EPIDEMIOLOGY OF TYPE 1 DIABETES: MONTH AND SEASON OF BIRTH. IMPLICATIONS FOR ETIOLOGY

By

LETITIA HOWARD PERDUE

A Thesis Submitted to the Graduate Faculty of

WAKE FOREST GRADUATE SCHOOL OF ARTS AND SCIENCES

In Partial Fulfillment of the Requirements

For the Degree of

MASTER OF SCIENCE

In the Health Services Research Program

August 2011

Winston-Salem, North Carolina

Approved By:

Lynne Wagenknecht, Dr.P.H., Advisor

Ralph D'Agostino, Jr., Ph.D., Chair

Katherine Poehling, M.D., M.P.H.

Beverly Snively, Ph.D.

DEDICATION

I would like to dedicate this thesis to my loving and supportive family. Without their support through this long process, completion of this thesis would never have been possible. Their support, sometimes emotional, sometimes statistical, has allowed me to move forward with this aspect of my professional career and I will be forever grateful. Thank you Chuck and Madeline, Mom and Dad, Annie Green and Marjorie.

ACKNOWLEDGMENTS

I would like to thank Drs. Lynne Wagenknecht, Katherine Poehling and Beverly Snively not only for their help and input into this thesis project, but also for working with me under tight timelines and supporting me through this process. I also appreciate the support of the Type 1 Diabetes Genetics Consortium (T1DGC) Coordinating Center team including Dr. Stephen Rich, Joan Hilner, June Pierce, Elizabeth Sides, Hoa Teuschler, and the T1DGC Steering Committee and Network Coordinators for allowing me the opportunity to contribute to this project and for their support and guidance throughout this project and thesis. I am also extremely appreciative for the support and encouragement over the past years from the entire Public Health Sciences Division, especially recognizing Dr. Walter Ambrosius and Judy Bahnson.

Last, but not least, I am very grateful for the time and effort of the investigators, staff and participants in the Type 1 Diabetes Genetics Consortium. Without their continued devotion to this nine-year endeavor, the T1DGC project could not have been possible.

TABLE OF CONTENTS

LISTS OF TABLES AND FIGURES

CHAPTER III

ABSTRACT

Aims/hypothesis: The aim of this study was to investigate whether proportion of type 1 diabetic births differed by month and season. We hypothesized that more births occur during the spring and summer months in all populations, except in low-prevalence populations.

Methods: Using type 1 diabetic participants recruited for the Type 1 Diabetes Genetics Consortium, we compared the observed number of births to the expected number of births in Australia, Canada, Poland, Spain and the United States. Reference populations were drawn from the Center for Disease Control (CDC) and the United Nations (UN) databases. Monthly and seasonal differences in the proportion of type 1 diabetic births were assessed by Poisson regression. The regression models were stratified by nationality, gender and race, where possible.

Results: Differences in birth patterns by month and season were not observed in the overall type 1 diabetic population. In the United States, a statistically significant difference for birth month was found with more type 1 diabetics born in June and August than expected.

Conclusions: These results suggest that monthly or seasonal influences may contribute to the development of type 1 diabetes. This finding could support the hypothesis that viruses occurring during pregnancy, specifically in the summer and fall months, a time of increased viral activity, may contribute to the monthly differences. However, other hypotheses such as environmental factors post-birth

are possible. Future research should investigate seasonality of birth patterns during known times of viral epidemics.

CHAPTER ONE

Introduction

Proposed Cause of Type 1 Diabetes

Type 1 diabetes mellitus, previously called insulin-dependent diabetes or juvenile-onset diabetes, develops when the immune system destroys pancreatic β-cells. The pancreatic β-cells make insulin, which regulates an individual's blood glucose. Onset of type 1 diabetes typically occurs during childhood or early adulthood; although onset can occur later in some individuals.[1] Type 1 diabetes has a multi-factorial origin involving a combination of genetic, biological, and environmental factors resulting in a wide spectrum of incidence rates between various populations with distinct variation by race and ethnicity.

The genetic influence on type 1 diabetes is primarily associated with the human leukocyte antigen (HLA) region of chromosome 6, namely *HLA-DR3* and *HLA-DR4* alleles. Nearly 98% of persons with type 1 diabetes have *DR3* and/or *DR4* and persons with both alleles are particularly susceptible to develop type 1 diabetes.[2-3] While genetic susceptibility appears necessary, it is not sufficient to cause the development of the disease. The concordance for type 1 diabetes in monozygous twin pairs is only about 36%.[2, 4] Additionally, incidence varies among persons with the same genotype. While genetics plays a role in development of type 1 diabetes, more than 80% of cases of type 1 diabetes occur in individuals with no family history of the disease.[2, 5]

Racial and ethnic background represents one of the most significant determinants for development of type 1 diabetes. Past research has shown that

Caucasians have a higher incidence rate than African Americans, Asians, and Hispanics. Gender, however, does not appear to be a significant determinant of type 1 diabetes.

The development of type 1 diabetes also depends on biological influences such as the presence of autoantibodies to islet cell antigens. There are two peaks for age of onset of type 1 diabetes. The first is in early childhood (0-4 years of age) and the second is around puberty (10-14 years of age). Onset of type 1 diabetes often occurs in winter and spring months.[2]

Several environmental factors have been suggested to contribute to the development of type 1 diabetes. These include intrauterine infections, dietary intake of certain nutrients and possible toxic food components, short duration of breastfeeding, early exposure to cows' milk proteins, vitamin D deficiency, maternal age, birth order, and socioeconomic status.

The combination of these influences leads the individual's immune system to attack and destroy the β-cells in the pancreas that produce insulin, ultimately leading to the development of type 1 diabetes. More than 90% of the β-cells must be destroyed prior to development of type 1 diabetes. This latency period further leads to the challenge of understanding the etiology of type 1 diabetes.

The discrepant incidence rates among populations, the increase in risk at puberty and the more frequent onset of type 1 diabetes during the winter, all suggest that while genetic and biological influences are important, viruses, nutrition, and other socioeconomic factors may also be involved in the development of type 1 diabetes.

Epidemiology of Type 1 Diabetes

In children younger than 14 years of age, 0.02% of the global population has been diagnosed with type 1 diabetes. Incidence of type 1 diabetes is increasing in many countries, with an estimated annual increase of 3%. This translates to 70,000 new cases of type 1 diabetes worldwide.[6]

Within the United States, type 1 diabetes is the third most prevalent chronic disease of childhood, affecting 0.3% of the general population by 20 years of age and a lifetime risk of nearly 1%.[7] The total number of persons with type 1 diabetes in the United States is estimated to be between 300,000 – 500,000 individuals. Estimates of prevalence among United States children vary but cluster around 1.7 per 1,000 and equate to approximately 123,000 children with type 1 diabetes.[8] Within the United States, the prevalence of type 1 diabetes varies by ethnic group. The estimated prevalence in non-Hispanic white children younger than 20 years has ranged between 1.0 - 2.9 per 1,000, whereas in the other racial and ethnic groups, this prevalence is estimated to range from 0.2 – 2.1 per 1,000.[9]

Among chronic childhood diseases, the incidence of type 1 diabetes is higher than any other chronic disease of youth, including all childhood cancers. Within the United States, the incidence is estimated to be increasing at the rate of 2 - 5% per year.[10]

Incidence rates of type 1 diabetes vary dramatically throughout the world. The highest reported incidence rates are in the Scandinavian countries, particularly Finland, as well as in Sardinia, Italy. In these areas, incidence rates

as high as 45 per 100,000 per year have been reported.[2, 11-16] These rates are more than 15 times greater than the incidence rates found in Asian, Hispanic, and Native American populations, where incidence rates are generally 3 per 100,000 or less.[2, 11, 17-22] Incidence rates in the United States, Australia and other European countries are intermediate, ranging from 3-19 per 100,000 per year.[2, 16, 22]

Ethnically heterogeneous populations, such as the United States and Canada, show differences in incidence rates per 100,000 based on ethnicity, ranging from 3.3 in African Americans to 20.6 in Caucasians.[7,16,23-25] However, in ethnically homogenous populations, such as Japan, the incidence rates show little variation between geographical areas within the country.[8, 26] Table I summarizes the incidence rates reported worldwide.

Table I. Reported incidence rates of type 1 diabetes in children ≤ 14 years of age worldwide (per 100,000 per year)[27]

Country	Incidence Rates (95% CI)
Africa	
Algeria	5.7 (3.6 - 8.5)
Sudan	5.0 (3.7 – 6.5)
Mauritius	1.4 (0.8 – 2.1)
Asia	
China (Shanghai)	0.7 (0.5 – 0.9)
China (Beijing)	0.9 (0.7 – 1.1)
China (Changsha)	0.3 (0.2 – 0.4)
China (Hong Kong)	1.3 (0.8 - 2.2)
Israel	6.0 (5.4 – 6.7)
Japan (Okinawa)	1.4 (0.8 – 2.2)
Pakistan	0.7 (0.4 – 1.0)
Russia	6.0 (5.2 – 6.9)
Europe	
Austria	9.6 (8.8 – 10.3)
Denmark	15.5 (13.3 – 18.0)
Finland	36.5 (34.8 – 38.3)
France	8.5 (7.9 – 9.1)
Germany	11.0 (10.3 – 11.7)
Italy (Sardinia)	36.8 (33.7 – 40.0)
Italy (Eastern Sicily)	11.7 (9.8 – 13.9)
Lithuania	7.4 (6.6 – 8.3)
Luxemburg	11.4 (8.1 – 15.6)
The Netherlands	13.0 (11.7 – 14.4)
Norway	21.2 (19.2 – 23.3)
Poland (Krakow)	6.1 (5.4 – 6.9)
Romania	5.0 (4.1 – 6.1)
Slovakia	8.5 (7.8 – 9.3)
Slovenia	7.9 (6.7 – 9.2)
Spain	12.5 (11.6 – 13.5)
Sweden	27.5 (26.4 – 28. 7)
United Kingdom (Oxford)	17.8 (16.2 – 19.5)
United Kingdom (Ireland)	19.7 (17.8 – 21.8)
North America	
Canada (Alberta)	24.0 (20.6 – 27.8)
United States (Allegheny County, PA)	17.8 (15.5 – 20. 3)
United States (Jefferson County, AL)	15.0 (12.2 – 18.2)

United States (Chicago, IL)	11.7 (10.5 – 13.1)
South America	
Brazil	8.0 (5.5 – 11.1)
Chile	1.6 (1.3 – 2.0)
Paraguay	0.9 (0.7 – 1.1)
Venezuela	0.1 (0.1 – 0.2)
Central America and West Indies	
Barbados	2.0 (0.3 – 6.4)
Cuba	2.9 (2.6 – 3.2)
Dominica	5.7 (1.5 – 14.7)
Mexico	1.5 (0.7 – 2.9)
Oceania	
Australia	14.5 (13.4 – 15.6)
New Zealand (Auckland)	12.9 (10.9 – 15.3)
New Zealand (Canterbury)	21.9 (17.3 – 27.3)

Gender differences in incidence and prevalence have not been found consistently; however, some studies report that for Caucasians, males have a slighter higher incidence rate, whereas in non-Caucasians, a slight excess is seen in females.[8]

Rationale to Focus on Birth Patterns in Type 1 Diabetes

With the increase in incidence of type 1 diabetes and the significant economic costs associated with this disease, understanding the etiology of this disease is critical. Differences in the proportion of births of children who eventually develop type 1 diabetes by season, as compared to the general population, suggest that environmental factors operating around the antenatal and perinatal period could contribute to the development of type 1 diabetes. Geographical and temporal variations in the birth patterns of children with type 1 diabetes suggest a potential interaction between seasonality and risk, where an environmental factor with periodic or episodic features could be linked to the development of type 1 diabetes.

Previous studies have hypothesized that mothers who conceive during the yearly season of certain viral epidemics transmit the viruses to the fetus. Thirty-two days after implantation, and throughout the remainder of fetal life, the pancreatic endocrine cells develop and organize into the islets of Langerhans.[28] If the mother contracts a virus that is pathogenic to the β-cells, depending upon the frequency and amount of damage to the β-cells during pregnancy, the child may be predisposed to type 1 diabetes at some point during their life. If the

mother transmits antibodies, rather than the virus to the fetus, the baby may be protected.

Due to the racial and ethnic differences in incidence rates, analysis of birth patterns by race and ethnicity is important. By understanding whether seasonal or monthly differences exist in the number of births of children who eventually develop type 1 diabetes in any population, and identifying the populations where the differences are present, advancements in the understanding of the epidemiology of type 1 diabetes can be furthered.

Potential Mechanisms Linking Enteroviruses and Type 1 Diabetes

Enteroviruses (EVs) are RNA viruses that commonly cause human diseases. Each year, an estimated 10-15 million symptomatic enterovirus infections occur in the United States.[29] The link between enteroviruses and development of type 1 diabetes has not been confirmed, however enteroviruses may affect the development of type 1 diabetes given that enteroviruses infect and damage β-cells and that the gene for the immune system receptor for enteroviruses (1F1H1) has been identified as a risk gene for type 1 diabetes. This hypothesis is supported by past research where EV proteins have been detected in the pancreas of type 1 diabetic patients and by studies that have shown similar seasonality patterns of autoantibody appearance, onset of type 1 diabetes, and presence of enteroviruses.[30] This seasonal pattern of enteroviruses typically increases in the summer and fall months, peaking in August.[31]

The viral hypothesis states that mothers, who conceive during the months with higher presence of viral infections (summer and fall), are more likely to become infected during pregnancy and transmit this virus to the fetus. Therefore, given a normal 40-week gestation period, children born in the spring and summer are more likely to develop type 1 diabetes because fetal development occurred during a period of peak enterovirus activity.

Past Research Investigating Effects of Enterovirus on Development of Type 1 Diabetes

Among the over 90 enterovirus serotypes described, coxsackie B5 enterovirus has been suggested to contribute to the future development or progression of type 1 diabetes. In the United States, the National Enterovirus Surveillance System has found that the coxsackie B5 enterovirus displays an epidemic pattern of circulation, increasing every 3-6 years, and usually lasting for one year. The summer-fall seasonality displayed in the coxsackie B5 enterovirus is more pronounced than the seasonality pattern displayed in other enteroviruses.[31]

In Finland, the Diabetes Prediction and Prevention study found that enterovirus infections were more frequently detected in participants testing positive for diabetes-associated antibodies than in matched controls.[32] The Trial to Reduce IDDM in Genetically at Risk (TRIGR) and Childhood Diabetes in Finland (DiME) projects, both also conducted in Finland, found significant differences between pregnant mothers of children who subsequently developed type1 diabetes. The TRIGR study[33] found a greater number of infections in

mothers of children who subsequently developed type 1 diabetes, and the DiME study[34] found that mothers of children who subsequently developed type 1 diabetes were more likely to have enterovirus antibodies present. Similar results have been found in Sweden, but were not duplicated in another study conducted in Finland.[35-36] In each of these studies, samples were collected from the mother at the end of the first trimester.

In Birmingham, Alabama, a significant increase was seen in the incidence of type 1 diabetes that corresponded with an epidemic of the coxsackie B virus.[37] Researchers in Slovakia found that children with type 1 diabetes were significantly more likely to test positive for coxsackie antibodies. Similar to the pattern in the United States, these researchers found that coxsackie infections occurred more frequently in September and less frequently in March.[38]

Past Research Investigating Effects of Vitamin D on Development of Type 1 Diabetes

Exposure to vitamin D has been suggested as an environmental factor that is protective against the development of type 1 diabetes. Vitamin D can either be supplied through exposure to sunlight through ultraviolet radiation or through food and supplements. Insufficient maternal vitamin D levels during a critical fetal period could lead to an increase in the proportion of births of children who subsequently develop type 1 diabetes during the spring and summer months.

Type 1 diabetes, in addition to other autoimmune diseases, is more prevalent in higher latitudes, where exposure to ultraviolet radiation is lower.[39]

Researchers in Australia examined the association between latitude and prevalence of immune related disorders and found that the prevalence of type 1 diabetes was negatively correlated with latitude.[40] Supplementation of vitamin D has been shown to reduce the risk of developing type 1 diabetes.[41-42] However, vitamin D research is confounded by differences in sunlight exposure, milk consumption, and the common use of vitamin D supplements.

Past Research on Seasonality of Birth Patterns in Other Autoimmune Diseases

Disproportionate numbers of births by season, as compared with the general population, have been reported in multiple autoimmune diseases, including type 1 diabetes, Graves' disease, Hashimoto's hypothyroidism, Crohn's disease, atopic disease, allergic rhinitis, and asthma.[43-45] The presence of these patterns, while not necessarily consistent across all autoimmune diseases, do suggest a common trigger in the initiation of the autoimmune process.

Birth patterns for patients with atopic disease and asthma have shown an increase in births during the fall and winter months; while for allergic rhinitis, the increase was found in winter and spring months.[44-45] Researchers in Denmark saw a peak in births occurring in August and a trough in March for persons who later developed Crohn's disease.[46]

Past Research on Seasonality of Onset Patterns in Type 1 Diabetes

Onset of type 1 diabetes appears to have a seasonal pattern, with fewer cases diagnosed in the summer months and peaks during the winter and spring months.[2, 11, 47-51] In the worldwide WHO Diamond Study, 42 (40%) of the 105 centers showed a significant seasonal pattern in the onset of type 1 diabetes,

with 28 (27%) of all centers showing a peak in onset during the winter months and 33 (31%) of all centers showing a trough during the summer months. Centers with higher incidence were more likely to exhibit the seasonal pattern. Four (10%) of the forty-two centers were located in the Southern Hemisphere, and two of these four centers showed an opposite monthly pattern with a similar seasonal pattern of peaks in their winter months and a trough in their summer months.[52]

Previous Research on Birth Patterns in Type 1 Diabetes Outlining the Background for the Current Study

Previous research on birth patterns in type 1 diabetes has shown mixed results. Differences in proportion of births by month or season have been observed more frequently in populations with high or medium incidence rates than in those with low incidence rates. Ethnically homogeneous populations are more likely to demonstrate differences in birth rates than heterogeneous populations. In some populations, monthly or seasonal differences have not been observed in overall population, but only in gender-specific type 1 diabetic populations.

Birth month differences based on incidence of type 1 diabetes. In Finland and Sardinia, the two regions with the highest reported incidence rates, Songini et al. found the birth pattern for individuals with type 1 diabetes was significantly different from that of the general population, with more individuals who subsequently developed type 1 diabetes born during the summer and fall months,[53] although other research has not replicated this finding.[54-55]

In populations with high incidence of type 1 diabetes (10-20 per 100,000), such as Scandinavia, Great Britain, Germany and New Zealand, results are mixed; however, many populations reveal a seasonal birth pattern for individuals who subsequently develop type1 diabetes, with most populations, but not all, demonstrating peaks in the summer months and troughs in winter months.

The EURODIAB study, using data from 16 regions throughout Europe, all primarily with high incidence of type 1 diabetes, did not find an overall statistically significant seasonal variation, though they observed a non-significant trend with increased births in the autumn months. When analyzing each region separately, a significant seasonality pattern was only found in Great Britain, where the peak in births during the spring months was different from the peak in the other seasons. Grouping regions by incidence rates did not show a seasonal effect.[54,56]

Within the United States, the SEARCH for Diabetes in Youth study found significant peaks in the number of births for individuals who subsequently develop type1 diabetes occurring from April through July, with troughs during the months of November through February. This pattern was consistent after stratifying by gender, race (black, white, other) and age (0-9 years, 10-18 years), where all sub-populations showed peaks in spring or early summer and troughs in late fall or winter. After stratifying by region of the United States, a similar pattern was observed in the northern United States, however, this pattern was not observed in the southern study regions.[57] Similarly, in Great Britain and Sweden, a significant difference was found when comparing the birth pattern of

individuals who subsequently develop type1 diabetes to that of the general population, with more individuals who subsequently developed type1 diabetes being born during the spring and summer, and fewer born during the winter months.[58-60] This same seasonal pattern, although the months are reversed (Southern Hemisphere), has been observed in New Zealand, where an increase in births of individuals who subsequently develop type1 diabetes was observed during the spring and summer months.[61]

Germany, another country with high incidence rates of type 1 diabetes, has shown inconsistent results. The EURODIAB study[54, 56] found a similar pattern of births for individuals who subsequently develop type1 diabetes and that of the general population. However, within Germany, in Berlin, a peak in the number of births of individuals who subsequently develop type1 diabetes was observed during the spring and summer months.[62] Within Baden-Wurttemberg, Germany, significant troughs in number of births of individuals who subsequently develop type1 diabetes was observed during the spring and summer[63]; however, within this same city, the EURODIAB study found no overall differences.[54,56]

Seasonal patterns of births of individuals who subsequently develop type1 diabetes differing from that of the general population have been observed in populations with intermediate incidence rates (5-10 per 100,000). Several Eastern Europe countries have shown a reduced number of births of individuals who subsequently develop type1 diabetes during the winter months and an increased number during the spring months.[64-67]

However, research in populations with low (≤5 per 100,000) incidence of type 1 diabetes, such as those in Turkey[68] and Japan[69] have not found statistically different seasonality pattern of births of individuals who subsequently develop type1 diabetes from that of the general population. However, in China[70] another population with low incidence of type 1 diabetes, Ye et al., reported troughs in the number of births of children who subsequently develop type1 diabetes during the spring and summer months, with peaks during the fall and winter months.

Birth month differences based on ethnic heterogeneity of population. Laron et al.[71] used incidence data to compare ethnically homogenous and ethnically heterogeneous populations with high, intermediate or low incidence of type 1 diabetes. They found that in homogenous populations, with varying incidence rates (such as Ashkenazi Jew, Arab, Sardinia, and New Zealand), the seasonality of birth pattern for individuals who subsequently develop type1 diabetes showed peaks in the spring or summer months. This pattern was not found in ethnically heterogeneous populations, such as the United States and Australia.

The two primary ethnic groups in Israel have different incidence rates; the Arab population has a low incidence (2.9 per 100,000), whereas the Jewish population has medium incidence (10-18 per 100,000). Researchers found that the Jewish type 1 diabetic population had a peak in the number of births in the spring, with a trough in the winter months. No difference was observed among the Arab population.[72]

Birth month differences in gender-specific sub-populations. The EURODIAB study found a seasonality pattern in regions in the combined data for males with type 1 diabetes, but not for females with type 1 diabetes.[54,56] This finding was not replicated in the country-specific data with the exception of Great Britain and Luxembourg.[54] In the Netherlands, the pattern of births of individuals who subsequently develop type1 diabetes differed from that of the general population for males, with peaks of type 1 diabetic births occurring in the spring months; however, these differences were not observed in the female or overall population.[73]

In Ireland, females with type 1 diabetes were found to have a different seasonal birth pattern than that of the general population; however, while a seasonal pattern was observed in the male population, this was not significantly different from that of the general male population.[74]

In summary, the inconsistencies among nationalities and genders regarding the presence of seasonality of birth patterns all suggest that future research needs to be conducted in order to better understand the impact of birth month on the etiology of this disease. If a peak is observed in the proportion of type 1 diabetic births, the peak is most commonly found in the summer months. Table II summarizes previous research of birth pattern differences.

Table II. Summary of previous research investigating birth patterns in type 1 diabetics

Country/Nationality	Years of Birth	Years of Diagnosis	N type 1 diabetic population	Peak
China (Shanghai)[70]		1976 – 1997	136	Fall/Winter
Israel (Jewish)[72]		1980 - 1993	987	Spring/Summer
Germany (Berlin)[62]		1990 – 2000	570	Spring/Summer
Italy (Sardinia)[53]		1989-1998	1928	Summer/Fall
Italy (Sicily)[75]		1989 – 1998	273	Summer/Fall
The Netherlands[73]	1959 – 1990		2633	Winter/Spring
Slovakia[65]	1974 – 1997	1989 – 1997	1186	Fall
Sweden[59]	1962 – 1992		1248	Summer
Ukraine[64]	1960 – 2003		20,117	Spring
United Kingdom[54,56]	1974 – 1994		5997	Summer
United Kingdom[58]	1974 – 1988		4665	Spring/Summer
New Zealand (Canterbury)[61]		1982 – 1996	275	Summer
Israel (Arab)[72]		1980 - 1993	108	Non-significant
Japan[69]		1986 – 1990	1260	Non-significant
Austria[54,56]	1974 – 1994		895	Non-significant
Czech Republic[54,56]	1974 – 1994		1512	Non-significant
Denmark[76]	1973 – 1977		837	Non-significant
Denmark[54,56]	1974 – 1994		296	Non-significant
Germany (Baden-Wuerttemberg)[54,56]	1974 – 1994		1303	Non-significant
Italy (Sardinia)[54,56]	1974 – 1994		886	Non-significant
Italy (Sardinia)[55]	1974 - 1992		425	Non-significant
Italy (Lazio)[54,56]	1974 – 1994		471	Non-significant
Lithuania[54,56]	1974 – 1994		486	Non-significant
Luxembourg[56]	1974 – 1994		72	Non-significant
Malta[56]	1974 – 1994		98	Non-significant

Poland[54,56]	1974 – 1994		448	Non-significant
Romania[54,56]	1974 – 1994		185	Non-significant
Slovakia[54,56]	1974 – 1994		889	Non-significant
Spain[54,56]	1974 – 1994		914	Non-significant
Sweden (Stockholm) [54,56]	1974 – 1994		520	Non-significant
Turkey [68]		1985 – 2001	353	Non-significant
United Kingdom (N. Ireland) [54,56]	1974 – 1994		462	Non-significant

Specific Aims and Hypothesis

The viral hypothesis assumes that certain maternal viral infections may trigger the autoimmune process in genetically susceptible fetuses. The specific aims are to provide an assessment of whether the number of births for individuals who subsequently develop type1 diabetes differs by month or season, overall, by nationality, and according to gender and race (defined as non-Hispanic white and other race/ethnicity). By understanding whether a seasonal birth pattern is present in any population, and identifying the populations where a seasonal birth pattern is present, advancements in the understanding of the epidemiology of type 1 diabetes can be furthered. The assumptions of the viral hypothesis in the Type 1 Diabetes Genetics Consortium population will be used to address the following specific aims.

1. In Australia, Canada, Poland, Spain, and the United States, to determine whether the proportion of births of individuals who subsequently develop type1 diabetes differs by month, and season, after accounting for birth patterns in the general population and controlling for important covariates (nationality and decade of birth).

   Hypothesis: A peak in the proportion of births of individuals who subsequently develop type1 diabetes will be observed in the spring and summer months, with a trough in the fall and winter months. These differences will be observed both overall, and nationality-specific.
2. Within the United States population, to determine whether the proportion of births of individuals who subsequently develop type1 diabetes differs by

month, and season, within gender-specific populations after accounting for the proportion of overall births by month and season.

Hypothesis: A peak in the proportion of births of individuals who subsequently develop type1 diabetes will be observed in the spring and summer months, with a trough in the fall and winter months, in both genders.

3. Within the United States population, to determine whether proportion of births of individuals who subsequently develop type1 diabetes differs by month, and season, within race-specific (non-Hispanic white, other race/ethnicity) populations after accounting for the proportion of overall births by month and season.

   Hypothesis 1: For the non-Hispanic white population, a peak in the proportion of births of individuals who subsequently develop type1 diabetes will be observed in the spring and summer months, with a trough in the fall and winter months.

   Hypothesis 2: Differences in proportion of births of individuals who subsequently develop type1 diabetes will not be observed in the other race/ethnicity population, due to the low incidence of type 1 diabetes in these populations.

Summary

As the Type 1 Diabetes Genetics Consortium (T1DGC) is an international study spanning over thirty countries, it provides the ideal sample in which to evaluate the presence of seasonality of birth patterns among individuals with type

1 diabetes across regions and ethnicities. By understanding whether a seasonality of birth pattern is present in any of these populations, and identifying the populations where a seasonality of birth pattern is present, advancements in the understanding of the epidemiology of type 1 diabetes can be furthered.

Reference List

1. Centers for Disease Control and Prevention. National diabetes fact sheet: general information and national estimates on diabetes in the United States, 2003. Rev ed. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, 2004.

2. Dorman JS, McCarthy BJ, O'Leary LA, Koehler AN. Risk Factors for Insulin-Dependent Diabetes. In: Harris MI, Cowie CC, Stern MP, et al. *Diabetes in America.* Bethesda, MD: NIH Publication; 1995: 165-178.

3. Wolf E, Spencer KM, Cudworth AG. The genetic susceptibility to type 1 (insulin dependent) diabetes: analysis of the HLA-DR association. *Diabetologia.* 1983; 24(4): 224-230.

4. Olmos P, A'Hern R, Heaton DA, et al. The significance of the concordance rate for type 1 (insulin-dependent) diabetes in identical twins. *Diabetologia.* 1988; 31(10): 747-750.

5. WHO Multinational Project for Childhood Diabetes Group. Familial insulin-dependent diabetes mellitus (IDDM) epidemiology: standardization of data for the DIAMOND Project. *Bulletin of the World Health Organization.* 1991; 69(6): 767-777.

6. International Diabetes Foundation. Type 1 diabetes incidence. http://da3.diabetesatlas.org/index5c31.html. Accessed April 25, 2011.

7. Rewers M, LaPorte RE, King H, Tuomilehto J. Trends in the prevalence and incidence of diabetes: insulin-dependent diabetes mellitus in childhood. *World Health Stat Q.* 1988; 41(3-4): 179-189.

8. LaPorte RE, Matsushima M, Chang Y. Prevalence and incidence of insulin-dependent diabetes. In: Harris MI, Cowie CC, Stern MP, et al. *Diabetes in America.* Bethesda, MD: NIH Publication; 1995: 37-46.

9. Siemiatycki J, Colle E, Campbell S, Dewar R, Aubert D, Belmonte MM. Incidence of IDDM in Montreal by ethnic group and by social class and comparisons with ethnic groups living elsewhere. *Diabetes.* 1988; 37(8): 1096-1102.

10. Silink M. Childhood diabetes: a global perspective. *Horm Res.* 2002; 57(suppl 1): 1-5.

11. Karvonen M, Tuomilehto J, Libman I, LaPorte R. A review of the recent epidemiological data on the worldwide incidence of type 1 (insulin-

dependent) diabetes mellitus. World Health Organization DIAMOND Project Group. *Diabetologia.* 1993; 36(10): 883-892.

12. Tuomilehto J, Lounamaa R, Tuomilehto-Wolf E, et al. Epidemiology of childhood diabetes mellitus in Finland – background of a nationwide study of type 1 (insulin-dependent) diabetes mellitus. The Childhood Diabetes in Finland (DiMe) Study Group. *Diabetologia.* 1992; 35(1): 70-76.

13. Dahlquist G, Blom L, Holmgren G, et al. The epidemiology of diabetes in Swedish children 0-14 years—a six year prospective study. *Diabetologia.* 1985; 28(11): 802-808.

14. Joner G, Søvik O. Increasing incidence of diabetes mellitus in Norwegian children 0-14 years of age 1973-1982. *Diabetologia.* 1989; 32(2): 79-83.

15. Muntoni S, Songini M. High incidence of IDDM in Sardinia. Sardinian Collaborative Group for Epidemiology of IDDM. *Diabetes Care.* 1992; 15(10): 1317-1322.

16. Diabetes Epidemiology Research International Group. Geographic patterns of childhood insulin-dependent diabetes mellitus. *Diabetes.* 1988; 37(8): 1113-1119.

17. Bao MZ, Wang JX, Dorman JS, Trucco M. HLA-DQ beta non-ASP-57 allele and incidence of diabetes in China and the USA. *Lancet.* 1989; 2(8661): 497-498.

18. Savage PJ, Bennett PH, Senter RG, Miller M. High prevalence of diabetes in young Pima Indians: evidence of phenotypic variation in a genetically isolated population. *Diabetes.* 1979; 28(10): 937-942.

19. Yang Z, Wang K, Li T, et al. Childhood diabetes in China: enormous variation by place and ethnic group. *Diabetes Care.* 1998; 21(4): 525-529.

20. Rueda OA, Libman IM, Bustamante NA, Valdes CR, LaPorte RE. Low incidence of IDDM in children of Veracruz-Boca del Rio, Veracruz. *Diabetes Care.* 1998; 21(8): 1372-1373.

21. Serrano-Rĩos M, Goday A, Larrad TM. Migrant populations and the incidence of type 1 diabetes mellitus: an overview of the literature with a focus on the Spanish-heritage countries in Latin America. *Diabetes Metab Res Rev.* 1999; 15: 113-132.

22. EURODIAB ACE Study Group. Variation and trends in incidence of childhood diabetes in Europe. *Lancet.* 2000; 355: 873-876.

23. SEARCH for Diabetes in Youth Study Group. The burden of diabetes mellitus among US Youth: prevalence estimates from the SEARCH for Diabetes in Youth Study. *Pediatrics.* 2006; 118: 1510-1518.

24. Lipman TH. The epidemiology of type 1 diabetes in children 0-14 yr of age in Philadelphia. *Diabetes Care.* 1993; 16(6): 922-925.

25. Tull ES, Roseman JM, Christian CL. Epidemiology of childhood IDDM in U.S. Virgin Islands from 1979 to 1988. Evidence of an epidemic in early 1980s and variation by degree of racial admixture. *Diabetes Care.* 1991; 14(7): 558-564.

26. Japan IDDM Epidemiology Study Group. Lack of regional variation in IDDM risk in Japan. *Diabetes Care.* 1993; 16(5): 796-800.

27. Karvonen M, Viik-Kajander M, Moltchanova E, et al. Incidence of childhood type 1 diabetes worldwide. *Diabetes Care.* 2000; 23(10): 1516-1526.

28. Schoenwolf GC. *Larsen's Human Embryology.* 4th ed. Philadelphia, PA: Elsevier Health Sciences; 2008.

29. Strikas RA, Anderson L, Parker RA. Temporal and geographic patterns of isolates of nonpolio enteroviruses in the United States, 1970—1983. *J Infect Dis.* 1986; 153: 346-351.

30. Taurianine S, Oikarinen S, Oikarinen M, Hyöty. Enteroviruses in the pathogenesis of type 1 diabetes. *Semin Immunopathol.* 2011; 33(1): 45-55.

31. Khetsuriani N, LaMonte-Fowlkes A, Oberste MS, Pallansch MA. Enterovirus Surveillance – United States, 1970-2005. https://www.cdc.gov/mmwr/preview/mmwrhtml/ss5508a1.htm. Accessed April 25, 2011.

32. Salminen K, Sadeharju K, Lönnrot M, Vähäsalo, et al. Enterovirus infections are associated with the induction of β-cell autoimmunity in a prospective birth cohort study. *Journal of Medical Virology.* 2003; 69: 91-98.

33. Sadeharju K, Hämäläinen AM, Knip M, Lönrot M, et al. Enterovirus infections as a risk factor for type I diabetes: virus analyses in a dietary intervention trial. *Clin Exp Immunol.* 2003; 132: 271-277.

34. Hyoty H, Hiltunen M, Knip M, Laakkone M, et al. A prospective study of the role of coxsackie B and other enterovirus infection in the pathogenesis of IDDM. *Diabetes.* 1995; 44(6): 652-657.

35. Viskari HR, Roivainen M, Reunanen A, Pitkäniemi J, et al. Maternal first-trimester enterovirus infection and future risk of type 1 diabetes in the exposed fetus. *Diabetes.* 2002; 51: 2568-2571.

36. Dahlquist GG, Ivarsson S, Lindberg B, Forsgren M. Maternal enteroviral infection during pregnancy as a risk factor for childhood IDDM: a population-based case-control study. *Diabetes. 1995;* 44: 408-413.

37. Wagenknecht LW, Roseman JM, Herman WH. Increased incidence of insulin-dependent diabetes mellitus following an epidemic of coxsackievirus B5. *American Journal of Epidemiology.* 1991; 133(10): 1024-1031.

38. Mikuleckỳ M, Michalkova D, Petrovičovả A. Coxsackie infection and births of future diabetic children: year, seasonality and secularity. *Journal of Pediatric Endocrinology & Metabolism.* 2000; 13: 523-527.

39. Keen H, Ekoe JM. The geography of diabetes mellitus. *Br Med Bull.* 1984; 40(4): 359-365.

40. Staples JA, Ponsonby AL, Lim LL, McMichael AJ. Ecologic analysis of some immune-related disorders, including type 1 diabetes in Australia: latitude, regional ultraviolet radiation, and disease prevalence. *Environmental Health Perspectives.* 2003; 111(4): 518-523.

41. Pozzilli P, Manfrini S, Crinỏ A, Picardi A, et al. Low levels of 25-hydroxyvitamin D_3 and 1, 25-dihydroxyvitamin D_3 in patients with newly diagnosed type 1 diabetes. *Horm Metab Res.* 2005; 37: 680-683.

42. Zipitis CS, Akobeng AK. Vitamin D supplementation in early childhood and risk of type 1 diabetes: a systematic review and meta-analysis. *Arch. Dis. Child.* 2008; 93: 512-517.

43. Krassas GE, Tziomalos K, Pontikides N, Lewy H, Laron Z. Seasonality of month of birth of patients with Graves' and Hashimoto's diseases differs from that in the general population. *European Journal of Endocrinology.* 2007; 156: 631-636.

44. Nilsson L, Björkstẻn B, Hattevig G, Kjellman B, Sigrs N, Kjellman NM. Season of birth as a predictor of atopic manifestations. *Arch. Dis. Child.* 1997; 76: 341-344.

45. Aberg N. Birth season variation in asthma and allergic rhinitis. *Clinical and Experimental Allergy.* 1989; 19: 643-648.

46. Sørensen HT, Pedersen L, Nørgård B, Fonager K, Rothman KJ. Research pointers: does month of birth affect risk of Crohn's disease in childhood and adolescence? *BMJ.* 2001; 323: 907.

47. Wagenknecht LE, Roseman JM, Alexander WJ. Epidemiology of IDDM in black and white children in Jefferson County, Alabama, 1979-1985. *Diabetes.* 1989; 38(5): 629-633.

48. Joner G, Søvik O. Incidence, age at onset and seasonal variation of diabetes mellitus in Norwegian children, 1973-1977. *Acta Paediatr Scand.* 1981; 70(3): 329-335.

49. LaPorte RE, Tejima N, Dorman JS, Cruickshanks KJ. Differences between blacks and whites in the epidemiology of insulin-dependent diabetes mellitus in Allegheny County, Pennsylvania. *Am J Epidemiol.* 1986; 123(4): 592-603.

50. Fishbein HA, LaPorte RE, Orchard TJ, Drash AL, Kuller LH, Wagener DK. The Pittsburgh insulin-dependent diabetes mellitus registry: seasonal incidence. *Diabetologia.* 1982; 23(2): 83-85.

51. Elamin A, Omer MI, Zein K, Tuvemo T. Epidemiology of childhood type 1 diabetes in Sudan, 1987-1990. *Diabetes Care.* 1992; 15(11): 1556-1559.

52. Moltchanova EV, Schreier N, Lammi N, Karvonen M. Seasonal variation of diagnosis of type 1 diabetes mellitus in children worldwide. *Diabetic Medicine.* 2009; 26: 673-678.

53. Songini M, Casu A, The Sardinian Collaborative Group for Epidemiology of IDDM, Ashkenazi I, Laron Z. Seasonality of birth in children (0-14 years) and young adults (0-29 years) with type 1 diabetes mellitus in Sardinia differs from that in the general population. *Journal of Pediatric Endocrinology & Metabolism;* 2001: 14: 781-783.

54. McKinney PA on behalf of the EURODIAB Seasonality of Birth Group. Seasonality of birth in patients with childhood type 1 diabetes in 19 European regions. *Diabetologia;* 2001: 44(Suppl 3): B67-B74.

55. Muntoni S, Wäänänen S, McKinney PA, Law G, Bodansky HJ, Muntoni S. The seasonal distribution of birth of patients with insulin-dependent diabetes mellitus in Sardinia. *Diabetologia;* 1999: 42 (Suppl 1): A86/312.

56. Rothwell PM, Gutnikov SA, McKinney PA, et al. Seasonality of birth in children with diabetes in Europe: multicentre cohort study. *BMJ.* 1999; 319: 887-888.

57. Kahn HS, Morgan TM, Case LD, Dabelea D, et al. Association of type 1 diabetes with month of birth among U.S. Youth. *Diabetes Care.* 2009; 32(11): 2010-2015.

58. Rothwell PM, Staines A, Smail P, Wadsworth E, McKinney P. Seasonality of birth of patients with childhood diabetes in Britain. *BMJ.* 1996; 312: 1456-1457.

59. Samuelsson U, Johannson C, Ludvigsson J. Month of birth and risk of developing insulin dependent diabetes in south east Sweden. *Arch Dis Child.* 1999; 81: 143-146.

60. Dahlquist GG, Kallen BA. Time-space clustering of date at birth in childhood-onset diabetes. *Diabetes Care.* 1996; 19(4): 328-332.

61. Willis JA, Scott RS, Darlow BA, Lewy H, Ashkenazi I, Laron Z. Seasonality of birth and onset of clinical disease in children and adolescents (0-19 years) with type 1 diabetes mellitus in Canterbury, New Zealand. *Journal of Pediatric Endocrinology & Metabolism.* 2002; 15: 645-647.

62. Kordonouri O, Shuga N, Lewy H, Ashkenazi I, Laron Z. Seasonality of month of birth of children and adolescents with type 1 diabetes mellitus in Berlin differs from the general population. *Eur J Pediatr.* 2001; 161: 291-292.

63. Neu A, Kehrer M, Ashkenazi I, Laron Z. Seasonality of birth in children (0-14 years) with diabetes mellitus type 1 in Baden-Wuerttemberg, Germany. *Journal of Pediatric Endocrinology & Metabolism.* 2000; 13: 1081-1085.

64. Vaiserman AM, Carstense B, Voitenko VP, Tronko MD, et al. Seasonality of birth in children and young adults (0-29 years) with type 1 diabetes in Ukraine. *Diabetologia.* 2007; 50: 32-35.

65. Mikuleckỳ M, Michalkovå D, Hlava P. Seasonality of births of Slovak IDDM children. *Diabetologia;* 1999: 42 (Suppl 1): A86/314.

66. Mikuleckỳ M, Minårik P, Michalkovå D. Insulin gene profile cycles with season of birth of future diabetic children and their relatives. *Journal of Pediatric Endocrinology & Metabolism.* 2004; 17(5): 727-730.

67. Ursic-Bratina N, Battelino T, Kkžišnik C, Laron-Kenet T, Ashkenazi I, Laron Z. Seasonality of birth in children (0-14 years) with type 1 diabetes

mellitus in Slovenia. *Journal of Pediatric Endocrinology & Metabolism.* 2001; 14(1): 47-52.

68. Evliyaoğlu O, Öcal G, Cetinkaya E, et al. No seasonality of birth in children with type 1 diabetes mellitus in Ankara, Turkey. *Journal of Pediatric Endocrinology & Metabolism.* 2002; 15(7): 1033-1034.

69. Kida K, Mimura G, Ito T, et al. Incidence of type 1 diabetes mellitus in children aged 0-14 in Japan, 1986-1990, including an analysis for seasonality of onset and month of birth: JDS study. *Diabetic Medicine.* 2000; 17: 59-63.

70. Ye J, Chen RG, Ashkenazi I, Laron Z. Lack of seasonality in the month of onset of childhood IDDM (0.7-15 years) in Shanghai, China. *Journal of Pediatric Endocrinology & Metabolism.* 1998; 11(3): 461-464.

71. Laron Z, Lewy H, Wilderman I, Casu A, et al. Seasonality of month of birth of children and adolescents with type 1 diabetes mellitus in homogenous and heterogeneous populations. *IMAJ.* 2005; 7: 381-384.

72. Laron Z, Shami I, Nitzan-Kaluski D, Ashkenazi I. Month of birth and subsequent development of type 1 diabetes (IDDM). *Journal of Pediatric Endocrinology & Metabolism.* 1999; 12(3): 397-402.

73. Jongbloet PH, Groenewoud HM, Hirasing RA, Van Buuren S. Seasonality of birth in patients with childhood diabetes in the Netherlands. *Diabetes Care.* 1998; 21(1): 190-191.

74. Roche EF, Lewy H, Hoey HM, Laron Z. Differences between males and females in the seasonality of birth and month of clinical onset of disease in children with type 1 diabetes mellitus in Ireland. *Journal of Pediatric Endocrinology & Metabolism.* 2003; 16(5): 779-782.

75. Fichera G, Arpi ML, Squatrito S, Purrello F, Ashkenazi I, Laron Z. Seasonality of month of birth of children (0-14 years old) with type 1 diabetes mellitus in the district of Catania, Sicily. *Journal of Pediatric Endocrinology & Metabolism.* 2001; 14(1): 95-96.

76. Bock T, Pedersen CR, Vølund A, Pallesen C, Buschard K. Perinatal determinants among children who later develop IDDM. *Diabetes Care.* 1994; 17(10): 1154-1157.

CHAPTER TWO

Birth Patterns of United States Children with Type 1 Diabetes

Letitia H. Perdue, Beverly M. Snively, Katherine A. Poehling,
Lynne E. Wagneknecht

Wake Forest School of Medicine

Corresponding author:
Letitia Perdue
Wake Forest School of Medicine
Medical Center Boulevard
Winston-Salem, NC 27157
Telephone: 336-716-1336
Fax: 336-713-5249
lperdue@wakehealth.edu

The following manuscript is to be submitted to Diabetologia in August 2011. Stylistic variations are due to the requirements of the journal. Ms. Letitia H. Perdue analyzed the data and prepared the manuscript. Drs. Beverly M. Snively, Katherine A. Poehling and Lynne E. Wagneknecht assisted Ms. Perdue in an advisory and editorial capacity and assisted in developing the analysis plan for this study.

ABSTRACT

Aims/hypothesis The aim was to investigate whether differences exist in the proportion of children who eventually develop type 1 diabetes by month and season of birth. We hypothesized that the season of birth of children who eventually develop type 1 diabetes more often will be spring and summer in all populations, with the exception of low-prevalence populations.

Methods Using 500 US participants born during 1990-2000 and recruited for the Type 1 Diabetics Genetics Consortium, we compared the observed number of births to the expected number of births, derived from Center for Disease Control (CDC) statistics. Monthly and seasonal differences in the proportion of type 1 diabetic births were assessed by Poisson regression, using the overall population, as well as gender- and race-specific populations.

Results In the overall US population, more births of children who eventually developed type 1 diabetes occurred in June and August than expected. Although no statistical difference was observed in either gender- or race-specific sub-populations, similar trends were observed in all sub-populations. No significant difference by season was observed.

Conclusions/interpretations The summer months had higher than expected numbers of births of children who eventually developed type 1 diabetes due to increases in the number of births during August. These results suggest that monthly or seasonal influences may contribute to the development of type 1 diabetes. This finding could support the hypotheses that viruses occurring during

the perinatal or antenatal period contribute to the monthly differences; however, other hypothesis such as environmental factors post-birth are possible.

Keywords Type 1 diabetes, seasonality of birth, United States

Abbreviations Center for Disease Control (CDC), Type 1 Diabetes Genetics Consortium (T1DGC)

Introduction

Type 1 (insulin-dependent) diabetes mellitus has a multi-factorial origin involving a combination of genetic and environmental factors resulting in a wide spectrum of incidence rates among populations around the world. The range of incidence rates, the increase in risk at puberty and the more frequent onset of type 1 diabetes during the winter months, all suggest that environmental factors such as viruses and nutrition may be involved in the development of type 1 diabetes.

The genetic influence of type 1 diabetes is primarily associated with the human leukocyte antigen (HLA) region of chromosome 6, namely *HLA-DR3* and/or *HLA-DR4* alleles. Nearly 98% of persons with type 1 diabetes have *DR3* and/or *DR4* and individuals with both alleles are particularly susceptible to develop type 1 diabetes.[1-2] While genetic susceptibility appears necessary, it is not sufficient to cause the development of the disease. The concordance for type 1 diabetes among monozygous twin pairs is only about 36%.[1, 3] Additionally, incidence varies among persons with the same genotype. While genetics plays a role in development of type 1 diabetes, more than 80% of cases of type 1 diabetes occur in individuals with no family history of the disease. [1, 4] These findings suggest that, in addition to genetics, the environment plays a role in the development of type 1 diabetes.

Geographical and temporal variations in both birth month and month of diagnosis for children with type 1 diabetes suggest a potential relationship between environment and onset, where an environmental factor with cyclic

features could be linked to the development of type 1 diabetes. One explanation for a seasonal pattern in birth months is given by the viral hypothesis. This hypothesis states that women who are pregnant during the months with higher presence of viral infections, specifically the summer and fall months, are more likely to transmit these viruses to the fetus and this infection may initiate an autoimmune process in the pancreas that may ultimately lead to the development of type 1 diabetes.[5]

Assuming a 40-week gestational period, our hypothesis is that more type 1 diabetics will be born in the spring and summer months because fetal development occurs during the most common seasons for viral epidemics, specifically summer and fall. Seasonal patterns in birth month of individuals who subsequently develop type 1 diabetes have been observed more frequently in high or medium incidence populations, or in ethnically homogenous populations. Primarily, the peaks have been observed in the number of spring or summer births, supporting this viral hypothesis. Understanding the overall etiology of this disease is critical for prediction and ultimately, prevention of type 1 diabetes.

Past research on seasonality of birth patterns among individuals with type 1 diabetes has shown mixed results.[6-21] However, if a peak is observed in the proportion of type 1 diabetic births, the peak is most commonly found in the summer months. Significant peaks in the number of births for children who subsequently develop type 1 diabetes have been observed during the summer months in regions of Great Britain, Sweden, New Zealand, Sardinia, Eastern European countries, and in the Jewish population in Israel.[6-16] However, these

differences have not been observed among persons with type 1 diabetes in the Turkey, Japan, China, Denmark, Germany, and the Arab population in Israel.[7, 17-20] In the Netherlands, seasonal birth patterns differing from that of the general population were observed among boys, but not girls, with type 1 diabetes.[21]

Prior research has primarily focused on ethnically homogenous populations. It is unknown whether seasonal patterns are present in ethnically heterogeneous populations like the United States. Within the United States, the SEARCH for Diabetes in Youth study is one of the only studies that has investigated birth patterns among children who developed type 1 diabetes. Kahn et al. found a significant peak in the number of births of children who subsequently develop type 1 diabetes occurring from May through January, with a trough during the months of November through February. This pattern was consistent after stratifying by gender, race (black, white, other) and age (0-9 years, 10-18 years), where all sub-populations showed peaks in the spring or early summer and troughs in late fall or winter.[22]

The variation in prevalence of type 1 diabetes across race and ethnic backgrounds suggest that investigating heterogeneous populations can help to better understand the epidemiology of type 1 diabetes. The SEARCH for Diabetes in Youth overall prevalence rate for type 1 diabetes in the United States is 1.03 – 2.88 in the non-Hispanic white population (children between the ages of 0-9 and 10-19, respectively). This was higher than in the overall US population, with prevalence rates of 0.76 and 1.54, in the respective age categories.[23] The discrepant prevalence rates and the lack of research in birth patterns of type 1

diabetics within the United States suggest that this is an ideal population with which to study this question. Therefore, we set out to answer the following questions:

1) In a United States population, does the proportion of births of individuals who subsequently develop type 1 diabetes differ by month and season?
2) In a United States population, does the proportion of births of individuals who subsequently develop type 1 diabetes differ by month and season, for non-white Hispanics and other race/ethnicities?
3) In a United States population, does the proportion of births of individuals who subsequently develop type 1 diabetes differ by month and season, for males and females?

We hypothesize that the proportion of births of individuals who subsequently develop type 1 diabetes will be greater in the spring and summer months (March – August), in the overall United States population, in the gender-specific populations, and in the non-Hispanic white United States population. In the low prevalence population ("other" race/ethnicity group), we hypothesize that there will be no difference between the percentage of births of individuals who subsequently develop type 1 diabetes by month.

Methods

Study Population: The Type 1 Diabetes Genetics Consortium The Type 1 Diabetes Genetics Consortium (T1DGC) was an international effort to discover genes that modify the risk of type 1 diabetes and expand upon the existing genetic resources for type 1 diabetes. Participants were recruited over a 6-year recruitment period (2004-2010) from 4 regional networks consisting of over 200 clinics representing 34 countries. The T1DGC recruited type 1 diabetic participants regardless of duration of disease. T1DGC design and study methods have been described previously.[24-25] Fifty-two clinics, representing 27 states within the United States, contributed to the T1DGC. Recruitment for the T1DGC was restricted to affected sibling pair families (at least two children with type 1 diabetes in the family) except in low-prevalence populations where trio families (one child with type 1 diabetes and both biological parents), cases, and controls were recruited.

Ethnicity and race was self-reported by the participant, or their parent or guardian (Appendix A). Ethnicity was defined as Hispanic origin or not of Hispanic origin. Race codes were identified based on a modified version of the racial/ethnic groupings from the Australian 2000-2001 census.[27] Participants could record up to three race codes; however, only the primary race code was used in these analyses. For purposes of these analyses, participants were defined as non-Hispanic white (American Caucasian) or "other" race/ethnicity.

The clinics within the United States recruited 2,797 participants with type 1 diabetes. In order to decrease the possible influence of related individuals, analyses were restricted to include only one participant from each family. The first child in each family diagnosed with type 1 diabetes was selected for use in these analyses (1,215 participants). The type 1 diabetic population was further restricted by only including participants selecting one of the following race codes: North American, no further designation; African American; American Caucasian; Native North American; Mexican American; or North American, not elsewhere classified (1,071 participants). All participants had month of birth recorded. Due to the years of available reference data, only those participants whose year of birth was between 1990 – 2007 were included (540 participants). Due to small sample sizes representing type 1 diabetic participants born from 2001 – 2007, these participants were excluded (40 participants; leaving 500 participants born between 1990 and 2000 for analyses purposes).

Reference birth populations We accessed the United States Center for Disease Control (CDC) database of births for the years 1990 – 2000 to represent the expected number of births, by month.[27] The non-Hispanic white population was defined as both parents identifying as non-Hispanic white.

Statistical Analysis The T1DGC was a prevalence study design, where the number of type 1 diabetics included in the analyses does not represent all individuals who subsequently develop type 1 diabetes born during a specified

year. In order to account for this, the expected number of individuals who subsequently develop type 1 diabetes born (b) each year (*y*), for each month (*m*) was derived by the following formula.

$$b_{my} = \frac{n_{my}}{N_y} \times B_y$$

In this formula, n represents the number of reference population births for *y* year, representing *m* month; N represents the total number of reference population births for *y* year; B represents the total number of individuals with type 1 diabetes in the T1DGC population for *y year;* and b represents the expected number of individuals with type 1 diabetes for year *y*, representing month *m*. The expected and observed number of type 1 diabetics per month was totaled among all available years. These calculations were derived overall and by gender and race in order to account for different birth rates among the selected groups.

To assess the effect of month of birth on likelihood of developing type 1 diabetes, after controlling for year of birth, race, and gender, the data were analyzed with the use of a Poisson regression, with the logarithm of the overall births as an offset. Interaction terms (race by month of birth; gender by month of birth) were included to assess whether birth patterns differed by gender or race. The interactions were tested in the model for statistical significance by a backward-selection procedure and only statistically significant covariates ($p \leq 0.1$) were included in the final model. All main effects were forced to remain in the model (month of birth, year of birth, race, and gender).

The base model was:

$$\log\left(\frac{\text{type I diabetic births}}{\text{reference population births}}\right) = \beta 0 + \beta 1\text{year of birth} + \beta 2\text{gender} + \beta 3\text{race} + \beta 4\text{month of birth} + \beta 5\ \text{gender} * \text{month of birth} + \beta 6\ \text{race} * \text{month of birth}$$

The data were assessed for over dispersion. Stratified subgroup analyses were performed for gender- and race- specific populations. We used the SAS statistical program, version 9.2 (SAS Institute).

Birth months were grouped into seasons, defined as: winter (December, January, February); spring (March, April, May); summer (June, July, August); and fall (September, October, November). Season of birth was substituted for month of birth and assessed using similar modeling techniques. Tests were run using the overall population, as well as gender- and race-specific subpopulations.

In the modeling, month (or season) of birth, year of birth, race and gender were defined as categorical variables. Reference populations were set as December (winter), year of birth 2000, white, and male. Likelihood ratio statistics were used to evaluate the overall effect of month (or season) of birth, year of birth, race, and gender, and the interaction terms. Model-based estimates of incidence rate ratios and confidence intervals were calculated from parameter estimates.

Results

The non-Hispanic white type 1 diabetic population consisted of 333 individuals. The “other” race/ethnicity population consisted of 167 participants: 85 participants identifying themselves as non-Hispanic, African American (50.9%); 39 participants identifying themselves as Hispanic, Mexican American (23.4%); 23 participants identifying themselves as non-Hispanic, North American, no further designation (13.8%); 10 participants identifying themselves as Hispanic, American Caucasian (6.0%); 7 participants identifying themselves as Hispanic, North American, no further designation (4.2%); 1 participant identifying his or herself as non-Hispanic Native North American Indian (0.6%); 1 participant identifying his or herself as non-Hispanic, North American, not elsewhere classified (0.6%); and 1 participant identifying his or herself as Hispanic, African American (0.6%);. The type 1 diabetic population used in these analyses is described, by race/ethnicity and gender, in Table I.

Table I. Type 1 diabetic population descriptive statistics

Population	Non-Hispanic Whites	"Other" Race/ Ethnicity	Males	Females	Overall
N type 1 diabetic population	333	167	265	235	500
Average age at onset (years)	5.1 ± 3.3	6.6 ± 3.5	5.5 ± 3.4	5.8 ± 3.5	5.6 ± 3.4
Average age at enrollment (years)	11.6 ± 3.0	11.3 ± 3.1	11.7 ± 3.1	11.2 ± 3.1	11.5 ± 3.1
Average duration (years)	6.5 ± 3.6	4.7 ± 3.4	6.3 ± 3.6	5.4 ± 3.5	5.9 ± 3.6
Average number of affected siblings in family[a]	2.0 ± 0.2	1.4 ± 0.5	1.9 ± 0.4	1.8 ± 0.4	1.9 ± 0.4
% with *DR3* and/or *DR4*	94.6%	79.6%	90.9%	88.1%	89.6%

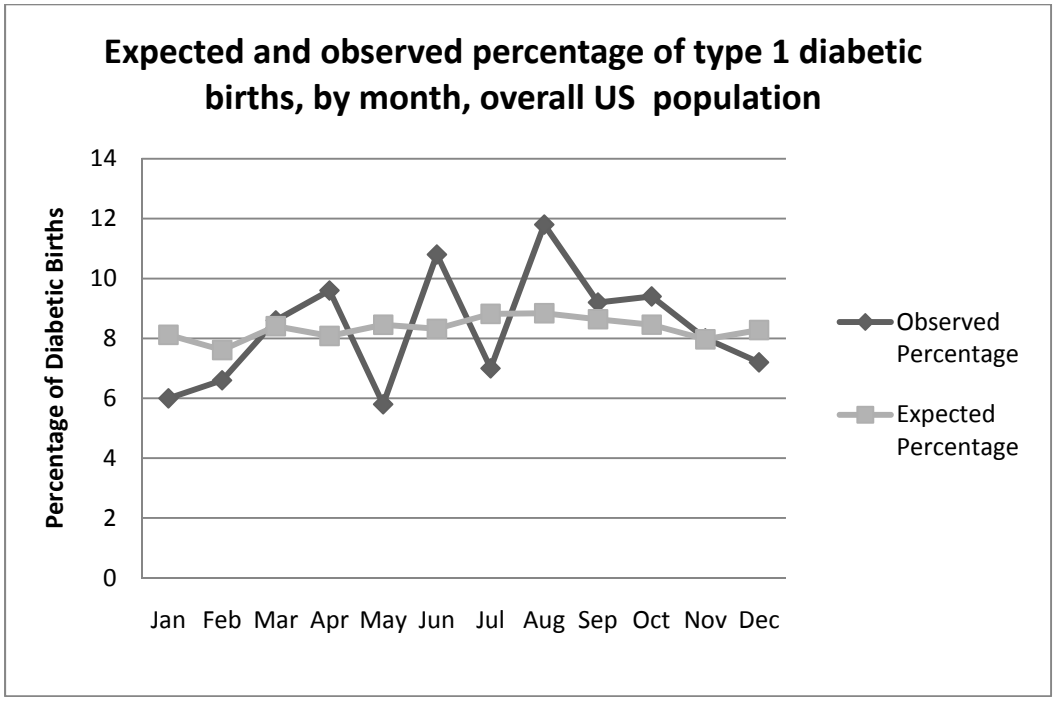
[a]31 participants excluded due to missing information

Month of Birth Percentage of births by month for the type 1 diabetic and CDC reference population, by race/ethnicity, gender. and overall are described in Table II and graphically in Figure 1. Peaks in the number of births of individuals who subsequently develop type 1 diabetes are observed during the months of June and August, with a trough from December – February.

Table II. Percentage of births by month for the type 1 diabetic (T1DGC) and CDC reference population, by race/ethnicity, gender and overall US population

Birth Month	Non-Hispanic White		"Other" Race/Ethnicity		Male		Female		Overall	
	T1DGC % (N)	CDC %	T1DGC % (N)	CDC %	T1DGC % (N)	CDC %	T1DGC % (N)	CDC %	T1DGC % (N)	CDC %
Jan	7.2% (24)	7.9%	3.6% (6)	8.3%	6.8% (18)	8.1%	5.1% (12)	8.1%	6.0% (30)	8.1%
Feb	6.3% (21)	7.6%	7.2% (12)	7.6%	6.0% (16)	7.6%	7.2% (17)	7.6%	6.6% (33)	7.6%
Mar	9.3% (31)	8.6%	7.2% (12)	8.2%	9.4% (25)	8.4%	7.7% (18)	8.4%	8.6% (43)	8.4%
Apr	9.0% (30)	8.7%	10.8% (18)	7.8%	10.9% (29)	8.1%	8.1% (19)	8.1%	9.6% (48)	8.1%
May	6.6% (22)	8.7%	4.2% (7)	8.1%	5.3% (14)	8.5%	6.4% (15)	8.4%	5.8% (29)	8.4%
Jun	11.4% (38)	8.5%	9.6% (16)	8.2%	10.6% (28)	8.3%	11.1% (26)	8.3%	10.8% (54)	8.3%
Jul	5.7% (19)	8.8%	9.6% (16)	8.8%	6.0% (16)	8.8%	8.1% (19)	8.8%	7.0% (35)	8.8%
Aug	11.4% (38)	8.8%	12.6% (21)	8.9%	10.9% (29)	8.8%	12.8% (30)	8.9%	11.8% (59)	8.8%
Sep	9.3% (31)	8.6%	9.0% (15)	8.7%	11.3% (30)	8.6%	6.8% (16)	8.7%	9.2% (46)	8.6%
Oct	9.3% (31)	8.4%	9.6% (16)	8.6%	8.7% (23)	8.0%	10.2% (24)	8.5%	9.4% (47)	8.5%
Nov	7.5% (25)	7.8%	9.0% (15)	8.2%	7.2% (19)	8.0%	8.9% (21)	8.0%	8.0% (40)	8.0%
Dec	6.9% (23)	8.0%	7.8% (13)	8.6%	6.8% (18)	8.3%	7.7% (18)	8.3%	7.2% (36)	8.3%
Overall (N)	333	~36.5 million	167	~36.4 million	265	~37.3 million	235	~35.6 million	500	~72.9 million

Figure 1. Expected and observed percentage of type 1 diabetic births, by month, overall US population



The Poisson regression model allowed the researchers to investigate the effect of month of birth, while controlling for year of birth, gender, and race. No adjustment for over dispersion was necessary. The interaction terms gender by month and race by month were non-significant and thus, excluded from the final model. Birth month was found to contribute to the proportion of type 1 diabetics born ($p = 0.03$). Year of birth ($p < 0.001$) and race ($p < 0.001$) were found to significantly contribute to the proportion of type 1 diabetics born, however gender was not found to be significant ($p = 0.43$).

Our model-based estimates indicate that a person born in June has 1.47 times (95% CI, 0.96 to 2.24) the chance of developing type 1 diabetes as compared to a person born in December. Individuals born in August have 1.52 times (95% CI, 1.007 to 2.308) the chance of developing type 1 diabetes as compared to individuals born in December.

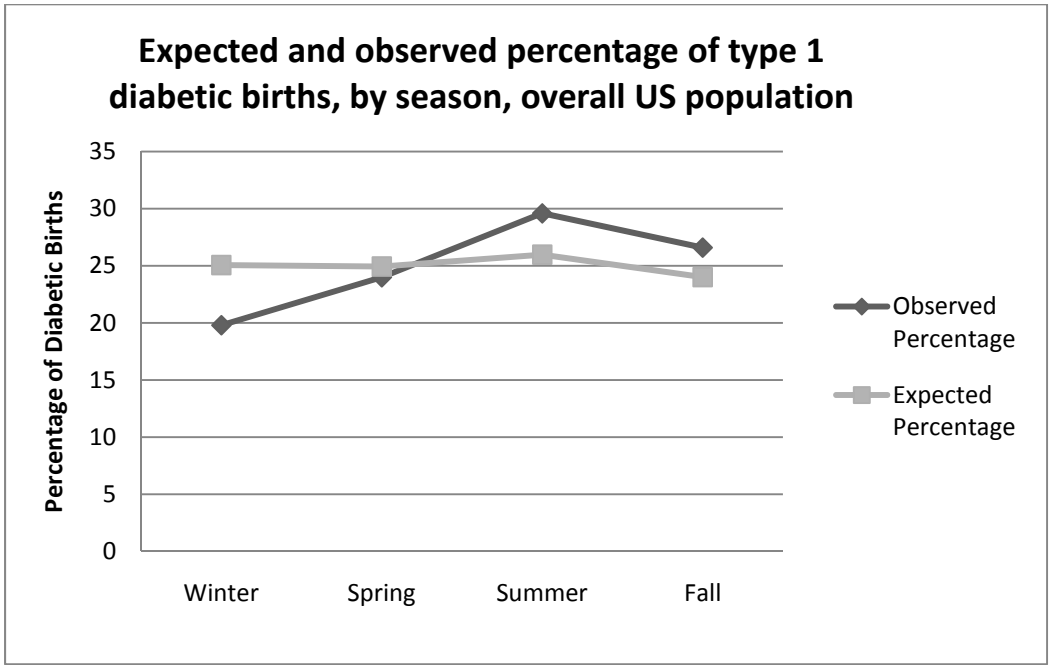
In gender-stratified models, month of birth did not significantly contribute to the proportion of diabetics born. Race and year of birth significantly contributed to proportion of diabetics for both genders. In ethnic-stratified models, month of birth did not significantly contribute to the number of type 1 diabetics.

Season of Birth Percentages of births by season for the type 1 diabetic (T1DGC) and CDC reference population, by race/ethnicity, gender and overall are described in Table III and Figure 2. A peak in the number of births of individuals who subsequently develop type 1 diabetes can be observed during the summer and fall months, with a trough in the winter months.

Table III. Percentage of births by season for the type 1 diabetic (T1DGC) and CDC reference population, by race/ethnicity, gender and overall US population

Season of Birth	Non-Hispanic White		"Other" Race/Ethnicity		Male		Female		Total	
	T1DGC % (N)	CDC %	T1DGC % (N)	CDC %	T1DGC % (N)	CDC %	T1DGC % (N)	CDC %	T1DGC % (N)	CDC %
Winter	20.4% (68)	23.6%	18.6% (31)	24.5%	19.6% (52)	24.0%	20.0% (47)	24.0%	19.8% (99)	24.0%
Spring	24.9% (83)	25.6%	22.2% (37)	24.2%	25.7% (68)	24.9%	22.1% (52)	24.9%	24.0% (120)	24.9%
Summer	28.5% (95)	26.1%	31.7% (54)	25.9%	27.5% (73)	26.0%	31.9% (75)	26.0%	29.6% (148)	26.0%
Fall	26.1% (87)	24.7%	27.5% (46)	25.5%	27.2% (72)	25.0%	26.0% (61)	25.1%	26.6% (133)	25.1%

Figure 2. Expected and observed percentage of type 1 diabetic births, by season, overall US population



In the model substituting season of birth for month of birth, the interaction terms gender by season of birth and race by season of birth were not significant and excluded from the final model. There was a trend, albeit non-significant ($p = 0.08$) for season of birth to contribute to the proportion of type 1 diabetic births. Gender ($p = 0.43$) did not significantly contribute to the proportion of type 1 diabetic births. Race ($p < 0.001$) and year of birth ($p < 0.001$) were found to significantly contribute to the proportion of type 1 diabetic births. No adjusting for over dispersion was necessary.

Our model based estimates indicate that a person born in the summer months has 1.37 times (95% CI, 1.06 to 1.77) the chance of developing type 1 diabetes as compared to a person born during the winter months. An individual born in the spring months has 1.15 times (95% CI, 0.88 to 1.50) the chance of

developing type 1 diabetes as compared to an individual born in the winter months and an individual born in the fall months has 1.29 times (95% CI, 0.99 to 1.67) the chance of developing type 1 diabetes as compared to an individual born in the winter months.

In gender-stratified models, season of birth did not significantly contribute to the proportion of diabetics born for either males or females. Race and year of birth significantly contributed to proportion of diabetics for both genders. In ethnic-stratified models, season of birth did not significantly contribute to the number of type 1 diabetics.

Discussion

The main finding was that month of birth significantly contributed to the proportion of type 1 diabetic births. Individuals born in August have 1.52 times (95% CI, 1.007 to 2.308) the chance of developing type 1 diabetes as compared to individuals born in December. While there was a trend toward a peak in the proportion of type 1 diabetic births occurring during the summer months, and trough in the proportion of type 1 diabetic births in the winter months, a significant difference was not found between seasons of birth. The peaks in the summer and troughs in the winter months are consistent with past research where similar peaks and troughs have been found.[6, 12, 16, 28-29]

Similar non-significant trends were observed in the gender- and race-specific populations. Differences in the birth patterns for males have been found in some populations, although this has not been found in other populations.[21] Low prevalence populations, such as the "other" race/ethnicity population used in this analyses, have not shown differences in month of birth, suggesting that low power precludes the ability to identify monthly differences or other factors contribute to the etiology of type 1 diabetes.[18-20]

The increase in the number of births of individuals who subsequently develop type 1 diabetes during June and August supports our hypothesis that environmental effects occurring during periods of increased viral exposure (summer and fall) during the perinatal period may contribute to the development of type 1 diabetes. Specifically, pregnancies beginning in September and November were at greatest risk of a child who ultimately developed type 1 diabetes. Additionally, the trough of type 1 diabetic births observed during the winter months (December – February), associated with implantation during the months of March through May, suggest fetal development occurring during a period of low viral exposure. These seasonal differences were not significant, although this could be due to the decrease of proportion of type 1 diabetic births occurring during the month of July or to the natural variation of severity and timing of viral epidemics.

If a consistent seasonal pattern was present, one would expect to see this in the results. However, the significant year effect in both the model with season of birth and the model with month of birth suggest that the number of type 1

diabetics varied by year. The average age at onset (5.6 ± 3.4 years), age at enrollment (11.5 ± 3.1 years), and duration of disease (5.9 ± 3.6 years) are lower than in the overall population of individuals with type 1 diabetes, partially due to the inclusion of those type 1 diabetics born between the years of 1990 – 2000. Other possible explanations could be attributed to the decreased amount of time to develop the disease in this young population and the recruitment timeline for this type 1 diabetic population. Fewer individuals with type 1 diabetes were recruited from the more recent birth years than the older birth years. Another possible reason for this significant effect could be due to viral epidemics that may have occurred in this population during a specific year.

The cohort used for this study is a highly selected, genetically pre-disposed population. This is evident in the higher average number of affected siblings per family (1.9 ± 0.4). The average number of affected siblings in the family was lower in the other race/ethnicity population (1.4 ± 0.5) than in the non-Hispanic white populations (2.0 ± 0.2) due to recruitment criteria for this study. However, the percentage of participants in this study carrying one or both of the *DR3* and *DR4* alleles (89.6%) can give us some confidence in the ability to extend the findings of this study with the overall type 1 diabetic population, as other research has found that nearly 98% of type 1 diabetic participants carry one or more of these alleles.[1-2] Due to the genetically-susceptible type 1 diabetic population, generalizing these findings to the overall US type 1 diabetic population must be cautioned since the population used in this analyses may

require less of an environmental stimulus for future development of type 1 diabetes.

Due to difference in recruitment criteria and ascertainment bias of type 1 diabetes between the non-white Hispanic and “other” race/ethnicity populations, the significant race effect could be an artifact of the recruitment criteria. Recruitment criteria for the non-Hispanic white participants and participants from “other” race/ethnicities differed in this collection. Furthermore, it is well established that the incidence and prevalence of type 1 diabetes differs by race/ethnicity.

The heterogeneous nature of the United States provides an ideal population in which to control additional variables that may confound the presence or absence of an effect of birth month on the likelihood to develop type 1 diabetes. The inflexible coding of race and ethnicity within the T1DGC and small sample sizes within race/ethnicity categories required the collapsing of these into one category and did not allow inclusion of those type 1 diabetics who may have described themselves as Asian. Therefore, the population used for analyses represents many, but not all, type 1 diabetics within the United States. By grouping all other race/ethnicities together, any differences in the month of birth patterns in one specific racial grouping may have been hidden by grouping all races together.

In summary, the differences in the proportion of type 1 diabetic births by month found in the overall United States population support our hypothesis that environmental factors in pregnant mothers of type 1 diabetics contribute to the

likelihood of developing type 1 diabetes in this population. Further research should investigate seasonality of birth patterns during known times of viral epidemics in order to determine if the viral hypothesis is supported and if enteroviruses are transmitted from the mother to the fetus.

Type 1 diabetes is a multi-factorial disease, with evidence for a strong genetic component and less consistent support for environmental influences. Understanding the potential contribution of environmental factors during the antenatal and prenatal periods is critical to detangling the etiology of type 1 diabetes. Examination of type 1 diabetic birth patterns is an important step in appreciating the environmental contribution to the development of the disease.

References

1. Dorman JS, McCarthy BJ, O'Leary LA, Koehler AN. Risk Factors for Insulin-Dependent Diabetes. In: Harris MI, Cowie CC, Stern MP, et al. *Diabetes in America.* Bethesda, MD: NIH Publication; 1995: 165-178.

2. Wolf E, Spencer KM, Cudworth AG. The genetic susceptibility to type 1 (insulin dependent) diabetes: analysis of the HLA-DR association. *Diabetologia.* 1983; 24(4): 224-230.

3. Olmos P, A'Hern R, Heaton DA, et al. The significance of the concordance rate for type 1 (insulin-dependent) diabetes in identical twins. *Diabetologia.* 1988; 31(10): 747-750.

4. WHO Multinational Project for Childhood Diabetes Group. Familial insulin-dependent diabetes mellitus (IDDM) epidemiology: standardization of data for the DIAMOND Project. *Bulletin of the World Health Organization.* 1991; 69(6): 767-777.

5. Khetsuriani N, LaMonte-Fowlkes A, Oberste MS, Pallansch MA. Enterovirus Surveillance – United States, 1970-2005. https://www.cdc.gov/mmwr/preview/mmwrhtml/ss5508a1.htm. Accessed April 25, 2011.

6. Dahlquist GG, Kallen BA. Time-space clustering of date at birth in childhood-onset diabetes. *Diabetes Care.* 1996; 19(4): 328-332.

7. Laron Z, Shami I, Nitzan-Kaluski D, Ashkenazi I. Month of birth and subsequent development of type 1 diabetes (IDDM). *Journal of Pediatric Endocrinology & Metabolism.* 1999; 12(3): 397-402.

8. McKinney PA on behalf of the EURODIAB Seasonality of Birth Group. Seasonality of birth in patients with childhood type 1 diabetes in 19 European regions. *Diabetologia;* 2001: 44(Suppl 3): B67-B74.

9. Mikuleckỳ M, Michalkovå D, Hlava P. Seasonality of births of Slovak IDDM children. *Diabetologia;* 1999: 42 (Suppl 1): A86/314.

10. Mikuleckỳ M, Minårik P, Michalkovå D. Insulin gene profile cycles with season of birth of future diabetic children and their relatives. *Journal of Pediatric Endocrinology & Metabolism.* 2004; 17(5): 727-730.

11. Rothwell PM, Gutnikov SA, McKinney PA, et al. Seasonality of birth in children with diabetes in Europe: multicentre cohort study. *BMJ.* 1999; 319: 887-888.

12. Samuelsson U, Johannson C, Ludvigsson J. Month of birth and risk of developing insulin dependent diabetes in south east Sweden. *Arch Dis Child.* 1999; 81: 143-146.

13. Songini M, Casu A, The Sardinian Collaborative Group for Epidemiology of IDDM, Ashkenazi I, Laron Z. Seasonality of birth in children (0-14 years) and young adults (0-29 years) with type 1 diabetes mellitus in Sardinia differs from that in the general population. *Journal of Pediatric Endocrinology & Metabolism;* 2001: 14: 781-783.

14. Ursic-Bratina N, Battelino T, Kkžišnik C, Laron-Kenet T, Ashkenazi I, Laron Z. Seasonality of birth in children (0-14 years) with type 1 diabetes mellitus in Slovenia. *Journal of Pediatric Endocrinology & Metabolism.* 2001; 14(1): 47-52.

15. Vaiserman AM, Carstense B, Voitenko VP, Tronko MD, et al. Seasonality of birth in children and young adults (0-29 years) with type 1 diabetes in Ukraine. *Diabetologia.* 2007; 50: 32-35.

16. Willis JA, Scott RS, Darlow BA, Lewy H, Ashkenazi I, Laron Z. Seasonality of birth and onset of clinical disease in children and adolescents (0-19 years) with type 1 diabetes mellitus in Canterbury, New Zealand. *Journal of Pediatric Endocrinology & Metabolism.* 2002; 15: 645-647.

17. Bock T, Pedersen CR, Vølund A, Pallesen C, Buschard K. Perinatal determinants among children who later develop IDDM. *Diabetes Care.* 1994; 17(10): 1154-1157.

18. Evliyaoğlu O, Öcal G, Cetinkaya E, et al. No seasonality of birth in children with type 1 diabetes mellitus in Ankara, Turkey. *Journal of Pediatric Endocrinology & Metabolism.* 2002; 15(7): 1033-1034.

19. Kida K, Mimura G, Ito T, et al. Incidence of type 1 diabetes mellitus in children aged 0-14 in Japan, 1986-1990, including an analysis for seasonality of onset and month of birth: JDS study. *Diabetic Medicine.* 2000; 17: 59-63.

20. Ye J, Chen RG, Ashkenazi I, Laron Z. Lack of seasonality in the month of onset of childhood IDDM (0.7-15 years) in Shanghai, China. *Journal of Pediatric Endocrinology & Metabolism.* 1998; 11(3): 461-464.

21. Jongbloet PH, Groenewoud HM, Hirasing RA, Van Buuren S. Seasonality of birth in patients with childhood diabetes in the Netherlands. *Diabetes Care.* 1998; 21(1): 190-191.

22. Kahn HS, Morgan TM, Case LD, Dabelea D, et al. Association of type 1 diabetes with month of birth among U.S. Youth. *Diabetes Care.* 2009; 32(11): 2010-2015.

23. SEARCH for Diabetes in Youth Study Group. The burden of diabetes mellitus among US Youth: prevalence estimates from the SEARCH for Diabetes in Youth Study. *Pediatrics.* 2006; 118: 1510-1518.

24. Hilner JE, Perdue LH, Sides EG, et al. Designing and implementing sample and data collection for an international genetics study: the Type 1 Diabetes Genetics Consortium (T1DGC). *Clinical Trials.* 2010; 7(Suppl 1): S5-S32.

25. Perdue LH, Albret A, Aldrich A, et al. Quality control of phenotypic forms data in the Type 1 Diabetes Genetics Consortium. *Clinical Trials.* 2010; 7(Suppl 1): S46-S55.

26. Australian Bureau of Statistics. Australian Standard Classification of Cultural and Ethnic Groups (2000-2001). http://www.ausstats.abs.gov.au/ausstats/free.nsf/0/CAFD9A578C421AEFCA256C0F0001D603/$File/12490_2000-01.pdf. Accessed April 25, 2011.

27. Centers for Disease Control and Prevention. National Center for Health Statistics. VitalStats. http://www.cdc.gov/nchs/vitalstats.htm. Accessed April 25, 2011.

28. Laron Z, Lewy H, Wilderman I, Casu A, et al. Seasonality of month of birth of children and adolescents with type 1 diabetes mellitus in homogenous and heterogeneous populations. *IMAJ.* 2005; 7: 381-384.

29. Rothwell PM, Staines A, Smail P, Wadsworth E, McKinney P. Seasonality of birth of patients with childhood diabetes in Britain. *BMJ.* 1996; 312: 1456-1457.

Appendix A

a. Are you *(Is your child)* Latino, Hispanic, or of Spanish origin?

☐ Yes

☐ No

☐ Not Applicable

b. Which of the following best describes your *(child's)* race (or ethnic origin)?

HAND PARTICIPANT CUE CARD AND RECORD PARTICIPANT'S RESPONSES.

☐☐☐ Primary

☐☐☐

☐☐☐

CHAPTER THREE

Discussion

Summary of Previous Findings

The Type 1 Diabetics Genetics Consortium (T1DGC) provides a unique opportunity to investigate whether the proportion of diabetic births differs by month and season of birth in multiple nationalities and ethnicities. The previous research uses this population to investigate whether differences exist between months, and seasons, of birth within the United States population, using the Center for Disease Control (CDC) data as the reference population. This reference group allowed researchers to investigate the overall US birth population, as well as look at birth patterns in gender-specific and race-specific populations. For purposes of the previous analyses, race was defined as non-Hispanic white and all "other" racial/ethnic groups.

Birth month was found to be a significant predictor of development of type 1 diabetes, using a Poisson regression model, controlling for gender, race, and year of birth. Birth month was not found to contribute to development of type 1 diabetes when examining the sub-populations (males, females, non-Hispanic whites and "other" races/ethnic groups). Season of birth was not found to contribute to development of type 1 diabetes, either in the overall US populations or any of the sub-populations.

A trough in the number of type 1 diabetic births was observed during the months of December through February (winter months), and a peak in proportion of births occurring in June and August. These peaks and troughs were

consistently seen in all sub-populations, although none of these differences were significant and greater differences between observed and expected were seen in some sub-populations. Due to the small sample sizes in these sub-populations, further research is needed to confirm whether the non-significant differences observed in these sub-populations can be replicated.

To take advantage of the unique worldwide collection of individuals with type 1 diabetes recruited to the T1DGC, preliminary analyses of nationality-specific birth patterns among individuals with type 1 diabetes were undertaken. The Poisson regression modeling was repeated using type 1 diabetic and reference populations from Australia, Canada, Poland, Spain and the United States. Other countries included in the T1DGC were excluded due to small sample sizes or lack of overlap for year of birth in the reference population. The previous research included only type 1 diabetic participants born between the years of 1990 – 2000, and included a reference population based on the Center for Disease Control database.[1] The current analyses expands the years of birth included and uses the United Nations database as the reference population.[2] The United Nations database includes statistics for the United States based on the United States census data.

Additional Analyses

Introduction. The current analyses focus on 5 nationalities: Australia, Canada, Poland, Spain, and the United States. These nationalities represent intermediate to very high incidence rates. Reported incidence rates within Poland, a country with intermediate incidence of type 1 diabetes, range from 5.0 to 6.1 per 100,000

per year. Incidence rates within Australia (14.5 per 100,000 per year), Spain (12.5 per 100,000 per year) and Canada (24.0 per 100,000) represent high to very high incidence of type 1 diabetes.[3] Within the United States, incidence rates vary by race/ethnicity. The SEARCH for Diabetes in Youth Study reports incidence rates varying from 6.4 – 23.6 per 100,000 depending on a person's race/ethnic background. Incidence rates in non-Hispanic white children were reported as 23.6 per 100,000 per year[4], however rates were lower among African-American US children (15.7 per 100,000 per year)[5] and Hispanic children (14.1 – 16.2 per 100,000 per year).[6] In US children identifying themselves as Asian/Pacific Islander incidence rates were much lower, ranging from 6.4 – 7.4 per 100,000 per year.[7]

Methods.

Study Population: The Type 1 Diabetes Genetics Consortium. The Type 1 Diabetes Genetics Consortium provided adequate sample sizes in Australia, Canada, Poland, Spain and the United States to allow preliminary investigation of the birth patterns in the type 1 diabetic population. Recruitment for the T1DGC in these countries was restricted to affected sibling pair families (at least two children with type 1 diabetes in the family) except in low-prevalence populations where trio families (one child with type 1 diabetes and both biological parents), cases, and controls were recruited. Australia, Poland and Spain recruited only affected sibling pair families, while Canada and the United States recruited affected sibling pair families, trio families, cases, and controls.

As with the previous analyses, although participants self-reported up to three race codes, only the primary race code was used in analyses. Race codes were identified based on a modified version of the racial/ethnic groupings from the Australian 2000-2001 census.[8] Race codes were grouped into nationalities for purposes of these analyses. Number of participants with type 1 diabetes recruited, by race designation and nationality, are described in Table I.

Table I. Type 1 diabetic participants recruited, by assigned nationality and race designation

Nationality	Race designation	N type 1 diabetic participants
Australia	Australian Peoples, no further designation	126
	Australian	298
	Australian Aboriginal	7
	Total	**431**
Canada	Canadian	229
	French Canadian	37
	Total	**266**
Poland	Polish	394
	Total	**394**
Spain	Spanish	305
	Total	**305**
United States	North American, no further designation	127
	African American	499
	American Caucasian	1727
	Native North American Indian	2
	Mexican American	113
	North American, not elsewhere classified (includes Bermudan, Inuit, Métis)	1
	Total	**2469**

Within these nationalities, 3,865 participants with type 1 diabetes were recruited. In order to decrease the possible influence of related individuals, analyses were restricted to included only one participant from each family. The first child in each family diagnosed with type 1 diabetes was selected for use in these analyses (1,753 participants). Only one of these participants was excluded because month of birth was missing (1,752). Due to small sample sizes of participants born after 1999, these birth years were excluded from analyses (1675 participant were included in analyses). Only those participants whose year of birth overlapped with the available reference birth year data were included (1,350 participants were included in analyses). Table II describes the recruited type 1 diabetic population, by nationality, and the restrictions placed on this population for analyses purposes. Number of participants with type 1 diabetes used in analyses, by race designation and nationality are described in Table III.

Table II. Type 1 diabetic population and restrictions for analyses, by nationality

	Australia	Canada	Poland	Spain	United States	Overall
# type 1 diabetics recruited	431	266	394	305	2469	3865
# unique families	212	131	190	148	1072	1753
# type 1 diabetics with month of birth available	212	131	190	148	1071	1752
# type 1 diabetics born before 2000	206	129	184	148	1008	1675
# type 1 diabetics with appropriate year of birth reference population (N for analyses)	**164**	**84**	**154**	**90**	**858**	**1350**
Birth years included	1971, 1978-99	1970-71, 1973-90, 1992-97, 1999	1973 1975-76, 1978-98	1970-85, 1987-88, 1991-93 1996, 1998	1970-75, 1978-99	

Table III. Type 1 diabetic participants used in analyses, by assigned nationality and race designation

Nationality	Race designation	N type 1 diabetic participants
Australia	Australian Peoples, no further designation	50
	Australian	111
	Australian Aboriginal	3
	Total	**164**
Canada	Canadian	72
	French Canadian	12
	Total	**84**
Poland	Polish	154
	Total	**154**
Spain	Spanish	90
	Total	**90**
United States	North American, no further designation	54
	African American	93
	American Caucasian	668
	Native North American Indian	1
	Mexican American	41
	North American, not elsewhere classified (includes Bermudan, Inuit, Métis)	1
	Total	**858**

Reference birth populations We accessed the United Nations database of births for the years 1970 – 1999 to represent the expected number of births, by month.[2] Data were available for Australia, representing the years 1971-2003 (excluding 1972, 1973, 1974, 1976, and 1977), Canada, representing the years 1970-2005 (excluding 1972, 1991 and 1998); for Poland, representing 1973-2007 (excluding 1977 and 2006); for Spain, representing 1970-2007 (excluding 1986, 1989, 1990 and 2006); and for the United States, representing 1969-2006 (excluding 1976 and 1977).

Statistical Analysis The T1DGC was a prevalence study design, where the number of type 1 diabetics included in the analyses does not represent all individuals who subsequently develop type 1 diabetes born during a specified year. In order to account for this, the expected number of individuals who subsequently develop type 1 diabetes born (b) each year (*y*), for each month (*m*) was derived by the following formula.

$$b_{my} = \frac{n_{my}}{N_y} \times B_y$$

In this formula, n represents the number of reference population births for *y* year, representing *m* month; N represents the total number of reference population births for *y* year; B represents the total number of individuals with type 1 diabetes in the T1DGC population for *y* year*;* and b represents the expected number of individuals with type 1 diabetes for year *y*, representing month *m*. The expected and observed number of type 1 diabetics per month was totaled among all available years.

Birth years were grouped into decades (1970s, 1980s and 1990s) due to the large span of birth years. To assess the effect of month of birth on likelihood of developing type 1 diabetes, after controlling for nationality and decade of birth, the data were analyzed with the use of a Poisson regression, with the logarithm of the overall births as an offset. The interaction term nationality by month of birth was included to assess whether birth patterns differed by nationalities. Following the modeling performed in the previous analysis, the interaction was tested in the model for statistical significance by a backward-selection procedure and was included in the model only if statistically significant ($p \leq 0.1$). All main effects were forced to remain in the model (month of birth, decade of birth, nationality). The base model was:

$$\log\left(\frac{\text{type I diabetic births}}{\text{reference population births}}\right) = \beta 0 + \beta 1 \text{decade of birth} + \beta 2 \text{nationality} + \beta 3 \text{month of birth} + \beta 5 \text{ nationality} * \text{month of birth}$$

The data were assessed for over dispersion. Stratified subgroup analyses were performed for nationality- specific populations. We used the SAS statistical program, version 9.2 (SAS Institute).

Birth months were grouped into seasons, defined as: winter (December, January, February); spring (March, April, May); summer (June, July, August); and fall (September, October, November). Season of birth was substituted for month of birth and assessed using similar modeling techniques. Tests were run overall and nationality-specific. For the overall tests, the months were reversed in

Australia, so that the seasons were consistent with the other four Northern Hemisphere countries.

In the modeling, month (or season) of birth, decade of birth, and nationality were defined as categorical variables. Reference populations were set as December (winter), decade of birth 1990s and for nationality, the United States. Likelihood ratio statistics were used to evaluate the overall effect of month (or season) of birth, decade of birth, nationality, and the interaction term. Model-based estimates of incidence rate ratios and confidence intervals were calculated from parameter estimates.

Results. The type 1 diabetic and reference population used in these analyses is described by nationality, in Table IV.

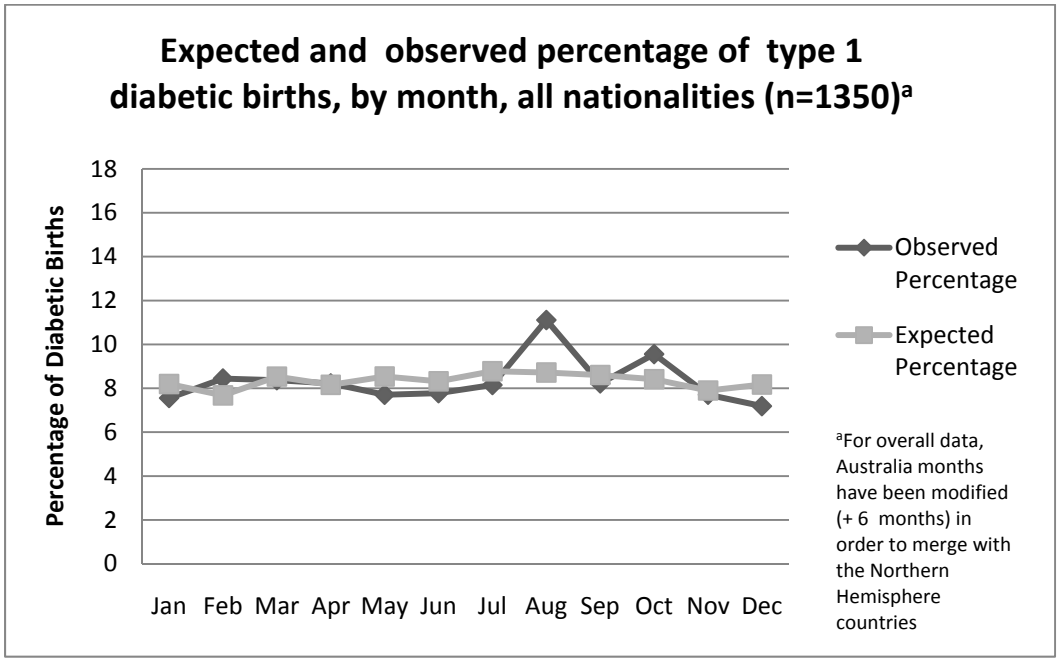
Table IV. Type 1 diabetic and reference population descriptive statistics

Population	Australia	Canada	Poland	Spain	United States	Overall
Type 1 diabetic population						
N	164	84	154	90	858	1350
N (1970s)	14	23	19	55	96	207
N (1980s)	79	32	80	23	285	499
N (1990s)	71	29	55	12	477	644
% male	47.6%	47.6%	48.1%	51.1%	53.0%	51.3%
Average age at onset (years)	5.9 ± 4.0	7.7 ± 5.0	7.8 ± 4.7	9.8 ± 6.2	7.0 ± 4.5	7.2 ± 4.7
Average age at enrollment (years)	16.3 ± 5.9	19.8 ± 8.6	17.6 ± 5.8	26.3 ± 7.0	16.5 ± 7.1	17.5 ± 7.3
Average duration (years)	10.3 ± 6.1	12.2 ± 7.6	9.8 ± 5.3	16.4 ± 7.6	9.5 ± 6.9	10.3 ± 6.9
Average number of affected siblings in family[a]	2.1 ± 0.3	2.1 ± 0.3	2.1 ± 0.4	2.1 ± 0.4	2.0 ± 0.5	2.0 ± 0.4
% with *DR3* and/or *DR4*	98.8%	89.3%	90.9%	93.3%	90.9%	91.9%
Reference Population						
N	5,711,845	9,982,957	14,077,992	12,342,311	104,244,966	146,360,071
N (1970s)	722,955	3,226,868	3,267,100	6,576,862	26,814,565	40,608,350
N (1980s)	2,423,127	3,749,214	6,561,729	3,859,108	37,530,540	54,094,198
N (1990s)	2,565,763	3,006,875	4,249,163	1,906,341	39,899,861	51,628,003

[a]44 participants excluded due to missing information

Month of Birth, Figure 1 displays the expected and observed percentages of type 1 diabetics, by month, summed over the years for the overall population. A peak in the number of births of individuals who subsequently develop type 1 diabetes can be observed in August.

Figure 1. Expected and observed percentage of type 1 diabetic births, by month, all nationalities



Figures 2 through 6 display the expected and observed percentages of type 1 diabetics, by month, summed over the years for each nationality. Percentage of births by month for the type 1 diabetic population and UN reference population, by nationality, are described in Table V.

Figure 2. Expected and observed percentage of type 1 diabetics, by month, Australia

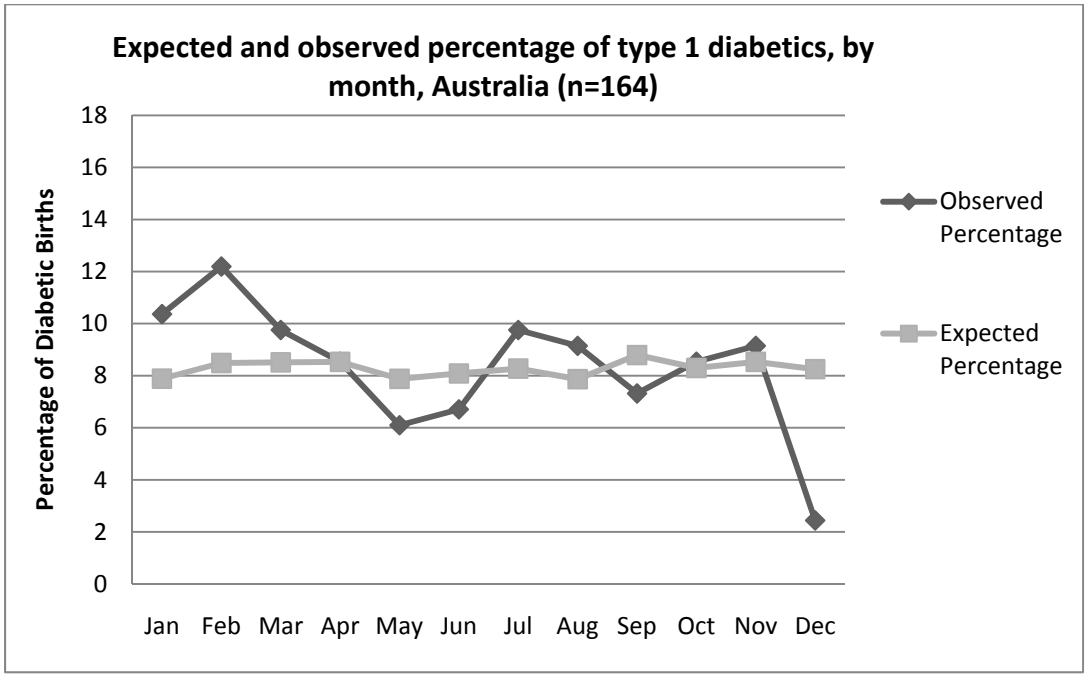


Figure 3. Expected and observed percentage of type 1 diabetic births, by month, Canada

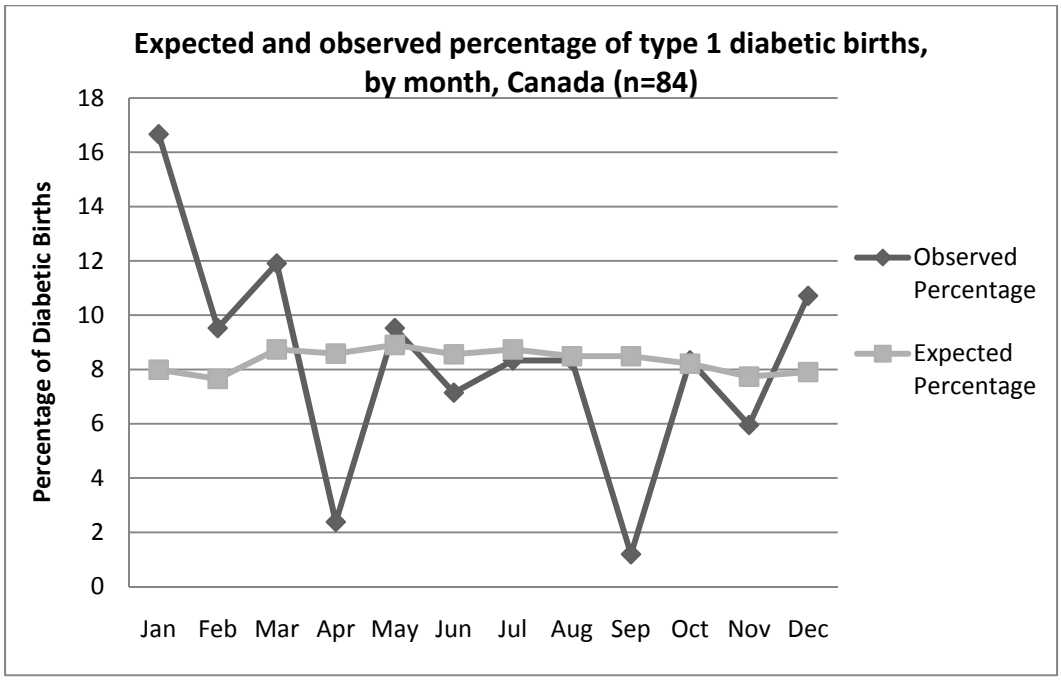


Figure 4. Expected and observed percentage of type 1 diabetic births, by month, Poland

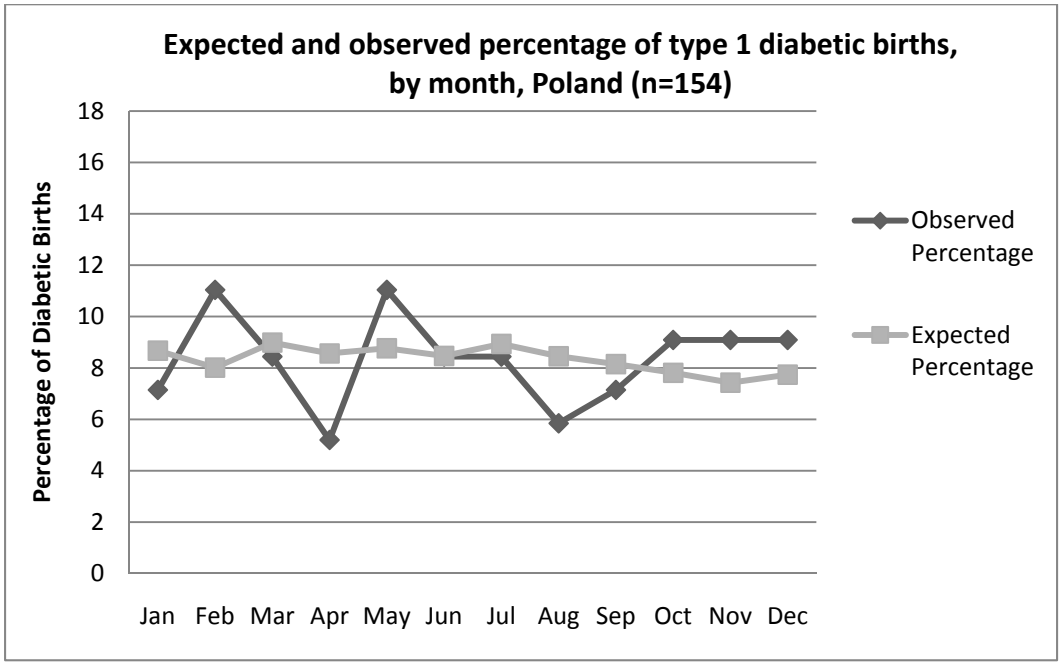


Figure 5. Expected and observed percentage of type 1 diabetic births, by month, Spain

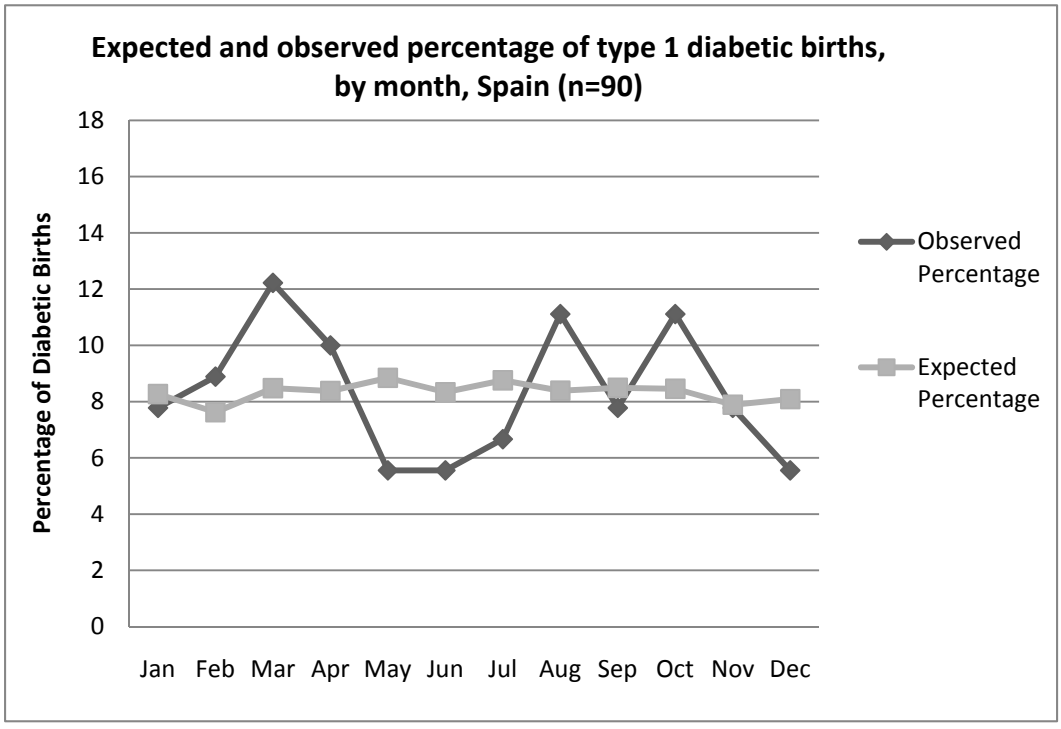


Figure 6. Expected and observed percentage of type 1 diabetic births, by month, United States

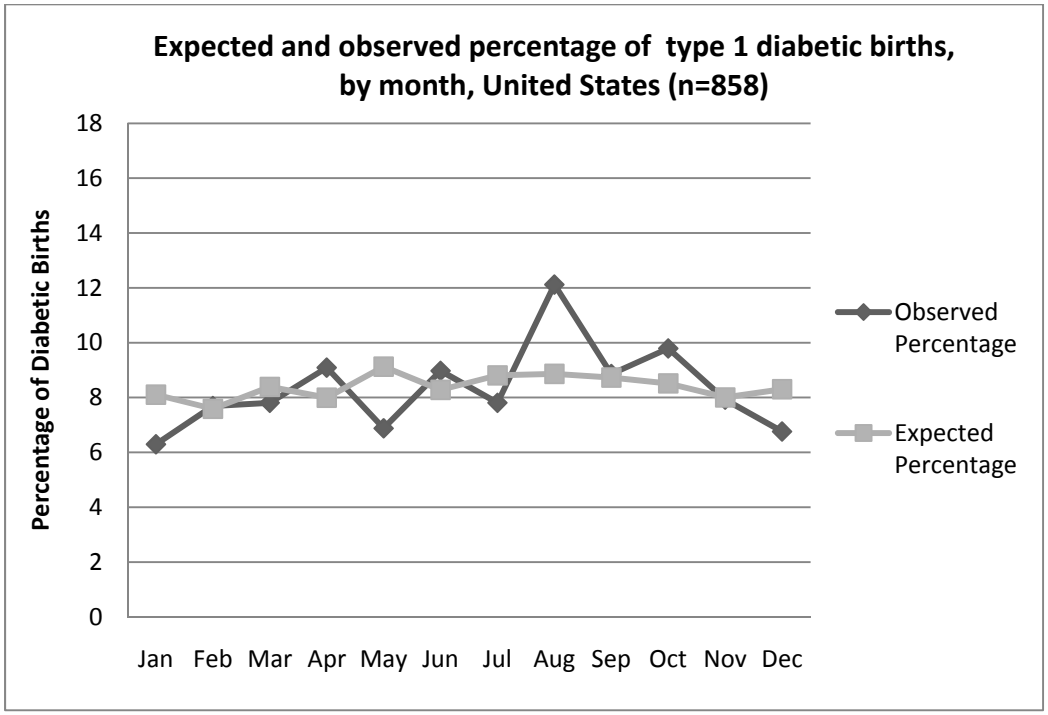


Table V. Percentages of births by month for the type 1 diabetic (T1DGC) and UN reference population, by nationality, and overall population

Birth Month	Australia		Canada		Poland		Spain		United States		Overall[a]	
	T1DGC % (N)	UN %	T1DGC % (N)	UN %	T1DGC % (N)	UN %	T1DGC % (N)	UN %	T1DGC % (N)	UN %	T1DGC % (N)	UN %
Jan	9.8% (16)	8.3%	16.7% (14)	8.0%	7.1% (11)	8.7%	7.8% (7)	8.3%	6.2% (54)	8.1%	7.6% (102)	8.2%
Feb	9.2% (15)	7.9%	9.5% (8)	7.6%	11.0% (17)	8.0%	8.9% (8)	7.6%	7.7% (66)	7.6%	8.4% (114)	7.7%
Mar	7.3% (12)	8.8%	11.9% (10)	8.7%	8.4% (13)	9.0%	12.2% (11)	8.5%	7.8% (67)	8.4%	8.4% (113)	8.5%
Apr	8.5% (14)	8.3%	2.4% (2)	8.6%	5.2% (8)	8.6%	10.0% (9)	8.4%	9.1% (78)	8.0%	8.2% (111)	8.1%
May	9.2% (15)	8.5%	9.5% (8)	8.9%	11.0% (17)	8.8%	5.6% (5)	8.9%	6.9% (59)	8.3%	7.7% (104)	8.5%
Jun	2.4% (4)	8.3%	7.1% (6)	8.5%	8.4% (13)	8.4%	5.6% (5)	8.3%	9.0% (77)	8.2%	7.8% (105)	8.3%
Jul	10.4% (17)	8.5%	8.3% (7)	8.7%	8.4% (13)	8.9%	6.7% (6)	8.7%	7.8% (67)	8.8%	8.1% (110)	8.8%
Aug	12.2% (20)	8.5%	8.3% (7)	8.5%	5.8% (9)	8.4%	11.1% (10)	8.4%	12.1% (104)	8.9%	11.1% (150)	8.8%
Sep	9.8% (16)	8.5%	1.2% (1)	8.5%	7.1% (11)	8.1%	7.8% (7)	8.5%	8.9% (76)	8.7%	8.2% (111)	8.6%
Oct	8.5% (14)	8.5%	8.3% (7)	8.2%	9.1% (14)	7.8%	11.1% (10)	8.4%	9.8% (84)	8.5%	9.6% (129)	8.4%
Nov	6.1% (10)	7.9%	6.0% (5)	7.8%	9.1% (14)	7.4%	7.8% (7)	7.9%	7.9% (68)	8.0%	7.7% (104)	7.9%
Dec	6.7% (11)	8.1%	10.7% (9)	7.9%	9.1% (14)	7.8%	5.6% (5)	8.1%	6.8% (58)	8.3%	7.2% (97)	8.2%

[a] Months for Australia are reversed, so that the seasons were consistent with the other four Northern Hemisphere countries.

The Poisson regression model allowed the researchers to investigate the effect of month of birth, while controlling for decade of birth and nationality. Nationality ($p < 0.001$) and decade of birth ($p < 0.001$) were found to significantly contribute to the proportion of type 1 diabetics born. Month of birth ($p = 0.12$) and the interaction between nationality and month of birth ($p=0.07$) were not found to significantly contribute to the proportion of type 1 diabetics born.

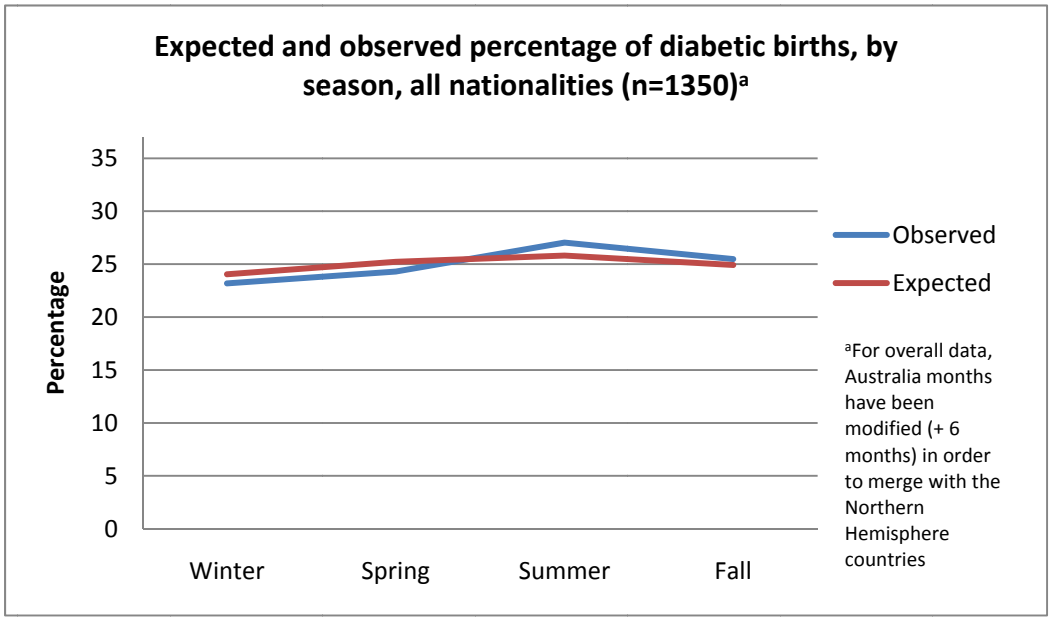
In the model stratified by nationality, month of birth significantly contributed to the proportion of diabetics born for Canada ($p = .02$) and the United States only ($p = 0.02$). Within Canada, our model-based estimates indicate that a person born in April has 0.20 times (95% CI, 0.04 to 0.94) the chance of developing type 1 diabetes as compared to a person born in December. Individuals born in September have 0.10 times (95% CI, 0.01 to 0.81) the chance of developing type 1 diabetes as compared to individuals born in December. Within the United States, our model-based estimates indicate that a person born in August (95% CI, 1.22 to 2.32) has 1.68 times the chance of developing type 1 diabetes as compared to a person born in December; a person born in October has 1.42 times (95% CI, 1.01 to 1.98) the chance of developing type 1 diabetes as compared to a person born in December.

Decade of birth significantly contributed to the proportion of diabetics born in Poland and the United States.

Season of Birth. Figure 7 displays the observed and expected percentages of type 1 diabetics, by season, summed over the years for the overall population. A slight peak in the number of births of individuals who subsequently develop type

1 diabetes can be observed in the summer months, with a trough during the winter months.

Figure 7. Expected and observed percentage of type 1 diabetic births, by season, all nationalities



Figures 8 through 12 display the expected and observed percentages of type 1 diabetics, by season, summed over the years for each nationality. Percentage of births by season for the type 1 diabetic population and UN reference population, by nationality are described in Table VI.

Within the Australian population, births of individuals who subsequently develop type 1 diabetes were equally proportioned to each season. In Canada, a peak was observed in the winter months, with a trough in the fall months. A peak can also be observed in the winter months in the Poland diabetic population. In Spain, the peak is observed in the spring months. In the United States population, peaks occur during the summer and fall months, with a trough in the

number of births of individuals who subsequently develop type 1 diabetes occurring in the winter months.

Figure 8. Expected and observed percentage of type 1 diabetic births, by season, Australia

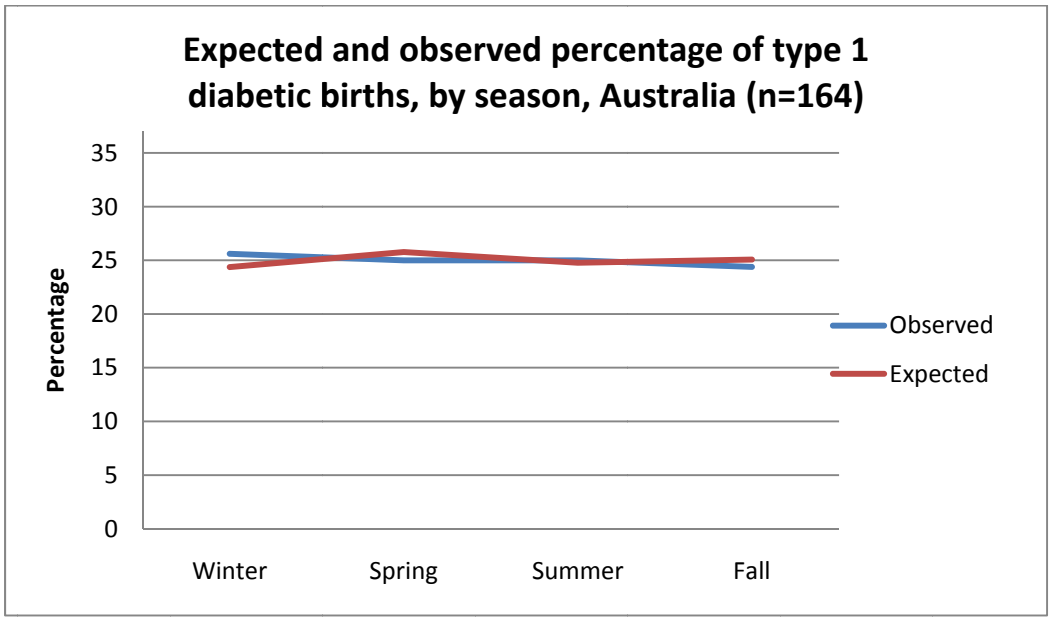


Figure 9. Expected and observed percentage of type 1 diabetic births, by season, Canada

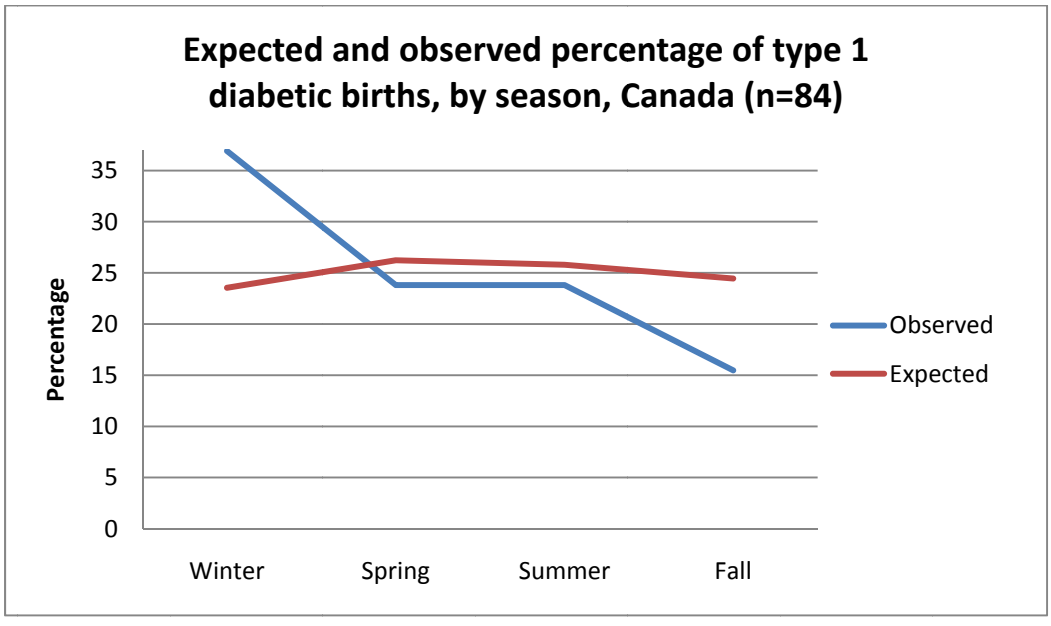


Figure 10. Expected and observed percentage of type 1 diabetic births, by season, Poland.

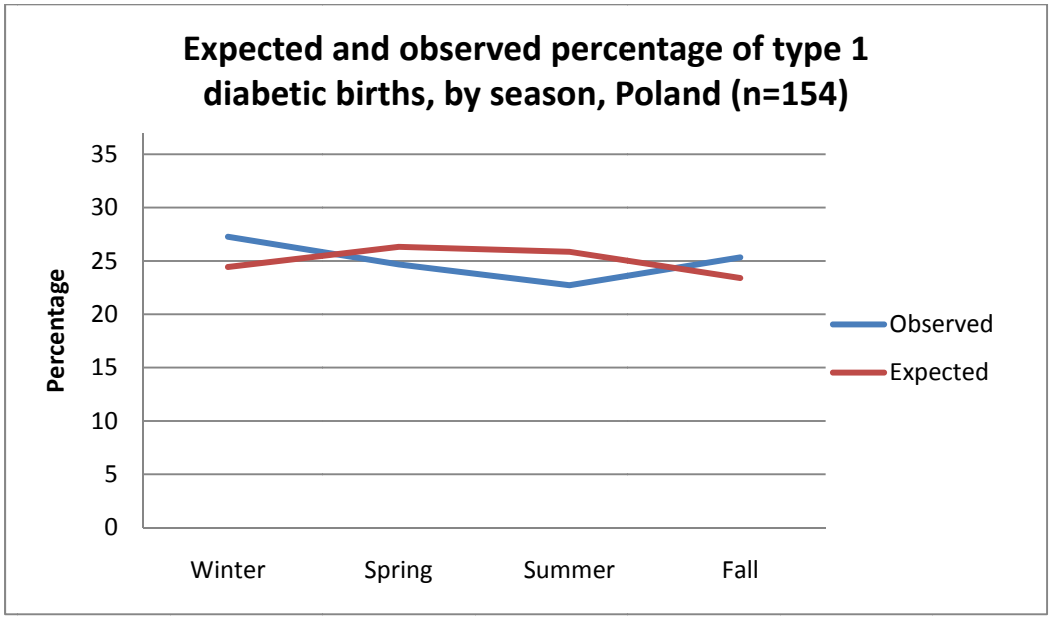


Figure 11. Expected and observed percentage of type 1 diabetic births, by season, Spain

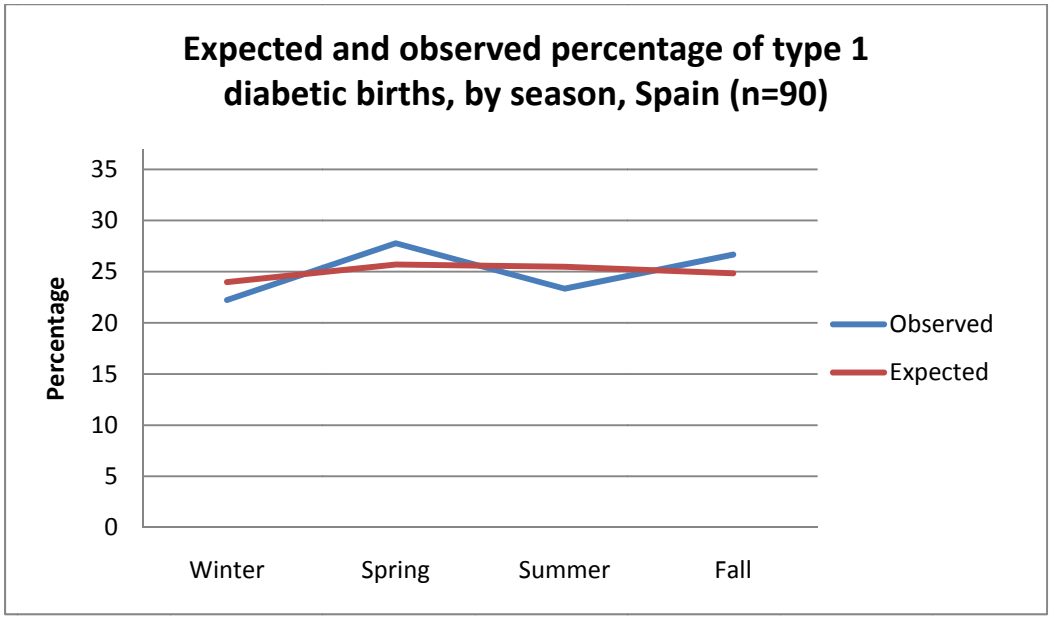


Figure 12. Expected and observed percentage of type 1 diabetic births, by season, United States

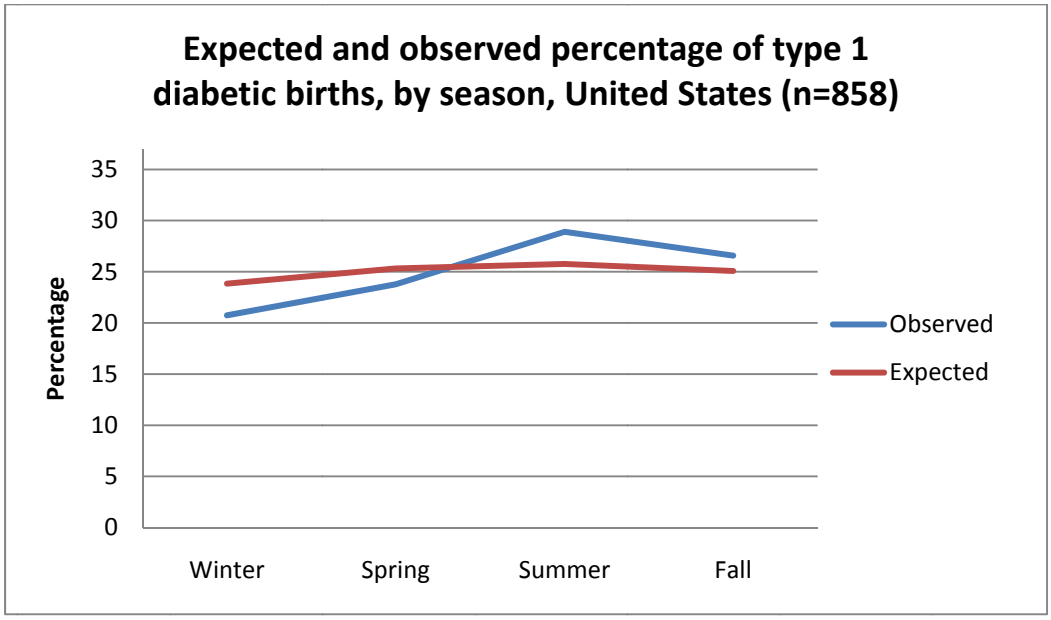


Table VI. Percentages of births by season for the type 1 diabetic (T1DGC) and UN reference population, by nationality, and overall population

Season of Birth	Australia		Canada		Poland		Spain		United States		Overall[a]	
	T1DGC % (N)	UN %	T1DGC % (N)	UN %	T1DGC % (N)	UN %	T1DGC % (N)	UN %	T1DGC % (N)	UN %	T1DGC % (N)	UN %
Winter	25.0% (41)	25.2%	36.9% (31)	23.5%	27.3% (42)	24.4%	22.2% (20)	24.0%	20.7% (178)	24.1%	23.2% (313)	24.1%
Spring	24.4% (40)	24.9%	23.8% (20)	26.2%	24.7% (38)	26.5%	27.8% (25)	25.8%	23.8% (204)	24.7%	24.3% (328)	25.1%
Summer	25.6% (42)	24.2%	23.8% (20)	25.7%	22.7% (35)	25.8%	23.3% (21)	25.5%	28.9% (248)	25.9%	27.0% (365)	25.8%
Fall	25.0% (41)	25.6%	15.5% (13)	24.5%	25.3% (39)	23.4%	26.7% (24)	24.8%	26.6% (228)	25.3%	25.5% (344)	25.0%

[a] Months for Australia are reversed, so that the seasons were consistent with the other four Northern Hemisphere countries.

In the overall model substituting season of birth for month of birth, season of birth ($p = 0.59$) did not significantly contribute to the proportion of type 1 diabetic births. Nationality ($p < 0.001$) and decade of birth ($p < 0.001$) significantly contributed to the proportion of type 1 diabetics born. The interaction between nationality and season was not significant ($p = 0.15$).

In the model stratified by nationality, season of birth significantly contributed to the proportion of diabetics born only for Canada ($p = .03$). Within the United States, the data suggests that season of birth may influence proportion of diabetics, although results were not statistically significant ($p = 0.053$). Within Canada, our model based estimates indicate that a person born in the fall months has 0.40 times (95% CI, 0.21 to 0.77) the chance of developing type 1 diabetes as compared to a person born in the winter months. A person born in the spring months has 0.58 times (95% CI, 0.33 to 1.01) the chance, and a person born in the summer months has 0.59 times (95% CI, 0.34 to 1.03) the chance of developing type 1 diabetes as compared to a person born in the winter months.

Decade of birth significantly contributed to the proportion of diabetics born in Poland and the United States.

Discussion. The main finding was that neither month of birth or season of birth contributed to the likelihood of developing type 1 diabetes, in the overall population. Within Canada, a significant difference in the proportion of type 1 diabetic births was seen, by month and season, with more type 1 diabetic births occurring during the winter months. Within the United States population, a

significant difference in the proportion of births of individuals who subsequently develop type 1 diabetes was seen by month, with increases in the number of births of individuals who subsequently develop type 1 diabetes in August and October.

Although the overall trend was not statistically significant, the peak seen in the summer months (specifically August) was primarily due to the larger sample size from the United States type 1 diabetic population (Figures 1 and 6). Similarly, a trough was seen in the overall study population in December and January; this was again driven by the United States type 1 diabetic population.

Due to available sample size in the remaining populations (Australia, Canada, Poland, and Spain), the percentages of observed type 1 diabetic births showed more variability throughout the year. Both Canada and Poland had an increase in the number of births of individuals who subsequently develop type 1 diabetes occurring during the winter months, although this was not significant in Poland. Smaller samples were included in analyses for all sub-populations, with the exception of the United States.

The differences in proportion of births of individuals who subsequently develop type 1 diabetes in the United States confirms the previous findings where the CDC reference data for the period 1990 – 2000 was used in analyses. Even with the addition of twenty years of data and the use of a different reference population, month of birth appears to contribute to the likelihood of development type 1 diabetes. Specifically, in each analysis, the individuals born during the

month of August was found to be at higher risk for future development of type 1 diabetes.

The Type 1 Diabetes Genetics Study was a prevalence study, and as such, participants were recruited regardless of duration of disease and the population spanned many birth years. Thus, if a consistent seasonal pattern was present, one would expect to see this in the results. However, the sample sizes in any specific year were small; and as such, years had to be combined into decades for the regression model. Therefore, viral epidemics that may have occurred in a population during a specific year could not be detected.

The type 1 diabetic population used in analyses was fairly evenly split between males and females (51.3% males). The average age at onset was 7.2 ± 4.7 years; however, the average age was lower in the Australian population and higher in the Spanish population. Likewise, age at enrollment and duration of disease was higher in the Spanish type 1 diabetic population (26.3 ± 7.0 and 16.4 ± 7.6, respectively) than in the overall T1DGC population (17.5 ± 7.3 and 10.3 ± 6.9, respectively). The population from the T1DGC is a highly genetically susceptible population, evident in the average number of affected siblings per family (2.0 ± 0.4) and the percent carrying either the *DR3* and/or the *DR4* allele (91.9%).

As previous research has shown, seasonality of birth patterns may vary by race and gender. Due to the recruitment criteria for the T1DGC, these analyses were unable to investigate the differences between Caucasian and other race/ethnicities within the same country. Due to reference data available, we

were unable to investigate the differences by gender. Use of national census data would allow analysis by gender to be performed, although combining nationalities may not be possible using this as a reference population.

In conclusion, we found consistent differences in seasonality of birth patterns found in the United States population, using both the CDC and the United Nations data, supporting our hypothesis that environmental factors in pregnant mothers of type 1 diabetics may contribute to the likelihood of developing type 1 diabetes in this population. This has implications for the viral hypothesis, such that increased viral activity, known to occur during the summer and fall months, in pregnant women, may lead to an increase risk of type 1 diabetes. However, it is unknown if the differences observed are due to prenatal environmental factors, or post-natal environmental effects. Further research should investigate seasonality of birth patterns during known times of viral epidemics in order to determine if the viral hypothesis is supported and if enteroviruses are transmitted to from the mother to the fetus.

Strengths and Limitations of this Study

The T1DGC is a worldwide recruitment of persons and families affected with type 1 diabetes. Many of the countries and nationalities included have limited or no research conducted on seasonality of birth patterns in individuals with type 1 diabetes. This study provided an opportunity to investigate whether birth patterns differ from the general population. The research on this topic has produced mixed results. The T1DGC was one of the first studies to encompass a large number of nations, previously understudied. By standardizing eligibility

criteria and data collection procedures, pooling of populations for analyses and comparison of results is possible.

The type 1 diabetic population used in this study was a more genetically susceptible population than the overall type 1 diabetic population. Thus, even though the monthly birth pattern for this group of type 1 diabetics was different than that of the general population, it is difficult to generalize this finding to all type 1 diabetics. However, given that genetics do play a role in development of type 1 diabetes, generalizing these finding to the type 1 diabetic population as a whole, may not be unwarranted. While it has been suggested that nearly 98% of all type 1 diabetics carry the *HLA DR3* or *DR4* gene, [9-10] only 92% of the T1DGC population used in this population carried one or both of these genes.

Ethnicity was self-reported and the ethnicity groups used by the T1DGC were based on nationalities as defined by the Australian 2000-2001 census.[3] Participants were not asked to identify themselves according to the National Institutes of Health (NIH) race groups (*i.e.,* White, Black or African American, Asian, American Indian or Alaskan native, Native Hawaiian or Pacific Islander). The race codes were specific to nationality and included categories such as Polish, British, and French Canadian. Therefore, the researchers could not group these participants into NIH racial categories without concern about admixture within the population. A finer classification system and one that was not based on self-report may have been more important in some countries than others.

Future Research

At the time of analyses, a full T1DGC data set was not available. Future research within the Consortium should investigate the seasonality of birth patterns using the entire available sample set. This would permit the inclusion of more nationalities and would increase the sample sizes for included nationalities. Many recruiting sites within the Consortium represent nationalities that have had little or no research conducted on birth patterns in individuals with type 1 diabetes.

Differences in the proportion of type 1 diabetics born by month, and season, have been reported more frequently in high incidence populations. The current analyses used only nationalities with medium or high incidence of type 1 diabetes. Future research should take into account the underlying disease prevalence in comparing the birth patterns of individuals with type 1 diabetes to the general population.

Type 1 diabetes is a multi-factorial disease, with evidence for a strong genetic component and less consistent support for environmental influences. Understanding the potential contribution of environmental factors during the antenatal and prenatal periods is critical to detangling the etiology of type 1 diabetes. Examination of type 1 diabetic birth patterns is an important step in appreciating the environmental contribution to the development, and ultimately, prevention, of this disease.

Reference List

1. Centers for Disease Control and Prevention. National Center for Health Statistics. VitalStats. http://www.cdc.gov/nchs/vitalstats.htm. Accessed April 25, 2011.

2. United Nations Statistics Division. United Nations Demographic Yearbook 26 Nov 2010. http://unstats.un.org/unsd/demographic/default.htm. Accessed April 25, 2011.

3. Karvonen M, Viik-Kajander M, Moltchanova E, et al. Incidence of childhood type 1 diabetes worldwide. *Diabetes Care.* 2000; 23(10): 1516-1526.

4. Bell RA, Mayer-Davis EJ, Beyer JW, D'Agostino RB, et al. Diabetes in non-Hispanic white youth. Prevalence, incidence, and clinical characteristics: the SEARCH for Diabetes in Youth Study. *Diabetes Care.* 2009; 32 (2): S102-111.

5. Mayer-Davis EJ, Beyer JW, Bell RA, Dabelea D, et al. Diabetes in non-African-American youth. Prevalence, incidence, and clinical characteristics: the SEARCH for Diabetes in Youth Study. *Diabetes Care.* 2009; 32 (2): S112-122.

6. Lawrence JM, Mayer-Davis EJ, Reynolds K, Beyer J, et al. Diabetes in Hispanic American youth. Prevalence, incidence, and clinical characteristics: the SEARCH for Diabetes in Youth Study. *Diabetes Care.* 2009; 32 (2): S123-132.

7. Liu LL, Yi JP, Beyer J, Mayer-Davis EJ, Beyer JW, D'Agostino RB, et al. Type 1 and type 2 diabetes in Asian and Pacific Islander US Youth: the SEARCH for Diabetes in Youth Study. *Diabetes Care.* 2009; 32 (2): S133-140.

8. Australian Bureau of Statistics. Australian Standard Classification of Cultural and Ethnic Groups (2000-2001). http://www.ausstats.abs.gov.au/ausstats/free.nsf/0/CAFD9A578C421AEFCA256C0F0001D603/$File/12490_2000-01.pdf. Accessed April 25, 2011.

9. Dorman JS, McCarthy BJ, O'Leary LA, Koehler AN. Risk Factors for Insulin-Dependent Diabetes. In: Harris MI, Cowie CC, Stern MP, et al. *Diabetes in America.* Bethesda, MD: NIH Publication; 1995: 165-178.

10. Wolf E, Spencer KM, Cudworth AG. The genetic susceptibility to type 1 (insulin dependent) diabetes: analysis of the HLA-DR association. *Diabetologia.* 1983; 24(4): 224-230.

Wake Forest School of Medicine

CURRICULUM VITAE

NAME: Letitia Howard Perdue, BA, CCRP

CURRENT ACADEMIC TITLE:

Project Manager I

ADDRESS: Public Health Sciences
Department of Biostatistical Sciences
WC-21
Medical Center Boulevard
Winston-Salem, NC 27157

PHONE: 336-716-1336

EDUCATION:

2005 – Present	Enrolled in Master of Health Services Research Program (M.S. degree anticipated August 2011) Wake Forest University Graduate School of Arts and Sciences Winston-Salem, North Carolina
1997 - 2001	Bachelor of Arts in Psychology St. Mary's College of Maryland St. Mary's City, Maryland

PROFESSIONAL MEMBERSHIPS AND SERVICE:

Society of Clinical Trials

Society of Clinical Research Associates

JOURNAL ARTICLES:

1. Hilner JE, **Perdue LH**, Sides EG, Pierce JJ, Wagner AM, Aldrich A, Loth A, Albret L, Wagenknecht LE, Nierras C, Akolkar B, T1DGC. Designing and implementing sample and data collection for an international genetics study: the Type 1 Diabetes Genetics Consortium. *Clin Trials.* 2010; 7 (Suppl 1): S5-S32.
2. Hall MA, King NM, **Perdue LH**, Hilner JE, Akolkar B, Greenbaum CJ, McKeon C, T1DGC. Biobanking, consent, and commercialization in

international genetics research: the Type 1 Diabetes Genetics Consortium. *Clin Trials.* 2010; 7 (Suppl 1): S33-S45.
3. **Perdue LH**, Albret L, Aldrich A, Loth A, Sides EG, Dove A, Wagner AM, Waterman R, Pierce JJ, Akolkar B, Steffes MW, Hilner JE, T1DGC. Quality control of phenotypic forms data in the Type 1 Diabetes Genetics Consortium. *Clin Trials.* 2010; 7 (Suppl 1): S46-S55.
4. Bingley PJ, Williams AJ, Colman PG, Gellert SA, Eisenbarth G, Yu L, **Perdue LH**, Pierce JJ, Hilner JE, Nierras C, Akolkar B, Steffes MW, T1DGC. Measurement of islet cell antibodies in the Type 1 Diabetes Genetics Consortium: efforts to harmonize procedures among the laboratories. *Clin Trials.* 2010; 7 (Suppl 1): S56-S64.
5. Rosinger S, Nutland S, Mickelson E, Varney MD, Boehm BO, Olsem GJ, Hansen JA, Nicholson I, Hilner JE, **Perdue LH**, Pierce JJ, Akolkar B, Nierras C, Steffes MW, T1DGC. Collection and processing of whole blood for transformation of peripheral blood mononuclear cells and extraction of DNA: the Type 1 Diabetes Genetics Consortium. *Clin Trials.* 2010; 7 (Suppl 1): S65-S74.
6. Mychaleckyj JC, Noble JA, Moonsamy PV, Carlson JA, Varney MD, Post J, Helmberg W, Pierce JJ, Bonella P, Fear AL, Lavant E, Louey A, Boyle S, Lane JA, Sali P, Kim S, Rappner R, Williams DT, **Perdue LH**, Reboussin DM, Tait BD, Akolkar B, Hilner JE, Steffes MW, Erlich HA, T1DGC. HLA genotyping in the international Type 1 Diabetes Genetics Consortium. *Clin Trials.* 2010; 7 (Suppl 1): S75-S87.
7. ACCORD Study Group, ACCORD Eye Study Group, Chew EY, Ambrosius WT, Davis MD, Danis RP, Gangaputra S, Greven CM, Hubbard L, Esser BA, Lovato JF, **Perdue LH**, Goff DC Jr, Cushman WC, Ginsberg HN, Elam MB, Genuth S, Gerstein HC, Schubart U, Fine LJ. Effects of medical therapies on retinopathy progression in type 2 diabetes. *N Engl J Med.* 2010; 363 (3): 233-244.
8. Ambrosius WT, Danis RP, Goff DC Jr, Greven CM, Gerstein HC, Cohen RM, Riddle MC, Miller ME, Buse JB, Bonds DE, Peterson KA, Rosenberg YD, **Perdue LH**, Esser BA, Seaquist LA, Felicetta JV, Chew EY, for the ACCORD Study Group. Lack of association between the thiazolidinediones and macular edema in type 2 diabetes: the ACCORD eye substudy. *Arch Ophthalmol.* 2010; 128 (3): 312-318.
9. Brown WM, Pierce JJ, Hilner JE, **Perdue LH**, Lohman K, Li L, de Bakker PI, Irenze K, Ziaugra L, Mirel DB, for the Type 1 Diabetes Genetics Consortium. Overview of the Rapid Response Data. *Genes Immun.* 2009; 10 (Suppl 1): S5-S15.
10. Brown WM, Pierce JJ, Hilner JE, **Perdue LH**, Lohman K, Lu L, Venkatesh RB, Hunt S, Mychaleckyj JC, Delouskas P, for the Type 1 Diabetes Genetics Consortium. Overview of the MHC fine mapping data. *Diabetes Obes Metab.* 2009; 11 (Suppl 1): 2-7.
11. Chew EY, Ambrosius WT, **Howard LT**, Greven CM, Johnson S, Danis RP, Davis MD, Genuth S, Domanski M, for the ACCORD Study Group. Rationale, design and methods for the Action to Control Cardiovascular

Risk in Diabetes Eye Study (ACCORD-Eye). *American Journal of Cardiology.* 2007; 99: 103i – 111i.

ABSTRACTS/SCIENTIFIC EXHIBITS:

1. **Perdue LH**, Griffin LP, King MD, Erickson K, Ferguson E, Bahnson JL, Lang W & Espeland MA (May 2011). "Data collection and storage for online screening prior to consent." Presentation at the Society for Clinical Trials, Vancouver, BC, Canada.
2. Griffin LP, **Perdue LH**, King MD, Erickson K, Ferguson E, Bahnson JL, Lang W & Espeland MA (May 2011). "Participant data entry for a web based data management system." Presentation at the Society for Clinical Trials, Vancouver, BC, Canada.
3. **Perdue LH**, Ambrosius WT, Danis RP & Chew EY (May 2011). "The challenges of recruiting for an ancillary study initiated after an ongoing clinical trial." Presentation at the Society for Clinical Trials, Vancouver, BC, Canada.
4. King, NP, Hall MA, **Perdue LH**, Hilner J, Greenbaum CJ, McKeon C, Howell S & Mehra N (May 2008).
   "Biobanking, Consent, and Commercialization in International Genetics Research." Presentation at the Translating ELSI, Cleveland, OH.
5. Williams D, **Howard L**, Pierce J & Hilner J (May 2007). "Collaborative effort to facilitate large DNA sample shipments." Presentation at the Society for Clinical Trials, Montreal, QC, Canada.
6. Hilner JE, Pierce JJ, **Howard LT**, Sides EG, Beck SR, Davis C & Steffes M. (May 2005). "Monitoring data quality in an international study: The Type 1 Diabetes Genetics Consortium." Presentation at the Society for Clinical Trials, Portland, OR.
7. Hilner JE, **Howard LT**, Hanson K, Aldrich A, Loth A, Wagner A, Withers H & Wagenknecht LE. (May 2004). "Implementing international data collection: The Type 1 Diabetes Genetics Consortium." Presentation at the Society for Clinical Trials, New Orleans, LA.
8. Sutton KL & **Howard LT**. (May 2001). "A cross-section, cross-gender study of ability to accurately perceive basic vocal emotion." Presentation to St. Mary's College of Maryland as part of the St. Mary's Project.
9. **Howard LT**, Lazarus C, Sutton KL & Glidden LM. (April 2001). "Individual differences in the longitudinal course of depression in mothers rearing children with developmental disabilities." Poster presented at the Society for Research in Child Development, Minneapolis, MN.