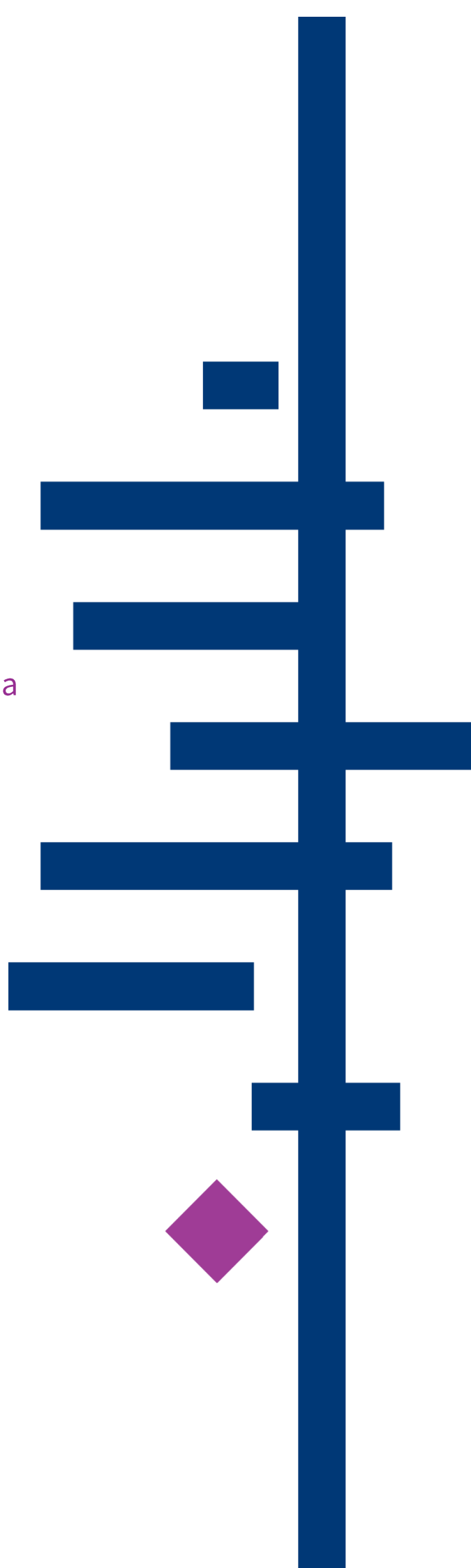


Anogenital warts: Incidence, prevalence, self-reported history & quality of life

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Executive Summary

Introduction

This systematic review aimed to update and expand upon a previously published review. The previous review included studies that reported incidence, prevalence and self-reported history of anogenital warts (AGW) in the general adult population, published from January 2001 to January 2012. Abstracts from relevant conferences 2009-2011 were also included. Studies were excluded if the adult population considered did not include at least ages 20 through to 40 years of age or if they focused on immuno-compromised or high-risk populations or children less than 15 years of age.

Objectives

The current review extended the search for publications from January 2012 to June 2016. Data were extracted and combined with those reported in the previous review. Inclusion criteria for this search were widened: studies were included whether or not they included ages 20-40 and HIV+ men and women were included as a special interest population.

In addition, the current review considered health-related quality of life (HRQoL) amongst people with AGW. Studies were included that compared HRQoL, health status and health utilities amongst people with AGW and amongst people with other HPV-related diseases, healthy controls or population norms measured by validated, standardised instruments, and published between 1998 and September 2016.

The risk of bias was assessed for all studies included in both the previous review and the current review.

Results

44 studies were identified in the search for studies reporting incidence, prevalence and self-reported history and added to the 37 reported in the previous review.

Incidence

The update search identified 14 studies reporting incidence of AGW. Data from these were combined with data from the 19 studies in the previous review. The risk of bias in included studies was judged overall to be low for the majority of studies and dimensions.

For HIV negative adult men, as defined in the previous review (including at least 20-40 years of age) incidence of “new” or incident AGW ranged from 77/100,000 to 453/100,000, higher than the previous review. For men of all ages, incidence ranged from 77/100,000 to 560/100,000. For younger men (≤ 30) incidence was higher, ranging from 130/100,000 to 560/100,000.

For HIV negative adult women as defined in the previous review incidence of new AGW ranged from 76/100,000 to 430/100,000, similar to the previous review. For women of all ages, incidence ranged from 76/100,000 to 1,030/100,000. For younger women (≤ 30) incidence was higher, ranging from 320/100,000 to 1,030/100,000.

For HIV negative adult men and women combined as defined in the previous review, incidence of new AGW ranged from 85/100,000 to 205/100,000, similar to the previous review. Incidence ranged from 85/100,000 to 790/100,000 in all ages, and from 230/100,000 to 790/100,000 in younger people.

No new studies were identified that reported incidence of recurrent AGW. Incidence ranged from 47/100,000 to 163/100,000 in adult men, from 23/100,000 to 110/100,000 in adult women, and 43/100,000 to 133/100,000 in adult men and women combined.

Incidence of any AGW ranged from 37/100,000 to 331/100,000 in adult men, from 40/100,000 to 251/100,000 in adult women, and 160/100,000 to 289/100,000 in adult men and women combined, similar to the previous review.

Incidence estimates for new AGW in adult women and any AGW in adult men, women and men and women combined were lower when studies were excluded that included data from settings where AGW detection is more likely (e.g. settings where genital examinations are routine) and settings where AGW prevalence may be expected to be higher (eg. sexually transmitted infection clinics).

Only one study was identified that reported an estimate of incidence in HIV+ individuals. Based upon data from a Taiwanese national health insurance database, incidence of new AGW in men and women combined was 1,389/100,000.

Prevalence

The update search identified 13 studies reporting prevalence of AGW. Data from these were combined with data from the 14 studies in the previous review. The risk of bias in prevalence studies was judged to be high for some dimensions in most studies. The most common risks of bias related to case definition, the validity of outcome measurement, and the representativeness of populations and sampling frames.

Prevalence estimates ranged from 0.014% to 13.7% in men, 0.023% to 10% in women, and from 0.019% to 17% in men and women combined when all settings were considered. These estimates are higher in range than in the previous review. Estimates were reduced when high-detection and high-prevalence settings were omitted: from 0.014% to 1.3% in men, 0.023% to 0.9 % in women, and from 0.019% to 1.1% in men and women combined

Amongst HIV positive populations, prevalence estimates range from 7.3% to 31% for men, 2.8% to 3.7% for women, and 1.6% to 17% for men and women combined. For estimates including men, most data came from high-detection and high-prevalence settings or populations.

Health-related quality of life

Sixteen reports from 14 studies were identified that compared HRQoL, health status and health utilities amongst people with AGW and amongst people with other HPV-related diseases, healthy controls or population norms. The identified studies suggest that AGW have a significant impact on overall health related quality of life, in particular in terms of anxiety and depression.

Only one study was found that compared health status in people with AGW and people with both malignant and non-malignant HPV-related disease. Malignant disease (cervical and anal cancer and head and neck squamous cell carcinoma) was associated with the most marked reduction in health

status. Health utility values for AGW were better than malignant disease, but worse than atypical squamous cells of undetermined significance (ASC-US) and cervical intraepithelial neoplasia (CIN). Mean EQ-5D index scores were significantly lower in people with AGW than healthy controls.

These findings were supported by three of four studies that compared AGW with non-malignant HPV-related disease, in which the mean total burden of disease as measured by the HIP questionnaire was greater amongst women with AGW than those with other conditions.

In studies that compared overall health status in people with AGW with general population norms, mean EQ-5D health status index scores were lower in three of four, and reported as significantly so in two. Mean perceived health status measured by the EQ-5D VAS was significantly lower than population norms in three studies. In one study that used the WHO Quality of Life questionnaire, overall quality of life was poorer in people with AGW than healthy controls.

The factors contributing to the overall decrement in health status measures appear to be primarily associated with anxiety and depression, and to a lesser degree discomfort and pain. Higher proportions of people with AGW reported some or severe problems with anxiety and depression than population norms in all five studies that compared individual EQ-5D dimensions. The same was true for pain and discomfort in three of five studies. In two studies that reported SF36 health status values, mental health scores were markedly lower than population norms.

Conclusions

AGW represent a significant public health burden, particularly in younger HIV negative adults and in HIV positive men and women. AGW lead to significantly diminished health-related quality of life, particularly in terms of anxiety and depression and pain and discomfort.

Summary of Findings: Incidence & prevalence of AGW in males (not including HIV+)

Outcome	Range of estimates		Number & nature of studies & size of included populations	Certainty of the evidence (GRADE)	Notes
	Lowest	Highest			
Incidence of new AGW (all ages)	77 / 100,000	560 / 100,000	<ul style="list-style-type: none"> 16 studies¹, total N > 29,500,000⁽¹⁻¹⁴⁾ Belgium, Brazil, Canada, Hong Kong, Denmark, Germany, Mexico, Spain, Sweden, UK, USA 9 studies used national/regional administrative databases, 5 medical records, 1 prospectively collected clinic data, 1 genital examinations of population sample 	⊕○○○ VERY LOW ²	<ul style="list-style-type: none"> Seven studies did not report size of study population
Incidence of new AGW (adults as defined in the previous review, including at least 20-40 years)	77 / 100,000	453 / 100,000	<ul style="list-style-type: none"> 14 studies¹, total N > 29,300,000^(1, 3-13) Belgium, Brazil, Canada, Hong Kong, Denmark, Germany, Mexico, Spain, Sweden, UK, USA 8 studies used national/regional administrative databases, 4 medical records, 1 prospectively collected clinic data, 1 genital examinations of population sample 	⊕○○○ VERY LOW ²	<ul style="list-style-type: none"> Estimates based upon administrative or medical record reviews were broader, and in particular higher, than in the previous review. Seven studies did not report size of study population
Incidence of new AGW (≤30 years)	130/100,000	560 / 100,000	<ul style="list-style-type: none"> 2 studies, total N = 231,249^(2, 14) Sweden (ages 15-23), USA (ages 11-29) 1 regional administrative database, 1 medical records 	⊕○○○ VERY LOW ²	<ul style="list-style-type: none"> Incidence estimates were higher in younger males than in the adult population as defined in the previous review.
Incidence of recurrent AGW (adults, including at least 20-40 years)	47 / 100,000	163 / 100,000	<ul style="list-style-type: none"> 2 studies, N not reported^(3, 4) Spain, UK Retrospective medical records data 	⊕○○○ VERY LOW ²	<ul style="list-style-type: none"> Neither study reported size of study population
Prevalence of AGW, all settings	0.014 %	13.70 %	<ul style="list-style-type: none"> 14 studies, total N > 3,600,000^(3, 7, 10, 15-25) Australia, Brazil, Canada, China, Denmark, Germany, Hungary, Italy, Mexico, Peru, South Korea, Spain, USA, Vietnam 2 national/regional administrative databases, 5 medical records, 4 prospectively collected clinic data, 2 genital examinations of population sample 	⊕○○○ VERY LOW ²	<ul style="list-style-type: none"> Many studies included data from STI and sexual health clinics. Three studies did not report size of study population
Prevalence of AGW, high-detection and high-prevalence settings omitted³	0.014 %	1.3 %	<ul style="list-style-type: none"> 5 studies, total N > 3,500,000^(7, 20, 21, 23, 25) Canada, Italy, South Korea 2 national/regional administrative databases, 2 medical records, 1 prospectively collected clinic data 	⊕⊕○○ LOW ⁴	<ul style="list-style-type: none"> One study did not report size of study population
Self-reported history of AGW, lifetime	0.27%	7.9%	<ul style="list-style-type: none"> 8 surveys (representative population samples), total N = 122,933(26-33) Australia, Czech Republic, Denmark, Slovenia, UK, USA 	⊕○○○ VERY LOW ⁵	-

Self-reported history of AGW, previous 12 months	0.5%	1.2%	<ul style="list-style-type: none"> 3 surveys (representative population samples), total N = 45,206 ^(27, 32, 34) Australia, China, Denmark 	⊕○○○ VERY LOW ⁵	-
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¹Estimates from one study (Nsouli-Maktabi 2013) omitted as outlier. Study focussed on military population with estimated incidence of 2,164/100,000 in males

²Downgraded three levels: data are from observational studies; high proportion of studies are in settings or populations with uncertain generalisability to general population.

³High-detection settings include clinical and research settings where genital examinations are routine. High-prevalence settings include settings where AGW prevalence may be expected to be higher, such as sexually transmitted infection clinics.

⁴Downgraded two levels: data are from observational studies

⁵Downgraded three levels: data are from observational studies; case definition is self-report.

Summary of Findings: Incidence & prevalence of AGW in females (not including HIV+)

Outcome	Range of estimates		Number & nature of studies & size of included populations	Certainty of the evidence (GRADE)	Notes
	Lowest	Highest			
Incidence of new AGW (all ages)	76 / 100,000	790 / 100,000	<ul style="list-style-type: none"> 17 studies ¹, total N > 29,600,000 ^(1-14, 35) Belgium, Canada, Hong Kong, Denmark, Germany, Spain, Sweden, UK, USA 9 studies used national/regional administrative databases, 6 medical records, 2 prospectively collected clinic data 	⊕○○○ VERY LOW ²	<ul style="list-style-type: none"> Eight studies did not report size of study population
Incidence of new AGW (adults as defined in the previous review, including at least 20-40 years)	76 / 100,000	430 / 100,000	<ul style="list-style-type: none"> 15 studies ¹, total N > 29,400,000 ^(1, 3-13, 35) Belgium, Canada, Hong Kong, Denmark, Germany, Spain, Sweden, UK, USA 8 studies used national/regional administrative databases, 5 medical records, 2 prospectively collected clinic data 	⊕○○○ VERY LOW ²	<ul style="list-style-type: none"> Estimates are similar to previous review. Eight studies did not report size of study population
Incidence of new AGW (≤30 years)	230 / 100,000	790 / 100,000	<ul style="list-style-type: none"> 2 studies, total N = 231,249 ^(2, 14) Sweden (ages 15-23), USA (ages 11-29) 1 study used national/regional administrative databases, 1 medical records 	⊕○○○ VERY LOW ²	<ul style="list-style-type: none"> Estimates are higher in younger females than in the adults as defined in previous review.
Incidence of recurrent AGW (adults, including at least 20-40 years)	23 / 100,000	110 / 100,000	<ul style="list-style-type: none"> 5 studies, total N > 98,605 ^(3, 4, 35-37) France, Germany, Italy, Spain, UK 3 studies used medical records, 2 prospectively collected clinic data 	⊕○○○ VERY LOW ²	<ul style="list-style-type: none"> Four studies did not report size of study population
Prevalence of AGW (all ages), all settings	0.023%	10.0%	<ul style="list-style-type: none"> 21 studies, total N > 3,900,000 ^(3, 7, 10, 15, 17, 20, 21, 23, 25, 35, 38-48) Australia, Brazil, Canada, China, Czech Republic, France, Germany, Hungary, Italy, Mexico, Nigeria, Peru, Spain, South Korea, USA, Vietnam 2 studies used national/regional administrative databases, 6 medical records, 7 prospectively collected clinic data, 6 genital examinations of population sample 	⊕○○○ VERY LOW ²	<ul style="list-style-type: none"> Three studies did not report size of study population
Prevalence of AGW (all ages), high-detection and high-prevalence settings omitted ³	0.023%	0.9%	<ul style="list-style-type: none"> 6 studies, total N > 3,500,000 ^(7, 20, 21, 23, 25, 43) Canada, Denmark, Germany, Italy, South Korea 2 national/regional administrative databases, 2 medical records, 1 prospectively collected clinic data, 1 genital examinations of population sample 	⊕⊕○○ LOW ⁴	<ul style="list-style-type: none"> One study did not report size of study population
Self-reported history of AGW, lifetime (all ages)	0.36%	12.0%	<ul style="list-style-type: none"> 9 surveys (representative population samples), total N = 157,383 ^(27-29, 31, 33, 43, 49-52) Argentina, Australia, Brazil, Czech Republic, Denmark, Germany, Iceland, Norway, Slovenia, Sweden, UK, USA 	⊕○○○ VERY LOW ⁵	-

Self-reported history of AGW, previous 12 months (all ages)	0.3%	2.0%	<ul style="list-style-type: none"> 2 surveys (representative population samples), total N = 22,306 ^(27, 34) Australia, China 	⊕○○○ VERY LOW ⁵	-
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¹Estimates from one study (Nsouli-Maktabi 2013) omitted as outlier. Study focussed on military population with estimated incidence of 1,928/100,000 in females

²Downgraded three levels: data are from observational studies; high proportion of studies are in settings or populations with uncertain generalisability to general population.

³High-detection settings include clinical and research settings where genital examinations are routine. High-prevalence settings include settings where AGW prevalence may be expected to be higher, such as sexually transmitted infection clinics.

⁴Downgraded two levels: data are from observational studies

⁵Downgraded three levels: data are from observational studies; case definition is self-report.

Summary of Findings: Incidence & prevalence of AGW in HIV+ populations

Outcome	Range of estimates		Number of studies & size of included populations (denominator)	Certainty of the evidence (GRADE)	Notes
	Lowest	Highest			
Incidence of new AGW – men & women (all ages)	1,389 (95% CI (1306-1476))		<ul style="list-style-type: none"> 1 study, N = 15,123 ⁽⁵³⁾ Taiwan National Health Insurance Research database 	⊕⊕⊕⊕ LOW ¹	
Prevalence of AGW – men (all ages)	7.3%	31.0%	<ul style="list-style-type: none"> 3 studies, total N = 1,075 ⁽⁵⁴⁻⁵⁶⁾ Brazil, Spain All prospective studies in HIV or infectious disease clinics 	⊕⊕⊕⊕ VERY LOW ²	<ul style="list-style-type: none"> In two studies 26% and 55% of HIV+ men, were heterosexual, not reported in the third study One study reported prevalence estimates of 15% in heterosexual men, 28% in MSM Antiretroviral therapy (ART) use was 55% in the study reporting 7.3% prevalence and 83% reporting 15% (heterosexual) and 28% (MSM) ART use levels not reported in third study, but AGW associated with <95% ART adherence and longer time since HIV diagnosis
Prevalence of AGW – women (all ages)	2.8%	3.7%	<ul style="list-style-type: none"> 2 studies, total N = 1,398 ^(57, 58) Studies in Brazil, Tanzania 1 study medical records at maternity unit, 1 study participants in a multivitamins trial 	⊕⊕⊕⊕ VERY LOW ³	<ul style="list-style-type: none"> ART use was not reported in one study, all women were ART-naïve in the other
Prevalence of AGW – men & women (all ages)	1.6%	17.0%	<ul style="list-style-type: none"> 6 studies, total N = 1,783 ⁽⁵⁹⁻⁶⁴⁾ Studies in Chile, China, Sri Lanka, Turkey, UK, USA 5 studies in populations of HIV or infectious disease clinics, 1 medical records review of hospital inpatient and outpatient records 	⊕⊕⊕⊕ VERY LOW ²	<ul style="list-style-type: none"> ART use was inconsistently reported. Three studies reported levels of use as 18%, 71% & 76% CD4 cell counts were inconsistently reported. Two studies reported median CD4 counts of 320 & 433 cells/mul

¹ Downgraded two levels: data are from an observational study

² Downgraded three levels: data are from observational studies; most studies are in settings or populations with uncertain generalizability to general HIV+ population.

³ Downgraded three levels: data are from observational studies; one study abstract only, with uncertain methodology.

Summary of Findings: Health related quality of life measures in people with AGW (not including HIV+)

Outcome	Plain language summary	Measurements				Number and location of studies & size of included populations (denominator)	Certainty of the evidence (GRADE)	Notes
Health utility in AGW versus other malignant and non-malignant HPV-related disease (time trade-off)	Men and women with AGW rate their own health status as better than people with HPV-related cancers, but worse than people with HPV-related non-cancerous or precancerous disease	Mean health utility values:				1 study N = 600 ^(65, 66) (Italy)	⊕⊕⊕⊕ LOW ¹	<ul style="list-style-type: none">Time trade-off (TTO) is a validated method for determining health utility values, typically used in calculating QALY values. Higher values indicate better health status.
		CIN 1 ASC-US CIN 2/3 AGW HNSCC Cerv. Cancer Anal cancer	(0.83, SD 0.22) (0.83, SD 0.24) (0.81, SD 0.27) (0.78, SD 0.27) (0.69, SD 0.30) (0.58, SD 0.31) (0.50, SD 0.26)					
Health status in AGW versus other non-malignant HPV-related disease (HPV Impact Profile [HIP] questionnaire)	The impact of AGW on peoples’ psychological and emotional well-being and their social and personal lives may be worse than the impact of other non-cancerous or precancerous HPV-related disease.	Mean HIP score for four studies				4 studies ⁽⁶⁷⁻⁶⁹⁾ N = 4,027 (Australia, China, Taiwan, UK)	⊕⊕⊕⊕ LOW ¹	<ul style="list-style-type: none">The HIP questionnaire measures the psychosocial burden of HPV-related disease. It comprises 7 psychosocial dimensions: worries and concerns; emotional impact; sexual impact; self-image; partner issues and transmission; interactions with doctors; and health control and life impact. Higher scores indicate a greater psychosocial impact.
		AGW CIN 2/3 CIN 1 CIN1/2/3 VIN 2/3 Abnormal cytology Abnormal cytology HPV+ Norm cytology	51 44 42 - 44 - - 22	52 - - 49 - 44 46 33	63 - - 48 - 44 49 28			
Health status in AGW versus general population norms (mean EQ-5D index)	The overall health status (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) of people with AGW may be lower than is normal for the general population.	Mean EQ-5D index for four studies				4 studies ⁽⁷⁰⁻⁷⁴⁾ N = 2,357 (Canada, UK)	⊕⊕⊕⊕ VERY LOW ²	<ul style="list-style-type: none">The EQ-5D is a validated and widely used generic measure of health status, consisting of five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Higher scores indicate better health status.
			AGW	Population norm				
		Men & women	90	89				
		Men	81	89				
		Women	77	89				
		Men & women	79	89				
		Men & women	76	82				
		Men	88	92				
		Women	87	93				
		Men & women	87	93				

Self-reported health state in AGW versus general population norms (mean EQ-5D VAS)	People with AGW perceive themselves to have much poorer general health than is normal for the general population.	Mean EQ-5D VAS for three studies			3 studies ^(70, 71, 73, 75) N = 2,742 (Canada, China, UK)	⊕000 VERY LOW ²	<ul style="list-style-type: none"> The EQ-5D VAS is a visual analogue scale in which respondents indicate their perceived health state at the time of answering on a scale from 0 to 100 (0, worst imaginable health state; 100, best imaginable health state).
		Men & women	78	85			
		Men	78	82			
		Women	76	83			
		Men & women	77	83			
		Men	69	81			
		Women	62	79			
Proportions of people with AGW reporting some or severe problems with anxiety or depression compared with population norms	People with AGW report more problems with anxiety and depression than is normal for the general population.	Proportion reporting some or severe problems with anxiety / depression in five studies			5 studies ^(70, 71, 73, 75-77) N = 2,911 (Canada, China, Netherlands, UK)	⊕000 VERY LOW ²	<ul style="list-style-type: none"> In the EQ-5D questionnaire, respondents indicate whether they are experiencing any or severe problems with anxiety or depression.
		Men & women	41%	19%			
		Men & women	26%	16%			
		Men	50%	5%			
		Women	62%	7%			
		Men & women	56%	6%			
		Men	43%	26%			
		Women	61%	32%			
		Men & women	56%	30%			
		Men	14%	8%			
Proportions of people with AGW reporting some or severe problems with pain or discomfort compared with population norms	People with AGW may have more problems with pain and discomfort than is normal for the general population.	Proportion reporting some or severe problems with pain / discomfort in five studies			5 studies ^(70, 71, 73, 75-77) N = 2,911 (Canada, China, Netherlands, UK)	⊕000 VERY LOW ²	<ul style="list-style-type: none"> In the EQ-5D questionnaire, respondents indicate whether they are experiencing any or severe problems with pain or discomfort.
		Men & women	21%	27%			
		Men & women	25%	21%			
		Men	21%	7%			
		Women	28%	11%			
		Men & women	25%	9%			
		Men	45%	26%			
		Women	49%	30%			
		Men & women	47%	28%			
		Men	8%	21%			
		Women	27%	30%			

¹Downgraded two levels: data are from observational studies

²Downgraded three levels: data are from observational studies; some studies are in settings or populations with uncertain generalisability to general population, or adjustment for prognostic factors is uncertain.

ASC-US: atypical squamous cells of undetermined significance. CIN: cervical intraepithelial neoplasia. HNSCC: head and neck squamous cell carcinoma. HSIL: high grade squamous intraepithelial lesion. LSIL: low grade squamous intraepithelial lesion. Abnormal cytology: any abnormal cytology, HPV status unknown. Abnormal cytology HPV+: abnormal cytology with positive HPV test

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