

# Association between human papillomavirus vaccines and serious adverse events in adolescent girls: A nationwide large-scale cohort study and self-controlled risk interval analysis

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## Backgrounds

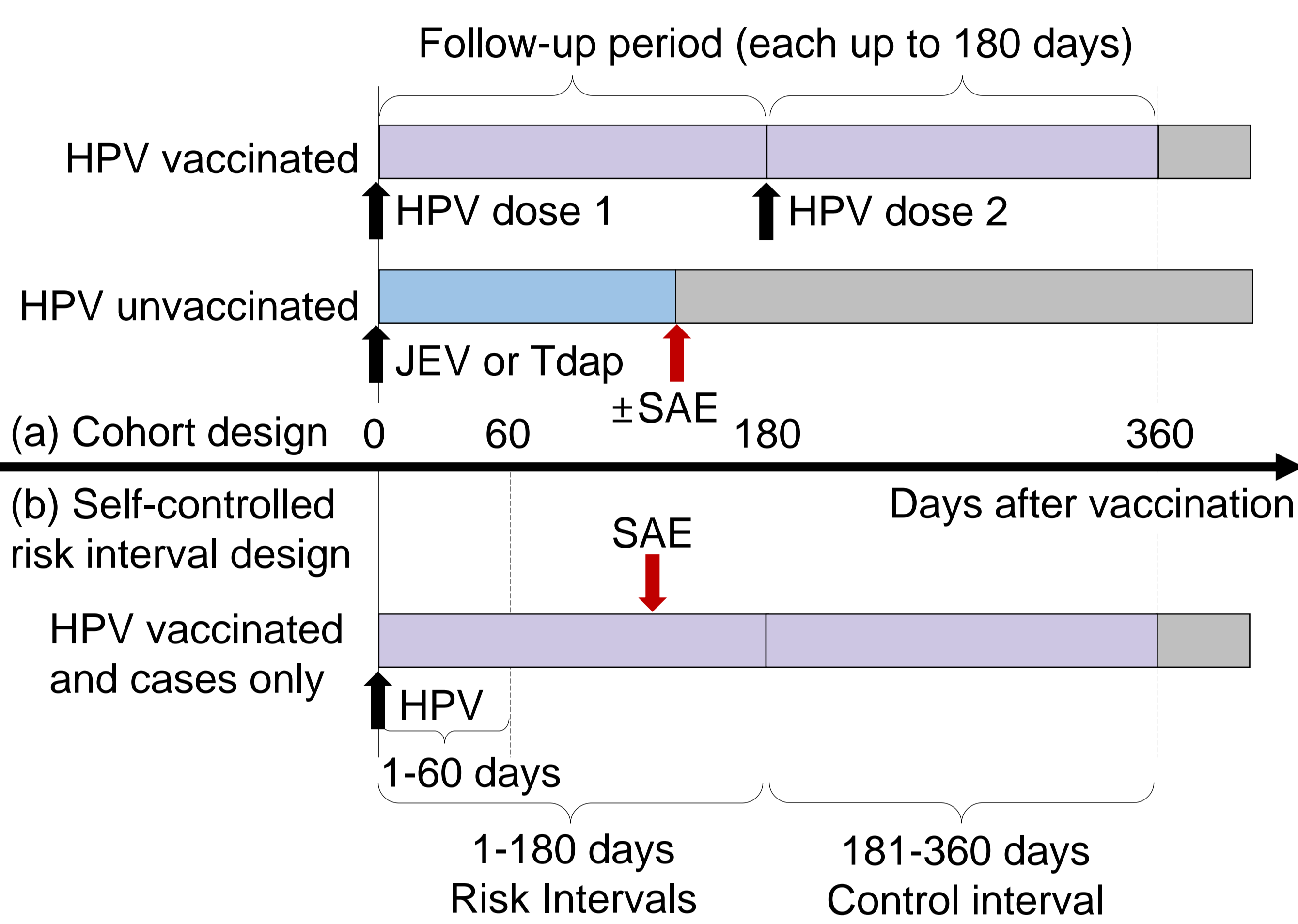
- Most suspected serious adverse events (SAEs) of human papillomavirus (HPV) vaccines, which have been of concern and a barrier to HPV vaccination, were neurological and autoimmune diseases.
- Prior studies presented the risk of various autoimmune-related SAEs after HPV vaccination, which remains controversial.

## Objectives

- To evaluate the association between human papillomavirus (HPV) vaccination and serious adverse events (SAEs) in female adolescents in South Korea.

## Methods

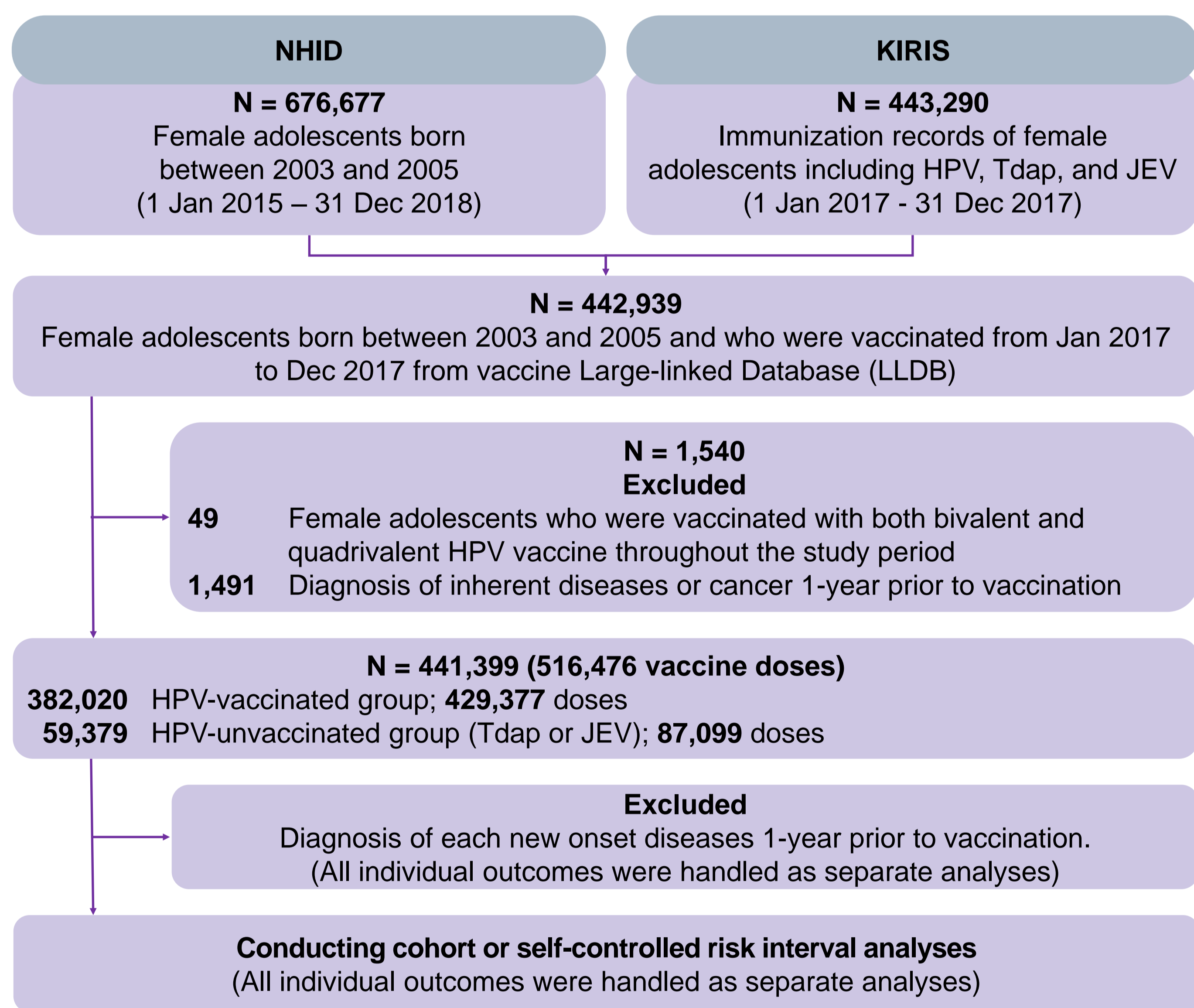
### 1 Overview of the cohort (a) and SCRI (b) study designs.



- **Data source:** A large-linked database (LLDB) created by linking the Korea Immunization Registry Information System (KIRIS) and the National Health Insurance Database (NHID).
- **Study design:** A cohort and self-controlled risk interval (SCRI) analyses were conducted with a 180-day risk period for each individual outcome.
- **Study population:** Female adolescents born between 2003 and 2005 and who were vaccinated with HPV, JEV (Japanese encephalitis vaccine), or Tdap (Tetanus-diphtheria-acellular pertussis).
- **Vaccination:** HPV vaccine. JEV or Tdap was selected as comparator vaccine.
- **Main outcome measure:** 33 SAEs including endocrinal, gastrointestinal, cardiovascular, neurological, autoimmune-related disorders.
- **Statistical analysis:** (a) **Cohort design:** Incidence rate ratios were estimated using Poisson regression. (b) **SCRI design:** Relative risks were estimated using conditional logistic regression.

## Results

### 2 Flow chart of enrollment in the large-linked databases by linking the Korea Immunization Registry Information System with the National Health Information Database between January and December 2017.



### 3 Association between HPV vaccination and SAEs in both the cohort and SCRI analyses among female adolescents born in 2003–2005 and vaccinated in 2017.

	Cohort Adjusted Rate Ratio (95% CI)	SCRI Adjusted Relative Risk (95% CI)
<b>Endocrinal</b>		
Graves' disease	0.58(0.27-1.22)	0.63(0.44-0.91)
Hashimoto's thyroiditis	1.18(0.64-2.19)	0.87(0.65-1.15)
Hyperthyroidism	1.04(0.68-1.58)	0.80(0.66-0.96)
Hypothyroidism	1.21(0.91-1.61)	0.77(0.69-0.87)
<b>Gastrointestinal</b>		
Crohn's disease	0.61(0.22-1.70)	0.92(0.57-1.48)
Ulcerative colitis	0.80(0.16-4.04)	0.58(0.25-1.36)
Peptic ulcer diseases	1.11(0.99-1.24)	0.94(0.89-0.99)
Pancreatitis	0.92(0.68-1.24)	0.80(0.69-0.91)
<b>Cardiovascular</b>		
Venous thromboembolism	0.59(0.15-2.38)	0.73(0.34-1.60)
Vasculitis	0.80(0.40-1.60)	0.86(0.61-1.21)
Hypotension	1.19(0.81-1.75)	0.73(0.63-0.85)
<b>Musculoskeletal</b>		
Bechet's syndrome	0.74(0.15-3.66)	1.18(0.54-2.57)
Juvenile arthritis	1.86(0.64-5.38)	1.43(0.89-2.30)
Rheumatoid arthritis	0.94(0.66-1.33)	0.77(0.66-0.90)
<b>Neurological</b>		
Bell's palsy	0.48(0.24-0.97)	0.84(0.51-1.36)
Epilepsy	1.14(0.79-1.65)	0.90(0.76-1.06)
Narcolepsy	0.21(0.04-1.01)	0.28(0.12-0.65)
Paralysis	0.56(0.14-2.29)	1.60(0.55-4.62)
Migraine	1.19(1.03-1.37)	0.85(0.80-0.90)
Guillain-Barré syndrome	0.03(0.00-0.35)	0.67(0.11-3.99)
Optical neuritis	0.98(0.42-2.31)	0.98(0.64-1.50)
Neuralgia and neuritis	1.04(0.67-1.62)	0.89(0.73-1.09)

- There was no significant increase in the risk of Hashimoto's thyroiditis (rate ratio 1.18, 95% CI: 0.64 to 2.19), which had previously been shown an increased risk in the meta-analysis.
- While the risk associated with migraine was significantly increased in cohort analysis (rate ratio 1.19, 95% CI: 1.03-1.37), the result of the SCRI analysis (relative risk 0.85, 95% CI: 0.80-0.90) presented no evidence with adjusting potential confounders.

## Conclusions

- Of the 33 SAEs, none showed a significant increase in risk in both cohort and SCRI analyses, indicating that the association between SAEs and HPV vaccination was weak.



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