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Hazard of complex regional pain syndrome following human papillomavirus vaccination among adolescent girls in the United States: a case-cohort analysis of insurance claims data

Nadja A Vielot[1], **Sylvia Becker-Dreps**[1,2]

[1]Department of Family Medicine, School of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

[2]Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

Abstract

Objectives: Complex regional pain syndrome (CRPS) cases have followed human papillomavirus (HPV) vaccination, but no causal link has been established.

Methods: Using insurance claims, the authors observed unvaccinated 11-year-old girls for CRPS diagnoses. The authors used time-dependent Cox regression to identify health-related CRPS predictors using diagnosis codes. Next, the authors identified HPV vaccinations using procedural codes. HPV vaccination and CRPS predictors were considered time-dependent covariates to estimated adjusted hazard ratios (HR) and 95% confidence intervals (CI) for CRPS, 30, 90, and 180 days post-vaccination.

Results: 1,232,572 girls received 563 unique CRPS diagnoses. In a 10% sub-cohort of 123,981 girls accounting for potential confounders and predisposing risk factors (i.e. injury, infection, mental illness, primary care use), CRPS hazard was not significantly elevated 30 days (HR: 0.90, 95% CI: 0.46, 1.73), 90 days (HR: 1.17, 95% CI: 0.83, 1.65), or 180-days post-vaccination (HR: 1.11, 95% CI: 0.83, 1.47).

Conclusion: The results support the safety and continued administration of HPV vaccines to adolescents.

Corresponding author: Nadja A Vielot, Aycock Family Medicine Building, 590 Manning Drive, Chapel Hill, NC 27599, USA, Tel.: +1 (443) 825-5975, nadjavielot@unc.edu.

Author contributions

NA Vielot conceived of the study design, performed all data processing and statistical analyses, and led manuscript preparation. S Becker-Dreps provided subject matter expertise and guidance on study design, and assisted with manuscript preparation. Both authors have reviewed and approved the final manuscript.

Declaration of interests

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Keywords

complex regional pain syndrome; human papillomavirus; girls; vaccination; safety; insurance claims

1. Introduction

In the United States, the Centers for Disease Control and Prevention (CDC) recommends universal human papillomavirus (HPV) vaccination to 11 and 12-year-olds for the prevention of cervical cancer and HPV-associated cancers of other anatomical sites [1]. Pre- and post-licensure studies consistently demonstrate high vaccine efficacy and suggest no association between HPV vaccination and severe adverse events; most reactions are mild, and while syncope is a rare adverse event associated with HPV vaccination, it is not considered severe [1,2]. However, Japanese media reported 50 cases of girls experiencing symptoms of Type I complex regional pain syndrome (CRPS) following HPV vaccination in 2013, and a case report was published in 2014 [3]. No etiological analyses were performed to suggest a link between vaccination and CRPS symptoms in these girls, nor was a biologically-plausible mechanism or risk window between vaccination and CRPS symptoms established; symptoms began over five months following the initiation of HPV vaccination, on average [3]. Furthermore, the various health-related factors that are predictors of CRPS, such as recent physical trauma to the affected limb (e.g. sprains, strains, surgeries), infections, and mental health disorders, were not considered as possible factors in the development of CRPS symptoms [4,5].

Despite these limitations of the research, the Japanese government suspended its recommendation for HPV vaccination in June 2013, and adolescent coverage of HPV vaccination fell from over 80% to less than 5% by the end of 2014 [6]. Similar reactions were observed in Denmark, which saw adolescent HPV vaccine coverage decline by half following an increase in adverse events reporting and anecdotal evidence for adverse events beginning in 2013 [7]. To our knowledge, no population-based studies have assessed the risk of CRPS in adolescent girls, accounting for the complex illness histories that often affect CRPS patients. This data is critical to emphasize the safety profile of HPV vaccination and promote uptake of this potentially life-saving intervention, particularly in the context of widespread anti-vaccination campaigns and resulting vaccine hesitancy.

We present here the results of the first known epidemiological study of the association between HPV vaccination and CRPS incidence in adolescent girls in the United States using insurance claims. We identified diagnoses that were positively associated with CRPS, and then, using a case-cohort design, we estimated the relative 30-day, 90-day, and 180-day hazards of CRPS following HPV vaccination. We conditioned on diagnoses that indicate the presence of comorbidities, and aimed to identify potential risk windows for CRPS onset.

2. Patients and methods

2.1. Data source

The IBM MarketScan® Commercial Database captures patient-level medical claims for over 200 million unique enrollees in the United States since 1995 [8]. The MarketScan database provides patient demographic data; duration of insurance enrollment; claims for medical diagnoses, procedures, and prescriptions using International Classification of Disease – 9th Revision (ICD-9), Current Procedural Terminology (CPT), Healthcare Common Procedure Coding System (HCPCS), and national drug codes (NDC), respectively; and dates of medical services. We obtained monthly enrollment tables for all MarketScan enrollees and all insurance claims made between January 1, 2005 and December 31, 2014 from the Cecil G. Sheps Center for Health Services Research.

2.2. Study population

The study period began June 29, 2006 – the date when the Advisory Committee on Immunization Practices voted in favor of HPV vaccination in girls – and ended December 31, 2014. The full cohort included girls who 1) turned 11 years of age during the study period; 2) had no prior claims for HPV vaccination or CRPS; and 3) had at least one year of continuous insurance plan enrollment prior to the 11th birthday (lookback period). For the case-cohort analysis, we created a sub-cohort based on the full cohort to improve the efficiency of the models for estimating the relative hazard of CRPS. The sub-cohort included all CRPS cases and a random 10% sample of all girls in the cohort at the start of follow-up.

2.3. Exposure, outcome, and covariate ascertainment

The primary outcome was a diagnosis of CRPS, based the ICD-9 codes for reflex sympathetic dystrophy (ICD-9 codes 337.2, 337.2X) and algoneurodystrophy or Sudeck's atrophy (ICD-9 code 733.7). The exposure of interest was a claim for bivalent or quadrivalent HPV vaccination, based on CPT codes 90650 and 90649, respectively. The outcome and exposure were both coded as binary indicator variables for incidence of CRPS and receipt of a dose of HPV vaccine (present=1; absent=0). HPV vaccination was considered a time-dependent exposure in order to establish risk windows for CRPS, as well as to account for multiple doses. To estimate the 30-day risk of CRPS, HPV vaccination status was coded as absent at the start of follow-up; present for the full monthly interval in which the claim was made, and absent in subsequent intervals. To estimate the 90-day and 180-day risk of CRPS, HPV vaccination status was coded as present for the monthly interval in which the claim was made and in the two and five subsequent monthly intervals, respectively [9]. Multiple HPV vaccine doses were coded multiple times following this scheme for each risk window. We conducted a sensitivity analysis to assess the hazard of CRPS at any time following initiation of HPV vaccination, by considering girls exposed in all subsequent monthly intervals following the first claim for HPV vaccination.

Potential confounders included diagnoses that were positively associated with CRPS as identified from a preliminary risk factor assessment, which are also corroborated as CRPS risk factors in the literature. These diagnoses may also be associated with HPV vaccination given their association with receipt of health care, and are thus potential confounders. We

coded these diagnoses as static covariates at baseline and time-dependent covariates during follow-up. Baseline covariate values (present=1; absent=0) were based on the presence of an insurance claim for that diagnosis in the one-year lookback period prior to the start of follow-up. Time-dependent covariate values (present=1; absent=0) were based on the presence of an insurance claim for that diagnosis during follow-up; a covariate was coded as present for the monthly interval in which the claim was made and in all subsequent monthly intervals.

2.4. Statistical analysis

We observed girls from the 11th birthday (start of follow-up) until the date of a claim for a CRPS diagnosis, or until censoring at disenrollment or at the end of the study period. For girls with multiple insurance enrollment periods, we restricted observation to the enrollment period that included the 11th birthday. For the risk factor analysis, time-dependent Cox models estimated unadjusted hazard ratios (HR) and 95% confidence intervals (CI) for the association between each diagnosis and CRPS incidence in the full cohort. We combined similar diagnoses into composite variables, and estimated unadjusted HRs for the new composite variables. We identified the diagnoses most strongly associated with CRPS that were also corroborated as risk factors in the literature [4,10–12], and defined baseline and time-dependent covariates for these diagnoses, as described above, based on inclusive lists of ICD-9, CPT, and prescription drug codes (Appendices 1–4).

To estimate the relative hazard of CRPS following HPV vaccination in the case-cohort sample, we fit time-dependent Cox models to estimate crude and adjusted HRs and 95% CIs for the association of HPV vaccination with incident CRPS. We specified models to estimate the hazard of CRPS for each risk window, and we up-weighted non-cases in the final models by the inverse of the sampling fraction (i.e. 1/0.10=10). Adjusted models conditioned on baseline and time-dependent covariates.

We conducted all analyses in SAS version 9.3 (SAS Institute, Cary, North Carolina, USA). The Institutional Review Board at the University of North Carolina at Chapel Hill approved the analysis of secondary data.

3. Results

The full cohort included 1,232,572 girls and the 10% sub-cohort included 123,418 girls. The median duration of follow-up in the sub-cohort was 1.7 years (interquartile range: 0.8–3.3 years), and nearly one-quarter of participants received at least one dose of HPV vaccine during follow-up. We identified 563 CRPS cases for an incidence rate of 20/100,000 person-years (Table 1). The case-cohort sample size including the 10% sub-cohort and all cases was 123,981.

The diagnoses positively associated with incident CRPS in the full cohort are shown in the Figure. Injury to a lower limb was the strongest predictor of CRPS (HR: 12.4, 95% CI: 10.4, 14.7). Injuries to other body parts, accidents, and operations and procedures were also strongly associated with CRPS (Figure). We also identified psychological disorders, infections, and use of primary care as risk factors for CRPS diagnosis that have also been

identified in the scientific literature. We defined baseline and time-dependent covariates for an experience of trauma, mental illness, infection, and use of primary care (Appendix 1–4). Respiratory and gastrointestinal diagnoses were likely to be subsumed under infections, and we did not include these as independent covariates. As pain is a prerequisite for a CRPS diagnosis, we did not include pain as an independent covariate.

The 30-day adjusted relative hazard of CRPS following HPV vaccination was 0.90 (95% CI: 0.43, 1.73), the 90-day adjusted relative hazard was 1.17 (0.83, 1.65), and the 180-day adjusted relative hazard was 1.11 (95% CI: 0.83, 1.47) (Table 2). In the sensitivity analysis including the unlimited risk window, the adjusted relative hazard suggested a 24% reduced hazard of CRPS at any time following HPV vaccination (HR: 0.76, 95% CI: 0.62, 0.94).

4. Discussion

To our knowledge, this is the first population-based, epidemiological study to estimate the association between HPV vaccination and CRPS in adolescents in the United States. The hazard of CRPS was not significantly elevated in the days following HPV vaccination, irrespective of the number of doses received and the length of time elapsed since vaccination, and we identified a large number of health-related predictors of CRPS among adolescent girls. Our results are consistent with those summarized by the European Medicines Agency and World Health Organization, including evidence from clinical trials and post-licensure surveillance, that HPV vaccination does not increase the risk of CRPS in adolescents [2,13]. Comorbidities and health care use may be associated with both CRPS diagnosis and receipt of HPV vaccination, inducing time-dependent confounding in etiological studies of CRPS. Our study emphasizes the need to condition on underlying health conditions in studies of CRPS risk, and particularly known risk factors for CRPS.

While case reports have described pediatric CRPS cases following vaccination [14–19], future research and clinical management of patients should consider patient medical history to identify possible alternative causes of CRPS cases that arise post-vaccination. Proposed mechanisms for CRPS include the activation of immune pathways that cause the pain, heat, redness, and swelling that is common in acute CRPS. Injuries can lead to excessive cytokine production in individuals with autoinflammatory disorders [20], and antibodies produced in response to infectious agents can stimulate autoantibodies against nervous system tissues in individuals with autoimmune disorders [20,21]. Use of primary care, including phone or email consultations with providers and requests for laboratory analyses, was elevated in a sample of Danish women seeking care for adverse events following HPV vaccination, suggesting a role for underlying or prior diseases in CRPS incidence [10]. The role of mental illness in CRPS is controversial, due in part to lack of studies measuring the presence of mental illness prior to CRPS onset [22]. However, mood disorders and stressful life events have been reported among CRPS cases [22,23], including in over one-third of our sample (data not shown). Current recommendations for CRPS treatment, including physical therapy and psychotherapy, have led to long-term resolution of symptoms in most pediatric CRPS cases [4,5,24].

Because CRPS diagnosis is clinical, the inability to validate ICD-9 codes as proxies for CRPS is a limitation of our study. Diagnosis codes for the signs and symptoms required to make a CRPS diagnosis are typically not available from outpatient insurance claims, and specific codes do not exist for all signs and symptoms implicated in CRPS diagnosis (e.g. coolness in the affected limb). The presence of an ICD-9 code for CRPS may simply reflect a provisional diagnosis, and thus it is possible that our CRPS incidence is over-estimated. Two studies, in which CRPS cases identified from healthcare databases were validated using information found in medical records and expert review, found that 43–65% of insurance claims for CRPS did not fulfill the diagnostic criteria outlined by the International Association for the Study of Pain [25,26]. Both studies included a wide array of diagnoses that were compatible with CRPS, as well as cases referred for CRPS diagnosis [25] and patients prescribed medications used exclusively for CRPS treatment [26]. The high sensitivity but potentially low specificity of these case definitions may have led to an overestimation of CRPS cases. It is also possible that CRPS incidence can be underestimated if patients do not receive a timely or accurate diagnosis from a specialist trained in pediatric CRPS diagnosis. Our study mitigated this limitation by including risk windows well beyond what is considered biologically plausible by experts, including an unlimited risk window following HPV vaccination. We were also unable to determine if trauma occurred in the same limb(s) affected by CRPS, due to missing data on which limb was affected by CRPS symptoms. Future research should conduct expert medical record reviews of CRPS cases to assist in describing the pathophysiology of the disease and to assess the frequency of pre-existing comorbidities in CRPS cases. To this end, the quality of medical records must be improved to provide evidence of signs and symptoms used in CRPS diagnosis; a preliminary review of the medical records of CRPS cases diagnoses in a large university-wide health system found inconsistent and inadequate reporting of the diagnostic criteria (data not shown).

The primary strength of this study is the ability to identify many cases of a rare disease using a large nation-wide insurance claims database. Time-to-event models estimated relative CRPS hazards within pre-specified windows following vaccination, indicating that CRPS risk is not elevated within the first six months following a vaccination event and undermining the biological plausibility of vaccine-induced CRPS. Finally, ours is the first epidemiological study to condition on comorbidities that were present prior to CRPS diagnosis when assessing the association of HPV vaccination with CRPS.

5. Conclusions

Our results support continued administration of HPV vaccines in the United States, following CDC recommendations for injection procedures, managing local reactions, syncope, and anaphylaxis, and reporting adverse events to the CDC’s vaccine safety surveillance system.

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Appendix

Appendix 1.

Diagnoses and procedures that define the presence of physical trauma

Diagnosis	Description	ICD-9 Codes
Fracture	Pelvis	808, 808.x, 808.xx
	Trunk	809, 809.x
	Upper body: Trunk, shoulder, arm, wrist, hand, finger	810.x–819.x
	Lower body: Thigh, leg, knee, ankle, toe	820.x–828x
	Unspecified bones	829, 829.x
Dislocation	Upper body: Shoulder, elbow, wrist, finger	831.x–834.x
	Lower body: Hip, knee, ankle, foot	835.x–838.x
	Other, multiple dislocations	839, 839.x, 839.xx
Sprain, strain	Upper body: Shoulder, arm, elbow, wrist, hand	840.x–842.x
	Lower body: hip, thigh, leg, knee, ankle, foot	843.x–846.x
	Other, unspecified parts of back	847, 847.x
	Other ill-defined	848, 848.x
Road vehicle accidents	Traffic accident	E81, E81.x, E81.xx
	Non-traffic accident	E82, E82.x, E82.xx
Procedure	**Description**	**CPT/HCPCS Codes**
Surgeries, treatment of fractures and dislocations	Upper body: Shoulder, elbow, arm, wrist, hand, finger	23000–26989
	Lower body: Pelvis, thigh, leg, knee, ankle, foot, toe	26990–28899
	Extracranial nerves, peripheral nerves, autonomic nervous system	64400–64999
Casting, splinting, strapping	Upper body: Body, shoulder, arm, wrist, hand, finger	29000–29280
	Lower body: Hip, leg, knee, foot	29305–29590
	Cast: Removal, revision	29700–29799
Medical equipment	Immobilization devices	L21x–L39x, L43x, L46x
	Canes, crutches, walker, wheelchair, gait trainer	E0100–E0149, E0950–E1298, E2201–E2633, K0001–K0902
	Cast, splint supplies	Q4001–Q4051

Appendix

Appendix 2.

Diagnoses, procedures, and prescription drugs that define the presence of mental illness

Diagnosis	**ICD-9 Codes**
Transient mental disorders	293, 293.x, 293.xx
Schizophrenic disorders	295, 295.x, 295.xx
Episodic mood disorders	296, 296.x, 296.xx
Delusional disorders	297, 297.x
Non-organic psychoses	298, 298.x
Anxiety, dissociative, and somatoform disorders	300, 300.x, 300.xx,
Personality disorders	301, 301.x, 301.xx
Physiological malfunction arising from mental factors	306, 306.x, 306.xx
Special syndromes or symptoms, not elsewhere classified (including sleep disorders, eating disorders, pain disorders)	307, 307.x, 307.xx
Acute reactions to stress	308, 308.x,
Adjustment disorders	309, 309.x, 309.xx
Non-psychotic mental disorders	310, 310.x, 310.xx
Depressive disorder, not elsewhere classified	311
Conduct disorders	312, 312.x, 312.xx
Emotional disturbance	313, 313.x, 313.xx
Hyperkinetic disorders	314, 314.x, 314.xx
Procedure	**CPT Codes**
Psychotherapy, psychiatric diagnostic examination	908xx, G007x, G008x, G0090-G0094, 4060f, 4062f, G0410, G0411
Prescription	**Generic Drug Name**
Anti-anxiety drugs	Alprazolam, buspirone, hydroxizine, lorazepam
Antidepressant drugs	Amitriptyline, bupropion, citalopram, clomipramine, desipramine, doxepin, duloxetine, escitalopram, fluoxetine, imipramine, mirtazapine, nortriptyline, paroxetine, phenelzine, sertraline, tranylcypromine, trazodone, venlafaxine
Antipsychotic drugs	Aripiprazole, chlorpromazine, clozapine, fluphenazine, haloperidol, lithium, olanzapine, paliperiodone, perphenazine, prochlorperazine, quetiapine, risperidone, thiothixine, trifluoperazine, ziprasidone
Sleep aids	Chloral hydrate, estazolam, eszopiclone, ramelteon, temazepam, zaleplon, zolpidem,
Hyperactivity, narcolepsy drugs	Amphetamine salt combination, atomoxetine, dexmethylphenidate, dextroamphetamine, lisdexamfetamine, methylphenidate, modafinil

Appendix

Appendix 3.

Diagnoses and prescription drugs that define the presence of infections

Diagnosis	**ICD-9 Codes**
Intestinal infectious diseases	001.xx–009.xx
Tuberculosis	010.xx–018.xx

Diagnosis	ICD-9 Codes
Zoonotic bacterial diseases	020.xx–027.xx
Other bacterial diseases	030.xx–041.xx
Human immunodeficiency virus (HIV)	042.xx–044.xx
Poliomyelitis and other non-arthropod-borne viral diseases of central nervous system	045.xx–049.xx
Viral diseases accompanied by exanthem	050.xx–059.xx
Arthropod-borne viral diseases	060.xx–066.xx
Other diseases due to viruses and chlamydiae	070.xx–079.xx
Rickettsioses and other arthropod-borne diseases	080.xx–088.xx
Syphilis and other venereal diseases	090.xx–099.xx
Other spirochetal diseases	100.xx–104.xx
Mycoses	110.xx–118.xx
Helminthiases	120.xx–129.xx
Other infectious and parasitic diseases	130.xx–136.xx
Late effects of infectious and parasitic diseases	137.xx–139.xx
Antibiotic Drug Class	
Aminoglycosides	
Antifungals	
Cephalosporins	
Beta-lactam antibiotics	
Chloramphenicols	
Erythromycin & Macrolides	
Penicillins	
Tetracyclines	

Appendix

Appendix 4.

Diagnoses and procedures that define the use of primary care

Diagnosis	ICD-9 Code
Health supervision of infant or child	V20
General medical examination	V70
Procedure	**CPT Code**
Initial comprehensive preventive medicine visit, 5–11yo	99383
Initial comprehensive preventive medicine visit, 12–17yo	99384
Initial comprehensive preventive medicine visit, 18–39yo	99385
Preventive medicine visit, established patient 5–11yo	99393
Preventive medicine visit, established patient 12–17yo	99394
Preventive medicine visit, established patient 18–39yo	99395

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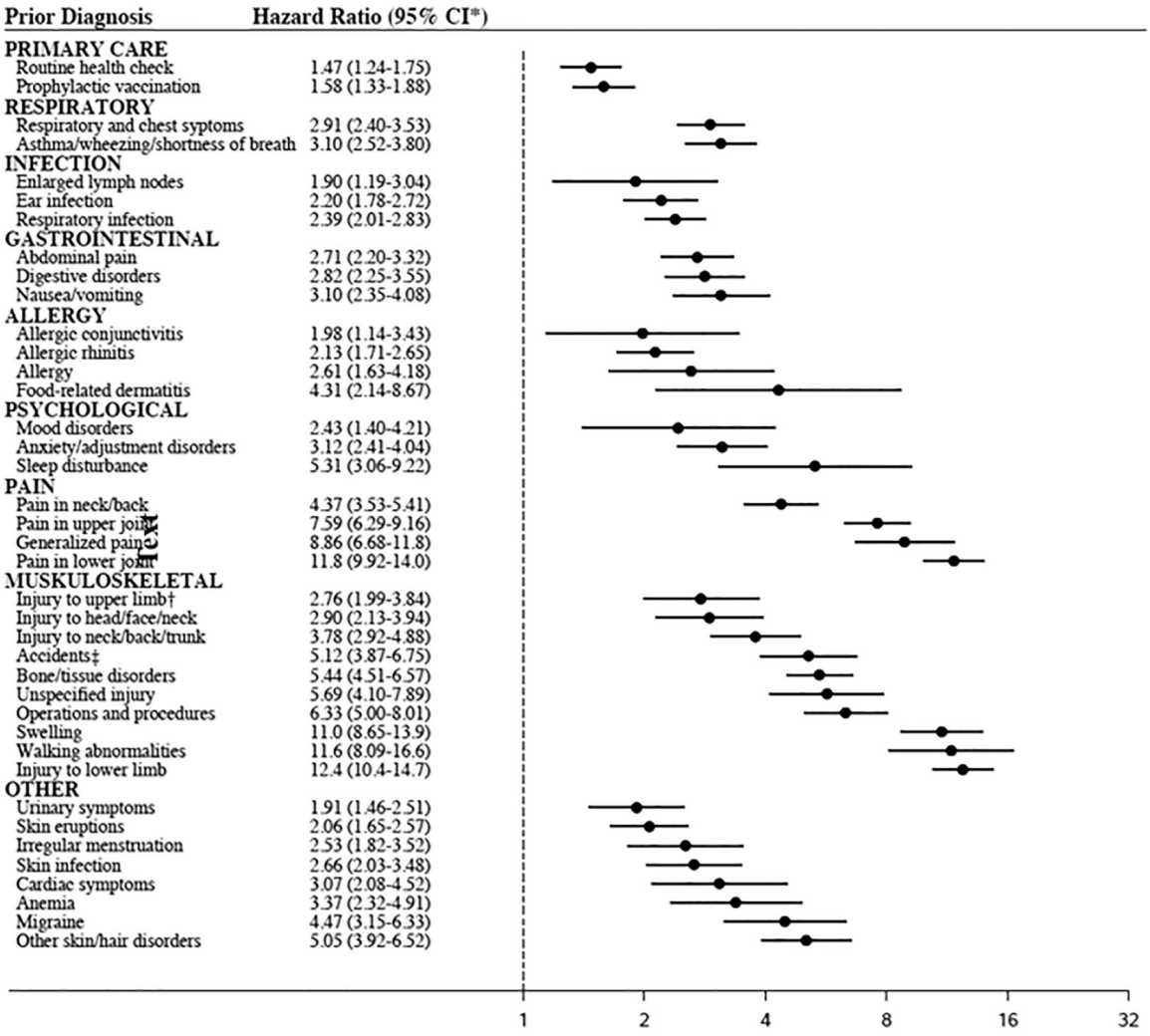

Figure.

Relative hazard of CRPS following common diagnoses in adolescent girls, 2006–2014 (n=1,232,572). The forest plot shows the hazard ratios and 95% confidence intervals for a diagnosis of complex regional pain syndrome (CRPS) following the most common diagnoses that were observed in the full cohort of adolescent girls.

Table 1.

Incidence of HPV vaccination and complex regional pain syndrome among adolescent girls, 2006–2014 (N=123,981)

Median duration of follow-up (IQR), years	1.7 (0.8, 3.3)
Receipt of HPV vaccination during follow-up	n (%)
None	47,558 (76.5)
One dose	4,351 (7.0)
More than one dose	10,256 (16.5)
Number of CRPS events *	563
Incidence rate (95% CI) of CRPS per 100,000 person-years	20.0 (18.4, 21.7)

Abbreviations: IQR=interquartile range; CRPS=complex regional pain syndrome; CI=confidence interval

*CRPS cases include diagnoses of reflex sympathetic dystrophy and algoneurodystrophy.

Table 2.

Relative hazard of CRPS in the 30 and 90 days following HPV vaccination (N=123,981)

	30-day relative hazard of CRPS	
	Crude HR (95% CI)	Adjusted HR * (95% CI)
HPV vaccination		
No	1.0 (ref)	1.0 (ref)
Yes	0.93 (0.48, 1.80)	0.90 (0.46, 1.73)
	90-day relative hazard of CRPS	
	Crude HR (95% CI)	Adjusted HR * (95% CI)
HPV vaccination		
No	1.0 (ref)	1.0 (ref)
Yes	1.27 (0.90, 1.79)	1.17 (0.83, 1.65)
	180-day relative hazard of CRPS	
	Crude HR (95% CI)	Adjusted HR * (95% CI)
HPV vaccination		
No	1.0 (ref)	1.0 (ref)
Yes	1.25 (0.94, 1.66)	1.11 (0.83, 1.47)
	Relative hazard of CRPS at any time following vaccination	
	Crude HR (95% CI)	Adjusted HR * (95% CI)
HPV vaccination		
No	1.0 (ref)	1.0 (ref)
Yes	1.22 (1.00, 1.49)	0.76 (0.62, 0.94)

Abbreviations: HPV = human papillomavirus; CRPS = complex regional pain syndrome; HR=hazard ratio; CI=confidence interval

* HR adjusted for baseline and follow-up covariates for physical trauma, infection, mental illness, and use of primary care.