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Comparison of the incidence of diabetes in United States and Indian youth: An international harmonization of youth diabetes registries

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Abstract

Objective: Comparison of incidence, across diabetes registries, has the potential to inform hypotheses for risk factors. We sought to compare the incidence of type 1 (T1D) and type 2 diabetes (T2D) in the SEARCH for Diabetes in Youth (SEARCH) in the U.S. to the Registry of Diabetes with Young Age at Onset (YDR) in India.

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Methods: We harmonized data from both registries to the Observational Medical Outcomes Partnership (OMOP) Common Data Model (v5). Data were from physician-diagnosed diabetes incident cases <20 years of age (2006–2012). Denominators were from census and membership data. Incidence was calculated for each of the registries and compared by type and within age and sex categories using a 2-sided, skew-corrected inverted score test.

Results: Incidence of T1D was higher in SEARCH (21.2 cases/100,000 [95% CI:19.9, 22.5]) than YDR (4.9 cases/100,000 [95% CI:4.3, 5.6]). Incidence of T2D was also higher in SEARCH (5.9 cases/100,000 [95% CI:5.3, 6.6] in SEARCH vs 0.5 cases/100,000 [95% CI:0.3, 0.7] in YDR. The age distribution of T1D cases was similar across registries, whereas T2D was higher at an earlier age in SEARCH. Sex differences existed in SEARCH only, with a higher rate of T2D among females.

Conclusion: The incidence of youth-onset T1D and T2D was significantly different between registries. Additional data are needed to elucidate whether the differences observed represent diagnostic delay, differences in genetic susceptibility, or differences in distribution of risk factors.

Keywords

diabetes in youth; incidence; India; United States; descriptive epidemiology of diabetes

Introduction

While dependent on the timeframe and population under study, the incidence of diabetes in youth has increased worldwide over the past two decades, for both type 1 diabetes and type 2 diabetes.[1–5] Increases in type 2 diabetes are believed to be attributable, at least in part, to an increase in obesogenic environment,[6,7] whereas factors contributing to the overall increase in type 1 diabetes remain elusive. Still, much of the literature documenting the increase in youth-onset diabetes has been documented in developed countries. Less is known about the incidence of diabetes in youth in developing countries, possibly due to a lack of infrastructure for identifying cases in a systematic manner. However, comparing incidence of youth-onset diabetes across countries has the potential to generate hypotheses for possible factors contributing to the differences observed. For example, differences observed could be evaluated relative to differences in the distribution of known risk factors in the countries examined. Comparisons could also lead to hypotheses generation of novel risk factors. These comparisons could also serve to inform the relative public health burden of diabetes as compared to other countries, thus directing resource allocation.

A challenge in examining and contrasting the incidence of diabetes between countries is that estimates obtained may not be comparable. Any differences in estimates observed could be attributable to differences in the populations examined, but also differences in the case ascertainment approach and under-reporting of cases due to differences in infrastructure for accounting of cases. Comparisons of incidence and the demographic factors associated with differences in incidence estimates obtained are facilitated by harmonization of data across the countries examined.

In 2006, the Indian Council of Medical Research established the Registry of Diabetes with Young Age at Onset (YDR), with the objective of characterizing the descriptive epidemiology and burden of complications in youth-onset diabetes in India.[8] With the development of this registry, there was an opportunity to compare youth-onset type 1 and type 2 diabetes incidence in India to that of other countries.

In the United States (U.S.), the SEARCH for Diabetes in Youth study has maintained a registry of incident, youth-onset diabetes cases since 2002.[9] In the present study, we sought to compare the incidence of youth-onset diabetes in both the U.S. and India, using a common data model to harmonize data elements and re-ascertainment of cases to evaluate and account for the potential for possible under-ascertainment bias in incidence estimates. Examination of differences in incidence by diabetes type and age distribution could lead to hypothesis-generation of factors contributing to changes in disease incidence over time.

Methods

Ascertainment of cases in SEARCH

Population-based cases of youth-onset diabetes in the U.S. were ascertained through the SEARCH for Diabetes Study in Youth (SEARCH) registry. Since 2002, youth-onset (<20 years) cases of non-gestational diabetes have been systematically ascertained in five regions of the U.S., including geographic regions within Washington, Ohio, South Carolina, and Colorado, and a health management organization-based site within Southern California. The SEARCH registration of cases informs national estimates of disease incidence, prevalence and trends across time.[10] Case reports are validated through medical record review to confirm physician diagnosis of diabetes. Following case validation and deletion of duplicate reports, cases were registered centrally. Diabetes type was abstracted from medical records based on physician documentation of diabetes type within 6 months of initial diagnosis. For incident years 2006–2012, cases were ascertained within 30 months of the year in which diagnosis was made. Centrally-registered cases were invited to participate in a brief survey to collect information on demographic factors, including age at diagnosis, race and ethnicity. Age at diagnosis, race, and sex were obtained from the participant survey, unless this data was missing, in which case data were obtained from medical record abstraction. For race, if both survey and medical record data were missing this information, race was imputed from the predominant race corresponding to the individual’s geocoded census block. Informed consent from parents, and assent from children, where relevant, was obtained prior to completion of the survey. Consent was implied for surveys completed by mail or on-line. As described elsewhere, completeness of case ascertainment for the four regionally-based sites was evaluated using the capture-recapture method and has demonstrated consistent case ascertainment across time, with a range of completeness between 92–94% for type 2 diabetes and 99% for type 1 diabetes.[10,11] Local Institutional Review Boards at each of the five SEARCH clinical sites reviewed and approved the study protocol.

Ascertainment of cases in YDR

Incident cases of youth-onset (≤25 years) diabetes in India were ascertained through the Registry of People with Diabetes with Youth Age at Onset (YDR). YDR is implemented through regional collaborating centers that serve as centralized repositories for reporting centers within the region. Data from the regional centers is transmitted to the Technical Coordinating Unit at the All India Institute Medical Sciences to compile and analyze data obtained. For this study, type 1 and type 2 diabetes cases <20 years at diagnosis, identified in the regional centers for New Delhi and Chennai from 2006–2012, were included. Cases were restricted to those cases registered within 30 months of the date of diagnosis in the incident year of diagnosis. YDR defined diabetes according to presence of fasting plasma glucose ≥126 mg/dl and/or 2 hour post-load plasma glucose ≥200 mg/dl. Diabetes type was determined by clinical judgement.[8] Patient demographic, socioeconomic, and clinical factors were recorded at the time of case registration. Case re-ascertainment in YDR was conducted through a systematic process of identifying all cases within a subset of the reporting centers through record abstraction and comparing the cases identified to those previously identified to obtain counts of confirmed cases, newly identified cases, and registered cases not identified through the re-ascertainment process. The number of cases missed and proportion of cases missed were calculated using capture-recapture methods[12]. The proportion of cases missed, by age and sex and within type and region, was used to estimate the average annual incidence of diabetes by sex and age, within type, within the YDR regions of New Delhi and Chennai, and for both regions combined. Average annual incidence was calculated by averaging the number of cases for each year across 2006–2012 and dividing this by the population census. Annual incidence was averaged to generate the average annual incidence across all years combined).

Estimation of incidence and comparisons between SEARCH and YDR

Cases in SEARCH and YDR included incident type 1 and type 2 cases identified from 2006 through 2012. Denominators for incidence calculations were obtained from census data corresponding to the respective case ascertainment areas. For SEARCH, this data is collected through the U.S. Census Bureau and includes youths <20 years of age on December 31st of the incident year and who are civilian residents of the geographic catchment area of the SEARCH site. Count data are available by county according to age, sex, race and ethnicity. For the health-plan based SEARCH site, participant addresses were geocoded to Census blocks to estimate racial and ethnic distributions by age and sex.[10] For SEARCH participants residing on Native American reservations, Indian Health Services usage data, obtained from the previous 3 years, was used to construct denominators.[10] For YDR, region-based age and sex count data, for establishing the denominators were available through the Ministry of Home Affairs, Government of India Census data. The India Census is completed every 10 years and denominator data to inform incidence estimates were available at the district level, which corresponds to the catchment area of the YDR registration centers in New Delhi and Chennai. The most recent data available were used (2011 Census).[12]

Prior to calculation of incidence estimates, local registry structures and values were harmonized and transformed into the Observational Medical Outcomes Partnership (OMOP) Common Data Model (v5) as described in a prior paper in this volume.[13] Once data were transformed, common queries were executed locally. Aggregated summary data was shared between registries. Within each of the registries, we first examined annual incidence of diabetes, by type, across the period 2006–2012. Crude annual incidence (two-year moving average) was calculated within each of the sites. The average annual diabetes incidence was calculated for each registry and compared across registries by type and within age and sex categories. Crude and adjusted (adjusted for incomplete ascertainment) incidence rates for YDR were calculated. The 2-sided, skew-corrected inverted score test was used to assess for differences in average, annual incidence across the two registries by sex and age at diagnosis, and within diabetes type.

Results

Capture-recapture indicates 99.3% of type 1 and 92.1% of type 2 cases are successfully identified in SEARCH.[10] Case re-ascertainment in YDR indicated that 78% of type 1 diabetes cases were identified during the initial ascertainment process. For type 2 diabetes, 83.5% of cases were identified during the initial ascertainment process. Completeness of case registry varied by age, type and region (Supplementary Tables 1–3). For type 1 diabetes, the proportion under-ascertained increased with decreasing age. A higher proportion of cases were missed in New Delhi than in Chennai (Supplementary Tables 1–2). Thus, both crude incidence rates and rates adjusted for ascertainment were calculated for YDR.

Incidence rates by age, sex and within type are presented in Tables 1–2. The overall, average annual incidence of type 1 diabetes in SEARCH, for the period 2006–2012 was 21.2 cases/100,000 (95% CI: 19.9, 22.5) (Table 1). In YDR, the overall, crude and adjusted average annual incidence of type 1 diabetes was 4.0 cases/100,000 (95% CI: 3.6, 4.5) and 4.9 cases/100,000 (95% CI: 4.3, 5.6), respectively (Table 1). In SEARCH, for type 2 diabetes, the average annual incidence rate was 5.9 cases/100,000 (95% CI: 5.3, 6.6) (Table 2). For YDR, the crude average annual incidence of type 2 diabetes was 0.4 cases/100,000 (95% CI: 0.3, 0.6). Adjustment for under-ascertainment of cases marginally increased the incidence estimate (0.5 /cases/100,000 [95% CI: 0.3, 0.7]) (Table 2). For both type 1 and type 2 diabetes, the average annual incidence was significantly higher in SEARCH as compared to YDR ($p < 0.0001$ for both type 1 and type 2 diabetes) (Tables 1–2).

When examining incidence by age at onset for type 1 diabetes, the age distribution was similar between the two registries (Table 1). Conversely, for type 2 diabetes, the age distribution was shifted to a younger age at onset in SEARCH as compared to YDR (Tables 1–2). With the exception of ages 0–4 for type 2 diabetes only, the incidence of both type 1 and type 2 diabetes was significantly higher across both sex and all age groups in SEARCH as compared to YDR ($p<0.0001$ for all) (Table 1). Of note, while the ratio of females to males were similar across registries for type 1 diabetes, the female to male ratio was different for type 2 diabetes. Specifically, while the incidence of type 2 diabetes in females was nearly twice that of males in SEARCH (7.5 cases/100,000 in females versus 4.4 cases/100,000 in males), the female to male ratio in YDR was equivalent (adjusted incidence of 0.5 cases/100,000 in both females and males) (Table 2).

Discussion

Comparison of a center-based registry of youth-onset diabetes in India and a population-based registry of youth-onset diabetes in the U.S. indicates that the incidence of type 1 and type 2 diabetes in youth is significantly different between these two countries. Incidence of diabetes in youth, irrespective of type, is significantly higher in the U.S.. Examination of differences by age and sex distributions, and within type, finds differences between these two registries, as well. While the relative distributions were similar for type 1 diabetes, peak incidence of type 2 diabetes generally occurred at an earlier age in SEARCH. It may be that risk factors for developing type 2 diabetes are more prevalent at an earlier age in the U.S., or, it may be that there is greater diagnostic delay for type 2 diabetes in India.[14] The prevalence of obesity in youth is lower in India than in the U.S.,[15] suggesting that the differences in age distribution may, in part, be attributable to differences in distribution of obesogenic lifestyle factors.

The ratio of incidence by sex was also significantly different for type 2 diabetes. Females experience a higher incidence of type 2 diabetes as compared to males in the U.S.. Again, this suggests that lifestyle factors may contribute. Differences in health seeking behaviors, could also differ by country,[16] although it is unknown whether this would extend to health seeking behaviors on behalf of children.

South Asians, in particular, are believed to have increased susceptibility for developing type 2 diabetes, demonstrating increased insulin resistance at comparable body mass index as compared to other population groups.[17,18] While differences in type 1 diabetes incidence may be attributable, in part, to differences in racial distributions across the two countries, additional data are needed to evaluate this further. Census data in the U.S. preclude estimating incidence in South Asians only using data available in SEARCH. However, in restricting SEARCH incidence rates to Asian/Pacific Islanders only, differences between registries was attenuated, with an incidence of 7.8 cases/100,000 youth (95% CI: 5.2, 11.8) in SEARCH Asian/Pacific Islanders only as compared to the 4.9 cases/100,000 youth (95% CI: 4.3, 5.6) (adjusted) in YDR. Still, racial differences may not full explain the differences observed. For example, in a study conducted in the UK, comparing diabetes incidence in South Asians versus non-South Asians, there was no significant difference in incidence of diabetes for children and young adults (ages 0–29), although within diabetes type, South Asian youth exhibited significantly higher incidence of type 2 diabetes and lower incidence of type 1 diabetes.[19]

Assessment of case ascertainment completeness in YDR suggests that under-ascertainment is a challenge, particularly for New Delhi and among younger age groups with type 1 diabetes. While we presented adjusted estimates to account for possible under-ascertainment, the process of re-ascertainment is imperfect and some additional cases may have been missed. The reporting centers in YDR rely upon a variety of sources for case confirmation. Many sites rely upon paper-based records and some records may be incomplete. YDR registers all diagnosed cases, however some cases may not be identified if there is diagnostic delay and the child dies as a result.[20] Given the extreme poverty in some areas of India, this could be a contributing factor in differences observed as well.[21] Indeed, we estimated 53.3% (95% CI: 50.7, 55.8) of type 1 diabetes cases were missed in the 0–4 year age group for type 1 diabetes in New Delhi (Supplementary Table 2).

The differences in youth-onset diabetes observed for SEARCH and YDR illustrate that there is much still to learn and understand about diabetes. The distribution of risk factors for diabetes, particularly type 2 diabetes, is likely very different in the U.S. compared to India.[22] However, in urban areas in particular, this pattern may be shifting as youth in India adopt more obesogenic dietary and behavioral patterns. New Delhi, as compared to Chennai, is more urban and type 2 diabetes incidence was observed to be lower in New Delhi. Additional research is needed to evaluate whether these differences could be attributable to lifestyle factors. In conclusion, the difference in incidence of diabetes in youth observed for SEARCH and YDR may lead to new hypotheses for understanding diabetes. Differences in racial distribution may contribute to differences observed, underscoring that genetic susceptibility is important, but not precluding the possibility that cultural norms within racial-identity groups could also contribute. Registry differences in environmental factors contributing to type 2 diabetes are likely, with the U.S. likely providing a more obesogenic environment for youth and at an earlier age. Indeed, as described elsewhere in this issue (Hockett et al), the proportion of obese youth was higher in the SEARCH registry as compared to YDR for Type 2 diabetes (78.9% in SEARCH versus 36.6% in YDR). Diagnostic delays or under-ascertainment of cases for YDR could contribute to the differences in incidence observed, but more work is needed to elucidate this further.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

API	Asian/Pacific Islander
CI	Confidence Interval
OMOP	Observational Medical Outcomes Partnership
YDR	Registry of People with Diabetes with Youth Age at Onset
U.S.	United States

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Table 1.

Average of annual incidence of youth-onset, type 1 diabetes in SEARCH and YDR-New Delhi and Chennai regions (2006–2012)

	SEARCH			YDR – New Delhi and Chennai				
Type 1 diabetes	**Average annual Cases (n)**	**Denominator (Millions)**	**Crude incidence rate/100,000 (95% CI)**	**Average annual Cases (n)**	**Denominator (Millions)**	**Crude incidence rate/100,000 (95% CI)**	**Adjusted* incidence rate/100,000 (95% CI)**	**p-value comparing crude incidence rates**
Overall Incidence	1,063	5.025	21.2 (19.9, 22.5)	299	7.445	4.0 (3.6, 4.5)	4.9 (4.3, 5.6)	<0.0001
Sex								
Female	498	2.459	20.2 (18.5, 22.1)	141	3.475	4.1 (3.4, 4.8)	4.9 (4.1, 5.9)	<0.0001
Male	566	2.566	22.0 (20.3, 23.9)	158	3.970	4.0 (3.4, 4.6)	4.9 (4.1, 5.8)	<0.0001
Age at diagnosis								
0–4	172	1.222	14.1 (12.1,16.3)	50	1.676	3.0 (2.3, 3.9)	3.8 (1.8, 5.9)	<0.0001
5–9	345	1.228	28.1 (25.3, 31.2)	92	1.821	5.0 (4.1, 6.2)	6.2 (4.9, 7.7)	<0.0001
10–14	383	1.250	30.7 (27.8, 33.9)	97	1.956	4.9 (4.1, 6.0)	6.0 (4.8, 7.3)	<0.0001
15–19	162	1.325	12.3 (10.5,14.3)	60	1.992	3.0 (2.4, 3.9)	3.8 (2.9, 4.9)	<0.0001

* adjusted for under-ascertainment

Table 2.

Average of annual incidence of youth-onset, type 2 diabetes in SEARCH and YDR-New Delhi and Chennai regions (2006–2012)

	SEARCH			YDR – New Delhi and Chennai				
Type 2 diabetes	**Average annual Cases (n)**	**Denominator (Millions)**	**Crude incidence rate/100,000 (95% CI)**	**Average annual Cases (n)**	**Denominator (Millions)**	**Crude incidence rate/ 100,000 (95% CI)**	**Adjusted incidence rate/100,000 (95% CI)**	**p-value comparing crude incidence rates**
Overall Incidence	297	5.025	5.9 (5.3, 6.6)	32	7.445	0.4 (0.3, 0.6)	0.5 (0.3,0.7)	<0.0001
Sex								
Female	185	2.459	7.5 (6.5, 8.7)	16	3.475	0.5 (0.3, 0.7)	0.5 (0.3,0.9)	<0.0001
Male	112	2.566	4.4 (3.6, 5.2)	17	3.970	0.4 (0.3, 0.7)	0.5 (0.3,0.8)	<0.0001
Age at diagnosis								
0–4	1	1.222	0.0 (0.0, 0.4)	0	1.676	0.0 (0.0, 0.3)	--	NA
5–9	14	1.228	1.1 (0.7,1.9)	2	1.821	0.1 (0.0, 0.4)	0.1 (0.0,0.4)	<0.0001
10–14	134	1.250	10.7 (9.1,12.7)	9	1.956	0.5 (0.2, 0.9)	0.5 (0.2,1.0)	<0.0001
15–19	148	1.325	11.2 (9.5,13.2)	21	1.992	1.1 (0.7, 1.6)	1.3 (0.8,2.0)	<0.0001