SEASONAL VARIATION OF TYPE 1 DIABETES DIAGNOSIS IN CHILDREN, ADOLESCENTS AND YOUNG ADULTS IN KENYATTA NATIONAL HOSPITAL - RETROSPECTIVE COHORT STUDY

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H58/36080/2019
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2022

DECLARATION

I declare that this dissertation is my original work and has not been presented for the award of a degree in any other university.

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DEDICATION

I dedicate this work to;

- All children, adolescents and young adults with diabetes type 1.
- My family for their encouragement and support.

COLLABORATING INSTITUTIONS

1. KENYATTA NATIONAL HOSPITAL
2. UNIVERSITY OF NAIROBI

ACKNOWLEDGEMENT

I sincerely thank the following

- My supervisors Dr. Lucy Mungai and Prof.Dalton Wamalwa for their guidance and support.
- My dad Joseph Kariuki and late mum Salome Wangu for their parental guidance, persistence and love for academic pursuit and excellence.
- My family and children for their support.
- Members of the Department of Paediatrics and Child Health for their support during this study process.
- Staff at the Health Records Department Kenyatta National Hospital for their support.
- My statistician Joshua Atunga for his continued assistance in data management.

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ABBREVIATIONS

CMV	Cytomegalovirus
DKA	Diabetic Keto-Acidosis
FAO	Food and Agriculture Organization
HB_{A1c}	Glycated Hemoglobin
HCO^{-3}	Bicarbonate
HUS	Hemolytic Uremic Syndrome
IDDM	Insulin Dependent Diabetes Mellitus
IDF	International Diabetes Federation
JF	January-February
JJA	June-July-August
KNH	Kenyatta National Hospital
MAM	March-April-May
MHC	Major Histocompatility Complex
MODY	Maturity Onset Diabetes of the Young
NIDDM	Non-Insulin Dependent Diabetes Mellitus
NRI	National Rainfall Index
OND	October-November-December
T1DM	Type 1 Diabetes Mellitus
TEDDY	The Environmental Determinants of Diabetes in the Young
WHO	World Health Organization

DEFINITION OF TERMS

Season-each of the four divisions of the year (MAM, OND, JJA and JF) marked by particular weather patterns primarily by amount of rainfall.

Precipitation-amount of rainfall in a given duration

National Rainfall Index- it is a determination of how much average rainfall or precipitation that has fallen over a specific area or region.

Molecular mimicry-possibility of foreign antigens being similar genetically or structurally wit self-antigens leading to autoimmunity.

Kussmaul breathing - (deep, heavy, non-labored rapid breathing), fruity breath odour (due to acetone)

Allele-different forms of a gene that cause differences in individuals.

ABSTRACT

Background-The most commonly diagnosed endocrine disorder in adolescents, children and young adults is T1DM. The prevalence of T1DM in Kenya is rising with an estimated 1,694 children and adolescents having T1DM (IDF Diabetes Atlas 2019). Seasonal variation is an environmental factor that triggers type 1 diabetes onset in genetically predisposed children. Studies done show an increased type 1 diabetes diagnosis in cold seasons for particular age groups compared to warm seasons.

Objectives-The study aimed to determine the seasonal variation of T1DM diagnosis in children, adolescents and young adults in diabetes clinic in KNH between 2009 to 2021 and its correlation with the various age categories and geographical patterns.

Methodology-This was a retrospective cohort study carried out at diabetic clinic at Kenyatta National Hospital among children, adolescents and young adults who at the point of diagnosis with T1DM were aged between 0 - <25 years between 2009 to 2021.Demographic data (age, sex), age at diagnosis with T1DM, month and season of diagnosis and patient's geographical origin were recorded in a data collection form. The outcomes of interest were the seasonal variation in the diagnosis of T1DM based on sex, age and age categorization, geographical origin, month and season of diagnosis of T1DM.Data was analyzed based on age, sex and month, season of diagnosis and geographical origin. Age categorization of 5 year intervals at 0-4 years, 5-9 years, 10-14 years, 15-19 years and 20-24 years were used and seasonal and geographical origin were compared. Categorical variables were summarized into proportions and continuous variables into medians where applicable. Statistical analytical methods using available software R Studio was used to inference any association and strength or significance of the associations thereof in seasonality of diagnosis of T1DM. Statistical tests were interpreted at 5% level of significance (p value less or equal to 0.05) and findings presented in form of tables, graphs and charts.

Results-A total of 1,250 patient charts were identified by health records using ICD 10 code for T1DM diagnosis. Out of these 379 were consecutively sampled and included in the study and analyzed. The median age was 9 years with an interquartile range of 3-12 years. There were 201(53%) males and 178(47%) females. The data was grouped into six age categories ages: 10-14 years were the majority at 35.1% (n=133) followed by those aged 0-4 years at 29% (n=110). Participants aged 20-24 years were the least at 4.5% (n = 17).Four Kenyan seasons were used as per Kenya Meteorological Department namely MAM or *"long rains"* season, OND or *"short rains"* season , JJA &S or *"cool dry"* season and JF or *hot and dry*

season. Among the four seasons, JJA&S had the highest diagnosed cases at 37.5% followed by MAM at 27.4%. JF season had the least diagnoses at 16.4%.In the 12 months of the year, March had the highest percentage of cases at 12.1% followed by August and September at 11.3% each. The month of November had the least diagnoses at 3.2%.To determine seasonality of the data decomposition of additive time series to was done using two approaches. The first was a time series plot of the monthly decomposed data for each year from 2009 to 2021 and the second involved time series plot of the four Kenyan seasons decomposed data for each year from 2009 to 2021.In both, repeating patterns of highs (peaks) and lows (troughs) was observed in the seasonal panel related to the months and seasons of the year, which suggested seasonality in the data. A significant statistical association between gender and season of diagnosis was established ($p<0.01$) with more females in the MAM season. There was also an association between the various age categorization at diagnosis and seasonality ($p=0.04$).It was also established that there was a significant association between the place of residence (urban vs rural) and season of diagnosis ($p=0.004$).

Conclusion-In this study we observed seasonality of T1DM in children, adolescents and young adults attending KNH diabetic clinic. This is the first study exploring seasonality of T1DM in Kenya. The study alludes to the role of environmental factors in triggering T1DM diagnosis. The study also provides a basis for evaluation of the time varying environmental variables such as rainfall precipitation, temperature, seasonal viral and bacterial infections and specific geographical points of locations in regards to onset of T1DM diagnosis.

1. INTRODUCTION

1.1 Introduction and Classification of Diabetes Mellitus

Diabetes mellitus is a disorder of metabolism that exhibits with persistent hyperglycaemia with altered metabolism of carbohydrate, fat and protein arising from absolute or relative anomalies in insulin secretion, its action or both(1). The diabetes mellitus main forms are characterized by insulin deficiency and insulin resistance. The two broad categories are T1DM and T2DM.T1DM arises from insulin deficiency due to pancreatic Beta-cell damage whereas T2DM is due to insulin resistance at insulin action sites with variation in impairment of Beta-cell function(6–8). Both T1DM and T2DM commence with an abnormal phase of homeostasis of glucose as the disease progresses. T1DM arises from absolute or near-absolute insulin deficiency(2,9–12). T2DM is exhibited by varying degrees of impaired insulin secretion, resistance to insulin and increased glucose production(8,10,13,14). Distinct metabolic and genetic defects in insulin secretion and/or insulin action at action sites lead to the common observance of hyperglycemia in T2DM with potential implications in therapeutics. T2DM begins as a duration of abnormal homeostasis of glucose categorized as impaired glucose tolerance (IGT) or impaired fasting glucose (IFG).

Diabetes classification is as shown in Table 1 (2,10,11)

Table 1: Aetiologic Classification of Diabetes Mellitus

I. T1DM – destruction of βeta-cell finally leading to absolute insulin deficiency e.g., due to immune mediated mechanisms, environmental factors, idiopathic
II. T2DM -insulin resistance and/or insulin deficiency.
III. Defects of βeta-cell function e.g., MODY, organelle dysfunction, chromosomal abnormalities, micronutrient responsive diabetes
IV. Chemical or drug induced e.g., Diazoxide, cyclosporine, tacrolimus, β-Adrenergic blockers, glucocorticoids, L-Asparaginase, Vacor (rodenticide), alpha-Interferon, Dilantin, Phenytoin
V. Exocrine pancreas disorders e.g., pancreatectomy, pancreatitis, cystic fibrosis
VI. Infections e.g., Rubella, CMV, HUS

VII.Variants of T2DM -acquired defects of insulin action, insulin action genetic defects, Cushing, pheochromocytoma, Anti-insulin receptor antibodies

VIII. Syndromes of genetic origin with diabetes and insulin deficiency/insulin resistance e.g., Klinefelter syndrome, Turner syndrome, Down syndrome, Prader-Willi syndrome

IX. Gestational diabetes

X. Neonatal diabetes

1.2 Type 1 Diabetes Mellitus

Formerly called juvenile diabetes or IDDM. Manifests as deficiency of endogenous insulin that is relative or absolute. There is full dependence on exogenous insulin.

There are 4 phases or stages in the natural history of diabetes (2,9,10):

1. Preclinical -βeta-cell autoimmune process with gradual insulin secretion defect,
2. Clinical-there is beginning of clinical features of diabetes,
3. Remission that is transient "honeymoon phase," and
4. Diabetes that's established-there is either acute with or without chronic complications with reduced expectancy of life.

The commencement is mainly in children, age (median) 7-15 yrs., but may present at any age.

1.3 Epidemiology of T1DM

The incidence of T1DM has consistently increased. T1DM represents approximately 10% of all diabetes mellitus. T1DM is the most common type of diabetes mellitus in children and new cases of T1DM are also been diagnosed in adults and about half of all new cases of T1DM present as adults(2,6,15). T1DM new cases vary among many different ethnic populations ranging from 0.7 in 100,000 per year in Karachi (Pakistan) to more than 40 in 100,000 per year in Finland. Data from Western Europe show a 2-5% annual increase in T1DM incidence, whereas 9% in some eastern and central European countries. The highest rate of increase is in young children. In school-age children in United States the prevalence is about 1.9 in 1,000, with an increase of 1 in 1,430 children at 5 years of age and 1 in 360

children at 16 years of age. T1DM occurrence among African Americans is 30-60% that of white Americans. In the United States the annual new cases rate is approximately 19.7 in 100,000 among children aged less than10 years and 18.6 in 100,000 of children aged more than 10 years. Both male and female children are equally affected. In some low-risk populations there is some slight female predominance such as the Japanese. With socioeconomic status there is no apparent association. Presentation peaks are seen in in 2 age groups: 5-7 years and puberty. The prevalence of T1DM in Kenya is rising with an estimated 1,694 children and adolescents (0-19 years) having T1DM (IDF Diabetes Atlas 2019).(1)

1.4 Pathophysiology of T1DM

Some individuals who are genetically prone to developing diabetes get exposed to environmental factors. Environmental factors (viruses, season) and genetic susceptibility contribute to the pathogenesis(6,16). In T1DM there is pancreatic islet βeta cells destruction through an autoimmune process. T1DM susceptibility is controlled genetically by the MHC II genes alleles expressing human leukocyte antigens (HLAs). Genetically prone individuals have autoantibodies to βeta-cell antigens such as antibodies to glutamic acid decarboxylase, insulin autoantibody (IAA), islet cell cytoplasm (ICA), and ICA512 that are detected in serum. The autoantibodies can be detected way before any T1DM onset. There may also be other associated diseases of autoimmune nature such as thyroid inflammation, Addison disease and celiac disease. Some of the patients with T1DM, the destruction of the βeta-cell is not immune related. This subtype of diabetes is different from established aetiology of destruction of βeta-cell such as ionizing radiation, pancreatectomy, defects of mitochondrial gene, chemicals or drugs, and viruses is found in Asian or African origin patients. This subtype that is non immune mediated can present with ketoacidosis and have prolonged remission periods (“honeymoon phase”) with deficiency of insulin that is relative, such as that seen in T2DM patients. Insulin deficiency leads to T1DM onset with symptoms and signs. Some βeta cells that are viable are still present at the time of diagnosis and they may excrete insulin that is just enough to cause to a remission that is partial (“honeymoon phase”) of T1DM but as time progresses, there is total destruction of all βeta cells with insulin deficiency that is absolute and the individual is totally dependent on exogenous insulin for survival.

T1DM natural history has some or all of the following stages(2,11,15):

1. Autoimmunity initiation.
2. Preclinical autoimmune process with progressive loss of βeta-cell function.
3. Clinical onset of T1DM.
4. Remission that is transitory (honey moon phase).
5. Established diabetes.
6. Complications development.

Since all children and young adults with proof of autoimmune process do not proceed to diabetes illness is an indication that there are “checkpoints” or points of action at which the autoimmune process can be reversed or stopped before it proceeds to diabetes illness. Thus T1DM can be prevented or attempts of prevention made by intervening in the preclinical stage.

2. LITERATURE REVIEW

2.1 Risk Factors of T1DM

2.1.1 Genetic Factors

The prevalence in the general population in the United States is only 0.4% whereas that in siblings approach 6% (15 times more). If the father has diabetes the risk is 5-6% and if the mother has diabetes its 3-4%., The concordance rate in dizygotic twins ranges from 6-10%, whereas that in monozygotic twins it is at 30-65% (5 to 6 times more). About 50% of monozygotic twins with T1DM are discordant. For a child with diabetes the genetic susceptibility of the parents is approximately 3%. In 85% of newly diagnosed T1DM patients, there is no family member with T1DM(2,11).

2.1.2 Environmental Factors

Approximately half of monozygotic twins are not concordant for T1DM.There are differences in rural and urban areas inhabited by similar ethnic group. There are notable changes in new cases of T1DM that occur with migration. The same ethnic group can have a higher number of new cases diagnosed if they migrate to another region. Occurrence of seasonality as an environmental factor influencing onset of T1DM is noted. The TEDDY study will give more information on these environmental factors. In the causation of T1DM some of the environmental factors that play a role are: (3);

a. Congenital rubella syndrome-associated βeta -cell autoimmune destruction in up to 70%, with T1DM development in up to 40% of children infected. It may take up to 20 years in genetically susceptible individuals.
b. Viral infections-none has been isolated or implicated yet but likely mechanisms involve infection of βeta -cells by viruses causing lysis and antigens release, antigen presenting cells direct infection leading to further cytokines release and “molecular mimicry”.
c. Mumps virus-causes βeta -cell autoimmune destruction and thus causation of T1DM.
d. Enteroviruses-patients with T1DM have increased enterovirus infections and prenatal blood samples of a high enterovirus infection in patients who subsequently develop T1DM.
e. Hygiene hypothesis-Lack of exposure to childhood illnesses and infectious agents may raise a child’s chances of developing autoimmune diseases including T1DM.

f. Psychological stress- psychologic situations that are stressful can trigger T1DM development. Stress hormones secreted overwhelm the reduced capacity of insulin secretion.
g. Diet- breastfeeding can lower the risk of T1DM development. Cow's milk and gluten may increases gut "leakiness" of the already immature gut to antigens in cow's milk. Bovine serum albumin and Beta-lacto globulin in cow's milk are implicated. Infants fed on whey-based formulas have reduced incidence of developing T1DM. Vitamin D, ascorbic acid, omega-3 fatty acids, vitamin E and zinc have been associated with reduced risk.

2.2 Clinical Presentation and Diagnosis of T1DM

Intermittent polyuria or nocturia develops when glucose in serum is greater than renal threshold and persistent diuresis with nocturnal enuresis with polydipsia occurs with further chronic hyperglycaemia(2,10,11).Glycosuria also occurs and may lead to urinary tract infections. Hyperphagia occurs as a compensatory mechanism to lost calories in urine (glycosuria). Weight loss occurs due to loss of body water, loss of body fat and reduced subcutaneous fat tissue. Body literally starves due to loss of unused calories (CHO)-about 250gm of CHO is lost in urine as glucose leading to body starvation since the hyperphagia cannot replace the full body caloric intake. They also present with dehydration since about 5 litres of body water is lost in urine. Fat metabolism leads to accumulation of ketoacids which causes abdominal discomfort or true pain, nausea and vomiting. Dehydration worsens because there is oral intake impairment due to nausea and vomiting with worsening weakness and orthostasis.

Ketoacidosis makes the symptoms worse and causes deep, non-labored, heavy rapid breathing (Kussmaul breathing), acetone breath thas has a fruity odour. Q-T interval prolongation on ECG with reduced neurocognitive function and eventually loss of consciousness. New onset T1DM progresses to DKA in 20-40% of children-this happens faster in younger children. When the limited insulin secretory capacity is overwhelmed by counter regulatory hormones there is further deterioration which may be worsened by comorbid illnesses or trauma. DKA arises from metabolic anomalies in either severe insulin deficiency and/or insulin inaction at insulin sites made worse by counter regulatory hormones released during stressful conditions

characterized by ketonaemia, ketonuria, high anion gap ketoacidosis, reduced serum bicarbonate (CO_2) and pH and high serum osmolality.

DKA is classified as per the table below (Table 2)(2,9,11):

Table 2-DKA Classification and T1DM diagnostic criteria

Parameter	**Normal/No DKA**	**Mild**	**Moderate**	**Severe**
Bicarbonate (mmol/L)	<28	<20	<15	<10
pH	<7.45	<7.35	<7.25	<7.15
Clinical signs and symptoms	No noted changes clinically, normal	Alert and oriented and fatigued,	Kussmaul type of breathing; oriented, arousable sleepy;	Kussmaul type of breathing or depressed breathing and sensorium to sleepy to coma

In diagnosis of T1DM hyperglycaemia needs to be confirmed and the presence or absence of DKA is also ascertained and evaluation of electrolyte abnormalities and in obese children always consider T2DM.A baseline HbA_{1c} is also done. Testing for autoimmunity can be done in well-resourced centres and associated autoimmune disorders can also be sought such as celiac disease and thyroiditis.

The diagnostic criteria for T1DM is as per the below criteria(2,9–11);

1. Plasma glucose concentration ≥11.1 mmol/L (200 mg/dL) with classic symptoms of T1DM, or
2. Fasting plasma glucose concentration ≥7.0 mmol/L (≥126 mg/dL), or
3. 2-hour post prandial glucose ≥11.1 mmol/L (≥200 mg/dL) during an OGTT, or
4. HbA1c greater than or equal to 6.5%.

2.3 Seasonal Variation in diagnosis of T1DM

Seasonal variation is an environmental factor that triggers T1DM onset in genetically prone children and studies done show an increased T1DM diagnosis in cold seasons for particular age groups compared to warm seasons.

In Wisconsin a study by Allen et al (17) on the incidence as well as differences in rural to urban variation of seasonality of T1DM was done. It was a retrospective study covering the period 1970-1979 amongst a study population of 370 aged 0-29 years, between two counties in Wisconsin-Dane and La Crosse. The population base was considered as the mean populations within the study duration within the boundaries of those counties. Urban population was distinguished based on both total population (>10,000 persons) and density of population (>=1000 persons per square mile or 386 persons per kilometer squared of municipalities). The total cases of newly diagnosed diabetes requiring insulin over the study duration in all community hospitals in the two counties was determined. Cases residing outside the boundaries of the study area were excluded.

For the incidence, 307 newly diagnosed patients were identified.268 resided within the boundaries of the two counties -La Crosse County (22%) and Dane County (78%). Incidence rates of the county populations both rural and urban were compared, and since the two counties had an identical age-adjusted incidence rates of 14/100,000, data from both counties were merged. Of the cases 57.5% were males and their age-specific new cases rates exceeded that of females in every 5-year age group. The age-adjusted new cases rate for males of 16.4/100,000 was different significantly ($p = 0.006$) from that of females of 11.6/100,000. Peak T1DM incidence for males was at age group 10 to 14 years followed by that in females in the same age range with an increasing gradient for age to peak incidence observed in both males and females, with a decrease in females after the peak. Average age at T1DM diagnosis for females was 13.8 years and for males 14.0 years. New cases rates among males in urban region was higher consistently than for males rural region. Among rural and urban females, there were no differences in rates and there was no wide variance between rural and urban males.

There was an observation in seasonal trends in the month of diagnosis.31% or 95 cases were observed in the fourth quarter and in early spring a smaller peak was also observed. Males aggregated at ages 10 to 19 years and in the quarter four of the year 38% of cases were diagnosed. There was a smaller peak in March identical to that seen for the total cases. There were significant seasonal trends for males aged 10 to 19 years and total cases.

A study in Greece by Kalliora et al (18) on seasonal variation of T1DM diagnosis in Greek children was done. It was a retrospective study between 1978-2008 where 1148 children aged 0.1 to 16.4 years, 544 females and 604 males attending two centres and diagnosed with T1DM were studied and the average age was 8.32±5.01 years. Patients were from both rural and urban regions. Birth date and date of diagnosis of T1DM were retrieved from the patient's file and grouped as per the birth month or diagnosis of T1DM and Cold months were identified as Jan, Feb, Nov and Dec, moderate months were identified as Mar, Apr, Sept and Oct, and warm months as May, Jun, Jul and Aug. They were in addition categorized as per season at the time of diagnosis or birth: Autumn to Winter (Sept to Feb), Spring to Summer (Mar to Aug). They were also categorized as per age at the time of diagnosis: aged less than 3 years and more than 3 years. Presentation of data was as percentages or means ± 1 standard deviation. Pearson chi square test assessed significance in all two way and goodness of fit tables, with a significance set at $p<0.05$ and statistical analyses done using SPSS 11.0 software.

The cold months had statistically significant more children diagnosed with T1DM compared to warm months and moderate months had intermediate values (moderate vs. warm (p=0.09), cold vs. moderate (p=0.0192), cold vs. warm (p=0.001). Children diagnosed with T1DM were higher during the cold months (p=0.001): 55.79% of boys and 56.25% of girls diagnosed during Autumn to Winter with 44.21% of boys and 43.75% of girls diagnosed in Spring to Summer (p=0.001).

Differences observed were not significant with regard to the clinical presentation of T1DM.During spring to summer (52.83%) there were more children born with T1DM than in autumn to winter (47.17%) months (p=0.004). Of the girls born during the Spring to Summer (52.21%) and those born during the Autumn-Winter (47.79%) months (p=0.08) there was no significant statistical difference. For boys born during the Spring to Summer (53.31%) and those born in Autumn to Winter (46.69%) months (p=0.02) there was a statistically significant difference. For those more than 3 years age group more were diagnosed in the cold months in comparison to the warm months (p=0.007).Those less than 3 years age group, more were diagnosed in the warm months in comparison to the cold months (p=0.026).For these two age groups of more than 3 years and less than 3 years, there was no observed seasonality in the dates of birth.
Peak values occurred during the cold months with a significant incidence of T1DM diagnoses in both males and females. The high incidence of T1DM during the cold months could reinforce the theory that environmental factors such as infectious agents may act as triggers in the onset of T1DM with signs and symptoms of T1DM, possibly hastening an autoimmunity that may have commenced even before. The study also revealed that in children less than 3 years old compared with those more than 3 years the pattern of seasonality is different, with the peak incidence of those less than 3 years observed in warm months, and which is not easy to explain.

Another worldwide study in 53 countries from 105 centres named WHODiaMond study (19) on the T1DM diagnosis seasonality was based on the new cases data collected by the WHO Diabetes Mondiale (WHODiaMond) Project in 0 to 14 year-old children where 31,091 cases of T1DM were submitted over the period 1990 to 1999 against an average population of 40.5 million of diabetics within that age group. Incidence seasonality patterns were also determined for age- and sex-specific groups. There were three age groups of 0 to 4 years, 5 to 9 years, and 10 to 14 years of age.

105 centres in 53 countries submitted data for at least 1 year, so that the purpose of examining seasonality. There was an assumption that for each centre the monthly cases followed Poisson distribution with adjustment for the length of the month and population at risk.

There was significant seasonality in 42 centres ($P < 0.05$) in T1DM incidence when there was pooling of data for sex and age. Centres with peaks in months of winter (Oct to Jan) were 28 and those with dips in months of summer (Jun to Aug) were 33. Two centres in the southern hemisphere showed a peak in Jul to Sept and a dip in Jan to Mar. Centres further away from the equator were likely to demonstrate seasonality ($P = 0.000283$). Boys exhibited significant seasonality in more centres more often than girls (33 vs. 26 centres). Further grouping of the data into age groups 0 to 4 years, 5 to 9 years and 10 to 14 years of age, the incidence in the older age groups, 5 to 14 years old, showed significant seasonality than that in the youngest age group 0 to 4 years.

A retrospective study in Scotland by J.A. Mooney et al (20) on seasonality of T1DM in children and its alterations by holidays and weekends between 1984 to 2001 with 4517 (2407 males and 2110 females) children aged 0 to 14 years.

There was evidence of seasonality in children more than 4 years of age with proportions of 19.5% to 25.7% and peak between mid-Dec and mid-Jan. There were fewer cases over holiday periods and weekends, with less cases in Dec compared with Nov and Jan, and with the fewest cases in Jul (main Scottish holiday month). Mondays and Fridays were the most common days for case presentation were. There were three categories of age groups; 0 to 4, 5 to 9 and 10 to 14 years. Month standardization was done by month correction to 31 days by multiplying the 30-day months by 1. 033 and Feb figure by 1.097. The youngest age group exhibited no seasonality.

A retrospective study in Yaoundé Cameroon by Lontchi-Yimagou et al on seasonality in diabetes diagnosis in association with precipitation and temperature (21) in 4 centres between 2000 to 2008 with a total of 3232 cases showed that there was an association between climate variations using the 2000 to 2008 precipitation and temperature from the national meteorological database and newly diagnosed diabetes patients or decompensated diabetics hospitalization admissions.

Variations in climate for the duration of the study with regards to precipitation and temperature (mean, median and max) were done. There were several groups. One was as per

the month of attendance to the hospital. The other was as per the year attended to during the duration of the study and the season they were attended to: Nov to Feb (long dry season); Mar to Jun (long rainy season); Jul and Aug (short dry season); Sep and Oct (short rainy season). Oct had the highest precipitation [estimated 239mm (minimum 9mm-maximum239mm) and the also corresponds with the highest cases of newly diagnosed [n=366 (minimum 234mm –maximum 366mm) and decompensated diabetes patients [n=99 (minimum 46-maximum 99). The rainy seasons had majority of the admissions (51 %) compared to the dry seasons (49 %).

Spaans et al (22) did a study on seasonality of diagnosis of T1DM in Netherlands (Young Dudes 2) among children aged 0 to 14 years which was a retrospective observational study between 2009-2011 with an average of 676 children per year diagnosed with T1DM for the 3 years of study with an average population of 0-14 years in the 3 years of study of 2, 909,537 implying a yearly T1DM incidence rate (IR) of 23.2 per hundred thousand children(ptc). There was a significant difference in the yearly IR ($p = 0.03$) between seasons: 6.6 ptc in autumn, 6.4 ptc in winter, 5.4 ptc in summer and 4.9 ptc in spring. This pattern was observed in girls and boys and was part of the Young DUtch Diabetes Estimates (DUDEs) initiative. The seasons were defined as follows: spring (March, April and May), winter (December), autumn (September, October, November January and February), summer (June, July and August). There were three age categories: 0 to 4 years, 5 to 9, and 10 to 14 years. There was a higher incidence rate seen in the winter and autumn and a lower incidence rate in summer and spring indicating seasonality ($p=0.03$). During the study period the average annual incidence rate was 23.2 ptc for girls and 23.3 ptc for boys with no statistical significance. There was a lower incidence rate in age group 0–4 years for all the seasons as compared with the age groups 5-9/10-14 years which had a higher incidence rate for all the seasons with the highest incidence occurring in winter.

3.0 STUDY JUSTIFICATION AND UTILITY

T1DM manifestation in children not only depends on genetic predisposition but also environmental factors (diet, exercise, infections) (3) that trigger the disease, seasonality being one of them. It is important to determine the seasonal variation in T1DM diagnosis in order to understand the factors influencing seasonal incidence of T1DM.Kenya has 4 main seasons as per Kenya Meteorological Department – (*Mutai et al*.) , (5) Mar to Apr to May (MAM) *"long rains"* season, Oct to Nov to Dec (OND) *"short rains"* season , June to Jul to Aug (JJA) *"cool dry"* period that often times extends to September (except for parts of the western and coastal portions of the country that experience appreciable amounts of rainfall in this season) and January-February being basically *hot and dry*.

A Kenyan based study would determine if the observed associations in other studies are similar and if so, what preventive public health measures associated with the seasons can be taken in regards to public information, education and information to mitigate a rise or further suppress the observed seasonal incidence. In addition, on the curative aspect, do we need to be more prepared and ready to diagnose and treat T1DM promptly in some seasons than others? Such a study has not been done locally. Since all children and young adults with proof of autoimmune process do not proceed to diabetes points to the fact that there are points of intervention or "checkpoints" at which the autoimmunity can be reversed or stopped before it finally is diabetes thus raising the chances of intervening in the preclinical stage thus preventing T1DM. Such a study would add more to studies that are trying to determine environmental factors that trigger T1DM in genetically prone individuals such as the TEDDY cohort prospective study (USA, Finland, Germany and Sweden, 2004 to 2025).

3.1 Research Question

Research Question-What is the seasonal variation of T1DM diagnosis in children, adolescents and young adults in diabetes clinic in Kenyatta National Hospital?

3.2 Research Objective

3.2.1 Primary Objective

To determine the seasonal variation of T1DM diagnosis in children, adolescents and young adults in diabetes clinic in KNH from 2009 to 2021.

3.2.2 Secondary Objective

To describe the seasonal variation of the various age categories and geographical patterns of T1DM diagnosis in children, adolescents and young adults in diabetes clinic in KNH between 2009 to 2021.The study period between 2009 to 2021 was selected because of the following reasons;

i. The KNH computerized health information system provided data as from 2009 onwards. No data was available prior to this.
ii. Hard copy registers of diabetes patients were available and provided information on patients under care even as from 2009 some of whom are still on follow up at the diabetes clinic.
iii. To accommodate the sample size for purposes of attaining the desired power of the study.

4. RESEARCH METHODOLOGY

4.1 Study Design

This was a retrospective cohort study where patient information was obtained from patients file.

4.2 Study Site

The study was conducted mainly at Kenyatta National Hospital health records department. KNH is located in Nairobi and is a national referral, teaching and research hospital with a bed capacity of 1800 and has been in operation since pre-independence in 1901 when it was first operationalized as the Native Civil Hospital later renamed King George the sixth in 1952 and later renamed KNH following independence. It receives patients from other hospitals within and outside Kenya for specialized health care. Kenyatta National Hospital is the national referral hospital in Kenya. The hospital has a range of specialized outpatient clinics of which the diabetes clinic is one of them. The hospital is a national referral hospital serving the whole country and by virtue of its location mainly Nairobi County and its metropolitan area comprised of Kiambu, Machakos, Murang'a and Kajiado Counties.

Based at the ground floor room number 19 is the Health Records department. Upon discharge or death the patients file is taken to the department where it's coded manually and then the codes are keyed in a computerized system as per ICD 10 codes and retrieved when needed. KNH Ethics and Research Committee must approve of any research being conducted in KNH.

4.3 Study Population

Children, adolescents and young adults aged between 0 - <25 years with T1DM.

4.4 Inclusion Criteria

- Patients diagnosed with T1DM in KNH aged 0- <25 years.
- Patients diagnosed with T1DM in KNH from the years 2009-2021.

4.5 Exclusion Criteria

- Any patient who was 25 years and above.
- Diabetes associated with genetic syndromes
- Diabetes associated with drug therapy.

4.6 Sample Size Determination

- The sampling method chosen was consecutive sampling.
- Sample size calculation:

$$n = \frac{(Z)^2 p(1-p)}{MOE^2} = \frac{1.96^2 \times (0.5602 \times 0.4398)}{0.05 \times 0.05} = \frac{0.94647788793}{0.0025} = 378$$

Z-standard deviation at 95% confidence interval

p-sample proportion using the Maria I Kalliora et al (18) study in Greece an average proportion of 56.02% were diagnosed with T1DM during the cold season and an average proportion 43.98% diagnosed in the warm season.

MOE-margin of error or probability value

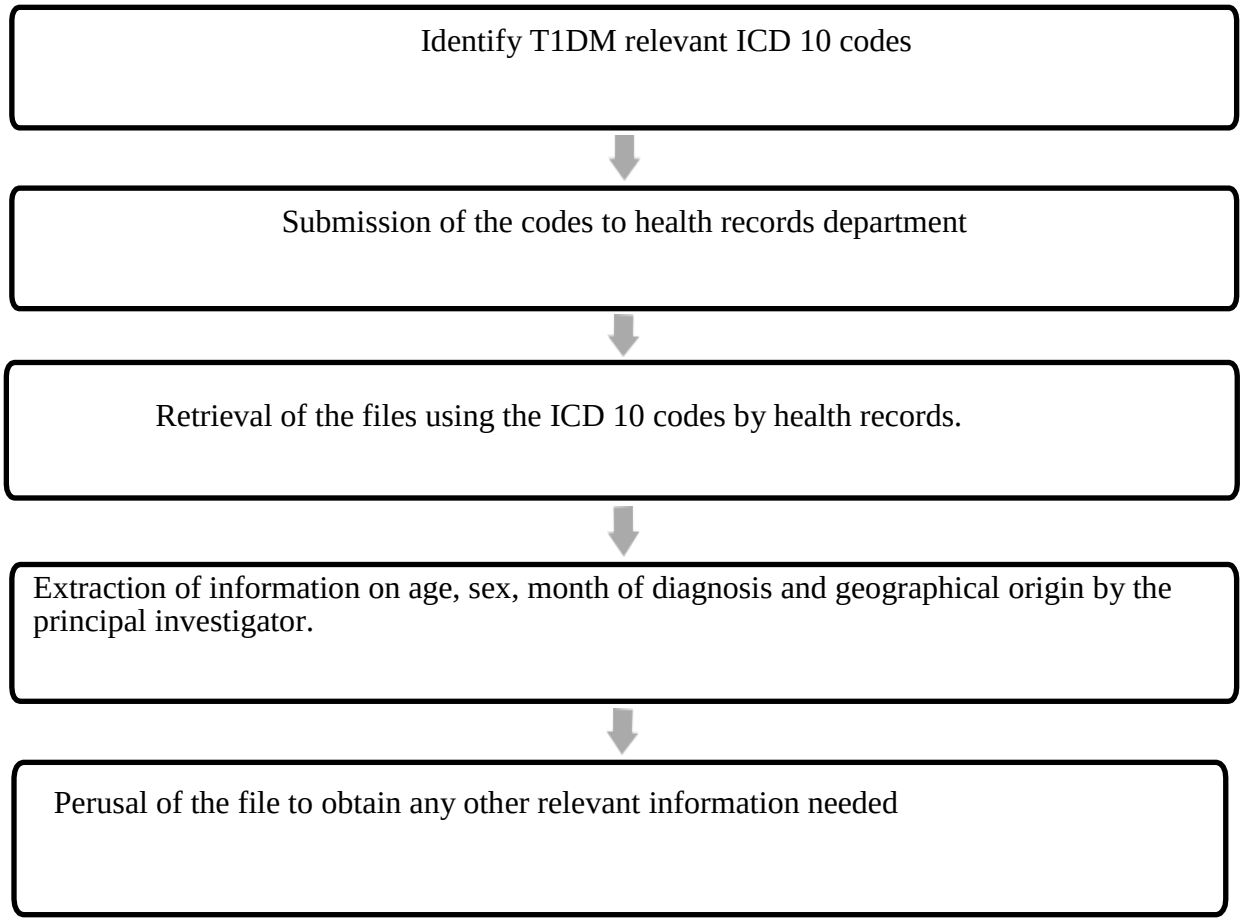
4.7 Patient Enrollment Procedure

Files of patients with Type 1 diabetes mellitus were retrieved from the health records department by the health records staff using appropriate ICD 10 codes for Type 1 Diabetes. Mortality files were also retrieved. Once the files were retrieved, extraction of information on age, sex, month of diagnosis and geographical origin was done by the principal investigator using the data collection tool in Appendix 2.

Retrieval of this information was done at the Health Records Department in a particular room allocated to researchers.

To ensure protection of records, files were not allowed to be removed from the health records department. Files were retrieved in small batches of between twenty five (25) to thirty five (35) files to minimize disruption of services for active patients. The above is represented in a flowchart in figure 1.

Figure 1: Patient Enrollment Procedure.



4.8 Data Management and Analysis

After retrieving the files from the Health records Department at KNH, the relevant information was collected by the principal investigator using the data collection sheet in Appendix 2.The demographic and clinical characteristics data was then entered in the data analysis tool in Appendix 5 by the principal investigator for capture of frequency or proportion for final analysis.

Age categorization using 5 years intervals at 0-4, 5-9, 10-14, 15-19 and 20-24 years and seasonal and geographical variations were compared. A summary of the categorical data was

analyzed and presented as proportions while continuous variables were analyzed and presented as medians where applicable.

Test associations were done using Chi Square and Fischer's exact test. Statistical analytical methods using available software R Studio was used for analysis and make inferences of any association and strength or significance of the associations thereof in seasonality of diagnosis of T1DM.Statistical tests were interpreted at level of significance of 5% ($p <= 0.05$). Study findings were presented in form of graphs, tables and charts.

5. ETHICAL CONSIDERATION

Approval to commence and continue with this study was sought and granted by the University of Nairobi Department of Paediatrics and Child Health. Ethical approval was obtained from University of Nairobi and Kenyatta National Hospital Ethics and Research Committee (UON/KNH-ERC).

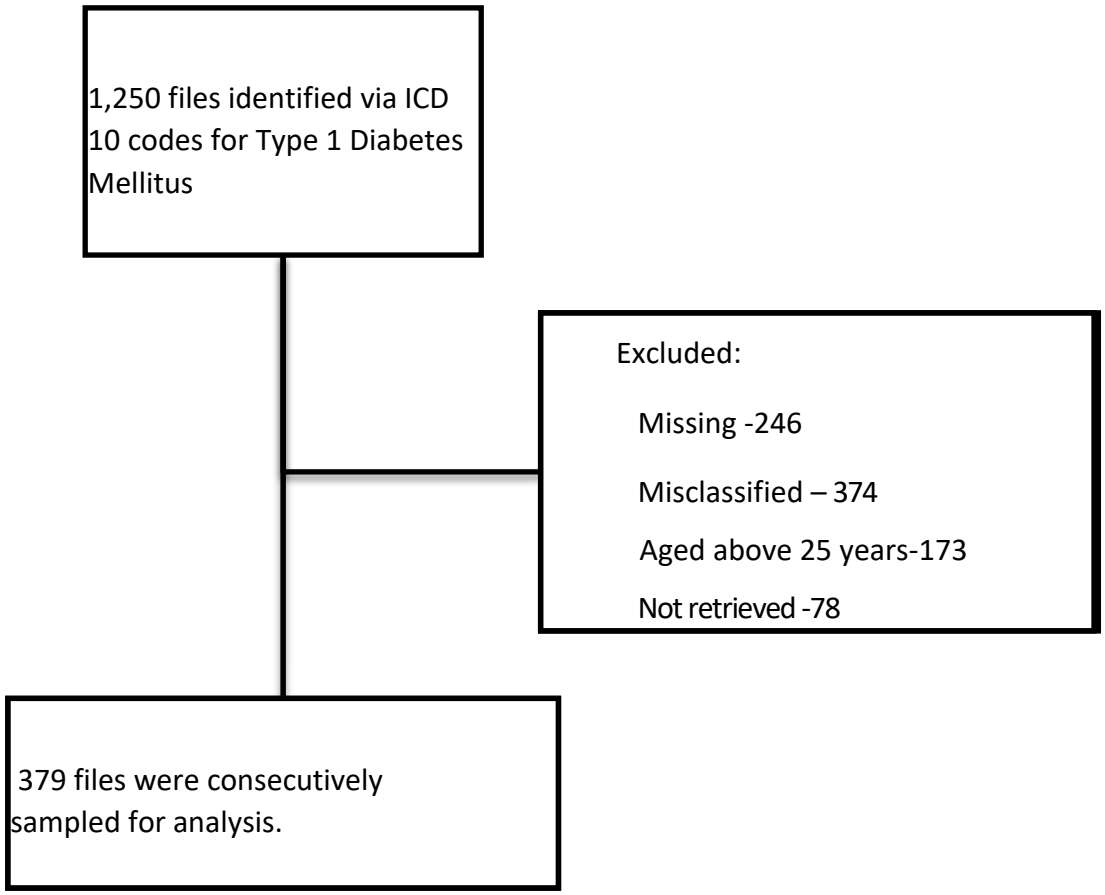
6. RESULTS

Using the ICD 10 codes for Type 1 Diabetes Mellitus in Appendix 1, a total of 1,250 files were listed from the system in health records department from 2009 to 2021.A total of 871 files were excluded as follows:

- 173 files were patients aged above 25 years.
- 374 were misclassified files with different diagnosis captured as Type 1 Diabetes Mellitus. This arose primarily during inputting of the codes during the initial coding process. This was relayed to the health records.
- 246 files could not be traced at all by the health records during the process of file retrieval despite being present in the list generated by ICD 10 codes for Type 1 Diabetes Mellitus.
- After reaching the desired sample size of 379 which was consecutive or total enumerative sampling method, 78 files were not retrieved from the totals of 1,250 files generated by health records using ICD 10 codes.

The above study process is represented in the flow chart Figure 2 below.

Figure 2: Study Procedure



6.1 Baseline Characteristics

Table 3: Baseline Characteristics

Variable	Frequency	Percentage (%)
Gender: Female	178	47.0
Male	201	53.0
Age categories at diagnosis: 0-4 years	110	29.0
5-9 years	91	24.0
10-14 years	133	35.1
15-19 years	28	7.4

20-24 years		17	4.5
Place of residence:	Rural	162	42.7
	Urban	217	52.3
Age distribution: Median age = 9.0 years, Mean = 8.6 years, Interquartile Range = 3-12 years.			
Family characteristics			
Family history of diabetes:	No	261	68.9
	Yes	118	31.1
Father has diabetes:	No	356	93.9
	Yes	23	6.1
Mother has diabetes:	No	363	95.5
	Yes	17	4.5
Sibling has diabetes:	No	376	99.2
	Yes	3	0.8
Family history of T1DM:	No	330	87.1
	Yes	49	12.9
Clinical characteristics			
Patient had polyphagia:	No	307	81.0
	Yes	72	19.0
Patient had polyuria:	No	99	26.1
	Yes	280	73.9
Patient presented in COMA:	No	359	94.7
	Yes	20	5.3
Patient had polydipsia:	No	153	40.4
	Yes	226	59.6
Plasma glucose >= 11.1:	No	3	99.2
	Yes	376	0.8
Fasting blood sugar>= 7.0:	No	206	54.5

	Yes	173	45.5
HBA1c >= 6.5%:	No	344	90.8
	Yes	35	9.2
Status	Alive	369	97.3
	Dead	10	2.7

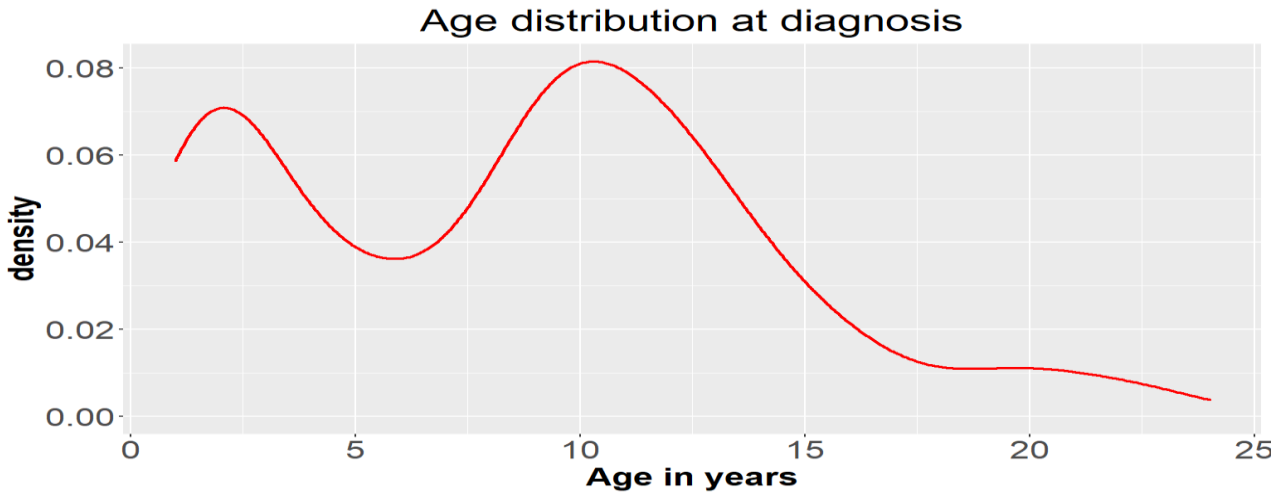
This study had a total sample of 379 participants and data was collected from the year 2009 to 2021. This was sequential data for diagnosis of type 1 diabetes mellitus for children, adolescents and young adults below 25 years. Data was extracted from patient's records at Kenyatta National Hospital.

The majority of the participating patients were males 53.0% (n = 201) while the rest were females. The data was grouped in to six age categories where those who were aged 10-14 years were the majority at 35.1% (n=133) followed by those aged 0-4 years at 29% (n=110). Participants aged 20-24 years were the least at 4.5% (n = 17).

The median age of the participants was 9.0 years. The mean age was 8.6 years. The majority of the participants 52.3% (n = 217) were from urban areas while the rest were from the rural areas.

6.2 Distribution of Age at Diagnosis

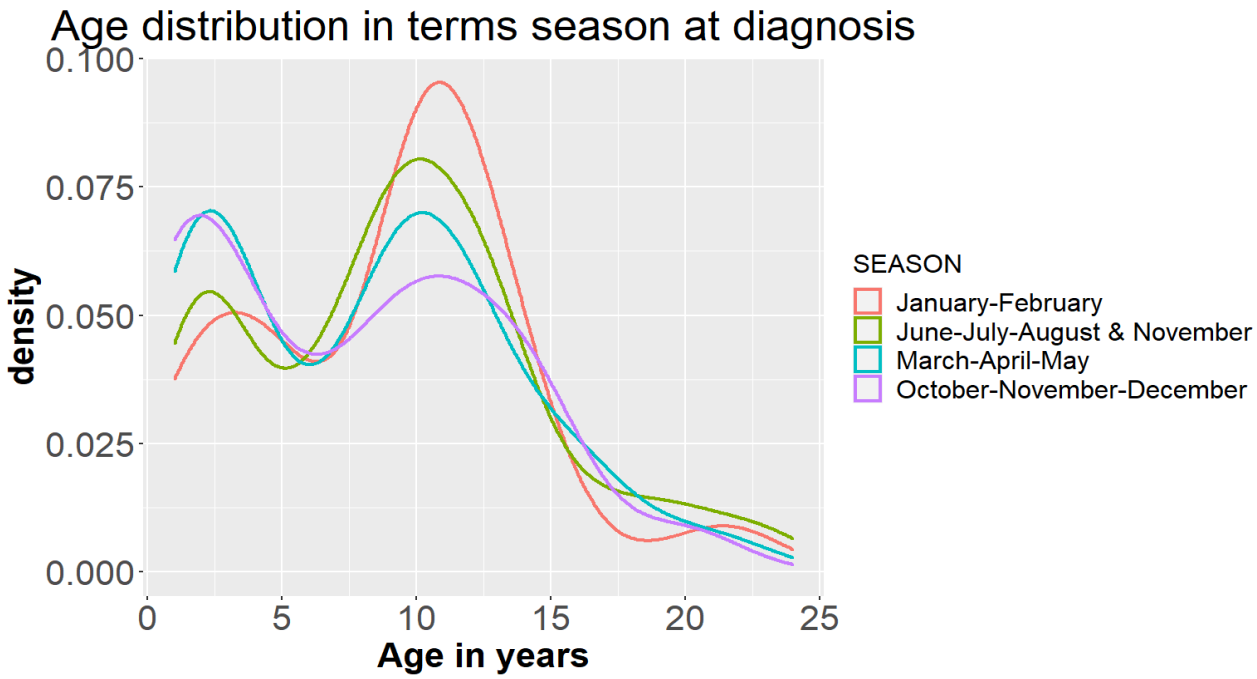
Figure 3: Density Plot of age at Diagnosis



The age at diagnosis of type 1 diabetes mellitus was right skewed with median 9.0 years and interquartile range 3-12 years.

6.3 Distribution of Age at Diagnosis and Seasons

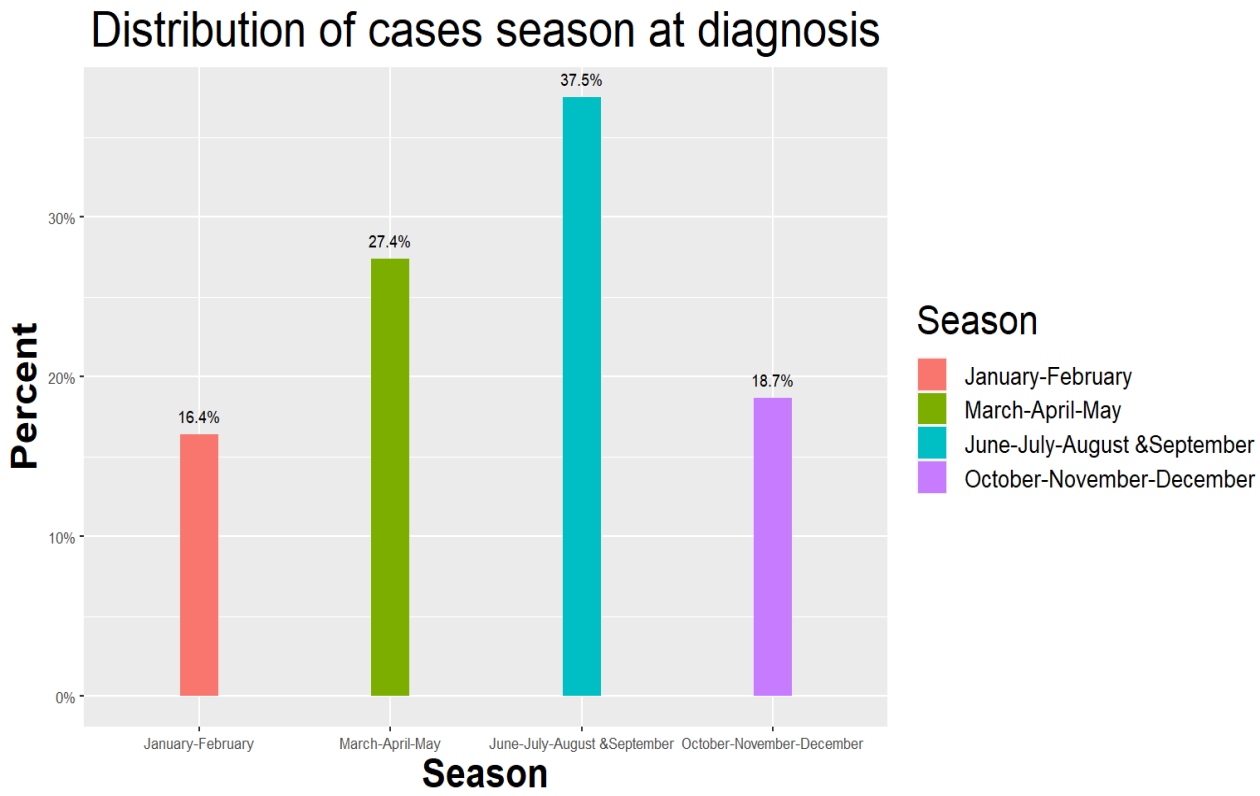
Figure 4: Density plot showing distribution of age at diagnosis with their respective seasons



The density plot in figure 5 above shows that for all the seasons, majority of the diagnoses were made around age 12 years and that January/February led in the bulk of the diagnoses

6.4 Distribution of cases according to season at diagnosis

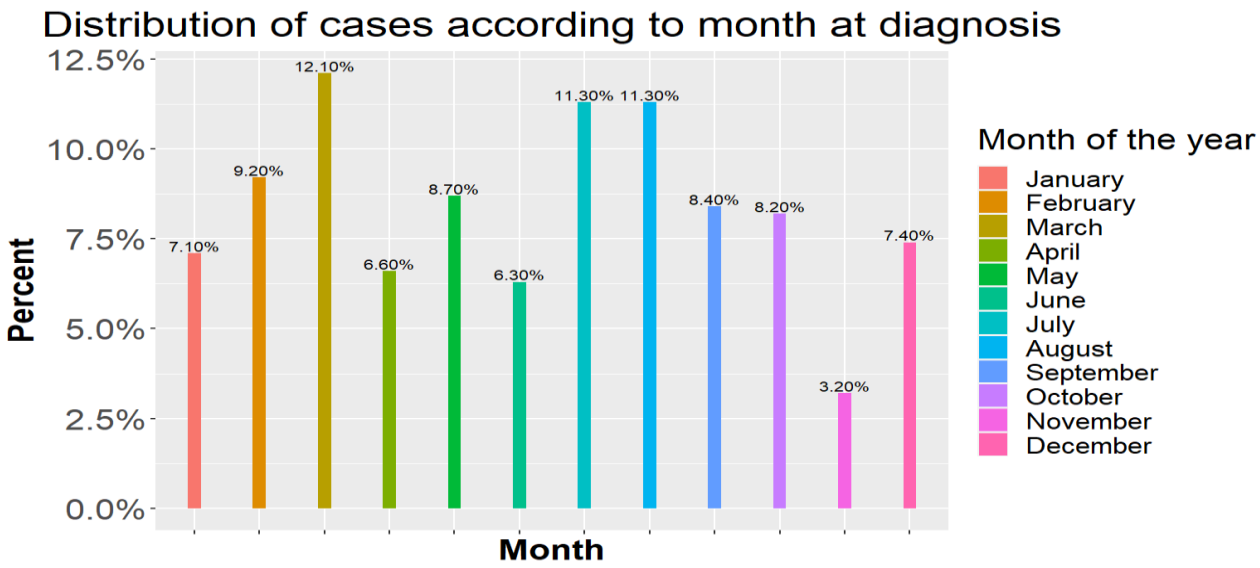
Figure 5: Distribution of cases in the four seasons



Among the four seasons, June/July/August/September had the highest diagnosed cases at 37.5% followed by March/April/May at 27.4%. January/February had the least diagnoses at 16.4%.

6.5 Distribution of cases as per the month of diagnosis

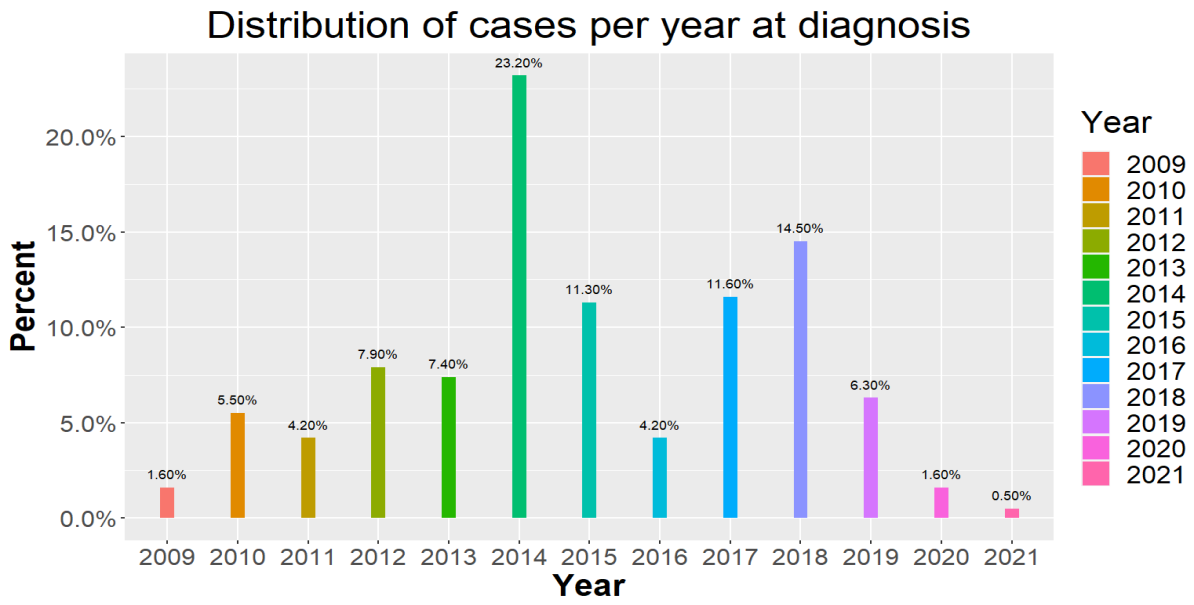
Figure 6: Bar graph showing distribution of cases over the 12 months



In the 12 months of the year, March had the highest percentage of cases at 12.1 followed by July and August at 11.3% each. The month of November had the least diagnoses at 3.2%.

6.6 Distribution of cases per year of diagnosis

Figure 7: Distribution of cases per year of diagnosis



In terms of yearly distribution of diagnoses, 2014 had the majority of cases at 23.2% followed by the year 2018 at 14.5%. The year 2021 had the least cases at 0.5% of the total.

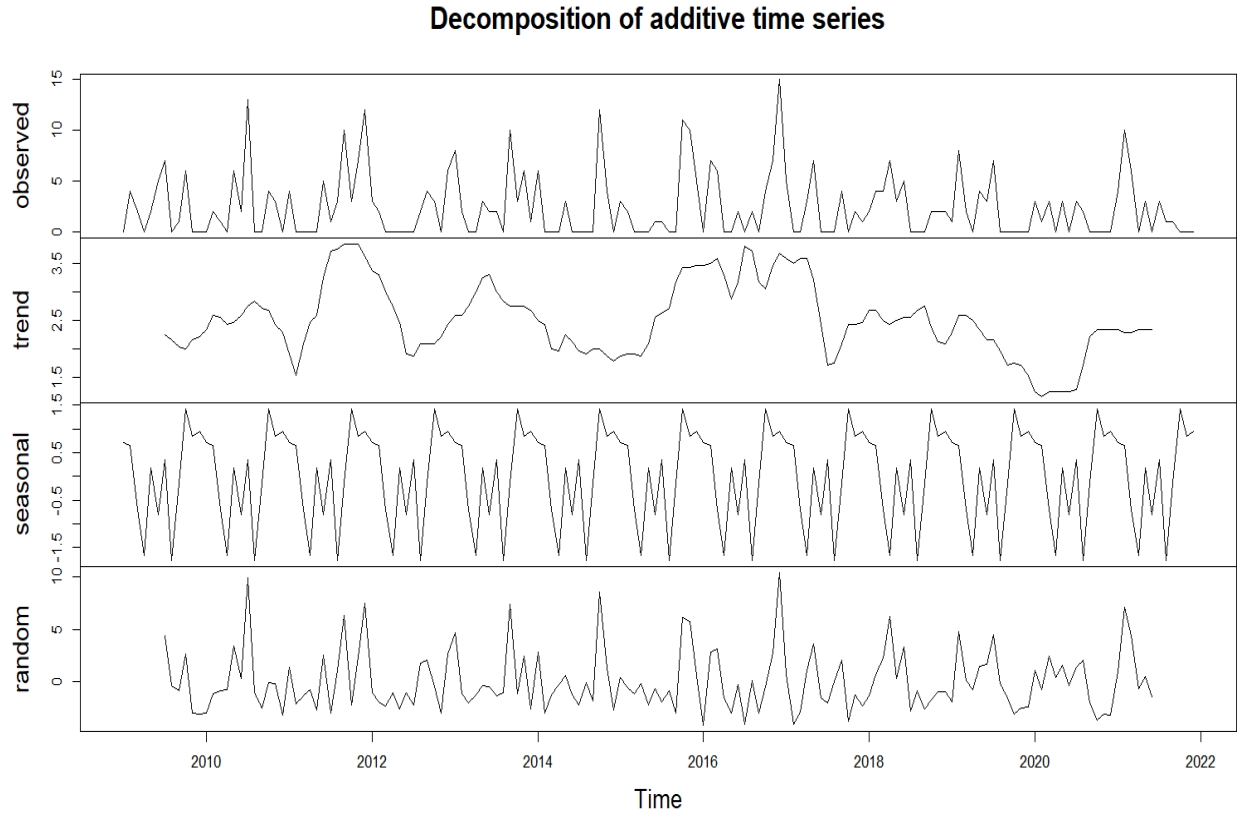
6.7 Seasonal Variation of T1DM diagnosis in children, adolescents and young adults in diabetes clinic in KNH from 2009 to 2021.

6.7.1 Seasonality determination

Decomposition of additive time series to determine seasonality was done using two approaches:

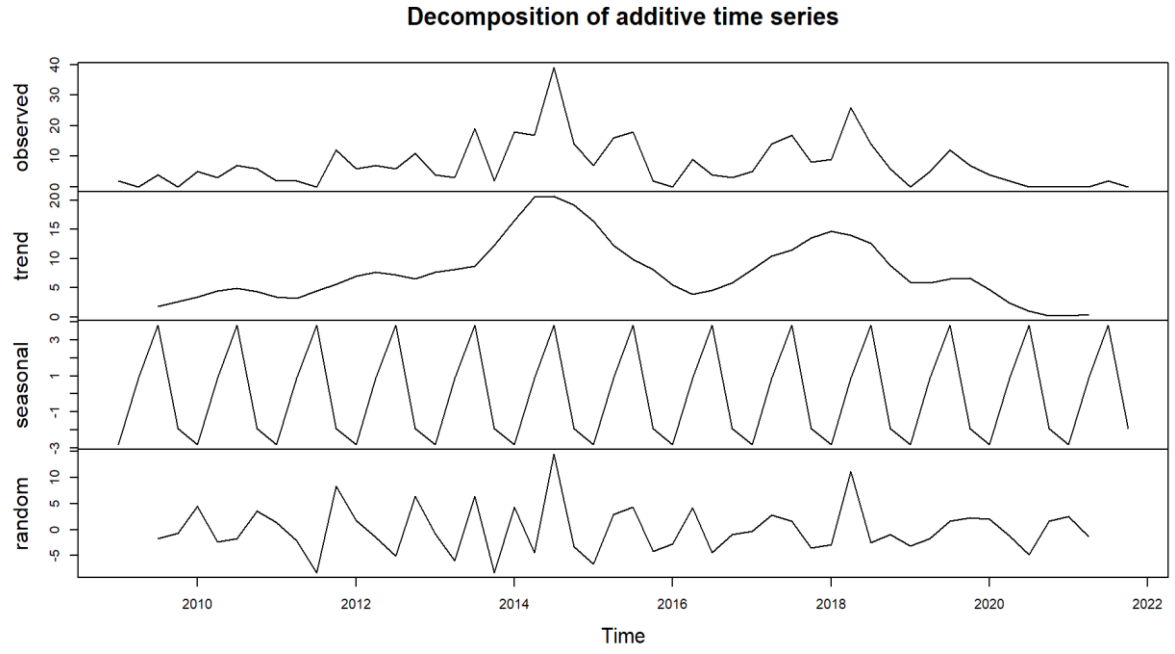
1. Time series plot of the monthly decomposed data for each year from 2009 to 2021.
2. Time series plot of the four seasons per year decomposed data for each year from 2009 to 2021.

Figure 8: Time series plot of the monthly decomposed data for each year from 2009 to 2021



The top panel of Figure 8 shows the distribution of the monthly cases. The second panel is the trend component. The third panel shows that the seasonal factor is the same for each year with a regularly repeating patterns of highs (peaks) and lows (troughs) was observed related to the months of the year, which suggests seasonality in the data.

Figure 9: Time series plot of the four seasons per year decomposed data for each year from 2009 to 2021.

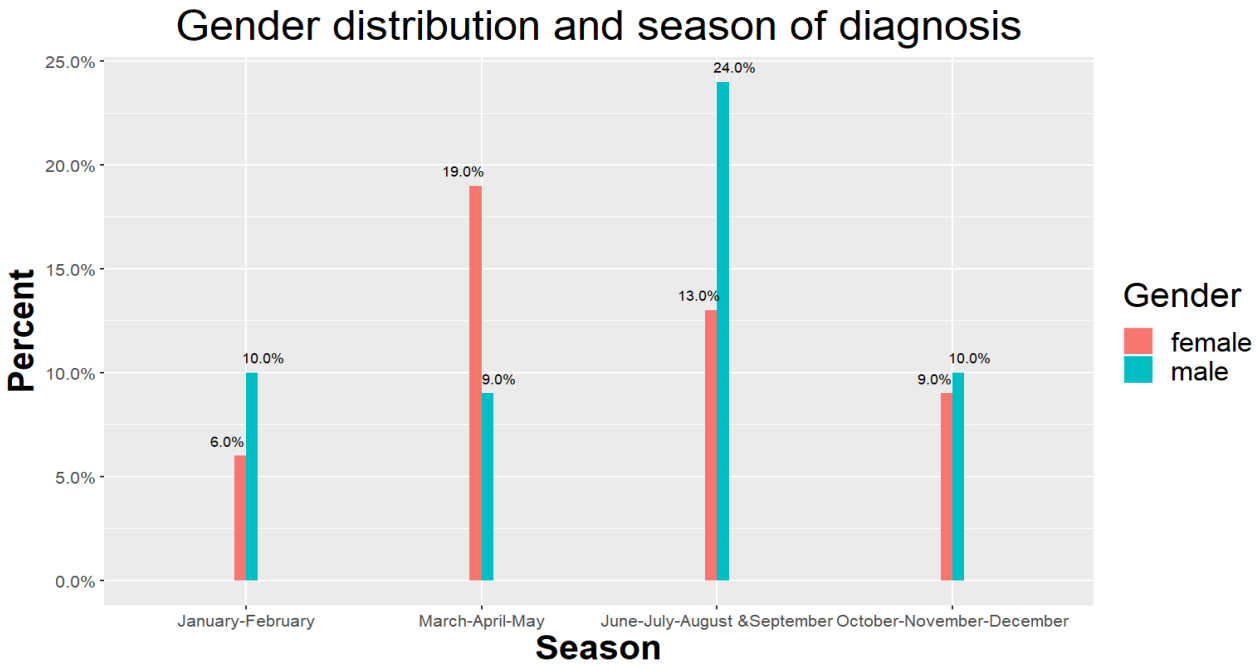


The top panel of Figure 9 shows the distribution of the monthly cases. The second panel is the trend component. The third panel shows that the seasonal factor is the same for each year with a regularly repeating patterns of highs (peaks) and lows (troughs) was observed related to the four seasons of the year, which suggests seasonality in the data

6.8 Seasonal variation of the various age categories and geographical patterns of T1DM diagnosis in children, adolescents and young adults in diabetes clinic in KNH from 2009 to 2021.

6.8.1 Association between gender at diagnosis and season

Figure 10: Gender distribution as per season of diagnosis



In all the four seasons except March/April/May, the males recorded the highest number of cases. Of the 37.0% of cases recorded in June/July/August/September, 24.0% were males while the rest were females

To check whether there is significance difference in season of diagnosis between males and females, we did a Pearson's chis square.

Table 4: Chi square test for association between gender and season of diagnosis

Gender	**Season of Diagnosis**			
	JF	MAM	JJAS	OND
Male	39	33	92	37
Female	23	71	50	34
Chi square test	**p-value < 0.01 (95% CI)**			

H_0: There is no association between gender and season of diagnosis

H_1: There is an association between gender and season of diagnosis

The p-value of less than 0.05 at 95% confidence level leads us to reject the null hypothesis thus there is a significant statistical association between gender and season of diagnosis.

6.8.2 Association between age at diagnosis and season

Table 5: Association between age and season at diagnosis

Age category in years	**Season at diagnosis**			
	JF	MAM	JJAS	OND
0 - 4 years	12	36	34	28
5 - 9 years	12	26	39	14
10 - 14 years	33	28	50	22
15 - 19 years	3	12	14	7
20 - 24 years	2	2	5	0
Fisher's exact test	**p-value = 0.04 (95% CI)**			

H_0: There is no association between age and season of diagnosis

H_1: There is an association between age and season of diagnosis

Fisher's exact test was used to test significance in the association between age categories and season of diagnosis. Based on the p-value of 0.04 at 95% confidence level, we reject the null hypothesis and conclude that there was an association between age at diagnosis and the season.

6.8.3 Association between area of residence and season at diagnosis

Table 6: Chi square test of association between place or residence and season at diagnosis

Age category in years	Season at diagnosis			
	JF	MAM	JJAS	OND
Rural	29	36	75	22
Urban	33	68	67	49
Chis square test	**p-value = 0.004 (95% CI)**			

H_0: There is no association between place of residence and season of diagnosis

H_1: There is an association between place of residence and season of diagnosis

The Pearson's chis square p-value of 0.04 is <0.05 at 95% confidence level. We reject the null hypothesis and conclude that there was significant association between place of residence and season at diagnosis.

7.0 DISCUSSION

This was the first Kenyan study to evaluate seasonal patterns of T1DM diagnoses in children and adolescents. We retrospectively examined all case diabetes mellitus Type 1 diagnosed in Kenyatta National Hospital and determined if the cases had a seasonality pattern based on the four main Kenyan seasons of Mar to Apr to May (MAM) *"long rains"* season, Oct to Nov to Dec (OND) *"short rains"* season , June to Jul to Aug (JJA) *"cool dry"* period that often times extends to September (except for parts of the western and coastal portions of the country that experience appreciable amounts of rainfall in this season) and January-February being basically *hot and dry* (5) .

We found a clear pattern consistent with seasonality in the presentation of cases of Type 1 diabetes mellitus diagnosed in this population. Relatively more cases were diagnosed in the JJA season which coincides with cool dry season which extends into September as well as the MAM season which coincides with the long rainy season. A similar observation was made in Eric Lontchi et al study in Yaounde Cameroon (21).A possible explanation to this could be the sedentary lifestyle of less activity that children, adolescents and young adults adopt in the long rainy and cold seasons triggering the illness in the genetically predisposed. Another environmental factor could be viral infections which are seasonal such as flu and whose incidence increases in the rainy and cold seasons as found out in the TEDDY study (3) .It is plausible that the rainy season is also associated with infectious diseases such as malaria which can trigger the onset of T1DM in genetically predisposed individuals. Diabetes is frequently associated with infections as seen in clinical practice. Winter or cold months could support the hypothesis that infections may act as precipitating factors in the clinical manifestation of the disease, possibly accelerating an autoimmune process that may have been initiated months or years before as expounded in Maria I. Kalliora et al study in Greek children (18) .Although Kenya being a tropical country does not have clearly defined climatic seasons such as winter or summer, there exists variations in temperature ,rainfall and humidity which are likely to influence disease patterns.

Other environmental factors implicated in the TEDDY study (3) include hygiene hypothesis that postulates that lack of exposure to childhood illnesses and infectious agents may raise a child's chances of developing autoimmune diseases including T1DM. Psychological stress is also another environmental factor that explains that psychologic situations that are stressful can trigger T1DM development where stress hormones secreted overwhelm the reduced

capacity of insulin secretion. Another important environmental factor is diet where breastfeeding can lower the risk of T1DM development. Cow's milk and gluten may increases gut "leakiness" of the already immature gut to antigens in cows' milk. Bovine serum albumin and beta-lacto globulin in cow's milk are implicated. Infants fed on whey-based formulas have reduced incidence of developing T1DM. Vitamin D, ascorbic acid, omega-3 fatty acids, vitamin E and zinc have been associated with reduced risk. High calorie diets have also been implicated in T1DM onset especially in genetically predisposed individuals.

The study also found males to be more affected than females in most of the seasons ($p<0.01$).This was also found to be the case in E.V Moltchanova et al study (19) .

The study did find out higher cases in urban than rural setting ($p=0.004$).A similar finding was observed in C. Allen et al (17) where seasonal trends were significant for total cases ($p=0.05$) and a striking difference in seasonal variation by month of diagnosis was observed between urban and rural cases (Chi Square $0.025 < p < 0.05$).

The study highlights the role of seasonality in presentation and diagnosis of T1DM in the population of children, adolescents and young adults served by Kenyatta National Hospital. In addition there was a significant statistical indication that there was seasonal variation in the various age categories ($p=0.04$) as well as gender ($p=0.01$). It is reasonable to assume that the Kenyatta National Hospital represents a wide range of children with T1DDM since for most of the period of data studied it was the only public setting with established paediatric endocrinology services. An important limitation is that children who could have died before referral or managed in other facilities are not represented in the current study.

8. STUDY STRENGTHS

This study being the first to explore the seasonality of diabetes diagnosis in Kenya highlighted seasonal variation in diagnosis of T1DM in children, adolescents and young adults in Kenyatta National Hospital a similar observation made in other studies.

9. STUDY LIMITATIONS

A large number of files were excluded from the study due to misclassification. This was due to errors during inputting of codes into the health records system noted after files were retrieved. These errors were communicated to the team at the Health Information Department.

Several files were missing contributing to a significant amount of missing data.

This being a retrospective study, there was heavy reliance on the availability and accuracy of the medical records.

In addition the sample selection was not random for the total population in Kenya and precise geographical origin data for each patient is needed

10. CONCLUSIONS AND RECOMMENDATIONS

Seasonal variation on diagnosis of T1DM was established and indeed is a real phenomenon. There was association between age-categorisation at diagnosis and seasonality at diagnosis of T1DM.Seasonal variation in T1DM is dependent on the geographical position since there was significant association between place of residence (urban and rural) and seasonality at diagnosis of T1DM.

The results of the study support the concept of seasonality in T1DM diagnosis, implying a possible relationship between clinical expression of T1DM and various environmental factors such as seasons and climatic conditions.

The study demonstrated the median age of commencement being 12 years which was within the known commencement median age of T1DM diagnosis of 7-15 yrs.

This study being the first to explore the seasonality of diabetes diagnosis in Kenya opens an opportunity to further look into the time varying environmental variables such as rainfall precipitation, temperature, seasonal viral and bacterial infections and specific geographical points of locations in regards to onset of T1DM diagnosis.

There is need for preventive public health measures to reduce exposure associated with the seasonal effects can be taken. Emphasis on a more active lifestyle and not too much consumption of high calorie diets. There is need to be more prepared and ready to diagnose and treat T1DM promptly in some seasons than others especially the cold and rainy seasons. There is need to investigate points of intervention or “checkpoints” thus raising the chances of intervening in the preclinical stage of T1DM diagnosis. In addition public awareness for the public to be vigilant that these cases are likely to be more in long rainy and cold seasons especially in genetically predisposed individuals more so those with a family history of diabetes.

There is need to enhance ICD 10 coding for T1DM and other diseases by the health records to avoid errors encountered and also imperative to have cloud backups of health records information in case of information communication and technology equipment failure.

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APPENDICES

APPENDIX 1-ICD 10 Diagnosis of T1DM

E10 Type 1 Diabetes Mellitus

Includes.
diabetes (mellitus):

- brittle
- juvenile-onset
- ketosis-prone

Excludes.:
diabetes mellitus (in):

- malnutrition-related (E12.-)
- neonatal (P70.2)
- pregnancy, childbirth and the puerperium (O24.-)

glycosuria:

- NOS (R81)
- renal (E74.8)

impaired glucose tolerance (R73.0)
postsurgical hypoinsulinaemia (E89.1)

APPENDIX 2-Data Collection Form

STUDY TITLE: SEASONAL VARIATION IN DIAGNOSIS OF T1DM IN CHILDREN, ADOLESCENTS AND YOUNG ADULTS AT KENYATTA NATIONAL HOSPITAL

Section 1

Study Number	
Date	

Date of Birth	Day	Month	Year
Current Age (Years)			
Sex	U	M	F
Date of Diagnosis of T1DM	Day	Month	Year
Age at Diagnosis of T1DM	Year(s)	Month(s)	
Month of Diagnosis of T1DM			
Geographical Region of Stay at Diagnosis			

Section 2

Year of Birth					
Month of Birth					
Year of Diagnosis					
Month of Diagnosis					
Age Category	0-4	5-10	11-14	15-19	20-24
Geographical region of stay /County at Diagnosis					
Season at time of Diagnosis	MAM	OND	JJA-S	JF	
Season at time of Birth	MAM	OND	JJA-S	JF	
Seasonal Average Temperature at Diagnosis	MAM	OND	JJA-S	JF	

Seasonal Average Precipitation at Diagnosis	MAM	OND	JJA-S	JF
Family History of Diabetes	YES		NO	
Sibling with Diabetes	YES		NO	
Father is Diabetic	YES		NO	
Mother is Diabetic	YES		NO	

Section 3

Diagnosis confirmed by	Tick
Plasma Glucose >=11.1mmo/L	
Fasting Plasma Glucose >=7.0mmol/L	
Two-hour post load glucose >=11.1mmo/L	
HbA1c >=6.5%	

Section 4

Status	Y/N	Date of Death	Age at Death

Alive			
Dead			

APPENDIX 3: Budget

Item	**Unit**	**Amount (KShs)**
Principal investigator	1	Nil
Research Assistant/Data Clerk	1	15,000
Statistician	1	30,000
Anti-Plagiarism fee/ERC fee	1	4,000
Stationery and printer supplies	1	3,000
Photocopying	1	2,000
Telephone airtime	1	3,000
Dissemination/Publication		30,000

Miscellaneous		10,000
TOTAL		**97,000**

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Email: uonknh_erc@uonbi.ac.ke
Website: http://www.erc.uonbi.ac.ke
Facebook: https://www.facebook.com/uonknh.erc
Twitter: @UONKNH_ERC https://twitter.com/UONKNH_ERC

KENYATTA NATIONAL HOSPITAL
P O BOX 20723 Code 00202
Tel: 726300-9
Fax: 725272
Telegrams: MEDSUP, Nairobi

Ref: KNH-ERC/A/17

17th January, 2022

Dr. Michael Kariuki
Reg. No. H58/36080/2019
Dept. of Paediatrics and Child Health
Faculty of Health Sciences
University of Nairobi

KENYATTA NATIONAL HOSPITAL APPROVED 17 JAN 2022 KNH/UoN-ERC P.O. Box 20723 - 00202, NAIROBI

Dear Dr. Kariuki,

RESEARCH PROPOSAL: SEASONAL VARIATION OF TYPE I DIABETES DIAGNOSIS IN CHILDREN, ADOLESCENTS AND YOUNG ADULTS IN KENYATTA NATIONAL HOSPITAL (P670/08/2021)

This is to inform you that KNH-UoN ERC has reviewed and approved your above research proposal. Your application approval number is **P670/08/2021.** The approval period is 17th January 2022 – 16th January 2023.

This approval is subject to compliance with the following requirements;

i. Only approved documents including (informed consents, study instruments, MTA) will be used.
ii. All changes including (amendments, deviations, and violations) are submitted for review and approval by KNH-UoN ERC.
iii. Death and life threatening problems and serious adverse events or unexpected adverse events whether related or unrelated to the study must be reported to KNH-UoN ERC 72 hours of notification.
iv. Any changes, anticipated or otherwise that may increase the risks or affected safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH-UoN ERC within 72 hours.
v. Clearance for export of biological specimens must be obtained from relevant institutions.
vi. Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. Attach a comprehensive progress report to support the renewal.
vii. Submission of an executive summary report within 90 days upon completion of the study to KNH-UoN ERC.

Prior to commencing your study, you will be expected to obtain a research license from National Commission for Science, Technology and Innovation (NACOSTI) https://research-portal.nacosti.go.ke and also obtain other clearances needed.

Yours sincerely,

PROF. M.L. CHINDIA
SECRETARY, KNH-UoN ERC

c.c. The Dean-Faculty of Health Sciences, UoN
The Senior Director, CS, KNH
The Chairperson, KNH- UoN ERC
The Assistant Director, Health Information, KNH
The Chair, Dept. of Paediatrics and Child Health, UoN
Supervisors: Dr. Lucy N. Wainaina Mungai, Dept. of Paediatrics and Child Health, UoN
Prof. Dalton Wamalwa, Dept. of Paediatrics and Child Health, UoN