent class (modal assignment) (Wang and Wang, 2012). A rule of thumb for a good classification is when the modal assignment probability is higher than 0.70 (Nagin, 2005). Another common criterion used was the entropy, which measures the accuracy of classification of Governorates into latent classes. The value ranges from zero to one, the closer the value to one the more accurate the classification is. It is suggested that an entropy of more than 0.80 is high, 0.60 is medium and 0.40 is low (Clark, 2010).

3.4.2.5 Defining and labelling the latent classes

Similar to examining the factor loadings and labelling the factors in the EFA, the probabilities are examined and the latent classes are labelled in the LCA. The higher the probability for a given Governorate on a given class the more likely it is that it belongs to it. This is also aided by a probability plot that is provided within Mplus. The plot provides a visual representation of how each indicator variable relates to each class in terms of the probability. It is crucial and a sign that the LCA model has succeeded if the resulting classes are clearly interpretable. The main objective of the LCA is to group homogenous observations or, in this case, Governorates together in separate classes. Consequently, the researcher should be able to define each class by the pattern of item-response probability in that class (Wang and Wang, 2012). If one class is not interpretable or does not make sense, the LCA model then should be discarded despite a good model fit.

3.4.2.6 Predicting the class membership of Governorates

The final step in LCA is to predict the resulting latent classes, similarly to predicting the factors in an EFA. This is readily done in Mplus by specifying `save = cprobabilities` under the save section of the command lines. A new file is generated that contains the probability of each Governorate belonging to each class, with a column for every class, and finally a categorical latent class variable that specifies to which class each Governorate belongs (based on the probabilities) (Geiser, 2010).

3.5 Direct Acyclic Graph and regression analyses

3.5.1 Direct Acyclic Graph

Prior to modelling, a Directed Acyclic Graph (DAG) was constructed to understand the influence of the variables on the disease outcome. A DAG shows independence between the variables by drawing nodes, whereby the connections between these nodes imply a causal influence. These connections are directed with an arrow to better indicate which variable influences the other (Thornley et al., 2013).

Figure 3.5 shows the DAG for the association between the exposure of interest (PM) and the outcome (childhood cancers). Confounding variables are identified by removing the arrow between the exposure and the outcome. However, there is no direct arrow in between, because 'infections' is on the causal pathway, since PM is a proxy measure for infections. Therefore, the arrow between PM and infections is removed, and an examination of a potential unblocked backdoor path between PM and childhood cancers was performed. It can be seen that SES is considered a confounder and should be adjusted for. Furthermore, age and sex are confounders between infections and childhood cancers and should also be adjusted for. The stratification of age and sex and the use of an expected number of cases automatically adjusts the two variables, so there is no need to include them in the regressions as separate variables. The regression analysis phase commenced in light of this DAG.

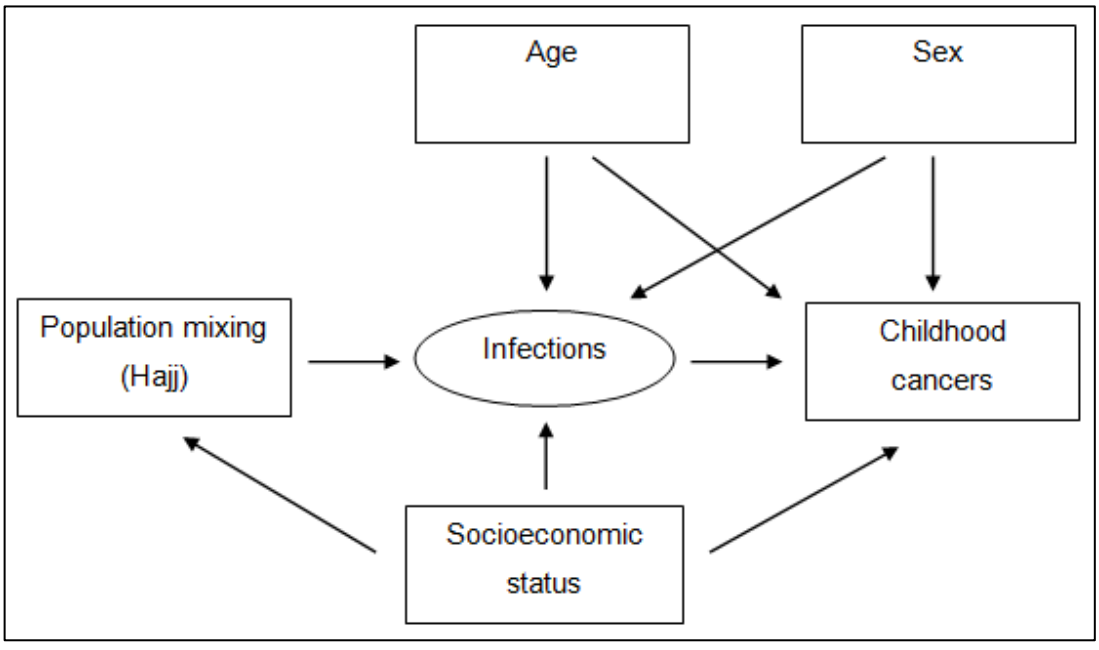


Figure 3.5: Identification of confounding variables between exposure and outcome

3.5.2 Poisson regression

The use of ordinary linear regression for the analysis of a number of rare diseases such as cancers occurring in children and adolescents is inappropriate, because the distributions of the counts are not normally distributed and, therefore, the standard errors of the model will be inaccurate. A Poisson model and its extension, the Negative Binomial (NB) model are used with data sets such as these (Petrie and Sabin, 2013). Nonetheless, the data were checked for normality, and the distribution was found to be highly skewed, with a high number of zero cell counts. Therefore, the Poisson model was used as a first step.

Poisson regression is a member of the class of generalised linear models (GLMs). Similar to the linear regression model, it consists of a linear combination of explanatory variables to the right side of the equation, and the outcome of interest is log transformed to the left side of the equation. The basic model is given by:

$$ln(r) = a + b_1 x_1 + b_2 x_2 + ... + b_j x_j \qquad \textbf{Equation 3.17}$$

Where, $ln(r)$ are the log rates of the disease, and the term a is the constant, and x_j is the *j*th explanatory variable, and the b_j s are the estimated Poisson coefficients (Petrie and Sabin, 2013).

The regression was performed in Stata (StataCorp, 2011b). The software models the actual number of observed counts as opposed to the rate, while the log of the person-year at risk enters the model as an offset (Petrie and Sabin, 2013).

The assumption underlying the Poisson regression is that the range of values are non-negative (therefore the Poisson distribution is always skewed to the right), and it also assumes that the variance is equal to the mean. Consequently, it does not account for any overdispersion of the data, i.e., the variance is greater than the mean thus violating the underlying assumption. If the data is overdispersed, then it is better to use the NB model instead (Petrie and Sabin, 2013).

3.5.3 Negative binomial regression

Since the Poisson regression assumes that the variance is equal to the mean, it does not account for any overdispersion of the data. This is common when there are a large number of zeros, as is the case within the Saudi cancer data. The NB model accounts for the overdispersion of the dependent variable by assuming that there is unobserved variance amongst observations with the same predicted value,

which leads to a larger variance of the distribution of the outcome, more than can be accounted for by a simple Poisson, though the mean is not affected (Little, 2013).

A useful feature of the NB model is that the Poisson model is nested within it. The main differences between the Poisson and the NB is that the NB model has an α parameter that is estimated along with the other model parameters and which measures the overdispersion numerically. If the α is equal to zero then there is no overdispersion and the model reduces to the simpler Poisson model. If however, α > 0, then this indicates that overdispersion does exist and is accounted for. The interpretation of the model coefficients are the same as the Poisson model. Also, the variance in the NB model is larger than the variance of the Poisson, though the means are the same (Little, 2013).

Inspection of the data both visually by a histogram and statistically showed there is overdispersion. Therefore, the NB model was used, in which the alpha parameter that is estimated alongside the models' parameters all showed a value of > 0, thereby confirming the overdispersion in the outcome.

The data were arranged in strata of years, age and sex by Governorates. Univariable analysis was performed on each of the PM, SES and year variables to assess which to include in the multivariable analyses (Appendix H). The PM was modelled as a binary variable to be able to distinguish the effect of the exposure to Hajj, which happens in Makkah, on the incidence of cancers when compared to the rest of the Saudi Governorates each year. This was the only feasible method for assessing the effect of Hajj given the limited availability of the data. Further, three sets of regressions were performed for every disease category using SES as the main independent variable. The first included the standardised index of SES as a continuous variable, as derived by the EFA from this study. The second set included the use of the same standardised index, but using quintiles of the SES variable and model as a categorical variable. The third set included the use of the categorical classes of SES as derived by the LCA approach. These three sets were utilised to look for the effect of SES on the incidence of each cancer group. The second class 'upper middle class' category was chosen as the reference group for the SES, since it included the majority of Governorates, whereas for the quintiles of SES, the reference group was chosen as the most affluent category, since all quintiles had similar numbers of Governorates, thus by choosing the most affluent it is easier to compare. The model diagnostics included inspection of likelihood ratio tests, AICs and BICs.

4 Results: Descriptive analyses and mapping

All data presented relate to cancers in children and young adults reported in the calendar years 1994 to 2008 in Saudi Arabia, and are in the order in which they appear in the methods.

4.1 Demographic characteristics, incident cases and incidence rates

4.1.1 Demographics

Demographics details the number of incident cases of cancers by age group and sex between 1994 and 2008. For males the highest numbers are found to be in the 0-4, and 10-14 age groups (26.86% and 20.53% respectively), and the lowest numbers are found in the 15-19 age group (16.19%). For females, the numbers are higher in the 0-4 and the 20-24 age groups (25.78% and 23.92% respectively). For both sexes, the majority of incident cases are in the 0-4 age group (26.36%) and the lowest number of cases is in the 5-9 age group (16.36%). Generally, however, incident cases are higher in males than in females (53.81% and 46.19% respectively).

Table 4.1: Incident cases and incidence rates (per 100,000) of all cancers in Saudi Arabia by age group and sex, 1994-2008

Age group	Male (%)	Rates	Female (%)	Rates	Total (%)	Rates
0-4	2,479 (26.86)	13.78	2,042 (25.78)	11.51	4,521 (26.36)	12.65
5-9	1,655 (17.93)	8.89	1,150 (14.52)	6.28	2,805 (16.36)	7.60
10-14	1,895 (20.53)	10.79	1,500 (18.94)	8.13	3,395 (19.80)	9.43
15-19	1,494 (16.19)	9.76	1,334 (16.84)	8.85	2,828 (16.49)	9.31
20-24	1,706 (18.49)	11.53	1,895 (23.92)	14.36	3,601 (21.00)	12.86
Total	9,229 (53.81)	10.95	7,921 (46.19)	9.57	17,150 (100)	10.27

4.1.2 Incident cases

Tables 4.2 and 4.3 detail the incident cases of cancers for males and females by age groups between 1994 and 2008 for the main diagnostic groups according to the ICCC-3. For males, in the 0-4 age group, the most commonly occurring types of cancers were leukaemias, CNS tumours and lymphomas (38.60%, 11.86% and 11.62% respectively). However for females within the same age group, the highest numbers of incident cases were for leukaemias, neuroblastomas and CNS tumours (37.86%, 11.61% and 10.87% respectively). For the 5-9 age group, the most common types of cancers were leukaemia, lymphomas and CNS tumours (34.50%, 29.00% and 15.89% respectively) for males, and leukaemias, CNS tumours and lymphomas (36.96%, 19.48% and 14.96% respectively) for females. Lymphomas were the most commonly occurring cancers in the 10-14 age group (30.61%), followed by leukaemias and malignant bone tumours (26.28% and 12.19% respectively) in males, which were also the most common types in females (26.40%, 24.27% and 13.13% respectively). Similarly, lymphomas, leukaemias and malignant bone tumours in males were the most occurring for the 15-19 age group (33.47%, 23.43% and 12.45% respectively). However, for females the most common cancers were lymphomas, followed by epithelial tumours, and leukaemias (28.64%, 26.39% and 14.24% respectively). For males in the 20-24 age group, lymphomas were the most occurring cancer (30.30%) followed by epithelial tumours (19.81%) and leukaemias (17.76%). For females, the most common cancers were epithelial tumours (44.17%) followed by lymphomas and leukaemias (22.37% and 10.61% respectively). No cases were reported for retinoblastomas in either gender for the 15-19 and 20-24 age groups.

Table 4.2: Incident cases of main diagnostic groups for males in Saudi Arabia by age and main diagnostic group, 1994-2008

	Age group (years)											
Diagnostic group	**0-4**	**(%)**	**5-9**	**(%)**	**10-14**	**(%)**	**15-19**	**(%)**	**20-24**	**(%)**	**Total**	**(%)**
Leukaemias	957	(38.60)	571	(34.50)	498	(26.28)	350	(23.43)	303	(17.76)	2,679	(29.03)
Lymphomas	288	(11.62)	480	(29.00)	580	(30.61)	500	(33.47)	517	(30.30)	2,365	(25.63)
CNS	294	(11.86)	263	(15.89)	222	(11.72)	91	(6.09)	110	(6.45)	980	(10.62)
Neuroblastomas	229	(9.24)	39	(2.36)	15	(0.79)	4	(0.27)	5	(0.29)	292	(3.16)
Retinoblastomas	189	(7.62)	12	(0.73)	3	(0.16)	0	(0)	0	(0)	204	(2.21)
Renal tumours	177	(7.14)	39	(2.36)	16	(0.84)	10	(0.67)	11	(0.64)	253	(2.74)
Hepatic tumours	49	(1.98)	10	(0.60)	20	(1.06)	12	(0.80)	17	(1.00)	108	(1.17)
Malignant bone tumours	25	(1.01)	80	(4.83)	231	(12.19)	186	(12.45)	122	(7.15)	644	(6.98)
Soft tissue sarcomas	149	(6.01)	94	(5.68)	109	(5.75)	101	(6.76)	125	(7.33)	578	(6.26)
Germ cell tumours	63	(2.54)	12	(0.73)	37	(1.95)	53	(3.55)	116	(6.80)	281	(3.04)
Other epithelial tumours	27	(1.09)	36	(2.18)	139	(7.34)	169	(11.31)	338	(19.81)	709	(7.68)
Unspecified neoplasms	19	(0.77)	11	(0.66)	11	(0.58)	14	(0.94)	32	(1.88)	87	(0.94)
Other	13	(0.52)	8	(0.48)	14	(0.74)	4	(0.27)	10	(0.59)	49	(0.53)
Total	2,479	(26.86)	1,655	(17.93)	1,895	(20.53)	1,494	(16.18)	1,706	(18.48)	9,229	(100)

Table 4.3: Incident cases of main diagnostic groups for females in Saudi Arabia by age and main diagnostic group, 1994-2008

	Age group (years)											
Diagnostic group	**0-4**	**(%)**	**5-9**	**(%)**	**10-14**	**(%)**	**15-19**	**(%)**	**20-24**	**(%)**	**Total**	**(%)**
Leukaemias	773	(37.86)	425	(36.96)	364	(24.27)	190	(14.24)	201	(10.61)	1,953	(24.66)
Lymphomas	162	(7.93)	172	(14.96)	396	(26.40)	382	(28.64)	424	(22.37)	1,536	(19.39)
CNS	222	(10.87)	224	(19.48)	153	(10.20)	86	(6.45)	75	(3.96)	760	(9.59)
Neuroblastomas	237	(11.61)	40	(3.48)	18	(1.20)	6	(0.45)	7	(0.37)	308	(3.89)
Retinoblastomas	193	(9.45)	4	(0.35)	2	(0.13)	0	(0)	0	(0)	199	(2.51)
Renal tumours	209	(10.42)	56	(4.87)	12	(0.80)	7	(0.52)	22	(1.16)	306	(3.86)
Hepatic tumours	31	(1.52)	5	(0.43)	9	(0.60)	10	(0.75)	12	(0.63)	67	(0.85)
Malignant bone tumours	19	(0.93)	71	(6.17)	197	(13.13)	89	(6.67)	51	(2.69)	427	(5.39)
Soft tissue sarcomas	96	(4.70)	62	(5.39)	84	(5.60)	96	(7.20)	91	(4.80)	429	(5.42)
Germ cell tumours	58	(2.84)	38	(3.30)	88	(5.87)	94	(7.05)	123	(6.49)	401	(5.06)
Other epithelial tumours	16	(0.78)	42	(3.65)	163	(10.87)	352	(26.39)	837	(44.17)	1,410	(17.80)
Unspecified neoplasms	21	(1.03)	7	(0.61)	10	(0.67)	17	(1.27)	23	(1.21)	78	(0.98)
Other	5	(0.24)	4	(0.35)	4	(0.27)	5	(0.37)	29	(1.53)	47	(0.59)
Total	2,042	(25.78)	1,150	(14.52)	1,500	(18.94)	1,334	(16.84)	1,895	(23.92)	7,921	(100)

4.1.3 Overall age-sex standardised incidence rates

The indirect and direct age-sex standardised rates for leukaemias, lymphomas, CNS tumours and other cancers are presented in Table 4.4. The rates are given as per 1,000,000 person years. The rate for ALL in Saudi Arabia was 18.50 per 1,000,000 person years (Table 4.4). In direct standardisation for the World, European or US standard population the incidence rate dropped slightly to 17.86 per 1,000,000, 18.15 per 1,000,000 and 17.62 per 1,000,000 person years, respectively. The age-sex standardised rates also dropped for BL and CNS tumours. However, for CML, NHL and the 'other cancers' group, the incidence was raised when standardising to the World, European or US population. The increased incidence is more marked for the 'other cancers' group, where the indirect rate was 41.17 per 1,000,000 person years (95%CI=40.20-42.14), and the direct rates for the World, European and US standard population were 42.25, 42.72 and 41.92 per 1,000,000 person years. The differences are more marked when the age-sex adjusted incidence rates are standardised to the US standard population, this may be due to differences in the age structure between the US and Saudi Arabia in the 0-24 age group.

Table 4.4: Overall age-sex standardised incidence rates per 1,000,000 for 0-24 year olds in Saudi Arabia

Diagnostic group		Standardisation			
		Indirect	Direct to standard population of		
			World	Europe	US
Leukaemia					
ALL	O[a]	3,091	…	…	…
	Rate	18.50	17.86	18.15	17.62
	95% CI	17.85-19.16	17.22-18.49	17.50-18.80	16.99-18.24
AML	O[a]	985	…	…	…
	Rate	5.90	5.89	5.92	5.88
	95% CI	5.53-6.27	5.52-6.26	5.55-6.29	5.51-6.25
CML	O[a]	265	…	…	…
	Rate	1.59	1.66	1.67	1.65
	95% CI	1.40-1.78	1.46-1.86	1.46-1.87	1.45-1.85
Other	O[a]	291	…	…	…
	Rate	1.74	1.63	1.66	1.62
	95% CI	1.54-1.94	1.45-1.82	1.46-1.85	1.43-1.80
Lymphoma					
HL	O[a]	2,175	…	…	…
	Rate	13.02	13.10	12.97	13.23
	95% CI	12.47-13.57	12.55-13.66	12.41-13.52	12.67-13.80
NHL	O[a]	1,150	…	…	…
	Rate	6.88	6.98	6.95	7.00
	95% CI	6.49-7.28	6.57-7.38	6.54-7.35	6.59-7.41
BL	O[a]	410	…	…	…
	Rate	2.45	2.31	2.34	2.29
	95% CI	2.22-2.69	2.09-2.54	2.11-2.56	2.07-2.51
Other	O[a]	166	…	…	…
	Rate	0.99	1.03	1.04	1.02
	95% CI	0.84-1.14	0.87-1.19	0.88-1.20	0.86-1.18
CNS tumours	O[a]	1,740	…	…	…
	Rate	10.42	10.17	10.21	10.11
	95% CI	9.93-10.91	9.68-10.70	9.73-10.70	9.63-10.59
Other groups	O[a]	6,877	…	…	…
	Rate	41.17	42.25	42.72	41.92
	95% CI	40.20-42.14	41.24-43.26	41.70-43.74	40.92-42.92

[a] Observed cases

4.1.4 Age-sex standardised incidence rates and ratios by Governorate

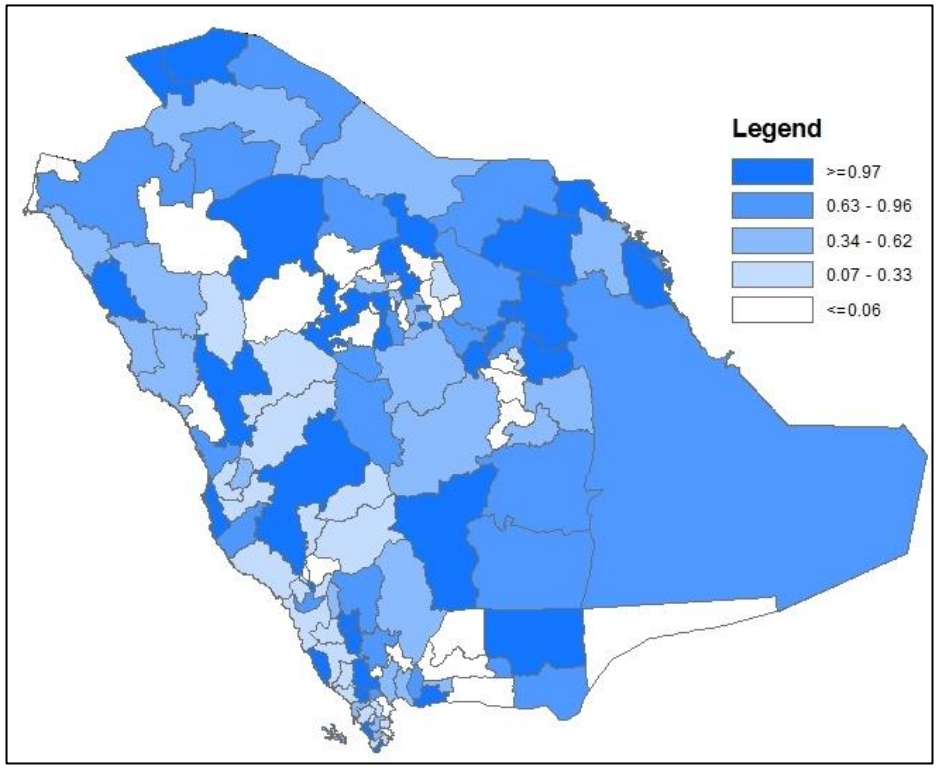
The age-sex standardised incidence rates and the SIRs along with the 95% confidence intervals for each disease category were computed in young people aged under 24 years in Saudi Arabian Governorates, but have not been given. The SIRs have been used in disease mapping and funnel plots.

4.1.4.1 Disease mapping

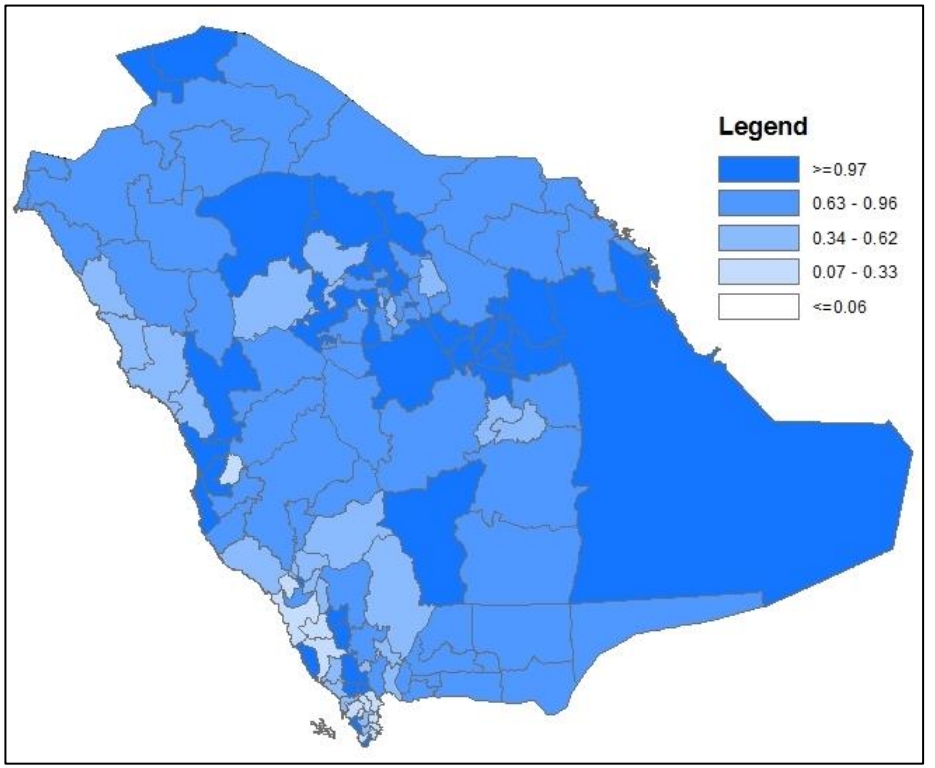
Figure 4.1 shows the crude and SEB smoothed SIRs for ALL. For the crude SIRs, the number of expected cases in the three large Governorates of Riyadh, Jeddah and Dammam were lower than the observed, which is reflected in the high SIRs of these Governorates. There were 23 Governorates with no cases present, providing an SIR of zero. For the SEB smoothed rates, the SIR of one Governorate shrunk towards the mean of its neighbouring Governorates. For example, Badr in the western coast had an estimated SIR of zero due to having no observed cases of ALL. However, after the SEB smoothing, the estimated smoothed SIR became 0.55. The smoothed map shows a pattern of high incidence in the central region of Riyadh, as well as in the Eastern province, Jeddah, Medinah and in the Northern Border region of Toraif and Qurayyat.

Figure 4.2 shows the crude and smoothed SIRs for AML. For the crude SIRs, a total of 47 Governorates had no observed cases reported. However, the Governorate with the highest SIR of 2.95 was Toraif (95%CI = 1.08 - 6.41), located in the Northern Border province, due to having 6 observed cases compared to the 2.04 expected, which are small numbers. After smoothing, the SIR for Toraif shrank to 1.47. The smoothed map in general, shows a clearer pattern of AML incidence, in which incidence remains high in the north eastern, central and south eastern regions of the country. In the south, Baha, Abha and Jazan Governorates have a persistent high incidence of AML after smoothing.

a) Crude SIRs

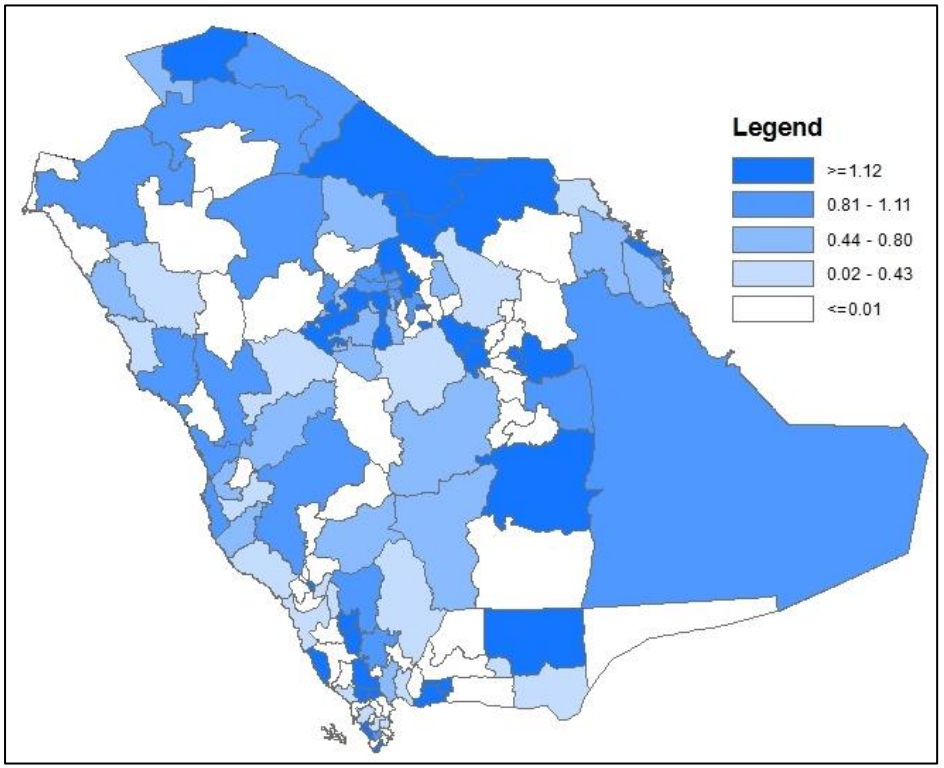


b) Smoothed SIRs



Figures 4.1: Crude and smoothed age-sex standardised incidence ratios (SIRs) of acute lymphoblastic leukaemias registered from 1994 to 2008 in young people under the age of 24 years by Saudi Governorates

a) Crude SIRs



b) Smoothed SIRs

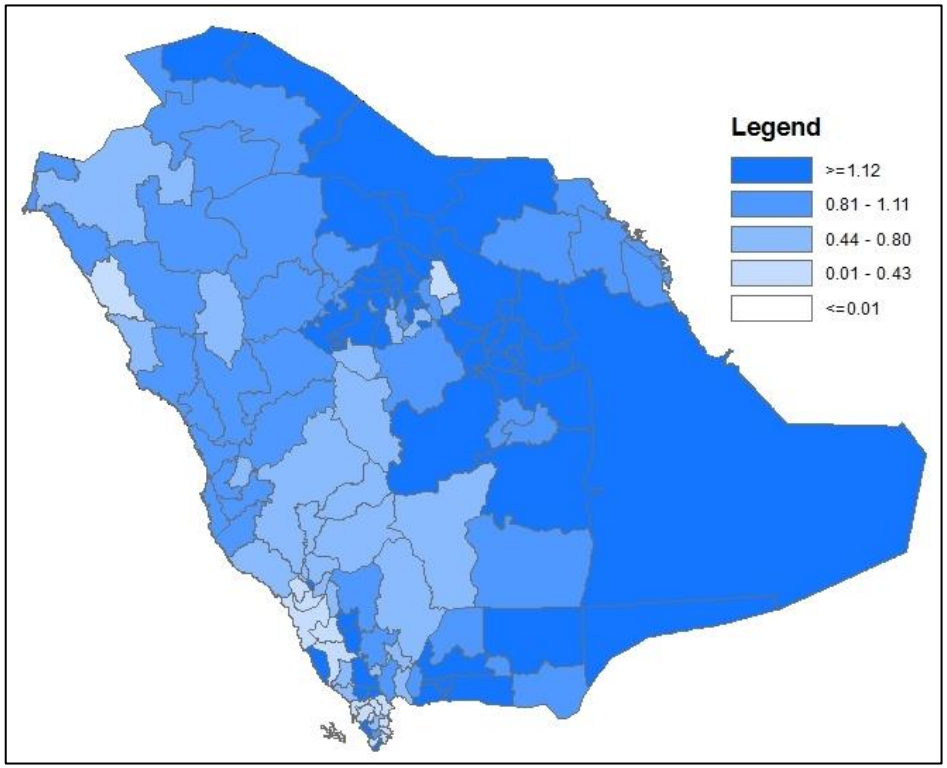


Figure 4.2: Crude and smoothed age-sex standardised incidence ratios (SIRs) of acute myeloid leukaemias registered from 1994 to 2008 in young people under the age of 24 years by Saudi Governorates

Figure 4.3 shows the crude and SEB smoothed SIRs for CML. For the crude SIR, no clear pattern of incidence can be seen. The Governorates with the highest SIRs were found in Herimla, Rayth and Kamel, these are characterised as small sparsely populated Governorates. The high SIRs were due to having one observed case of CML within the 15-year study period, compared to an expected number of cases of below 0.25 in each of these Governorates. Other Governorates with a high SIR included Qurayyat and Abha. The SEB smoothed map has imposed a much clearer pattern of incidence, in which only Qurayyat and Abha Governorates retain a high SIR. The majority of the other Governorates have an estimated smoothed SIR between 0.72 and 1.30.

Figure 4.4 gives the crude and smoothed SIRs of the ‘other leukaemias’ group. Many Governorates had no cases (n=74). Those with a high SIR are scattered in the country, in the north in Toraif and Skaka, in the west in Medinah and Jeddah and in the south in Baha and Bishah, and some of the neighbouring areas of these Governorates had zero cases, hence no discernible pattern can be deduced. However, the SEB smoothed map shrunk the high SIRs towards the mean of the neighbouring Governorates, which resulted in a much clearer pattern of incidence. Only the Zolfi and Ola Governorates keep their SIR of zero, since all their neighbouring Governorates also had an SIR of zero in the crude SIR map.

a) Crude SIRs

b) Smoothed SIRs

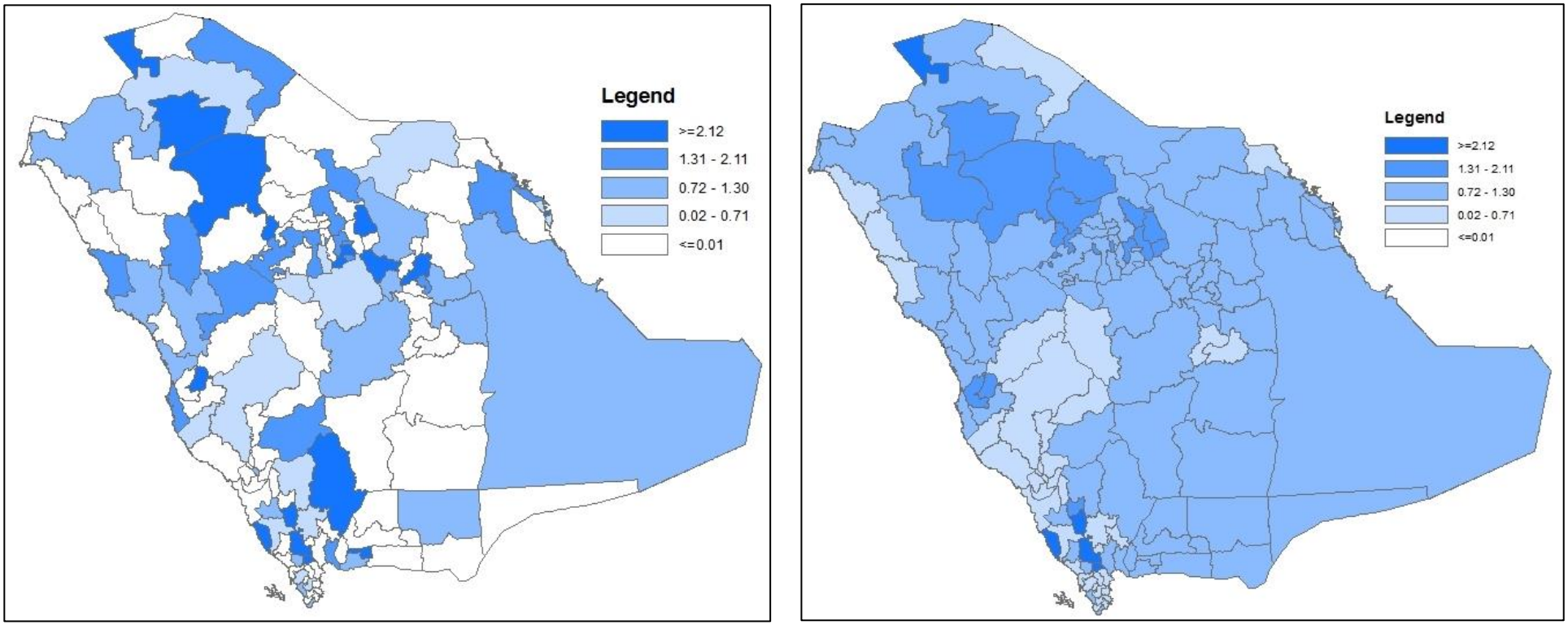


Figure 4.3: Crude and smoothed age-sex standardised incidence ratios (SIRs) of chronic myeloid leukaemias registered from 1994 to 2008 in young people under the age of 24 years by Saudi Governorates

a) Crude SIRs

b) Smoothed SIRs

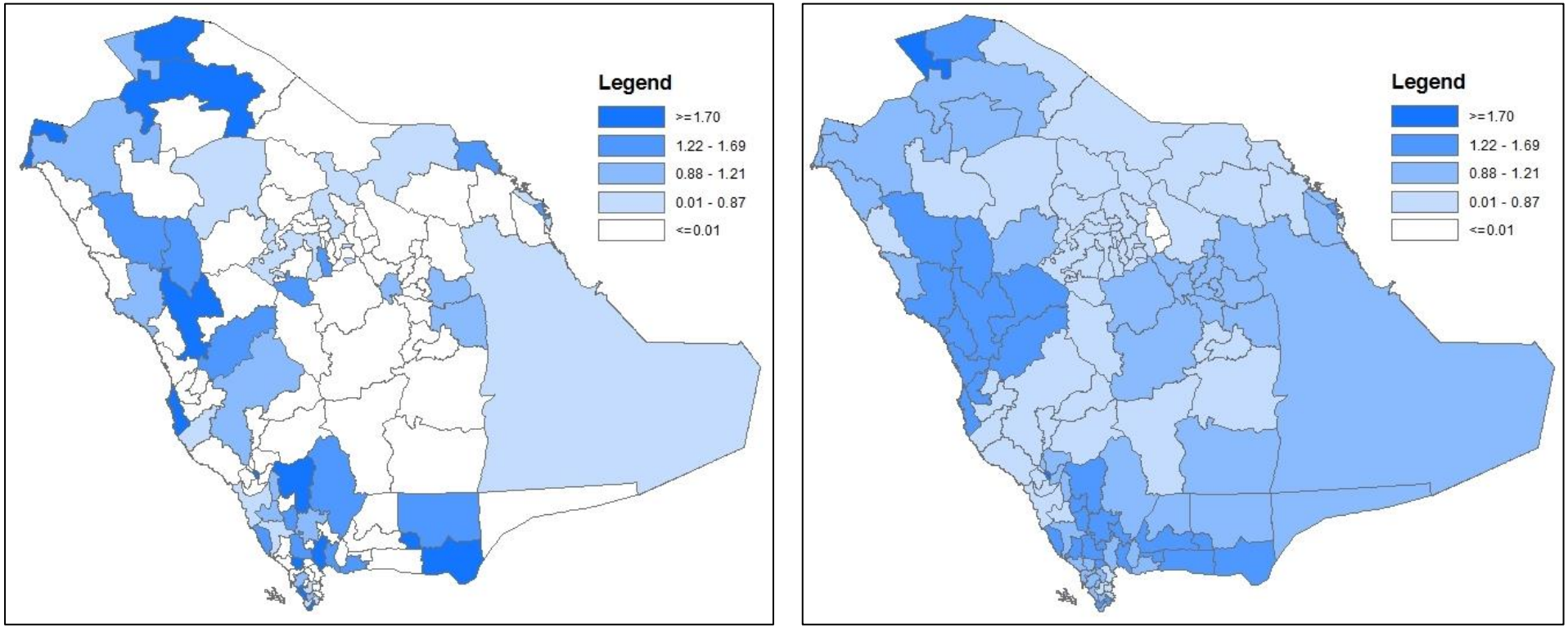
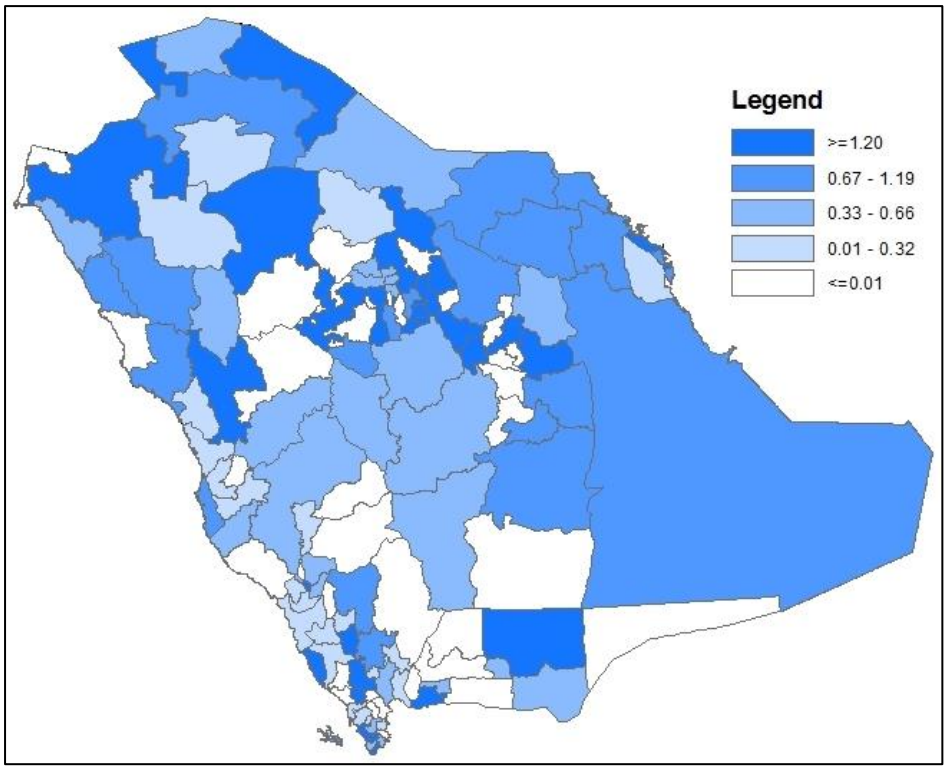


Figure 4.4: Crude and smoothed age-sex standardised incidence ratios (SIRs) of 'other leukaemias' registered from 1994 to 2008 in young people under the age of 24 years by Saudi Governorates

Figure 4.5 shows the crude and SEB smoothed SIRs for HL. Herimla had the highest SIR of 3.88 (95%CI = 1.06 - 9.94), followed by Baha (SIR=2.20, 95%CI = 1.26 - 3.57). There were 34 Governorates with zero cases present, which is reflected in an estimated SIR of zero (Figure 4.5a). The smoothed map has shrunk the extreme estimates of the SIRs, thereby increasing the incidence in their surrounding Governorates (Figure 4.5b). The SIR of Herimla has decreased and is no longer in the highest quintile, but the SIR of Baha remains high. The general pattern of incidence can be seen as gradually increasing from the south-western Governorates of Majardah and Qunfudhah towards the highest SIRs in the north in Hail, Skaka and Arar.

For NHL, the crude and SEB smoothed SIRs are shown in Figure 4.6. There is little discernible spatial pattern in the crude SIRs (Figure 4.6a). The Governorates with extremely high SIRs are scattered in the north in Qurayyat and Skaka, in the capital Riyadh, in the west in Yanbu and Jeddah, in the south in Baha, Abha and Najran and Selayil and in the eastern province in Khobar and Bqeeq. The SEB smoothed maps have shrunk the extreme estimates of SIRs and increased the incidence of NHL in the Governorates which previously had an SIR of zero, providing a clearer more discernible pattern. Although, Governorates such as Qurayyat, Riyadh, Bqeeq, Abha, Jeddah and Baha still maintain a high SIR.

a) Crude SIRs



b) Smoothed SIRs

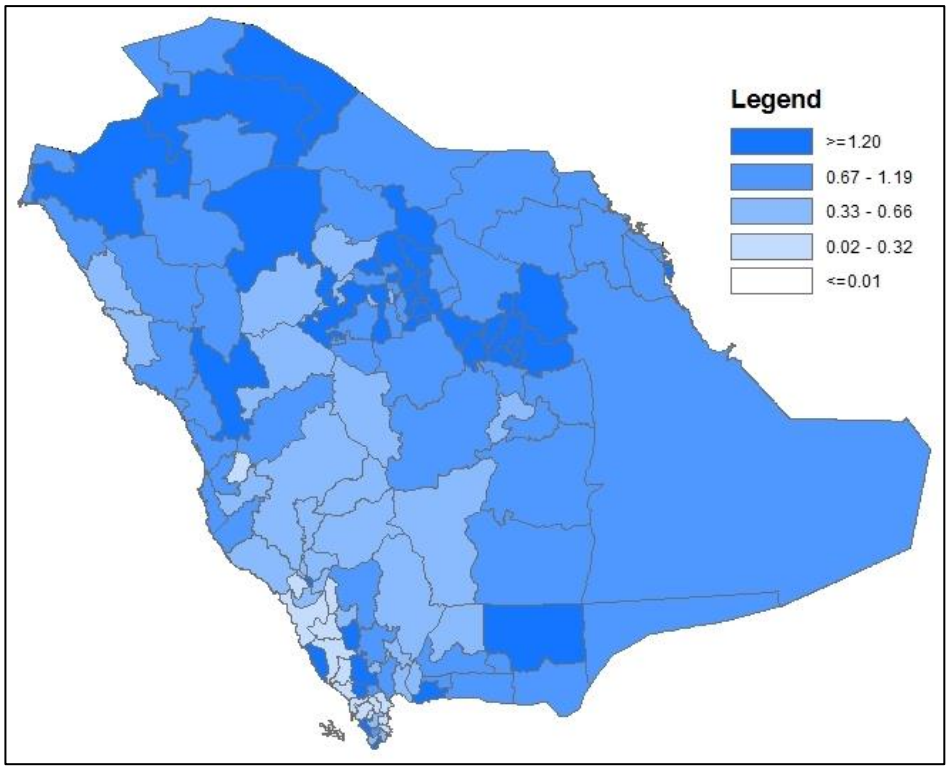
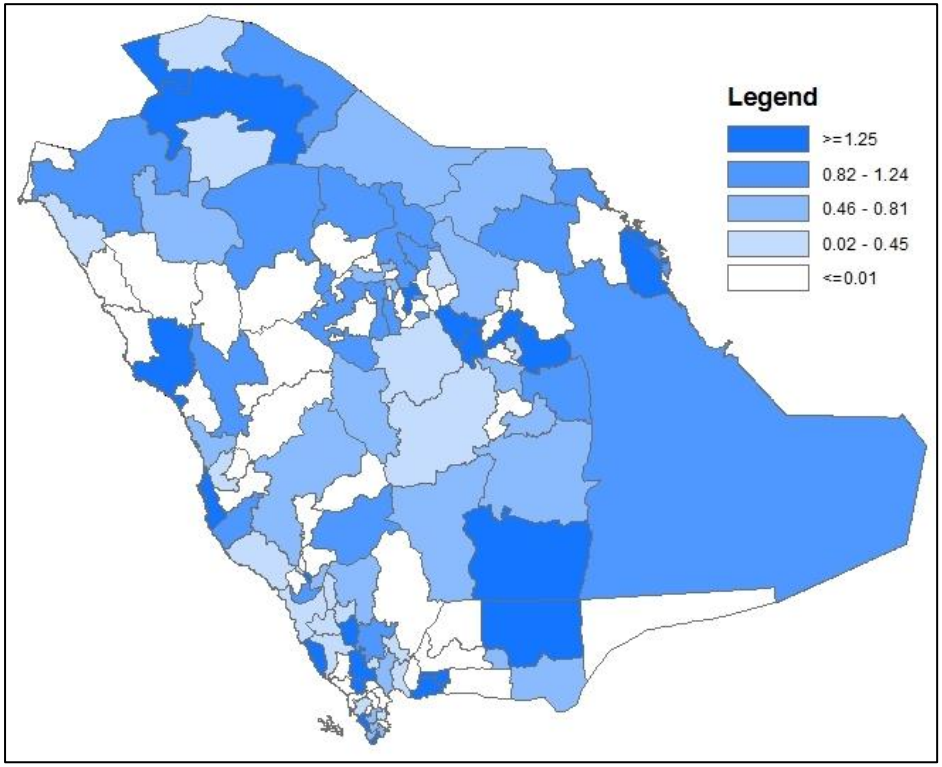


Figure 4.5: Crude and smoothed age-sex standardised incidence ratios (SIRs) of Hodgkin's lymphoma registered from 1994 to 2008 in young people under the age of 24 years by Saudi Governorates

a) Crude SIRS



b) Smoothed SIRs

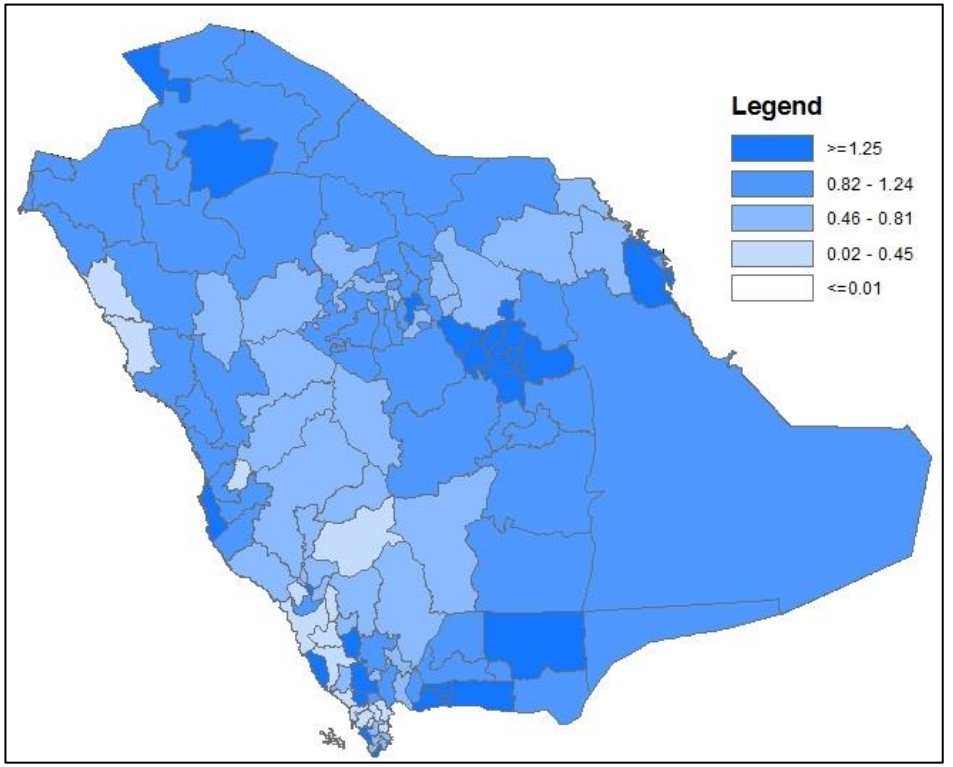
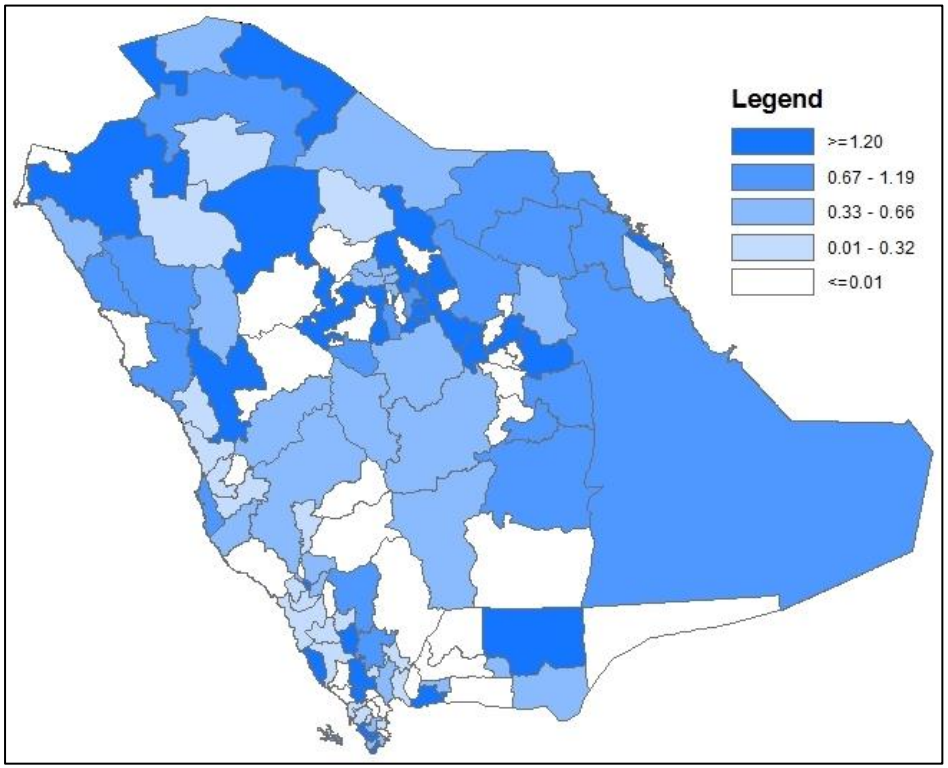


Figure 4.6: Crude and smoothed age-sex standardised incidence ratios (SIRs) of non-Hodgkin's lymphoma registered from 1994 to 2008 in young people under the age of 24 years by Saudi Governorates

Figure 4.7 shows the crude and SEB smoothed SIRs for BL. The expected number of cases for the majority of the Governorates was low and there was a total of 60 Governorates with no cases of BL present, resulting in a crude SIR of zero. The majority of which are concentrated in sparsely populated rural areas in the south and central areas of the country. Some are adjacent to Governorates with extremely high SIRs, hence little spatial patterns can be seen. The spatially smoothed map (Figure 4.7a) shows an increase in SIRs for all Governorates that had a crude SIR of zero. Although, many still retain an extremely high SIR, such as Riyadh, Hail and Arar in the north, as well as Najran and Abha in the south.

Figure 4.8 presents the crude and SEB smoothed estimates of the SIRs for the 'other lymphomas' group. The number of expected cases is low in all Governorates compared to other disease categories, where the highest is 29.15 for Riyadh (SIR = 1.03, 95%CI = 0.69 - 1.47). There are 82 Governorates with no cases present, which is reflected in an estimated crude SIR of zero. There is little discernible pattern for incidence, since the Governorates with the highest SIRs are scattered within the country. The SEB smoothed map (Figure4.8b) has shrunk the extreme estimates, thereby increasing the SIRs of their surrounding Governorates, revealing a much clearer pattern. Incidence is low in the majority of the southern Governorates. The Governorates with the highest incidence are concentrated on the western coast in Jeddah, Makkah, Rabegh, Yanbu and Amluj, and in the north in Qurayyat, Toraif and Arar. The Zolfi, Wadi Dawaser and Kamel Governorates keep their zero SIRs even after smoothing.

a) Crude SIRs



b) Smoothed SIRs

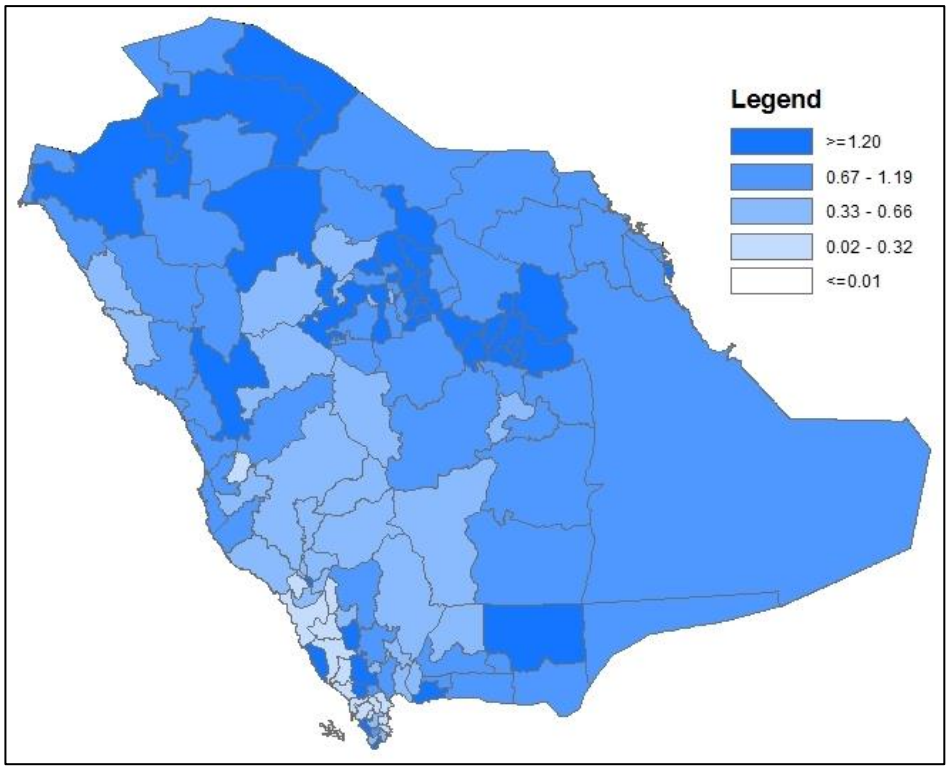


Figure 4.7: Crude and smoothed age-sex standardised incidence ratios (SIRs) of Burkitt's lymphoma registered from 1994 to 2008 in young people under the age of 24 years by Saudi Governorates

a) Crude SIRs

b) Smoothed SIRs

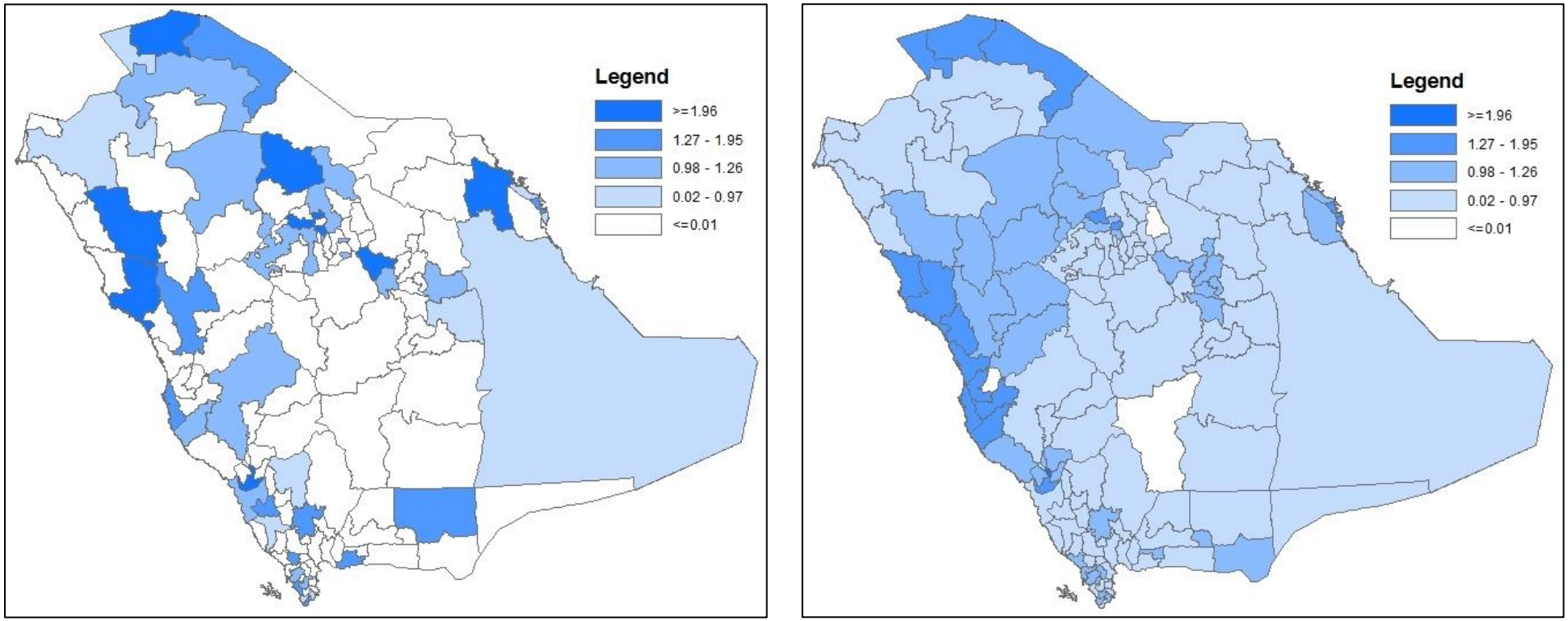
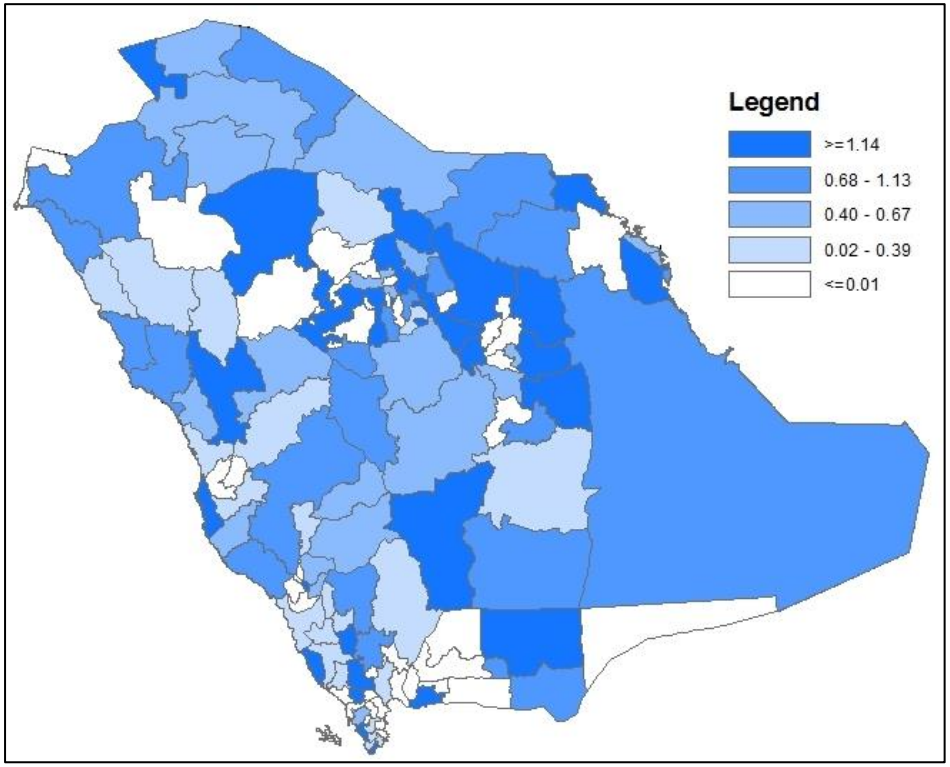


Figure 4.8: Crude and smoothed age-sex standardised incidence ratios (SIRs) of 'other lymphomas' registered from 1994 to 2008 in young people under the age of 24 years by Saudi Governorates

Figure 4.9 presents the crude and smoothed estimates for CNS tumours. The highest quintile of SIRs was found in the highly populated Governorates of Riyadh, Jeddah, Dammam, Hail, Buraidah, Madinah and Baha, as well as in the sparsely populated Governorates such as Qurayyat and Riyadh Khobaraa. Both high and low populated Governorates are adjacent to others with SIRs of zero due to no cases being present, hence no spatial pattern can be seen. However, the SEB smoothed map (Figure 4.9b), has shrunk the extreme estimates, and therefore a concentration of Governorates with high SIRs can be seen in the central region, as well as in the west in Yanbu, Badr and Madinah. Governorates with low SIRs are mostly seen in the south western region in Qunfudhah, Qilwah and Sarat Abaida.

For the 'all other cancers' group, the crude and SEB smoothed SIRs are presented in Figure 4.10. Only 15 Governorates have an SIR of zero due to no cases present, and all of these are surrounded by Governorates with an SIR in the highest quintile. The highest SIR was found in Shaqraa, which is located in the central province of Riyadh (SIR = 4.30, 95%CI = 3.05 - 5.87), followed by Baha (SIR = 2.20, 95%CI = 1.70 - 2.81). The SEB smoothed map (Figure 4.10b), presents a clearer pattern of incidence, in which the high SIRs have shrunk towards the mean of the neighbouring areas, thereby increasing the SIRs for those areas. The entire eastern provinces, along with Governorates from the Riyadh province, maintain a high SIR after smoothing. A slightly lower incidence is seen in the north and in Governorates in the south. Though, Baha and Shaqraa have a persistently high SIR.

a) Crude SIRs



b) Smoothed SIRs

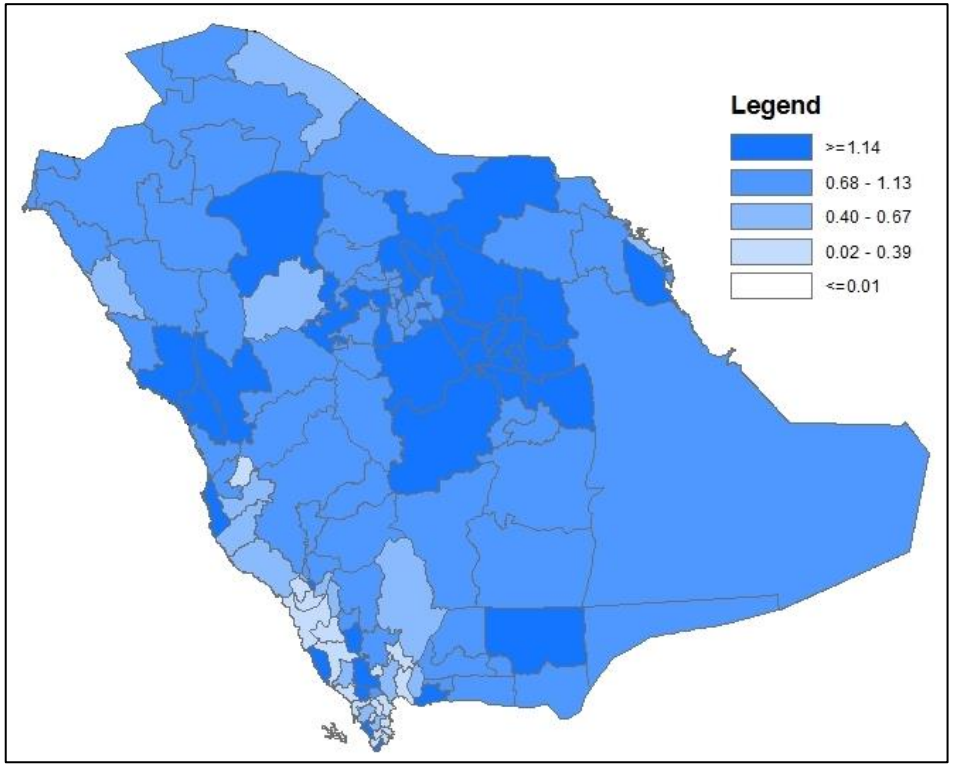


Figure 4.9: Crude and smoothed age-sex standardised incidence ratios (SIRs) of CNS tumours registered from 1994 to 2008 in young people under the age of 24 years by Saudi Governorates

a) Crude SIRs

b) Smoothed SIRs

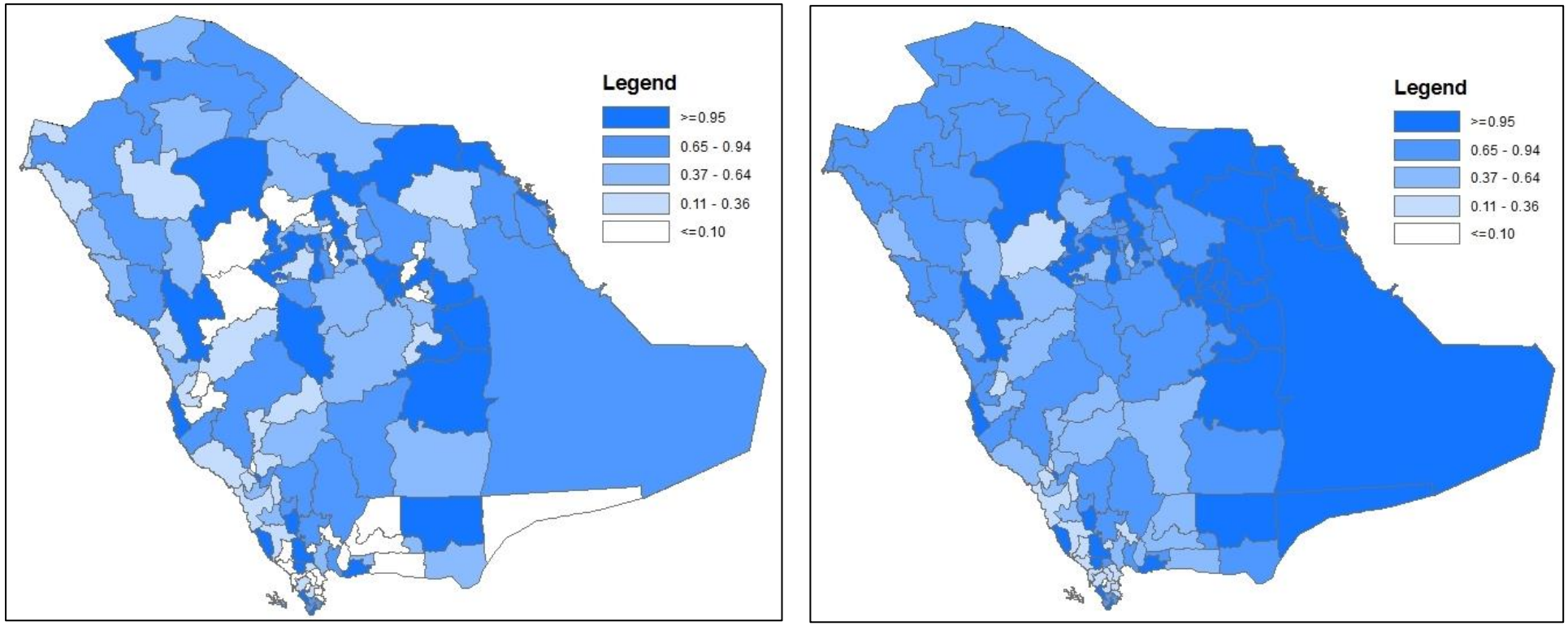


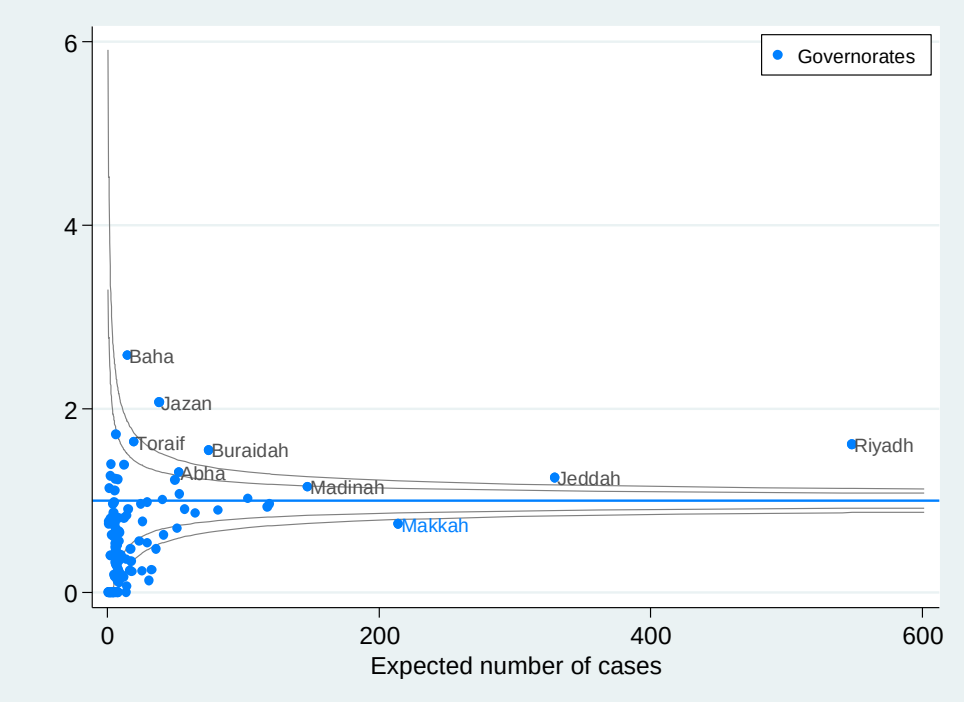
Figure 4.10: Crude and smoothed age-sex standardised incidence ratios (SIRs) of 'all other cancers' registered from 1994 to 2008 in young people under the age of 24 years by Saudi Governorates

4.1.4.2 Funnel plots

Figure 4.11 gives the crude and smoothed funnel plots for SIRs for ALL. The plot reflects the SIRs mapped in Figure 4.1 (Figure 4.1a), where Baha, Jazan, Buraidah, Jeddah and Riyadh had extremely high SIRs placing them outside the upper 99.8% control limit. The majority of Governorates however, were within both control limits. The smoothed SIRs were also given (Figure 4.1b), which show a slight reduction in the extreme SIRs, for example the SIRs of Baha and Jazan have been smoothed from 2.58 and 2.07 to 2.48 and 2.01 respectively. Also, the smoothing has raised the SIRs in the Governorates with low values.

Funnel plots for AML are given in Figure 4.12. The SEB smoothed plot (Figure 4.12), clearly shows a reduction in SIRs, such as the SIRs for Toraif and Aflaj which have been reduced from 2.95 and 2.67 to 1.47 and 1.28 respectively, thus these Governorates are no longer above the 99.8% control limit. Similarly, for CML and the ‘other leukaemias’ group, the number of Governorates with zero cases decreased in the smoothed plots in Figures 4.13 and 4.14. Several Governorates with extremely high SIRs such as Herimla and Rayth for CMLs and Toraif and Bishah for the ‘other leukaemias’ group decreased within the control limits. Of importance is the Makkah Governorate, which was found to have an SIR below one for all types of leukaemia before and after smoothing. In fact, for ALL, both the crude and smoothed SIRs were below the lower 99.8% control limit.

a) Crude SIRs



b) Smoothed SIRs

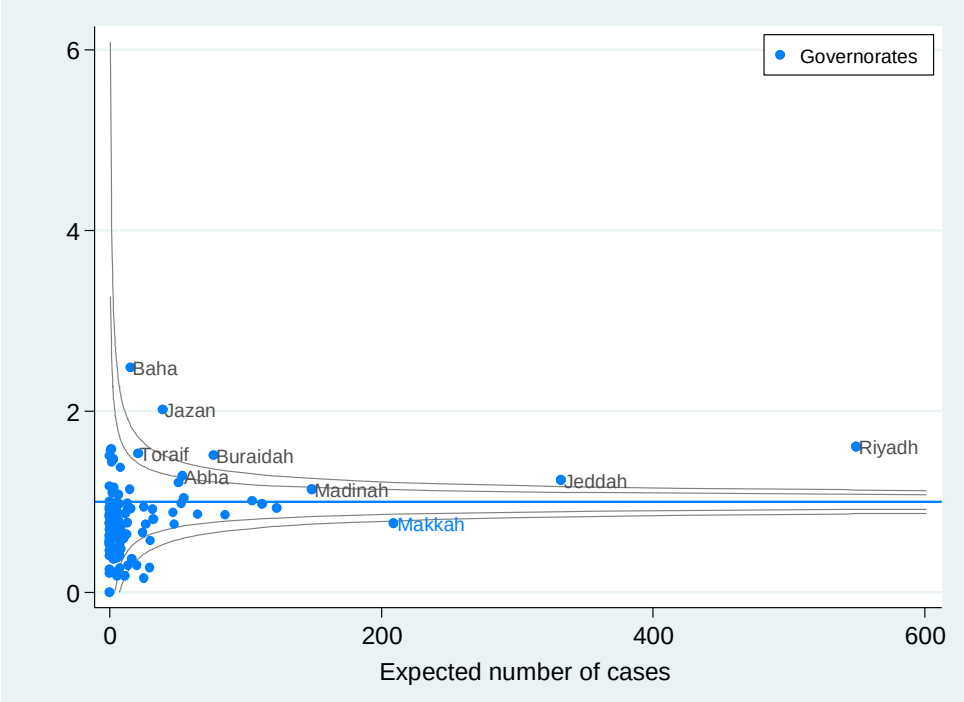
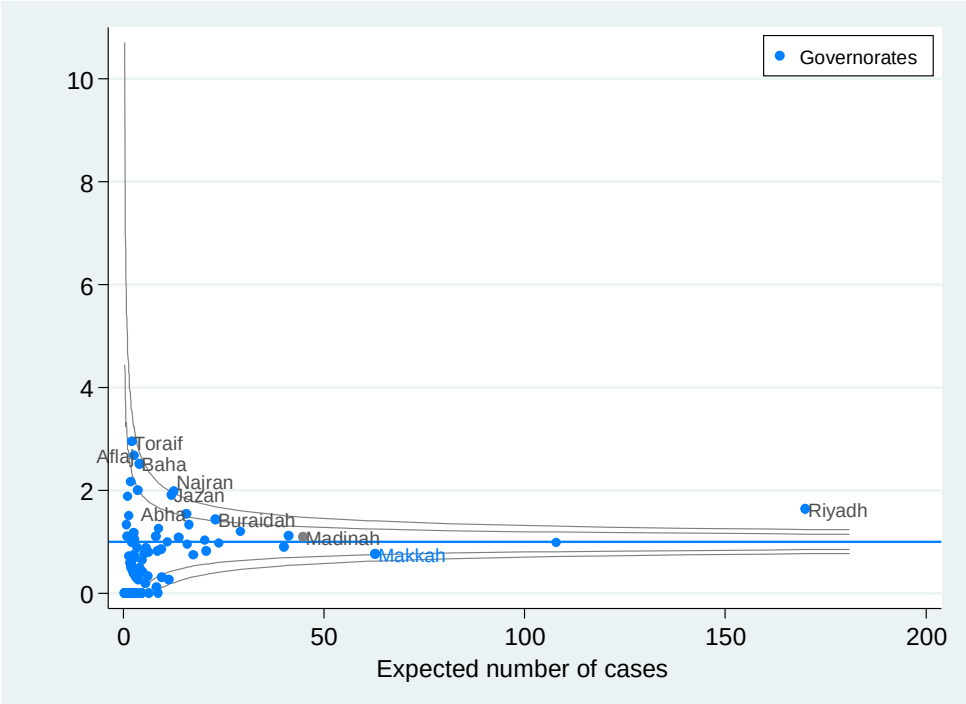


Figure 4.11: Funnel plots of crude and smoothed age-sex standardised incidence ratios (SIRs) of acute lymphoblastic leukaemia registered from 1994 to 2008 in young people under the age of 24 years by Saudi Governorates

a) Crude SIRs



b) Smoothed SIRs

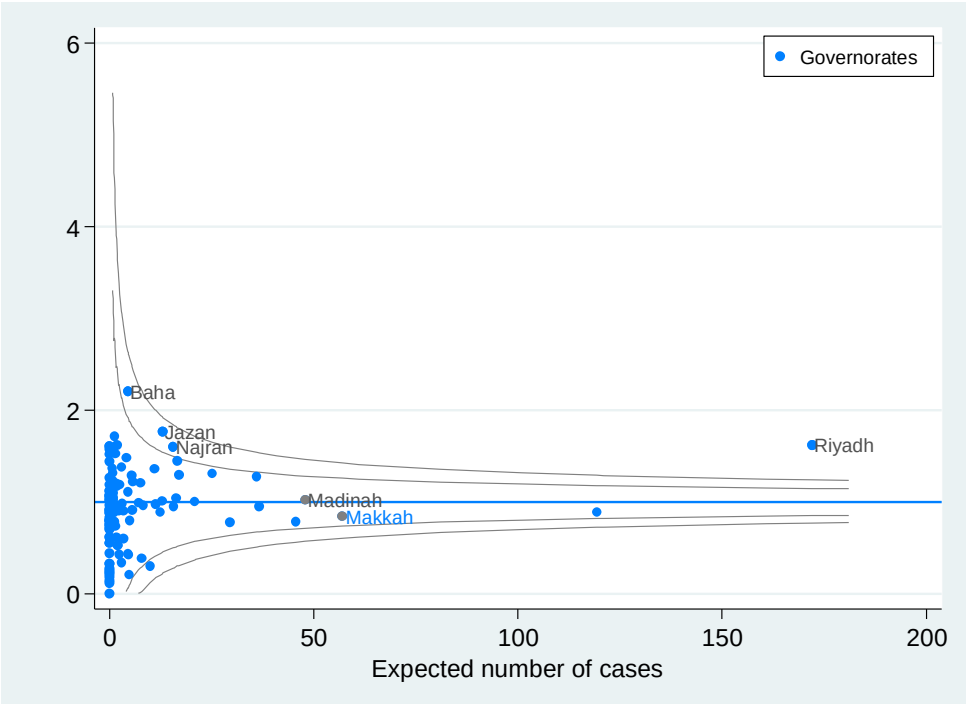
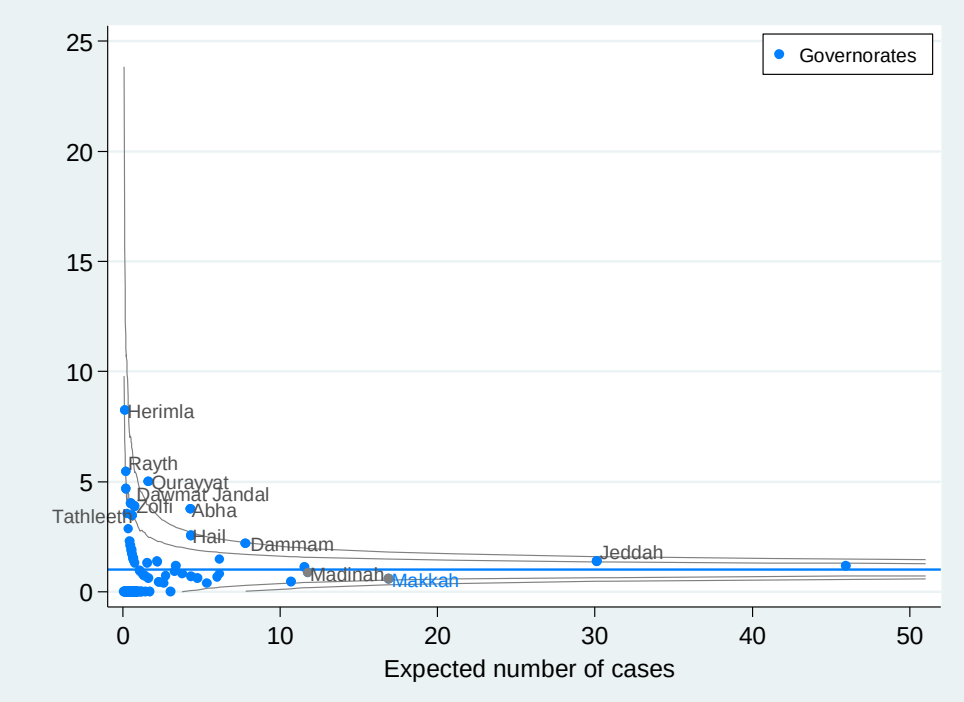


Figure 4.12: Funnel plots of crude and smoothed age-sex standardised incidence ratios (SIRs) of acute myeloid leukaemia registered from 1994 to 2008 in young people under the age of 24 years by Saudi Governorates

a) Crude SIRs



b) Smoothed SIRs

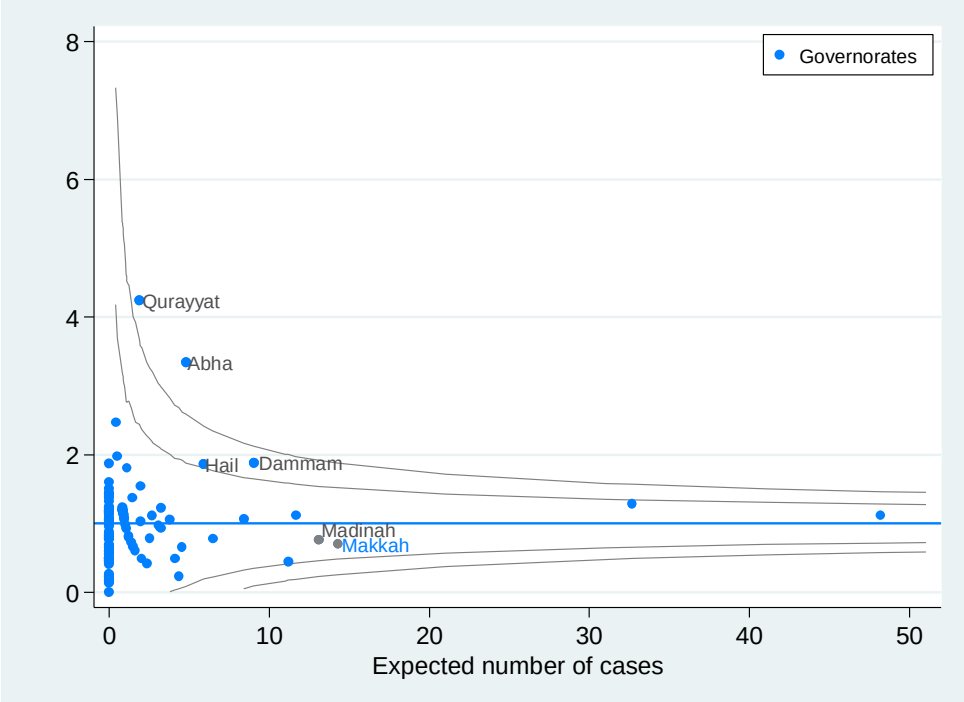
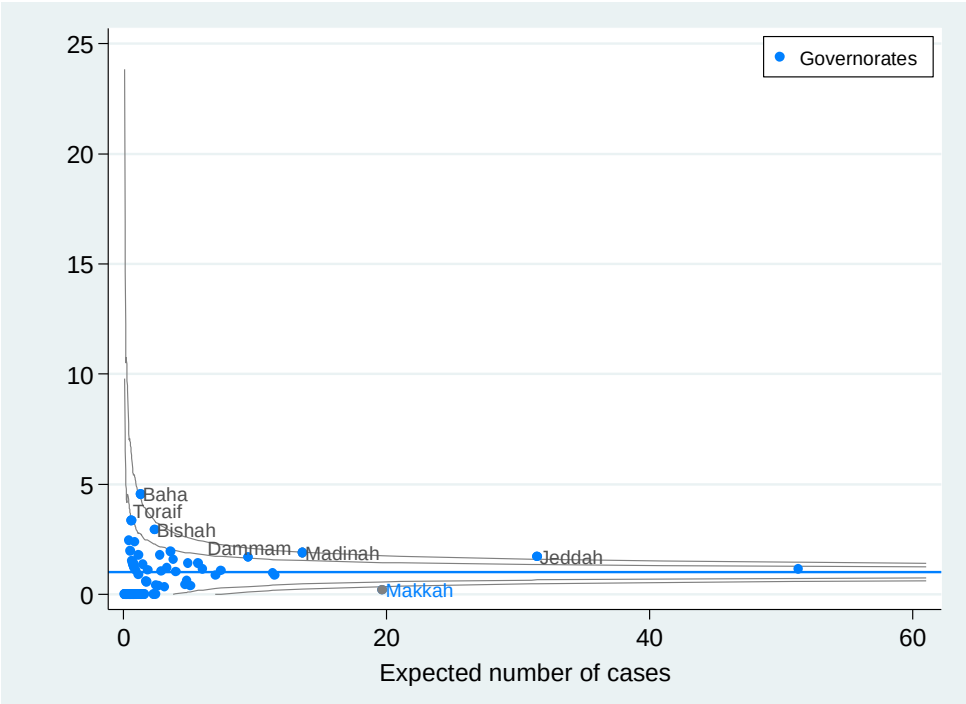


Figure 4.13: Funnel plots of crude and smoothed age-sex standardised incidence ratios (SIRs) of chronic myeloid leukaemia registered from 1994 to 2008 in young people under the age of 24 years by Saudi Governorates

a) Crude SIRs



b) Smoothed SIRs

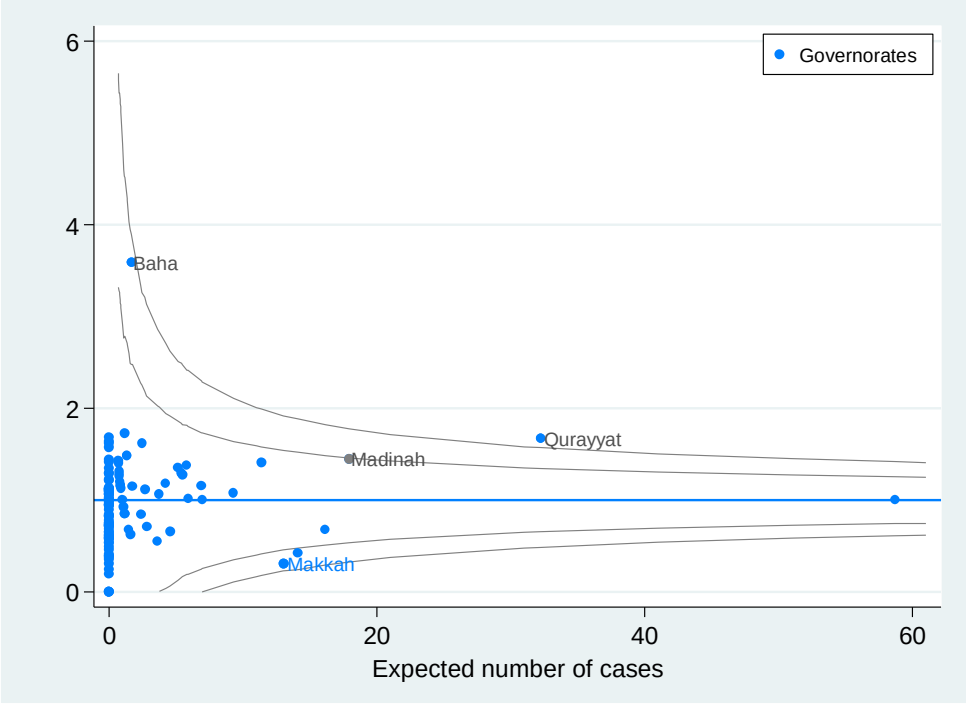
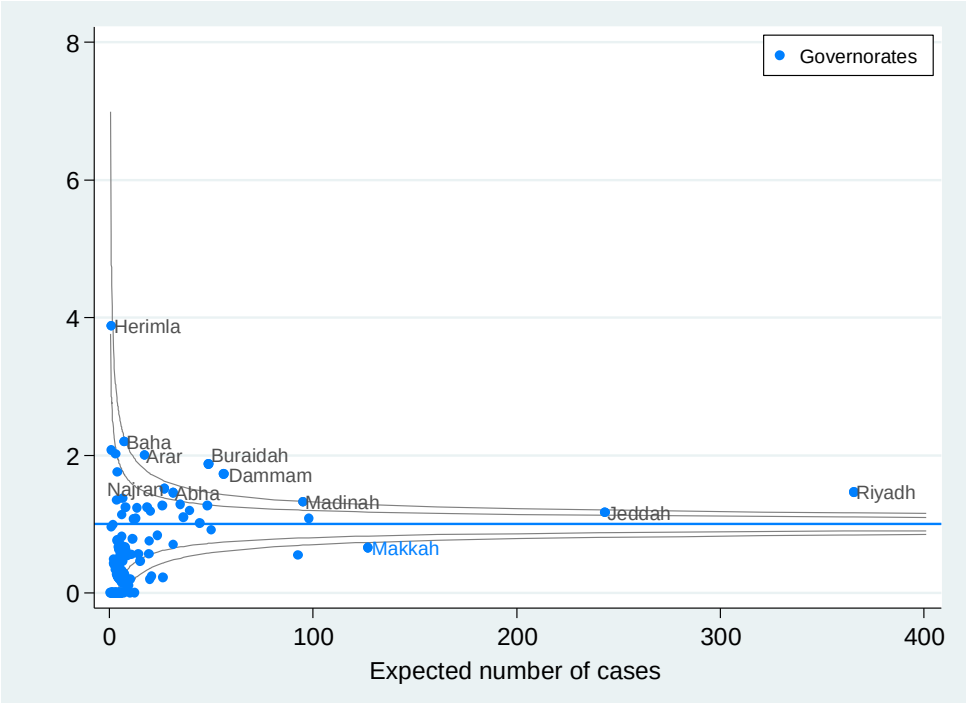


Figure 4.14: Funnel plots of crude and smoothed age-sex standardised incidence ratios (SIRs) of 'other leukaemias' registered from 1994 to 2008 in young people under the age of 24 years by Saudi Governorates

Figure 4.15 and 4.16 plot the crude and SEB smoothed SIRs for HL and NHL respectively. The expected cases for HL are highest amongst all types of lymphomas. The plot clearly shows that Herimla had the highest incidence rate (SIR=3.80), followed by Baha (SIR=2.19). Following smoothing, the extremely high SIRs decreased, but the highest reduction was for the Herimla Governorate (smoothed SIR=1.51), which decreased to below the upper control limit, due to having a low population compared to other Governorates. Similarly for NHL, Bqeeq had the highest reduction in SIR after SEB smoothing.

Figure 4.17 plots the crude and SEB smoothed SIRs for BL. The Raas Tanourah, Uhd Masarha, Baha, Sarat Abaida and Abha Governorates had SIRs above the 95% control limit. After SEB smoothing (Figure 4.17b), the Governorates with the lower populations, such as Raas Tanourah, Uhd Masarha, Shaqraa and Sarat Abaida had the highest reduction in SIRs. Furthermore, the number of Governorates with zero SIRs was reduced. For the ‘other lymphomas’ group (Figure 4.18), the number of expected cases was relatively low. The SEB smoothing reduced the number of Governorates with zero cases.

a) Crude SIRs



b) Smoothed SIRs

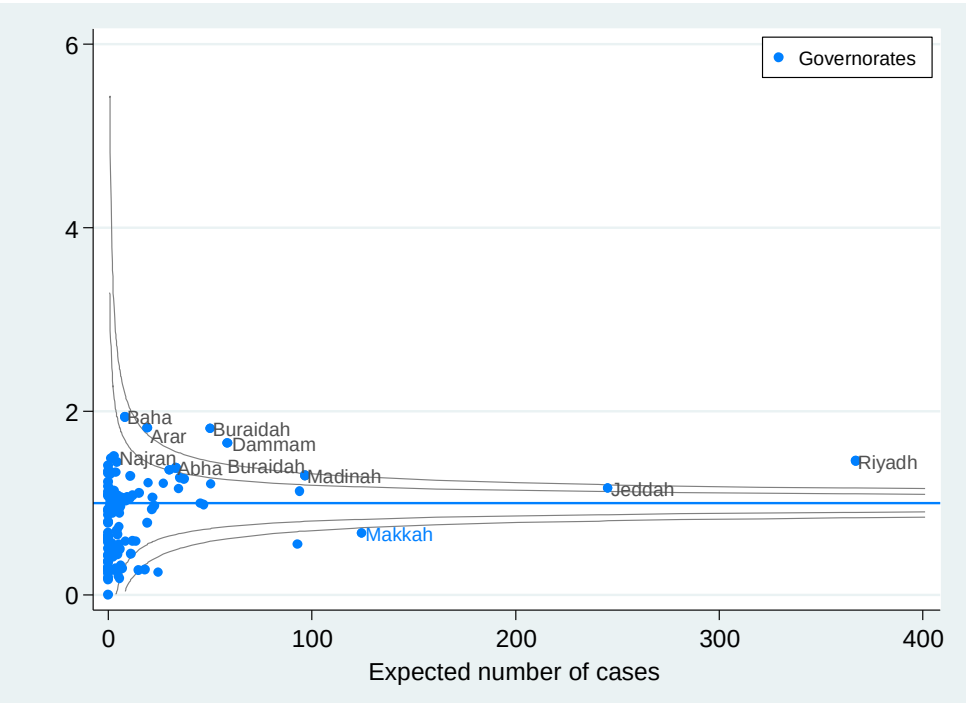
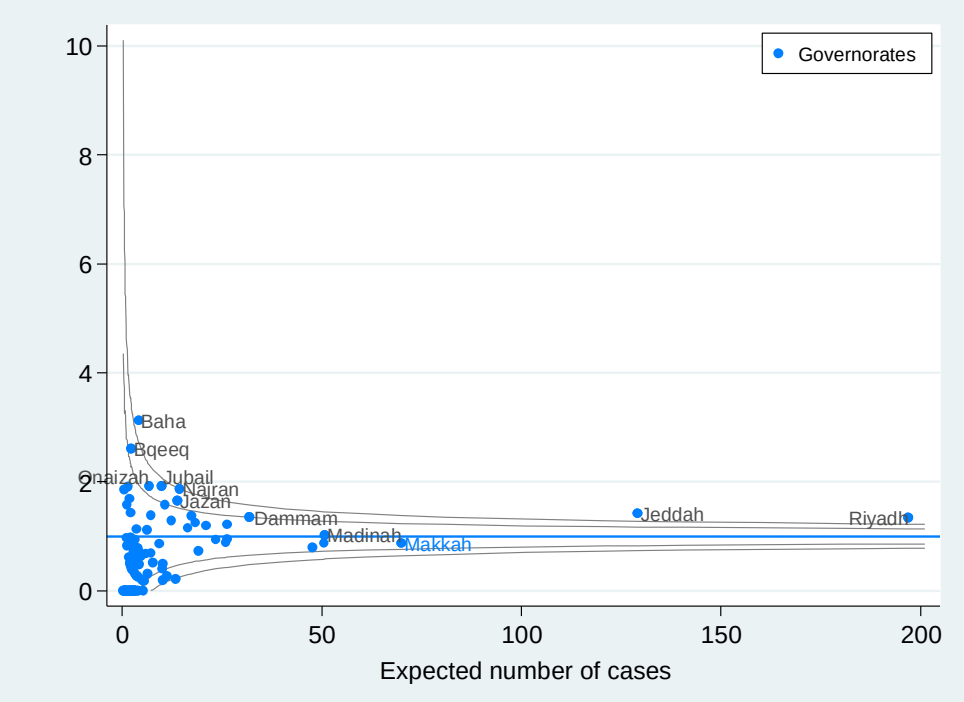


Figure 4.15: Funnel plots of crude and smoothed age-sex standardised incidence ratios (SIRs) of Hodgkin's lymphoma registered from 1994 to 2008 in young people under the age of 24 years by Saudi Governorates

a) Crude SIRs



b) Smoothed SIRs

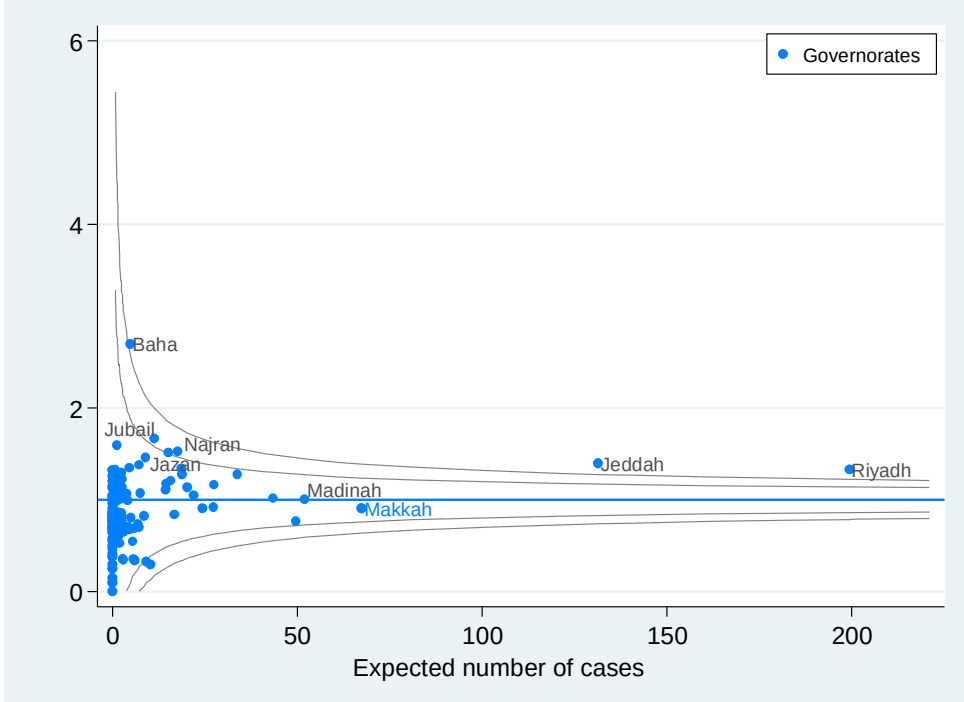
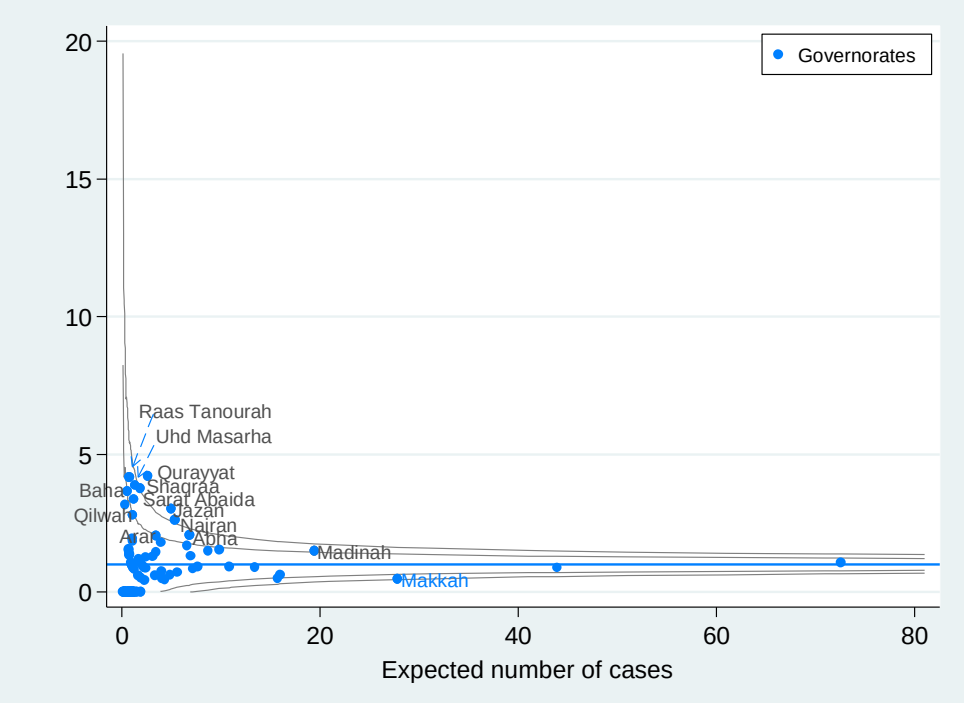


Figure 4.16: Funnel plots of crude and smoothed age-sex standardised incidence ratios (SIRs) of non-Hodgkin's lymphoma registered from 1994 to 2008 in young people under the age of 24 years by Saudi Governorates

a) Crude SIRs



b) Smoothed SIRs

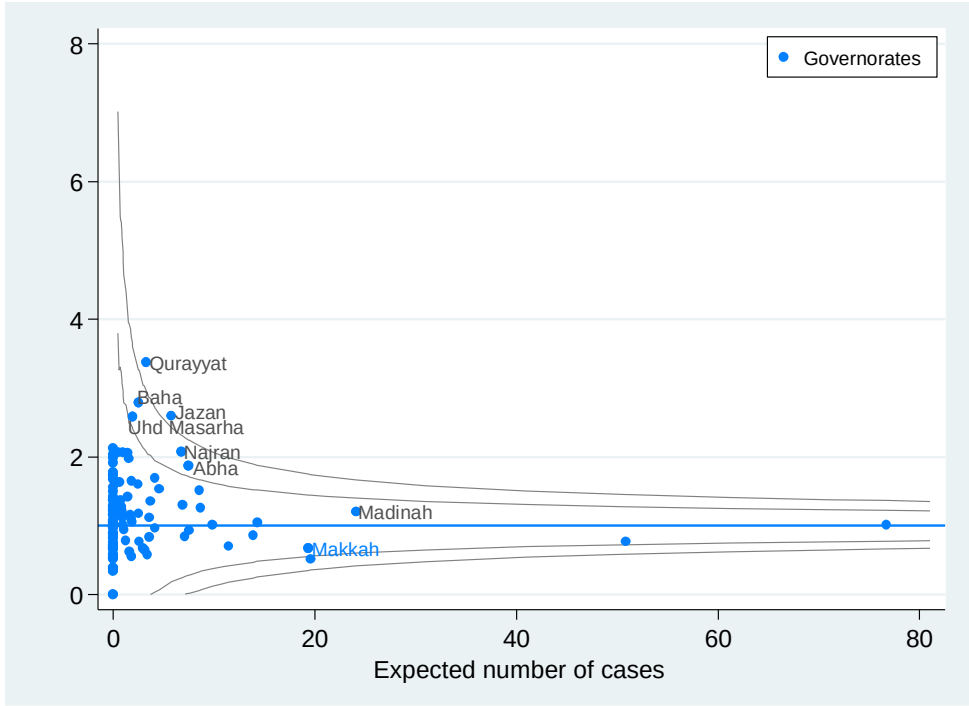
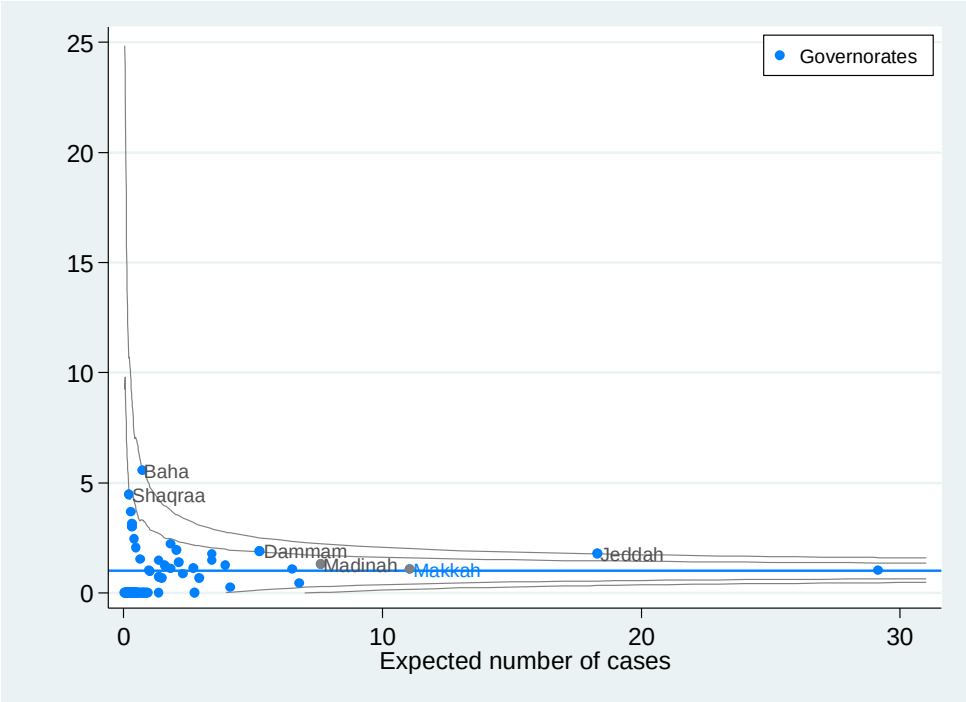


Figure 4.17: Funnel plots of crude and smoothed age-sex standardised incidence ratios (SIRs) of Burkitt's lymphoma registered from 1994 to 2008 in young people under the age of 24 years by Saudi Governorates

a) Crude SIRs



b) Smoothed SIRs

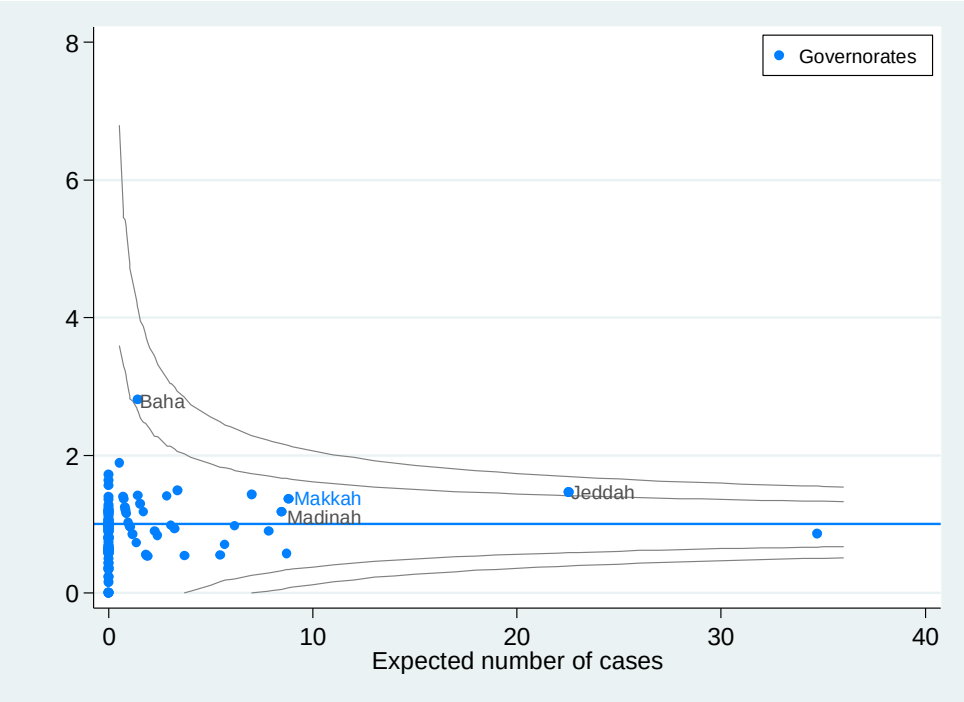
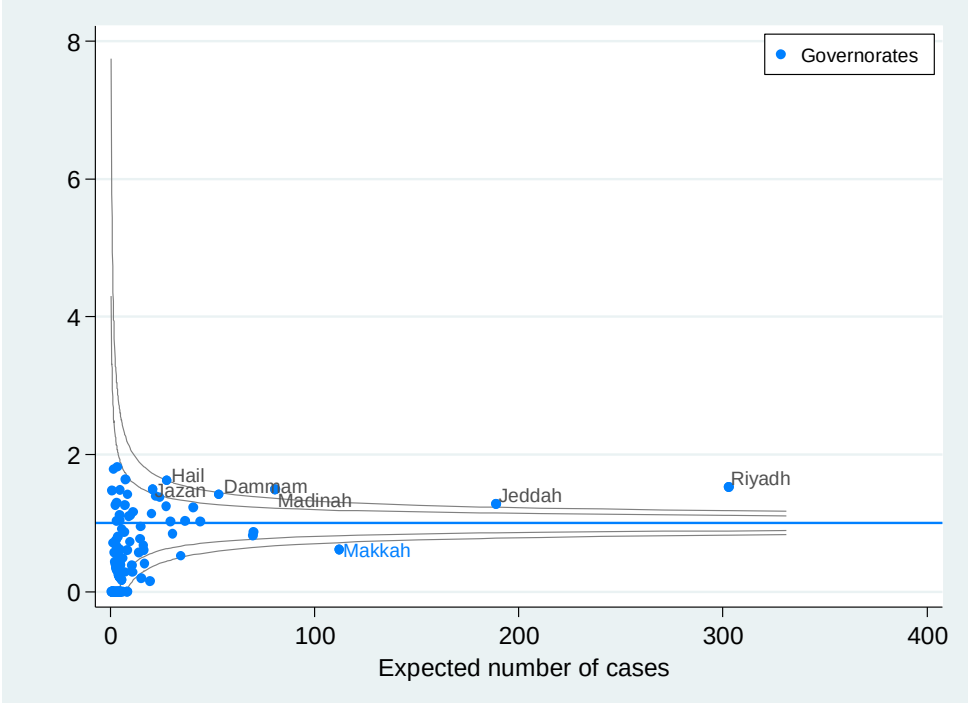


Figure 4.18: Funnel plots of crude and smoothed age-sex standardised incidence ratios (SIRs) of 'other lymphomas' registered from 1994 to 2008 in young people under the age of 24 years by Saudi Governorates

Figure 4.19 plots the crude and SEB smoothed SIRs for CNS tumours. The SEB smoothing shrunk the SIRs of the Governorates with extreme SIRs. However, those with high population numbers such as Riyadh, Jeddah and Madinah still maintain high SIRs above the upper 99.8% control limit. The number of Governorates with zero SIRs, due to no cases present, decreased. Although, the Makkah Governorate maintains a low SIR below the lower control limits, even after smoothing.

For the ‘all other cancers’ group, Figure 4.20 shows the crude and SEB smoothed SIRs on funnel plots. The number of expected cases is high and exceeds 1000 cases for Riyadh. The SEB smoothing reduced the Shaqraa Governorate from 4.30 to 2.70. Additionally, Raas Tanourah was reduced to below the upper control limit. Furthermore, Makkah keeps a low SIR that is below the lower control limits, both before and after smoothing.

a) Crude SIRs



b) Smoothed SIRs

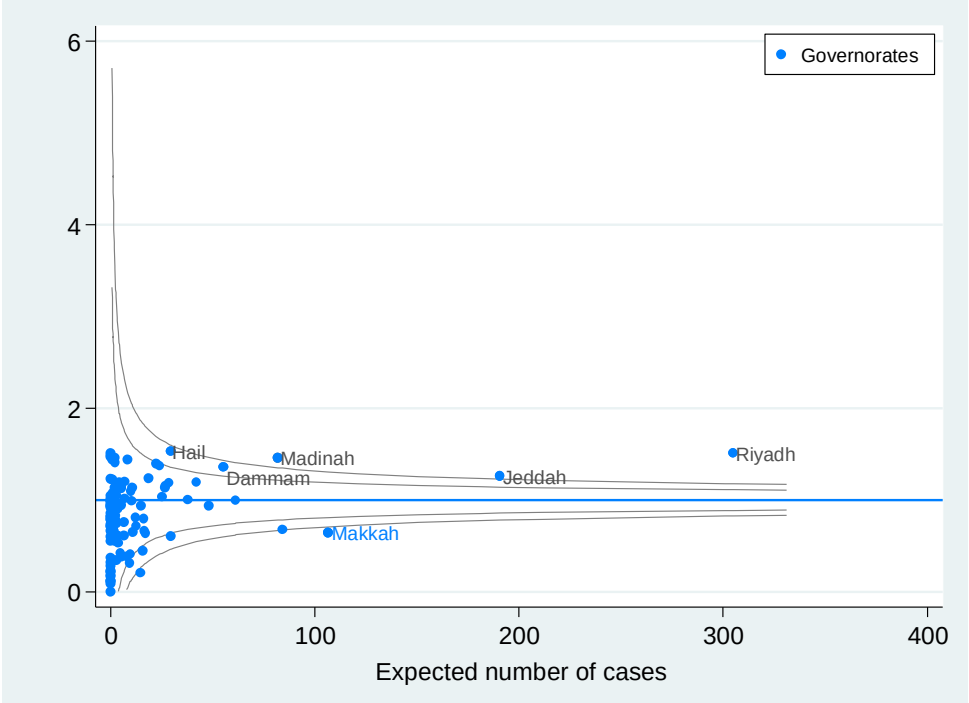
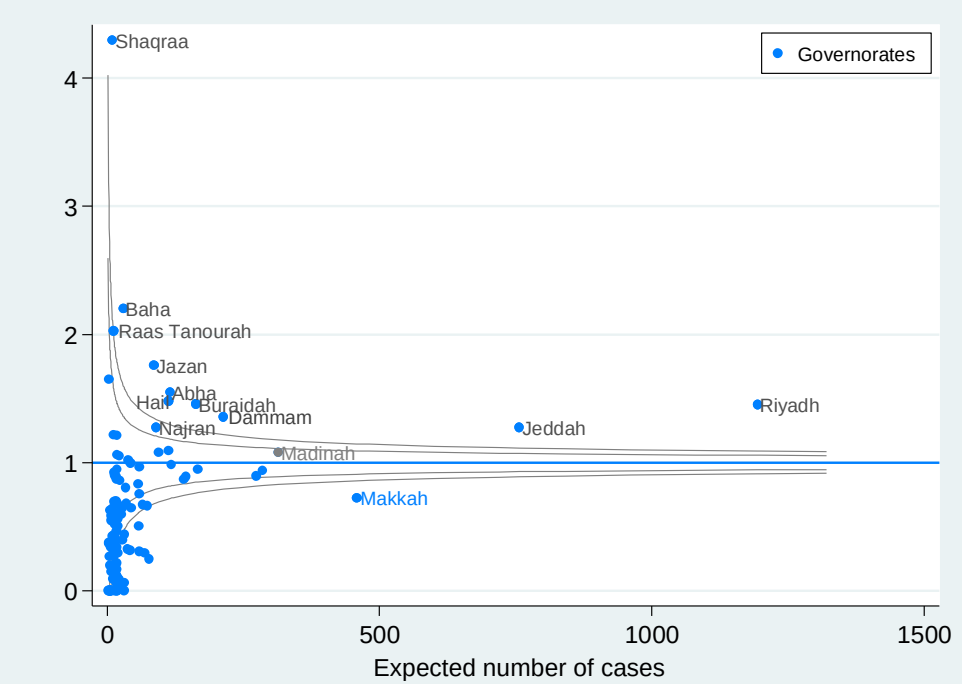


Figure 4.19: Funnel plots of crude and smoothed age-sex standardised incidence ratios (SIRs) of central nervous system tumours registered from 1994 to 2008 in young people under the age of 24 years by Saudi Governorates

a) Crude SIRs



b) Smoothed SIRs

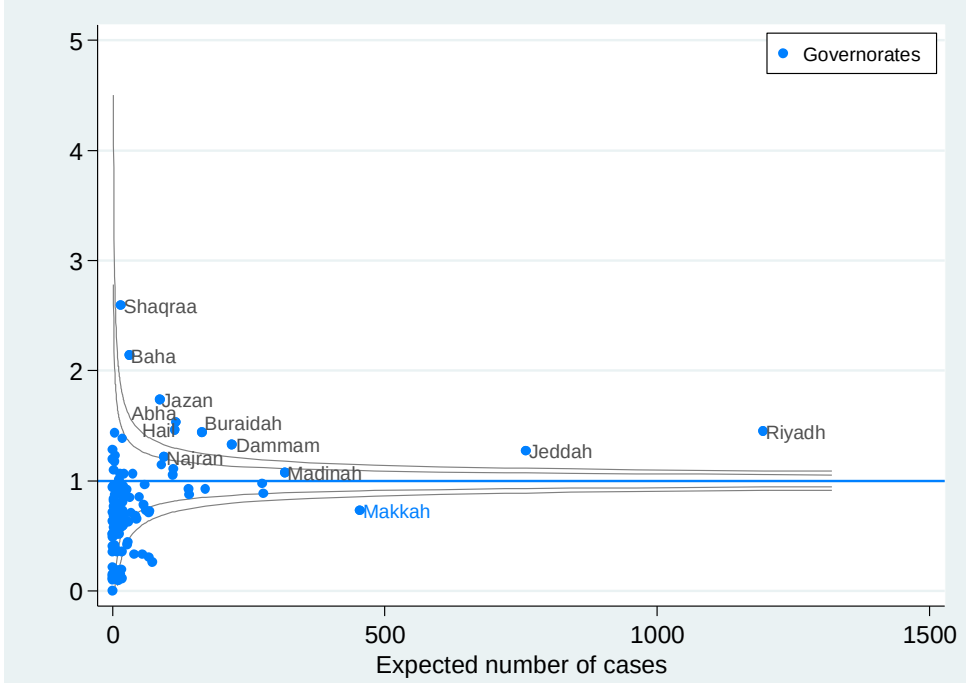


Figure 4.20: Funnel plots of crude and smoothed age-sex standardised incidence ratios (SIRs) of 'all other cancers' registered from 1994 to 2008 in young people under the age of 24 years by Saudi Governorates

4.1.5 Annual increase in Hajj

Figure 4.21 shows the annual increase in Hajj pilgrimage relative to the increase in the child and young adult population aged less than 24 years. The young adult Saudi population continues to increase; it had almost reached 13 million by the year 2008. The number of pilgrims also continues to increase, although there was a sudden drop in 1999.

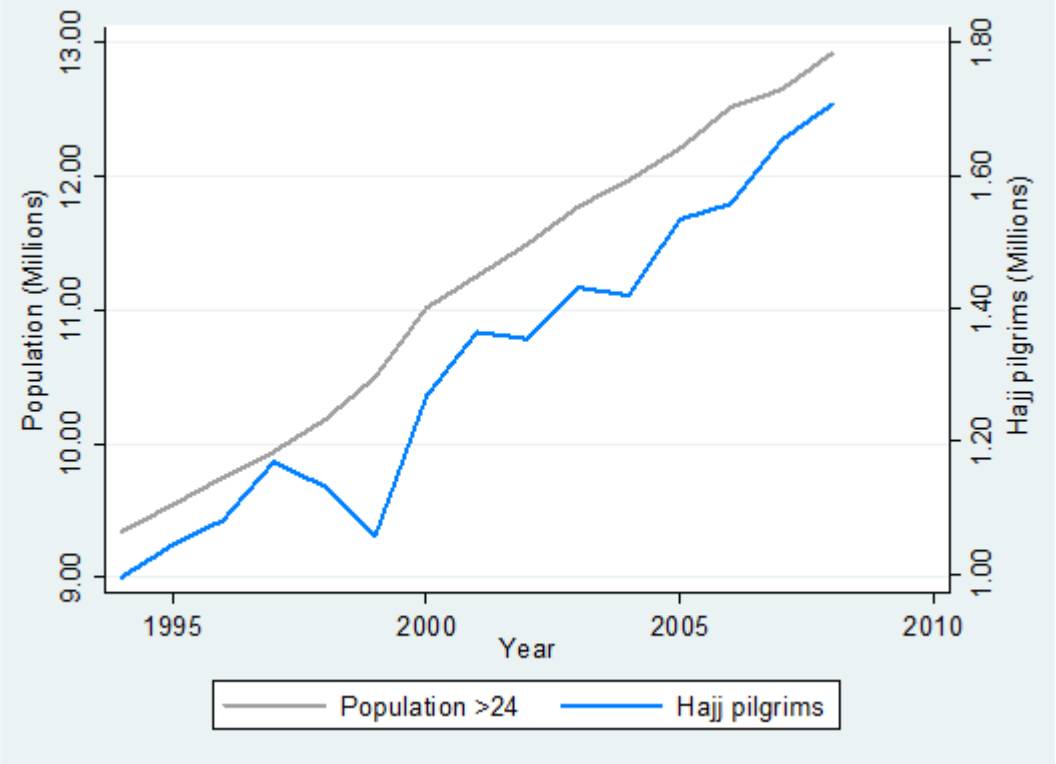


Figure 4.21: Increase in childhood and young adult population (<24) and Hajj pilgrims in Saudi Arabia between 1994 and 2008

5 Results: Indices of socioeconomic status

The data presented here is from the 2004 national census data. Details of all analytical methods were given in Chapter 3.

5.1 Data cleaning and descriptive statistics

5.1.1 Descriptive statistics

Table 5.1 details the descriptive statistics on the available variables from the 2004 national census of Saudi Arabia. Aggregating variables such as the ‘two or more cars’ variable has led to the distribution being more normally distributed. For the educational status category, the lowest mean was found for those with a higher education, i.e. a masters and a PhD (0.003). This variable is also positively skewed (skewness= 2.56) and its kurtosis is high (12.47), indicating a high peaked non-normal distribution. Further, the maximum proportion for a Governorate with higher education was only 0.019. For employment status, the average number of people in the labour force was 0.485 (SD=0.08), where the minimum number in a Governorate was high (0.32). For the type of housing and housing tenure categories, both the ‘other type of housing’, which indicated people living in tents or slums, and ‘other tenure’, which indicated whether the home is provided by a charity, are very small, in which the mean and SD for these variables were only 0.10 (SD=0.07) and 0.01 (SD=0.01), respectively. No Governorate had a minimum value of 0.00 for the household amenities category. The lowest minimum value was 0.03 for the ‘no TV available’ variable.

Table 5.1: Descriptive statistics of the proportions of indicator variables from the 2004 census of Governorates in Saudi Arabia

	Socioeconomic indicators	Mean	SD	Skewness	Kurtosis	Min	Max
Educational status	Illiterate	0.215	0.078	0.352	2.960	0.050	0.455
	Read and write	0.191	0.032	1.189	9.517	0.098	0.360
	*Illiterate or can read and write**	0.407	0.096	0.439	3.741	0.189	0.735
	Primary	0.210	0.021	-1.386	6.547	0.124	0.243
	Intermediate	0.168	0.028	-0.954	5.175	0.051	0.229
	Secondary	0.119	0.040	0.255	3.152	0.036	0.227
	*School degree**	0.498	0.067	-0.565	4.683	0.224	0.662
	Diploma	0.030	0.011	0.220	3.083	0.004	0.062
	University	0.061	0.027	0.710	3.948	0.005	0.156
	*Diploma and university**	0.091	0.035	0.357	3.697	0.015	0.208
	Masters	0.002	0.002	2.649	13.157	>0.00	0.014
	PhD	>0.00	>0.00	2.272	9.307	>0.00	0.005
	*Higher education**	0.003	0.002	2.556	12.467	>0.00	0.019
Employment status	In the labour force	0.485	0.075	0.324	2.642	0.315	0.662
	Students	0.177	0.030	-0.540	3.943	0.057	0.237
	Housewives	0.267	0.051	0.514	3.227	0.167	0.410
	Retired	0.036	0.011	0.117	2.629	0.009	0.064
	Other employment	0.032	0.018	0.862	3.376	0.003	0.089
Type of housing	Traditional house	0.443	0.229	0.390	1.962	0.038	0.896
	Villa	0.204	0.136	0.209	1.701	0.010	0.512
	Traditional house/villa floor	0.078	0.059	0.784	2.747	0.005	0.237
	Apartment	0.173	0.143	1.517	4.942	0.007	0.644
	Other type of housing	0.100	0.071	2.730	15.513	0.013	0.546

	Socioeconomic indicators	Mean	SD	Skewness	Kurtosis	Min	Max
Tenure of housing	House owned	0.573	0.146	-0.321	2.378	0.249	0.843
	House rented	0.266	0.122	0.798	3.532	0.007	0.631
	House provided	0.150	0.090	1.414	5.578	0.026	0.510
	Other tenure	0.010	0.012	3.334	15.910	>0.00	0.077
Car availability	No car available	0.292	0.092	0.789	3.006	0.121	0.532
	One car	0.464	0.074	0.359	3.295	0.020	0.694
	Two cars	0.166	0.046	-0.441	2.927	0.006	0.265
	Three cars	0.051	0.026	-0.044	1.715	0.006	0.102
	Four cars	0.016	0.010	0.280	1.971	>0.00	0.044
	Five cars	0.005	0.004	1.008	3.876	>0.00	0.021
	Six cars	0.001	0.001	1.139	4.958	>0.00	0.007
	Seven cars	>0.00	>0.00	1.536	6.761	>0.00	0.003
	Eight cars	>0.00	>0.00	1.163	3.485	>0.00	>0.00
	Nine cars	>0.00	>0.00	1.804	6.626	>0.00	>0.00
	Ten or more cars	>0.00	>0.00	1.419	5.624	>0.00	0.001
	*Two or more cars**	0.242	0.083	-0.333	2.079	0.033	0.387
Household amenities	Phone not available	0.468	0.196	0.669	2.664	0.133	0.968
	TV not available	0.217	0.127	1.302	5.399	0.038	0.721
	PC not available	0.807	0.113	-0.963	3.935	0.438	0.988
	Internet not available	0.878	0.087	-1.364	5.162	0.583	0.993
	Library not available	0.847	0.088	-0.707	3.153	0.571	0.988
	Satellite not available	0.635	0.172	-0.576	3.141	0.131	0.979
	Video not available	0.780	0.135	-0.858	3.258	0.352	0.982
	Video game not available	0.775	0.099	-0.341	2.850	0.489	0.970

*Aggregated variables used in the analyses.

5.2 Standardised index of socioeconomic status

The EFA method was used to formulate the index. The results are presented in the same order as they were explained in Chapter 3.

5.2.1 Data checks

The Bartlett's test of sphericity and the Kaiser-Meyer-Olkin (KMO) test results are presented in Table 5.2. The KMO test result is above 0.70 indicating that the results are in the middling area and are suitable for EFA. Also, the Bartlett's test is significant, also showing that the data is suitable for EFA.

Table 5.2: Bartlett's test of sphericity and the Kaiser-Meyer-Olkin's test results

Test statistic	Result
Kaiser-Meyer-Olkin test	0.727
Bartlett's test of sphericity	P value > 0.01

5.2.2 Factor extraction and factor retention

The principal factor method was used to extract the factors. The initial factors extracted are available in Table 5.3. The initial extraction produced the same number of factors as there were indicator variables. Since 29 indicator variables were used, then 29 factors were extracted, each explaining a certain proportion of the common variance. The eigenvalue is highest for the first factor, because it is the factor that contributes more to the overall factor solution, i.e. explains the common variance more than the other factors. The eigenvalue then starts to diminish. The decision on the number of factors to retain was made based on three criteria. First, the scree plot in Figure 5.1, which plotted all 29 factors that were extracted. From the plot, the four factors on the steep slope are the meaningful factors. This is because after the fourth factor, the eigenvalues start to level off. Therefore, the remaining extracted factors may be discarded.

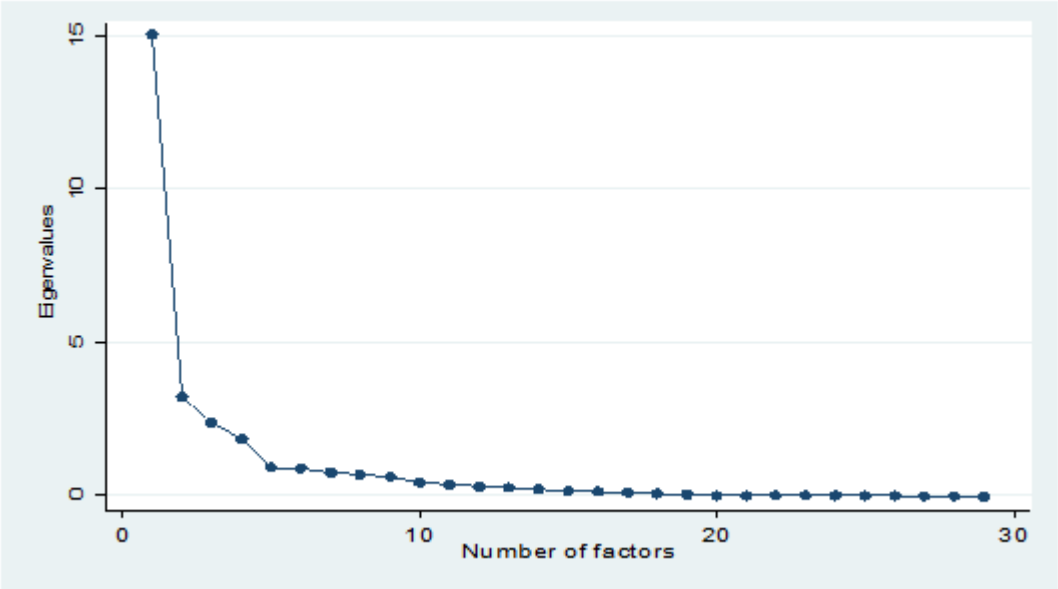


Figure 5.1: Scree plot of eigenvalues of the extracted factors

The second criterion is the Kaiser rule of retaining only the eigenvalues that are above one. Table 5.3 shows the eigenvalues for the 29 factors obtained from the initial extraction. It also shows the proportion as well as the cumulative proportion of the common variance that is explained by each factor. Based on the Kaiser rule, and since only the first four factors have eigenvalues that are above one, then only these factors will be retained. The final criterion is the interpretability of each factor. The interpretation of the factors is based on the factor loading of each variable in each factor (Table 5.4). Factor 4 is difficult to interpret and therefore it is safe to drop it. Only one indicator (one car available) loads highly on that factor, and if dropped the variable loads highly on Factor 2 which is more interpretable.

Table 5.3: Factors extracted from the initial extraction stage

Factor	Eigenvalue	Proportion	Cumulative
Factor 1	15.03	0.52	0.52
Factor 2	3.21	0.11	0.64
Factor 3	2.39	0.08	0.72
Factor 4	1.84	0.06	0.79
Factor 5	0.91	0.03	0.82
Factor 6	0.88	0.03	0.85
Factor 7	0.75	0.02	0.88
Factor 8	0.69	0.02	0.90
Factor 9	0.61	0.02	0.92
Factor 10	0.43	0.01	0.94
Factor 11	0.37	0.01	0.95
Factor 12	0.30	0.01	0.96
Factor 13	0.25	0.00	0.97
Factor 14	0.21	0.00	0.98
Factor 15	0.15	0.00	0.99
Factor 16	0.13	0.00	0.99
Factor 17	0.09	0.00	0.99
Factor 18	0.06	0.00	1.00
Factor 19	0.03	0.00	1.00
Factor 20	0.00	0.00	1.00
Factor 21	0.00	0.00	1.00
Factor 22	0.00	0.00	1.00
Factor 23	0.00	0.00	1.00
Factor 24	0.00	0.00	1.00
Factor 25	0.00	0.00	1.00
Factor 26	-0.00	-0.00	1.00
Factor 27	-0.00	-0.00	1.00
Factor 28	-0.01	-0.00	1.00
Factor 29	-0.04	-0.00	1.00

Table 5.4: The factor loadings of variables on the extracted factors

Variables	Factor 1	Factor 2	Factor 3	Factor 4
Illiterate or can read/write	-0.89	-0.16	-0.11	0.05
School degree	0.75	0.28	0.12	-0.16
Diploma or university	0.93	-0.07	0.09	0.17
Higher education	0.83	-0.21	-0.16	-0.02
In the labour force	0.66	-0.08	-0.63	0.11
Students	0.18	0.35	0.73	0.23
Housewives	-0.77	-0.03	0.27	-0.38
Retired	-0.52	0.14	0.32	0.17
Other employment	-0.53	-0.22	0.42	0.08
Traditional house	-0.61	-0.36	0.28	0.05
Villas	0.32	0.55	-0.10	0.24
Traditional house or villa floor	0.46	0.29	0.09	0.16
Apartment	0.69	-0.12	0.01	-0.47
Other type of housing	-0.41	0.11	-0.79	0.15
House owned	-0.70	0.00	0.43	0.05
House rented	0.70	0.00	-0.04	-0.46
House provided	0.16	0.09	-0.68	0.48
Other tenure of housing	0.18	-0.72	0.33	0.30
No car available	-0.09	-0.88	-0.14	0.54
One car available	0.04	0.17	0.11	-0.93
Two/more cars available	0.06	0.82	0.05	0.22
Phone available	0.78	0.24	-0.04	0.00
TV available	0.81	-0.20	0.22	0.00
PV available	0.95	-0.00	0.12	0.03
Internet available	0.92	0.02	0.05	-0.06
Library available	0.86	0.11	0.03	-0.10
Satellite available	0.84	-0.09	0.00	-0.14
Video available	0.91	0.04	-0.04	0.06
Video games available	0.94	0.08	0.11	0.01

5.2.3 Factor rotation

Figure 5.2 presents the non-rotated factor solution for the three factors. Factor loading plots help in visually identifying variables with high loadings on specific variables. The non-rotated factor solution does not present a distinguishable pattern of loadings of the indicator variables. Interpretation of these factors proved to be difficult as some factors had high loadings on two factors, for example the ‘rented home’ and ‘living in apartment’ variables had a high loading on both Factor 1 and Factor 2. Therefore, these factors were rotated using the oblique factor rotation method.

Figure 5.3 presents the rotated factor solution. The rotation made it possible to distinguish between the high and low loadings of factors. For example, in the first plot of Factor 1 against Factor 2, high loadings for Factor 1 were seen for the availability of household items, such as a PC, TV and satellite, also, a high loading was found for the ‘living in apartments’ and ‘in the labour force’ variables. Furthermore, high loadings on Factor 2 were seen for ‘having two or more cars’ and living in ‘villas’. In the plot of Factor 2 against Factor 3, a clear distinction can be made for the variables with high loadings on Factor 3, these were for ‘other employment’, ‘traditional house’ and the house tenure is ‘owned’. The ‘students’ variable happened to have a high loading on both Factor 2 and Factor 3.

This plot is a reflection of the table of loadings available in Table 5.5. Inspection of the factor loadings from this table, and from the loading plots made it possible to label the factors. Factor 1 was labelled ‘middle class’, Factor 2 ‘affluent class’ and Factor 3 ‘deprived class’.

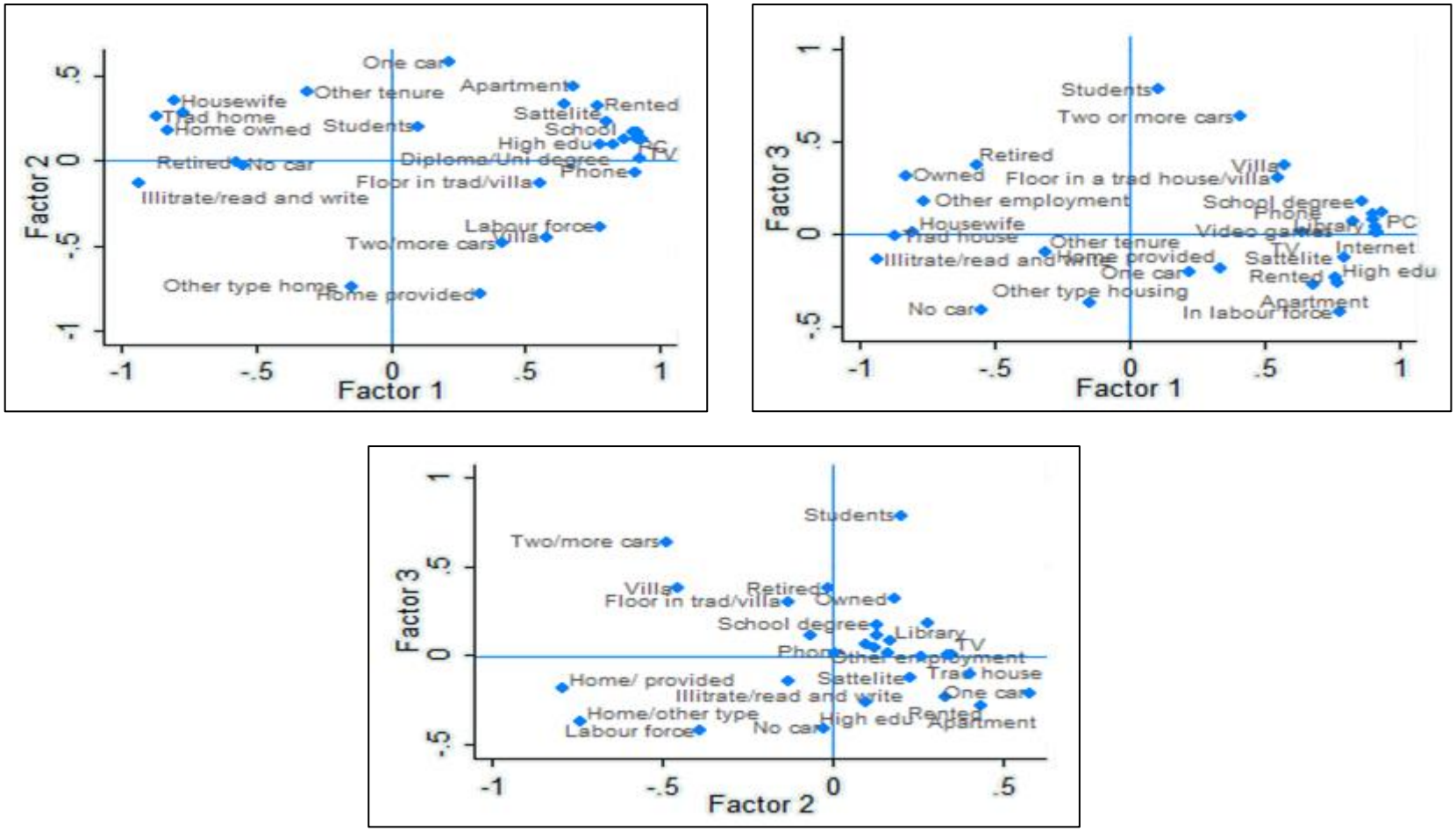


Figure 5.2: Factor loadings from the non-rotated factor solution

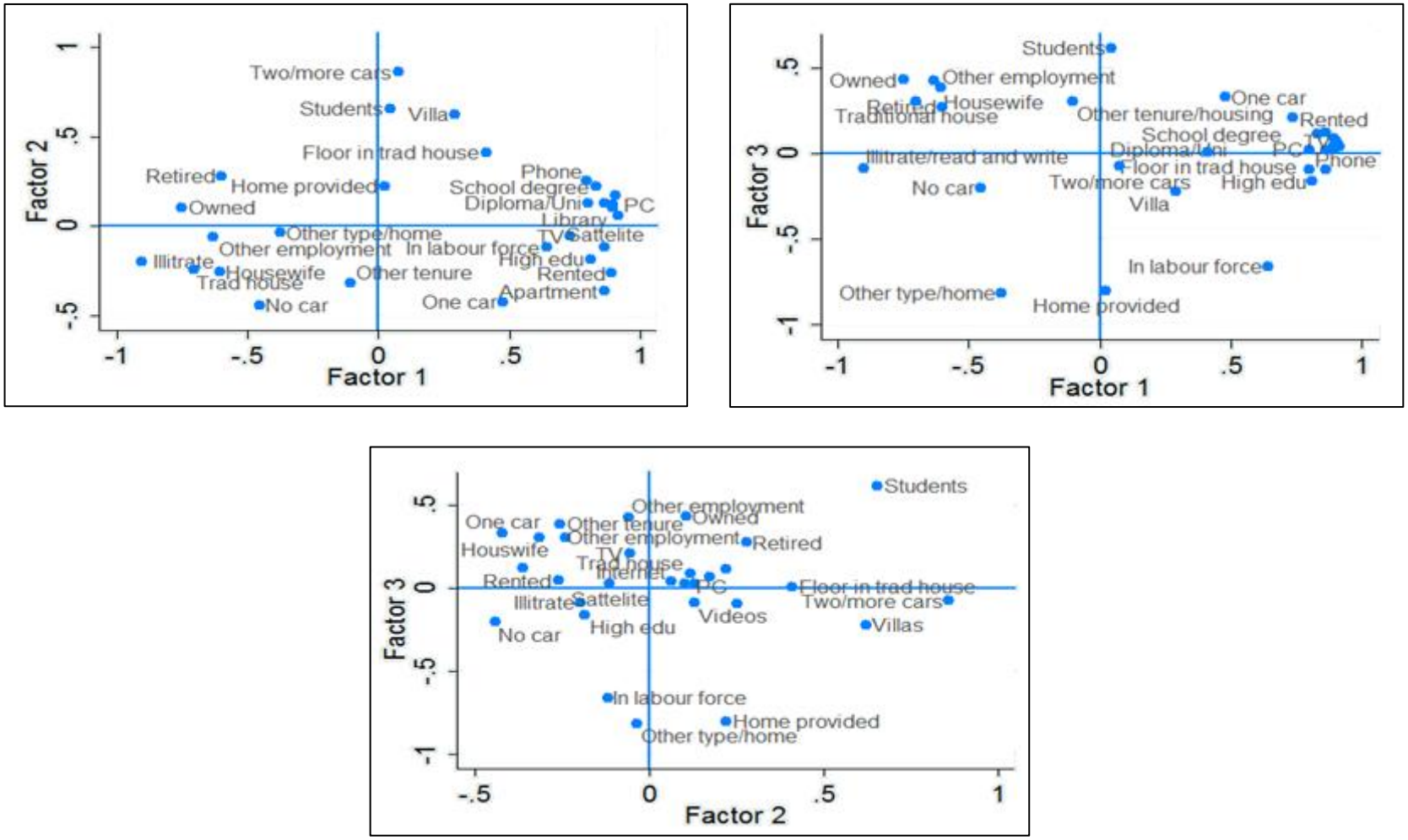


Figure 5.3: The factor loadings from the rotated factor solution

Table 5.5: The rotated factor loadings of variables on the extracted factors

Variables	Middle class	Affluent class	Deprived class
Illiterate or can read and write	-0.90	-0.20	-0.08
School degree	0.83	0.22	0.11
Diploma and University	0.80	0.13	0.03
Higher education	0.81	-0.18	-0.16
In the labour force	0.64	-0.12	-0.66
Students	0.04	0.66	0.62
Housewives	-0.61	-0.25	0.39
Retired	-0.60	0.28	0.28
Other employment	-0.63	-0.06	0.43
Traditional house	-0.70	-0.24	0.31
Villas	0.29	0.62	-0.22
Traditional house or villa floor	0.41	0.41	0.01
Apartment	0.86	-0.36	0.12
Other type of housing	-0.38	-0.04	-0.81
House owned	-0.75	0.11	0.43
House rented	0.89	-0.26	0.05
House provided	0.02	0.22	-0.80
Other tenure of housing	-0.11	-0.31	0.31
No car available	-0.45	-0.44	-0.20
One car available	0.48	-0.42	0.33
Two or more cars available	0.08	0.86	-0.07
Phone available	0.80	0.25	-0.09
TV available	0.74	-0.06	0.21
PV available	0.90	0.12	0.09
Internet available	0.92	0.06	0.04
Library available	0.90	0.10	0.03
Satellite available	0.86	-0.11	0.03
Video available	0.86	0.13	-0.09
Video games available	0.91	0.17	0.07

5.2.4 Initial index and standardised index

The proportion of the common variance explained for the three factors was used as a weight in the initial index equation (Equation 3.9). Table 5.6 gives the proportions for each of the three factors.

Table 5.6: Proportion of the common variance explained by each factor

Factors	Variance	Proportion
Factor 1	14.63252	0.5158
Factor 2	4.29528	0.1514
Factor 3	4.04424	0.1426

The initial index equation (Equation 3.9) produces an index of the 118 Governorates that range between 131.25 for the most affluent Governorate to 0 for the most deprived. For ease of interpretation, this index was standardised by applying Equation 3.10. Appendix I gives detailed results of both the initial and the standardised index.

5.3 Classes of socioeconomic status

The LCA method was used to formulate the index. The results are presented in the same order as they were explained in Chapter 3.

5.3.1 Deciding the number of classes

The model fit indices for the one- to four-class models are presented in Table 5.7. Both the two- and four-class solutions have entropy very close to one (0.98), indicating that the accuracy of classification is excellent. Also, the LMR-LRT and BLRT tests resulted in a significant P-value, indicating that these two class models are better than a k-1 class model. However, the AIC, BIC and ABIC were lower in the four-class solution, hence giving it more preference than a two-class model. Also, the four-class solution is more interpretable, as it groups the Governorates into four clear homogenous groups, rather than two groups. Hence, the four-class model was chosen. Specifying a five-class model would not allow the model to converge.

Table 5.7: Fit statistics for latent class analysis

Number of classes	Number of free parameters	Log likelihood (H0) value	Akaike Information Criterion (AIC)	Bayes Information Criterion (BIC)	Adjusted BIC	Entropy	Lo-Mendell-Rubin likelihood ratio test (LMR-LRT)	Bootstrap Likelihood Difference test (BLRT)
One class	22	977	-1910	-1849	-1919	n/a	n/a	n/a
Two classes	34	1318	-2568	-2474	-2581	0.98	0.00	0.00
Three classes	46	1415	-2739	-2611	-2757	0.95	0.41	0.00
Four classes	58	1567	-3018	-2857	-3040	0.98	0.02	0.00

5.3.2 Examining the quality of latent class membership

The class membership of each Governorate is decided by means of modal assignment probability. If the probability is very high and the class separation is large, then the class membership is of high quality. Appendix J provides the final class four-class solution, as well as the modal assignment probability. It can be seen that the class separation is large. Therefore, the quality of modal assignment is very good. A further measure of the quality of class membership is the entropy (Table 5.7). The entropy is very high for the four-class solution (0.98) indicating that the classification of the classes is very much accurate.

5.3.3 Defining and labelling classes

Figure 5.4 gives the probability plot for the four-class solution. This plot is used to define and label each class. Since the indicator variables chosen are the disadvantage variables, the lower the probability of each variable the greater the affluence indicated. Class 1 shows a low probability in all indicators except for the 'living in a floor of the traditional or villa' variable and the 'house not owned' variable, indicating that Class 1 represents the most affluent Governorates and has been labelled 'the affluent class'; this includes 11.1% of the Governorates. Class 4 is shown to have the highest probability of all variables except for 'living in a floor of a traditional house or villa' and 'house not owned' variables, thereby indicating that this variable represents the most deprived Governorates, and includes 11.01% of Governorates. Class 2 is labelled 'upper middle class' and includes 44.91% of Governorates. Class 3 is labelled 'lower middle class' and includes 33.05% of Governorates and finally Class 4 is labelled 'the deprived class' and includes 11.01% of Governorates.

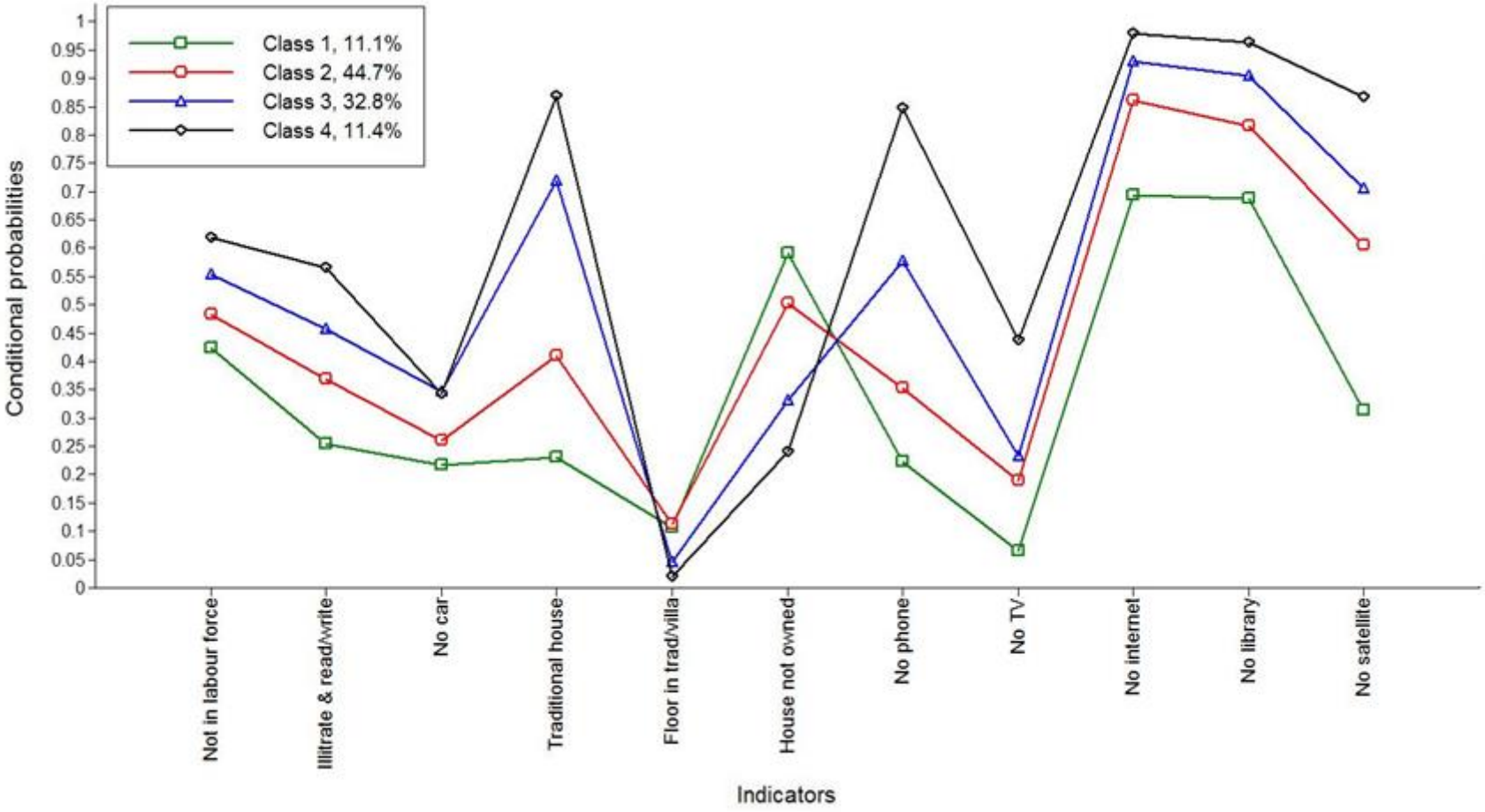
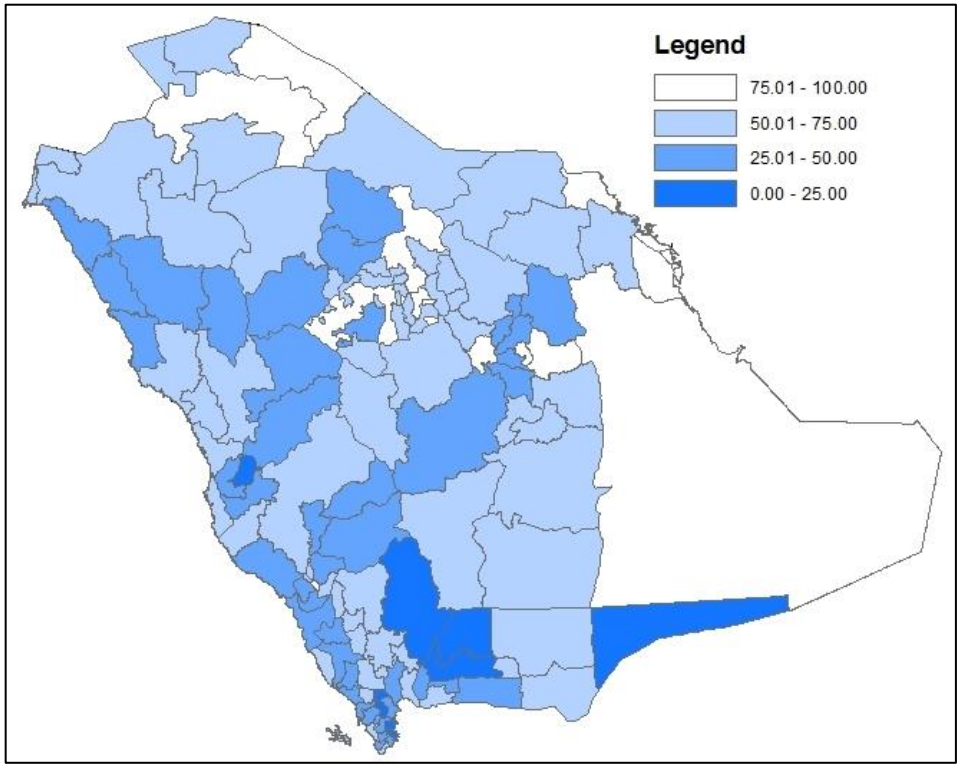


Figure 5.4: Probability plot of disadvantage in Saudi Arabia

5.3.4 Geographical mapping of both indices

Figures 5.5a and 5.5b present the results of both indices geographically. For the standardised index, the most affluent Governorates were found to cluster in the eastern province in the Governorates of Ahsa, Jubail, Dammam, Khobar and Qatif as well as in the capital Governorate of Riyadh and in the north in Arar and Skaka. In the western region, no Governorate, not even Jeddah, was found to be within the most affluent Governorates, although Jeddah had a score of 74.39 which is very close to the cut-off point used to classify Governorates in map (a). The most deprived Governorates are seen to cluster in the south with Governorates such as Tathleeth, Kharkheer, Yadmah and Thaar. Governorates that lie within the lower middle range of affluence are seen to form a belt between Romah in the central region towards Raniah in the south western region, and on the western Red Sea coast in the Leeth, Qilwah, Belgarn, Qunfudhah, Majardah, Darb Jazan and Samtah, as well as in the north western Governorates, including Dhebaa, Wajh, Ola, Amluj and Hinakiyah. For the class index, a very similar pattern of affluence is clearly seen. There are very minor changes, in the north Arar and Skaka are not classified in the affluent class, also Governorates such as Riyadh, Khobaraa, Ghazalah, Khaibar, and Kharkheer are classified as deprived rather than low middle class.

a) Standardised index



b) Class index

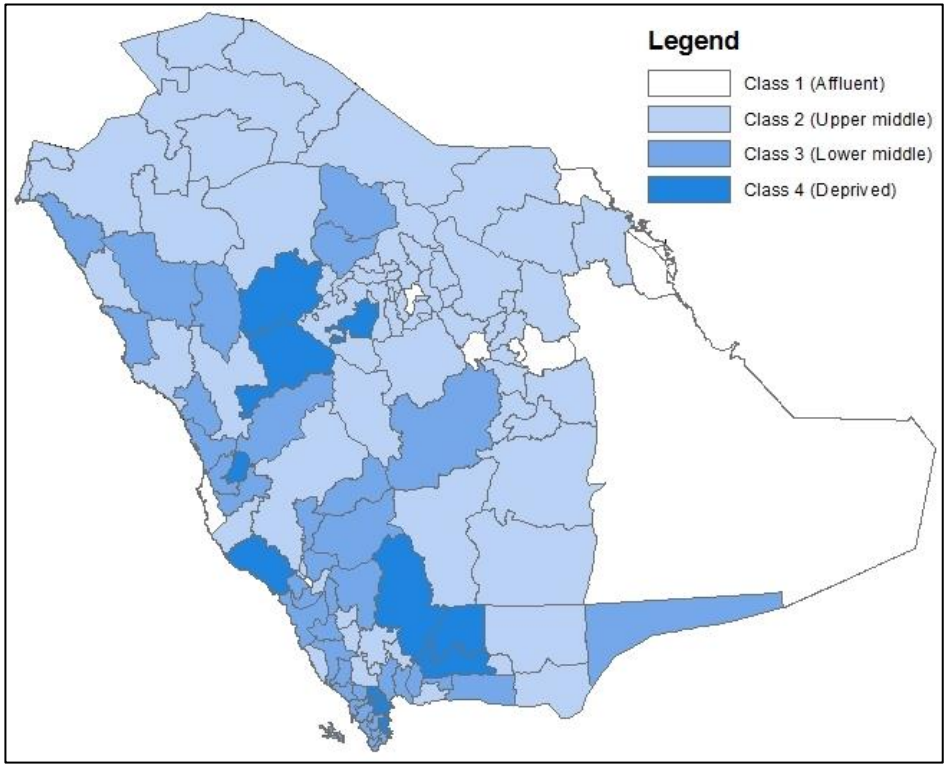


Figure 5.5: Geographical representation of the standardised index and the class index for Saudi Governorates

5.3.5 Comparing distributions of both indices

Figure 5.6 shows the distributions of both the standardised index and the class index through a box and whisker plot. The median for Class 1 is around a score of 85 for the standardised index, indicating that both indices point towards the same Governorates as affluent. The median for Class 2 is around 64 for the standardised index. The upper whisker overlaps with the lower whisker of Class 1, thereby signifying that a few Governorates considered affluent in the standardised index are classified as upper middle class in the class index. There is also one outlier for the Governorate of Wajh which is considerably low in the standardised index. The lower whisker overlaps with the inter-quartile range for Class 3 indicating that these two classes include Governorates with very close scores in the continuous index. For Class 3, the median is around 44 for the standardised index. An outlier is found for the Governorate of Kharkheer which is the most deprived Governorate in the standardised index having a score of 0. Class 4 includes a range of scores between 47 and 17.81, which is the lowest score before the 0 point, and therefore includes the lower spectrum of the deprived Governorates in the standardised index, except for Kharkheer.

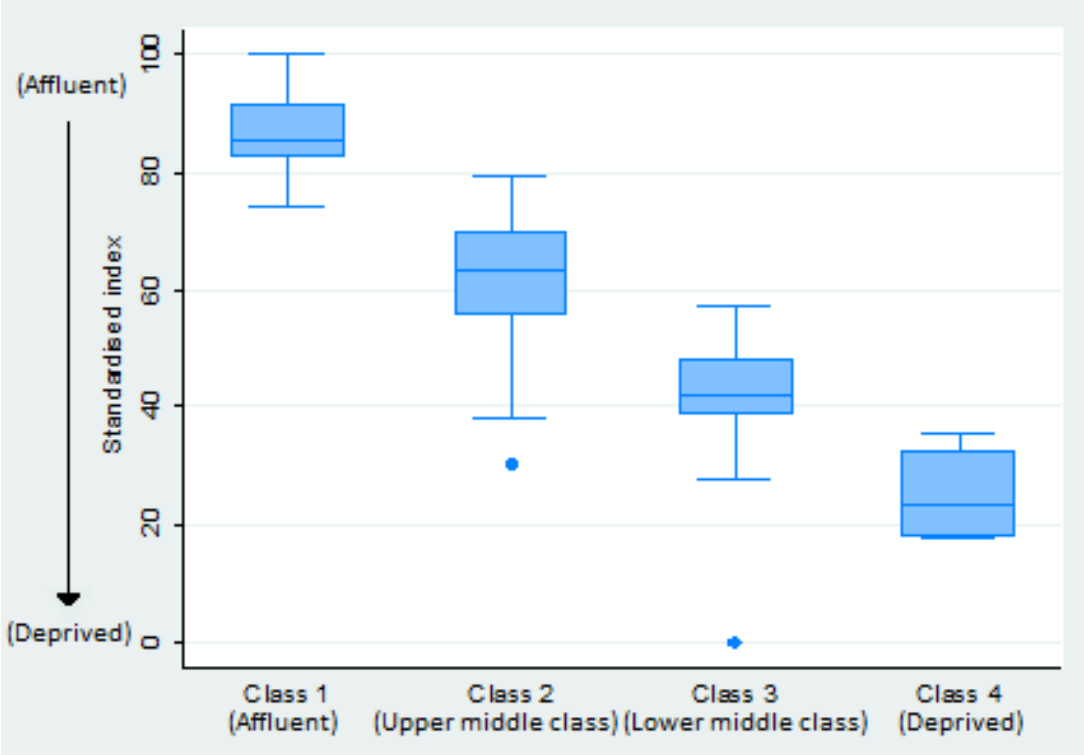


Figure 5.6: Boxplots of the continuous standardised socioeconomic index and the categorical class socioeconomic index for Saudi Governorates

The linear pattern in the distribution of the box plots shows that the two indices point towards the same Governorates as either affluent or deprived, except for minor differences expressed in the whiskers and outliers.

6 Results: Regression analyses of population mixing and socioeconomic status, sensitivity analyses and ascertainment of cases

All data presented are for the calendar years from 1994 to 2008 and are presented in the order in which they appear in the methods. Analytical methods were dealt with in Chapter 4.

6.1 Regression analyses

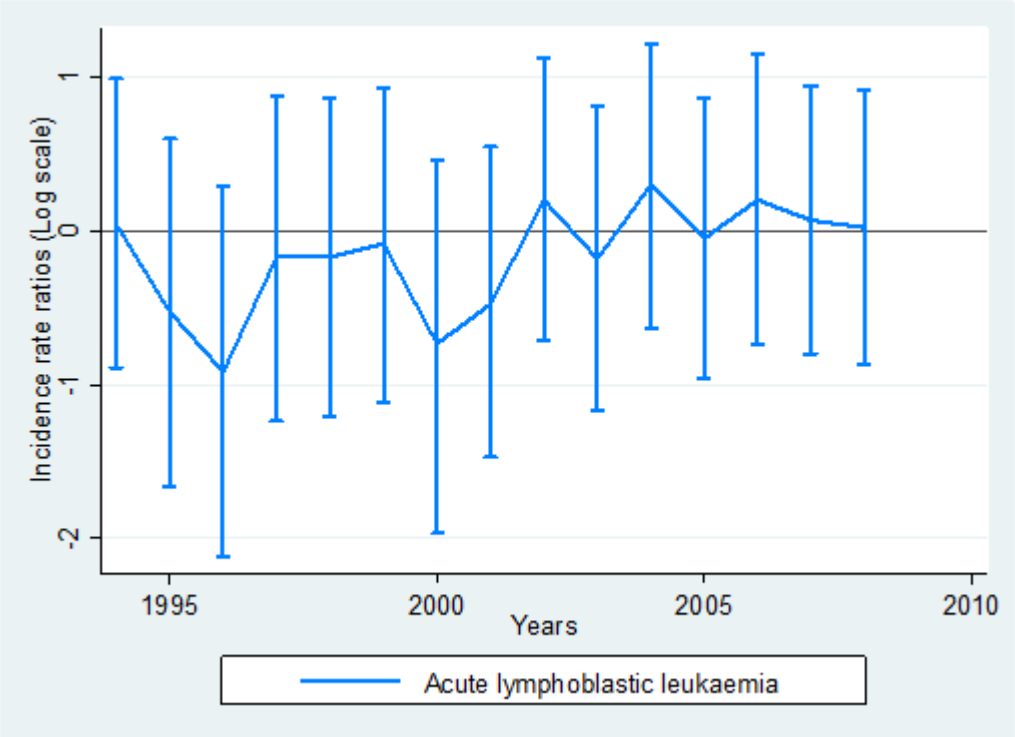
The first attempt at regression involved a Poisson regression. However, the data exhibited a large overdispersion that the Poisson model was simply not able to account for, as well as a large number of zero cells. It was also found that $\alpha > 0$, indicating that Poisson was not an ideal method and therefore the negative binomial model was used instead.

The univariable analysis showed that only the SES variables were statistically significant ($P<0.00$). Nevertheless, the PM variable was modelled by year of diagnosis to check for any variation in incidence. The IRR for PM and its relative 95%CI for all diagnostic groups were plotted in Figures 6.1-6.4. The IRRs have been log transformed to show a clearer picture, hence the point of no effect is zero.

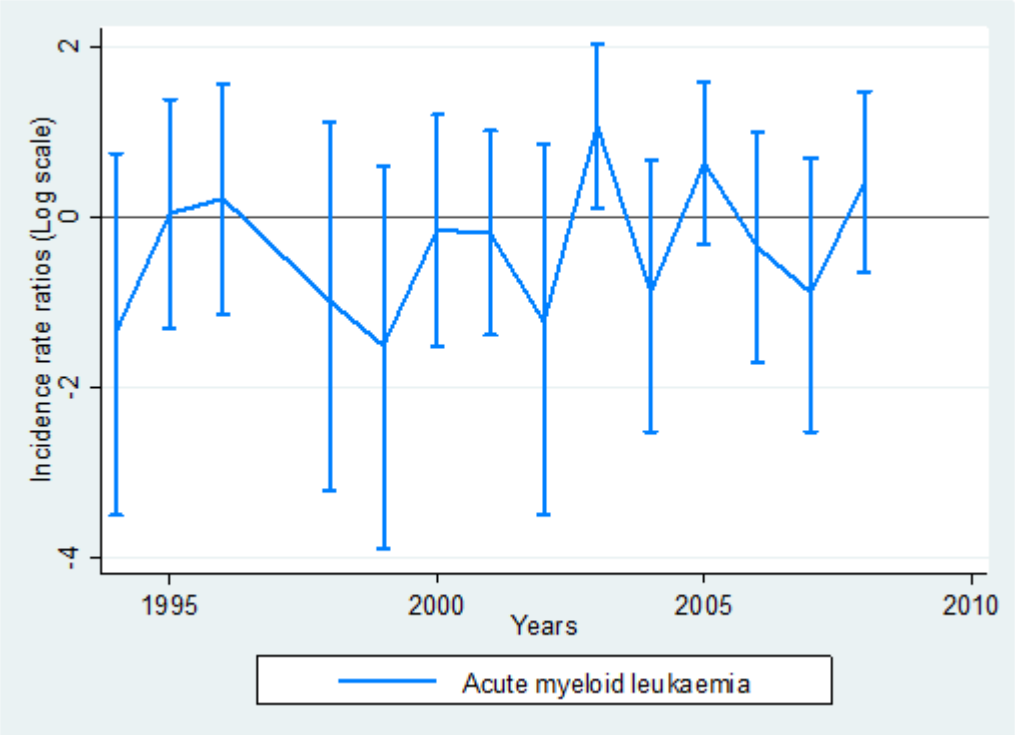
The figures clearly showed that PM in Makkah compared to the rest of the Governorates has no significant effect on the incidence of all diagnostic groups. Only for CNS in the year 1997 is there a borderline significant elevated risk (Non-logged IRR = 2.43, 95%CI = 0.99 - 5.98, logged IRR = 0.88, 95%CI = -0.01 - 1.78). For CML, other leukaemias group, BL and other lymphomas group, some years had no cases reported in Makkah.

Figure 6.1: Incidence rate ratios of leukaemias diagnosed in Saudis aged <24 years corresponding to population mixing by year of diagnosis

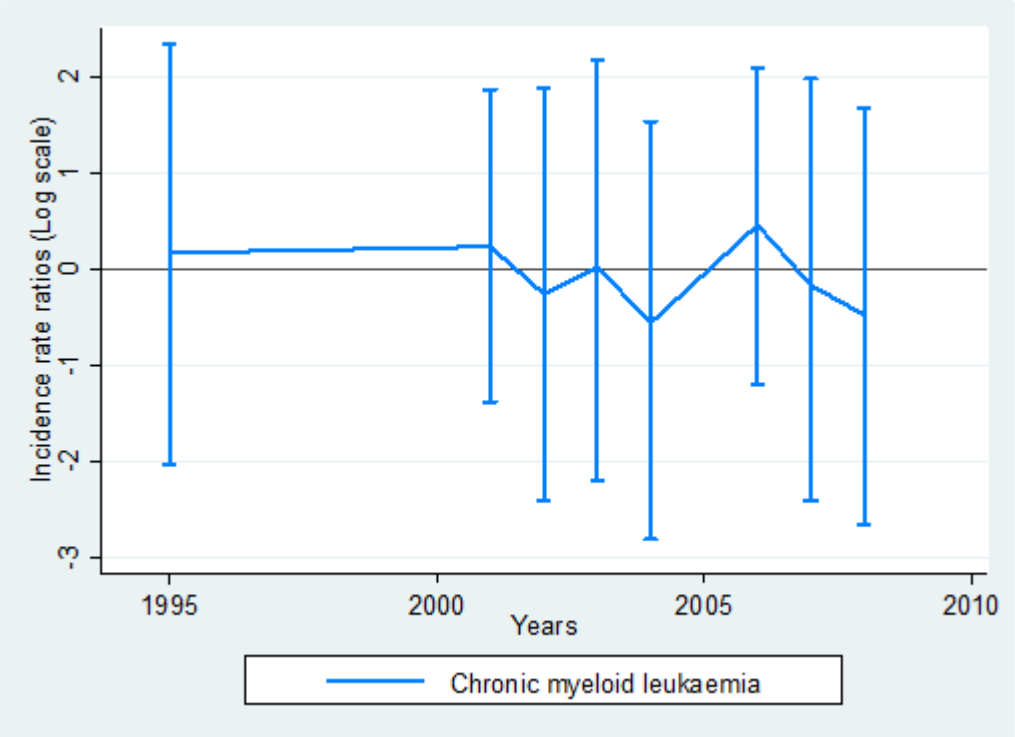
a) Acute lymphoblastic leukaemia



b) Acute myeloid leukaemia



c) Chronic myeloid leukaemias



d) Other leukaemias

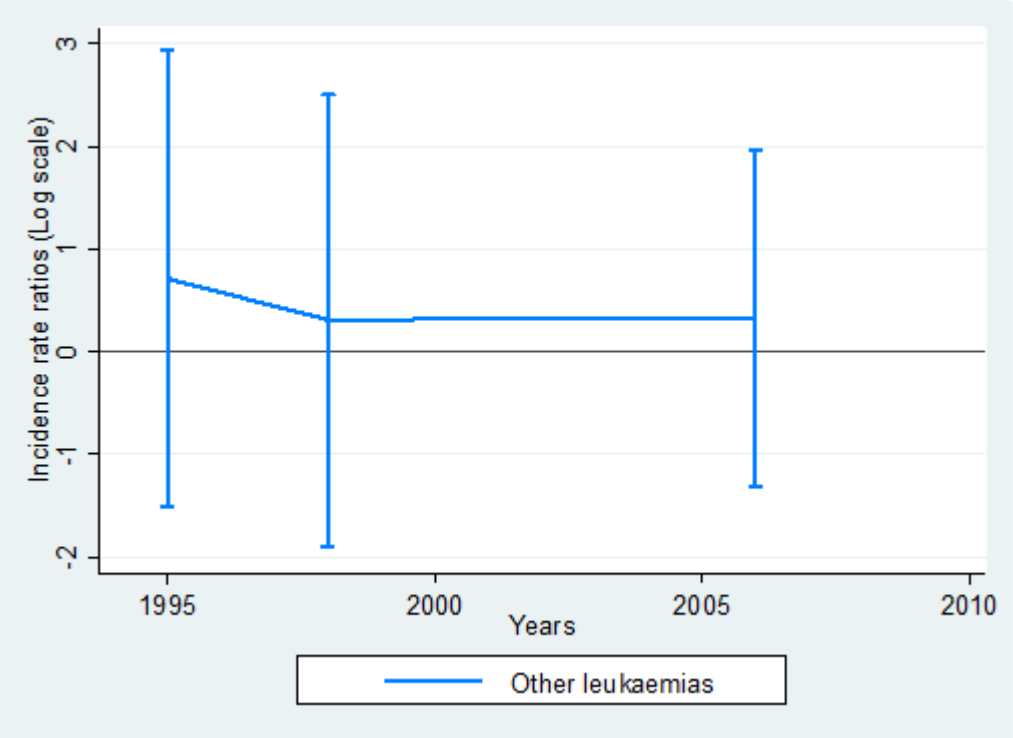
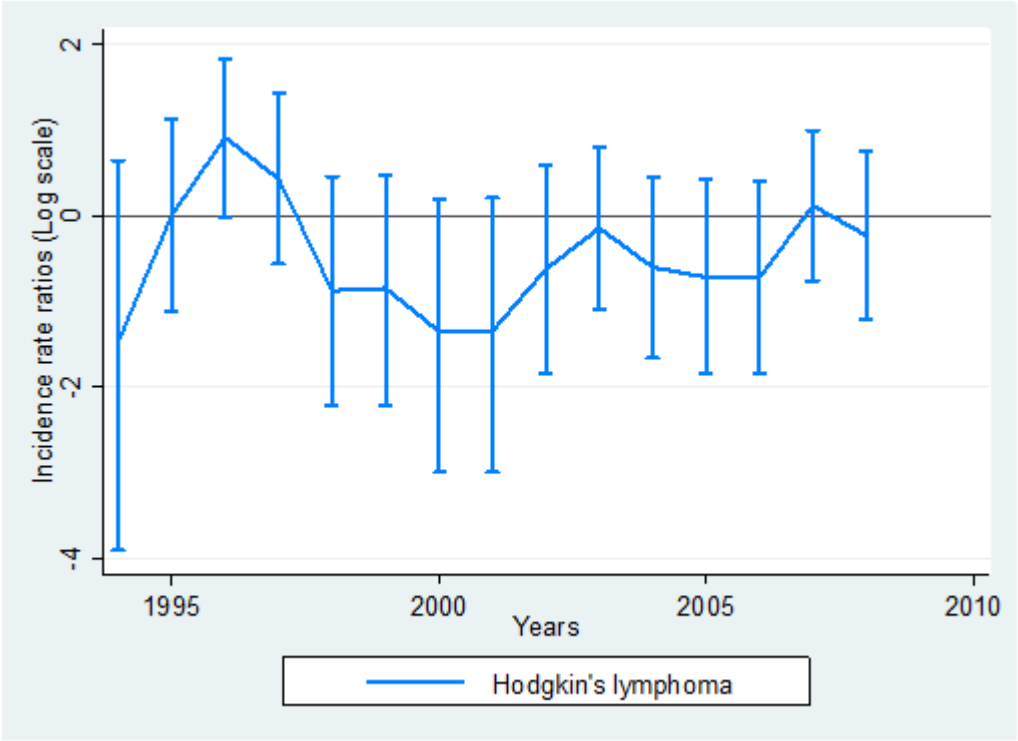
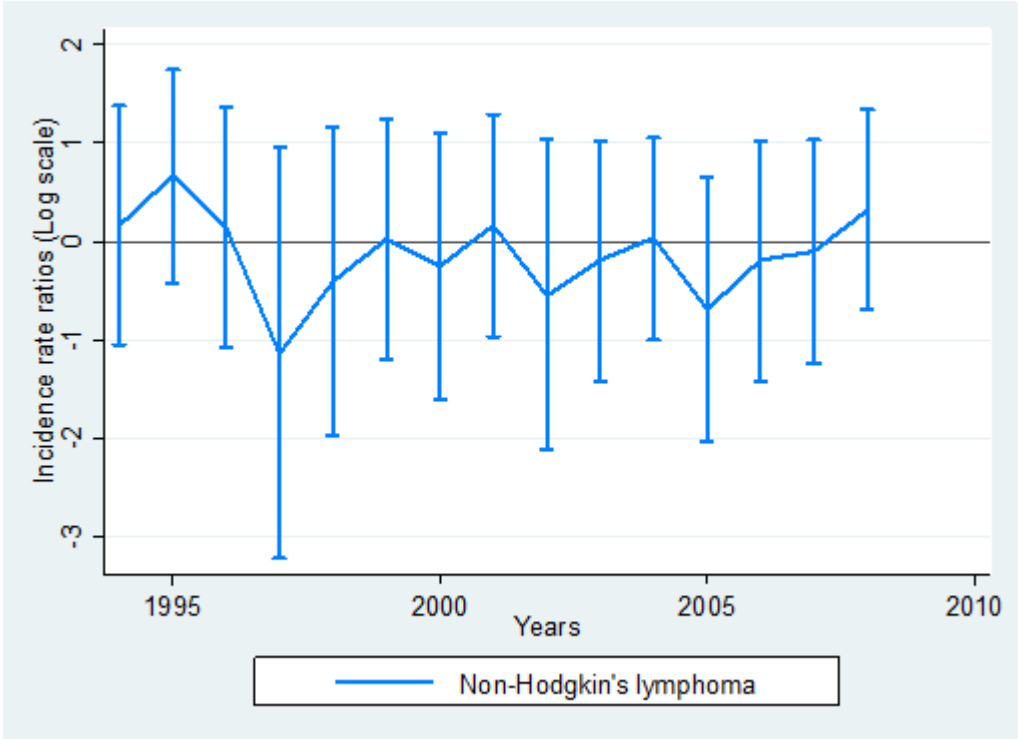


Figure 6.2: Incidence rate ratios of leukaemias diagnosed in Saudis aged <24 years corresponding to population mixing by year of diagnosis

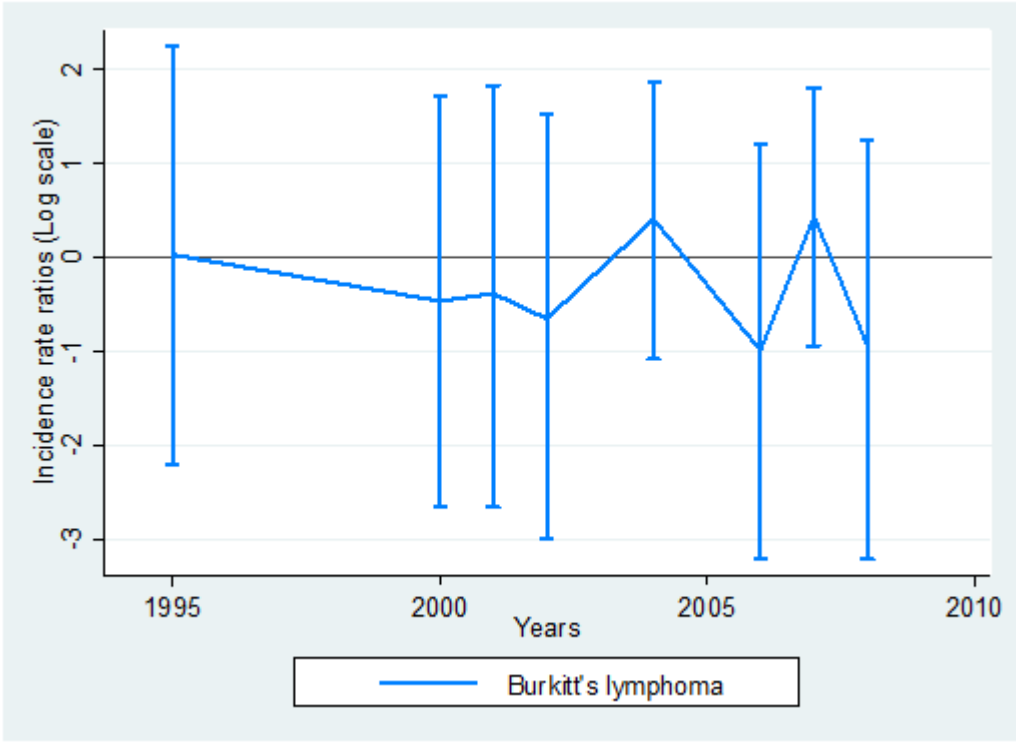
a) Hodgkin's lymphoma



b) Non-Hodgkin's lymphoma



c) Burkitt's lymphoma



d) Other lymphomas

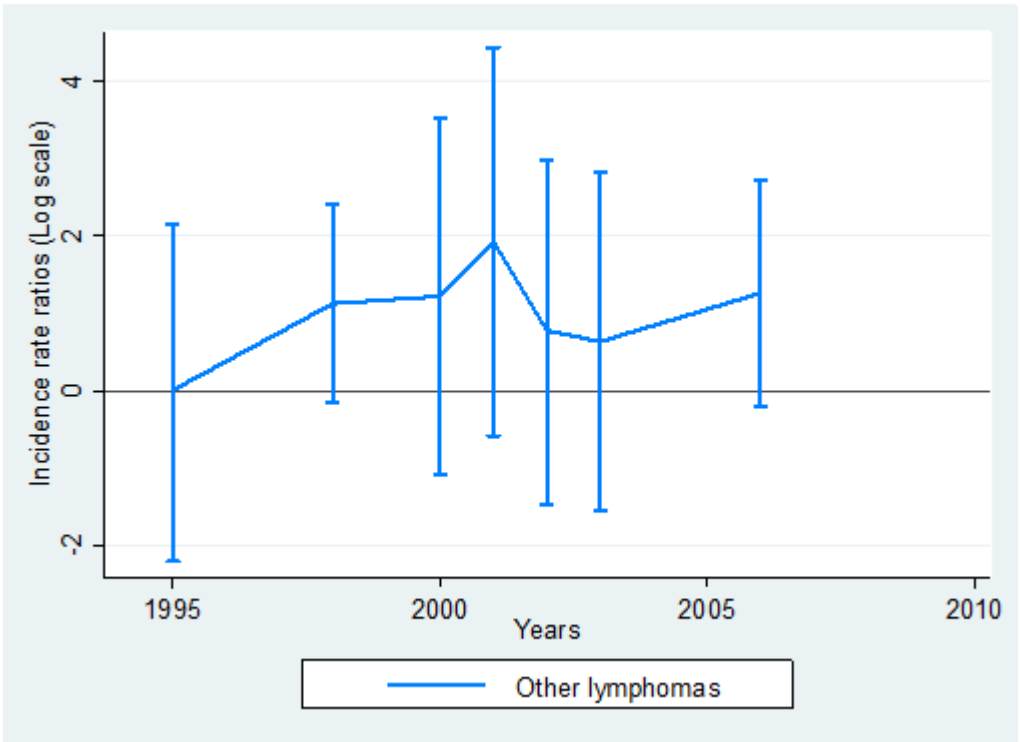


Figure 6.3: Incidence rate ratios of central nervous system tumours diagnosed in Saudis aged <24 years corresponding to population mixing by year of diagnosis

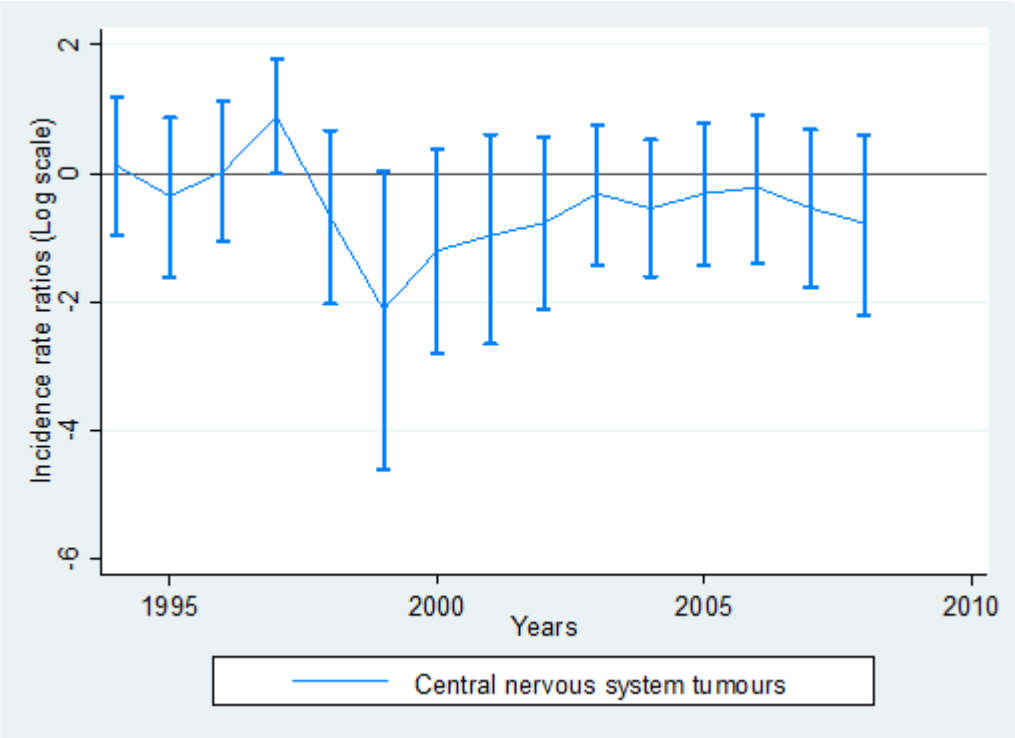
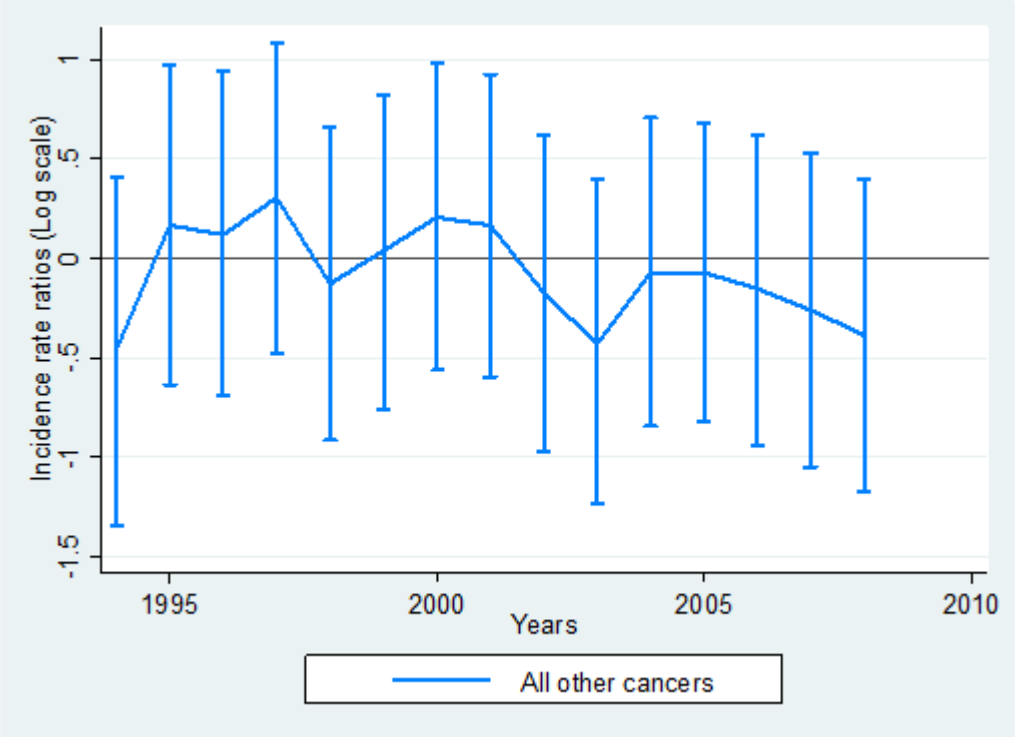


Figure 6.4: Incidence rate ratios of other cancers diagnosed in Saudis aged <24 years corresponding to population mixing by year of diagnosis



The second set of regressions examined the association between SES and young people's cancers. Since the NB regression models were fitted using the observed counts of cases in each Governorate using the log of the expected cases as the offset from the age-sex incidence rates (Chapter 4), the age and sex variables were automatically adjusted. Tables 6.1a to 6.1c show the results of these regression models.

Table 6.1a presents the regression results for all types of leukaemias. For ALL there was a significant increase in ALL with the increase of affluence of SES classes, where the most affluent class had an IRR of 1.38 (95%CI = 1.23 -1.54), and the most deprived class had an IRR of 0.17 (95%CI = 0.10 - 0.29). The use of the continuous standardised index in the second model shows a significant increase of the IRR with increasing affluence (IRR = 1.26, 95%CI = 1.22 - 1.30). The third model used quintiles of the standardised index and modelled it as a categorical variable. Similar to the SES class index, there is a significant reduction of incidence of ALL within the most deprived quintiles (IRR= 0.14, 95% CI= 0.10 – 0.21). Although the reduction in incidence is non-linear, there still remains the general decrease.

For CML the association with the SES classes is U-shaped, where the most affluent class had a non-significant positive association (IRR = 1.27, 95%CI = 0.97 - 1.67), the incidence then dropped to 0.42 in the lower middle class 95%CI = 0.24 - 0.72) and finally increased slightly to 0.65 (95%CI = 0.26 - 1.61). A similar pattern is found for CML in the third model for the quintiles of SES.

Table 6.1b presents the regression results for all types of lymphomas. For HL and NHL, a significant linear decrease in incidence with decreasing affluence is seen with both diseases. The incidence drops to 0.02 for HL and 0.08 for NHL in the most deprived classes (95%CI = 0.00 - 0.11 and 95%CI = 0.02 - 0.27, respectively). The same statistically significant linear relationship is found in the third model for the SES quintiles for both diseases.

Table 6.1c presents the regression results for CNS and all other types of cancers. For both groups, the incidence is higher in affluent classes and quintiles and gradually decreases for the lower classes and quintiles.

The model fit statistics for all models have shown that the p-value for the goodness of fit chi-square statistic were statistically significant, indicating good model fit.

Table 6.1: IRRs and 95% CI for Saudis aged <24 years diagnosed with cancer (1994 to 2008) associated with socioeconomic status in all Saudi Governorates using negative binomial regression

a) Leukaemias

		Types of leukaemias							
		Acute lymphoblastic		Acute myeloid		Chronic myeloid		Other leukaemias	
Models/Variables [a]	**Range**	IRR	95% CI	IRR	95% CI	IRR	95% CI	IRR	95% CI
Model 1: SES class index									
Model fit: 3 df (*p* value)		215.37 (<0.01)		88.24 (<0.01)		22.30 (<0.01)		23.41 (<0.01)	
SES classes	Affluent	1.38	(1.23-1.54)	1.25	(1.07-1.47)	1.27	(0.97-1.67)	1.50	(1.15-1.97)
		1	(-)	1	(-)	1	(-)	1	(-)
	↓	0.55	(0.47-0.64)	0.46	(0.35-0.61)	0.42	(0.24-0.72)	0.90	(0.60-1.37)
	Deprived	0.17	(0.10-0.29)	0.19	(0.08-0.44)	0.65	(0.26-1.61)	0.13	(0.01-0.93)
Model 2: Standard. SES index									
Model fit: 1 df *(p* value)		247.43 (<0.01)		96.32 (<0.01)		22.64 (<0.01)		19.67 (<0.01)	
SES standardised index	Continuous	1.26	(1.22-1.30)	1.24	(1.19-1.30)	1.21	(1.11 -1.31)	1.18	(1.09-1.28)
Model 3: Quintiles of standardised index									
Model fit: 4 df (*p* value)		335.94 (<0.01)		123.40 (<0.01)		47.42 (<0.01)		37.26 (<0.01)	
SES quintiles	Affluent	1	(-)	1	(-)	1	(-)	1	(-)
		0.59	(0.52-0.67)	0.83	(0.69-0.99)	0.45	(0.31-0.65)	0.53	(0.37-0.75)
	↓	0.71	(0.60-0.84)	0.58	(0.43-0.78)	0.33	(0.16-0.64)	0.70	(0.44-1.14)
		0.24	(0.18-0.31)	0.21	(0.13-0.33)	0.24	(0.11-0.53)	0.39	(0.21-0.73)
	Deprived	0.14	(0.10-0.21)	0.19	(0.10-0.33)	0.37	(0.17-0.79)	0.15	(0.04-0.48)

[a] All models show overdispersion that is not sufficiently accounted for by Poisson regression $\alpha \neq 0$ indicating that a negative binomial model is appropriate.

b) Lymphomas

		Types of lymphomas							
		Hodgkin's		Non-Hodgkin's		Burkitt's		Other lymphomas	
Model/Variables	**Range**	IRR	95%CI	IRR	95%CI	IRR	95%CI	IRR	95%CI
Model 1: SES class index									
Model fit: 3 df (*p* value)		259.90 (<0.01)		138.21(<0.01)		16.47 (<0.01)		16.34 (<0.01)	
SES classes	Affluent	1.28	(1.13-1.44)	1.38	(1.19-1.60)	0.81	(0.64-1.03)	1.39	(0.98-1.95)
	↓	1	(-)	1	(-)	1	(-)	1	(-)
		0.41	(0.34-0.50)	0.43	(0.33-0.57)	0.73	(0.53-1.01)	0.79	(0.45-1.37)
	Deprived	0.02	(0.00-0.11)	0.08	(0.02-0.27)	0.19	(0.06-0.61)	0.00	(0-.)
Model 2: Standard. SES index									
Model fit: 1 df (*p* value)		263.67 (<0.01)		132.07 (<0.01)		9.67 (<0.01)		9.81 (<0.01)	
ES standardised index	Continuous	1.31	(1.26-1.36)	1.28	(1.22-1.34)	1.10	(1.03-1.17)	1. 16	(1.05-1.29)
Model 3: Quintiles of standardised index									
Model fit: 4 df (*p* value)		323.42 (<0.01)		175.35 (<0.01)		24.62 (<0.01)		16.48 (<0.01)	
SES quintiles	Affluent	1	(-)	1	(-)	1	(-)	1	(-)
	↓	0.59	(0..51-0.67)	0.70	(0.59-0.83)	0.74	(0.56-0.98)	0.88	(0.60-1.30)
		0.46	(0.37-0.57)	0.54	(0.41-0.71)	0.93	(0.64-1.35)	0.56	(0.27-1.17)
		0.20	(0.15-0.27)	0.19	(0.12-0.29)	0.64	(0.41-0.99)	0.55	(0.26-1.13)
	Deprived	0.14	(0.09-0.22)	0.11	(0.05-0.22)	0.23	(0.10-0.52)	0.09	(0.01-0.71)

[a] All models show overdispersion that is not sufficiently accounted for by Poisson regression $\alpha \neq 0$ indicating that a negative binomial model is appropriate.

c) Central nervous tumours and other types of cancers

		Types of cases			
		Central nervous system tumours		Other types of cancer	
Model/Variables	**Range**	IRR	95%CI	IRR	95%CI
Model 1: SES class index					
Model fit: 3 df (*p* value)		155.02 (<0.01)		422.12 (<0.01)	
SES classes	Affluent	1.24	(1.09-1.42)	1.30	(1.19-1.42)
	↓	1	(-)	1	(-)
		0.43	(0.34-0.53)	0.52	(0.47-0.58)
	Deprived	0.20	(0.11-0.36)	0.16	(0.11-0.23)
Model 2: Standardised SES index					
Model fit: 1 df (*p* value)		152.93 (<0.01)		454.94 (<0.01)	
SES standardised index	Continuous	1.25	(1.20-1.30)	1.26	(1.23-1.29)
Model 3: Quintiles of standardised SES index					
Model fit: 4 df (*p* value)		200.85 (<0.01)		543.47 (<0.01)	
SES quintiles	Affluent	1	(-)	1	(-)
	↓	0.71	(0.61-0.82)	0.72	(0.66-0.79)
		0.54	(0.43-0.68)	0.62	(0.55-0.70)
		0.24	(0.18-0.34)	0.27	(0.23-0.32)
	Deprived	0.18	(0.11-0.28)	0.20	(0.16-0.25)

[a] All models show overdispersion that is not sufficiently accounted for by Poisson regression $\alpha \neq 0$ indicating that a negative binomial model is appropriate

6.2 Sensitivity analyses

6.2.1 Socioeconomic classes

Sensitivity analyses were conducted in order to understand how the SES classes variable and the year variable affects the resulting IRR. Therefore, the modal probabilities that were used to assign Governorates into their respective classes were introduced into the model in place of the SES classes. Table 6.2 presents the regression results.

It was found that modelling the modal probabilities for the SES classes had little to no effect on the resulting incidence of all cancers. The direction and significance of the associations in all groups have not changed.

Table 6.2: IRRs and 95% CI for Saudis aged <24 years diagnosed with cancer (1994 to 2008) associated with socioeconomic status using the negative binomial regression

		Types of leukaemias							
		Acute lymphoblastic		Acute myeloid		Chronic myeloid		Other leukaemias	
Variables [a]	**Range**	IRR	95% CI	IRR	95% CI	IRR	95% CI	IRR	95% CI
Model fit: 3 df (*p* value)		216.03 (<0.01)		88.29 (<0.01)		22.28 (<0.01)		22.65 (<0.01)	
Modal probabilities of SES	Affluent	1.36	(1.21-1.52)	1.25	(1.07-1.46)	1.27	(0.96-1.67)	1.50	(1.15-1.97)
	↓	1	(-)	1	(-)	1	(-)	1	(-)
		0.55	(0.47-0.65)	0.46	(0.35-0.61)	0.42	(0.24-0.72)	0.90	(0.59-1.37)
	Deprived	0.16	(0.09-0.27)	0.21	(0.09-0.45)	0.63	(0.25-1.57)	0.16	(0.02-0.92)
		Types of lymphomas							
		Hodgkin's		Non-Hodgkin's		Burkitt's		Other lymphomas	
Variables [a]	**Range**	IRR	95% CI	IRR	95% CI	IRR	95% CI	IRR	95% CI
Model fit: 3 df (*p* value)		256.07 (<0.01)		140.61 (<0.01)		17.68 (<0.01)		17.08 (<0.01)	
Modal probabilities of SES	Affluent	1.27	(1.12-1.43)	1.38	(1.19-1.61)	0.80	(0.63-1.01)	1.40	(0.99-1.97)
	↓	1	(-)	1	(-)	1	(-)	1	(-)
		0.41	(0.33-0.50)	0.44	(0.34-0.57)	0.73	(0.53-1.02)	0.81	(0.46-1.43)
	Deprived	0.04	(0.01-0.13)	0.07	(0.02-0.25)	0.18	(0.05-0.58)	0.00	(0.00-.)[b]
		Central nervous system and other cancers							
		Central nervous system				Other cancers			
Variables [a]	**Range**	IRR		95% CI		IRR		95% CI	
Model fit: 3 df (*p* value)		156.72 (<0.01)				423.14 (<0.01)			
Modal probabilities of SES	Affluent	1.25		(1.09-1.42)		1.29		(1.18-1.41)	
	↓	1		(-)		1		(-)	
		0.43		(0.34-0.53)		0.52		(0.47-0.58)	
	Deprived	0.19		(0.10-0.35)		0.16		(0.11-0.23)	

[a] All models show overdispersion that is not sufficiently accounted for by Poisson regression $\alpha \neq 0$ indicating that a negative binomial model is appropriate.

[b] The number of cases are too low to come up with reliable results

6.2.2 The effect of the large cities

The largest and most affluent Governorates in the country are Riyadh, Jeddah and Dammam (Appendix I and J). These three Governorates also have an excess of cases in almost all diagnostic groups. These three Governorates were excluded from the analysis to examine any differences in the IRRs. Table 6.3 presents the results from this analysis.

The removal of the three large Governorates had an immediate effect on the incidence in the most affluent classes for all leukaemias groups (Table 6.3a). The incidence dropped from a significant 1.38 (95%CI = 1.23 - 1.54) (Table 6.3a) to a non-significant 1.14 (95%CI = 0.98 - 1.33). No major changes were found in the most deprived classes. The results for AML and the other leukaemias group demonstrated a very similar trend to that of ALL. For CML however, the direction of the association of incidence in the most affluent class was reversed from positive to negative, although it remained non-significant. Furthermore, the removal of the large Governorates improved model fit, where the chi-square goodness-of-fit test was lower.

Table 6.3b gives the results for lymphomas. The incidence for NHL remains markedly increased in the most affluent class (IRR =1.31, 95%CI = 1.06 - 1.60). In the third model for all lymphomas, the pattern of incidence in the SES quintiles remains the same as the pattern in Table 6.2b.

The results for CNS and all other cancers groups are given in Table 6.3c. The incidences of both groups were non-significant in the most affluent class. However, for the lower middle class and the deprived class the incidence of both groups remain significantly reduced. Similar to leukaemias and lymphomas, the pattern of incidence in the third model for the SES quintiles remains the same for both groups.

This analysis shows that the large metropolitan Governorates play a major role in the increased and significant incidence of cancers in the most affluent classes. However, after the removal of these Governorates, there still appears to be a pattern of increased incidence in the affluent classes.

Table 6.3: IRRs and 95%CI for Saudis aged <24 years diagnosed with cancer (1994 to 2008) associated socioeconomic status in all Saudi Governorates excluding Riyadh, Jeddah and Dammam

a) Leukaemias

		Types of leukaemias							
		Acute lymphoblastic		Acute myeloid		Chronic myeloid		Other leukaemias	
Models/Variables [a]	**Range**	IRR	95% CI*	IRR	95% CI*	IRR	95% CI*	IRR	95% CI*
Model 1: SES class index									
Model fit: 3 df (*p* value)		140.03 (<0.01)		60.37 (<0.01)		12.65 (<0.01)		9.61 (<0.05)	
SES classes	Affluent	1.14	(0.98-1.33)	1.05	(0.83-1.32)	0.97	(0.63-1.50)	1.12	(0.73-1.71)
	↓	1	(-)	1	(-)	1	(-)	1	(-)
		0.55	(0.47-0.64)	0.46	(0.35-0.61)	0.42	(0.24-0.72)	0.90	(0.60-1.37)
	Deprived	0.17	(0.10-0.29)	0.19	(0.08-0.44)	0.65	(0.26-1.61)	0.13	(0.01-0.93)
Model 2: Standard. SES index									
Model fit: 1 df *(p* value)		166.51 (<0.01)		58.00 (<0.01)		13.15 (<0.01)		11.72 (0.01)	
SES standardised index	Continuous	1.24	(1.20-1.29)	1.22	(1.16-1.29)	1.19	(1.08 -1.31)	1.17	(1.07-1.29)
Model 3: Quintiles of standardised index									
Model fit: 4 df (*p* value)		237.50 (<0.01)		93.45 (<0.01)		29.61 (<0.01)		23.28 (<0.01)	
SES quintiles	Affluent	1	(-)	1	(-)	1	(-)	1	(-)
	↓	0.70	(0.60-0.80)	0.90	(0.74-1.11)	0.50	(0.33-0.75)	0.54	(0.36-0.82)
		0.79	(0.66-0.94)	0.66	(0.49-0.90)	0.40	(0.20-0.77)	0.72	(0.43-1.21)
		0.26	(0.20-0.34)	0.21	(0.13-0.35)	0.24	(0.10-0.55)	0.46	(0.25-0.87)
	Deprived	0.17	(0.11-0.25)	0.21	(0.12-0.39)	0.41	(0.19-0.90)	0.18	(0.05-0.57)

[a] All models show overdispersion that is not sufficiently accounted for by Poisson regression $\alpha \neq 0$ indicating that a negative binomial model is appropriate.

b) Lymphomas

		Types of lymphomas							
		Hodgkin's		Non-Hodgkin's		Burkitt's		Other lymphomas	
Models/Variables [a]	**Range**	IRR	95% CI	IRR	95% CI	IRR	95% CI	IRR	95% CI
Model 1: SES class index									
Model fit: 3 df (*p* value)		206.70 (<0.01)		101.93 (<0.01)		16.85 (<0.01)		9.12 (<0.05)	
SES classes	Affluent	1.13	(0.96-1.33)	1.30	(1.06-1.60)	0.74	(0.51-1.08)	0.94	(0.53-1.66)
	↓	1	(-)	1	(-)	1	(-)	1	(-)
	↓	0.41	(0.34-0.50)	0.43	(0.33-0.57)	0.73	(0.53-1.01)	0.79	(0.45-1.37)
	Deprived	0.02	(0.00-0.11)	0.08	(0.02-0.27)	0.19	(0.06-0.61)	0.00	(0.00-.)*
Model 2: Standard. SES index									
Model fit: 1 df (*p* value)		202.17 (<0.01)		105.82 (<0.01)		12.30 (<0.01)		5.82 (<0.05)	
SES standardised index	Continuous	1.31	(1.26-1.36)	1.29	(1.23-1.36)	1.13	(1.05-1.22)	1.16	(1.02-1.31)
Model 3: Quintiles of standardised index									
Model fit: 4 df (*p* value)		253.26 (<0.01)		137.23 (<0.01)		27.66 (<0.01)		10.27 (<0.05)	
SES quintiles	Affluent	1	(-)	1	(-)	1	(-)	1	(-)
	↓	0.60	(0.51-0.70)	0.74	(0.61-0.90)	0.63	(0.46-0.86)	0.86	(0.53-1.39)
	↓	0.48	(0.38-0.59)	0.55	(0.41-0.73)	0.80	(0.54-1.19)	0.66	(0.31-1.41)
	↓	0.22	(0.16-0.30)	0.20	(0.13-0.32)	0.60	(0.38-0.93)	0.66	(0.31-1.41)
	Deprived	0.15	(0.10-0.24)	0.12	(0.06-0.24)	0.21	(0.09-0.49)	0.12	(0.01-0.87)

[a] All models show overdispersion that is not sufficiently accounted for by Poisson regression $\alpha \neq 0$ indicating that a negative binomial model is appropriate.

c) Central nervous system tumours and other types of cancers

		Central nervous system tumours and other cancers			
		Central nervous system		Other cancers	
Models/Variables [a]	**Range**	IRR	95% CI	IRR	95% CI
Model 1: SES class index					
Model fit: 3 df (*p* value)		105.77 (<0.01)		319.79 (<0.01)	
SES classes	Affluent	0.90	(0.74-1.09)	1.12	(1.00-1.25)
	↓	1	(-)	1	(-)
		0.43	(0.34-0.53)	0.52	(0.47-0.58)
	Deprived	0.20	(0.11-0.36)	0.16	(0.11-0.23)
Model 2: Standard. SES index					
Model fit: 1 df *(p* value)		90.69 (<0.01)		342.88 (<0.01)	
SES standardised index	Continuous	1.22	(1.17-1.27)	1.25	(1.22-1.28)
Model 3: Quintiles of standardised index					
Model fit: 4 df (*p* value)		145.99 (<0.01)		414.38 (<0.01)	
SES quintiles	Affluent	1	(-)	1	(-)
	↓	0.80	(0.68-0.94)	0.83	(0.75-0.92)
		0.61	(0.48-0.77)	0.69	(0.60-0.78)
		0.27	(0.20-0.38)	0.30	(0.25-0.36)
	Deprived	0.20	(0.13-0.31)	0.23	(0.18-0.29)

[a] All models show overdispersion that is not sufficiently accounted for by Poisson regression $\alpha \neq 0$ indicating that a negative binomial model is appropriate.

6.3 Case ascertainment

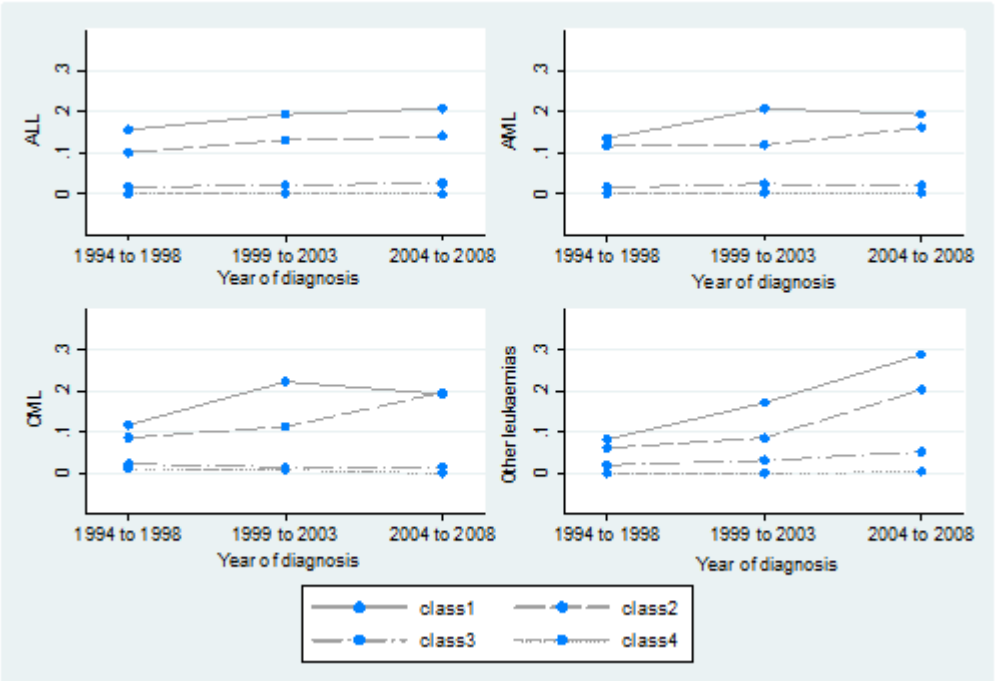
6.3.1 Proportion of cases over time

The very low IRR in the most deprived Governorates prompted the examination of case ascertainment of the Saudi Cancer Registry (SCR). Initially, the proportion of cases of each cancer category by socioeconomic class was plotted over time in three five-year blocks. These plots are shown in Figures 6.5a to 6.5c.

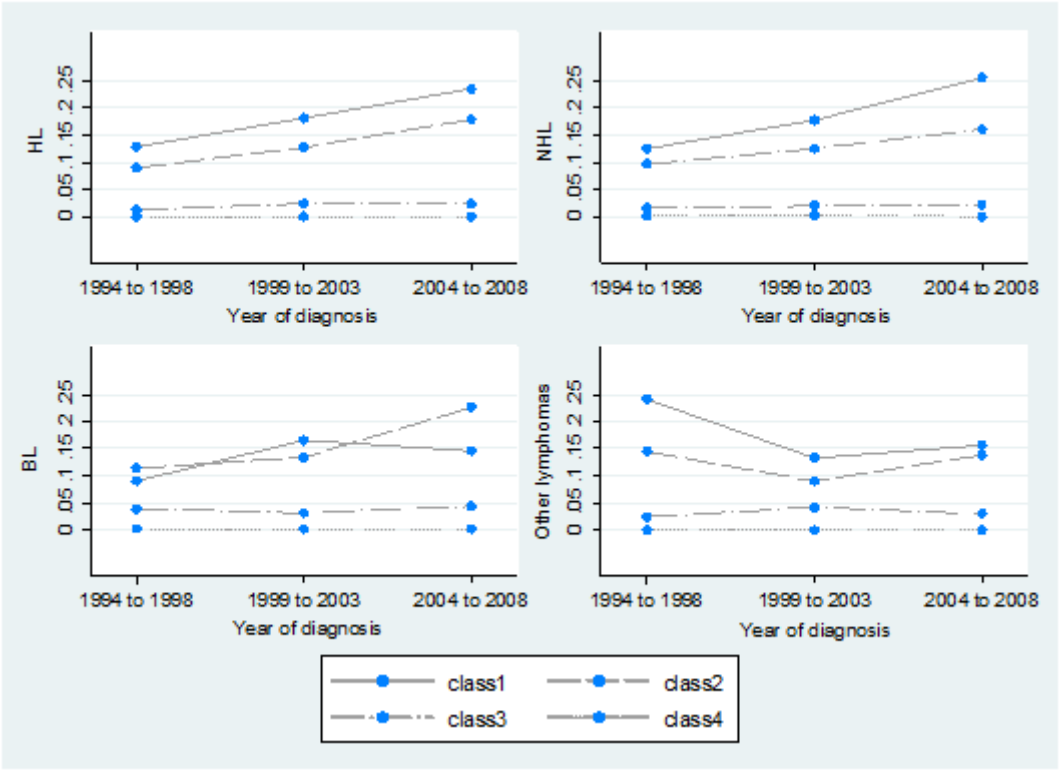
It can be seen that only ALL had a slight increase in Classes 1 and 2 (the more affluent Governorates) throughout the 15-year study period. However, a marked increase in Classes 1 and 2 was found for other leukaemias, HL, NHL, CNS and all other tumours group. For CML and BL, the proportion of cases increased to its highest peak in the period 1999-2003, and then slightly reduced in the period 2004-2008. However, Class 2 exhibited a steady increase in incidence in the period 2004 to 2008 that is equal to Class 1 for CML and higher than Class 1 for BL. It was revealed that only the proportion of the other lymphoma group for Class 1 and 2 decreased throughout the study period.

For Classes 3 and 4 that represent the lower middle class Governorates and the deprived Governorates, however, the proportion of cases was very low. Class 4 exhibited little to no change across the three time periods. Further, a large gap exists between the two upper classes and the two lower classes, which is marked in all cancer groups except for the other leukaemia groups.

a) Leukaemias



b) Lymphomas



c) Central nervous system tumours and other types of cancers

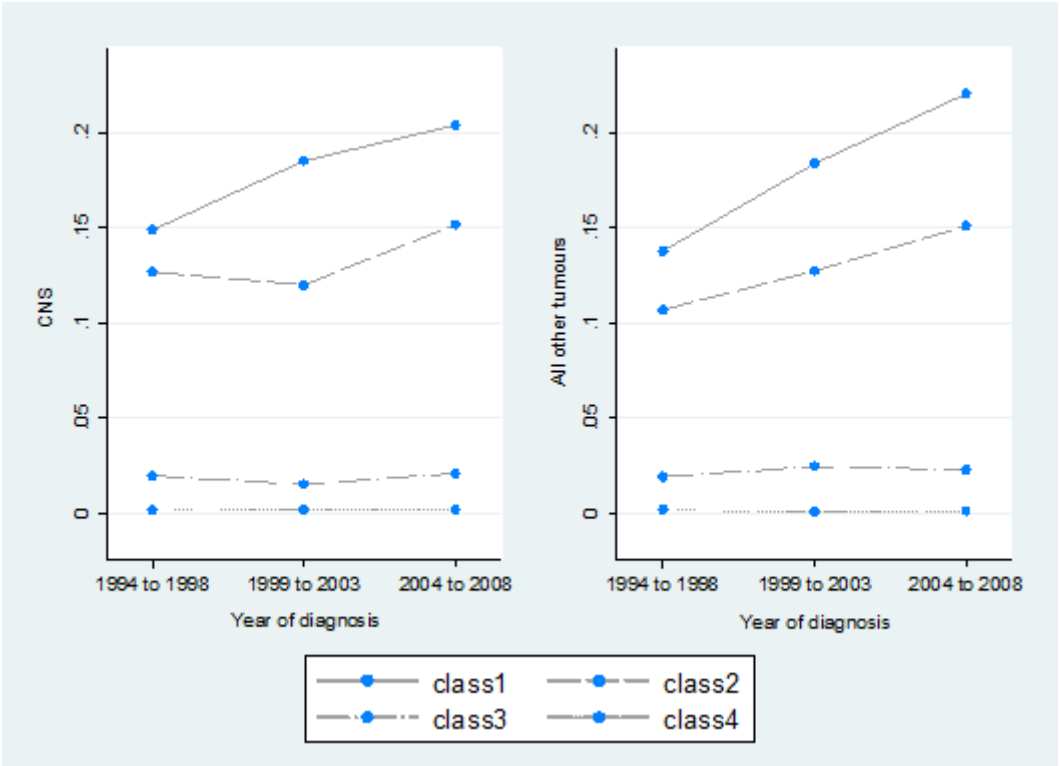


Figure 6.5: Proportion of cancer cases in Saudi Governorates by socioeconomic classes over time

6.3.2 Incidence rates by years

New cancer registries tend to have low case ascertainment in their early years. Figure 6.6 shows the incidence rates of all cancer categories year by year from 1994 to 2008, and Figure 6.7 shows the incidence rates of all cancer categories by the three five-year blocks. The figures show that the incidence rates are not stable, especially in the period between 1994 and 2003. However, a marked increase or reduction can be expected with just an additional case, as a result of the rarity of leukaemias and lymphomas. Nonetheless, the incidence rates are more stable in the years following 2003, except for ALL which shows further fluctuation.

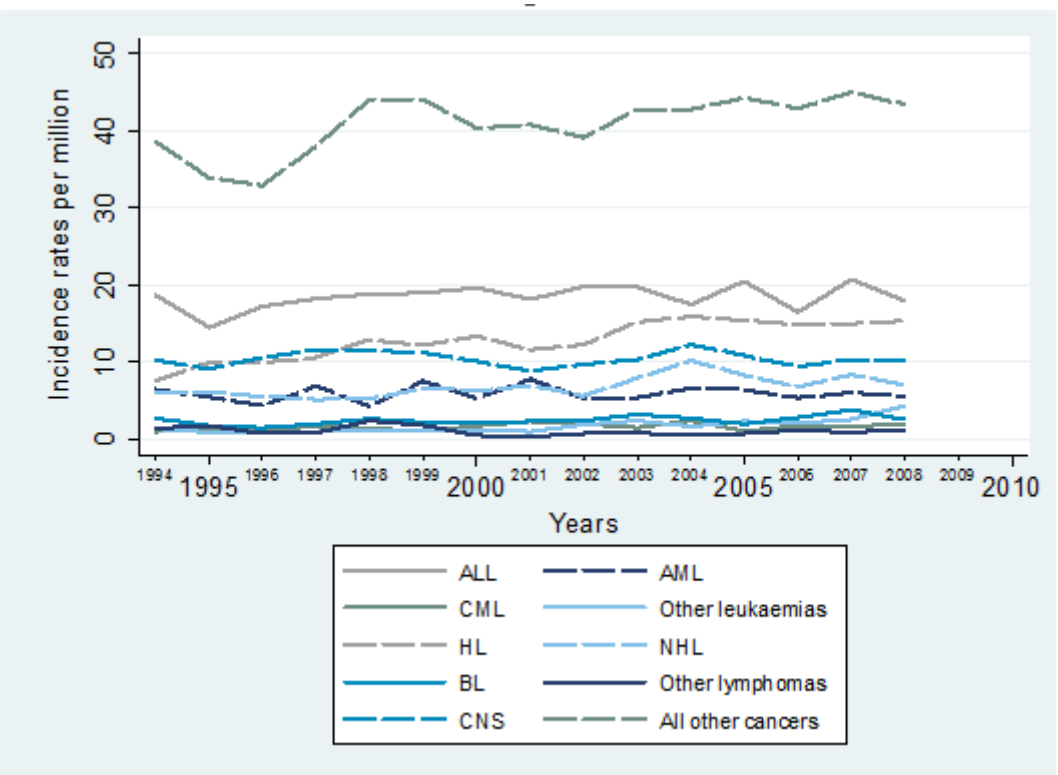


Figure 6.6: Incidence rates of childhood and adolescent cancers by year of diagnosis

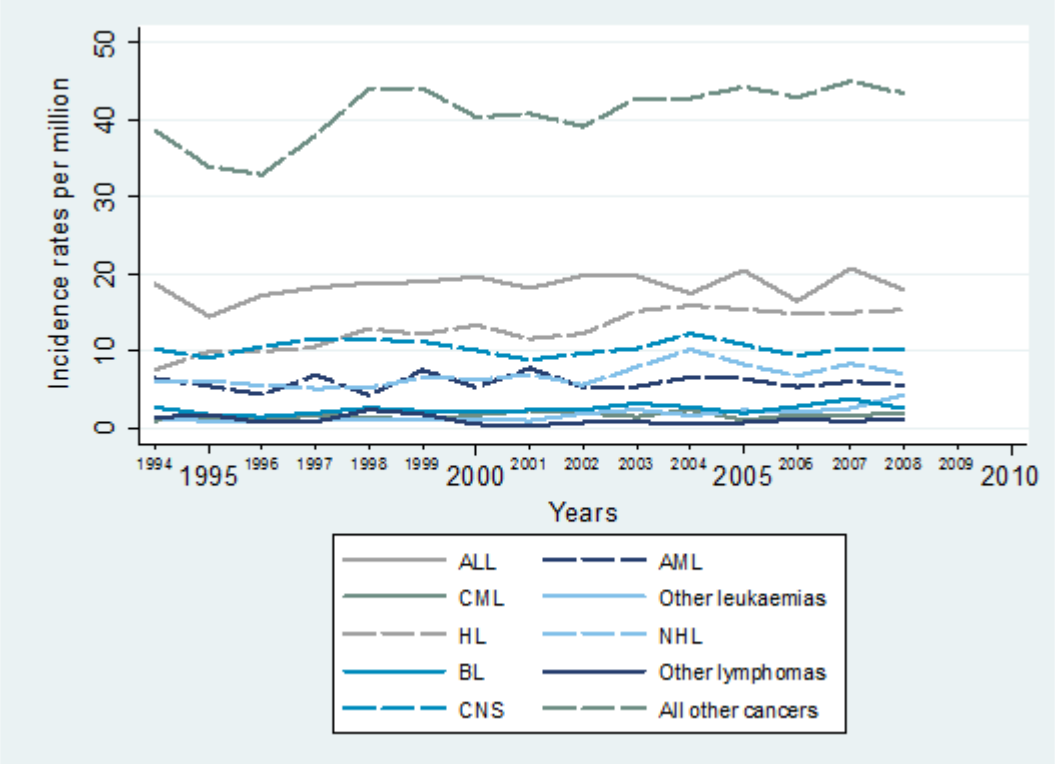


Figure 6.7: Incidence rates of childhood and adolescent cancers by three five-year blocks

6.3.3 Comparison with the US

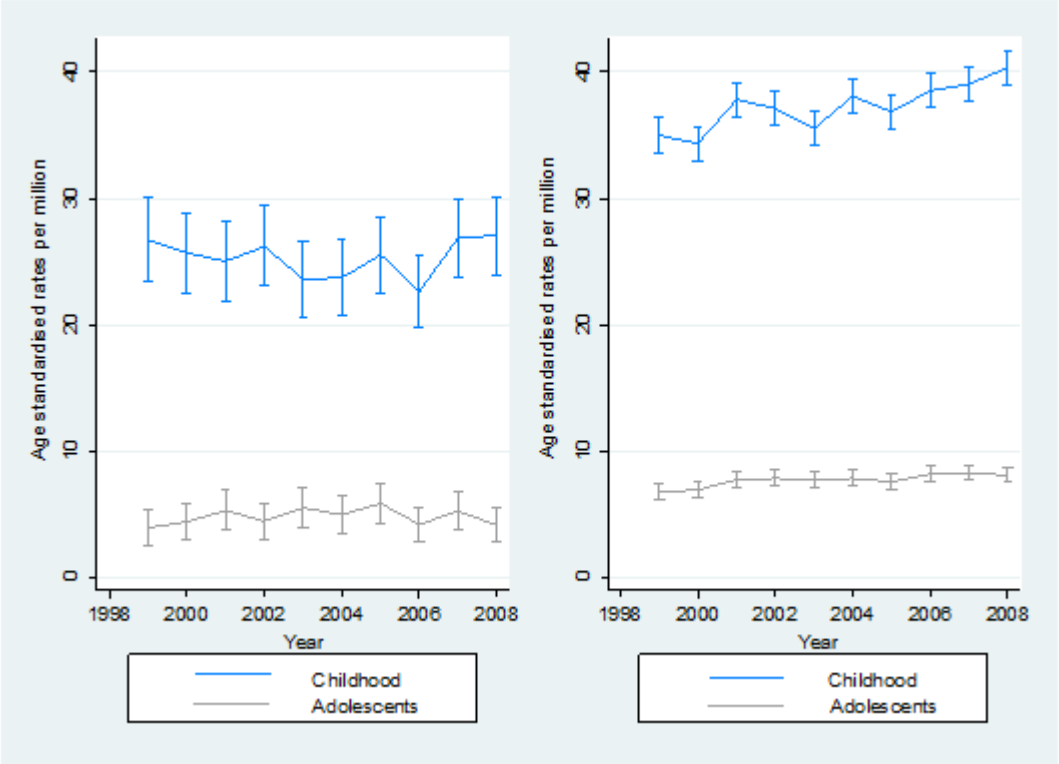
The age standardised incidence rates of cancers in Saudi Arabia between 1999 and 2008 were compared with those of the US and are shown in Figures 6.8 (a-d) along with their 95% CI. These rates are standardised to the US standard population. Figure 6.8a shows the age standardised rates for children and adolescent groups with leukaemias. For the US, a marked steady increase in incidence of leukaemia for both age groups is seen. However, for Saudi Arabia, although there is fluctuation in incidence, the rate is observed to be almost the same in 1999 as in 2008. Furthermore, the 95% CI is very wide rendering the results to be unreliable. The wide CI is likely to be the result of the very low numbers of cases.

Figure 6.6b shows the age-standardised incidence rates for lymphomas. It can be seen that there is a marked difference between the two countries. In the US, the age-standardised rates in adolescents and children are very close, also the fluctuation is minimal. However, in Saudi Arabia, a large gap in incidence between

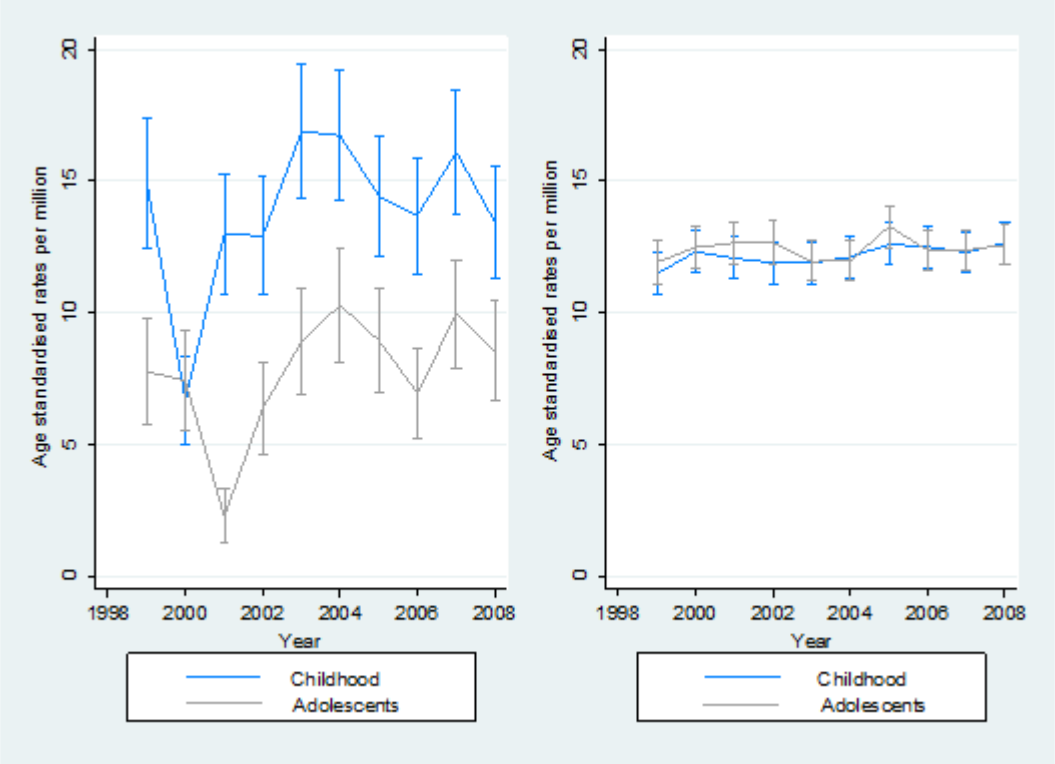
children and adolescents can be observed, as well as a large fluctuation by year of diagnosis. Furthermore, the wide CI is an indicator of the low number of cases.

Figures 6.8c and 6.8d show the rates for CNS and the all other cancers group. The rates in Saudi for both age groups are lower than for the US. In addition, there is a marked reduction in the incidence for the childhood category for the other cancers group in the year 2000 in Saudi, however, in the US the incidence increases.

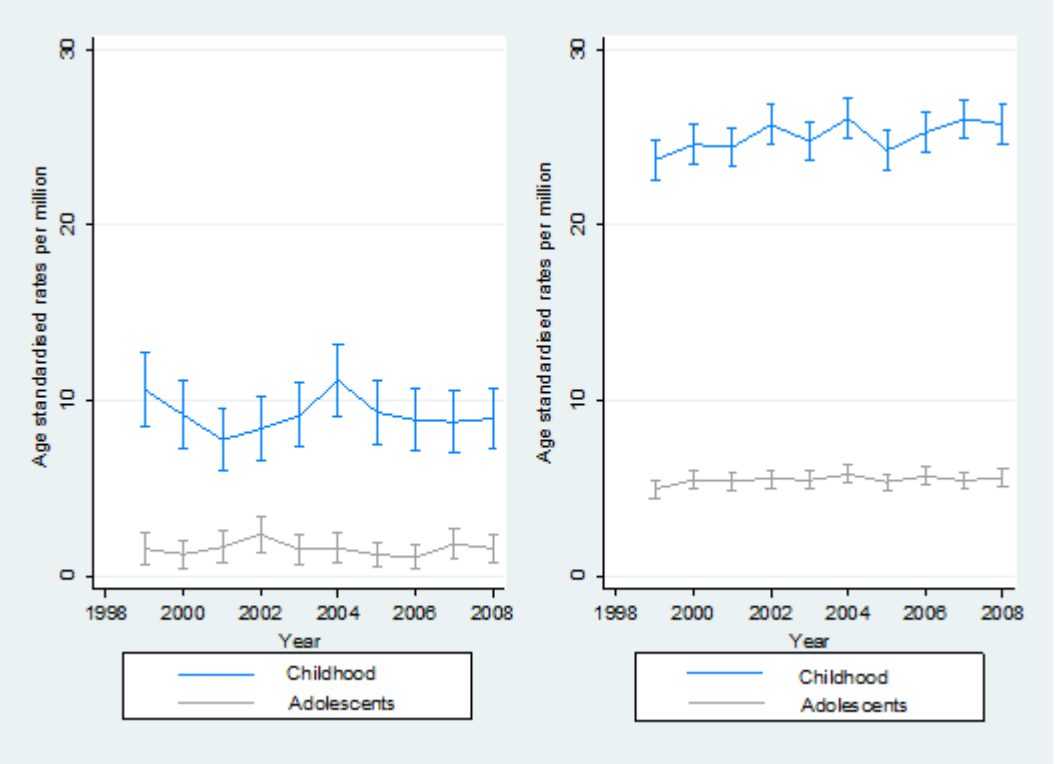
a) All leukaemias



b) All lymphomas



c) Central nervous system tumours



d) All other types of cancers

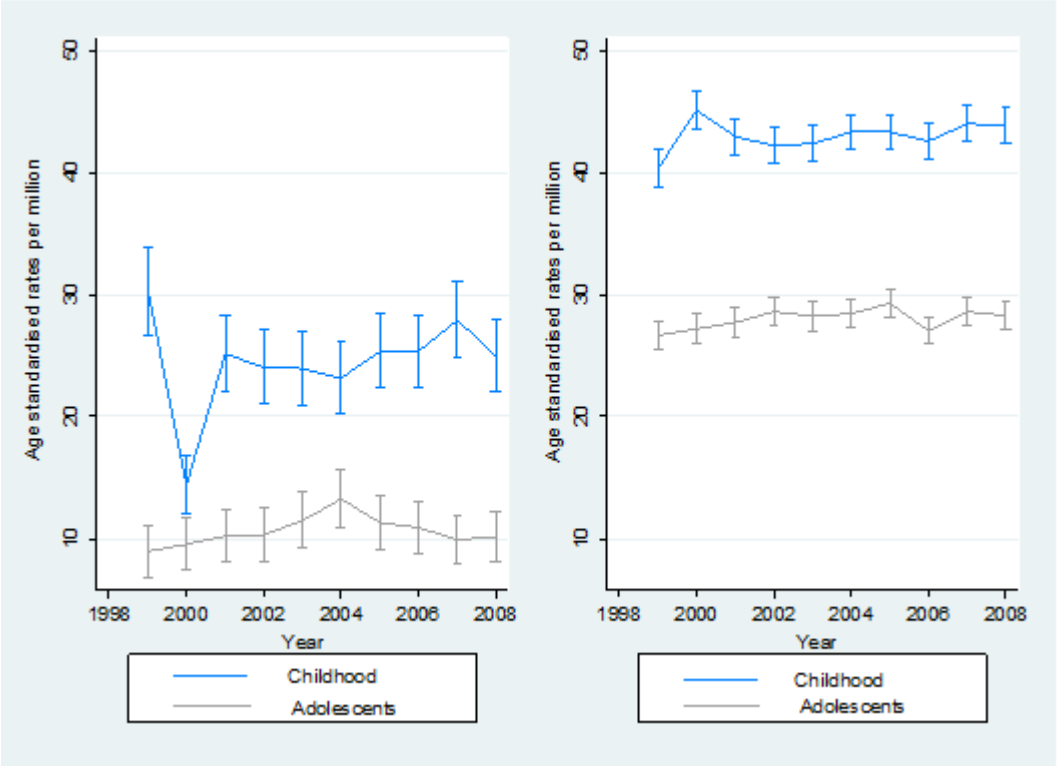


Figure 6.5: The age-standardised rates of cancers in under and over 14 years of age for Saudi Arabia (left) and the United States (right) standardised to the US standard population

7 Discussion

7.1 Discussion of results

This study is the first to quantify childhood and young adult cancers in Saudi Arabia as a separate group. It is novel in that it analysed incidence in these groups over a period of 15 years from 1994 to 2008, as well as derived two area-based measures of SES for Saudi Arabia that were used in the subsequent analysis to address the effects of SES and PM in terms of Hajj. These indices may also be used in other health and social research studies. The results from this thesis address the aims set out in Chapter 1.

- **Describe the pattern of incidence of childhood and young adult cancers particularly leukaemias, lymphomas and central nervous system (CNS) tumours across Saudi Arabia, as well as produce international comparisons.**

This study has successfully quantified the incidence of cancers in these age groups for all diagnostic groups defined by the ICCC-3, as reported to the SCR between the years 1994 and 2008. Incident cases and incidence rates reported revealed that incidence of cancers was more pronounced in males specifically for leukaemias, lymphomas and CNS tumours in the 0-4 age group. The most common diagnostic group reported for both genders was leukaemias, with higher cases found in the 0-4 age group, which is similar to international patterns of incidence (Stiller, 2007, Valery et al., 2014, Stiller and Parkin, 1996).

This study has also been successful in producing international comparisons for the three main diagnostic groups through direct age-sex standardisation using three different standard populations, i.e. World standard, European standard and the US standard. The rates for ALL were higher when standardising to the Saudi population. This may be a result of the relatively younger population of Saudi Arabia, where cancer incidence is mostly accounted for by ALL. There are slight differences in rates when using different standard populations, due to the different age structures. For example, the European standard gives equal weights for ages 5 to 54 and the US standard gives more weight to older age groups. This explains the larger differences found when standardising to the US standard population, especially for the leukaemias group.

It has been possible to compare these findings with a previous study that computed age-sex standardised rates for children and young adults aged less than 24 years in Northern England, and also standardised to the world standard population (Feltbower et al., 2009). For ALL, AML, HL and NHL the age-sex standardised rate in Northern England was markedly higher than in Saudi (26.9, 7.6, 14.7 and 9.5 per million compared to 17.86, 5.89, 13.10 and 6.98 per million, respectively). These differences are likely to be due to comparing an economically developed country with an economically developing country, where incidence is higher in developed countries, where higher levels of hygiene and social isolation are found due to higher levels of affluence (Jemal et al., 2011). It should be stressed that underlying factors associated with behavioural factors and social lifestyle may have also contributed to the difference, although this is less likely in younger cancer sufferers. Under reporting due to poor case-ascertainment or under-diagnosis could have played a role in these low rates.

- **Aim 2: Describe the geographical variation in incidence of these cancers.**

This study aimed to describe the variation in incidence of leukaemias, lymphomas and CNS tumours in children and young people within the first 15 years of reporting by the SCR, and has successfully achieved this aim. For each diagnostic group the SIRs were calculated and mapped for all of the 118 Governorates of Saudi Arabia. The maps showed little discernible pattern prior to smoothing, whereby 14 Governorates had an SIR of zero due to no observed cases being reported within them for all diagnostic groups. These Governorates are Badae, Dayer, Dhurma, Ghazalah, Harth, Kamel, Khabash, Kharkheer, Oyoon Jawaa, Quraa, Rejal Almaa, Thaar, Thadeq and Yadmah. All have one common attribute in that they are geographically small rural areas with small population sizes. This suggests that under-reporting and/or under-diagnosis may have played role. In general, one might assume that Governorates in close proximity to each other will have similar SIRs thereby revealing a pattern of incidence. However, the maps of crude SIRs did not reveal any discernible pattern which necessitated spatial smoothing.

Furthermore, for all diagnostic groups Governorates with larger population sizes such as Riyadh, Jeddah and Dammam showed constantly high SIRs. This is more likely to be due to statistical rather than biological phenomena. The extremely high numbers of observed cases compared to the expected cases in these three Governorates is likely to be due to the availability of referral centres that offer

patients from outside these Governorates cancer-related care, especially for the Riyadh Governorate. Consequently, these patients provide a temporary address as being one of the three Governorates rather than their permanent address, hence leading to misclassification bias. This could potentially cause an overestimate of the IRRs in these Governorates, and an underestimate in the rural Governorates.

This observation is further supported by the fact that other Governorates with high SIRs are the capital Governorates of their relative Provinces. Each of the 13 provinces in Saudi Arabia is made up of several Governorates, one of which is named the “Amarah” or the capital of that province. This capital Governorate is highly populated compared to the rest of the Governorates within that province, and provides secondary health care services. It is not uncommon for patients to report the capital Governorate as their place of residence rather than the actual ‘rural’ Governorate. These capital Governorates include Baha, Arar, Hail, Jazan, Najran, Abha, Buraidah, Skaka, Tabuk and Makkah. All were found to have moderate to high SIRs for all diagnostic groups.

Furthermore, it can be demonstrated that there are considerable differences in incidence across Governorates, which may reflect under-ascertainment or under-diagnosis, especially in rural areas, which may be due to limited geographical access to health services.

There have been no comparable studies in the mapping of childhood and young adult cancers in Saudi Arabia. Only two studies have examined the geographical distribution of cancer incidence in Saudi Arabia by utilising data from the web-based atlas developed in 2013 (Al-Ahmadi and Al-Zahrani, 2013a, Al-Ahmadi, 2013, Al-Ahmadi and Al-Zahrani, 2013b). However, both looked at only the most common types of cancers reported between 1998 and 2004, and did not make it clear which age groups were represented. Most importantly, the rates were computed in cities only, not in all 118 Governorates and these rates were only crude, thus no indirect age-sex standardisation was performed. Consequently, these studies are not comparable to this work which has mapped indirectly estimated age-sex standardised rates of childhood and young adult cancers. Indirect rates should be used when making internal comparisons, for example when comparing the Governorates to each other.

- **Construct indices of SES, to be used in future research as well as in the subsequent analyses in this study, to adjust for the socioeconomic position of the Governorates under examination.**

This project has succeeded in producing two area-based measures of SES for the 118 Governorates of Saudi Arabia, which have been mapped for comparison. The two replicable indices of SES have been formulated using multiple socioeconomic indicators available from the 2004 national census data. These have shown that 8 out of 11 Governorates within the Eastern province are within the most affluent Governorates of the country. These are Qatif, Khobar, Rass Tanourah, Jubail, Dammam, Bqeeq, Ahsa and Khafji. The Eastern province hosts five major universities within the country, as well as ARAMCO, one of the world's largest oil companies. The Jubail Governorate in the northern part of the Eastern province is the largest industrial city in the Middle East. Therefore, it is logical to find these Governorates to be within the most affluent, especially when the Eastern provinces are the gateway to the rest of the Gulf countries. The major cities in the country, such as the capital Riyadh and Jeddah, as well as some of the capital Governorates of provinces such as Arar, Skaka and Buraidah, were also within the affluent ranking in the two indices.

The selection of indicators was extremely important. The analysis began with a close examination of what had been chosen to formulate indices in other countries. For example, the Townsend and Carstairs indices in the UK (Townsend et al., 1988, Carstairs and Morris, 1991), as well as the index in Italy (Tello et al., 2005) all utilised indicators available from national censuses. In contrast to the Saudi census, the censuses used in formulating these indices included indicators such as unemployment and overcrowding. Although the Saudi census does have a variable for employment status, this variable only shows the proportion in the labour force, and this includes the proportion of the population who are available for work, hence both employed and unemployed are included in that variable. Furthermore, the Saudi census collects information on the number of rooms per household, therefore the information necessary to create an overcrowding variable was available, but was not used to derive it. Thus, a decision was made that balanced what had to be included and what was available and accessible from the census.

Interestingly, the loadings of the variables on each factor show that the first factor labelled as 'Middle class' has better qualified constituents than Factor 2 'Affluent class' in terms of education. This is culturally justified where the highly educated are not usually wealthy, and the wealthy are not highly educated. Furthermore, the

student indicator had a dichotomy on two factors: Factor 2 labelled as ‘Affluent class’ and Factor 3 labelled as ‘Deprived class’. A Governorate that has a high proportion of students may indicate that it is either affluent or poor. This indicator covers the population aged greater than 15 years. Therefore, it includes both university students and mature students (over 21 years old) returning to schools to gain better jobs. Both of which may explain why the indicator loads highly onto the two factors.

Similar to the Townsend index (Townsend et al., 1988), the final numerical value assigned to each Governorate in the standardised index does not measure a specific object. The value provides an abstract measure of deprivation that is used to rank these Governorates. The standardised index method has been used to develop an index for Canada (Kishnan, 2010), India (Sekhar et al., 1991, Antony and Visweswara Rao, 2007), Japan (Fukuda et al., 2007) and the State of Mississippi in the USA (Hightower, 1978). However, none of these studies attempted to reconstruct the index using another statistical method for extra validity. The LCA approach was chosen to construct categorical classes of SES to be used in future analyses; hence, Saudi researchers have the choice between a continuous or a categorical index.

The study further explored the distribution of the two indices numerically and geographically, and showed very minor differences between them, adding further support to the pattern of affluence in the country. These indices can be added to Saudi disease registries such as the SCR, as well as for administrative purposes.

Since this is the first project to derive indices of SES, there are no comparable studies in Saudi Arabia or in the Gulf region, an area which is known for its wealth and high income per capita. In Kuwait, it was suggested that a person’s connectedness may be used as a surrogate for social class, rather than deriving a measure for SES, since it is considered a city state with very few areas that may be defined as truly rural or poor (Shah et al., 1999). This is not the case for Saudi Arabia, as it is a vast country with several Governorates considered extremely rural, and which lack higher educational institutions and specialised health organisations. It is a common perception that these rural areas are considered more deprived, whilst urban areas are the most affluent. This perception has been verified by these newly developed indices.

Comparing the results of these indices with those of Townsend and Carstairs (Townsend et al., 1988, Carstairs and Morris, 1991), which are usually calculated on the census ward level, it is seen that rural wards had lower scores indicating less

deprivation and urban areas had higher scores indicating more deprivation. In Saudi Arabia, however, rural areas had lower scores in the standardised index and were categorised as either the 'lower middle class' or 'most deprived class' in the categorical class index. Although it is important to remember that these indices are methodologically different and there were differences in the indicators chosen for analysis. It is one of the social characteristics of Saudi Arabia to centralise in one specific area that includes higher educational and specialised health services. These areas are often associated with more job opportunities for the unemployed, and usually have more economical and financial opportunities for those interested in business. Therefore, these areas are usually characterised by affluence.

The Saudi government has aimed to address centralisation in the large cities of the country. For example, very recently in 2013 work was done to develop the 'Waad Alshamal' industrial complex costing over £360 million, 25 kilometres from the rural Governorate of Toraif in the North. The complex will include seven world-scale phosphate processing plants and will create no less than 22,000 jobs (Bechtel, 2013). Also, the King Abdullah University of Science and Technology was developed in 2010 close to the non-urban Governorate of Rabegh on the west coast (KAUST, 2015). Such initiatives may alter the pattern of affluence, therefore, an update of the indices with the next published census may show changes, especially in these two areas.

- **Examine the effect of SES and Hajj on the incidence of childhood and young adult cancers in Saudi Arabia and interpret the findings in relationship to the PM hypothesis.**

After describing the variation in incidence and deriving measures of SES, this project then attempted to determine the effect that SES and Hajj might have on the incidence of these cancers. The main findings of this work are that Hajj as a measure of PM had no significant effect on any of the diagnostic groups, particularly ALL, NHL and CNS tumours, and that incidence was higher in affluent Governorates.

These findings are not supportive of the PM hypothesis as suggested by Kinlen (1988); they do however support the concept of herd immunity (Anderson and May, 1990), in which continuous mixing prior to the exposure of infection confers protection against leukaemia. The Hajj is a unique measure of PM, as it is an event that has been going on for over 1,400 years. Hence, people residing within Makkah are likely to have established herd immunity and have a primed immune system

due to continuous exposure to infections brought by pilgrims, in particular children who are continuously exposed to these infections in their early life.

For the ALL subtype, NHL and CNS tumours a linear association with SES was found where incidence was highest in the most affluent areas, compared to the most deprived. In comparing these results with those of others in the UK, it should be stressed that the rural areas in the UK are the most affluent, whilst in Saudi these areas are deprived. In light of this, this study is in agreement with that of others in England for children and young adults (Dickinson et al., 2002, Van Laar et al., 2014, Law et al., 2003) and in Yorkshire (Parslow et al., 2002). Furthermore, this association was observed in studies dealing with childhood DM, which is a disease thought to be parallel to ALL in terms of underlying aetiology and geographical distribution (McKinney et al., 2000, Feltbower et al., 2005). This association was found even after eliminating the three major Governorates of Riyadh, Dammam and Jeddah which were within the most affluent Governorates and had high SIRs.

These findings are supportive of the hygiene hypothesis (Strachan, 1989). If this hypothesis was operating, then affluent areas would have higher rates of cancers, particularly ALL which was demonstrated to be the case even after eliminating the most highly affluent areas. Also, the delayed infection hypothesis put forward by Greaves (1988) specifically relates to the childhood ALL subtype (but similar associations were found for NHL). These findings do not suggest an in utero event for ALL, however, the negative association between ALL and PM is consistent with the delayed infection hypothesis, where exposure to infections in early life is necessary to prime the immune system against abnormal responses to infections, whether symptomatic or asymptomatic (Wiemels et al., 1999a, Greaves, 1997). On the other hand, it is unlikely that this is the only explanation for the marked association between ALL and NHL incidence and affluence. Factors such as poor case-ascertainment and/or limited access to health organisations are believed to have played a role in the highly rural areas. However, these findings warrant further investigation.

It should be noted that these findings were not able to clearly distinguish whether deprivation or the rurality of these deprived Governorates played a role in the observed association. According to both the PM (Kinlen, 1988, Kinlen, 1995) and delayed infection hypotheses (Greaves, 1997), susceptibility is conferred upon individuals who are isolated either geographically, i.e. residing in rural areas, or socially due to higher affluence. It should be noted that no Governorate is truly

isolated as there is a massive network of modern roads linking all parts of the country. The present study did not identify rural and deprived areas with a higher incidence of cancers, only affluent urban areas. This is in contrast to previous studies, such as that of Law et al. (2003) and Dickinson et al. (2002) in England, who found a non-significant elevated risk of both childhood ALL and NHL in rural areas. It is more likely however, that affluence has contributed more to these results, as it is the only common denominator between the urban areas in Saudi and the rural areas in the UK studies. Unfortunately, this study lacked data on the level of urbanicity of Governorates. Population-weighted population density was not available (Dorling and Atkins, 1995), and the use of normal population density was not appropriate for the purposes of this work, since populations are often centralised in one area of a Governorate, thus that data would not appropriately measure the density at which individuals live. Other unmeasured confounders may have also contributed to these results.

This work should be compared to previous studies with caution. Although the results were similar, it should be taken into account that the measure of PM used here is different in a few aspects. First, Hajj is an annual event that is confined in both time and space, as it takes place in a small geographical area and takes only five days to perform. Therefore, it is different to previous measures of PM, which measure migrants or commuting, as these are more permanent in nature. Furthermore, this work should not be compared to studies by Kinlen that retrospectively examined crude measures of PM in relatively isolated populations, since Makkah is a highly urbanised Governorate and the study included all 118 Governorates of Saudi Arabia, thus did not focus on clusters of leukaemia. This study provides support to the debate that the variation observed in the incidence of ALL and NHL may be attributed to early exposure to infection, for which Hajj may play a major role.

The pattern of incidence of AML, HL and CNS tumours does not follow that of ALL and NHL. Although incidence was highest in the most affluent Governorates, the association was not linear across the rest of the SES categories. There is no plausible explanation for these findings, although they do warrant further investigation on a more refined geographical scale. The estimates for CML, other leukaemias group, BL and other lymphomas group give little information due to small numbers.

The marked association with SES has raised suspicions about case-ascertainment especially in the rural/deprived Governorates. Hence, case-ascertainment was

explored to the extent available by the cancer data by plotting the proportion of each diagnostic group by SES by year. The findings further point towards poor case-ascertainment in these areas where the proportion was very low regardless of the year of diagnosis. Plotting incidence rates by year, the rates were found to be more stable following the year 2003, which may indicate improvement in reporting of cases. Furthermore, age standardised rates for the two groups of children aged 0-14 and young adults aged 15-24 in both Saudi Arabia and the US standardised to the US standard population showed marked differences. First, the rates in Saudi, especially for lymphomas and other types of cancer, were unstable and were accompanied by relatively wide CIs particularly for lymphomas, which may reflect the low number of cases for that group. For these two groups of cancers, there was a drop in incidence in 2001 and 2002 that could only be explained by issues of poor reporting or under-diagnosis. Although, there may well be true differences in incidence between the two countries, where one is developed and the other is developing. Only one study explored case-ascertainment in one major hospital in Riyadh during the first year of reporting, using the capture re-capture method, and found that the overall rate of case-ascertainment was only 68% (Al-Zahrani et al., 2003). This rate is very low compared to international cancer registries, for example in the Netherlands case-ascertainment of three major registries found an overall rate of 98.3% (Schouten et al., 1994), and in the UK case-ascertainment was higher than 99% (Kroll et al., 2011a). However, these are relatively old registries, whilst the study on the SCR ascertainment only focused on the first year of reporting. No other data study has explored case-ascertainment in later years to check for possible improvement. The established methods for case-ascertainment such as capture-recapture and independent case-ascertainment were beyond the scope of this work.

7.2 Discussion of data sources

7.2.1 Data from the cancer register

The (Saudi Cancer Registry) SCR is the only source of data that has been used to investigate environmental risk factors proposed in the aetiology of cancers. The registry collects data on cases of all ages diagnosed with cancer while resident within Saudi Arabia. The process of data collection continues prospectively, and the registry has reported more than 135,000 cases throughout the period 1994 to 2008. The topography, morphology and other diagnostic details of cases are collected from hospital medical records, histopathological reports and death records by trained registrars. The quality of population-based registries depends on both the completeness and validity of the data. The major challenge the registry is facing concerns incompleteness of medical records, completeness of ascertainment and acquiring qualified oncology registrars. A further challenge is that many patients seek medical treatment in the larger cities such as Riyadh, Jeddah and Dammam where there are more specialised hospitals, thereby only reporting their temporary address. This greatly increases the rates in these Governorates which do not reflect the underlying rates of disease at a geographical level (Al-Eid et al., 2007a).

A population-based registry such as the SCR should aim to report every single case occurring within its catchment area, i.e. within the borders of Saudi Arabia 100% case ascertainment should be achieved. For Saudi Arabia, the level of case ascertainment for the cases reported from all regions of the country is yet to be examined. There has been only one attempt at examining case ascertainment of cancers reported to the SCR for the year 1994, and this used the capture-recapture method for one major referral hospital in Riyadh. The study concluded that the ascertainment rate from medical records was 51%, from pathology reports the rate was 53% and from death certificates the rate was 17%. The study also concluded that the overall rate from all sources was 68%. These results are not surprising considering these rates were taken for the first year of actual reporting (Al-Zahrani et al., 2003).

There are several methods to check for the validity or quality of the collected data, such as re-abstracting and re-coding a sample of the data to ensure that none are invalid. In any case, each registry should develop its own internal checks for ensuring the validity of their data. For the SCR, these checks include verification of site and morphology data, as well as case linkage between a tumour and a patient (Al-Eid et al., 2007a).

Relevant to this work is patient addresses. The addresses obtained from patients are largely P.O. boxes that are centralised which do not indicate the actual geographical location of patients; this data is not disclosed for patient confidentiality reasons. The location of patients, however, in the majority of cases was given at a Governorate level, or sometimes at a district level. It is not likely that during the data collection process there was a requirement to give the exact location of patients. Therefore, it was structurally impossible to obtain data on a finer geographical scale. This is very different to data from the UK cancer registry which provides data on several geographical levels.

7.2.2 The census data and the Hajj data

To date, five censuses have been conducted in Saudi Arabia by the Central Department for Statistics and Information (CDSI), these were in 1962, 1974, 1992, 2004 and 2010. The first census of 1962 is rarely used officially as it did not cover the entire population, but the second census of 1974 is considered the first comprehensive census in Saudi history (CDSI, 2004a). There are no official statements about the coverage of the censuses conducted in the later years. Although, the population figures between 2004 and 2010 are consistent with natural increase figures, indicating that the population figures for 2004 are valid (Bel-Air, 2014).

For the Hajj data, the number of foreign pilgrims entering the country is assumed to be 100% accurate, since Saudi customs require a Hajj visa. However, the validity of the number of pilgrims from within the country has not been officially reported.

7.3 Discussion of methods

7.3.1 Disease classification

The published reports of cancer incidence from the SCR are only based on the ICD-10 classification, rather than on the ICCC-3 classification for the childhood category. This is not best practice, because for the childhood population (less than 15 years of age) classification of cancers should be based on histology rather than topography, therefore the ICCC-3 classification is more suitable for that age group as it also permits international comparisons to be made. For the adolescents and young adults group (aged between 15 and 24 years), the Birch et al. (2002) disease classification was produced; this takes into account the most frequent cancers occurring within this age group and those that are rare in children, such as carcinomas (Birch et al., 2002).

Although the current study targeted patients of less than 25 years of age, which includes both children and young adults, it used the ICCC-3 classification, primarily for two reasons. First, any classification system should represent the most important age groups numerically, and that was the childhood population. Secondly, the use of one rather than two classifications ensures consistency in analyses and interpretation.

7.3.2 Geographical mapping

Examination of geographical patterns of disease incidence is one element of the classic triad in descriptive epidemiology of time, person and place. Place is a surrogate for environmental, lifestyle and possibly genetic factors that may underlie patterns of occurrence of a disease across populations. Geographical mapping conveys direct visual information on the spatial distribution of a disease and can easily identify subtle patterns that may be missed if the same data is presented in a tabular form.

Of importance is selection of the appropriate administrative unit for mapping. This study used Governorates as the administrative unit for mapping, which was mainly due to the fact that measures of PM are by definition on an area level. Also, there were data limitations of the SCR on smaller geographical levels and data accessibility of the census data. In addition, the selection of appropriate data classifications within the maps is extremely important. The ArcGIS mapping software offers several types of classification schemes such as equal interval and quantiles. The classification method used in this work was the quantile method,

which placed equal numbers of Governorates into each of five classes i.e. fifths. Therefore, each class contained 20% of Governorates. Quantiles are often preferred over other methods in the mapping of epidemiological and disease data for the simplicity and intuitiveness in map reading (Brewer and Pickle, 2002). The spatially smoothed maps share the same legend as the non-smoothed to aid in map comparisons and interpretation.

Disease mapping in Saudi Arabia is a relatively new field. Interest has recently been sparked with the development of a web-based cancer atlas for Saudi Arabia in 2013, which is yet to be made available for public use (Al-Ahmadi, 2013). The atlas however, is limited to cancer data between 1998 and 2004, and only includes incidence rates and age-standardised rates to the world standard population. Also, the atlas is limited by only including the most common types of cancer reported by the SCR. This study is the first to geographically map SIRs of all major ICCC subgroups of disease categories that were reported to the SCR, from the first year of cancer reporting in 1994 to 2008, for a well-defined young adult population, as well as the first to ever apply spatial smoothing to these rates.

7.3.3 Possible drawbacks of disease mapping

Although the SIR was chosen as a risk estimate for disease occurrence in the Choropleth maps, it must be noted that it does not imply absolute risk. It merely compares the number of observed cases to the number of expected cases calculated from the age-sex specific incidence for a specified area. The SIRs are easily understandable and more precise than crude incidence rates (Esteve, 1994). However, similar to other risk estimates, this method may suffer from chance variations in incidence, especially in Governorates with very low numbers of observed cases. This is a particular problem when dealing with rare diseases, where thousands of individuals are required before one single case is expected occur (Bruce et al., 2013). This leads to spuriously highlighted high or low areas of risk. In this study, despite the fact that the geographical unit is relatively broad, i.e. Governorates, and the study spanned a period of 15 years between 1994 and 2008, some Governorates have extremely low numbers of cases, and 23 had no cases at all. Also, some Governorates have very low population numbers. Therefore, some degree of chance variation may be found. In fact, the CIs of some SIRs include unity, hence a chance variation does exist.

Therefore, the standard statistical method of spatial empirical Bayes smoothing was used, as that takes into account the very low population numbers, thus adjusting

the SIRs by shrinking them to the means of the neighbouring Governorates. This decreases the likelihood of presenting unusually high or low risks and reveals patterns that would have been otherwise missed (Clayton and Kaldor, 1987). Therefore, with the use of smoothing to correct for small population numbers, the advantages of the SIRs as a comparative method outweigh its potential limitations.

7.3.4 Exploratory factor analysis

In the process of deriving indices of SES, EFA was chosen because it does not require *a priori* hypothesis about the data, in fact it is used to formulate hypotheses (Fabrigar and Wegener, 2012). Since this is the first attempt at measuring SES for Saudi Arabia it seemed reasonable to explore the data using this technique. Furthermore, this method, as well as the formulas used to calculate the scores, has been used in Canada (Kishnan, 2010), India (Sekhar et al., 1991, Antony and Visweswara Rao, 2007), Japan (Fukuda et al., 2007) and in construction of an index for the state of Mississippi in the United States of America (Hightower, 1978), and the methods are well documented within the literature. Some have used principal component analysis (Kishnan, 2010, Vyas and Kumaranayake, 2006), however the principal component analysis is used as a data reduction technique only.

There are three common criteria to consider upon deciding the number of factors to retain after the initial extraction of the factors. First, the Guttman-Kaiser rule which describes the truly existing factors as the factors with eigenvalues above one (Kaiser, 1960, Guttman, 1954). This is the most commonly used method within the literature; but is mistakenly used on its own. A scree-plot is also used, it plots the eigenvalues and the number of factors and is determined by the point at which the plotted values start to level off (Cattell, 1966). The most important criterion is the interpretability. In this study, the scree plot and eigenvalues found four factors to retain, but the fourth factor was not interpretable. In this situation it is reasonable to drop the fourth factor and keep the first three factors that are interpretable (Bandalos, 2009). As stated by Worthington and Whittaker (2006), “In the end, researchers should only retain a factor if they can interpret it in a meaningful way, no matter how solid the evidence for its retention based on the empirical criteria” (p.822). Therefore, although the fourth factor satisfied the first two conditions, it was not interpretable even after rotation and was dropped.

The initial factor extraction usually yields factors that are difficult to interpret. A very common procedure is to rotate the factor axes to achieve a simple structure,

whereby the factor loadings will become either higher or lower than the loadings obtained from the initial extraction, hence the factors will be easier to interpret. Two types of rotations are available, orthogonal and oblique. It is a common misconception amongst researchers to regard orthogonal rotation as the “best” method (Bandalos, 2009). Indeed, most of the previous methodological papers on SES using EFA employed an orthogonal rotation without commenting on the assumptions of the factors or the rationale behind that choice (Fukuda et al., 2007, Kishnan, 2010, Hightower, 1978). It is always safer to consider the factors as not being perfectly independent, hence using an oblique rotation rather than an orthogonal one (Preacher and MacCallum, 2003). In any case, an oblique rotation will default to an orthogonal if the factors are truly uncorrelated, but the factors will be allowed to correlate if it is necessary to achieve the simple structure, therefore an oblique rotation was used in this study.

7.3.4.1 Possible drawbacks of EFA

A commonly reported limitation of EFA is the high level of subjectivity that arises from the several methodological decisions the researcher makes in a single analysis. Thus, the accuracy of the results depends on the quality of these decisions (Beavers et al., 2013). Therefore, ideally EFA should not be used on its own unless for exploratory reasons.

There is no consensus on the minimum sample size required. However, normality checks are necessary in small samples, because non-normal distributions produce an underestimate of the variance of a variable. Though, in large samples, i.e. a sample of greater than 100, the underestimates of variances disappears if the variables are positively skewed. If the variables are negatively skewed, then a sample size of greater than 200 is required (Tabachnick and Fidell, 2007). Therefore, since the variables obtained from the CDSI are either normally distributed, or positively skewed, and since the sample size is greater than 100 (N=118), no transformations were performed on the skewed data.

7.3.5 Latent class analysis

The LCA statistical method was chosen to classify the Governorates into homogenous groups. Unlike EFA, it is not only used for exploratory purposes, but is also used as a confirmatory statistical technique, i.e. results from an LCA model should confirm that of previous latent analysis (Geiser, 2010). In this work, LCA was

used to confirm and validate the results from the EFA. Although confirmatory factor analysis (CFA) could have been used, LCA was chosen due to the resulting categorical variables. Therefore, two indices of SES have been derived, one continuous and the other categorical. The use of LCA in relation to SES is not new since previous studies have utilised LCA to derive indices of SES, such as the index derived from a cross-sectional survey in the Philippines (Dahly, 2010), as well as the derivation of three socioeconomic classes on the neighbourhood level in Portugal (Alves et al., 2013).

The LCA is aimed at grouping observations or Governorates based on the pattern of item responses, therefore it is a person-centred approach to latent analysis. The main assumption underlying LCA is conditional independence, i.e. the indicator variables are mutually independent once the categorical variable, i.e. SES class variable is conditioned out. Furthermore, LCA may be used when indicator variables are non-normal. In fact, LCA captures non-normal outcomes, especially if there is a sound theory underlying the non-normality of the variables, for example if the variable is non-normal due to different response patterns from the observations. Hence, skewness is a result of the variable belonging to two or more classes. Therefore, log transforming the variables may lead to loss of information (Beng, 2003).

7.3.5.1 Possible drawbacks of LCA

The first issue encountered in this work was model convergence in Mplus. This is a complication that is encountered in iterative estimation procedures such as that found in LCA. It is often found that one set of parameter starting values does not make it possible to find the solution with the best log likelihood, and thus the model converges on the local likelihood maximum which results in inaccurate parameter estimates. Furthermore, the local maximum problem is more frequent in models with four or more extracted classes (Geiser, 2010). In this work, the problem of local maximum was encountered and the starting values had to be increased to 1000. Also, the highest number of classes extracted was four classes, because when five classes were set to be extracted, the model only converged on the local maximum, regardless of the number of starting values.

Also, sample size was a further limitation. The data set used here contained a small number of observations (N=118) relative to the number of indicator variables (n=29). Therefore, the number of variables had to be reduced to allow for the rule of thumb of 10 observations per indicator. Thus, the indicator variables were reduced

to only 11. The choice of variables was based on the disadvantaged variables only. This is similar to the variable selection used in UK indices such as the Carstairs and Townsend indices, in which the disadvantaged variables, such as low social class and overcrowding were used. This allowed proper model convergence and derivation of sensible and interpretable results comparable with the results of the EFA.

7.3.6 Regression analyses

The NB regression was chosen because a useful feature of the NB model is that the Poisson model is nested within it. The main differences between the Poisson and the NB is that the NB model has an α parameter that is estimated along with the other model parameters, and which measures the overdispersion numerically. If the α is equal to zero then there is no overdispersion and the model reduces to the simpler Poisson model. If however, the $\alpha > 0$, then this indicates that overdispersion does exist and is accounted for. The interpretation of the model coefficients are the same as the Poisson model. Also, the variance in the NB model is larger than the variance of the Poisson, though the means are the same (Little, 2013).

7.3.6.1 Other models considered for use

A further type of model that was considered for use was the zero-inflated Poisson (ZIP) and the zero-inflated NB model (ZINB). These models account for excessive zeros within the data. This is done by modelling the data as having a mixture of two distributions, the first has a central location of zero (also known as structured zeros) and the other has a central location of none-zeros. The first distribution is modelled using logistic regression and the second is modelled using a Poisson model in the ZIP model or the NB in the ZINB (He et al., 2014).

Prior to using these models, it was important to consider their underlying assumptions. These models assume that the data is generated from two different populations, the first are those who have no probability of acquiring the outcome of interest, and therefore will always have a value of zero, and the second population produces a value of zero but with some probability. This assumption does not apply to the cancer data, since the data is generated from one population all with a probability of acquiring cancer. Therefore, these models were not appropriate for use with this data.

7.4 Strengths of the study

A major strength for this study is that it is the first to address cancers in the childhood and young adult groups in Saudi Arabia, no research has previously explored incidence in these age groups. It also addressed major gaps in knowledge related to Saudi health and social research. First, it has succeeded in producing two area-based measures of SES for the 118 Governorates of Saudi Arabia for the first time, and has set the basis for future research in this field. The fact that the two indices were derived from routinely collected independent census data makes it possible to replicate and update with the next published census. Previous researches on Saudi health data have not been able to adjust for area-based SES as none were available, and this has been a cited limitation (AlGhamdi et al., 2014). Secondly, it has used a nation-wide population-based cancer registry to identify cases from a well-defined age group. Therefore, it has the largest statistical power possible. Both the cancer data and the census data were used to come up with indirect age-sex standardised rates, hence it was possible to make comparisons in incidence between the Saudi Governorates for the first time, by mapping these rates and applying necessary spatial smoothing to identify patterns. Furthermore, it made use of the Hajj data in a novel way by considering it as a natural experiment, thereby studying any effect it may have on the incidence of childhood and young adult cancers.

7.5 Limitations of the study

This study design was an aggregation of cancer counts in childhood and young adults that have occurred at the Governorate level.

Such ecological studies that attempt to describe areas through a snapshot of data are subject to the ecological fallacy (Piantadosi et al., 1988). This occurs when conclusions on individuals are based on analysis of aggregated data. This may be exacerbated by the fact that areas under analysis are not small. However, the SCR does not give data on addresses as they are usually centralised P.O. Boxes that do not indicate an individual's address. The only possible location provided was the Governorate. One consequence of ecological studies is the inability to adjust for potential confounders such as breastfeeding, attendance to day care centres, etc. which can only be collected on an individual level.

One confounder that may have been used in this study design was population density, which has been previously used to measure urbanisation. The use of the normal population density measured by persons/square miles is not appropriate for use in this situation. This is because Governorates are extremely wide, and populations centralised in only one small area. One clear example is the Ahsa Governorate (Figure 3.2), which administratively includes the entire Empty Quarter desert, where only 18% of that Governorate is populated. The best possible approach to this problem was to obtain data on population-weighted population density, as suggested by Dorling and Atkins (1995). This measure of density, unlike the normal population density which is area weighted, is population weighted by measuring the density of where an average person lives. However, no such data has been derived for the Saudi Governorates.

With regards to the socioeconomic indices, one methodological issue is the modifiable aerial unit problem, whereby the choice of the geographical level of analysis is made solely on the basis of administrative and/or political convenience, rather than being based on sound empirical evidence (Schuurman et al., 2007). A further problem, especially with the socioeconomic class index, is misclassification bias. It is a problem that occurs with categorical variables by assigning each Governorate to a class, for example, assigning Riyadh to the affluent class, thereby assuming that all of the population of Riyadh are affluent, which is not true. One way to overcome these issues is to reproduce these indices on a smaller geographical scale.

There have also been some issues with data availability and data accessibility. Saudi census data for the Governorate level are not readily available to download

from the CDSI webpage. Only aggregated data for the province level is made available for use. On-site visits to the CDSI were made and formal letters by Ministry officials had to be written in order to access this data, which delayed the process of data analysis. Furthermore, the level of coverage was not publically published, therefore there is a level of uncertainty for 100% coverage, especially in the most rural areas. Similarly, the only figure of case-ascertainment published for the SCR was 68%, which only covered one referral hospital in Riyadh during the first year of reporting. This figure does not inspire confidence, especially as it is drawn from an area where incidence is already high. Rural areas with extremely low numbers of cases, or which have no cases at all, are likely to have a result of poor case-ascertainment. Cancer registries provide data on which epidemiologic research and health policies rely. Therefore, complete and high quality data is vital. Low case-ascertainment in research may give misleading results. Furthermore, this project did not examine the subgroups of childhood and young adults separately, and did not examine subgroups of CNS tumours due to time limitations.

In relation to the Hajj, the project originally aimed at creating a measure of PM through the Shannon Index of Diversity (Shannon, 1948), since high diversity of mixing was found to be associated with increased incidence of ALL in previous studies (Parslow et al., 2002, Law et al., 2003, Feltbower et al., 2005). However, data on the place of origin of pilgrims was kept by the Ministry of Interior and could not be released. Therefore, only the total numbers of pilgrims by year were used.

7.6 Recommendations and future work

This project has the set basis for work in the field of SES. For the purposes of this study and to facilitate data linkage with cancer cases, Governorates were chosen as the geographical unit of analysis. Although these newly developed indices are replicable with the next national census, further work should be done to analyse residential zip codes or districts, which will reveal a clearer pattern of affluence. Additionally, disease registries should incorporate these new developed socioeconomic indices into their data to be included into future analyses.

An excellent opportunity has risen with the introduction of the new postal system in 2011. The new system should facilitate the process of selecting smaller boundaries, for example, a residential zip code or district will enable assigning individuals to spatial locations. The smaller boundaries will ensure that the populations within these areas are less heterogeneous, which will increase the reliability of these analyses, and reduce the effects of the modifiable area unit problem and misclassification bias. Disease registries wishing to use area-based measures of SES should integrate these newly developed residential addresses into their databases for data linkage.

Moreover, data to create measures such as overcrowding and unemployment have been collected, but are not given. The inclusion of these variables in future indices will help to derive more precise indices. In addition, the CDSI will most likely be able to publish population-weighted population density data. This data has been used previously to adjust for its potential confounding effects, and should be included in future ecological analyses.

However, such work will be challenging to perform in light of the difficulties faced in data access during the data collection phase of the work. The CDSI should encourage the use of census data by publishing data online, on different geographical levels, as is the case with census data in other countries. For example, in the UK, census data are published by the Office of National Statistics in geographical levels as well as small output areas.

With regards to the cancer data, it is believed that registrars collect data given by patients in hospitals. Hospitals should encourage patients to provide a more precise location of patient residence, such as residential districts. This information will help with future analyses that aim to look for any associations with potential aetiological factors. It is recommended that the SCR examine case-ascertainment on a continuous basis, especially in the more rural Governorates, either through capture-

recapture methods or by independent case-ascertainment, although the latter was reported to be more accurate (Schouten et al., 1994).

This is the first project that has analysed age-sex standardised rates of cases reported between 1994 and 2008 in the 0-24 age group, and thus has set the basis for future studies surrounding incidence for this group. Future work should include analysis of smaller subgroups for example 0-4, 5-9, 10-14 and 15-24 year groups for better comparison with previous studies and to ascertain whether associations observed still hold on these subgroups.

7.7 Future planned publications

The results from Chapter 5 are already under review in the Journal of Public Health. In addition, work is ongoing for the preparation of a scientific paper from Chapter 6 to the British Journal of Cancer.

7.8 Conclusions

This study has set the basis for work on the incidence of childhood and young adult cancers, an age group which has received no attention in previous Saudi studies. Results showed that cancers were mostly accounted for by ALL in the 0-4 age range, which is similar to international patterns. Standardising leukaemias, lymphomas and CNS tumours to the world standard population demonstrated that Saudi had lower rates compared to the UK (Feltbower et al., 2009). The study has also shown that there is a difference in the incidence of all diagnostic groups across the Saudi Governorates. The very low incidences in the most deprived Governorates suggest that case-ascertainment and/or under-diagnosis may be attributed to limited access to health organisations.

In Saudi Arabia, no area-based measure of SES has been derived, and this has been set as a limitation in previous nation-wide studies (AlGhamdi et al., 2014). Therefore, this work aimed to derive two area-based measures of SES for the 118 Governorates that could be used to assess its effect upon the incidence of childhood and young adult cancers and interpret the results in light of the PM hypothesis. The two indices were developed with already established methodologies used to derive indices in other countries. The first was continuous and the second was categorical; they showed very similar patterns of affluence in which the large urban Governorates were more affluent and the smaller rural areas were more deprived. These indices were then used in the regression analyses to assess whether SES and PM in terms of Hajj had any associations with the incidence of leukaemias, lymphomas and CNS tumours.

The main findings from the regression analyses indicated that PM had no significant effect on ALL and all other diagnostic groups. Furthermore, incidence was higher with increasing affluence, which is in line with previous studies that adjusted for SES (Dickinson et al., 2002, Law et al., 2003, Van Laar et al., 2014, Parslow et al., 2002). It should be noted, however, that in these studies the affluent areas were rural, while in Saudi the affluent areas were urban. Therefore, although the findings were unable to distinguish whether rurality or affluence contributed to the findings, the fact that affluence is the only common factor gives more weight to its effect.

The findings from this study are not supportive of the PM hypothesis, but give support to the delayed infection hypothesis for two main reasons. The first is that incidence was higher in affluent Governorates where social isolation due to affluence may have delayed exposure to infections in early life. Secondly, in Makkah, the Hajj is an annual event where infections are one major side-effect. The

annual exposure of the residents of Makkah to these infections, especially for infants in early life, may have primed their immune system thereby reducing the risk of the second mutational event required for the development of overt leukaemia. However, case-ascertainment and under-diagnosis may have exacerbated these findings.

Future research is needed to confirm these results, especially in the childhood age group aged 0-14. However, careful consideration should be given to issues with case-ascertainment prior to any investigation to ensure valid conclusions.

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APPENDIX A Extended classification table of the International Classification of Childhood Cancers 3rd Edition

Site Group	ICD-O-3 Histology (Type)	ICD-O-2/3 Site	Recode for Extended Classification
I Leukemias, myeloproliferative diseases, and myelodysplastic diseases			
(a) Lymphoid leukemias			
(a.1) Precursor cell leukemias	9835, 9836, 9837	C000-C809	001
(a.2) Mature B-cell leukemias	9823, 9826, 9832, 9833, 9940	C000-C809	002
(a.3) Mature T-cell and NK cell leukemias	9827, 9831, 9834, 9948	C000-C809	003
(a.4) Lymphoid leukemia, NOS	9820	C000-C809	004
(b) Acute myeloid leukemias	9840, 9861, 9866, 9867, 9870-9874, 9891, 9895-9897, 9910, 9920, 9931	C000-C809	005
(c) Chronic myeloproliferative diseases	9863, 9875, 9876, 9950, 9960-9964	C000-C809	006
(d) Myelodysplastic syndrome and other myeloproliferative diseases	9945, 9946, 9975, 9980, 9982-9987, 9989	C000-C809	007
(e) Unspecified and other specified leukemias	9800, 9801, 9805, 9860, 9930	C000-C809	008
II Lymphomas and reticuloendothelial neoplasms			
(a) Hodgkin lymphomas	9650-9655, 9659, 9661-9665, 9667	C000-C809	009
(b) Non-Hodgkin lymphomas (except Burkitt lymphoma)			
(b.1) Precursor cell lymphomas	9727-9729	C000-C809	010
(b.2) Mature B-cell lymphomas (except Burkitt lymphoma)	9670, 9671, 9673, 9675, 9678-9680, 9684, 9689-9691, 9695, 9698, 9699, 9731-9734, 9761, 9762, 9764-9766, 9769, 9970	C000-C809	011
(b.3) Mature T-cell and NK-cell lymphomas	9700-9702, 9705, 9708, 9709, 9714, 9716-9719, 9767, 9768	C000-C809	012
(b.4) Non-Hodgkin lymphomas, NOS	9591, 9760	C000-C809	013

(c) Burkitt lymphoma	9687	C000-C809	014
(d) Miscellaneous lymphoreticular neoplasms	9740-9742, 9750, 9754-9758	C000-C809	015
(e) Unspecified lymphomas	9590, 9596	C000-C809	016
III CNS and miscellaneous intracranial and intraspinal neoplasms			
(a) Ependymomas and choroid plexus tumor			
(a.1) Ependymomas	9383, 9391-9394	C000-C809	017
(a.2) Choroid plexus tumor	9390	C000-C809	018
(b) Astrocytomas	9380	C723	019
	9384, 9400-9411, 9420, 9421-9424, 9440-9442	C000-C809	019
(c) Intracranial and intraspinal embryonal tumors			
(c.1) Medulloblastomas	9470-9472, 9474, 9480	C000-C809	020
(c.2) PNET	9473	C000-C809	021
(c.3) Medulloepithelioma	9501-9504	C700-C729	022
(c.4) Atypical teratoid/rhabdoid tumor	9508	C000-C809	023
(d) Other gliomas			
(d.1) Oligodendrogliomas	9450, 9451, 9460	C000-C809	024
(d.2) Mixed and unspecified gliomas	9380	C700-C722, C724-C729, C751, C753	025
	9382	C000-C809	025
(d.3) Neuroepithelial glial tumors of uncertain origin	9381, 9430, 9444	C000-C809	026
(e) Other specified intracranial and intraspinal neoplasms			
(e.1) Pituitary adenomas and carcinomas	8270-8281, 8300	C000-C809	027
(e.2) Tumors of the sellar region (craniopharyngiomas)	9350-9352, 9582	C000-C809	028
(e.3) Pineal parenchymal tumors	9360-9362	C000-C809	029
(e.4) Neuronal and mixed neuronal-glial tumors	9412, 9413, 9492, 9493, 9505-9507	C000-C809	030
(e.5) Meningiomas	9530-9539	C000-C809	031
(f) Unspecified intracranial and intraspinal neoplasms	8000-8005	C700-C729, C751-C753	032
IV Neuroblastoma and other peripheral nervous cell tumors			
(a) Neuroblastoma and ganglioneuroblastoma	9490, 9500	C000-C809	033

(b) Other peripheral nervous cell tumors	8680-8683, 8690-8693, 8700, 9520-9523	C000-C809	034
	9501-9504	C000-C699, C739-C768, C809	034
V Retinoblastoma	**9510-9514**	**C000-C809**	**035**
VI Renal tumors			
(a) Nephroblastoma and other nonepithelial renal tumors			
(a.1) Nephroblastoma	8959, 8960	C000-C809	036
(a.2) Rhabdoid renal tumor	8963	C649	037
(a.3) Kidney sarcomas	8964-8967	C000-C809	038
(a.4) pPNET of kidney	9364	C649	039
(b) Renal carcinomas	8010-8041, 8050-8075, 8082, 8120-8122, 8130-8141, 8143, 8155, 8190-8201, 8210, 8211, 8221-8231, 8240, 8241, 8244-8246, 8260-8263, 8290, 8310, 8320, 8323, 8401, 8430, 8440, 8480-8490, 8504, 8510, 8550, 8560-8576	C649	040
	8311, 8312, 8316-8319, 8361	C000-C809	040
(c) Unspecified malignant renal tumors	8000-8005	C649	041
VII Hepatic tumors			
(a) Hepatoblastoma	8970	C000-C809	042
(b) Hepatic carcinomas	8010-8041, 8050-8075, 8082, 8120-8122, 8140, 8141, 8143, 8155, 8190-8201, 8210, 8211, 8230, 8231, 8240, 8241, 8244-8246, 8260-8264, 8310, 8320, 8323, 8401, 8430, 8440, 8480-8490, 8504, 8510, 8550, 8560-8576	C220, C221	043
	8160-8180	C000-C809	043
(c) Unspecified malignant hepatic tumors	8000-8005	C220-C221	044
VIII Malignant bone tumors			
(a) Osteosarcomas	9180-9187, 9191-9195, 9200	C400-C419, C760-C768, C809	045
(b) Chondrosarcomas	9210, 9220, 9240	C400-C419, C760-C768, C809	046
	9221, 9230, 9241-9243	C000-C809	046
(c) Ewing tumor and related sarcomas of bone			
(c.1) Ewing tumor and Askin tumor of bone	9260	C400-C419, C760-C768, C809	047

	9365	C400-C419	047
(c.2) pPNET of bone	9363, 9364	C400-C419	048
(d) Other specified malignant bone tumors			
(d.1) Malignant fibrous neoplasms of bone	8810, 8811, 8823, 8830	C400-C419	049
	8812, 9262	C000-C809	049
(d.2) Malignant chordomas	9370-9372	C000-C809	050
(d.3) Odontogenic malignant tumors	9270-9275, 9280-9282, 9290, 9300-9302, 9310-9312, 9320-9322, 9330, 9340-9342	C000-C809	051
(d.4) Miscellaneous malignant bone tumors	9250, 9261	C000-C809	052
(e) Unspecified malignant bone tumors	8000-8005, 8800, 8801, 8803-8805	C400-C419	053
IX Soft tissue and other extraosseous sarcomas			
(a) Rhabdomyosarcomas	8900-8905, 8910, 8912, 8920, 8991	C000-C809	054
(b) Fibrosarcomas, peripheral nerve sheath tumors, and other fibrous neoplasms			
(b.1) Fibroblastic and myofibroblastic tumors	8810, 8811, 8813-8815, 8821, 8823, 8834-8835	C000-C399, C440-C768, C809	055
	8820, 8822, 8824-8827, 9150, 9160	C000-C809	055
(b.2) Nerve sheath tumors	9540-9571	C000-C809	056
(b.3) Other fibromatous neoplasms	9491, 9580	C000-C809	057
(c) Kaposi sarcoma	9140	C000-C809	058
(d) Other specified soft tissue sarcomas			
(d.1) Ewing tumor and Askin tumor of soft tissue	9260	C000-C399, C470-C759	059
	9365	C000-C399, C470-C639, C659-C768, C809	059
(d.2) pPNET of soft tissue	9364	C000-C399, C470-C639, C659-C699, C739-C768, C809	060
(d.3) Extrarenal rhabdoid tumor	8963	C000-C639, C659-C699, C739-C768, C809	061
(d.4) Liposarcomas	8850-8858, 8860-8862, 8870, 8880, 8881	C000-C809	062
(d.5) Fibrohistiocytic tumors	8830	C000-C399, C440-C768, C809	063
	8831-8833, 8836, 9251, 9252	C000-C809	063

(d.6) Leiomyosarcomas	8890-8898	C000-C809	064
(d.7) Synovial sarcomas	9040-9044	C000-C809	065
(d.8) Blood vessel tumors	9120-9125, 9130-9133, 9135, 9136, 9141, 9142, 9161, 9170-9175	C000-C809	066
(d.9) Osseous and chondromatous neoplasms of soft tissue	9180, 9210, 9220, 9240	C490-C499	067
	9231	C000-C809	067
(d.10) Alveolar soft parts sarcoma	9581	C000-C809	068
(d.11) Miscellaneous soft tissue sarcomas	8587, 8710-8713, 8806, 8840-8842, 8921, 8982, 8990, 9373	C000-C809	069
(e) Unspecified soft tissue sarcomas	8800-8805	C000-C399, C440-C768, C809	070
X Germ cell tumors, trophoblastic tumors, and neoplasms of gonads			
(a) Intracranial and intraspinal germ cell tumors			
(a.1) Intracranial and intraspinal germinomas	9060-9065	C700-C729, C751-C753	071
(a.2) Intracranial and intraspinal teratomas	9080-9084	C700-C729, C751-C753	072
(a.3) Intracranial and intraspinal embryonal carcinomas	9070, 9072	C700-C729, C751-C753	073
(a.4) Intracranial and intraspinal yolk sac tumor	9071	C700-C729, C751-C753	074
(a.5) Intracranial and intraspinal choriocarcinoma	9100	C700-C729, C751-C753	075
(a.6) Intracranial and intraspinal tumors of mixed forms	9085, 9101	C700-C729, C751-C753	076
(b) Malignant extracranial and extragonadal germ cell tumors			
(b.1) Malignant germinomas of extracranial and extragonadal sites	9060-9065	C000-C559, C570-C619, C630-C699, C739-C750, C754-C768, C809	077
(b.2) Malignant teratomas of extracranial and extragonadal sites	9080-9084	C000-C559, C570-C619, C630-C699, C739-C750, C754-C768, C809	078
(b.3) Embryonal carcinomas of extracranial and extragonadal sites	9070, 9072	C000-C559, C570-C619, C630-C699, C739-C750, C754-C768, C809	079
(b.4) Yolk sac tumor of extracranial and extragonadal sites	9071	C000-C559, C570-C619, C630-C699, C739-C750, C754-C768, C809	080

(b.5) Choriocarcinomas of extracranial and extragonadal sites	9100, 9103, 9104	C000-C559, C570-C619, C630-C699, C739-C750, C754-C768, C809	081
(b.6) Other and unspecified malignant mixed germ cell tumors of extracranial and extragonadal sites	9085, 9101, 9102, 9105	C000-C559, C570-C619, C630-C699, C739-C750, C754-C768, C809	082
(c) Malignant gonadal germ cell tumors			
(c.1) Malignant gonadal germinomas	9060-9065	C569, C620-C629	083
(c.2) Malignant gonadal teratomas	9080-9084, 9090, 9091	C569, C620-C629	084
(c.3) Gonadal embryonal carcinomas	9070, 9072	C569, C620-C629	085
(c.4) Gonadal yolk sac tumor	9071	C569, C620-C629	086
(c.5) Gonadal choriocarcinoma	9100	C569, C620-C629	087
(c.6) Malignant gonadal tumors of mixed forms	9085, 9101	C569, C620-C629	088
(c.7) Malignant gonadal gonadoblastoma	9073	C569, C620-C629	089
(d) Gonadal carcinomas	8010-8041, 8050-8075, 8082, 8120-8122, 8130-8141, 8143, 8190-8201, 8210, 8211, 8221-8241, 8244-8246, 8260-8263, 8290, 8310, 8313, 8320, 8323, 8380-8384, 8430, 8440, 8480-8490, 8504, 8510, 8550, 8560-8573, 9000, 9014, 9015	C569, C620-C629	090
	8441-8444, 8450, 8451, 8460-8473	C000-C809	090
(e) Other and unspecified malignant gonadal tumors	8590-8671	C000-C809	091
	8000-8005	C569, C620-C629	091
XI Other malignant epithelial neoplasms and malignant melanomas			
(a) Adrenocortical carcinomas	8370-8375	C000-C809	092
(b) Thyroid carcinomas	8010-8041, 8050-8075, 8082, 8120-8122, 8130-8141, 8190, 8200, 8201, 8211, 8230, 8231, 8244-8246, 8260-8263, 8290, 8310, 8320, 8323, 8430, 8440, 8480, 8481, 8510, 8560-8573	C739	093
	8330-8337, 8340-8347, 8350	C000-C809	093
(c) Nasopharyngeal carcinomas	8010-8041, 8050-8075, 8082, 8083, 8120-8122,	C110-C119	094

	8130-8141, 8190, 8200, 8201, 8211, 8230, 8231, 8244-8246, 8260-8263, 8290, 8310, 8320, 8323, 8430, 8440, 8480, 8481, 8500-8576		
(d) Malignant melanomas	8720-8780, 8790	C000-C809	095
(e) Skin carcinomas	8010-8041, 8050-8075, 8078, 8082, 8090-8110, 8140, 8143, 8147, 8190, 8200, 8240, 8246, 8247, 8260, 8310, 8320, 8323, 8390-8420, 8430, 8480, 8542, 8560, 8570-8573, 8940, 8941	C440-C449	096
(f) Other and unspecified carcinomas			
(f.1) Carcinomas of salivary glands	8010-8084, 8120-8157, 8190-8264, 8290, 8310, 8313-8315, 8320-8325, 8360, 8380-8384, 8430-8440, 8452-8454, 8480-8586, 8588-8589, 8940, 8941, 8983, 9000, 9010-9016, 9020, 9030	C079-C089	097
(f.2) Carcinomas of colon and rectum	8010-8084, 8120-8157, 8190-8264, 8290, 8310, 8313-8315, 8320-8325, 8360, 8380-8384, 8430-8440, 8452-8454, 8480-8586, 8588-8589, 8940, 8941, 8983, 9000, 9010-9016, 9020, 9030	C180, C182-C189, C199, C209, C210-C218	098
(f.3) Carcinomas of appendix	8010-8084, 8120-8157, 8190-8264, 8290, 8310, 8313-8315, 8320-8325, 8360, 8380-8384, 8430-8440, 8452-8454, 8480-8586, 8588-8589, 8940, 8941, 8983, 9000, 9010-9016, 9020, 9030	C181	099
(f.4) Carcinomas of lung	8010-8084, 8120-8157, 8190-8264, 8290, 8310, 8313-8315, 8320-8325, 8360, 8380-8384, 8430-8440, 8452-8454, 8480-8586, 8588-8589, 8940, 8941, 8983, 9000, 9010-9016, 9020, 9030	C340-C349	100
(f.5) Carcinomas of thymus	8010-8084, 8120-8157, 8190-8264, 8290, 8310, 8313-8315, 8320-8325, 8360, 8380-8384, 8430-8440, 8452-8454, 8480-8586, 8588-8589, 8940, 8941, 8983, 9000, 9010-9016, 9020, 9030	C379	101
(f.6) Carcinomas of breast	8010-8084, 8120-8157, 8190-8264, 8290, 8310, 8313-8315, 8320-8325, 8360, 8380-8384, 8430-	C500-C509	102

	8440, 8452-8454, 8480-8586, 8588-8589, 8940, 8941, 8983, 9000, 9010-9016, 9020, 9030		
(f.7) Carcinomas of cervix uteri	8010-8084, 8120-8157, 8190-8264, 8290, 8310, 8313-8315, 8320-8325, 8360, 8380-8384, 8430-8440, 8452-8454, 8480-8586, 8588-8589, 8940, 8941, 8983, 9000, 9010-9016, 9020, 9030	C530-C539	103
(f.8) Carcinomas of bladder	8010-8084, 8120-8157, 8190-8264, 8290, 8310, 8313-8315, 8320-8325, 8360, 8380-8384, 8430-8440, 8452-8454, 8480-8586, 8588-8589, 8940, 8941, 8983, 9000, 9010-9016, 9020, 9030	C670-C679	104
(f.9) Carcinomas of eye	8010-8084, 8120-8157, 8190-8264, 8290, 8310, 8313-8315, 8320-8325, 8360, 8380-8384, 8430-8440, 8452-8454, 8480-8586, 8588-8589, 8940, 8941, 8983, 9000, 9010-9016, 9020, 9030	C690-C699	105
(f.10) Carcinomas of other specified sites	8010-8084, 8120-8157, 8190-8264, 8290, 8310, 8313-8315, 8320-8325, 8360, 8380-8384, 8430-8440, 8452-8454, 8480-8586, 8588-8589, 8940, 8941, 8983, 9000, 9010-9016, 9020, 9030	C000-069, C090-C109, C129-C179, C239-C339, C380-C399, C480-C488, C510-C529, C540-C549, C559, C570-C619, C630-C639, C659-C669, C680-C689, C700-C729, C750-C759	106
(f.11) Carcinomas of unspecified site	8010-8084, 8120-8157, 8190-8264, 8290, 8310, 8313-8315, 8320-8325, 8360, 8380-8384, 8430-8440, 8452-8454, 8480-8586, 8588-8589, 8940, 8941, 8983, 9000, 9010-9016, 9020, 9030	C760-C768, C809	107
XII Other and unspecified malignant neoplasms			
(a) Other specified malignant tumors			
(a.1) Gastrointestinal stromal tumor	8936	C000-C809	108
(a.2) Pancreatoblastoma	8971	C000-C809	109
(a.3) Pulmonary blastoma and pleuropulmonary blastoma	8972, 8973	C000-C809	110
(a.4) Other complex mixed and stromal neoplasms	8930-8935, 8950, 8951, 8974-8981	C000-C809	111

(a.5) Mesothelioma	9050-9055	C000-C809	112
(a.6) Other specified malignant tumors	9110	C000-C809	113
	9363	C000-C399, C470-C759	113
(b) Other unspecified malignant tumors	8000-8005	C000-C218, C239-C399, C420-C559, C570-C619, C630-C639, C659-C699, C739-C750, C754-809	114

APPENDIX B Main classification table of the International Classification of Childhood Cancers 3rd Edition

Site Group	ICD-O-3 Histology (Type)	ICD-O-2/3 Site	Recode
I Leukemias, myeloproliferative diseases, and myelodysplastic diseases			
(a) Lymphoid leukemias	9820, 9823, 9826, 9827, 9831-9837, 9940, 9948	C000-C809	011
(b) Acute myeloid leukemias	9840, 9861, 9866, 9867, 9870-9874, 9891, 9895-9897, 9910, 9920, 9931	C000-C809	012
(c) Chronic myeloproliferative diseases	9863, 9875, 9876, 9950, 9960-9964	C000-C809	013
(d) Myelodysplastic syndrome and other myeloproliferative diseases	9945, 9946, 9975, 9980, 9982-9987, 9989	C000-C809	014
(e) Unspecified and other specified leukemias	9800, 9801, 9805, 9860, 9930	C000-C809	015
II Lymphomas and reticuloendothelial neoplasms			
(a) Hodgkin lymphomas	9650-9655, 9659, 9661-9665, 9667	C000-C809	021
(b) Non-Hodgkin lymphomas (except Burkitt lymphoma)	9591, 9670, 9671, 9673, 9675, 9678-9680, 9684, 9689-9691, 9695, 9698-9702, 9705, 9708, 9709, 9714, 9716-9719, 9727-9729, 9731-9734, 9760-9762, 9764-9769, 9970	C000-C809	022
(c) Burkitt lymphoma	9687	C000-C809	023
(d) Miscellaneous lymphoreticular neoplasms	9740-9742, 9750, 9754-9758	C000-C809	024
(e) Unspecified lymphomas	9590, 9596	C000-C809	025
III CNS and miscellaneous intracranial and intraspinal neoplasms			
(a) Ependymomas and choroid plexus tumor	9383, 9390-9394	C000-C809	031
(b) Astrocytomas	9380	C723	032
	9384, 9400-9411, 9420, 9421-9424, 9440-9442	C000-C809	032
(c) Intracranial and intraspinal	9470-9474, 9480, 9508	C000-C809	033

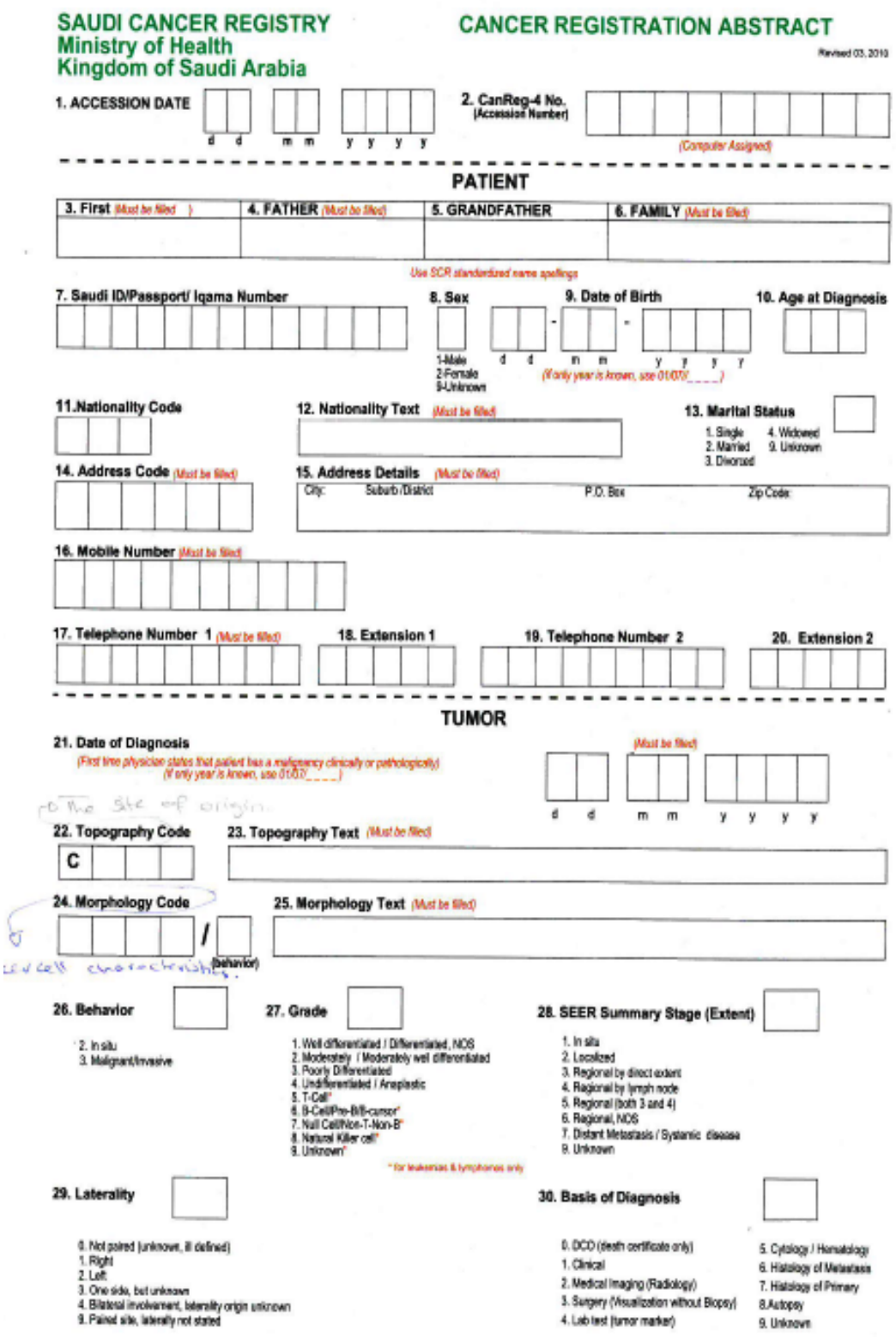
embryonal tumors	9501-9504	C700-C729	033
(d) Other gliomas	9380	C700-C722, C724-C729, C751, C753	034
	9381, 9382, 9430, 9444, 9450, 9451, 9460	C000-C809	034
(e) Other specified intracranial and intraspinal neoplasms	8270-8281, 8300, 9350-9352, 9360-9362, 9412, 9413, 9492, 9493, 9505-9507, 9530-9539, 9582	C000-C809	035
(f) Unspecified intracranial and intraspinal neoplasms	8000-8005	C700-C729, C751-C753	036
IV Neuroblastoma and other peripheral nervous cell tumors			
(a) Neuroblastoma and ganglioneuroblastoma	9490, 9500	C000-C809	041
(b) Other peripheral nervous cell tumors	8680-8683, 8690-8693, 8700, 9520-9523	C000-C809	042
	9501-9504	C000-C699, C739-C768, C809	042
V Retinoblastoma	**9510-9514**	**C000-C809**	**050**
VI Renal tumors			
(a) Nephroblastoma and other nonepithelial renal tumors	8959, 8960, 8964-8967	C000-C809	061
	8963, 9364	C649	061
(b) Renal carcinomas	8010-8041, 8050-8075, 8082, 8120-8122, 8130-8141, 8143, 8155, 8190-8201, 8210, 8211, 8221-8231, 8240, 8241, 8244-8246, 8260-8263, 8290, 8310, 8320, 8323, 8401, 8430, 8440, 8480-8490, 8504, 8510, 8550, 8560-8576	C649	062
	8311, 8312, 8316-8319, 8361	C000-C809	062
(c) Unspecified malignant renal tumors	8000-8005	C649	063
VII Hepatic tumors			
(a) Hepatoblastoma	8970	C000-C809	071
(b) Hepatic carcinomas	8010-8041, 8050-8075, 8082, 8120-8122, 8140, 8141, 8143, 8155, 8190-8201, 8210, 8211, 8230, 8231, 8240, 8241, 8244-8246, 8260-8264, 8310, 8320, 8323, 8401, 8430, 8440, 8480-8490, 8504, 8510, 8550, 8560-8576	C220, C221	072

	8160-8180	C000-C809	072
(c) Unspecified malignant hepatic tumors	8000-8005	C220, C221	073
VIII Malignant bone tumors			
(a) Osteosarcomas	9180-9187, 9191-9195, 9200	C400-C419, C760-C768, C809	081
(b) Chondrosarcomas	9210, 9220, 9240	C400-C419, C760-C768, C809	082
	9221, 9230, 9241-9243	C000-C809	082
(c) Ewing tumor and related sarcomas of bone	9260	C400-C419, C760-C768, C809	083
	9363-9365	C400-C419	083
(d) Other specified malignant bone tumors	8810, 8811, 8823, 8830	C400-C419	084
	8812, 9250, 9261, 9262, 9270-9275, 9280-9282, 9290, 9300-9302, 9310-9312, 9320-9322, 9330, 9340-9342, 9370-9372	C000-C809	084
(e) Unspecified malignant bone tumors	8000-8005, 8800, 8801, 8803-8805	C400-C419	085
IX Soft tissue and other extraosseous sarcomas			
(a)Rhabdomyosarcomas	8900-8905, 8910, 8912, 8920, 8991	C000-C809	091
(b) Fibrosarcomas, peripheral nerve sheath tumors, and other fibrous neoplasms	8810, 8811, 8813-8815, 8821, 8823, 8834-8835	C000-C399, C440-C768, C809	092
	8820, 8822, 8824-8827, 9150, 9160, 9491, 9540-9571, 9580	C000-C809	092
(c) Kaposi sarcoma	9140	C000-C809	093
(d) Other specified soft tissue sarcomas	8587, 8710-8713, 8806, 8831-8833, 8836, 8840-8842, 8850-8858, 8860-8862, 8870, 8880, 8881, 8890-8898, 8921, 8982, 8990, 9040-9044, 9120-9125, 9130-9133, 9135, 9136, 9141, 9142, 9161, 9170-9175, 9231, 9251, 9252, 9373, 9581	C000-C809	094
	8830	C000-C399, C440-C768, C809	094
	8963	C000-C639, C659-C699, C739-C768, C809	094
	9180, 9210, 9220, 9240	C490-C499	094

	9260	C000-C399, C470-C759	094
	9364	C000-C399, C470-C639, C659-C699, C739-C768, C809	094
	9365	C000-C399, C470-C639, C659-C768, C809	094
(e) Unspecified soft tissue sarcomas	8800-8805	C000-C399, C440-C768, C809	095
X Germ cell tumors, trophoblastic tumors, and neoplasms of gonads			
(a) Intracranial and intraspinal germ cell tumors	9060-9065, 9070-9072, 9080-9085, 9100, 9101	C700-C729, C751-C753	101
(b) Malignant extracranial and extragonadal germ cell tumors	9060-9065, 9070-9072, 9080-9085, 9100-9105	C000-C559, C570-C619, C630-C699, C739-C750, C754-C768, C809	102
(c) Malignant gonadal germ cell tumors	9060-9065, 9070-9073, 9080-9085, 9090, 9091, 9100, 9101	C569, C620-C629	103
(d) Gonadal carcinomas	8010-8041, 8050-8075, 8082, 8120-8122, 8130-8141, 8143, 8190-8201, 8210, 8211, 8221-8241, 8244-8246, 8260-8263, 8290, 8310, 8313, 8320, 8323, 8380-8384, 8430, 8440, 8480-8490, 8504, 8510, 8550, 8560-8573, 9000, 9014, 9015	C569, C620-C629	104
	8441-8444, 8450, 8451, 8460-8473	C000-C809	104
(e) Other and unspecified malignant gonadal tumors	8590-8671	C000-C809	105
	8000-8005	C569, C620-C629	105
XI Other malignant epithelial neoplasms and malignant melanomas			
(a) Adrenocortical carcinomas	8370-8375	C000-C809	111
(b) Thyroid carcinomas	8010-8041, 8050-8075, 8082, 8120-8122, 8130-8141, 8190, 8200, 8201, 8211, 8230, 8231, 8244-8246, 8260-8263, 8290, 8310, 8320, 8323, 8430, 8440, 8480, 8481, 8510, 8560-8573	C739	112

	8330-8337, 8340-8347, 8350	C000-C809	112
(c) Nasopharyngeal carcinomas	8010-8041, 8050-8075, 8082, 8083, 8120-8122, 8130-8141, 8190, 8200, 8201, 8211, 8230, 8231, 8244-8246, 8260-8263, 8290, 8310, 8320, 8323, 8430, 8440, 8480, 8481, 8500-8576	C110-C119	113
(d) Malignant melanomas	8720-8780, 8790	C000-C809	114
(e) Skin carcinomas	8010-8041, 8050-8075, 8078, 8082, 8090-8110, 8140, 8143, 8147, 8190, 8200, 8240, 8246, 8247, 8260, 8310, 8320, 8323, 8390-8420, 8430, 8480, 8542, 8560, 8570-8573, 8940, 8941	C440-C449	115
(f) Other and unspecified carcinomas	8010-8084, 8120-8157, 8190-8264, 8290, 8310, 8313-8315, 8320-8325, 8360, 8380-8384, 8430-8440, 8452-8454, 8480-8586, 8588-8589, 8940, 8941, 8983, 9000, 9010-9016, 9020, 9030	C000-C109, C129-C218, C239-C399, C480-C488, C500-C559, C570-C619, C630-C639, C659-C729, C750-C768, C809	116
XII Other and unspecified malignant neoplasms			
(a) Other specified malignant tumors	8930-8936, 8950, 8951, 8971-8981, 9050-9055, 9110	C000-C809	121
	9363	C000-C399, C470-C759	121
(b) Other unspecified malignant tumors	8000-8005	C000-C218, C239-C399, C420-C559, C570-C619, C630-C639, C659-C699, C739-C750, C754-C809	122
Not Classified by ICCC or in situ			**999**

APPENDIX C Saudi cancer registry data abstraction form



SAUDI CANCER REGISTRY
Ministry of Health
Kingdom of Saudi Arabia

CANCER REGISTRATION ABSTRACT

Revised 03, 2010

1. ACCESSION DATE (d d) (m m) (y y y y)

2. CanReg-4 No. (Accession Number) (Computer Assigned)

PATIENT

3. First (Must be filled)	4. FATHER (Must be filled)	5. GRANDFATHER	6. FAMILY (Must be filled)

Use SCR standardized name spellings

7. Saudi ID/Passport/ Iqama Number

8. Sex (1-Male, 2-Female, 9-Unknown)

9. Date of Birth (d d) - (m m) - (y y y y) (If only year is known, use 01/01/____)

10. Age at Diagnosis

11. Nationality Code

12. Nationality Text (Must be filled)

13. Marital Status (1. Single, 2. Married, 3. Divorced, 4. Widowed, 9. Unknown)

14. Address Code (Must be filled)

15. Address Details (Must be filled) City: Suburb /District P.O. Box Zip Code:

16. Mobile Number (Must be filled)

17. Telephone Number 1 (Must be filled)

18. Extension 1

19. Telephone Number 2

20. Extension 2

TUMOR

21. Date of Diagnosis (First time physician states that patient has a malignancy clinically or pathologically) (If only year is known, use 01/01/____) (Must be filled) (d d) (m m) (y y y y)

22. Topography Code C

23. Topography Text (Must be filled)

24. Morphology Code / (Behavior)

25. Morphology Text (Must be filled)

26. Behavior
2. In situ
3. Malignant/Invasive

27. Grade
1. Well differentiated / Differentiated, NOS
2. Moderately / Moderately well differentiated
3. Poorly Differentiated
4. Undifferentiated / Anaplastic
5. T-Cell*
6. B-Cell/Pre-B/B-cursor*
7. Null Cell/Non-T-Non-B*
8. Natural Killer cell*
9. Unknown*
* for leukemias & lymphomas only

28. SEER Summary Stage (Extent)
1. In situ
2. Localized
3. Regional by direct extent
4. Regional by lymph node
5. Regional (both 3 and 4)
6. Regional, NOS
7. Distant Metastasis / Systemic disease
9. Unknown

29. Laterality
0. Not paired (unknown, ill defined)
1. Right
2. Left
3. One side, but unknown
4. Bilateral involvement, laterality origin unknown
9. Paired site, laterality not stated

30. Basis of Diagnosis
0. DCO (death certificate only)
1. Clinical
2. Medical Imaging (Radiology)
3. Surgery (Visualization without Biopsy)
4. Lab test (tumor marker)
5. Cytology / Hematology
6. Histology of Metastasis
7. Histology of Primary
8. Autopsy
9. Unknown

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HOSPITAL

31. Date first seen at Source1 for this cancer (Must be filled) — d d / m m / y y y y

32. Source 1	33. Reporting Hospital Text	34. MRN 1	35. Path 1
36. Source 2	37. Referral Hospital Text	38. MRN 2	39. Path 2
40. Source 3	41. Referral Hospital Text	42. MRN 3	43. Path 3
44. Source 4	45. Referral Hospital Text	46. MRN 4	47. Path 4
48. Source 5	49. Referral Hospital Text	50. MRN 5	51. Path 5
52. Source 6	53. Referral Hospital Text	54. MRN 6	55. Path 6

FOLLOW-UP

56. Last Contact — d d / m m / y y y y

57. Status

1. Dead
2. Alive
9. Unknown

58. Cause of Death

1. Cancer
2. Other
3. Not Applicable
9. Unknown

59. Coder ID #

60. Data Entry ID #

Signature: _____

Signature: _____

QUESTIONS / QUERIES / PROBLEMS

APPENDIX D Example of phase 1: Converting morphology and topography codes to ICCC-3 extended classification

```
*A) LYMPHOID LEUKAEMIAS:


*a.1) PRECURSOR CELL LEUKAEMIAS:

gen phaseone = 1 if mor=="98353" & top=="1" | mor=="98353" &
top=="1" | mor=="98353" & top=="110" | mor=="98353" &
top=="111" | mor=="98353" & top=="111" | mor=="98353" &
top=="112" | mor=="98353" & top=="113" …

replace phaseone = 2 if mor=="98353" & top=="503" |
mor=="98353" & top=="504" | mor=="98353" & top=="505" |
mor=="98353" & top=="506" | mor=="98353" & top=="508" |
mor=="98353" & top=="509" | mor=="98353" & top=="51" …

replace phaseone = 3 if mor=="98363" & top=="1" |
mor=="98363" & top=="1" | mor=="98363" & top=="110" |
mor=="98363" & top=="111" | mor=="98363" & top=="111" |
mor=="98363" & top=="112" | mor=="98363" & top=="113" …

replace phaseone = 4 if mor=="98363" & top=="503" |
mor=="98363" & top=="504" | mor=="98363" & top=="505" |
mor=="98363" & top=="506" | mor=="98363" & top=="508" |
mor=="98363" & top=="509" | mor=="98363" & top=="51" …

replace phaseone = 5 if mor=="98373" & top=="1" |
mor=="98373" & top=="1" | mor=="98373" & top=="110" |
mor=="98373" & top=="111" | mor=="98373" & top=="111" |
mor=="98373" & top=="112" | mor=="98373" & top=="113" …

replace phaseone = 6 if mor=="98373" & top=="503" |
mor=="98373" & top=="504" | mor=="98373" & top=="505" |
mor=="98373" & top=="506" | mor=="98373" & top=="508" |
mor=="98373" & top=="509" | mor=="98373" & top=="51" …


*a.2) MATURE B-CELL LEUKAEMIAS:

replace phaseone = 7 if mor=="98233" & top=="1" |
mor=="98233" & top=="1" | mor=="98233" & top=="110" |
mor=="98233" & top=="111" | mor=="98233" & top=="111" |
mor=="98233" & top=="112" | mor=="98233" & top=="113" …

replace phaseone = 8 if mor=="98233" & top=="503" |
mor=="98233" & top=="504" | mor=="98233" & top=="505" |
mor=="98233" & top=="506" | mor=="98233" & top=="508" |
mor=="98233" & top=="509" | mor=="98233" & top=="51" …
```

```
replace phaseone = 9 if mor=="98263" & top=="1" |
mor=="98263" & top=="1" | mor=="98263" & top=="110" |
mor=="98263" & top=="111" | mor=="98263" & top=="111" |
mor=="98263" & top=="112" | mor=="98263" & top=="113" …

replace phaseone = 10 if mor=="98263" & top=="503" |
mor=="98263" & top=="504" | mor=="98263" & top=="505" |
mor=="98263" & top=="506" | mor=="98263" & top=="508" |
mor=="98263" & top=="509" | mor=="98263" & top=="51" …

replace phaseone = 11 if mor=="98323" & top=="1" |
mor=="98323" & top=="1" | mor=="98323" & top=="110" |
mor=="98323" & top=="111" | mor=="98323" & top=="111" |
mor=="98323" & top=="112" | mor=="98323" & top=="113" …

replace phaseone = 12 if mor=="98323" & top=="503" |
mor=="98323" & top=="504" | mor=="98323" & top=="505" |
mor=="98323" & top=="506" | mor=="98323" & top=="508" |
mor=="98323" & top=="509" | mor=="98323" & top=="51" …

replace phaseone = 13 if mor=="98333" & top=="1" |
mor=="98333" & top=="1" | mor=="98333" & top=="110" |
mor=="98333" & top=="111" | mor=="98333" & top=="111" |
mor=="98333" & top=="112" | mor=="98333" & top=="113" …

replace phaseone = 14 if mor=="98333" & top=="503" |
mor=="98333" & top=="504" | mor=="98333" & top=="505" |
mor=="98333" & top=="506" | mor=="98333" & top=="508" |
mor=="98333" & top=="509" | mor=="98333" & top=="51" …

replace phaseone = 15 if mor=="99403" & top=="1" |
mor=="99403" & top=="1" | mor=="99403" & top=="110" |
mor=="99403" & top=="111" | mor=="99403" & top=="111" |
mor=="99403" & top=="112" | mor=="99403" & top=="113" …

replace phaseone = 16 if mor=="99403" & top=="503" |
mor=="99403" & top=="504" | mor=="99403" & top=="505" |
mor=="99403" & top=="506" | mor=="99403" & top=="508" |
mor=="99403" & top=="509" | mor=="99403" & top=="51" …


*a.3) MATURE T-CELL AND NK CELL LEUKAEMIAS:

replace phaseone = 17 if mor=="98273" & top=="1" |
mor=="98273" & top=="1" | mor=="98273" & top=="110" |
mor=="98273" & top=="111" | mor=="98273" & top=="111" |
mor=="98273" & top=="112" | mor=="98273" & top=="113" …

replace phaseone = 18 if mor=="98273" & top=="503" |
mor=="98273" & top=="504" | mor=="98273" & top=="505" |
mor=="98273" & top=="506" | mor=="98273" & top=="508" |
mor=="98273" & top=="509" | mor=="98273" & top=="51" …

replace phaseone = 19 if mor=="98313" & top=="1" |
mor=="98313" & top=="1" | mor=="98313" & top=="110" |
```

```
mor=="98313" & top=="111" | mor=="98313" & top=="111" |
mor=="98313" & top=="112" | mor=="98313" & top=="113" …

replace phaseone = 20 if mor=="98313" & top=="503" |
mor=="98313" & top=="504" | mor=="98313" & top=="505" |
mor=="98313" & top=="506" | mor=="98313" & top=="508" |
mor=="98313" & top=="509" | mor=="98313" & top=="51" …


replace phaseone = 21 if mor=="98343" & top=="1" |
mor=="98343" & top=="1" | mor=="98343" & top=="110" |
mor=="98343" & top=="111" | mor=="98343" & top=="111" |
mor=="98343" & top=="112" | mor=="98343" & top=="113" …

replace phaseone = 22 if mor=="98343" & top=="503" |
mor=="98343" & top=="504" | mor=="98343" & top=="505" |
mor=="98343" & top=="506" | mor=="98343" & top=="508" |
mor=="98343" & top=="509" | mor=="98343" & top=="51" …

replace phaseone = 23 if mor=="99483" & top=="1" |
mor=="99483" & top=="1" | mor=="99483" & top=="110" |
mor=="99483" & top=="111" | mor=="99483" & top=="111" |
mor=="99483" & top=="112" | mor=="99483" & top=="113" …

replace phaseone = 24 if mor=="99483" & top=="503" |
mor=="99483" & top=="504" | mor=="99483" & top=="505" |
mor=="99483" & top=="506" | mor=="99483" & top=="508" |
mor=="99483" & top=="509" | mor=="99483" & top=="51" …


*a.4) LYMPHOID LEUKAEMIAS, NOS:

replace phaseone = 27 if mor=="98203" & top=="1" |
mor=="98203" & top=="1" | mor=="98203" & top=="110" |
mor=="98203" & top=="111" | mor=="98203" & top=="111" |
mor=="98203" & top=="112" | mor=="98203" & top=="113" …

replace phaseone = 28 if mor=="98203" & top=="503" |
mor=="98203" & top=="504" | mor=="98203" & top=="505" |
mor=="98203" & top=="506" | mor=="98203" & top=="508" |
mor=="98203" & top=="509" | mor=="98203" & top=="51" …


*---------------------------------*

*---------------------------------*

*GENERATE ICCC-E:

gen ICCCE = 001 if phaseone ==1 | phaseone==2 | phaseone==3 |
phaseone==4 | phaseone==5 | phaseone==6
```

APPENDIX E Example of phase 2: Converting morphology and topography codes to ICCC-3 main classification

```
*GENERATE ICCCM FROM ICCCE (For Leukaemias,
myeloproliferative diseases, and myelodysplastic diseases)

gen ICCCM = 011 if ICCCE==001 | ICCCE==002 | ICCCE==003 |
ICCCE==004
replace ICCCM = 012 if ICCCE==005
replace ICCCM = 013 if ICCCE==006
replace ICCCM = 014 if ICCCE==007
replace ICCCM = 015 if ICCCE==008

label define ICCCM 011 "Lmyphoid leukaemias" 012 "AML" 013
"CML" 014 "Myelodysplastic syndrome and other myeloid
diseases" 015 "Unspecified and other leukaemias"
label value ICCCM ICCCM
```

APPENDIX F Discrepancies found within the total number of households from each indicator group and the total number of households reported

Governorate	Households before	Discrepancies	Households after
Riyadh	724830	354	725184
Kharj	54926	-1	54925
Makkah	262973	93	263066
Jeddah	622047	252	622299
Madinah	176338	428	176766
Hinakiyah	9246	57	9303
Buraidah	81794	197	81991
Onaizah	23127	31	23158
Dammam	125097	131	125228
Ahsa	136239	56	136295
Jubail	37115	97	37212
Khobar	83237	102	83339
Abha	62724	131	62855
Khamis Mushayt	74086	347	74433
Sarat Abaida	9308	68	9376
Uhd Rofidah	17269	46	17315
Tabuk	82298	226	82524
Hail	50758	748	51506
Baqaa	6200	43	6243
Ghazalah	13946	47	13993
Arar	22186	200	22386
Rafha	9548	178	9726
Toraif	5704	43	5747
Jazan	38938	343	39281
Sabyaa	30878	368	31246
Abu Arish	19065	135	19200
Samtah	18891	176	19067
Harth	6087	104	6191
Dhamd	9601	109	9710
Reeth	1621	20	1641

Beesh	8835	125	8960
Farasan	2272	26	2298
Dayer	7067	198	7265
Uhd Masarha	10329	121	10450
Eidabi	7356	59	7415
Aridhah	8013	172	8185
Darb	8393	82	8475
Najran	44382	189	44571
Baha	16673	190	16863
Baljurashi	11137	217	11354
Mandaq	7621	104	7725
Mikhwah	10975	33	11008
Aqeeq	4798	65	4863
Quraa	5215	54	5269
Skaka	26538	275	26813
Qurayaat	16341	178	16519
Dawmat Jandal	5662	11	5673

APPENDIX G Commitment letter to Farsi GeoTech Company for use of Geographical Information System data

Division of Biostatistics
Leeds Institute of Genetics, Health and Therapeutics

Level 8, Worsley Building
University of Leeds
Leeds, LS2 9JT

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F: +44 (0) 113 343 4877
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UNIVERSITY OF LEEDS

17/04/2012

Dear Eng. Zaki Farsi,

I hereby confirm that the GIS maps kindly provided from your office to aid in my doctoral degree will not be used for any other purposes. They will be strictly used only for my research degree.

The GIS data will not be used for any other purposes, nor will it be spread to any third parties, and if done so, I understand the financial and legal requirements I will then endure.

Yours sincerely,

Reem Al Omar
Postgraduate research student

APPENDIX H Syntax of negative binomial regression analysis in Stata version 13

```
*Univariable analysis for ALL:
glm ALL, family(nbinomial) exposure(expALL) eform
glm ALL SES, family(nbinomial) exposure(expALL) eform
glm ALL PM, family(nbinomial) exposure(expALL) eform
glm ALL year, family(nbinomial) exposure(expALL) eform

--------------
-------------

*Regression analysis for PM for the year 1994:
glm ALL PM if year==1994, family(nbinomial) exposure(expALL)
eform

--------------
--------------

*Regression analysis for ALL and SES:
glm ALL SES, family(nbinomial) exposure(expALL) eform

--------------
--------------
# Where ALL = Acute lymphoblastic leukaemia
# PM = Population mixing binary variable
# expALL = Expected cases of ALL
```

APPENDIX I Initial and standardised index of Saudi Governorates

Province	Governorate	Initial index	Standardised index
Eastern Region	Qatif	131.25	100.00
Eastern Region	Khobar	122.70	97.02
Eastern Region	Rass Tanourah	113.03	93.64
Eastern Region	Jubail	106.89	91.50
Riyadh	Riyadh	104.71	90.74
Eastern Region	Dammam	104.08	90.52
Eastern Region	Bqeeq	89.92	85.59
Eastern Region	Ahsa	86.56	84.41
Eastern Region	Khafji	84.11	83.56
Qassim	Onaizah	82.63	83.04
Baha	Baha	80.88	82.43
Northern border	Arar	72.58	79.53
Jouf	Skaka	62.74	76.10
Riyadh	Dareiyah	60.72	75.40
Qassim	Buraidah	62.27	75.94
Jouf	Qurayaat	57.65	74.33
Makkah	Jeddah	57.83	74.39
Hail	Hail	58.07	74.48
Madinah	Madinah	56.78	74.02
Tabuk	Tabuk	57.32	74.21
Qassim	Rass	55.87	73.71
Aseer	Abha	55.92	73.72
Jouf	Dawmat Jandal	53.19	72.77
Qassim	Badae	50.97	72.00
Aseer	Khamis Mushayt	48.86	71.26
Madinah	Yanbu	47.68	70.85
Northern border	Toraif	45.62	70.13
Riyadh	Zolfi	42.84	69.16
Baha	Mandaq	40.32	68.28
Riyadh	Shaqraa	41.28	68.62
Makkah	Taif	38.50	67.65
Eastern Region	Hafr batin	38.80	67.76
Riyadh	Kharj	37.91	67.44
Baha	Baljurashi	36.02	66.78
Makkah	Makkah	36.65	67.01
Northern border	Rafha	29.70	64.58

Qassim	Asyah	30.24	64.77
Qassim	Midnab	28.53	64.17
Riyadh	Majmaah	27.64	63.86
Qassim	Shamssiyah	26.13	63.33
Aseer	Namas	20.62	61.41
Qassim	Bikairiah	20.17	61.26
Riyadh	Hotat bani tamim	19.64	61.07
Tabuk	Haql	21.86	61.84
Qassim	Riyadh Khobaraa	18.08	60.53
Aseer	Uhd Rofidah	17.03	60.16
Najran	Najran	13.95	59.09
Najran	Sharourah	10.69	57.95
Riyadh	Selayil	11.77	58.33
Baha	Quraa	6.25	56.40
Eastern Region	Noariyah	8.15	57.06
Jazan	Jazan	9.25	57.45
Riyadh	Afeef	11.28	58.15
Eastern Region	Qaryat Alya	3.06	55.29
Aseer	Belgarn	6.47	56.48
Riyadh	Dawadmi	4.79	55.89
Qassim	Oyoon Jawaa	4.80	55.90
Riyadh	Hareeq	-1.41	53.73
Riyadh	Aflaj	0.11	54.26
Jazan	Farasan	-2.01	53.52
Aseer	Dhahran Janoub	-2.21	53.45
Riyadh	Wadi Dawaser	-4.86	52.53
Tabuk	Tayma	-5.26	52.39
Makkah	Rabegh	-8.69	51.19
Aseer	Bishah	-11.21	50.31
Riyadh	Ghat	-8.80	51.15
Madinah	Badr	-12.09	50.00
Tabuk	Wajh	-12.38	49.90
Jazan	Abu Arish	-15.04	48.98
Baha	Mikhwah	-16.21	48.57
Tabuk	Amluj	-16.22	48.56
Makkah	Kholais	-18.29	47.84
Aseer	Sarat Abaida	-18.36	47.82
Riyadh	Romah	-24.33	45.73
Makkah	Jomoom	-26.44	45.00
Tabuk	Dhebaa	-25.71	45.25
Makkah	Khormah	-27.93	44.48
Jazan	Uhd Masarha	-31.48	43.24

Riyadh	Thadeq	-28.73	44.20
Aseer	Rejal Almaa	-31.72	43.16
Makkah	Raniah	-34.29	42.26
Aseer	Mahail	-32.13	43.02
Jazan	Beesh	-34.73	42.11
Jazan	Dhamd	-32.40	42.92
Baha	Qilwah	-34.97	42.03
Jazan	Sabyaa	-33.87	42.41
Makkah	Qunfudhah	-35.41	41.87
Madinah	Khaibar	-35.45	41.86
Madinah	Ola	-35.41	41.87
Hail	Baqaa	-39.79	40.34
Aseer	Majardah	-40.53	40.08
Riyadh	Mozahimyah	-40.18	40.21
Najran	Haboona	-46.51	38.00
Baha	Aqeeq	-44.39	38.74
Makkah	Torbah	-43.16	39.17
Jazan	Samtah	-45.51	38.35
Riyadh	Herimla	-46.16	38.12
Riyadh	Qowaiyah	-48.83	37.19
Hail	Shanan	-51.53	36.25
Najran	Badr Janoub	-56.75	34.43
Madinah	Hinakiyah	-54.67	35.15
Jazan	Darb	-56.06	34.67
Makkah	Leeth	-55.07	35.01
Qassim	Nabhanyah	-59.14	33.59
Hail	Ghazalah	-62.56	32.40
Madinah	Mahd	-66.19	31.13
Riyadh	Dhurma	-68.99	30.16
Najran	Khabash	-76.20	27.64
Jazan	Dayer	-77.09	27.33
Najran	Thaar	-85.75	24.31
Aseer	Tathleeth	-88.30	23.42
Makkah	Kamel	-90.79	22.55
Jazan	Harth	-103.39	18.16
Jazan	Aridhah	-103.08	18.27
Jazan	Eidabi	-103.60	18.09
Najran	Yadmah	-101.28	18.90
Jazan	Reeth	-104.40	17.81
Najran	Kharkheer	-155.46	0.00

APPENDIX J Modal class assignment and the final socioeconomic classes index of the Saudi Governorates

Region	Governorate	p1*	p2*	p3*	p4*	class
Eastern region	Khobar	1	0	0	0	1
Eastern region	Jubail	1	0	0	0	1
Eastern region	Dammam	1	0	0	0	1
Riyadh	Riyadh	1	0	0	0	1
Eastern region	Rass Tanourah	1	0	0	0	1
Eastern region	Qatif	1	0	0	0	1
Makkah	Jeddah	1	0	0	0	1
Qassim	Onaizah	0.999	0.001	0	0	1
Eastern region	Bqeeq	1	0	0	0	1
Riyadh	Dareiyah	0.998	0.002	0	0	1
Eastern region	Khafji	1	0	0	0	1
Eastern region	Ahsa	1	0	0	0	1
Baha	Baha	0.919	0.081	0	0	1
Tabuk	Tabuk	0	1	0	0	2
Madinah	Madinah	0.001	0.999	0	0	2
Madinah	Yanbu	0.234	0.766	0	0	2
Northern border	Arar	0.002	0.998	0	0	2
Riyadh	Kharj	0	1	0	0	2
Qassim	Buraidah	0	1	0	0	2
Riyadh	Shaqraa	0	1	0	0	2
Aseer	Khamis Mushayt	0	1	0	0	2
Aseer	Abha	0	1	0	0	2
Qassim	Rass	0	1	0	0	2
Makkah	Makkah	0	1	0	0	2
Jouf	Skaka	0	1	0	0	2
Qassim	Badae	0	1	0	0	2
Eastern region	Hafr batin	0	1	0	0	2
Hail	Hail	0	1	0	0	2
Jouf	Dawmat Jandal	0	1	0	0	2
Northern border	Toraif	0	1	0	0	2
Riyadh	Zolfi	0	1	0	0	2
Makkah	Taif	0	1	0	0	2
Jouf	Qurayyat	0	1	0	0	2
Qassim	Midnab	0	1	0	0	2
Riyadh	Majmaah	0	1	0	0	2
Baha	Baljurashi	0	1	0	0	2

Najran	Sharourah	0	1	0	0	2
Riyadh	Hareeq	0	1	0	0	2
Riyadh	Selayil	0	1	0	0	2
Riyadh	Hotat bani tamim	0	1	0	0	2
Tabuk	Haql	0	1	0	0	2
Qassim	Bikairiah	0	1	0	0	2
Najran	Najran	0	1	0	0	2
Qassim	Asyah	0	1	0	0	2
Riyadh	Ghat	0	1	0	0	2
Northern border	Rafha	0	1	0	0	2
Baha	Mandaq	0	1	0	0	2
Qassim	Oyoon Jawaa	0	1	0	0	2
Aseer	Uhd Rofidah	0	1	0	0	2
Aseer	Namas	0	1	0	0	2
Qassim	Shamssiyah	0	0.999	0.001	0	2
Eastern region	Noariyah	0	0.998	0.002	0	2
Riyadh	Herimla	0	1	0	0	2
Qassim	Riyadh Khobaraa	0	0.994	0.006	0	2
Riyadh	Aflaj	0	1	0	0	2
Riyadh	Mozahimyah	0	1	0	0	2
Riyadh	Wadi Dawaser	0	0.999	0.001	0	2
Eastern region	Qaryat Alya	0	0.998	0.002	0	2
Riyadh	Romah	0	1	0	0	2
Riyadh	Dawadmi	0	0.974	0.026	0	2
Riyadh	Afeef	0	0.986	0.014	0	2
Tabuk	Wajh	0	0.959	0.041	0	2
Tabuk	Tayma	0	1	0	0	2
Baha	Quraa	0	0.997	0.003	0	2
Riyadh	Thadeq	0	0.961	0.039	0	2
Riyadh	Dhurma	0	0.992	0.008	0	2
Jazan	Jazan	0	0.011	0.989	0	3
Makkah	Rabegh	0	0.018	0.982	0	3
Aseer	Belgarn	0	0	1	0	3
Tabuk	Dhebaa	0	0.001	0.999	0	3
Tabuk	Amluj	0	0.005	0.995	0	3
Jazan	Farasan	0	0	1	0	3
Aseer	Bishah	0	0	1	0	3
Aseer	Dhahran Janoub	0	0	1	0	3
Madinah	Ola	0	0	1	0	3
Madinah	Badr	0	0	1	0	3
Makkah	Khormah	0	0	1	0	3
Jazan	Abu Arish	0	0	1	0	3

Makkah	Raniah	0	0	1	0	3
Hail	Baqaa	0	0	1	0	3
Riyadh	Qowaiyah	0	0	1	0	3
Makkah	Kholais	0	0	1	0	3
Baha	Mikhwah	0	0	1	0	3
Aseer	Sarat Abaida	0	0	1	0	3
Makkah	Jomoom	0	0	1	0	3
Najran	Haboona	0	0	1	0	3
Makkah	Torbah	0	0	1	0	3
Hail	Shanan	0	0	1	0	3
Aseer	Rejal Almaa	0	0	1	0	3
Jazan	Sabyaa	0	0	1	0	3
Madinah	Khaibar	0	0	1	0	3
Baha	Aqeeq	0	0	1	0	3
Aseer	Mahail	0	0	1	0	3
Jazan	Beesh	0	0	1	0	3
Jazan	Uhd Masarha	0	0	1	0	3
Jazan	Dhamd	0	0	1	0	3
Makkah	Qunfudhah	0	0	0.982	0.018	3
Aseer	Majardah	0	0	0.999	0.001	3
Baha	Qilwah	0	0	0.973	0.027	3
Jazan	Darb	0	0	1	0	3
Najran	Badr Janoub	0	0	1	0	3
Madinah	Mahd	0	0	0.595	0.405	3
Jazan	Samtah	0	0	0.998	0.002	3
Najran	Khabash	0	0	1	0	3
Najran	Kharkheer	0	0	1	0	3
Madinah	Hinakiyah	0	0	0.003	0.997	4
Qassim	Nabhanyah	0	0	0	1	4
Makkah	Leeth	0	0	0	1	4
Hail	Ghazalah	0	0	0	1	4
Aseer	Tathleeth	0	0	0	1	4
Jazan	Dayer	0	0	0	1	4
Najran	Thaar	0	0	0	1	4
Makkah	Kamel	0	0	0	1	4
Najran	Yadmah	0	0	0	1	4
Jazan	Harth	0	0	0	1	4
Jazan	Eidabi	0	0	0	1	4
Jazan	Aridhah	0	0	0	1	4
Jazan	Reeth	0	0	0	1	4

*The probability of each Governorate belonging to a class.1