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ORIGINAL PAPER

# Childhood leukaemia incidence and trends in a Middle Eastern country during 1980–2014: a population-based study

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## Abstract

**Background** This retrospective cohort study examines the trends in childhood leukaemia age-standardized incidence rates (ASIRs) (per million person-years) using cases which were diagnosed at age 0–19 years from 1980 to 2014 and recorded in the Kuwait Cancer Control Center (KCCC) registry.

**Methods** Childhood leukaemia age-specific incidence rates overall and by sub-cohorts defined by age (0–4, 5–9, 10–14, and 15–19 years), sex (male, female) and nationality (Kuwaiti, non-Kuwaiti) were computed and age-standardized. Joinpoint regression models were used to evaluate trends in childhood leukaemia ASIRs. Average annual percent change (AAPC) and its 95% confidence interval (CI) were used to interpret the observed trends.

**Results** During the study period, 1077 childhood leukaemia cases of 32.3 million person-years were diagnosed. From 1980 to 2014, the average annual childhood leukaemia ASIR was 53.1 (95% CI 20.9, 85.2). Overall childhood leukaemia ASIRs significantly decreased on average by 6.8% per year (AAPC = −6.8; 95% CI −12.1, −1.1; $p = 0.02$) from 1980 to 1993, but a marginally significant increase in ASIRs from 1993 to 2014 was recorded (AAPC = 2.5; 95% CI −0.5, 5.5; $p = 0.10$). During the entire period, childhood leukaemia ASIRs trends significantly ($p < 0.05$) increased among 6 of 16 sub-cohorts, which was more pronounced among females and 10–14-year-old children.

**Conclusions** Overall, ASIRs significantly increased from 1993 to 2014, which specifically seems to be driven by an increase in ASIRs among females and 10–14 -year-old children. These increasing trends underscore the potential involvement of a range of exposures. Future studies on unravelling such factors may help develop preventive measures to minimize childhood leukaemia risk in this and similar settings in the region.

**Keywords** Childhood leukaemia · Incidence rates · Trends · Sub-cohort analysis · Joinpoint regression

## Introduction

Leukaemia is the most common cancer among children younger than 20 years. Approximately, one-third of leukaemia cases occur in children (age 0–14 years) and one-tenth of these in adolescents (age 15–19 years) (hereinafter referred to as children) [1]. Of leukaemia cases in children, approximately 80% are acute lymphoblastic leukaemia (ALL), primarily in children 1–4 years old, 17% acute myeloid leukaemia (AML) and 3% chronic myeloid leukaemia, with some variation in ALL and AML incidence rates worldwide [2–4]. The aetiology of childhood leukaemia is largely unknown. Both genetic and environmental risk factors have been implicated in the pathogenesis of this cancer of the haematopoietic system, but their implications have not been fully understood [5]. Some of the environmental factors which have been examined

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so far include ionizing radiation, electromagnetic fields, chemicals, infections, environmental tobacco smoke and maternal dietary habits, but hitherto only ionizing radiation has consistently been shown to be associated with childhood leukaemia [6]. Furthermore, based on temporal and geospatial patterning of cases and high population mixing, there is also cumulative evidence of an infectious aetiology of childhood leukaemia [7, 8]. Epidemiological evidence suggests that these possible mechanisms appear to account for only a modest fraction of all cases of childhood leukaemia [9].

A review of childhood leukaemia age-standardized incidence rates (ASIRs) (per million person-years) worldwide based on existing registries revealed a substantial variation within the countries (i.e. in the USA: 22.4–50.2; Canada: 37.9–43.8, China: 27.3) and regions (e.g. South America: 22.2–59.4; Europe: 31.0–49.2; Asia: 22.9–47.2; Oceania 32.2–49.9) [9]. ASIRs (per million person-years) of childhood leukaemia (lymphoid, myeloid) also vary substantially across the Middle Eastern countries, including Israel (26.6, 10.6), Saudi Arabia (29.6, 8.5) and Kuwait (37.5, 11.8) [10]. Nevertheless, efforts to assess global variations in childhood leukaemia incidence rates are hampered by the lack of population registries, disparities in diagnostic procedures, completeness of case ascertainment and competing risks such as infectious diseases among leukaemia-affected immunocompromised children [11]. Therefore, available evidence is inconsequential in linking childhood leukaemia risk variation to involvement of one or more risk factor [9].

In addition to geographical variations, examination of temporal trends in leukaemia and lymphoma incidence among children across European countries identified a significant linear average annual increase by 0.7–1.4% during the past several decades [12, 13]. Similarly in the USA, between 2007 and 2011, age-adjusted incidence rates of leukaemia among children (< 20 years) in almost all racial groups have shown upward trends [14]. A more recent study based on the data from 19 countries across the globe showed 0.66% and 0.93% average annual increase in leukaemia incidence among children (0–14 years) and adolescents (15–19 years), respectively, over the period 1991–2010 [15]. Amongst the Middle Eastern countries, only in Iraq has it been shown that the incidence rate (per million person-years) of childhood leukaemia increased from 26 (1993) to 122 (2006) with a somewhat declining trend thereafter [16]. Nonetheless, there is a paucity of comparable published data on the temporal variation in childhood leukaemia incidence from most Middle Eastern countries, including Kuwait. Therefore, this study evaluates trends in ASIRs (per million person-years) of childhood leukaemia diagnosed at age 0–19 years in Kuwait from 1980 to 2014 overall and by specific sub-cohorts defined by age, sex and nationality.

## Patients and methods

### Study setting, design and population

Kuwait is a small oil-rich country with a total approximate area of 18,000 $km^2$ and a total population of 4.25 million. Kuwait is located at the north-west corner of the Arabian Gulf, between latitudes 28° 45′ and 30° 05′ N and longitudes 46° 30′ and 48° 30′ E. The state is bounded by Saudi Arabia to the south and by Iraq to the north and west. Non-nationals constitute about 70% of the population, and resultantly, 80% of the labour force comprises migrants [17]. Amongst nationals, the male and female literacy rates (defined as individuals aged 10 years or more who can read and write) are 98.5% and 91.2%, respectively, with a sex ratio (male/female) of 1:1.04 at birth [18].

Administratively, Kuwait is divided into six governorates, and each governorate has a well-defined area, its population and comprises several demarcated districts. Medical services in each governorate comprise a network of primary health care clinics and a general public hospital. In addition, there are centralized specialty hospitals, including the Kuwait Cancer Control Center (KCCC). KCCC is the specialized cancer treatment hospital equipped with modern facilities for cancer diagnosis, treatment and follow-up. Nearly all suspected cancer patients are referred to KCCC. Cancer patients who are initially diagnosed and/or treated elsewhere are also referred to the KCCC for further follow-up. Health care at all levels is provided free of charge by the government to the nationals, whereas migrant residents have to pay a nominal fee to access medical services [19].

### Data sources

For this retrospective cohort study, the data on incident leukaemia (lymphoid, C91; myeloid, C92–94; not otherwise specified, NOS-C95 or lymphoid ICD-O-3 codes 9811–9837, 9940; myeloid codes 9742, 9840, 9860–9931, 9945–8; leukaemia NOS; codes 9800–9) cases aged 19 years or less, diagnosed (haematology and/or cytology) and registered in the Kuwait Cancer Control Center registry from January 1, 1980 to December 31, 2014 were obtained. For each patient, the dataset included date of birth, date of leukaemia diagnosis, age (years) at diagnosis, sex (male, female) and nationality (Kuwaiti or non-Kuwaiti). Annual estimates of the mid-year population stratified by age, sex and nationality (Kuwaiti, non-Kuwait) were obtained from the Public Authority for Civil Information Department, Ministry of Interior, Kuwait. The study protocol was approved by the Ethics Committee of the Ministry of Health, Kuwait.

## Statistical analysis

### Age-specific and age-standardized incidence rates

We computed an overall childhood leukaemia incidence rate (per million person-years) during the study period and the age-specific incidence rates (per million person-years) for 5-year age bands (0–4, 5–9,10–14, and 15–19 years) as the quotient of the number of cases and the number of person-years at risk in the respective sub-cohorts defined by cross-classification of the period of diagnosis (1980–1984, 1985–1989, 1990–1994, …, 2010–2014), sex (male and female) and nationality (Kuwaiti or non-Kuwaiti). Person-years were defined as mid-year population counts of each year in the relevant categories of age, sex and nationality. ASIRs (per million person-years) of childhood leukaemia were computed using World's Standard Population [20], first by year for unstratified data and then by sub-cohorts as defined above.

### Joinpoint regression analysis

Trends in the ASIRs (per million person years) of childhood leukaemia were evaluated using joinpoint regression analysis [21]. Joinpoint regression models assess the variation in the trends in incidence rates by identifying the combinations of trends that provide a statistically significantly better fit to a data series than a single trend line fitted by Poisson regression or time-series models [22, 23]. This procedure tends to determine the number of joinpoints that are adequate for assessing significant changes in incidence trends over time. Specifically, this technique is designed to identify the calendar year (joinpoint) wherein statistically significant abrupt change in temporal trends occurred [21]. First, we determined the overall trend, wherein the dependent variable was the age-standardized incidence rate (per million person-years) and the independent variable was calendar year (1980–2014). Next, we evaluated the trends in ASIRs (per million person-years) across the periods of diagnosis separately within age groups, sex and nationality. Subsequently, we evaluated the trends in sub-cohorts-specific ASIRs (per million person-years) wherein the independent variable was calendar year categorized as 5-year period (1980–1984, 1985–1989, … , 2010–2014), and sub-cohorts were defined by cross-classification of age categorized as 5-year brackets (0–4, 5–9, 10–14, and 15–19 years), sex (male or female) and nationality (Kuwaiti or non-Kuwaiti). Because of non-normal distribution of age-standardized rates, log transformation was used. The logarithm of the age-standardized rates was assumed to present a linear trend between joinpoints, with errors following a Poisson distribution. The analysis started with zero joinpoints (corresponding to a straight regression line) and tested whether one or more joinpoints were significant. Additional joinpoints were incrementally tested with a minimum of four observations between joinpoints. A default maximum number of joinpoints was set at three. Joinpoints were evaluated by the grid search and the Monte Carlo permutation method, with 4499 replicates and 0.05 as level of significance. Model estimates included the number of joinpoints as well as the slopes and intercepts for each regression line between two joinpoints or for entire period if no joinpoint detected. Additionally, annual percentage change (APC) for each identified trend and average annual percentage changes (AAPC), which is a weighted summary measure of the trend over a pre-specified fixed interval, and their 95% confidence intervals (CI) were estimated. Where a significant joinpoint was detected, AAPC along with its 95% CI was reported for each of the linear segments before and after the joinpoint, otherwise AAPC (95% CI) was reported for the entire study (1980–2014) in addition to graphs and average ASIRs (95% CI). Results of this analysis are reported as significant ($p < 0.05$) or marginally significant ($0.05 < p \leq 0.10$), and non-significant otherwise [24].

## Results

From January 1, 1980 to December 31, 2014, a total of 1077 childhood leukaemia cases were diagnosed of 32.3 million person-years at risk and registered in the KCCC registry. Of these cases, 57.6% were male, 52.1% Kuwaiti, 55.7% children (aged 14 years or less) and 44.3% adolescents (aged 15–19 years), hereafter labelled as children. Of 1077 childhood leukaemia patients, 848 (78.7%), 185 (17.2%) and 43 (0.1%) had lymphoid, myeloid and undifferentiated leukaemia, respectively. For the period 1980–2014, the average annual ASIR (per million person-years) of childhood leukaemia was 53.1 (95% CI 20.9, 85.2). Childhood leukaemia ASIRs fluctuated over the study period and varied by age, sex and nationality. Joinpoint regression modelling revealed that overall childhood leukaemia ASIRs (per million person-years) decreased by 6.8% per year on average from 1980 to 1993 (AAPC = −6.8; 95% CI −12.1, −1.1; $p = 0.02$). However, a marginally significant increase in the childhood leukaemia ASIRs was recorded from 1993 to 2014 (AAPC = 2.5; 95% CI −0.5, 5.5; $p = 0.10$) (Fig. 1).

The overall childhood age-band specific ASIRs ranged from lowest to highest for the children aged 0–4 years (ASIRs = 20.6; 95% CI 16.9, 24.3) and children aged 15–19 years (ASIRs = 46.4; 95% CI 36.9, 55.9). Furthermore, average annual ASIR (per million person-years) was higher for males than females (34.0; 95% CI 28.8, 39.1 versus 23.9; 95% CI 19.2, 28.6) and for Kuwaiti than non-Kuwaiti residents (30.7; 95% CI 25.9, 35.5 versus 27.1; 95% CI 21.7, 32.5) (Table 1). Joinpoint regression ASIRs analysis

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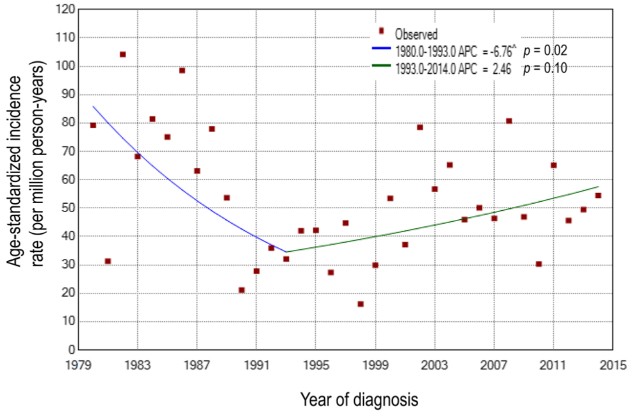


**Fig. 1** Observed and joinpoint regression model fitted age-standardized incidence rates of childhood leukaemia (all types) in Kuwait, 1980–2014

separately for age, sex and nationality revealed a significant joinpoint for age band 10–14 years for the period 1999–2014 (AAPC = 15.4; 95% CI 4.3, 27.6; $p = 0.03$) and female sex for the period 1980–2000 (AAPC = 21.0; 95% CI 1.1, 44.7) (Table 1, Fig. 2).

Joinpoint regression analysis by sub-cohorts revealed that, from 1980 to 2010, childhood leukaemia ASIRs statistically significantly increased in 6 of 16 sub-cohorts, including 0–4-year-old female Kuwaiti (AAPC = 7.1; 95% CI 1.8, 12.7; $p = 0.02$), 5–9-year-old both male (AAPC = 7.1; 95% CI 4.8, 9.3; $p < 0.01$) and female (AAPC = 4.5; 95% CI 0.1, 9.1; $p = 0.05$, marginally significant) Kuwaiti, 10–14-year-old female Kuwaiti (AAPC = 3.7; 95% CI 0.9, 6.6; $p = 0.02$) and 15–19-year-old both male (AAPC = 3.8; 95% CI 1.2, 6.5; $p = 0.01$) and female (AAPC = 3.4; 95% CI 1.1, 5.7; $p = 0.01$) Kuwaiti. From 1980 to 2010, though statistically marginally significant, an increased leukaemia risk was also experienced by 10–14-year-old male Kuwaiti children (AAPC = 5.5; 95% CI −0.2, 11.5; $p = 0.06$) (Table 2, Fig. 3). The remaining sub-cohorts did not have significant AAPC in childhood leukaemia ASIRs during the entire study period (Table 2).

## Discussion

Temporal variations in disease incidence are usually attributed primarily to changes in risk factors. The changes in disease incidence may also be influenced by improvement in diagnostic or classification procedures, differences in levels of ascertainment as might have happened during the Iraqi invasion and occupation of Kuwait in August 1990 [16], population mixing [25], in-migration and diversity of origin [26], merely a chance occurrence and/or indeed a true increase in disease risk. Since little is known about the aetiology of childhood leukaemia, it is imperative to correctly interpret incidence variations over time to determine whether such variations are due to changes in diagnostic or classification procedures, or whether they are related to putative causal factors. However, different risk factors may produce different time trends. Cancers that (primarily) have an infectious aetiology may show cyclical effects, whereas cancers that (primarily) have a non-infectious aetiology are more likely to show gradual monotonic increases (or decreases) over time [27]. This retrospective cohort study examines the trends in childhood leukaemia ASIRs (per

**Table 1** Number of new childhood leukaemia cases and world age-standardized incidence rate (ASIR) (per million person-years), average annual percentage change (AAPC) by age, sex and nationality in children aged 0–19 years, 1980–2014

| Characteristic | Cases (*n*) | ASIR (95% CI) | Trend 1 | | Trend 2 | |
|---|---|---|---|---|---|---|
| | | | AAPC (95% CI) | *p* value | AAPC (95% CI) | *p* value |
| Age (years) at diagnosis | | | | | | |
| 0–4 | 477 | 20.6 (16.9–24.3) | 2.2 (−8.5, 14.2) | 0.64 | 15.4 (4.3, 27.6)* | 0.03* |
| 5–9 | 255 | 23.0 (18.0–28.0) | 10.8 (−4.7, 28.8) | 0.14 | | |
| 10–14 | 193 | 25.7 (20.3–31.1) | 0.6 (−10.1, 10.0) | 0.84 | | |
| 15–19 | 152 | 46.4 (36.9–55.9) | 15.0 (−8.9, 45.1) | 0.18 | | |
| Sex | | | | | | |
| Male | 620 | 34.0 (28.8–39.1) | 6.3 (−7.8, 22.6) | 0.32 | −0.7 (−43.6, 74.9) | 0.96 |
| Female | 457 | 23.9 (19.2–28.6) | 21.0 (1.1, 44.7)* | 0.05* | | |
| Nationality | | | | | | |
| Kuwaiti | 561 | 30.7 (25.9–35.5) | 11.2 (−2.5, 26.8) | 0.09 | | |
| Non-Kuwaiti | 516 | 27.1 (21.7–32.5) | 7.2 (−10.1, 27.8) | 0.36 | | |

For age group 10–14, trends 1 and 2 spanned the periods 1980 to 1999 and 1999 to 2014, respectively. For female sex, trends 1 and 2 spanned the periods 1980 to 2000 and 2000 to 2014, respectively

*Statistically significant $p < 0.05$

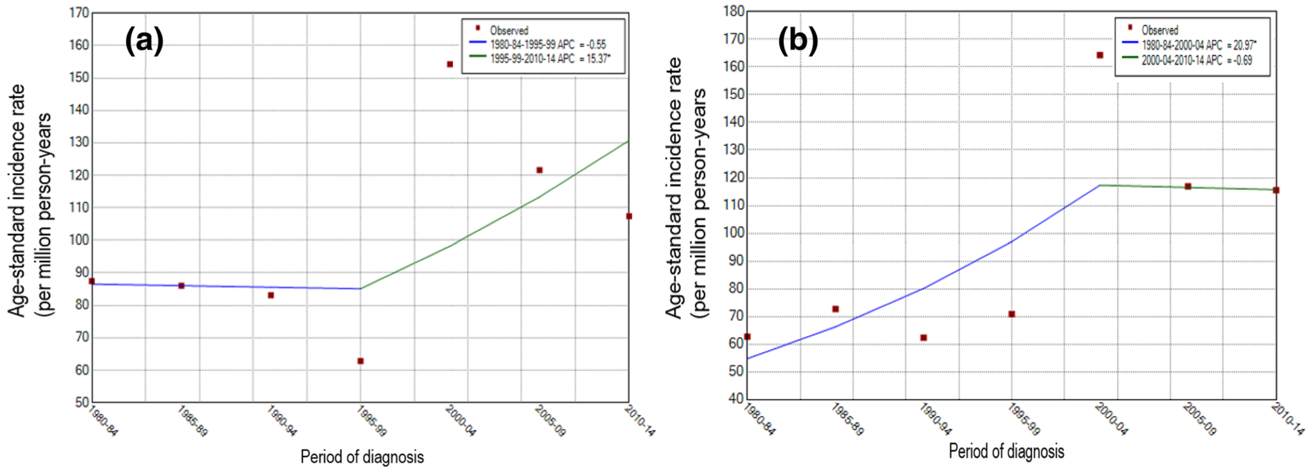


**Fig. 2** Significant joinpoints in temporal trends of childhood leukaemia age-standardized incidence rates (per million person-years) for **a** age (10–14 years) and **b** female sex in Kuwait, 1980–2014

**Table 2** Multivariable joinpoint regression analysis of trends in age-standardized incidence rates of childhood leukaemia (0–19 years) by sub-cohorts defined by age, sex and nationality, 1980–2014

| Synthetic sub-cohort characteristics [age (year) at diagnosis, sex, nationality] | Average annual percent change (1980–2014) | 95% confidence interval | *p* value |
|---|---|---|---|
| 0–4 years, male, Kuwaiti | 3.7 | −1.1, 8.7 | 0.10 |
| 0–4 years, female, Kuwaiti | 7.1^ | 1.8, 12.7 | 0.02 |
| 0–4 years, male, non-Kuwaiti | 1.7 | −6.1, 0.2 | 0.61 |
| 0–4 years, female, non-Kuwaiti | 1.6 | −5.5, 9.2 | 0.62 |
| 5–9 years, male, Kuwaiti | 7.1^ | 4.8, 9.3 | < 0.01 |
| 5–9 years, female, Kuwaiti | 4.5^ | 0.1, 9.1 | 0.05 |
| 5–9 years, male, non-Kuwaiti | −1.8 | −6.7, 3.4 | 0.41 |
| 5–9 years, female, non-Kuwaiti | −2.2 | −7.2, 3.2 | 0.34 |
| 10–14 years, male, Kuwaiti | 5.5 | −0.2, 11.5 | 0.06 |
| 10–14 years, female, Kuwaiti | 3.7^ | 0.9, 6.6 | 0.02 |
| 10–14 years, male, non-Kuwaiti | −0.3 | −4.7, 4.3 | 0.86 |
| 10–14 years, female, non-Kuwaiti | 0.9 | −1.7, 3.6 | 0.41 |
| 15–19 years, male, Kuwaiti | 3.8^ | 1.2, 6.5 | 0.01 |
| 15–19 years, female, Kuwaiti | 3.4^ | 1.1, 5.7 | 0.01 |
| 15–19 years, male, non-Kuwaiti | −2.4 | −7.6, 3.0 | 0.29 |
| 15–19 years, female, non-Kuwaiti | −0.7 | −5.6, 4.5 | 0.75 |

^Statistically significant trend

million person-years) using cases which were diagnosed at age 0–19 years between 1980 and 2014 and recorded in the KCCC registry.

## Magnitude of average annual ASIRs of childhood leukaemia in Kuwait and comparison with other populations

In the present work, childhood leukaemia ASIRs in Kuwait over a period of more than three decades are reported. From 1980 to 2014, 1077 children younger than 20 years were diagnosed with childhood leukaemia, of whom 57.6% were male and 52.1% Kuwaiti. During this period, the average annual ASIR (per million person-years) of childhood leukaemia was 53.1 in Kuwait. A previous analysis of the data from 2003 to 2007 for the same age group (0–19 years) in Kuwait showed an average annual ASIR (per million person-years) of lymphoid and myeloid leukaemia combined of 49.3 [10], which is somewhat lower than the figure found in the present analysis. Furthermore, in the present study, the average annual ASIR (per million person-years) of childhood leukaemia (lymphoid and myeloid combined) in comparison with the countries located in the same region is higher than the corresponding estimates reported from Saudi Arabia

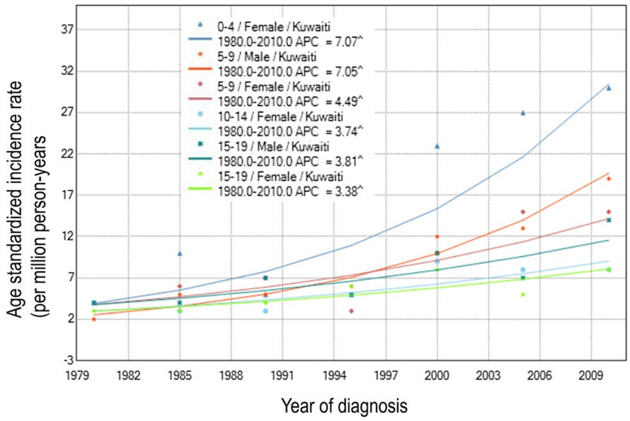


**Fig. 3** Incidence trends in age-standardized rates of childhood leukaemia (all types) by synthetic sub-cohorts defined by age (years) at diagnosis, sex and nationality among children in Kuwait, 1980–2014

(38.7) and Israel (47.2), but slightly lower than the estimate reported from Oman (60.7) [10, 28]. The average annual ASIRs of childhood leukaemia in other world's regions such as East Asia or Oceania included in this referred comparison nearly had the same range. However, countries included from the African region had lower average annual ASIR of childhood leukaemia than the countries in the Middle Eastern region, including Kuwait [10].

In the USA, from 2001 to 2009, the ASIR (per million person-years) of childhood leukaemia slightly varied among various racial/ethnic groups, including Hispanic (56.6), non-Hispanic (42.5) and White (47.9); more or less in the same range recorded in the present study, but substantially higher than the figure reported among African Americans (28.0) [29]. Between 2007 and 2014 in the USA, the average annual ASIR (per million person-years) of all types of leukaemia among children (< 20 years) was 49 [14, 30], slightly lower than the one reported in this study from Kuwait. In Europe, from 1991–2010, based on the data from 53 registries located in 19 European countries, the combined average annual ASIR (per million person-years) of leukaemia among children (0–14 years) was 46.9 (based on 48,458 paediatric cases), and among adolescents (15–19 years) was 23.6 (based on 4702 adolescents cases) [15]. Another international study based on the data collected from 2001 to 2010 by 153 registries located in 62 countries of various world regions reported leukaemia as the most common cancer among children (0–14 years) (average annual ASIR = 46.4 per million person-years, based on 92,085 cases) and the third most common cancer among adolescents (15–19 years) (average ASIR = 28.5 per million person-years, based on 155 cases). Furthermore, the average annual ASIRs (per million person-years) of leukaemia among children (0–14 years) and adolescents (15–19 years) varied widely across various world regions, including Sub-Saharan Africa (12.5; 19.0), North Africa (28.2; 26.4), Oceania (56.4; 43.0) and USA (65.4; 43.0, in White Hispanics) [31]. These variations of childhood leukaemia ASIRs across various world regions and diverse populations, among others, may be ascribed to disparities in the distribution of underlying risk factors such as genetics and environmental influences or combinations thereof, including prenatal and childhood exposure, genetic propensity, socio-economic differentials or an aberrant immune response to delayed infection with hitherto-unknown agents, the incidence of which may vary in different settings. It has been postulated that infection by these agents may trigger conversion of preleukaemic clones into overt precursor B-cell acute lymphocytic leukaemia [32, 33]. Furthermore, based on the average annual ASIRs reported in this study, Kuwait may be rated among the high-risk countries regarding childhood leukaemia incidence over a period of more than three decades.

## Trends in childhood leukaemia ASIRs in Kuwait and comparison with other populations

### Overall trend in ASIRs of childhood leukaemia

In this population-based registry study, trends in ASIRs (per million person-years) of leukaemia among children (0–19 years) from 1980 to 2014 are reported. Overall, from 1980 to 1993, there was statistically significant decrease in childhood leukaemia ASIRs (AAPC = −6.8), followed by a marginally significant increase in ASIRs (AAPC = 2.5) from 1994 to 2014. We are unaware of any published data from the Middle Eastern region that evaluated the AAPC in relation to changing incidence rates of childhood leukaemia to contrast with our results. However, a study from Iraq reported an increasing childhood leukaemia incidence rate (per million person-years) from 1993 (26) to 2006 (122) that then sharply declined in 2007 [16]. A study from Thailand documented an average annual ASIR (per million person-years) of childhood leukaemia as 32 with an increasing trend (AAPC = 1.7) from 1990 to 2011 [34], substantially lower than the estimates reported in the present study. In Italy, between 1976 and 2011, the incidence rates of childhood leukaemia showed statistically non-significant variation [35]. We are unaware of any published data on declining trend in childhood leukaemia risk in any paediatric/adolescent population during the same period as in this study i.e. 1980–1993. However, there was some evidence of deceleration of trends in overall cancer incidence during the 1990s in the USA [15]. In Europe, between 1978 and 1997, leukaemia incidence increased marginally (AAPC = 0.6), exclusively due to the 0.8% annual increase in acute lymphoblastic leukaemia. However, during the same period, declining trends were recorded for chronic myeloid leukaemia (AAPC = −0.4), other specified leukaemias (APPC = −0.6) and unspecified leukaemia (AAPC = −1.0) [1]. In the present study, compared with an overall increasing childhood leukaemia incidence rate from 1993 to 2014 (AAPC = 2.5) in most European countries, during a nearly comparable period (1991–2010), there was a relatively small but significantly increasing trend in leukaemia incidence rates among children (0–14 years) (AAPC = 0.66) and adolescents (15–19 years) (0.93) [15]. Similarly, in the USA, from 1975 to 2014, a significant increasing trend (AAPC = 1.7) in the age-adjusted incidence rate of all childhood leukaemia types among all races was recorded [30]. Thus far, in childhood leukaemia research, no single factor has been implicated other than ionizing radiation, which has been significantly linked to acute lymphoblastic leukaemia or acute myeloid leukaemia [5]. Most environmental risk factors have been found to be weakly and inconsistently associated with either form of acute childhood leukaemia [5, 36]. Nonetheless, secular changes in birth weight in Kuwait and elsewhere and exposure to some hitherto-unknown agent could possibly be the underlying reasons. Furthermore, in this study, an increasing trend in ASIRs over the period spanning from 1993 to 2014 could possibly be a surrogate for socio-economic status improvement, increased population mixing or lack of exposure to certain viruses, as speculated elsewhere, and/or it might in part represent variation in the ascertainment of leukaemia cases in successive decades [13, 37–39]. Additionally, during the Iraqi invasion in the summer of 1990, the Kuwaiti population was exposed to by-products of petroleum fires that were set by Iraqi troops evicted as a result of US military operations [40]. An analogous situation in the Basra region of neighbouring Iraq with environmental insults such as pyrophoric depleted uranium, leukaemogenic benzene and undifferentiated water and air pollution have been speculated as underlying agents for the increasing trend of leukaemia incidence from 1993 to 2006 [16].

### Trends in the incidence rates of childhood leukaemia by sub-cohort

Joinpoint regression analysis of trends revealed that, from 1980 to 2014, childhood leukaemia ASIRs significantly increased among 6 of 16 sub-cohorts, including 0–4-year-old female Kuwaiti (AAPC = 7.1), 5–9-year-old both male (AAPC = 7.1) and female (AAPC = 4.5) Kuwaiti, 10–14-year-old both male (AAPC = 5.5) and female (AAPC = 3.7) Kuwaiti and 15–19-year-old both male (AAPC = 3.8) and female (AAPC = 3.4) Kuwaiti children. Hence, the significantly increasing trend in childhood leukaemia ASIRs from 1993 to 2014 in this study primarily seems to be driven by increased leukaemia incidence among Kuwaiti children of both sexes and in almost all the age ranges considered. During the nearly comparable period from 1992 to 2013, an increase in the childhood leukaemia incidence rates with substantial variations in AAPCs by age, sex and race/ethnicity have also been recorded in the USA. For example, from 1992 to 2013, in all racial/ethnic groups, all leukaemia incidence rates were higher in males and the highest in children aged 1–4 years. Furthermore, the incidence rate of all leukaemias increased significantly both among Hispanic White children (APC = 0.96) and non-Hispanic White children (APC = 0.63), but not among non-Hispanic Black children or among non-Hispanic Asian children [41]. Another study from the USA reported racial variations in leukaemia incidence rates with significant APC (1.6) only for Hispanic children (0–19 years) [29]. Even in Europe, the increase in incidence was not constant by cancer type, region or over time; rather, there was a suggestion of stabilization in the trend for all cancers among adolescents in the whole of Europe [15]. During an overlapping period from 1978 to 2007 in 24 populations, the temporal trends in lymphoid and myeloid leukaemia incidence rates among children (age 0–19 years) generally did not change meaningfully. However, lymphoid leukaemia rates (per million person-years) during 2003–2007 in 54 populations in the same age range varied about tenfold, with the highest rates in US White Hispanics (50.2) and Ecuador (48.3), and the lowest in US blacks (20.4), Tunisia (17.7) and Uganda (6.9). Myeloid leukaemia rates varied only about fivefold, with the highest rates in the Philippines and Korea (14.0) and the lowest in Eastern Europe (5.9 in Serbia and 5.3 in Czech Republic) and Uganda (2.7) with the boy/girl average incidence rate ratio of two or less. Furthermore, it was noted that age-specific patterns were generally consistent within most countries worldwide [10]. Another relatively recent study based on globally collected data from large number of populations reported that leukaemia ASIRs among children and adolescents did not vary by regions/countries, but substantial variations in ASIRs within countries were recorded by age, sex and race/ethnicity [31]. In the present study, the differential propensity for childhood leukaemia risk among Kuwaiti versus non-Kuwaiti children may be ascribed to genetic differences and socio-economic status, as non-Kuwaiti children born to migrant parents from other Asian countries are economically most often less well off than Kuwaiti children. Previously, ethnic differences in the childhood leukaemia incidence rates have been shown in Kuwait and New Zealand [9]. Elsewhere, it has been shown that incremental temporal changes seem to be influenced by ethnicity/genetic and environmental factors. These variations in the childhood leukaemia risk were more conspicuous among children of European lineage than those of other ethnicities such as Asian or African lineage [4, 13, 42, 43]. As noted earlier, considering all the aetiological studies of childhood cancer, other than ionizing radiation, no single factor has been shown to be significantly associated with childhood leukaemia risk [13]. Nonetheless, it has been hypothesized that a shift towards increasing birth weight and exposure to infection might be underlying reasons [13, 44–46]. In parallel, it has been shown that there is a tendency towards increasing birth weight (> 4 kg) in Kuwait, which has an independent and significant link with a high prevalence of overweight (17.7%) and obesity (33.7%) among 6574 children (6–18 years) enrolled from 244 schools across all six governorates of Kuwait [47]. Analogously, therefore, increasing birth weight in Kuwait might have a link with increasing childhood leukaemia incidence rates, as conjectured earlier [13, 44–46]. However, this aspect needs further research. Furthermore, subgroups of the studied population affected by unfavourable trends in childhood leukaemia incidence could be the focus of further research to unravel the underlying risk factors.

The data presented in this study have some strengths and limitations, which should be considered when interpreting the results. This is perhaps the first study from a Middle Eastern country to examine and quantify the magnitude and trends in childhood leukaemia incidence rates over a period encompassing more than three decades. Some of the limitations of these data include (i) the possibility of classification errors over such an extended period and some degree of under-reporting of childhood leukaemia cases. However, the potential for such errors appears very minimal, since KCCC is the only national and centralized cancer diagnosis and treatment centre wherein these services are provided free of cost to Kuwaiti nationals and at nominal cost to non-Kuwaiti residents; (ii) During the summer of 1990, there was a disruption of health services due to the Iraqi invasion of Kuwait, until Iraqi troops were ejected by the USA-led military operation in 1991. During this period, childhood leukaemia cases might have been under-diagnosed and mis-diagnosed, or some childhood leukaemia cases might even have been missed. Additionally, many nationals and non-nationals temporarily left Kuwait around this period. Nevertheless, we assume that the number of such leukaemia cases must be very minimal. However, we do not have empirical evidence to support this contention; (iii) Cross-classification of leukaemia cases and person-years at risk by age, sex and nationality resulted in the sparse data in sub-cohorts. Therefore, sub-cohort-specific estimates of trends in incidence rates and corresponding trend lines appear somewhat unstable, potentially due to a sparse data bias [48]. However, in our data set, we did not have any cell frequency of five or less of leukaemia cases in a multiway contingency table resulting from the cross-classification of age, sex and nationality. Therefore, it was somewhat re-assuring that the greater than usual variability in the thinned data does not necessarily invalidate the results of this study. Pooling data from neighbouring countries with nearly similar settings may help overcome this sparse data issue.

In conclusion, our data suggest a substantial increase in the incidence rates of childhood leukaemia in Kuwait during the period 1993–2014, which seems to have been driven by increased incidence rates among female children and in the age group of 10–14 years. This differential increase in ASIRs by age and sex may not necessarily be due to exposure to some environmental risk factors or disease misclassification, since such factors would have had to increase the leukaemia risk at a greater rate among females and 10–14-year-old children. This differential increase in the incidence rates could possibly be due to changes in birth weight or alarmingly high prevalence of childhood obesity (40.9%) among 6–8-year-old Kuwaiti children [49], as hypothesized elsewhere [41]. Therefore, to design a potential prevention programme, future studies may contemplate identification of the range of potential risk factors and determine their relative contributions to childhood leukaemia risk in Kuwait. The resultant understanding of such factors may help develop effective preventive measures to minimize the childhood leukaemia risk in this and other similar settings in the region.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

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