Prevalence of Diabetes and Diabetic Nephropathy in a Large U.S. Commercially Insured Pediatric Population, 2002–2013

Lin Li,[1] Susan Jick,[1] Stefanie Breitenstein,[2] and Alexander Michel[3]

Diabetes Care 2016;39:278–284 | DOI: 10.2337/dc15-1710

OBJECTIVE

To estimate the prevalence of diabetes and diabetic nephropathy in a large population of U.S. commercially insured patients aged <18 years from 2002 to 2013.

RESEARCH DESIGN AND METHODS

Using the U.S. MarketScan Commercial Claims and Encounters Database, we identified 96,171 pediatric patients with diabetes and 3,161 pediatric patients with diabetic nephropathy during 2002–2013. We estimated prevalence of pediatric diabetes overall, by diabetes type, age, and sex, and prevalence of pediatric diabetic nephropathy overall, by age, sex, and diabetes type.

RESULTS

The annual prevalence of diabetes in the whole pediatric population increased from 1.86 to 2.82 per 1,000 during 2002–2013: 1.48 to 2.32 per 1,000 for type 1 diabetes and 0.38 to 0.67 per 1,000 for type 2 diabetes in 2002–2006 and then 0.56 to 0.49 per 1,000 thereafter. The annual prevalence of diabetic nephropathy in pediatric patients with diabetes increased from 1.16 to 3.44% for all cases and 0.83 to 2.32% for probable cases only in 2002–2013. Prevalence of diabetes and diabetic nephropathy was highest in patients aged 12 to <18 years. While prevalence of type 1 diabetes was higher in male than in female youth, prevalence of type 2 diabetes and diabetic nephropathy was higher in female than in male youth. There was no difference in prevalence of diabetic nephropathy by diabetes type.

CONCLUSIONS

The prevalence of diabetes and diabetic nephropathy increased in the U.S. MarketScan commercially insured pediatric population from 2002 to 2013. The prevalence of diabetes and diabetic nephropathy markedly increased starting at age 12 years.

Although type 1 diabetes accounts for a majority of childhood and adolescent diabetes, type 2 diabetes is becoming more common with the increasing rate of childhood obesity and it is estimated that up to 45% of all new patients with diabetes in this age-group have type 2 diabetes (1,2). With the rising prevalence of diabetes in children, a rise in diabetes-related complications, such as nephropathy, is anticipated. Moreover, data suggest that the development of clinical macrovascular complications, neuropathy, and nephropathy may be especially rapid among

[1]*Boston Collaborative Drug Surveillance Program, Boston University School of Public Health, Lexington, MA*
[2]*Global Clinical Development, Bayer Pharma AG, Wuppertal, Germany*
[3]*Global Epidemiology, Bayer Pharma AG, Berlin, Germany*

Corresponding author: Lin Li, linli07@bu.edu.

Received 3 August 2015 and accepted 26 October 2015.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc15-1710/-/DC1.

patients with young-onset type 2 diabetes (age of onset <40 years) (3–6). However, the natural history of young patients with type 2 diabetes and resulting complications has not been well studied. In the U.S., a large 10-year collaborative research project called SEARCH for Diabetes in Youth is currently ongoing and will probably answer several of these questions when results become available (7). Although it has been reported that prevalence of diabetes significantly increased from 2001 to 2009 among U.S. youth (8), current robust data on the frequency of diabetic nephropathy in patients <18 years old are lacking. Population-based data on the frequency of diabetic nephropathy in a U.S. pediatric population will inform clinicians about the need for diagnostic awareness and help develop effective treatments for pediatric patients with diabetes.

This study aimed to provide prevalence of diabetes and diabetic nephropathy in a large U.S. commercially insured population <18 years old from 2002 to 2013.

RESEARCH DESIGN AND METHODS

The data were derived from the MarketScan Commercial Claims and Encounters Database (CCE) of Truven Health Analytics, a large U.S.-based claims database (9–11). It contains data from 2002 through 2013 on ~30 million patients <65 years from >150 large employers geographically distributed throughout the U.S. that cover employees and their dependent family members. It has been reported that there is reasonable agreement on age, sex, and census region between the CCE database and the Current Population Survey respondents aged <65 years who participated in employer-sponsored private insurance (12). The CCE database contains basic demographic and enrollment data and information on paid claims for pharmaceuticals, medical services (with diagnoses recorded), and inpatient and outpatient procedures. Diagnoses are coded using the ICD-9-CM coding system. Procedures are coded using the Current Procedural Terminology, Fourth Edition, system and the Healthcare Common Procedure Coding system. Drug prescriptions are coded using the National Drug Code. These data have been used to conduct many studies in the areas of descriptive disease epidemiology and outcomes research on diabetes (9,10). This study was approved by the Boston University Medical Center Institutional Review Board.

Study Population

The study population comprised all patients who were <18 years old at any time between 2002 and 2013 in the CCE data. From this population, we identified those with diabetes, defined as those with *1*) one claim for an outpatient or inpatient diabetes diagnosis and two or more prescriptions for antidiabetes medications or *2*) records of two or more claims for an outpatient or inpatient diabetes diagnosis that were at least 30 days apart. The claims for diabetes could have been either primary or secondary diagnoses. We used these requirements to minimize the possibility of including misdiagnosed diabetes. The diagnosis date was the first recorded claim for diabetes or the first recorded antidiabetes treatment—whichever was earlier. We used ICD-9-CM; Current Procedural Terminology, Fourth Edition; and Healthcare Common Procedure Coding system codes to identify diabetes diagnoses and procedures (see Supplementary Table 1) and National Drug Code codes to identify the following antidiabetes medications: insulin, biguanides, thiazolidinediones, sulfonylureas, nonsulfonylurea secretagogues, α-glucosidase inhibitors, peptide analogs, and glycosurics. We excluded patients with one or more claim(s) for secondary diabetes, diabetes insipidus, or gestational diabetes mellitus before or on the earliest date of the recorded claim for diabetes.

Patients who had one or more prescription(s) for insulin and no prescriptions for another antidiabetes medication were classified as having type 1 diabetes, while those who filled prescriptions for noninsulin antidiabetes medications were considered to have type 2 diabetes. Among patients with no prescriptions for antidiabetes medications (29.1% of patients with diabetes), those aged ≤6 years at their first diagnosis of diabetes (0.98% of patients with diabetes), or those whose first two recorded claims were for type 1 diabetes (17.2% of patients with diabetes), were considered to have type 1 diabetes; otherwise, they were considered to have type 2 diabetes (10.9% of patients with diabetes). We used the cutoff age of 6 years because we found that, among patients with claims for antidiabetes medications, virtually all patients aged ≤6 years had type 1 diabetes.

Study Outcome

Among all pediatric patients with diabetes, we identified those who had one or more claim(s), while under age 18 years, for diabetic or other nephropathy and for chronic kidney disease (CKD) stages 1–5, unspecified CKD, end-stage renal disease (ESRD), proteinuria, renal dialysis, or kidney transplant that may have been related to diabetic nephropathy. These patients comprised the pool of potential diabetic nephropathy cases. (See Supplementary Table 2 for all relevant codes.) We then hierarchically separated all potential nephropathy cases into four exclusive groups according to the likelihood that they were true cases of diabetic nephropathy. These included patients with codes for *1*) diabetic nephropathy, *2*) nephropathy (including unspecific nephropathy, CKD stages 1–5 or unspecified, and ESRD), *3*) renal dialysis/kidney transplant, and *4*) proteinuria. We then hand-reviewed the electronic data of 50 randomly selected patients from each group. Through review of patients' electronic records and literature, we identified comorbidities associated with the presence of nephropathy. We excluded all patients with genetic kidney disease (such as polycystic kidney disease) or chromosomal anomalies recorded any time in their electronic data. We also excluded patients with claims for comorbidities associated with the risk of nephropathy, such as kidney cancer, protein metabolism disorder, or vesicoureteral reflux, before or on the earliest date of the recorded claim for nephropathy, as well as patients who had a single claim for nephropathy and also had one or more claim(s) for urinary tract disorders (such as infection or obstruction), septicemia/sepsis, and other conditions that may increase urinary albumin excretion within 30 days of the recorded nephropathy (13). (See Supplementary Table 3 for the complete codes.)

For each potential diabetic nephropathy case, we looked for claims for recurrent nephropathy diagnoses and screening or diagnostic tests for albuminuria and

supporting treatments (see Supplementary Table 4) to support the validity of the diagnosis. Patients with supporting codes for nephropathy were considered probable cases; otherwise, cases were considered possible. In addition, if patients had different types of nephropathy diagnoses in varying calendar years, we hand-reviewed their electronic data to find the most likely start date of nephropathy. Finally, patients with specific codes for diabetic nephropathy were considered specific cases, and patients with unspecific codes, including unspecific nephropathy, CKD stages 1–5 or unspecified, ESRD, renal dialysis/kidney transplant, and proteinuria, were considered unspecific cases.

Statistical Methods

To calculate prevalence, we estimated the number of patients age <18 years in each calendar year from 2002 to 2013 in the CCE data. A person contributed to the denominator of each year from the date they entered the database or 1 January 2002—whichever was later—until they reached the age of 18 years or left the database, the end of data collection, or 31 December 2013—whichever came first. For patients with diabetes, a person was counted from the earliest recorded claim for diabetes until the end of their record as described above. A person was included in the numerator of the appropriate calendar year in which they developed diabetic nephropathy and for each year thereafter until the end of their record, assuming that nephropathy persisted once it was diagnosed. The annual prevalence was estimated (separately for diabetes and diabetic nephropathy) as the number of prevalent cases in a given year divided by the number of pediatric patients insured at any time during that year.

We calculated annual prevalence of diabetes and 95% CIs using the Byar method (14) among the whole pediatric population and by diabetes type (type 1 and type 2 diabetes) and stratified by age (<2, 2 to <6, 6 to <12, and 12 to <18 years) and sex. We then calculated annual prevalence of diabetic nephropathy (with 95% CIs) among pediatric patients with diabetes overall and stratified by type of diabetic nephropathy (specific and unspecific cases), age, sex, and diabetes type. We repeated all analyses restricted to probable diabetic nephropathy cases only to understand the range of prevalence according to which nephropathy cases were included in the calculation. We also calculated annual prevalence of diabetic nephropathy (with 95% CIs) among the whole pediatric population. Finally, we used joinpoint regression, an analysis that assumes that rates of change are constant over time (15), to test for trends in prevalence of diabetes and diabetic nephropathy over the study period and estimated annual percent changes.

All analyses were conducted using SAS statistical software, version 9.3 (SAS Institute, Cary, NC), and Joinpoint Regression Program, version 4.2.0 (Statistical Research and Applications Branch, Surveillance Research Program, National Cancer Institute).

RESULTS

There were 149,223 patients aged <18 years at first diagnosis of diabetes in the CCE database from 2002 through 2013. After applicaton of the inclusion and exclusion criteria, 96,171 pediatric patients with diabetes were included in the final analysis. (See Supplementary Fig. 1 for details on selection process.) Type 1 diabetes accounted for a majority of the pediatric patients with diabetes (79%). Among these, 53% were male and 53% were aged 12 to <18 years at onset, while among patients with type 2 diabetes, 60% were female and 79% were aged 12 to <18 years at onset.

Prevalence of Diabetes

The overall annual prevalence of all diabetes increased from 1.86 to 2.82 per 1,000 during years 2002–2013; it increased on average by 9.5% per year from 2002 to 2006 and slowly increased by 0.6% after that (both *P* values <0.05). The prevalence of type 1 diabetes increased from 1.48 to 2.32 per 1,000 during the study period (average increase of 8.5% per year from 2002 to 2006 and 1.4% after that; both *P* values <0.05). The prevalence of type 2 diabetes increased from 0.38 to 0.67 per 1,000 during 2002 through 2006 (average increase of 13.3% per year; $P < 0.05$) and then dropped from 0.56 to 0.49 per 1,000 during 2007 through 2013 (average decrease of 2.7% per year; $P < 0.05$). (See Table 1 and Supplementary Fig. 2.)

Prevalence of any diabetes increased by age, with the highest prevalence in patients aged 12 to <18 years (ranging from 3.47 to 5.71 per 1,000 from 2002 through 2013). It was slightly higher in female than in male patients. The annual prevalence of type 1 diabetes also increased by age, with the highest prevalence in patients aged 12 to <18 years. Prevalence was slightly higher in male than in female patients. There were few patients with type 2 diabetes aged <6 years. The highest prevalence of type 2 diabetes was also observed in patients aged 12 to <18 years, and prevalence was higher in female than in male patients. (See Supplementary Table 5 for details.)

Prevalence of Diabetic Nephropathy

We identified 3,161 diabetic nephropathy cases. Among these, 1,509 cases (47.7%) were of specific diabetic nephropathy and 2,253 (71.3%) were classified as probable cases. The numbers of diabetic nephropathy cases in each study year are listed in Table 2.

The annual prevalence of diabetic nephropathy in pediatric patients with diabetes increased from 1.16 to 3.44% between 2002 and 2013; it increased by on average 25.7% per year from 2002 to 2005 and slowly increased by 4.6% after that (both *P* values <0.05). When we stratified by type of diabetic nephropathy, the annual prevalence increased by on average 25.4% per year from 2002 to 2005 for specific diabetic nephropathy (*P* value <0.05) and then decreased on average by 1.6% per year after that (*P* value = 0.2), while the annual prevalence of unspecific nephropathy increased on average by 28.7% per year from 2002 to 2005 and then by 11.2% per year after that (both *P* values <0.05). (See Table 3 and Supplementary Fig. 3.)

The annual prevalence of diabetic nephropathy increased by age, with the highest prevalence ranging between 1.62 and 4.30% in patients aged 12 to <18 years over the study period. The annual prevalence for all cases was slightly higher in female than in male patients. Prevalence was lower in probable compared with all diabetic nephropathy cases, by 21.4 to 32.6% depending on the year, but the prevalence still increased over time from 0.83 to 2.32% between 2002 and 2013. (See Table 4.) When we stratified by diabetes type, there was no significant difference in the annual prevalence of diabetic

Table 1—Annual prevalence of pediatric diabetes overall and by type of diabetes: U.S. MarketScan data, 2002–2013

	Number of patients with diabetes				Prevalence per 1,000 pediatric persons (95% CI)		
Year	All	Type 1	Type 2	Pediatric population (*N*)	All	Type 1	Type 2
2002	5,533	4,399	1,134	2,970,231	1.86 (1.81–1.91)	1.48 (1.44–1.53)	0.38 (0.36–0.40)
2003	9,425	7,489	1,936	4,695,851	2.01 (1.97–2.05)	1.59 (1.56–1.63)	0.41 (0.39–0.43)
2004	12,813	10,089	2,724	5,730,586	2.24 (2.20–2.27)	1.76 (1.73–1.80)	0.48 (0.46–0.49)
2005	13,851	10,854	2,997	5,806,847	2.39 (2.35–2.43)	1.87 (1.83–1.90)	0.52 (0.50–0.53)
2006	12,414	9,512	2,902	4,323,684	2.87 (2.82–2.92)	2.20 (2.16–2.24)	0.67 (0.65–0.70)
2007	19,904	15,576	4,328	7,763,597	2.56 (2.53–2.60)	2.01 (1.97–2.04)	0.56 (0.54–0.57)
2008	23,831	18,649	5,182	9,174,938	2.60 (2.56–2.63)	2.03 (2.00–2.06)	0.56 (0.55–0.58)
2009	27,977	22,007	5,970	10,494,444	2.67 (2.63–2.70)	2.10 (2.07–2.12)	0.57 (0.55–0.58)
2010	32,438	25,836	6,602	11,818,322	2.74 (2.71–2.77)	2.19 (2.16–2.21)	0.56 (0.55–0.57)
2011	36,528	29,199	7,329	13,427,193	2.72 (2.69–2.75)	2.17 (2.15–2.20)	0.55 (0.53–0.56)
2012	36,983	29,868	7,115	13,400,866	2.76 (2.73–2.79)	2.23 (2.20–2.25)	0.53 (0.52–0.54)
2013	30,542	25,218	5,324	10,847,056	2.82 (2.78–2.85)	2.32 (2.30–2.35)	0.49 (0.48–0.50)

nephropathy between patients with type 1 diabetes and patients with type 2 diabetes (data not shown).

Annual prevalence of diabetic nephropathy in the whole pediatric population increased from 2.15 to 9.70 per 100,000 for all cases and 1.55 to 6.55 per 100,000 for probable cases only from 2002 through 2013. (See Supplementary Fig. 4.)

CONCLUSIONS

According to the U.S.-based CCE data, the annual prevalence of type 1 diabetes in patients age <18 years increased from 1.48 to 2.32 per 1,000 from 2002 through 2013, while the annual prevalence of type 2 diabetes increased from 0.38 to 0.67 per 1,000 from 2002 through 2006 and then slowly decreased after that (0.56 to 0.49 per 1,000 in 2007–2013). The annual prevalence of diabetic nephropathy in pediatric patients with diabetes increased from 1.16 to 3.44% for all cases and 0.83 to 2.32% for probable cases only during the study period. Prevalence of diabetes and diabetic nephropathy was highest in patients aged 12 to <18 years. While prevalence of type 1 diabetes was higher in male than in female youth, prevalence of type 2 diabetes and diabetic nephropathy was higher in females.

There are limited data on the epidemiology of pediatric diabetes. Dabelea et al. (8) reported, based on data from the SEARCH for Diabetes in Youth study, that the annual prevalence of type 1 diabetes increased from 1.48 to 1.93 per 1,000 and from 0.34 to 0.46 per 1,000 for type 2 diabetes from 2001 to 2009 in U.S. youth. In our study, the annual prevalence of type 1 diabetes was 1.48 per 1,000 in 2002 and 2.10 per 1,000 in 2009, which is close to their reported prevalence. The annual prevalence of type 2 diabetes was 0.38 per 1,000 in 2002 and 0.57 per 1,000 in 2009 in our study, which is higher than they reported, but similar, and we both found that the annual prevalence of type 2 diabetes was higher in female than in male patients. In addition, Dabelea et al. reported that the annual prevalence of type 2 diabetes increased in 2001–2009, while we found that the annual prevalence of type 2 diabetes increased from 2002 to 2006 and slowly decreased thereafter. It should be noted that Dabelea et al. reported prevalence of type 2 diabetes only among youth aged 10–19 years. Differences in the source population, methods for identifying type 2 diabetes cases, and study period may explain these discrepancies. The incidence of type 1 diabetes has been separately reported to increase in Colorado youth aged 0–17 years from

Table 2—Annual number of diabetic nephropathy cases in U.S. MarketScan data, 2002–2013

	All	Type of diabetic nephropathy		Patient age (years)				Patient sex		Type of diabetes		Probable diabetic
Year	cases	Specific code	Unspecific code	<2	2 to <6	6 to < 12	12 to <18	Male	Female	Type 1	Type 2	nephropathy, %
2002	64	40	24	0	1	3	60	26	38	48	16	71.88
2003	151	100	51	0	1	10	140	59	92	113	38	77.48
2004	243	153	90	0	3	23	217	106	137	187	56	76.95
2005	329	203	126	0	4	30	295	150	179	255	74	73.56
2006	311	178	133	0	2	29	280	141	170	235	76	78.46
2007	483	272	211	1	3	47	432	224	259	363	120	78.88
2008	673	380	293	3	7	76	587	313	360	523	150	77.41
2009	836	427	409	0	9	107	720	384	452	646	190	74.88
2010	967	465	502	1	14	129	823	428	539	766	201	73.22
2011	1,110	488	622	0	10	139	961	510	600	888	222	71.35
2012	1,195	487	708	0	3	142	1,050	540	655	957	238	69.37
2013	1,052	400	652	0	5	92	955	468	584	868	184	67.49

Table 3—Annual prevalence of diabetic nephropathy in pediatric patients with diabetes for all cases and by type of diabetic nephropathy: U.S. MarketScan data, 2002–2013

	Number of diabetic nephropathy cases				Prevalence per 100 pediatric patients with diabetes (95% CI)		
Year	All	Specific case	Unspecific case	Number of patients with diabetes	All	Specific case	Unspecific case
2002	64	40	24	5,533	1.16 (0.89–1.48)	0.70 (0.50–0.96)	0.42 (0.27–0.63)
2003	151	100	51	9,425	1.60 (1.36–1.88)	1.03 (0.84–1.25)	0.52 (0.39–0.69)
2004	243	153	90	12,813	1.90 (1.67–2.15)	1.16 (0.98–1.36)	0.68 (0.55–0.84)
2005	329	203	126	13,851	2.38 (2.13–2.65)	1.41 (1.22–1.62)	0.88 (0.73–1.04)
2006	311	178	133	12,414	2.51 (2.23–2.80)	1.38 (1.18–1.59)	1.03 (0.86–1.22)
2007	483	272	211	19,904	2.43 (2.22–2.65)	1.32 (1.17–1.49)	1.02 (0.89–1.17)
2008	673	380	293	23,831	2.82 (2.61–3.05)	1.54 (1.39–1.70)	1.19 (1.06–1.33)
2009	836	427	409	27,977	2.99 (2.79–3.20)	1.47 (1.34–1.62)	1.41 (1.28–1.55)
2010	967	465	502	32,438	2.98 (2.80–3.18)	1.39 (1.27–1.52)	1.50 (1.37–1.64)
2011	1,110	488	622	36,528	3.04 (2.86–3.22)	1.29 (1.18–1.41)	1.65 (1.52–1.78)
2012	1,195	487	708	36,983	3.23 (3.05–3.42)	1.27 (1.16–1.39)	1.85 (1.71–1.99)
2013	1,052	400	652	30,542	3.44 (3.24–3.66)	1.26 (1.14–1.39)	2.05 (1.89–2.21)

1978–1988 to 2002–2004 (16), in Colorado youth aged 0–20 years from 1996 to 2010 (17), and among children aged 0–14 years in Philadelphia from 1985 to 2004 (18), which may at least partially explain the increase in prevalence of type 1 diabetes seen in this study.

Obesity is the most important risk factor for type 2 diabetes in youth, and the rise in pediatric obesity was accompanied by an increased prevalence of type 2 diabetes in children (19,20). Based on the National Health and Nutrition Examination Survey, Ogden et al. (21) recently reported that there were no significant changes in obesity prevalence in U.S. youth under the age of 20 years between 2003/2004 and 2011/2012, but there was a significant decrease in obesity among 2- to 5-year-old children. The period of the current study was 2002 through 2013, when the prevalence of obesity in U.S. youth remained stable and even decreased among children aged 2–5 years, which may at least partially explain our findings on the prevalence of type 2 diabetes. Type 1 diabetes is an autoimmune disease. Although an increase was also seen in the incidence and prevalence of type 1 diabetes in children (8,16–18), the causes for the increase are not clear. Dayal et al. (22) recently reported that there was no association between BMI and age at diagnosis in North Indian children with new-onset type 1 diabetes. In addition, it has been reported that the incidence of type 1 diabetes continued to rise in 2001–2008 in Australian youth aged 10–18 years, while the incidence of type 2 diabetes remained steady (23).

It has been reported that overt diabetic nephropathy and kidney failure caused by either type 1 or type 2 diabetes are uncommon during childhood or adolescence (24). In this study, the annual prevalence of diabetic nephropathy for all cases ranged from 1.16 to 3.44% in

Table 4—Annual prevalence of diabetic nephropathy in pediatric patients with diabetes for all cases stratified by age and sex and for probable cases only: U.S. MarketScan data, 2002–2003

	All cases						
	Age (years)*				Sex†		
Year	<2	2 to < 6	6 to <12	12 to <18	Male	Female	Probable cases only
2002	n/a	0.31 (0–1.72)	0.20 (0.04–0.60)	1.62 (1.23–2.08)	0.95 (0.62–1.39)	1.36 (0.96–1.87)	0.83 (0.61–1.11)
2003	n/a	0.18 (0–0.98)	0.40 (0.19–0.74)	2.21 (1.86–2.61)	1.26 (0.96–1.63)	1.94 (1.56–2.37)	1.24 (1.03–1.49)
2004	n/a	0.39 (0.08–1.13)	0.68 (0.43–1.02)	2.52 (2.19–2.88)	1.66 (1.36–2.01)	2.13 (1.79–2.52)	1.46 (1.26–1.68)
2005	n/a	0.55 (0.15–1.40)	0.81 (0.55–1.16)	3.14 (2.79–3.52)	2.18 (1.85–2.56)	2.57 (2.21–2.97)	1.75 (1.53–1.98)
2006	n/a	0.33 (0.04–1.19)	0.89 (0.59–1.28)	3.29 (2.91–3.70)	2.27 (1.91–2.67)	2.74 (2.35–3.19)	1.97 (1.73–2.23)
2007	2.44 (0.03–13.57)	0.35 (0.07–1.02)	0.89 (0.65–1.18)	3.15 (2.86–3.46)	2.24 (1.96–2.56)	2.61 (2.30–2.95)	1.91 (1.73–2.12)
2008	5.26 (1.06–15.38)	0.72 (0.29–1.49)	1.21 (0.95–1.51)	3.56 (3.28–3.86)	2.62 (2.34–2.92)	3.03 (2.73–3.36)	2.19 (2.00–2.38)
2009	n/a	0.79 (0.36–1.50)	1.46 (1.20–1.76)	3.70 (3.44–3.98)	2.73 (2.46–3.02)	3.25 (2.96–3.56)	2.24 (2.07–2.42)
2010	1.59 (0.02–8.83)	1.08 (0.59–1.82)	1.53 (1.28–1.82)	3.63 (3.39–3.89)	2.63 (2.39–2.89)	3.34 (3.06–3.63)	2.18 (2.02–2.35)
2011	n/a	0.70 (0.34–1.29)	1.51 (1.27–1.78)	3.73 (3.49–3.97)	2.78 (2.55–3.03)	3.30 (3.04–3.57)	2.17 (2.02–2.32)
2012	n/a	0.22 (0.04–0.64)	1.59 (1.34–1.87)	3.94 (3.71–4.19)	2.92 (2.68–3.17)	3.55 (3.28–3.83)	2.24 (2.09–2.40)
2013	n/a	0.44 (0.14–1.03)	1.29 (1.04–1.58)	4.30 (4.03–4.58)	3.04 (2.77–3.32)	3.86 (3.55–4.19)	2.32 (2.16–2.50)

Data are prevalence of diabetic nephropathy per 100 pediatric patients with diabetes (95% CI). n/a, not applicable because of zero cases. *P values <0.05 for years 2002 through 2013, χ^2 test. †P values <0.05 for years 2009 through 2013, χ^2 test.

pediatric patients with diabetes and was extremely low in the whole pediatric population (range 2.15 to 9.70 per 100,000), confirming that diabetic nephropathy is a very uncommon condition in youth aged <18 years. We observed that the prevalence of diabetic nephropathy increased in both specific and unspecific cases before 2006, with a leveling off of the specific nephropathy cases after 2005, while the unspecific cases continued to increase. The increased prevalence may be at least partly explained by our assumption that diabetic nephropathy persists once it is diagnosed. Currently, annual screening for albuminuria is recommended in children with a 5-year duration of type 1 diabetes (25). It is further recommended that urine albumin-to-creatinine ratio be monitored annually in children and adolescents with type 2 diabetes (26). Most cases (88.5%) of patients considered to have unspecific nephropathy were patients with proteinuria codes in the absence of any other nephropathy codes. One possible explanation for the continued increase in prevalence of unspecific nephropathy over time is that children who have had diabetes for a long time are more likely to be screened and found to have proteinuria, resulting in an increase in prevalence of unspecific diabetic nephropathy as defined in this study. A possible explanation for the plateau in the prevalence of specific diabetic nephropathy (those most likely to be true or severe cases) after 2005 is that improved management of diabetes over time has resulted in fewer cases of diabetic nephropathy. Incidence of nephropathy has been reported to have declined in patients with type 1 diabetes due to aggressive treatment regimens (27). There is also recognition in the literature that not every patient with diabetes with albuminuria necessarily has diabetic nephropathy, which may have resulted in a more appropriate diagnosis, which could explain some of the plateau in diabetic nephropathy prevalence (28). We also observed that the highest prevalence of diabetic nephropathy was in patients 12 to <18 years of age, which is consistent with knowledge that puberty is a major risk factor for diabetic nephropathy (24). In addition, we found that the annual prevalence of diabetic nephropathy was slightly higher in females than in males, which is also consistent with previous reports that female sex increases the risk of microalbuminuria in adolescents (29,30).

Compared with earlier studies, this study provides up-to-date estimates of prevalence of type 1 and type 2 diabetes in a large U.S. commercially insured pediatric population during years 2002–2013 including estimates of type 2 diabetes prevalence in very young patients. More importantly, we estimated prevalence of diabetic nephropathy and examined time trends across the study period, which we believe is the first study on prevalence of (diagnosed) diabetic nephropathy in this age-group. Use of the CCE data allowed us to evaluate prevalence across a long period of time and in a large widely geographically representative U.S. population.

Despite these strengths, this study has several limitations that should be considered. First, we cannot rule out the possibility of some misclassification of diabetes type, whereby, in some cases, physicians may have prescribed both insulin and noninsulin antidiabetes medications before making a final diagnosis. Using the data from the Pediatric Diabetes Consortium, Klingensmith et al. (31) recently reported that in the initial month after diagnosis of type 2 diabetes around 30% of patients were treated with insulin only. Thus, we may have misclassified a small proportion of type 2 cases as type 1 diabetes or vice versa. Despite this, we found that 9% of patients had onset of type 2 diabetes at age <10 years, consistent with the findings of Klingensmith et al. (8%), but higher than reported by the SEARCH for Diabetes in Youth study (<3%) (31,32). We also found that the prevalence of type 1 and type 2 diabetes among this commercially insured pediatric population were consistent with estimates reported from the SEARCH for Diabetes in Youth study (8). Second, there is no access to original clinical records in the CCE database; thus, validation of diabetic nephropathy was limited to electronic record review. Although we validated all potential cases by checking for supporting codes, there is still the possibility that some cases were misclassified, particularly for patients with a proteinuria diagnosis only because proteinuria may have been reversible for some patients in the early stage of diabetic nephropathy (13,33). In addition, we lack information on vigorous exercise, uncontrolled hypertension, and pronounced hyperglycemia, which may also increase the risk of proteinuria (13). Consequently, it is possible that some noncases were included as diabetic nephropathy cases. For this reason, we conducted an analysis restricted to patients with probable diabetic nephropathy. These results provide estimates that are likely lower than the true prevalence but provide context from which to evaluate the primary results. It is also possible that we missed some cases of diabetic nephropathy, since CKD is often not detected or diagnosed. Recognition of CKD has grown since 2003, a year after the new CKD stage classification system was published (34,35), so increased recording of the condition is expected, but it is the nature of any observational study that it can report only that which is diagnosed in regular practice; there is no active screening. In our study, the prevalence of specific diabetic nephropathy (most likely to be true or severe cases) decreased after 2005, which was unlikely to be explained by increased recognition of CKD. We also found, however, that the prevalence of diabetic nephropathy identified using unspecific ICD codes increased over the study period, which may be at least partly due to increased recognition of CKD regardless of cause. It is also important to note that CKD codes were not the only codes used to identify nephropathy cases. Third, while the CCE database is geographically largely representative of the U.S., not all socioeconomic groups are equally covered, e.g., families on social welfare and covered by Medicaid were not represented. Since obesity and type 2 diabetes are associated with social status, this needs to be considered when interpreting these results. In addition, we did not have race/ethnicity information in this study, so we were not able to estimate annual prevalence of diabetes and diabetic nephropathy by race/ethnicity. Finally, there was a marked change in the CCE pediatric population between 2006 and 2007: several medium-sized health plans stopped contributing data to the CCE in 2006, which explains the decrease in population size in that year. Twenty-five new contributors were added in 2007, which explains the steady rise in the population size from that time on. This should also be considered in

interpreting the results of the annual prevalence of diabetes and diabetic nephropathy around that time.

This study provides an estimate of the burden of diabetes and diabetic nephropathy in patients aged <18 years in a U.S.-based commercial claims database. The annual prevalence of diabetes increased over the study period mainly because of increases in type 1 diabetes. The annual prevalence of diabetic nephropathy also increased over the study period, although it is uncommon in pediatric patients with diabetes. The prevalence of diabetes and diabetic nephropathy markedly increased starting at age 12 years. There was no difference in prevalence of diabetic nephropathy by diabetes type.

Duality of Interest. This study was sponsored by Bayer Pharma AG. L.L. and S.J. received funding from Bayer Pharma AG to conduct the study. S.B. and A.M. are employees of Bayer Pharma AG. No other potential conflicts of interest relevant to this article were reported.

The sponsor had full access to the data but had no role in performing the data analysis.

Author Contributions. L.L., S.J., S.B., and A.M. conceptualized and designed the study, analyzed and interpreted data, and critically revised the manuscript. A.M. acquired data. S.J. obtained funding. L.L. and S.J. wrote the draft. L.L. performed statistical analysis. L.L. and S.J. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Craig ME, Jefferies C, Dabelea D, Balde N, Seth A, Donaghue KC; International Society for Pediatric and Adolescent Diabetes. ISPAD Clinical Practice Consensus Guidelines 2014. Definition, epidemiology, and classification of diabetes in children and adolescents. Pediatr Diabetes 2014;15(Suppl. 20):4–17
2. Pinhas-Hamiel O, Zeitler P. The global spread of type 2 diabetes mellitus in children and adolescents. J Pediatr 2005;146:693–700
3. Thanabalasingham G, Owen KR. Type 2 diabetes in the young: why we should worry. Practical Diabetes 2014;31:225–227
4. Dart AB, Martens PJ, Rigatto C, Brownell MD, Dean HJ, Sellers EA. Earlier onset of complications in youth with type 2 diabetes. Diabetes Care 2014;37:436–443
5. Luk AO, Lau ES, So WY, et al. Prospective study on the incidences of cardiovascular-renal complications in Chinese patients with young-onset type 1 and type 2 diabetes. Diabetes Care 2014;37:149–157
6. Song SH. Complication characteristics between young-onset type 2 versus type 1 diabetes in a UK population. BMJ Open Diabetes Res Care 2015;3:e000044
7. Hamman RF, Bell RA, Dabelea D, et al.; SEARCH for Diabetes in Youth Study Group. The SEARCH for Diabetes in Youth study: rationale, findings, and future directions. Diabetes Care 2014;37:3336–3344
8. Dabelea D, Mayer-Davis EJ, Saydah S, et al.; SEARCH for Diabetes in Youth Study. Prevalence of type 1 and type 2 diabetes among children and adolescents from 2001 to 2009. JAMA 2014; 311:1778–1786
9. MarketScan bibliography [Internet]. Available from http://interest.truvenhealth.com/content/DownloadLibrary-LifeSciences. Accessed 23 December 2014
10. Hansen L, Chang S. White paper. Health research data for the real world: the MarketScan Databases. Truven Health Analytics, 2012
11. Grosse SD, Boulet SL, Grant AM, Hulihan MM, Faughnan ME. The use of US health insurance data for surveillance of rare disorders: hereditary hemorrhagic telangiectasia. Genet Med 2014;16:33–39
12. Pickens G, Moldwin E, Marder WD. Healthcare spending index for employer-sponsored insurance: methodology and baseline results [Internet]. Available from http://truvenhealth.com/Portals/0/Assets/HealthInsights/TRU_15667_0415_HSI_ESI_WP.pdf. Accessed 15 September 2015
13. Gross JL, de Azevedo MJ, Silveiro SP, Canani LH, Caramori ML, Zelmanovitz T. Diabetic nephropathy: diagnosis, prevention, and treatment. Diabetes Care 2005;28:164–176
14. Rothman KJ, Boice JD Jr. Epidemiologic Analysis with a Programmable Calculator. Washington, DC, U.S. Govt. Printing Office, 1979 (NIH publ. no. 79-1649)
15. Kim HJ, Fay MP, Feuer EJ, Midthune DN. Permutation tests for joinpoint regression with applications to cancer rates. Stat Med 2000;19: 335–351
16. Vehik K, Hamman RF, Lezotte D, et al. Increasing incidence of type 1 diabetes in 0- to 17-year-old Colorado youth. Diabetes Care 2007; 30:503–509
17. Hummel K, McFann KK, Realsen J, Messer LH, Klingensmith GJ, Chase HP. The increasing onset of type 1 diabetes in children. J Pediatr 2012;161:652–7.e1
18. Lipman TH, Levitt Katz LE, Ratcliffe SJ, et al. Increasing incidence of type 1 diabetes in youth: twenty years of the Philadelphia Pediatric Diabetes Registry. Diabetes Care 2013;36:1597–1603
19. Hannon TS, Rao G, Arslanian SA. Childhood obesity and type 2 diabetes mellitus. Pediatrics 2005;116:473–480
20. Imperatore G, Boyle JP, Thompson TJ, et al.; SEARCH for Diabetes in Youth Study Group. Projections of type 1 and type 2 diabetes burden in the U.S. population aged <20 years through 2050: dynamic modeling of incidence, mortality, and population growth. Diabetes Care 2012; 35:2515–2520
21. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of childhood and adult obesity in the United States, 2011-2012. JAMA 2014;311: 806–814
22. Dayal D, Samprathi M, Jayaraman D, Kohat D, Bhalla AK. Secular trends of body mass index in North Indian children with Type 1 diabetes do not support the Accelerator Hypothesis. Clin Endocrinol (Oxf). 5 September 2015 [Epub ahead of print]. DOI: 10.1111/cen.129411
23. Tran F, Stone M, Huang CY, et al. Population-based incidence of diabetes in Australian youth aged 10-18 yr: increase in type 1 diabetes but not type 2 diabetes. Pediatr Diabetes 2014; 15:585–590
24. Bogdanović R. Diabetic nephropathy in children and adolescents. Pediatr Nephrol 2008;23: 507–525
25. American Diabetes Association. Standards of medical care in diabetes—2015. Diabetes Care 2015;38(Suppl. 1):S70–S76
26. Zeitler P, Fu J, Tandon N, et al.; International Society for Pediatric and Adolescent Diabetes. ISPAD Clinical Practice Consensus Guidelines 2014. Type 2 diabetes in the child and adolescent. Pediatr Diabetes 2014;15 (Suppl. 20):26–46
27. Nordwall M, Bojestig M, Arnqvist HJ, Ludvigsson J; Linköping Diabetes Complications Study. Declining incidence of severe retinopathy and persisting decrease of nephropathy in an unselected population of Type 1 diabetes-the Linköping Diabetes Complications Study. Diabetologia 2004;47:1266–1272
28. Sellers EA, Blydt-Hansen TD, Dean HJ, Gibson IW, Birk PE, Ogborn M. Macroalbuminuria and renal pathology in First Nation youth with type 2 diabetes. Diabetes Care 2009;32:786–790
29. Schultz CJ, Konopelska-Bahu T, Dalton RN, et al.; Oxford Regional Prospective Study Group. Microalbuminuria prevalence varies with age, sex, and puberty in children with type 1 diabetes followed from diagnosis in a longitudinal study. Diabetes Care 1999;22:495–502
30. Gallego PH, Bulsara MK, Frazer F, Lafferty AR, Davis EA, Jones TW. Prevalence and risk factors for microalbuminuria in a population-based sample of children and adolescents with T1DM in Western Australia. Pediatr Diabetes 2006;7:165–172
31. Klingensmith GJ, Connor CG, Ruedy KJ, et al.; Pediatric Diabetes Consortium. Presentation of youth with type 2 diabetes in the Pediatric Diabetes Consortium. Pediatr Diabetes. 8 May 2015 [Epub ahead of print]. DOI: 10.1111/pedi.12281
32. Pettitt DJ, Talton J, Dabelea D, et al.; SEARCH for Diabetes in Youth Study Group. Prevalence of diabetes in U.S. youth in 2009: the SEARCH for Diabetes in Youth study. Diabetes Care 2014;37:402–408
33. Son MK, Yoo HY, Kwak BO, et al. Regression and progression of microalbuminuria in adolescents with childhood onset diabetes mellitus. Ann Pediatr Endocrinol Metab 2015;20:13–20
34. U.S. Renal Data System. USRDS 2012 annual data report: atlas of chronic kidney disease and end-stage renal disease in the United States [Internet], 2012. Bethesda, MD, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases. Available from http://www.usrds.org/2012/view/v1_02.aspx. Accessed 10 September 2015
35. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 2002;39(Suppl. 1):S1–S266