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Regional Variation in The Incidence and Prevalence of Peyronie's Disease in The United States – Results from an Encounters and Claims Database

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Abstract

In recent years there have been more studies dedicated to Peyronie's disease (PD). However, prevalence and incidence are likely underestimated, with limited information on regional variation in the rate of diagnosis. In this study, we sought to estimate age and regional variation of the annual incidence and prevalence of PD in the United States. We reviewed data from the IBM MarketScan™ Claims and Encounters database between 2008–2017 for men ≥18 years. Inclusion required ≥1 medical claim with PD, identified by ICD-9 and ICD-10 codes or ≥1 claim for intralesional injection for PD, identified by Current Procedure Terminology (CPT) code. Overall average annual incidence was estimated at 20.9 cases per 100 000, with the highest rate of 41.6 cases per 100 000 observed in men 55–64 years (RR=8.2; p<0.0001). Geographically, the highest incidence rate was observed in the South (23.9 cases per 100,000 men; RR=1.30; p<0.0001). Across all ages, overall prevalence of PD showed a general upward trend, from 0.052% in 2008 to 0.096% in 2017. Our findings suggest men in the southern U.S. are diagnosed more with PD compared to other regions. Identification of associated factors may allow for a more proactive approach to diagnosis and management.

Introduction

Peyronie's disease (PD) is an acquired penile deformity characterized by fibrosis plaque formation within the penile tunica albuginea [1]. The condition is often associated with penile abnormalities such as pain with erection or intercourse, penile shortening, narrowing and/or curvature, erectile dysfunction and psychological distress [2–4]. A 2016 study by Stuntz, Perlaky, des Vignes, Kyriakides and Glass, using data from a multicenter database consisting of more than 3 million consumers reported the prevalence of PD in adult males

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in the U.S. to be approximately 11.8% [5]. Other studies report similar prevalence rates, and estimated incidence rate of 22.4–25.6 cases per 100,000 men, with the highest found in men 50 to 59 years old [5–8]. Some studies have observed an increased incidence of PD in individuals with certain conditions, thus presenting a possible link between these diseases and developing PD [9, 10].

There are currently, three population-based studies investigating epidemiological data of PD in the United States. In a county-wide longitudinal study using patient survey assessment and medical records that was conducted in 1991 by Lindsay, Schain. Grambsch, Benson, Beard and Kurland in Minnesota, 101 cases of PD were identified from 1950 to 1984 for an overall prevalence of 0.39% [6]. A second study examining PD prevalence was conducted via a web-based survey, and found 84 definitive PD cases and 199 probable PD cases among 238 men, for an estimated prevalence between 0.5% and 13% [8], suggesting the true prevalence of PD was significantly higher than what had previously been reported. Finally, in 2016, Stuntz, Perlaky, des Vignes, Kyriakides and Glass were the first to report prevalence of PD by geographic region and income, and observed that living in the southern U.S. was significantly associated with increased odds of having a definite or probable PD diagnosis [5].

These studies, though reporting similar results, provide limited information due to small sample size or use of self-reported surveys and may not be generalizable to a broader audience. In the present work, we examine prevalence and incidence of PD throughout the U.S. using a large insurance claims and encounters database. The primary objectives of this study include: (a) estimate the incidence and prevalence of PD diagnosis in the general U.S. population of adult men (b) examine and describe regional and age variation of incidence and prevalence of PD.

Materials and Methods

Study Design and Data Source

We conducted a retrospective study of data in the IBM MarketScan ™ Commercial Claims and Encounters database between January 1, 2008 to December 31, 2017. The MarketScan database contains de-identified longitudinal patient information and claims data on over 160 million covered individuals in the U.S [11]. The database provides individual-level demographic information, insurance features, financial information, inpatient and outpatient medical information and outpatient prescription drug data. Institutional Review Board (IRB) approval was not required for this study due to the de-identified nature of the dataset.

Patient Selection and Cohort Assignment

Adult men (≥ 18 years old) with a diagnosis of Peyronie's disease (PD) were identified for each calendar year during the study period. Individuals were required to have at least one claim of a PD diagnosis identified by the International Classification of Disease, 9th edition (ICD-9) or 10th edition (ICD-10) Clinical Modification code for PD {ICD-9-CM (607.85), ICD-10-CM (N48.6)} or one claim for intralesional injection for PD, identified by the Current Procedural Terminology code (CPT) code 54200 to be included in the patient

cohort. Index date was defined as the first physician visit with a diagnosis of PD during the enrollment period.

Incidence Cohort

One of the limitations of using a claims database for incidence estimation is the inability to know with certainty that the first claim identified in the dataset is indeed the first clinical diagnosis of disease. For this reason, we ran two incidence analyses with patient cohorts based on different continuous enrollment requirements; a main analysis cohort and a sensitivity analysis cohort. To be included in the main analysis cohort, individuals must have been continuously enrolled for at least 30 months (i.e., the specific calendar year of index diagnosis and at least 18 months prior to that), with no prior evidence of disease. For example, using the 30 months enrollment requirement, a patient identified with PD anytime in 2017 must have been enrolled during the entire 2016 period and at least 6 months during the 2015 period. For the sensitivity cohort, individuals were required to have been continuously enrolled for at least 18 months (i.e., the specific calendar year of diagnosis and at least 6 months prior to that), with no prior evidence of disease. The at-risk population for both groups had to satisfy the same continuous enrollment criteria. Because our cohort definition allowed for individuals within one cohort to have a varying number of enrollment months incidence rate was calculated as person-months.

Prevalence Cohort

The prevalence cohort was defined as men ≥ 18 years old with an ICD-9 or ICD-10 diagnosis code for PD or a CPT code for PD during the study period.

Geographic Regions

To examine geographic variation, we divided the U.S. into 4 regions; Northeast, Midwest, South and West, as defined by the U.S. Department of Commerce Economics and Statistics Administration U.S. Census Bureau [12]. We added a 5^{th} region- “Unknown” for patients with missing geographic information and those residing in areas within the U.S. such as Puerto Rico. See (Table 1) for a breakdown of states within each region.

Statistical Analysis

We calculated yearly incidence rates from 2010 to 2017 for the main analysis cohort and from 2009 through 2017 for the sensitivity analysis cohort. Claims data were reviewed yearly and patient demographic information (age-group and geographic region) were assessed on the index date. “Year” was converted into a binomial variable for *years before the introduction of Collagenase Clostridium histolyticum (CCh) (2008–2013)* and *years after (2014–2017*). Incident cases were modeled in a negative binomial regression with age-group, region, and *CCh* introduction as non-interacting cofactors. Separate models were fit for the main and sensitivity cohorts.

For the main analysis, incidence rate was calculated as the number of individuals with PD in a particular year divided by the total person-months contributed by all individuals who were continuously enrolled across the 30-months period with no prior PD diagnosis. The sensitivity analysis incidence rate was calculated as number of PD diagnoses in a particular

year divided by the total person-months contributed by those who were continuously enrolled across the 18-months period with no prior PD diagnosis. There was no blackout period for prevalence calculation, thus no separate cohorts were created. However, for more accurate calculation, taking into consideration people who were already diagnosed with PD prior to the study period, prevalence was calculated annually as, the number of PD diagnosis in unique individuals divided by the total number of men age ≥ 18 years who were enrolled for that year. Overall estimates for both incidence and prevalence were reported as well as estimates stratified by age-group and geographic region. All data transformations and statistical analysis were performed using R (version 3.5.3) (R Core Team) R Core Team (2019). SQL and R codes used to generate and analyze data is available upon request.

Results

Incidence Results

A total of 261,712 PD claims were identified in 94,876 unique men during the study period. About half of the individuals were men 55–64 years old and were located in the Southern U.S. (Table 2). In the main analysis, the incidence rate of PD in men ≥18 years old ranged between 19.6 and 23.0 per 100,000 per year. The highest average incidence rate of 41.6 per 100,000 per year was observed in men 55–64 years old, and the lowest average rate of 5.1 per 100,000 per year, in those 18–34 years old. When looking at geographic regions, the highest average incidence rate was observed in the Southern U.S., at 23.9 per 100,000 men per year and the lowest rate was observed in the Midwest at a rate of 18.6 per 100,000 men per year (Table 3, Figure 1). Age group, geographic region and introduction of *CCh* all had a significant effect on rates of PD Incidence (Table 4). Individuals with the highest risk were men age 55–64 years old (RR 8.21; 95%CI 7.77, 8.66; $p<0.001$) and those residing in the Southern U.S. (RR 1.30; 95%CI 1.25, 1.35; $p<0.001$).

Results from the sensitivity analysis showed higher overall incidence rates compared to the main analysis (31.1 per 100 000 men per year). However, the effects of age, region and *CCh* introduction remained the same, with men 55–64 years old and those residing in the Southern U.S. still having significantly higher PD incidence rates; 66.5 per 100 000 men per year and 35.6 per 100,000 men per year, respectively. Patient distribution and negative binomial regression analysis for sensitivity cohort are shown in Supplemental Tables 1 & 2.

Prevalence Results

Between 2008 and 2017, there were 132,078 prevalent cases of PD in adult men in the United States. Over the 10-year period, the distribution of cases across the age-groups and geographic regions varied, with about 46.6% and 42.5% of cases observed in men 55–64 years old and in the Southern U.S., respectively. The overall age-adjusted prevalence across the study period was estimated at 0.073%. The highest prevalence estimates were observed in men 55–64 years old (0.22%) and those residing in the Southern U.S. (0.083%), while the lowest rates were observed in men 18–34 years old (0.01%) and those residing in the Midwest (0.065%) (Table 5, Figure 2).

Discussion

This study reports incidence and prevalence of PD in the United States by age group and geographic region, using data from a large insurance claims and encounters database. Estimating epidemiological data on PD can be challenging, in part due to patients' reluctance to report their symptoms. Although there are three studies that have reported on prevalence of PD in the general U.S. population [5, 7, 9], there is a paucity of incidence reports. Additionally, previous studies were conducted in different subpopulations, or in single communities or cohorts that do not represent the general demographic of adult men in the U.S. In the present analysis, the age-adjusted average incidence of PD in the U.S. for adult men ≥18 years old is ~20.9 per 100,000 persons per year, which corresponds to a prior report by Lindsay. Schain, Grambsch, Benson, beard and Kurland in 1991 [6]. At this rate, there should be approximately 33,900 new cases of PD annually in the U.S.

PD prevalence increased with time from 0.05% in 2008 to 0.10% in 2017 with an age-adjusted average of 0.07% across the study period. In 2011 DiBenedetti, Nguyen, Zografos, Ziemiecki and Zhou observed a prevalence of 13% among men ≥18 years,[8] while Stuntz, Perlaky, des Vignes, Kyriakides and Glass in their 2016 study calculated a prevalence of 0.7% for definitive cases of PD and 11.0% for probable PD cases using a web-based, anonymized approach [5]. The age-adjusted prevalence in our study is lower than what has been previously reported, but is based on diagnoses in verified insurance claims [5, 6, 8]. However, when stratified by age group, our results mirror the trend observed in prior studies [5–8]; men between the ages of 55 and 64 years old have the highest prevalence of PD. Notably, Stuntz, Perlaky, des Vignes, Kyriakides and Glass observed that regionally, the highest prevalence of PD was in the Southern U.S. (13.8%) [5]. This conclusion is supported by our results, although the calculated prevalence in the Southern U.S. (0.083%) is lower than what was reported by Stuntz. While the exact association between geographic region and PD diagnosis is unclear, conditions such as hypertension, obesity, and diabetes, which have been previously linked to increased risk of PD [9–11, 13], are more prevalent in the Southern U.S [14]. Further work, however, is needed to strengthen this conclusion.

There was an increase in the incidence and prevalence of PD following the introduction of *CCh*. While we cannot say with certainty why we observed this trend, one could suggest that marketing strategies that emphasized the minimally invasive approach of intralesional injection coupled with the reported safety and efficacy of *CCh* [15] could have made patients more comfortable with addressing their symptoms. However, the finding in our study differs from the results in the study by Sun, Li and Eisenberg [16] where an increase in incidence and prevalence of PD was not observed after PD was introduced into the market.

A possible explanation for the variability in prevalence estimates may be due to differences in study design and methods used to derive estimates. For example, in the estimate reported by DiBenedetti, men who had been clinically diagnosed and/or treated, or had self-reported symptoms of PD were included [8]. Furthermore, data for both the DiBenedetti and Stuntz studies were collected through online patient self-reported surveys. With patient self-reported surveys, there is the risk of misinterpretation of symptoms, which could result in overreporting on the survey from capturing individuals with conditions that are similar to

but physiologically and diagnostically distinct from PD, such as congenital penile curvature or chordee.

The major strength of the present study is the use of a large insurance claims-based database. Epidemiologic results from this type of study are more generalizable than studies from single institutions or case reports. In addition, stratifying participants by age and geographic region provides a broad view of how disease presents across the country and permits future work that examines possible factors that could driving such variations. As opposed to studies using patient-reported data, the use of standard ICD-9-CM and ICD-10-CM diagnostic and procedure codes reduces the chances of including patients with similar but clinically and pathologically different conditions from our cohort. One of the limitations of our analysis is that it was limited to individuals with continuous enrollment; 30 months (main analysis) and 18 months (sensitivity analysis). In addition, our analysis only examines commercially insured patients ≥18 years old, and therefore cannot be generalized to men with other types of insurance, those with less stable insurance coverage and those without insurance coverage. Secondly, only patients who present for care are included in the data, so undiagnosed men and those with PD who do not enter the healthcare system are excluded. As such, our results likely represent underdiagnosis of PD across the U.S., especially in consideration of patients' reluctance to present to a healthcare provider for diagnosis and treatment of such a sensitive condition. Lastly, because claims-based databases rely on accurate administrative information, there remains the risk of coding and entry errors that affect the validity of the database. It is important to note that despite these limitations, the results presented here are useful in providing perspective on the incidence and prevalence of PD cases that enter the healthcare system, and to drawing awareness and assessing ways in which clinical practice can change towards identifying at risk individuals and implementing early intervention.

Conclusion

Men between the ages of 55 and 64 years old and those residing in the southern U.S. are more likely to have a diagnosis of PD compared to any other age-groups or geographic regions. A prevalence of 0.22% suggests that there are approximately 67 500 men between the age of 55 and 64 years old across the U.S. with PD, with approximately 12 750 new cases diagnosed annually. Regarding the significant regional variation observed, further work is required to investigate possible factors that may be driving such variation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix

Appendix

Author contributions: OM was responsible for study design, interpretation of results and manuscript writing. JH, RD and AC were responsible for data analysis, result interpretation and manuscript revision. AWP and JMH aided in study design and planning, result interpretation, and manuscript revision.

Conflicts of Interest:

Dr. Pastuszak declares the following conflict (s) of interest

1. Endo Pharmaceuticals – advisor, consultant, speaker, research support, fellowship support
2. Antares Pharmaceuticals – advisor
3. Bayer AG- speaker
4. Inherent Biosciences – advisor
5. Allotrope Medical – advisor
6. Woven Health – founder and leadership role
7. Vault Health – leadership role

Dr. Hotaling declares the following conflict(s) of interest

1. Endo pharmaceuticals – educational and research grants
2. Boston Scientific -educational grants
3. StreamDx, Nanonc, Andro360 -founder/own equity (early stage startups)
4. Inherent Biosciences – own equity
5. Turtle Health – advisor

Dr. Moghalu, Mr. Das, Dr. Horns and Mr. Campbell have no conflicts of interest to declare

Data Archiving

SQL and R codes used to generate and analyze data are available from the corresponding author upon reasonable request.

DISCLAIMER

All statements in this report, including its findings and conclusions are solely those of the authors and do not necessarily represent the views of the NIH or Endo Pharmaceuticals

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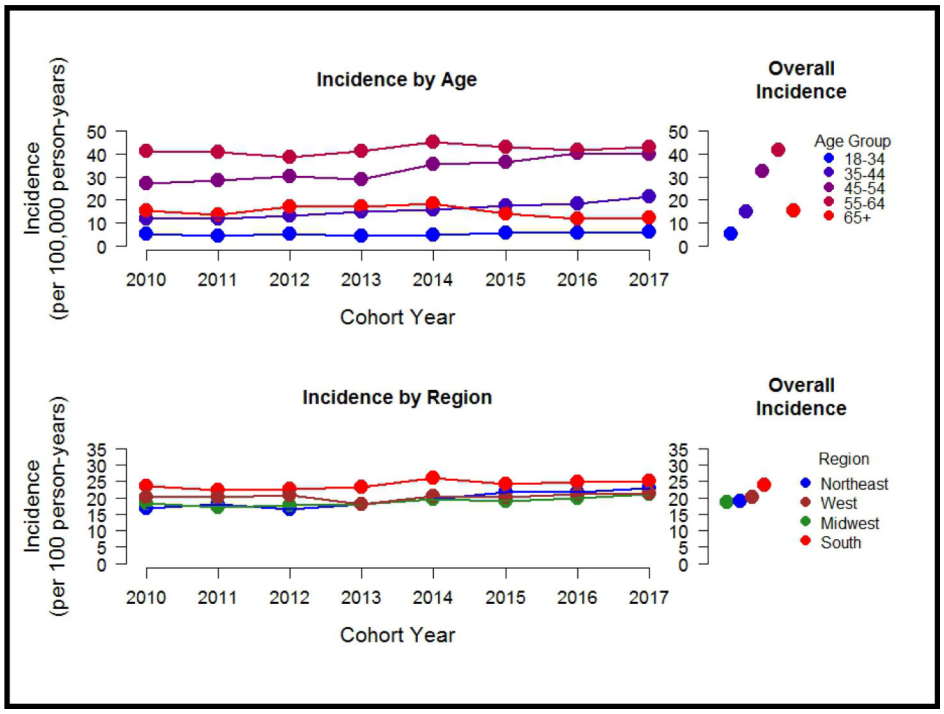

Figure 1:
Incidence of Peyronie's Disease - Stratified by Age Group and Geographic Region

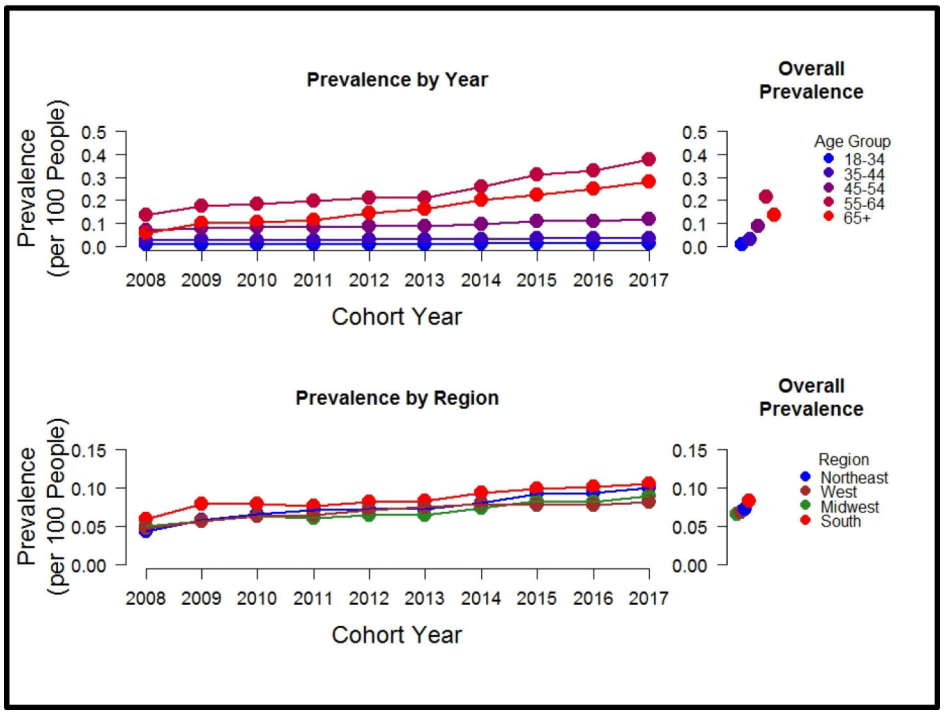

Figure 2:
Prevalence of Peyronie's Disease - Stratified by Age Group and Geographic Region

Table 1:

United States Geographic Regions and States

Northeast	**Midwest**	**South**	**West**
Connecticut	Indiana	Delaware	Arizona
Maine	Illinois	District of Columbia	Colorado
Massachusetts	Michigan	Florida	Idaho
New Hampshire	Ohio	Georgia	New Mexico
Rhode Island	Wisconsin	Maryland	Montana
Vermont	Iowa	North Carolina	Utah
New Jersey	Nebraska	South Carolina	Nevada
New York	Kansas	Virginia	Wyoming
Pennsylvania	North Dakota	West Virginia	Alaska
	Minnesota	Alabama	California
	South Dakota	Kentucky	Hawaii
	Missouri	Mississippi	Oregon
		Tennessee	Washington
		Arkansas	
		Louisiana	
		Oklahoma	
		Texas	

Table 2:

Patient Demographics * - Stratified by Age Group and Geographic Region

	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	Total
N	10082	13766	13973	15831	16862	13945	16278	10742	10594	10005	132078
Age Group, %											
18–34	5.4	4.8	4.7	4.8	5.1	4.8	4.7	4.8	4.8	5.4	4.9
35–44	10.4	9.2	8.7	8.3	8.4	8.6	7.7	7.9	7.8	7.9	8.5
45–54	29.1	27.2	27.8	26.5	26.0	25.1	25.3	25.8	26.0	27.4	26.5
55–64	45.9	46.6	46.2	46.5	45.8	44.7	47.1	48.2	48.1	48.7	46.6
≥ 65	9.2	12.2	12.6	14.0	14.7	16.8	15.2	13.3	13.2	10.6	13.5
Geographic Region, %											
Midwest	24.2	20.7	21.1	19.6	19.2	18.4	18.3	19.3	19.5	19.4	18.3
Northeast	13.0	15.7	18.3	20.0	18.9	18.6	21.2	18.8	17.4	18.6	19.8
South	42.9	44.3	41.6	40.2	41.0	37.6	38.8	46.6	48.6	48.4	42.5
West	16.0	15.1	17.2	17.2	18.7	22.7	19.1	14.8	14.0	13.4	17.2
Unknown/Other[a]	3.9	4.1	1.8	3.1	2.2	2.8	2.6	0.4	0.4	0.2	2.3

* Patients with ≥ 1 medical claims with diagnosis code for Peyronie's Disease, or procedural code for intralesional injection for Peyronie's disease. Some patients may have been identified in multiple calendar years. Continuous enrollment was not required.

[a] represents data with missing geographic information and areas within the U.S. such as Puerto Rico that do not fall into the 4 geographic regions.

Table 3:

Main Analysis: Yearly Incidence of Peyronie's Disease Stratified by Age Group and Geographic Region

	Annual Incidence rate per 100,000 person-years [b]								
	2010	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**Total**[c]
Age-group, %									
18 – 34	5.03	4.54	5.03	4.34	4.95	5.73	5.74	6.13	5.14
35 – 44	11.75	1.70	13.08	14.95	15.92	17.37	18.60	21.50	15.08
45 – 54	27.15	28.70	30.17	29.03	35.42	36.33	40.31	39.92	32.60
55 – 64	41.51	40.76	38.57	41.28	45.10	43.15	41.86	42.87	41.58
≥ 65	15.53	13.76	17.16	17.11	18.59	14.03	11.78	12.17	15.55
Geographic Region, %									
Midwest	18.31	17.21	17.59	17.97	19.61	18.96	20.01	21.24	18.59
Northeast	16.71	17.95	16.43	17.90	19.69	21.75	21.65	22.96	23.90
South	23.53	22.32	22.65	23.16	26.05	24.33	24.84	25.05	20.12
West	20.16	20.05	20.83	18.14	20.51	20.06	21.08	21.34	18.88
Unknown/Other[a]	20.32	17.58	22.33	19.61	20.13	12.52	32.93	22.60	21.76
Average (all age groups and region), %	**20.3**	**19.6**	**19.9**	**19.8**	**22.1**	**21.9**	**22.6**	**23.0**	**20.9**

[a] represents data with missing geographic information and areas within the U.S. such as Puerto Rico that do not fall into the 4 geographic regions.

[b] number of patients with 30 months of continuous enrollment, i.e. full year enrollment at year of inde4x diagnosis and 18 months prior without evidence of disease in prior months.

[c] Total incidence rates account for the overall rates across all the years

Table 4:

Main Analysis: Risk Analysis Using Multiple Negative Binomial Regression Model

	Incidence/RR	**Low 95%CI**	**High 95%CI**	**p-value**	**Descriptor**
INTERCEPT (age-group, pre-*CCh*, region)	3.4E-06	3.2E-06	3.6E-06	0	Incidence/Rate of having a PD diagnosis in men age 18–34+pre-*CCh*+Midwest Region
Age-group, years					
35–44	2.97	2.80	3.14	<0.001	Incidence/RR of having a PD diagnosis compared to men age 18–24 years
45–54	6.43	6.10	6.78	<0.001	
55–64	8.21	7.77	8.66	<0.001	
≥65	3.12	2.92	3.34	<0.001	
Geographic Region					
Northeast	1.02	0.97	1.07	0.494	Incidence/RR of having a PD diagnosis compared to men living in the Midwest
South	1.30	1..25	1.35	<0.001	
West	1.14	1.09	1.20	<0.001	
Unknown/Other[a]	1.13	1.02	1.25	0.0227	
Introduction of *CCh*					
After FDA approval	1.21	1.17	1.24	<0.001	Incidence/RR of having a PD diagnosis post FDA approval of *CCh* compared to pre-approval

RR, relative risk; FDA, Food and Drug Administration

[a] represents data with missing geographic information and areas within the U.S. such as Puerto Rico that do not fall into the 4 geographic regions.

[c] The FDA approved the use of *CCh* for treating PD in December 2013

Table 5:

Prevalence of Peyronie's Disease by Stratified by Age Group and Geographic Region

	Total	**# of PD diagnosis** [d]	**Prevalence of PD, %**
	181 586 920	132 078	0.073
Age-group			
18 – 34	63 418 711	6517	0.010
35 – 44	37 024 328	11 164	0.030
45 – 54	39 711 434	35 018	0.088
55 – 64	28 463 489	61 610	0.216
≥ 65	12 968 958	17 769	0.137
Geographic Region			
Midwest	40 161 673	26 212	0.065
Northeast	33 717 962	24 136	0.072
South	67 420 493	56 078	0.083
West	33 541 166	22 671	0.068
Unknown	6 745 626	2981	0.044

[d]total number of PD cases yearly, from 2008 to 2017