

Letters

RESEARCH LETTER

Cardiovascular Events in Women With Prior Cervical High-Grade Squamous Intraepithelial Lesion

Cancer and cardiovascular disease (CVD) are deeply interconnected.¹ In recent decades, several cohorts of adolescents and young adults (AYAs) with cancer have been established to investigate CVD,² but young women with cervical high-grade squamous intraepithelial lesion (HSIL) have rarely been



[Supplemental content](#)

included. HSILs are associated with human papillomavirus (HPV) infection³ and may contribute to atherosclerosis through systemic inflammation; proinflammatory cytokines upregulation; and promotion of endothelial dysfunction, arterial stiffness, and dysregulated lipid metabolism.⁴ We aimed to investigate cardiovascular risk and adverse outcomes among AYAs with prior cervical HSIL compared with matched controls (without cervical HSIL).

Methods | We used the Rebut study database, including all patients younger than 25 years recorded in the Swedish National Cancer Register (1958-2021), along with matched

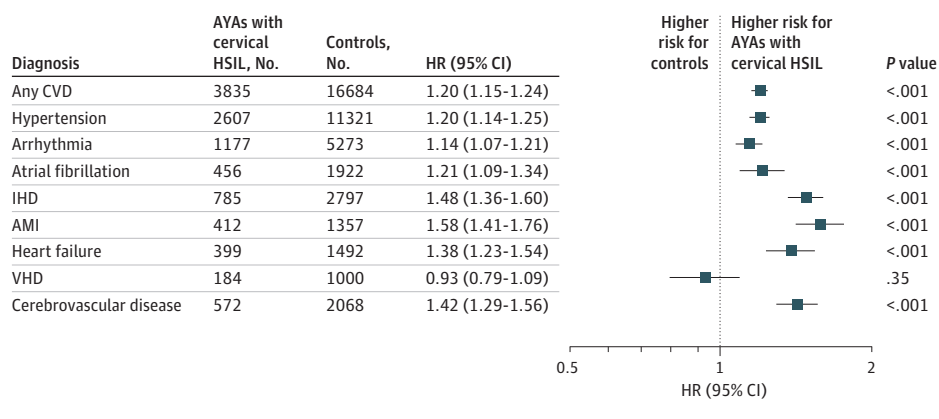
Table. Cardiovascular Risk Factors and Morbidity in AYAs With Prior Cervical HSIL and Matched Controls

Factor	Sample, No. (%)		P value
	AYAs with prior cervical HSIL (n = 29 960)	Controls (n = 149 606)	
Decade at index			
1958-1970	1351 (4.5)	6698 (4.5)	NA
1971-1980	5063 (16.9)	25 259 (16.9)	NA
1981-1990	4803 (16.0)	23 984 (16.0)	NA
1991-2000	3245 (10.8)	16 210 (10.8)	NA
2001-2010	3960 (13.2)	19 790 (13.2)	NA
2011-2021	11 538 (38.5)	57 665 (38.5)	NA
Cardiovascular risk factors			
Diabetes	934 (3.1)	4367 (2.9)	.06
CKD	146 (0.5)	680 (0.5)	.45
COPD	784 (2.6)	1684 (1.1)	<.001
Ever smoker	1436 (4.8)	4758 (3.2)	<.001
Missing data, No.	28 059	140 851	
Any CVD in mother ^a	12 223 (40.8)	58 989 (39.4)	<.001
Any CVD in father	14 207 (47.4)	69 283 (46.3)	<.001
CVD			
Any CVD ^a	3835 (12.8)	16 684 (11.2)	<.001
Time to CVD, median (IQR), y	33.3 (25.0-40.2)	33.1 (24.3-40.5)	.51
Age at any CVD, median (IQR), y	55.3 (47.1-62.3)	55.1 (46.4-62.5)	.67
Hypertension	2607 (8.7)	11 321 (7.6)	<.001
Age at hypertension, median (IQR), y	57.8 (51.2-64.0)	57.6 (50.2-63.9)	.07
Arrhythmias	1177 (3.9)	5273 (3.5)	.001
Age at arrhythmia, median (IQR), y	54.9 (41.8-63.4)	54.8 (41.8-63.5)	.99
Atrial fibrillation	456 (1.5)	1922 (1.3)	.001
Age at atrial fibrillation, median (IQR), y	61.2 (54.6-67.1)	62.2 (54.5-67.9)	.44
IHD	785 (2.6)	2797 (1.9)	<.001
Age at IHD, median (IQR), y	57.5 (50.5-63.9)	57.7 (51.0-64.7)	.22
MI	412 (1.4)	1357 (0.9)	<.001
Age at MI, median (IQR), y	58.7 (51.5-64.9)	58.1 (51.4-66.0)	.68
Heart failure	399 (1.3)	1492 (1.0)	<.001
Age at heart failure, median (IQR), y	60.9 (52.3-68.3)	60.8 (51.9-67.6)	.32
VHD	184 (0.6)	1000 (0.7)	.31
Age at VHD, median (IQR), y	61.1 (52.3-67.6)	58.9 (45.4-65.8)	.01
Cerebrovascular disease	572 (1.9)	2068 (1.4)	<.001
Age at cerebrovascular disease, median (IQR), y	58.0 (50.0-65.0)	58.7 (50.2-65.5)	.37

Abbreviations: AYA, adolescent and young adult; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; HSIL, high-grade squamous intraepithelial lesion; IHD, ischemic heart disease; MI, myocardial infarction; NA, not applicable; VHD, valvular heart disease.

^a Any CVD includes hypertension (*International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* [ICD-10] codes I10-I15), IHD (ICD-10 codes I20-I25), arrhythmia (ICD-10 codes I44-I49), heart failure and cardiomyopathy (ICD-10 codes I50 and I42), VHD (ICD-10 codes I34-I37), and cerebrovascular disease (ICD-10 codes I63, I64, and G45).

Figure. Forest Plot Comparing Risk of Cardiovascular Disease (CVD)



The hazard ratio (HR) plot shows 95% CIs on a logarithmic scale, comparing the risk of CVD between 29 960 adolescents and young adults (AYAs) with prior cervical high-grade squamous intraepithelial lesions (HSIL) and 149 606 matched controls in Sweden between 1958 and 2021. AMI indicates acute myocardial infarction; IHD, ischemic heart disease; VHD, valvular heart disease.

controls. The Swedish Ethics Review Authority approved the study and waived the informed consent requirement in accordance with Swedish legislation on data in national registries. We followed the [STROBE](#) reporting guideline.

We identified females aged 15 to 24 years with cervical HSIL (moderate or severe dysplasia and carcinoma in situ, corresponding to cervical intraepithelial neoplasia grade 2-3) and compared them with controls matched 1:5 by sex, age, and residence. Data were linked across multiple national population and high-quality health care registers: National Board of Health and Welfare Cancer Register (diagnosis and index time), Statistics Sweden, National Patient Register, SWEDHEART Registry, Swedish National Diabetes Register, and National Cause of Death Register.

Baseline characteristics were summarized descriptively. Cox proportional hazards regression models stratified on matched sets were used to estimate hazard ratios (HRs). Two-sided $P < .05$ indicated statistical significance. Data analysis was performed from June to August 2025 using R 4.3.2 (R Project for Statistical Computing).

Results | We included 29 960 female AYAs (median [IQR] age, 23 [22-24] years) with prior cervical HSIL and 149 606 matched controls. Cardiovascular risk factors and CVD are listed in the [Table](#). These AYAs had a higher risk of CVD (HR, 1.20; 95% CI, 1.15-1.24), with particularly elevated risks for myocardial infarction (MI; HR, 1.58; 95% CI, 1.41-1.76), heart failure (HR, 1.38; 95% CI, 1.23-1.54), and cerebrovascular disease (HR, 1.42; 95% CI, 1.29-1.56) (all $P < .001$) ([Figure](#)). Family history increased risk if the mother (HR, 1.11; 95% CI, 1.06-1.17; $P < .001$) and/or father (HR, 1.08; 95% CI, 1.03-1.14; $P < .001$) had any CVD diagnosis.

During follow-up, 3.1% of AYAs with prior cervical HSIL and 2.1% of controls died ($P < .001$). All-cause (HR, 1.52; 95% CI, 1.42-1.64; $P < .001$) and cardiovascular mortality (HR, 1.49; 95% CI, 1.29-1.71; $P < .001$) were higher among these AYAs. MI and sudden cardiac death were the leading causes of death, followed by acute respiratory distress and strangulation.

Cancer-specific mortality was infrequent but higher in AYAs with prior cervical HSIL than controls (HR, 2.24; 95% CI, 1.54-3.27; $P < .001$). The most common incident cancers after

5 years were skin, breast, and lung cancer, but gastrointestinal malignant neoplasms were the predominant cause of cancer-related deaths in both groups.

Discussion | This nationwide study demonstrated that AYAs with prior cervical HSIL faced increased CVD risk and mortality compared with matched controls. Young women with HPV infection often exhibit lifestyle and health factors (eg, smoking, obesity) associated with increased risk of CVD and mortality.⁵ We found that family history of CVD was more frequent among AYAs with prior cervical HSIL and a risk factor. MI was particularly prevalent and associated with mortality. These findings may be consistent with proposed mechanisms in which HPV is hypothesized to affect vascular inflammation and atherosclerosis.^{4,6}

Study limitations include that, given greater health care contact among women with HSIL, some degree of surveillance bias cannot be excluded. HPV-associated HSIL diagnostic era includes only a brief period for observing long-term CVD outcomes. Registry-based designs are inherently susceptible to selection, confounding, measurement, and reporting biases.

These findings warrant further research. Meanwhile, they support heightened clinical awareness regarding cardiovascular risk evaluation and prevention in women with prior HSIL.

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Author Contributions: Drs Hubbert and Singull had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition, analysis, or interpretation of data: Rodriguez-Wallberg, Holmberg, Keskisärkkä, Singull, Hubbert.

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Administrative, technical, or material support: Keskisärkkä, Singull, Hubbert.

Supervision: Rodriguez-Wallberg, Hedayati, Singull, Hubbert.

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Data Sharing Statement: See the [Supplement](#).

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