Supplementary materials

Table of Contents

1. Study protocols (including objectives, PICOS, bibliographic sources, literature search strings)

1.1. Objectives

1.1.1. Primary objectives

- To evaluate the accuracy to detect cervical precancer of hrHPV testing on samples taken by the woman her-self.
- To evaluate the potential to reach women who do not participate in the regular screening programme by offering self-samplers.

1.1.2. Secondary objectives

Accuracy
To assess the variation in the accuracy of HPV testing on self-samples by HPV assay, self-sampling device and transport medium.

Screening participation
To compare the test adequacy, test-positivity rate, adherence to follow-up, positive predictive value, detection rate of precancer in women participating in a self-sample strategy and those participating in a conventional strategy.

1.2. Clinical questions

1) Is testing for presence of high-risk types of the human papillomavirus (hrHPV) on vaginal samples taken by the woman herself as accurate to detect cervical pre-cancer than hrHPV testing on a cervical sample taken by a health professional?

2) Does the diagnostic accuracy of HPV testing on self-samples vary by HPV assay?

3) Does the diagnostic accuracy of HPV testing on self-samples vary by self-sampler or transport medium?

4) Is screening attendance higher when under-screened populations are offered a self-sampling device compared to usual practice?

1.3. PICOS components

1.3.1. PICOS 1: Clinical accuracy of HPV testing on self-samples

P*opulation*: women participating in cervical cancer screening, or women with cervical abnormalities detected previously and under follow-up, presenting at a colposcopy clinic.

Index test: hrHPV testing on a self-sample.

Comparator tests:
C1: hrHPV testing with the same assay on a clinician sample

Outcomes:
O1: absolute sensitivity and specificity for detection of CIN2+ or CIN3+ of the index test and of the comparator test.
O2: relative sensitivity and specificity for CIN2+ and CIN3+ of:
- hrHPV testing on a self-sample versus hrHPV testing on a clinician-sample

Covariates:
- HPV assay: amplification principle for the HPV assay (signal amplification, PCR), individual assay;
- Self-sampling device;
- Transport medium

Studies:
Cross-sectional diagnostic test accuracy studies where a vaginal self-sample and a cervical clinician-sample are taken and a hrHPV test is performed on the self-sample and on the clinician sample.
Randomised trials with hrHPV testing on a self-sample in one arm and on a clinician-sample in the other arm.

1.3.2. PICOS 2: Potential of strategies providing self-samplers to increase population coverage

P*opulation*: women who did not participate in the regular screening programme; women who did not respond to one or more previous invitations; women whose last screening is a long time ago; women belonging to under-screened communities.

Intervention: providing a self-sampling device for collection of a vaginal sample by the women her-self.
I1: "Mail-to-All": sending self-samplers to the woman's home address;
I2: "Opt-In": offering women the possibility to obtain a self-sampler: women can order a free self-sampling device; women can contact a service where they can get the self-sampling device;
I3. "Door-to-Door": Women are visited at home by a health care worker;
I4: women receive the self-sampling device when they contact a health service for whatever reason.

Control action:
C: standard procedure (invitation or reminder) or usual care where women have a sample taken by a clinician.

Outcomes:
O1: Response rate in intervention and control arms
O2: Relative response rate (intervention/control arms); response difference (intervention/control arms)
O3: proportion with unsatisfactory test results among screened women (arm1, arm2, ratio and difference)
O4: test-positivity rate among screened women with satisfactory sample (arm1, arm2, ratio and difference)
O5: adherence to further follow-up among screen-test positive women
O6: PPV for CIN2+ among screen-test positive women who complied with further follow-up
O7: detection rate of CIN2+ among all women, screened women, screen-positive women who complied to follow-up.

Studies:
Randomised controlled trials.
Controlled cohort studies

1.4. Literature retrieval strings

1.4.1. Clinical accuracy of HPV testing on self-samples

A. In Pubmed-Medline

#1: Cervix OR cervico* OR cervica*
#2: Cancer OR carcinoma OR neoplas* OR dysplas* OR CIN[tw] OR CINII*[tw] OR CIN2*[tw] OR CINIII*[tw] OR CIN3[tw] OR SIL[tw] OR SIL OR HSIL[tw] OR H-SIL OR LSIL[tw] OR L-SIL OR OR ‘‘low grade’’ OR low-grade OR mild OR equivocal OR borderline.
#3: #1 AND #2.
#4: HPV OR "Human Papillomavirus DNA Tests"[Mesh] OR ‘‘human papillomavirus’’ OR papillomavir* OR viral OR virus
#5: self-collection OR “self collection” OR self-sampling OR self-collect* OR self-sampl* OR self OR "Self-Examination"[Mesh]
#6: #4 AND #5
#7: #3 AND #6
#8: Publication Date to April 2018.
#9: #7 AND #8

B. In Embase

#1: 'cervix'/exp OR cervix OR cervico* OR cervica*
#2: 'cancer'/exp OR cancer OR 'carcinoma'/exp OR carcinoma OR neoplas* OR dysplas* OR cin OR 'cin2' OR 'cin3' OR sil OR hsil OR h+sil OR lsil OR l+sil OR 'low grade' OR low+grade OR mild OR equivocal OR 'borderline'/exp OR borderline
#3: 'hpv'/exp OR hpv OR 'human papillomavirus'/exp OR 'human papillomavirus' OR papillomavir* OR viral OR 'virus'/exp OR virus
#4: self+collection OR 'self collection' OR self+sampling OR 'self-sampling' OR self+collect* OR self+sampl* OR 'self'/exp OR self
#5: #1 AND #2 AND #3 AND #4

With the following limits:
- Map to preferred terminology (with spell check)
- Also search as free text
- Include sub-terms/derivatives (explosion search)
- Search publications: all years

C. In Cochrane Library

#1: Cervix or cervico* or cervica*
#2: Cancer or carcinoma or neoplas* or dysplas* or CIN or CIN2 or CIN3 or SIL or SIL or HSIL or H-SIL or LSIL or L-SIL or "low grade" or low-grade or mild or equivocal or borderline.
#3: HPV or ‘‘human papillomavirus’’ or papillomavir* or viral or virus
#4: self-collection or "self collection" or self-sampling or ‘‘self-sampling’’ or self-collect* or self-sampl* or self

With the following limits:
- Cochrane reviews (reviews + protocols)
- Other reviews

Search for word variations

1.4.2. Potential of strategies providing self-samplers to increase population coverage

In Pubmed-Medline

(Cervix OR cervical) AND (HPV OR papillomavirus) AND (self-sampling OR self sampling OR self-collection OR self collection) AND (screening OR coverage OR participation OR knowledge OR acceptance)

2. PRISMA flow charts of study retrieval and selection

2.1. Meta-analysis on accuracy of self-samples

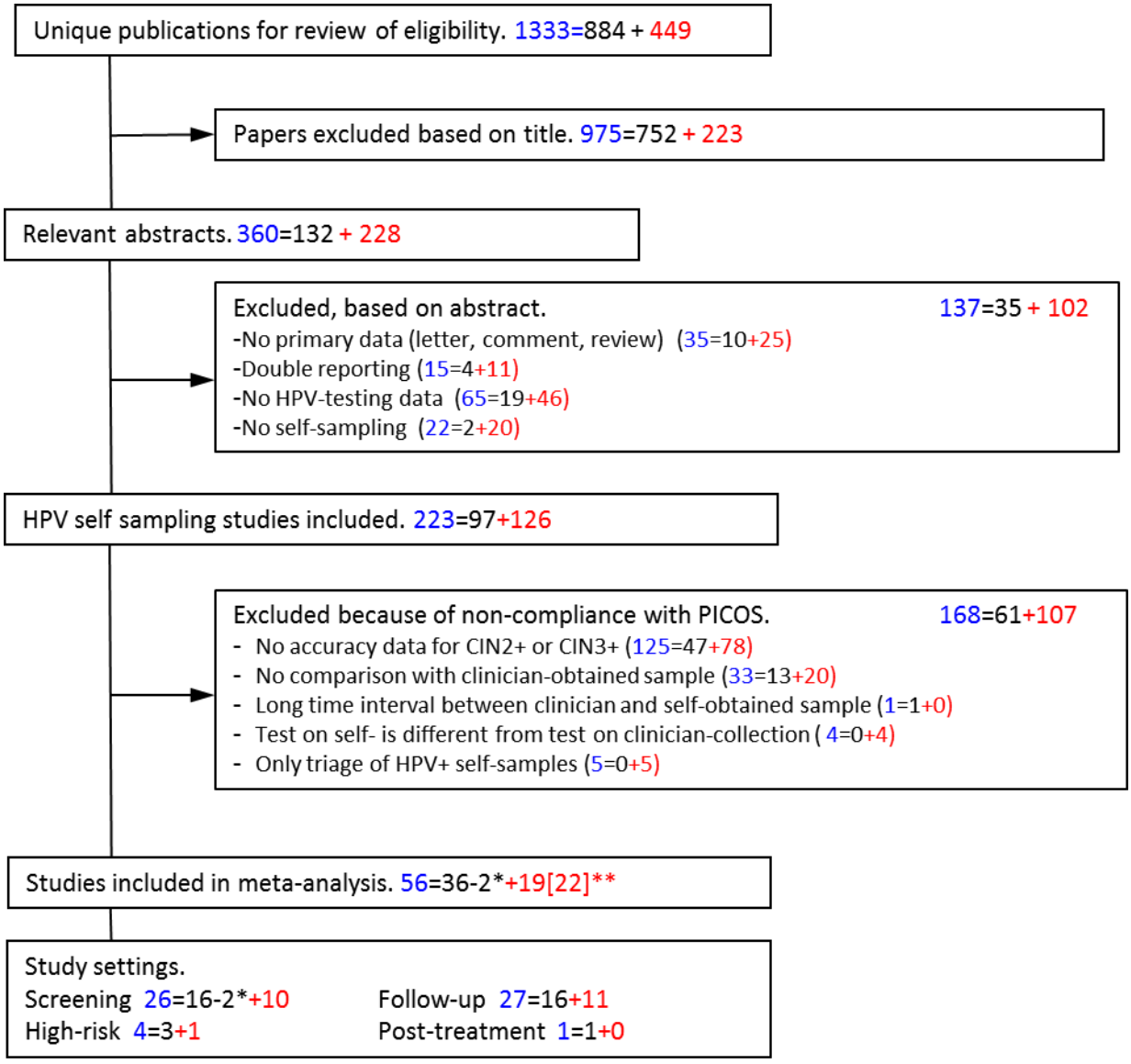


Figure 1. PRISMA flow chart summarizing the selection of eligible studies**.** Figures in black are those included in the search up to June 3, 2013[1], those in red concern new references retrieved up to April 15, 2018. The total number resulting from all searches are in blue.

* Two studies[2;3] included in the previous meta-analysis (Arbyn et al, Lancet Oncol 2014) [1] were excluded from the current updated review, since only cytology was performed on the clinician sample.
** One report included four studies[4].

2.2. Meta-analysis on the response to the offer of self-samples

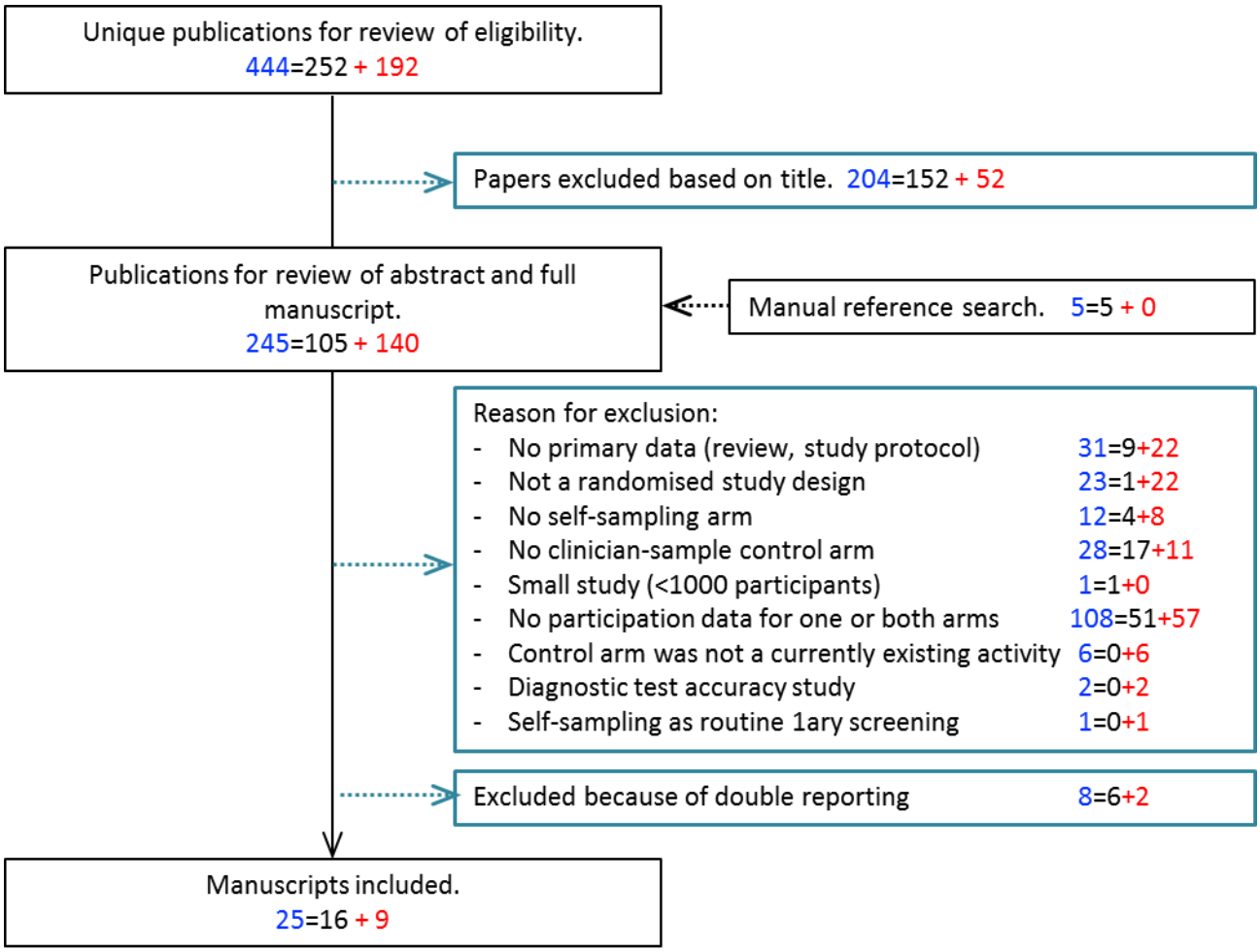


Figure 2. PRISMA flow chart summarizing the selection of eligible participation trials. Figures in black are those included in the search up to February 12, 2015[5], those in red are references retrieved up to April 15, 2018. References in blue are the sum of all searches.

Throughout this Supplementary File, information regarding studies added after the previous meta-analyses of Arbyn et al Lancet 2014[1] and Verdoodt et al Eur J Cancer 2015[5] are in red text whereas information from studies already included in these meta-analyses is in black text.

3. Characteristics of the studies included in the meta-analysis of the accuracy of hrHPV testing on self-samples

3.1. Study design/enrolled subjects

Table 1. Population and study characteristics (in black: studies included in the previous meta-analysis, in red: studies added between January 1, 2013 and April 15, 2018).

Author, year Country	**Study design**	**Population/ setting**	**Inclusion & exclusion criteria**	**Study size**	**Age**
1. Morrison, 1992 USA	Cross-sectional; All had self- & clinician samples	Follow up (colposcopy clinic)	Incl: - equivocal cervical cytology	25	Not specified
2. Hillemanns, 1999 Germany	Cross-sectional; All had self- & clinician samples	Follow up (colposcopy clinic)	Not specified	247	Not specified
3. Sellors, 2000 Canada	Cross-sectional; All had self- & clinician samples	Follow up (colposcopy clinic)	Incl: - equivocal cervical cytology	200	Mean: 31.5y (SD=9.4y) Range: ≥ 18y
4. Wright, 2000 South-Africa	Cross-sectional; All had self- & clinician samples	Screening	Incl: - unscreened for ≥ 3y	1415	Median: 39y Range: 35-65y
5. Belinson, 2001 China	Cross-sectional; All had self- & clinician samples	Screening	Excl: - pregnancy, history of cervical screening, pelvic radiation, or hysterectomy	1997	Mean: 39.1y (SE=3.16y)
6. Lorenzato, 2002 Brazil	Cross-sectional; All had self- & clinician samples	Screening (high-risk population)	Excl: - cervix removed - illness impeding participation	253	Mean: 38.1y (SD=13.7y) Median: 38y

Author, year Country	**Study design**	**Population/ setting**	**Inclusion & exclusion criteria**	**Study size**	**Age**
7. Nobbenhuis, 2002 The Netherlands	Cross-sectional; All had self- & clinician samples	- Follow up + healthy participants (colposcopy clinic)	Incl: - equivocal cervical cytology (very mild dyskaryosis or more severe results) - normal cervical cytology	71	Mean: 35y
8. Garcia, 2003 Mexico, Peru, USA	Cross-sectional; All had self- & clinician samples	Follow up (colposcopy clinic)	Excl: - history of hysterectomy, vaginal trauma or laceration - pregnancy	334	Mean: 36.9y
9. Salmeron, 2003 Mexico	Cross sectional; All had self- & clinician samples	Screening	Excl: - history of CIN2+ - hysterectomy - pregnancy	7868	Mean: 42.5y
10. Brink, 2006 The Netherlands	Cross-sectional; All had self- & clinician samples	- Follow up + healthy participants (colposcopy clinic)	Incl: - repeat equivocal cervical cytology	96	Median: 35y Range: 18-59y
11. Daponte, 2006 Greece	Clinical prospective evaluation study; All had self- & clinician samples	Follow up (colposcopy clinic)	Incl: - histologically proven cervical lesion Excl: - HIV-positivity	98	Not documented
12. Girianelli, 2006 Brazil	Cross-sectional; All had self- & clinician samples	Screening (high-risk population)	Incl: - unscreened for >3years Excl: - pregnancy - delivery <6months ago - never having had sexual intercourse - hysterectomy	1777	Median: 39y Mean: 39y Range: 25-59y
13. Holanda, 2006 Brazil	Cross-sectional; All had self- & clinician samples	Screening	Incl: - sexually active Excl: - pregnancy - hysterectomy	878	Range: 15-69y
14. Seo, 2006 South-Korea	Cross-sectional; All had self- & clinician samples	Follow up (colposcopy clinic)	Incl: - equivocal cervical cytology (ASC-US+)	118	Mean: 46.2y

Author, year Country	**Study design**	**Population/ setting**	**Inclusion & exclusion criteria**	**Study size**	**Age**
15. Szarewski, 2007 United Kingdom	Cross-sectional; All had self- & clinician samples	Screening	Excl: - history of ablative or excisional treatment of the cervix	920	Median: 29y (pop 1) Median: 41y (pop 2)
16. Qiao, 2008 China	Cross sectional; All had self- & clinician samples	Screening	Excl: - pregnancy - history of CIN, pelvic radiation, or hysterectomy	2530	Mean: 43y Range: 30-55y
17. Bhatla, 2009 India	Cross sectional; All had self- & clinician samples	Screening (high-risk population)	Incl: - sexually active women - persistent vaginal discharge, intermenstrual or postcoital bleeding or an unhealthy cervix Excl: - age <30 years - unmarried - hysterectomy or prior surgical procedures on the cervix - gross tumour on the cervix - pregnancy	546	Median: 36y
18. Balasubramanian, 2010 USA	Cross-sectional; All had self- & clinician samples	Screening (high-risk population)	Excl: - pregnancy - chronically immunecompromised - prior treatments for cervical neoplasia	1665	Median: 23y Range: 18-50y
19. Gustavsson, 2011 Sweden	Cross-sectional; All had self- & clinician samples	Follow up (colposcopy clinic)	Incl: - unscreened for ≥ 6years - HPV-positivity in a previous self-obtained sample §	50	Range: 39-60y
20. Taylor, 2011 South-Africa	Cross-sectional; All had self- & clinician samples	Post-treatment follow up + healthy participants	Incl: - subjects derived from randomized clinical trial evaluating the safety and efficacy of two screen-and-treat approaches for cervical cancer prevention - women who had undergone cryotherapy in the two screen and- treat groups + all women in the control group who did not undergo cryotherapy.	2670	Mean: 43y Range: 35-65y

Author, year Country	**Study design**	**Population/ setting**	**Inclusion & exclusion criteria**	**Study size**	**Age**
21. Twu, 2011 Taiwan	Cross-sectional; All had self- & clinician samples	Follow up (colposcopy clinic)	Incl: - unscreened for ≥ 3years Excl: - acute cervicitis or vaginitis - pregnancy - menstruating period - sexual intercourse <2d before the study	252	Median: 42y Range: 26-79y
22. Belinson, 2012 China	Cross-sectional; All had self- & clinician samples	Screening	Incl: - unscreened for ≥ 3years Excl: - pregnancy - hysterectomy - history of pelvic radiation	8556	Mean: 38.9y Range: 25-59y
23. Dijkstra, 2012 The Netherlands	Cross-sectional; All had self- & clinician samples	Follow up (colposcopy clinic)	Incl: - equivocal cervical cytology (moderate dyskaryosis or more severe results) - post-coital bleeding (normal cytology)	135	Median: 34y
24. Longatto-Filho, 2012 Argentina, Brazil	Cross-sectional and prospective cohort; All had self- & clinician samples	Screening	Incl: - consecutive series of women at their first visit to the clinic	12114	Mean: 37y***** Range: 14-67y*****
25. van Baars, 2012 The Netherlands	Cross-sectional; All had self- & clinician samples	Follow up (colposcopy clinic)	Incl: - equivocal cervical cytology	134	Mean: 40y Range: 21-66y
26-28. Zhao, 2012 China	Cross-sectional; All had self- & clinician samples	Screening	Incl: - sexually active - having an intact uterus - unscreened for ≥ 5years Excl: - pregnancy - history of CIN2+, or pelvic radiation	13004	Mean: 37.9y (SD=11.2y)
29. Darlin, 2013 Sweden	Cross-sectional; All had self- & clinician samples	Follow up (colposcopy clinic)	Incl: - equivocal cervical cytology	108	Mean: 34y Range: 18-65y

Author, year Country	**Study design**	**Population/ setting**	**Inclusion & exclusion criteria**	**Study size**	**Age**
30. Geraets, 2013 Spain	Cross-sectional; All had self- & clinician samples	Follow up (colposcopy clinic)	Incl: - equivocal cervical cytology	182	Median: 34y Range: 16-76y
31. Guan, 2013 China	Cross-sectional; All had self- & clinician samples	Screening	Incl: - VIA or VILI positive - VIA or VILI negative (random sample)	174	Not documented
32. Jentschke, 2013a Germany	Retrospective; All had self- & clinician samples	Follow up (colposcopy clinic)	Not documented	72	Mean: 37y Range: 16-68y
33. Jentschke, 2013b Germany	Retrospective; All had self- & clinician-samples	Follow up (colposcopy clinic)	Not documented	49	Mean: 36y Range: 18-68y
34. Nieves, 2013 Mexico	Cross-sectional; All had self- & clinician samples	Screening	Excl: - pregnancy - history of hysterectomy or pelvic irradiation	2049	Median: 39y Range: 30-50y
35. Zhao, 2013 China	Cross-sectional: All had self- & clinical-samples.	Screening	Excl: - previously diagnosed with cervical cancer - no cervix - pregnancy - unmarried - never having had sexual intercourse.	7421	Range: 25-65y.
36. Chernesky, 2014 Canada	Cross-sectional. All had self and clinician samples. Clinicians took also vaginal samples.	Follow-up (colposcopy clinic)	Not reported	580	Mean: 39y. Range: 18-63y.
37. Hesselink, 2014 The Netherlands	Clinical test validation study. Cases & controls contributed self- and clin samples.	Cases & controls from a screening population.	Cases with CIN2+. Controls: women with normal cytological findings who were without evidence of CIN2 in up to 2 years of follow-up monitoring.	70 CIN2+ cases, 824 controls.	Mean: 41y. Range: 30-60y.

Author, year Country	**Study design**	**Population/ setting**	**Inclusion & exclusion criteria**	**Study size**	**Age**
38-41. Jeronimo, 2014 India, Nicaragua, Uganda	Cross-sectional study in 3 countries: India (2 settings), Uganda, Nicaragua. All had self- & clinician samples.	Screening	Excl: -Never having had sexual intercourse (in Nicaragua, Uganda). In India: not married). -History of CIN or cervical cancer -Hysterectomy -Pregnancy until 3 months post-delivery	16,951	India, Nicara-gua: 30-59y. Uganda: 25-60y.
42. Wang, 2014 China	Cross-sectional; All had self- & clinician samples.	Follow up (colposcopy clinic)	Excl: -pregnancy -history of CIN, cervical cancer, hysterectomy	379	Range: 25-65y.
43. Zhang, 2014 China	Cross-sectional; All has self- & clinician samples	Screening	Women who participated in a multi-center screening programme. No details about the exclusion criteria.	806	Range: 16-54y.
44. Boggan, 2015 Haiti	Cross-sectional; All had self- & clinician-samples.	Screening	Incl: - sexual intercourse ≥1/lifetime Excl: - current pregnancy, hysterectomy, active menstruation.	1845	Mean: 41y. Range: 25-65y.
45. Porras, 2015 Costa Rica	Cross-sectional; All had self- & a subset had clinician samples.	HPV vaccine trial, 6M after enrolment.	- age 18-25y - sexually experienced women.	5109: self 615 among them also clin.	Mean: 22y. Range: 18-25y.
46. Chen, 2016 (a), Gen Mol China	Cross-sectional; All had self- & clinician samples.	Follow-up (colposcopy)	Incl: -18-56y -ASCUS+ and hrHPV positive (HC2).	197	Mean: 39 y. Range: 18-56y.
47. Chen, 2016 (b), J Ob Gyn China	Cross-sectional; All had self- & clinician samples.	Outpatient gyn clinic (one group had positive screening results and other no cervical lesions).	Incl: -≥ 18 y -½ patients with cervical lesions; ½ patients without cervical lesions or cervicitis Excl: - Lesion status categorized incorrectly.	202	Mean: 41y. Range: 21–79y.
48. Jentschke, 2016 Germany	Cross-sectional; All had self- & clinician samples.	Follow-up (colposcopy clinic)	Excl: - hysterectomy - pregnancy.	136	Mean: 36 y. Range: 17–78y.

Author, year Country	**Study design**	**Population/ setting**	**Inclusion & exclusion criteria**	**Study size**	**Age**
49. Qin, 2016 China	Cross-sectional; All had self- & clinician samples.	HIV clinic	Excl: - previously diagnosed with CIN - history of cervical cancer - hysterectomy - pregnancy	291	Mean: 39y. Range: 25-65y.
50. Stanczuk, 2016 Scotland	Cross-sectional; All had self- & clinician samples.	Screening	Excl: - previously diagnosed with CIN2+.	5,318	Mean: 41y. Range:18–76y.
51. Aiko, 2017 Japan	Cross-sectional; All had self- & clinician samples.	Follow-up (colposcopy clinic)	Incl: - Women with ASC-US+ - 20-69y - Visiting study colposcopy clinic Excl. - pregnancy - use of vaginal suppositories - history of conisation - cytology indicating cancer.	136	Range: 20-69y.
52. Asciutto, 2017 Sweden	Cross-sectional; All had self- & clinician samples.	Follow-up or symptomatic patients (colposcopy clinic)	Not documented.	218	Mean: 35y. Range: 19-71.
53. Catarino, 2017 Switzerland	Cross-sectional; All had self- & clinician samples.	Follow-up (colposcopy clinic)	Incl: ≥18y, understand instructions, informed consent. Excl: pregnancy, hysterectomy.	150	Median: 32y. Range: 18-69y.
54. Leeman, 2017 The Netherlands	Cross-sectional; All had self- &-clinician samples.	Follow-up (colposcopy clinic)	No details provided.	91	Range: 18-60y.
55. Asciutto, 2018 Sweden	Cross-sectional; All had self-, urine & clinician-samples.	Follow-up (colposcopy clinic)	Excl: hysterectomy, history gynecologic cancer, current cancer treatment.	176	Mean: 34y. Range: 20-68y.
56. Leinonen, 218 Norway†	Cross-sectional; All had 2 self-samples at home and a clinician-sample.	Patients with CIN3 or cancer received self-samples at home before visit for conisation.	Excl: women who did not have all specimens (2 self & 1 clin) or HPV tests.	187 CIN3 53 cancers	Mean: 38 y. Range: 21-80y.

* retrieved from Syrjänen, 2005 (Anticancer Research)

§ Sanner K, Wikstrom I, Strand A, Lindell M, Wilander E. Self-sampling of the vaginal fluid at home combined with high-risk hrHPV testing. Br J Cancer 2009; 101(5):871-874.

† Only women with CIN3+ included, therefore specificity cannot be assessed.

3.2. Details on test, collection devices, storage or transport media, verification disease status

Table 2. Characteristics of tests and disease verification (in black: studies included in the previous meta-analysis, in red studies added between 1 January 2013 and 15 April 2018).

Author, year	Tests	Assay	Sampling device	Storage medium	Golden standard	Test cut-off	Outcome
1. Morrison, 1992	Self: HRHPV Clin: hrHPV	PCR (L1 consensus)	Self: lavage (My-PAP)	ethanol carbowax	Colposcopy + colpo-directed biopsy - All participants	Not Specified	CIN2+
2. Hillemanns, 1999	Self: hrHPV Clin: hrHPV	HC2	Self: cytobrush Clin: cytobrush	Self: placed into a specimen collection tube	Colposcopy + colpo-directed biopsy and/or endocervical curettage - All participants	HC2: 1pg/ml	CIN2+
3. Sellors, 2000	Self: hrHPV Clin: hrHPV, cytology	hrHPV: HC2, PCR (L1 consensus) Cyto: cPap	Self: Dacron Polyester Swab Clin: soft cone-shaped cervical brush, Ayre spatula, and Dacron Polyester Swab	Self: STM Clin brush: STM Clin swab: sterile phosphate-buffered saline	Colposcopy + colpo-directed biopsy and/or endocervical curettage - All participants	HC2: 1pg/ml	CIN2+
4. Wright, 2000	Self: hrHPV Clin: hrHPV, cytology	hrHPV: HC2 Cyto: cPap	Self: Dacron Polyester Swab Clin: Accelon Combi Cervical Biosampler (cyto), conical brush (hrHPV)	STM	Colposcopy + colpo-directed biopsy/loop excision or endocervical curettage - Participants with at least one positive test result	HC2: 1pg/ml Cyto: ASCUS+, LSIL+	CIN2+
5. Belinson, 2001	Self: hrHPV Clin: hrHPV, cytology	hrHPV: HC2 Cyto: LBC (ThinPrep)	Self: Dacron Swab Clin: plastic spatula, endocervical brush	Self: STM Clin: PreservCyt	Colposcopy + colpo-directed biopsy + multiple random biopsies - All participants	HC2: 1 pg/ml	CIN2+
6. Lorenzato, 2002	Self: hrHPV Clin: hrHPV	PCR (L1 consensus, MY 9/11)	Self: cotton swab Clin: Ayre spatula, cytobrush	Self + clin: PBS	Colposcopy + colpo-directed biopsy - All participants	Not documented	CIN2+ CIN3+

Author, year	Tests	Assay	Sampling device	Storage medium	Golden standard	Test cut-off	Outcome
7. Nobbenhuis, 2002	Self: hrHPV Clin: hrHPV, cytology	hrHPV: PCR (GP 5+/6+) Cyto: cPap	Self: lavage Clin: lavage, Cervex-Brush	Self + Clin: PBS	Colposcopy + colpo-directed biopsy - All participants	Cyto: ASC-US+	CIN2+
8. Garcia, 2003	Self: hrHPV Clin: hrHPV, cytology	hrHPV: PCR (PGMY09/11, L1 consensus) Cyto: LBC (ThinPrep)	Self: cytobrush Clin: Ayre spatula and endocervical brush	Self: PreservCyt Clin: methanol buffer solution	Colposcopy + colpo-directed biopsy (+ endocervical curettage) - All participants	Cyto: ASCUS+	CIN2+
9. Salmeron, 2003	Self: hrHPV Clin: hrHPV, cytology	hrHPV: HC2 Cyto: cPap	Self: Dacron Swab Clin: conical cytobrush	Self + Clin: STM	Colposcopy + colpo-directed biopsy (+ endocervical curettage) - Participants with at least one positive test result	HPV: 1 pg/ml Cyto: ASC-US+	CIN2+
10. Brink, 2006	Self: hrHPV Clin: hrHPV, cytology	hrHPV: PCR – EIA (GP5+/6+) Cyto: LBC (SurePath)	Self: cervicovaginal lavage (Mermaid) Clin: endocervical brush	Self + Clin: SurePath	Colposcopy + colpo-directed biopsy - Participants with equivocal cytology ⌖	Cyto: ASC-US+, HSIL+	CIN2+
11. Daponte, 2006	Self: hrHPV Clin: hrHPV	PCR (*L1* and *E6* type-specific primers for HPV16)	Self +Clin: cytobrush	Self + Clin: PBS	Colposcopy + colpo-directed biopsy - All participants	Not documented	CIN2+
12. Girianelli, 2006	Self: hrHPV Clin: hrHPV, cytology	hrHPV: HC2 Cyto: cPap, LBC (Citoliq)	Self: conical brush Clin: conical brush (hrHPV, LBC), Ayre spatula and endocervical brush (cPap)	hrHPV: Citoliq	Colposcopy + colpo-directed biopsy - Participants with at least one positive test result - Systematic sample of 70 women with negative tests	HPV: 1pg/ml Cyto: ASC-US+	CIN2+
13. Holanda, 2006	Self: hrHPV Clin: hrHPV	HC2	Self: collection brush Clin: small conical brush	Self + Clin: UCM	Colposcopy + colpo-directed biopsy - All participants	1pg/ml	CIN2+
14. Seo, 2006	Self: hrHPV Clin: hrHPV	hrHPV DNA Chip	Self: Dacron Polyester Swab Clin: Dacron Polyester Swab	Not documented	Colposcopy + colpo-directed biopsy (+ endocervical curettage) or random biopsies - All participants		CIN2+ CIN3+

Author, year	Tests	Assay	Sampling device	Storage medium	Golden standard	Test cut-off	Outcome
15. Szarewski, 2007	Self: hrHPV Clin: hrHPV, cytology	hrHPV: HC2 Cyto: cPap	Self: cotton swab Clin Cyto: pointed spatula, endocervical brush Clin hrHPV: Cervical Sampler Brush	Not documented	Colposcopy + colpo-directed biopsy - Participants with at least one positive test result - Random sample (5%) of women with negative tests	HPV: 1 pg/ml Cyto: ASC-US+	CIN2+
16. Qiao, 2008	Self: hrHPV Clin: hrHPV, cytology	hrHPV: CareHPV Cyto: LBC (SurePath)	Self: vaginal brush (careHPV) Clin: nylon swab (LBC), cervical brush (care HPV)	- HPV: collection medium (QIAGEN) - LBC: SurePath	Colposcopy + colpo-directed biopsy and endocervical curettage - All participants	careHPV: 0.5 pg/ml, 1 pg/ml Cyto: ASC-US+, LSIL+	CIN2+ CIN3+
17. Bhatla, 2009	Self: hrHPV Clin: hrHPV, cytology	hrHPV: HC2, PCR (PGMY09/11) Cyto: cPap	Self: cervical sampling brush Clin: Ayre spatula and endocervical brush (cyto), cervical sampling brush (hrHPV)	HPV: STM	Colposcopy + colpo-directed biopsy - All participants	- HPV: 1pg/ml - Cyto: ASC-US+, LSIL+	CIN2+
18. Balasubramanian, 2010	Self: hrHPV Clin: hrHPV	HC2	Self: Dacron Swab Clin: Dacron Swab	hrHPV: STM	Colposcopy + colpo-directed biopsy or random biopsy - Participants with at least one positive test result - Random sample of women with negative tests	HPV: 1 pg/ml	CIN2+
19. Gustavson, 2011	Self: hrHPV Clin: hrHPV	PCR (primers for *E6/E7/L1*) *	Self: Viba-Brush Clin: cytobrush	Self + Clin: FTA cartridge	Colposcopy + colpo-directed biopsy - All participants	10 Geq/PCR	CIN2+
20. Taylor, 2011	Self: hrHPV Clin: hrHPV, cytology	hrHPV: HC2 Cyto: cPap, LBC (ThinPrep)	Self: Dacron Swab Clin: plastic spatula, cytobrush	Self: STM Clin: PreservCyt	Colposcopy + endocervical curettage and/or colpo-directed biopsy - All participants	HPV: 1 pg/mL Cyto: ASC-US+, LSIL+	CIN2+

Author, year	Tests	Assay	Sampling device	Storage medium	Golden standard	Test cut-off	Outcome
21. Twu, 2011	Self: hrHPV Clin: hrHPV	PCR (MY9/11 nested GP5+/6+), HPV Blot	Self: cytobrush Clin: Ayre spatula, cytobrush	Self + Clin: STM	Colposcopy + colpo-directed biopsy - participants with acetowhite lesions (VIA), or a positive cPap	- HPV Blot : 1-50 copies of HPV geq per PCR.	CIN2+ CIN3+
22. Belinson, 2012	Self: hrHPV Clin: hrHPV, cytology	Self hrHPV: Cervista, MALDI-TOF Clin hrHPV: HC2, Cervista, MALDI-TOF Clin cyto: cPap	Self: POI/NIH self-sampler, conical brush Clin: broom sampler	Self + clin: PreservCyt	Colposcopy + colpo-directed biopsy, or random biopsy and endocervical curettage - Participants with at least one positive test result	ASC-US	CIN3+
23. Dijkstra, 2012	Self: hrHPV Clin: hrHPV	PCR (GP5+/6+)	Self: Viba-Brush Clin: Viba-Brush, Cervex-Brush	Self + Clin: PreservCyt	Colposcopy + colpo-directed biopsy, or random biopsy (≥1) - All participants	Not documented	CIN2+
24. Longatto-Filho, 2012	Self: hrHPV Clin: hrHPV, cytology	hrHPV: HC2 Cyto: cPap, LBC (SurePath), LBC (Citoliq)	Self HPV: tampon Clin HPV: cervical swab Clin cyto: cervix brush (Surepath), DNA-Citoliq Brush	Self + Clin HPV: STM Clin Cyto: SurePath, Citoliq	Colposcopy + colpo-directed biopsy - Participants with at least one positive test result - Random sample (>5%) of women with negative tests **	HPV: 1pg/ml hrHPV Cyto: ASC-US+, LSIL+, HSIL+	CIN2+ cancer
25. van Baars 2012	Self: hrHPV Clin: hrHPV	SPF10-PCR, PCR (GP5+/6+)	Self: Evalyn-Brush Clin: Cervex-Brush	Self: FTA cartridge Clin: ThinPrep, SurePath	Colposcopy + colpo-directed biopsy - 44 out of 134 women (if histological result was available), for others follow-up cytology - All participants	Not documented	CIN2+ CIN3+
26-28. Zhao, 2012	Self: hrHPV Clin: hrHPV, cytology	hrHPV: HC2 Cyto: LBC (ThinPrep)	Self***: Dacron Swab Clin***: plastic spatula, endocervical brush	Self***: STM Clin***: SurePath for cyto; STM for HPV (see Belinson, IJC 2010)	Colposcopy + colpo-directed or random biopsy (4) - Participants with at least one positive test result	HPV: 1 pg/ml Cyto: ASC-US	CIN2+ CIN3+

Author, year	Tests	Assay	Sampling device	Storage medium	Golden standard	Test cut-off	Outcome
29. Darlin, 2013	Self: hrHPV Clin: hrHPV	PCR (GP5+/6+)	Self: coton swab Clin: Cervex-Brush Combi	Clin: PreservCyt	Colposcopy + colpo-directed biopsy - All participants	Not documented	CIN2+
30. Geraets, 2013	Self: hrHPV Clin: hrHPV	SPF10-PCR, PCR (GP5+/6+)	Self: Viba-Brush Clin: Cervex-Brush	Self: FTA cartridge Clin: PreservCyt	Colposcopy + colpo-directed biopsy - All participants	Not documented	CIN2+ CIN3+
31. Guan, 2013	Self: hrHPV Clin: hrHPV	Linear Array	cervical sampler brush	Self + Clin: FTA cartridge	Colposcopy + colpo-directed biopsy - All participants	Not documented	CIN2+
32/33. Jentschke, 2013 a & b	Self: hrHPV Clin: hrHPV, p16	hrHPV: HC2 P16: $p16^{INK4a}$ ELISA	Self: lavage (Delphi screener) Clin: Not documented	Self: buffered saline Clin: PreservCyt, Cervatec	Colposcopy + colpo-directed biopsy - All participants	Not documented	CIN2+ CIN3+
34. Nieves, 2013	Self: hrHPV Clin: hrHPV, cytology	hrHPV: HC2, APTIMA Cyto: LBC (Thinprep)	Self: POI/NIH self-sampler Clin: broom sampler	Self + Clin: PreservCyt	Colposcopy + colpo-directed cryoterapy or colpo-directed biopsy and/or multiple random biopsies - Participants with at least one positive test result	Cyto: ASCUS HPV: Not documented	CIN2+ CIN3+
35. Zhao, 2013	Self: hrHPV Clin: hrHPV, E6. VIA	hrHPV: HC2, *care*HPV. OncoE6 (only on clin).	Self & clin for cHPV: cone-shaped brush (Cervical Sampler, QIAGEN)∞. Clin for E6: polyester swab.	Self & clin for cHPV: CCM.	Colposcopy & targeted and random biopsies if one screen test was positive & 10% random selection of cotest-negative subjects.	RLU ≥1.0.	CIN2+ CIN3+
36. Chernesky, 2014	Self: hrHPV Clin: hrHPV	APTIMA HPV	Self: tapered round brush, cervix broom Clin: Cervex, APTIMA SCT	Self: APTIMA SCT Clin: Preserv-Cyt, APTIMA SCT, SurePath	Colposcopy on all. Colposcopy targeted biopsy if required.	APTIMA signal: ≥0.5	CIN2+

Author, year	Tests	Assay	Sampling device	Storage medium	Golden standard	Test cut-off	Outcome
37. Hesselink, 2014	Self: hrHPV Clin: hrHPV	hrHPV: HPV-Risk Test & GP5+/6+ PCR-EIA.	Self: Viba-Brush and Delphi Screener. Clin: Cervex	Self: PreservCyt: Delphi Screener SurePath: Viba-Brush. Clin: Preservcyt, SurePath.	Histology for cases; negative cyto & negative FU (2y) for controls.	C_T<36	CIN2+
38-41. Jeronimo, 2014	Self: hrHPV. Clin: hrHPV, Cytology. VIA.	hrHPV: *care*HPV cyto: conventional cyto.	Self HPV: cervical brush (digene cervical sampler). Clin HPV: cervical brush (digene cervical sampler). Clin cyto: Ayres spatula[€].	Self & clin: Digene collection media.	Colposcopy if at least one +screen test. Colpo-directed biopsy if colposcopic abnormality & ECC if required for diagnosis. Quality review of all CIN2+ & 10% negative biopsies (random).	HC2: RLU ≥1 Cyto: ASC-US+	CIN2+ CIN3+
42. Wang, 2014	Self: hrHPV Clin: hrHPV VIA	hrHPV: *care*HPV	Conical Cervical Sampler	DCM FTA card	Any positive results on HC2, *care*HPV, or VIA detection. Colposcopy + colpo-directed biopsy	*care*HPV: RLU ≥1.	CIN2+
43. Zhang, 2014	Self: hrHPV Clin: hrHPV	hrHPV: HC2 & LA	Not mentioned	Not mentioned	Colposcopy + colpo-directed biopsy. To all participants	Assumed HC2: RLU ≥1	CIN2+
44. Boggan, 2015	Self: hrHPV Clin: hrHPV	hrHPV: HC2	Self: Dacron brush Clin: Dacron brush	STM	Colposcopy + colpo-directed biopsy, with ECC if SCJ invisible; if HPV+ (on self or clin-samples).	Assumed HC2: RLU ≥1	CIN1+ CIN2+ CIN3+
45. Porras, 2015	Self: hrHPV Clin: hrHPV, cytology	Self: hrHPV: SPF10 PCR with HPVLiPA2; Clin hrHPV: same PCR, HC2. Cyto: LBC (ThinPrep)	Self: dry Dacron swab Clin: Cervex Brush	PreservCyt	Colposcopy + biopsy: immediate & if subsequent HPV/cyto+ observed up to 4Y at 6M intervals.	≥1 of 12hrHPV types	CIN2+
46. Chen, 2016 (a), Gen Mol Res	Self: hrHPV Clin: hrHPV	hrHPV: Cobas-4800, Seq HPV Assay, BMRT HPV Assay	Self and clin: conical brush (Qiagen)	Not documented	Colposcopy/biopsy, no details on all; gold standard undefined.	Not documented	CIN2+ CIN3+

Author, year	Tests	Assay	Sampling device	Storage medium	Golden standard	Test cut-off	Outcome
47. Chen, 2016 (b), J Ob Gyn Res	Self: hrHPV Clin: hrHPV	hrHPV: Abbott RealTime hrHPV (PCR) Cyto: LBC	Self: Evalyn brush Clin: cervical brush (cyto), Digene Female Swab Specimen Collection Kit (HPV)	Self: Dry for 16-18 W (Evalyn tube), then transferred to ThinPrep before PCR. Clin HPV: STM, then ThinPrep.	Colposcopy with directed or random biopsy on all.	Not documented	CIN2+ CIN3+
48. Jentschke, 2016	Self: hrHPV Clin: hrHPV, cytology	hrHPV: Abbott RealTime hrHPV PCR Cyto: LBC (ThinPrep)	Self: dry Evalyn Brush and dry Qvintip collection device Clin: broom-like device (Hologic). Order of 2 self-collection devices was alternated.	Dry, then transferred to PreservCyt	Colposcopy + colpo-directed biopsy, ECC if indicated. No biopsies taken for unsuspicious colposcopy.	As defined by manufacturer.	CIN2+ CIN3+
49. Qin, 2016	Self: hrHPV Clin: hrHPV, cytology	hrHPV: RealTime High-Risk HPV (Abbott *m2000*rt) Cyto: LBC (ThinPrep)	Self: conical brush (Qiagen) Clin: broom-brush	Self: FTA Elute card Clin: PreservCyt	Colposcopy on all + colpo-directed biopsy from colposcopically suspected lesions.	HPV: Not documented Cyto: ASC-US+	CIN2+
50. Stanczuk, 2016	Self: hrHPV Clin: hrHPV, cytology	hrHPV: Cobas 4800 Cyto: LBC (ThinPrep)	Self: Roche female swab sample packet. Clin: Cervex-Brush.	PreservCyt	Colposcopy and histology: - participants with high-grade abnormalities - participants with 2 low-grade or 3 borderline or 3 unsatisfactory cyto. Follow-up cyto: - borderline changes or low-grade cyto: repeat cyto after 6M.	Ct<40.	CIN2+ CIN3+

Author, year	Tests	Assay	Sampling device	Storage medium	Golden standard	Test cut-off	Outcome
51. Aiko, 2017	Self: hrHPV Clin: hrHPV, cytology	hrHPV: HC2 Cyto: cPap	Clin: Cytopic device (Matsunami Glass Ind.) for cyto; Digene HC2 DNA Collection Device for HPV. Self: Evalyn Brush	Not documented	Colposcopy on all, colposcopy-targeted biopsies & random biopsies if colposcopy normal & satisfactory; ECC if unsatisfactory colposcopy.	Not documented	CIN2+ CIN3+
52. Asciutto, 2017	Self: hrHPV Clin: hrHPV, cytology.	hrHPV: Cobas 4800 Cyto: LBC (ThinPrep)	Self: swab (Cobas® PCR Female Swab Sample Kit. Clin HPV: swab (Cobas® PCR Female Swab Sample Kit). Clin cyto: Cervex Combi Brush.	Self: Cobas PCR Female Swab Sample Kit. Clin HPV: Cobas® PCR Female Swab Sample Kit. LBC: PreservCyt.	Colposcopy on all, biopsies if indicated. If no biopsy, cytology was used as reference.	According to manufacturer's instructions.	CIN2+
53. Catarino, 2017	Self: hrHPV Clin: hrHPV, cytology.	hrHPV: Xpert HPV; part of clin sample also cobas 4800. Cyto: LBC (ThinPrep)	Self: dry, cotton swab in plastic tube. Clin: Cervex Brush	Self: dry, collection transferred to 0.9% NaCl in lab. Clin: PreservCyt.	Colposcopy on all, biopsy with ECC if necessary.	According to manufacturer's instructions.	CIN2+
54. Leeman, 2017	Self: hrHPV Clin: hrHPV	hrHPV: SPF10-DEIA-LIPA25 & GP5+/6+-EIA-LMNX	Self: Evalyn Brush Clin: Cervex	Self: Dry up to 3 months, then placed in vial with PreservCyt for shipment. Clin: PreservCyt.	All had colposcopy, all had colposcopy targeted biopsies, completed with random biopsies; ECC if unsatisfactory ECC.	Not documented.	CIN2+ CIN3+

Author, year	Tests	Assay	Sampling device	Storage medium	Golden standard	Test cut-off	Outcome
55. Asciutto, 2018	Urine: HPV Self: HPV Clin: HPV, LBC cytology	HPV: APTIMA Cyto: ThinPrep	Urine: first void urine Self: APTIMA Vaginal swab Clin: APTIMA Vaginal swab; LBC	Urine: APTIMA urine specimen collection kit. Self: APTIMA vaginal specimen collection kit. Clin; APTIMA vaginal specimen collection kit Clin cyto: PreservCyt.	Depending on colposcopy: punch biopsy or LLETZ.	APTIMA: as defined by manufacturer. Cyto: ASC-US+, LSIL+, HSIL+.	CIN2+
56. Leinonen, 2018	Self: HPV Clin: HPV	Self & clin: Anyplex II HPV28; cobas 4800, Xpert HPV. Clin: ThinPrep.	Self: Evalyn Brush & FLOQSwabs; Clin: brush not otherwise specified.	Self: dry transport of self-collection devices to lab. Clin: PreservCyt	Histology of the cone.	HPV: as defined by manufacturer.	CIN3+

⌗ (30 participants did not undergo colposcopy (likely part of the group of 32 healthy volunteers)

$ participants with a negative colposcopy, but abnormal cytology or a positive HPV-test, had a second colposcopy + four-quadrant biopsies + endocervical curettage

¥ women who had a positive HC2-test, and a random sample of women with a negative HC2-test or who were CIN2+

* Retrieved from: Moberg M, Gustavsson I, Gyllensten U. Real-time PCR-based system for simultaneous quantification of human papillomavirus types associated with high risk of cervical cancer. *J Clin Microbiol* 2003; 41(7):3221-3228.

** Retrieved from: Syrjanen K, Naud P, Derchain S, Roteli-Martins C, Longatto-Filho A, Tatti S et al. Comparing PAP smear cytology, aided visual inspection, screening colposcopy, cervicography and hrHPV testing as optional screening tools in Latin America. Study design and baseline data of the LAMS study. *Anticancer Res* 2005; 25(5):3469-3480.

∞ Information obtained from first author.

*** Retrieved from: Belinson et al, 127, 1151–1157 (2010), for SPOCC-III study.

€ Mentioned in Labani 2014, Eur J Obstet Gynaecol Reprod Biol 2014: 176: 75–79.

Abbreviations: ASC-US, Atypical Squamous Cells of Undetermined Significance; CCM: Care Collection Medium; CIN, Cervical Intraepithelial Neoplasia; colpo, colposcopy; cPap, conventional Pap smear; cyto, cytology; DCM: Digene Collection Medium; ECC: endo-cervical curettage; HPV, Human Papillomavirus; LBC, Liquid-Based Cytology; PBS, Phosphate Buffered Saline; STM, Specimen Transport Medium; UCM, Universal Collection Medium.

3.3. Used collection devices

Table 3. Devices used for self-sampling, grouped in five categories (in black: studies included in the previous meta-analysis, in red studies added).

Device group	Device	Manufacturer	Studies
Brush	careHPV cervical brush	Qiagen, Gaithersburg, MD, USA	Jer14
	Cervical brush	-	Hol06
	Conical brush. †	Qiagen (previously Digene Corporation), Gaithesburg, MD, USA -	Bha09, Laz11, Gir06, Bel12, Zha12a, Zha12b, Zha12c, Gua13, Zha13, Che14a, Wan14, Qin16
	Cyto-Brush	-	Hil99, Dap06, Twu11
	Cyto-Brush PLUS	Cooper Surgical, Trumbull, CT, USA	Gar03
	Dacron brush	Qiagen, Gaithersburg, MD	Bog15
	Evalyn Brush	Rovers Medical Devices B.V., Oss, the Netherlands	Van12, Che16b, Jen16, Aik17, Lee17
	POI self-sampler	-	Nie13
	POI/NIH self-sampler	-	Bel12
	Vaginal brush	-	Qia08, Dij12
	Viba-Brush	Vibabrush: Rovers Medical Devices B.V., Oss, Netherlands FTA cartridge: GE Healthcare, Buckinghamshire, United Kingdom	Gus11, Ger13, Hes14
Lavage	*Delphi Screener*	Delphi Bioscience, Scherpenzeel, the Netherlands	Jen13a, Jen13b, Hes14
	Lavage (15 ml)	-	Nob02
	Mermaid (5 ml)	(previous Delphi Screener)	Bri06
	MY-PAP (21ml)	Medtech, Bohemia, NY, USA	Mor92
Spatula	*Qvintip*	AprovixAB, Uppsala, Sweden	Wik11, Jen16
Swab	APTIMA vaginal swab	Hologic Inc, MA, USA	Asc18
	Cobas PCR Female Swab Sample Kit	Roche Molecular Diagnostics, Pleasanton, CA, USA	Asc17, Sta16
	Cotton swab	-	Lor02, Sza07, Dar13, Cat17
	Dacron swab	-	Sel00, Wri00, Bel01, Sal03, Seo06, Bal10, Tay11, Por15
	Flocked swab or FLOQSwab (ESwab®)	Copan, Brescia, Italy	Lei18
Tampon	Tampon	-	Lon12
Not documented	-	-	Zha14

† Also called "*Qiagen/Digene cervical sampler"*

3.4. Used media for transport and storage of cervical cell material

Table 4. Transport/storage media used (in black: studies included in the previous meta-analysis, in red studies added)**.**

	Author, year	Medium for self-sample/Recipient if dry collection	Medium used in laboratory
Transport media which conserve cells for cytological interpretation			
PreservCyt	Garcia, 2003	PreservCyt	
	Belinson, 2012	PreservCyt	
	Dijkstra, 2012	PreservCyt	
	Nieves, 2013	PreservCyt	
	Hesselink, 2014	PreservCyt media with Delphi Screener (lavage)	
	Porras, 2015	PreservCyt	
SurePath	Brink, 2006	SurePath	
	Hesselink, 2014	SurePath with Viba Brush	
Citoliq	Girianelli, 2006	Citoliq	
Storage media for virology			
STM*, UCM**, CCM^{ø}/DCM$^{\infty}$	Sellors, 2000	STM	
	Wright, 2000	STM	
	Belinson, 2001	STM	
	Salmeron, 2003	STM	
	Holanda, 2006	UCM	
	Qiao, 2008	Collection medium (QIAGEN)	
	Bhatla, 2009	STM	
	Balasubramanian, 2010	STM	
	Taylor, 2011	STM	
	Twu, 2011	STM	
	Longatto-Filho, 2012	STM	
	Zhao, 2012	STM	
	Zhao, 2013	CCM (=DCM)^{ß}	
	Jeronimo, 2014	DCM	
	Wang, 2014	DCM	
	Boggan, 2015	STM	
PBS***, buffered saline	Lorenzato, 2002	PBS	
	Nobbenhuis, 2002	PBS	
	Daponte, 2006	PBS	
	Jentschke, 2013a	Buffered saline	
Cobas	Stanczuk, 2016	Roche PCR media	
	Asciutto, 2017	Cobas PCR Female Swab Sample Kit	
APTIMA	Chernesky, 2014	APTIMA SCT ¶	
	Asciutto, 2018	Vaginal swab collection kit	
FTA cartridge			
	Gustavsson, 2011	FTA cartridge	Distilled water
	Geraets, 2013	FTA cartridge	Distilled water
	Guan, 2013	FTA cartridge	DEPC water
	Wang, 2014	FTA card	Sterile water
	Qin, 2016	FTA	DEPC$^{√}$ water
Dry transport			
	Hillemanns, 1999	Placed into a specimen collection tube	Not documented
	van Baars 2012	Capped Evalyn case	PreservCyt
	Darlin, 2013	Sterile cryotube	Not documented
	Chen, 2016 (b)	Dry for 16-18 weeks (Evalyn tube)	Transferred to PreservCyt before PCR

	Author, year	Medium for self-sample/Recipient if dry collection	Medium used in laboratory
	Jentschke, 2016	Evalyn tube Qvintip tube	PreservCyt Preservcyt
	Catarino, 2017	Plastic tube	Transferred to 0.9% NaCl in lab.
	Leeman, 2017	Evalyn Tube (dry collection)	PreservCyt
	Leinonen, 2018	Evalyn Tube & FLOQSwab	PreservCyt
Other (cannot be categorized)			
	Morrison, 1992	Ethanol carbowax	
	Jentschke, 2013b	Cervatec†	
Not documented			
	Seo, 2006	Not documented	
	Szarewski, 2007	Not documented	
	Wikstrom, 2011	Not documented	
	Zhang, 2014	Not documented	
	Chen, 2016 (a)	Not documented	
	Aiko, 2017	Not documented	

*STM, Specimen Transport Medium; **UCM, Universal Collection Medium; ***PBS, Phosphate-buffered saline; ºCCM, collection care medium; ᵒᵒDCM, Digene Care Medium; ßExtracted from Belinson, IJC 2010; √Diethyl Pyrocarbonate; ¶APTIMA SCT = APTIMA specimen collection and transportation kit.

A. Transport media which conserve cells for cytological interpretation

1. ThinPrep=PreservCyt
2. SurePath=AutoCyte
3. Citoliq

B. Storage media for virology

1. STM (specimen transport medium), UCM (universal transport medium), CCM (collection care medium), DCM (Digene care medium), Collection medium (QIAGEN)
2. PBS, buffered saline
3. Cobas, Cobas PCR Female Swab Sample Kit

C. Other

1. Ethanol carbowax
2. Cervatec†
3. APTIMA SCT (specimen collection and transportation kit)

D. Dry transport

E. FTA cartridge/card

3.5. Used hrHPV tests

Table 5. Used tests (abbreviations, manufacturer and study in which the tests were applied).

Abbreviation	Test	Manufacturer	Studies
AB	Abbott RT PCR hrHPV (Multiplex real-time PCR test that targets the (GP5+/6+) *L1 region* of 14 hrHPV types PCR)	Abbott Molecular, Inc., Des Plaines, IL, USA	Jen13b, Che16b, Jen16, Qin16
Anyplex HPV28	Anyplex II HPV28 (multiplex rtPCR targeting L1 of 28 HPV types with separated identification)	Seegene, Seoul, South Korea	Lei18
APTI	APTIMA (A multiplex *in vitro* nucleic acid amplification test targeting *E6/E7* mRNA from 14 hrHPV types)	Gen-Probe Inc., San Diego, CA, USA	Nie13, Che14, Asc18
BMRT	BMRT HPV PCR test	BioPerfectus Technologies, Taizhou, China	Che16a
cHPV	careHPV (A signal amplification method (simplified HC2) targeting 14 hrHPV types) [0.5]: cutoff at RLU>0.5 [1]: cutoff at RLU>1. Point-of-care test.	QIAGEN Corporation, Gaithersburg, MD, USA	Qia08, Zha13, Jer14, Wan14
cobas 4800	cobas 4800 HPV test (Target amplification by RT PCR using PGMY consensus primers, identifying, HPV16, HPV18 and 12 other hrHPV types)	Roche Molecular System, Pleasanton, CF, USA	Che16a, Sta16, Asc17, Lei18
Cvsta	Cervista (A signal amplification method by Invader chemistry using 3 ologinucleotide mixtures, together targeting 14 hrHPV types)	Hologic, Bedford, MA, USA	Bel12
DNAch	DNAchip (A broad spectrum PCR based on GP5+/6+PCR targeting the *L1 region* to detect and genotype 15 hrHPVs and 9 lrHPVs)	Biomedlab Co., Seoul, Korea	Seo06
GP5+/6+-EIA	PCR with GP5+/6+ primers with EIA recognition of amplicons hybridized with 14 oligo-nucleotids.	Diassy, Rijswijk, the Netherlands	Bri06, Dij12, VBaa12, Ger13, Lee17
GP5+/6+-LMNX	modified GP5+/6+ with Luminex read-out targeting the *L1 region* of hr- and lr HPVs)	Diassy, Rijswijk, the Netherlands	Dar13, Lee17

Abbreviation	Test	Manufacturer	Studies
HC2	Hybrid Capture-2 (A signal amplification method targeting 13 hrHPV types)	Qiagen Corporation, Gaithersburg, MD, USA	Hil99, Sel00, Wri00, Bel01, Sal03, Gir06, Hol06, Sza07, Bha09, Bal10, Laz11, Tay11, Wik11, Lon12, Zha12a, Zha12b, Zha12c, Jen13a, Jen13b, Nie13, Zha13, Zha14, Bog15, Por15†, Aik17
LBC-TP	Liquid-Based Cytology (ThinPrep)	Cytyc Corporation, Boxborough, MA, USA	Gar03, Bri06
LIPA25	SPF10-DEIA-LIPA	DDL, Voorburg, the Netherlands	vBa12, Ger13, Por15, Lee17
M-TOF	MALDI-TOF (GP5+/6+ based PCR with MALDI-TOF read out to detect *L1 region*)	AB SCIEX, Foster City, CA, USA	Bel12
NGS	Next Generation Sequencing. • SeqHPV assay	• BGI Shenzhen, China	Che16a
PCR other	Non-commercial PCR using primers, other than GP5+/6+:		
	MY9/11 (*L1 region*)		Mor92, Lor02,
	PGMY9/11 (*L1 region*)		Gar03, Bha09
LA	Linear Array (PGMY09/11 L1 consensus primer PCR test that identifies 37 HPV types by reverse line blot hybridization)	Roche MolecularSystems, Alameda, CA, USA	Gua13, Zha14
HPV Risk	Multiplex real-time PCR targeting a ~150-bp fragment of the E7 gene of 15 hrHPV types.	selfScreen, Amsterdam, the Netherlands	Hes14
Xpert HPV	Cartrige-based RT PCR targeting E6/7 genes of 14 hrHPV types. Point-of-care test.	Cepheid, Sunnyvale, CA, USA	Cat17, Lei18

† Only on clinician-taken sample.

The following hrHPV tests, assessed in the meta-analysis are considered as clinically validated for cervical cancer screening on clinician samples [6].

a) Based on signal amplification: Hybrid Capture, Cervista.
b) Based on target amplification by polymerase chain reaction (PCR): GP5+/5+ PCR-EIA, Abbott RT PCR hrHPV, Anyplex II HR[7], cobas 4800 HPV test, GP5+/6+-LMNX, Linear Array[8], HPV Risk assay, Xpert HPV[9].

4. Characteristics of the randomized trials comparing strategies including offering self-samples with control interventions

Table 6. Study characteristics of included RCTs fulfilling eligibility criteria.

Author, year Country	**Study design and population**	**Scenario of invitation in self-sampling arm**	**Scenario of invitation in control arm**	**N (Self-sampling arm)**	**N (Control arm)**	**Age range (years)**
1. Bais, 2007 The Netherlands	Randomized. Women who did not respond to the invitation for conventional screening and the first reminder 6 months later. No data on response stratified by screening history.	Direct mailing of the self-sampling kit.*	Invitation for conventional cytology with an explanatory letter.*	2,352	272	30-50
2. Gok, 2010 The Netherlands	Randomized. Women who did not respond to the invitation for conventional screening and the first reminder 6 months later. Whole population: 1st screen or screened 5 years ago. Subgroup: screened >7 years ago.	Direct mailing of the self-sampling kit, preceded by a notification. *	Invitation for conventional cytology, preceded by a notification.*	26,886	277	30-60
3. Giorgi-Rossi, 2011 Italy	Randomized. Women who did not respond to the invitation for conventional screening. No sufficient data on response stratified by screening history.	- Direct mailing of the self-sampling kit, preceded by a notification. - Women were offered the opportunity to receive the self-sampler device (by mail or picking it up at the clinic). If interested, they had to call a free toll number.	- Invitation for conventional cytology (prefixed date). - Invitation for hrHPV testing at the clinic (sample collected by a clinician).	- 616 - 622	- 619 - 616	35-65
4. Lazcano-Ponce, 2011 Mexico	Randomized. Women in poverty-reduction programme, with limited access to health services. No data on response stratified by screening history.	Door-to-door recruitment. Nurses performed home visits, in which a self-sample was taken by the woman herself.	Door-to-door recruitment. Nurses performed home visits, and made an appointment for conventional cytology in the clinic.	9,371	1,2731	25-65

Author, year Country	**Study design and population**	**Scenario of invitation in self-sampling arm**	**Scenario of invitation in control arm**	**N (Self-sampling arm)**	**N (Control arm)**	**Age range (years)**
5. Piana, 2011 France	Randomized. Women who did not respond to the invitation for conventional screening and had not had a cervical smear in ≥2y. No sufficient data on response stratified by screening history	Direct mailing of the self-sampling kit, preceded by a notification with an opt-out option.	Invitation for conventional cytology.	4,400	4,934	35-69
6. Szarewski, 2011 United Kingdom	Randomized. Women who did not respond to ≥2 invitations for conventional screening. No data on response stratified by screening history	Direct mailing of the self-sampling kit.¥	Invitation for conventional cytology.¥	1,500	1,500	25-64
7. Virtanen, 2011 Finland	Randomized. Women who did not respond to the invitation for conventional screening. No sufficient data on response stratified by screening history.	Direct mailing of the self-sampling kit, preceded by a notification (with an opt-out option).	Invitation for conventional cytology (pre-fixed appointment).	2,397	6,302	30-60
8. Wikstrom, 2011 Sweden	Randomized. Women who had not participated in screening for ≥6 years. No data on response stratified by screening history.	Direct mailing of the self-sampling kit, preceded by a notification. Afterwards an additional reminder to participate was sent.	Invitation for conventional cytology, within the framework of the organised screening programme.	2,000	2,060	39-60
9. Gok, 2012 The Netherlands	Randomized. Women who did not respond to the invitation for conventional screening and the first reminder. No data on response stratified by screening history.	Direct mailing of the self-sampling kit, preceded by a notification.*	Invitation for conventional cytology, preceded by a notification.*	25,561	261	30-60

Author, year Country	**Study design and population**	**Scenario of invitation in self-sampling arm**	**Scenario of invitation in control arm**	**N (Self-sampling arm)**	**N (Control arm)**	**Age range (years)**
10. Darlin, 2013 Sweden	Randomized. Women who had not had any cervical smears taken for >9y. No data on response stratified by screening history.	Direct mailing of the self-sampling kit. After one month, a reminder including another self-sampling kit was sent to non-responders.	Invitation for hrHPV testing at an outpatient clinic. The invitation included several alternative appointments. A reminder was sent to non-responders.	1,000	500	32-65
11. Sancho-Garnier, 2013 France	Randomized. Women who did not respond to the invitation for conventional screening and had not had a cervical smear in ≥2y. No data on response stratified by screening history.	Direct mailing of the self-sampling kit, preceded by a notification.	Invitation for conventional cytology at an outpatient clinic. The invitation included a list of centers performing the test.	8,829	9,901	35-69
12. Broberg, 2014 Sweden	Randomized. Women who did not respond to ≥4 invitations for conventional screening and did not have a registered Pap smear for ≥6y (30-53y), ≥7y (54y), or ≥8y (55-62y). Data on response stratified by screening history: screened ≤10 or >10y ago; never screened.	Women were offered the opportunity to receive a self-sampling kit (by mail). If interested, they had to return a coupon using a postage-free envelope. A reminder was sent if the kit was ordered but not returned, or after 10 weeks to women who did not respond.	No particular intervention was done. Women continued to receive annual invitations until a smear was registered.	800	4,000	30-62
13. Haguenoer, 2014 France	Randomized. Women who had not had a cervical smear in ≥3y, and did not respond to the invitation for conventional screening. No data on response stratified by screening history.	Direct mailing of the self-sampling kit.	- Invitation for conventional cytology. - No intervention.	1,999	- 2,000 - 1,999	30-65

Author, year Country	**Study design and population**	**Scenario of invitation in self-sampling arm**	**Scenario of invitation in control arm**	**N (Self-sampling arm)**	**N (Control arm)**	**Age range (years)**
14. Arrossi, 2015 Argentina	Cluster randomized. Women found at home. No data on response stratified by screening history.	Door-to-door recruitment. Community health workers performed home visits, in which a self-sample was taken by the woman herself.	Door-to-door recruitment. Community health workers performed home visits and advised women to go to a health centre for a clinician-collected sample for hrHPV testing.	3,049	4,018	≥30
15. Cadman, 2015 United Kingdom	Randomized. Women who did not respond to the invitation for conventional screening and the first reminder. Data on response stratified by screening history: screened 0-3y, 3-5y, 5-10y and >10y ago; never screened.	Direct mailing of the self-sampling kit.	Invitation for conventional cytology.	3,000	3,000	25-65
16. Giorgi-Rossi, 2015 Italy	Randomized. Women who did not respond to the invitation for conventional screening. No data on response stratified by screening history.	- Direct mailing of the self-sampling kit, preceded by a notification. - Women were invited by mail, to pick up a self-sampling device at the clinic.	- Invitation for conventional cytology at the clinic. - Invitation for hrHPV testing at the clinic (sample collected by a clinician).	- 4,516 - 4,513	- 1,998 - 3,014	30-64
17. Moses, 2015 Uganda	RCT. Women who lived or worked in target city and had access to a mobile telephone. Door-to-door recruitment. No data on response stratified by screening history.	Women were provided samples at place of recruitment and returned them to outreach workers.	Women were scheduled for VIA appointment and received a reminder call.	248	245	30-65

Author, year Country	**Study design and population**	**Scenario of invitation in self-sampling arm**	**Scenario of invitation in control arm**	**N (Self-sampling arm)**	**N (Control arm)**	**Age range (years)**
18. Enerly, 2016 Norway	Cohort study with random selection of women who did not have cytology, hrHPV or histology in more than 3 years. Targeted women attended information sessions. No data on response stratified by screening history.	Direct mailing of the self-sampling kit, preceded by a notification with an opt-out option.	Invitation (i.e., reminder) to complete liquid-based cytology sent to women not included in intervention group.	800	2,593	26-69
19. Racey, 2016 Canada	RCT. Women with current Ontario Health Insurance Program card and no cytology in ≥30 months. No data on response stratified by screening history.	Direct mailing of a self-sampling kit, preceded by a notification with choice to opt-out. Reminder phone call 1 month after kits were mailed.	C1: Invitation letter to schedule cytology appointment with primary C2: No invitation (opportunistic screening)	335	C1: 331 C2: 152	30–70
20. Sultana, 2016 Australia	RCT. Never-screened or under-screened women (not screened in the previous 2.5 years). Data on response stratified by screening history: screened >2.5y ago; never screened.	Direct mailing of a self-sampling kit, preceded by a notification with an opt-out option.	Invitation (never-screened) or reminder (underscreened) letters for cytology.	14,153= 7,075 un-screened; 7,078 under-screened	2,025= 1,014 un-screened; 1,011 under-screened	30-69
21. Zehbe, 2016 Canada	Cluster-RCT. Women from one of 11 community clusters (“bands”), First Nations communities (N-Canada). Community assistants set up contacts and information & promotion activities (Community assistants recruited at community events, radio, door-to-door, mail, band office, and health office networks). No clear data on response stratified by screening history..	- Arm A: Self-sampling offered in phase 1. - Arm B: Self-sampling offered in phase 2.	- Arm B: Pap smear collection offered in phase 1. - Arm A: Pap smear collection offered in phase 2.	404 (6 clusters)	430 (4 clusters)	25-69

Author, year Country	**Study design and population**	**Scenario of invitation in self-sampling arm**	**Scenario of invitation in control arm**	**N (Self-sampling arm)**	**N (Control arm)**	**Age range (years)**
22. Kitchener, 2017 United Kingdom	Cluster-randomized. Phase 2 of STRATEGIC trial. Women, due for their first invitation, who in phase 1 of STRATEGIC who did not respond to invitation letters (with or without pre-leaflet or with/without online booking) to screening after 6 months.	- A) Direct mailing of unrequested self-sampling kits - B) Direct mailing of requested self-sampling kits - C) Offered women choice between nurse navigator and self-sampling kit (not considered for syst. rev)	No intervention beyond standard invitation.	- A) SS to all: 1,141 (32 GPs) - B) SS requested: 1,290 (66 GPs)	3,782 (101 GPs)	20 (Grampian); 25 (Manchester)
23. Modibbo, 2017 Nigeria	RCT. Women living or working in target community not planning to move within 6 months. No data on response stratified by screening history.	Women attending a community event were given self-sampling kits to complete at home and to mail or drop them off at collection sites.	Women attending a community event were given hospital hrHPV test appointment.	200	200	≥30
24. Kellen, 2018 Belgium	RCT. Population-based RCT with 2 experimental arms and 2 controls arms, including women without screening record since 8 years. No data on response stratified by screening history.	1) Reminder mailing with self-sampling kit (mail-to-all); 2) Reminder mailing with self-sampling to be ordered (opt-in).	1) Reminder mailing inviting women to have a cytology specimen taken by a clinician (=routine intervention). 2) No invitation.	Mail-to-all: 9,118. Opt-in: 9,098.	Reminder letter: 8,830. No reminder: 8,849.	30-64
25. Tranberg, 2018 Denmark	Population-based RCT with 1 control arm and 2 experimental arms (mail-to-all & opt-in) including women who did not reply to a 1st invitation and were due to a 2nd reminder. Nested in Danish screening programme. Response rates stratified for regularly screened, under-screened and never screened subgroups. See Table 16 for definitions.	1) Reminder mailing with self-sampling kit; 2) Reminder mailing with self-sampling to be ordered (opt-in). Women were also offered the possibility to contact a GP for collection of cyto specimen. For both arms: reminder letter if response after 4m.	Reminder mailing inviting women to have a cytology specimen taken by a clinician.	Mail-to-all: 3,265. Opt-in: 3,264.	3,262	30-64

* A telephone helpline and/or website with information was available throughout the study.
¥ Study information was available in different languages as hard copy and on the internet.
Abbreviations: GP: general practitioner; HPV: human papillomavirus; RCT: randomized controlled trial; SS: self-sampling; VIA: visual inspection with acetic acid.

Table 7. Test, triage & follow-up characteristics of RCTs fulfilling eligibility criteria.

Author, year	Tests	Self-sampling device	Time of response assessment (months after invitation)	Triage of test+	Follow-up
1. Bais, 2007	PCR (GP5+/6+)	Cervicovaginal brush	6m	No triage	▪ Cytology + colposcopy + colpo-directed biopsy, in case of positive screen-test
2. Gök, 2010	HC2	Lavage (Delphi screener)	12m	Self-arm: cytology + repeat HPV	▪ Colposcopy + colpo-directed biopsy, in case of ASC-US+ ▪ Repeat testing (Pap + hrHPV) in 1y, in case of normal cytology or no cytology performed
3. Giorgi-Rossi, 2011	HC2	Lavage	3m	No triage	▪ Colposcopy + colpo-directed biopsy, in case of screen test+ and positive colposcopy ▪ Colposcopy + cytology in 1y, in case of screen test+ and negative colposcopy
4. Lazcano-Ponce, 2011	HC2	Cervicovaginal brush (Digene)	ND	No triage	▪ Colposcopy (free of charge) + colpo-directed biopsy, in case of screen test+
5. Piana, 2011	PCR	Not documented	ND	No triage	▪ Cytology and colposcopy + colpo-directed biopsy
6. Szarewski, 2011	HC2	Swab	6m	Cytology	▪ Colposcopy + colpo-directed biopsy, in case of triage test+ (or triage test-, by choice) (self-sampling arm) or screening test+ (control arm).
7. Virtanen, 2011	HC2	Lavage (Delphi screener)	ND	- <40y: cytology + repeat HPV - ≥40y: no triage	▪ <40y: Colposcopy + colpo-directed biopsy, in case of at least one positive triage test. Repeat testing (cytology + hrHPV) in 1y, in case of normal triage test. ▪ ≥40y: colposcopy + colpo-directed biopsy, in case of a positive screen test
8. Wikström, 2011	HC2	Swab	12m	No triage	▪ Self-arm: Colposcopy + biopsy; or cytology (with/without repeat hrHPV) ▪ Control arm: Colposcopy + biopsy, in case of HSIL+; repeat cytology in case of ASC-US or LSIL
9. Gök, 2012	HC2	Cervicovaginal brush	12m	Cytology	▪ Colposcopy + colpo-directed biopsy, in case of ASC-US+ ▪ Repeat testing (Pap + hrHPV) in 1y, in case of normal cytology
10. Darlin, 2013	PCR (GP5+/6+)	Not documented	ND	No triage	▪ Colposcopy + colpo-directed biopsy and LBC, in case of hrHPV.

Author, year	Tests	Self-sampling device	Time of response assessment (months after invitation)	Triage of test+	Follow-up
11. Sancho-Garnier, 2013	Abbott RT PCR	Swab (Dacron)	ND	Cytology	▪ Colposcopy + colpo-directed biopsy, in case of LSIL+
12. Broberg, 2014	HC2	Plastic swab (QvinTip)	ND	No triage	▪ Colposcopy + colpo-directed biopsy, in case of hrHPV-positivity and/or abnormal cytology.
13. Haguenoer, 2014	INNO-LiPa	Dry nylon flocked swab.	9m 12m	Cytology	▪ Colposcopy + colpo-directed biopsy in case of ASC-US+
14. Arrossi, 2015	HC2	Cervical brush (Qiagen)	6m	Self: no triage Control: cytology	▪ Colposcopy + colpo-directed biopsy, in case of hrHPV-positivity (self-sampling arm) or in case of hrHPV-positivity and ASC-US+ (control arm).
15. Cadman, 2015	HC2	Dacron Swab	3m	Cytology	▪ Colposcopy + colpo-directed biopsy, in case of abnormal cytology.
16. Giorgi-Rossi, 2015	HC2	Lavage (Delphi screener)	3m	Primary HPV: cytology (3/6 study centers), or no triage (3/6). Primary cytology: no triage.	▪ Colposcopy + colpo-directed biopsy in case of ASC-US+ (cytology triage, or primary cytology). Repeat HPV in case of normal cytology. ▪ Cytology, and colposcopy + colpo-directed biopsy in case of hrHPV+ (no triage). Repeat double testing in 3-6 months in case of normal colposcopy and HSIL, otherwise repeat testing in 1 year.
17. Enerly, 2016	CLART HPV2 test, HC2	Lavage (Delphi screener) / Evalyn brush (randomized)	ND	Self arm: cytology or hrHPV testing Control arm: cytology	For women with hrHPV-positive result on self-sample: scheduled appointment for collection of a cervical specimen that was co-tested (cytology &hr HPV).
18. Moses, 2016	Ecoli s.r.o real-time PCR test	Dracon swab	ND	VIA	▪ Self-test arm: Cryotherapy at VIA appointment, or colposcopy with treatment when indicated. ▪ VIA arm: Cryotherapy at the time of screening. Colposcopy and treatment referral when lesions were not appropriate for cryotherapy or when VIA was unsatisfactory.

Author, year	Tests	Self-sampling device	Time of response assessment (months after invitation)	Triage of test+	Follow-up
19. Racey, 2016	NML Luminex (linear array)	Dracon swab	ND	Cytology	Standard of care
20. Sultana, 2016	Cobas 4800	Nylon-tipped flocked swab	6m	HPV 16/18: No triage (directly to colposcopy) HPV other types: Cytology	Colposcopy with biopsy
21. Zebhe, 2016	Cobas 4800	Dracon swab	3m	Cytology: repeat in 6m HPV+: Cytology	Colposcopy
22. Kitchener, 2017	Cobas 4800	Lavage (Delphi Screener)/ Evalyn Brush	3m 6m 12m 18m	Cytology	Colposcopy if triage by cytology was positive. Usual triage as recommended in NHS programme if cytology positive in control arm. No triage results were presented.
23. Modibbo, 2017	(GP5+/6+-EIA PCR with LMNX genotyping)	Dry flocked swab	1m	ND	Treatment and follow-up
24. Kellen, 2018	RIATOL qPCR	Qvintip	12m	Cytology	Not documented.
25. Tranberg, 2018	SS arm: Cobas 4800. Control arm: SurePath cytology Cobas 4800 if 60-64y	Evalyn Brush	6m	SS arm: SurePath cytology.	FU as defined in Danish programme ASC-US/HPV+ & LSIL+ referred to colposcopy. If self HPV+ & NILM at 1st triage: repeat cytology & HPV at 12m.

Abbreviations: ASC-US+: atypical squamous cells of undetermined significance or more severe results; EIA: enzyme immunoassay; FU: follow-up; HC2: Hybrid Capture 2; hrHPV: high-risk human papillomavirus; LMNX: Luminex; LSIL+: low-grade squamous intraepithelial lesions or more severe disease; ND: not documented; PCR: polymerase chain reaction; NML: Canadian National Microbiology Laboratory; RCT: randomized controlled trial; SS: self-samplig; VIA: visual inspection with acetic acid.

5. Assessment of the quality of diagnostic studies

Table 8. Quality assessment of included studies according to the QUADAS* check list[10].

No	Author, year	P1 Enrolment**	P2 Exclusions	T1 Test cut-off	T2 Tests blinded	R1 Ref	R2 Ref blinded	R3 Incorp	F1 Delay reftest	F2 Part verif	F3 Diff verif	F4 Withdr explained	F5 Uninterpret tests reported	F6 Uninterpret ref reported	Patient selection	Test	Reference test	#Y	#U	#N	tot	%Y	%U	%N
1	Morrison, 1992	U	U	U	U	Y	U	Y	Y	Y	Y	Y	Y	Y	Mod	Mod	Low	8	5	0	13	0.62	0.38	0.00
2	Hillem, 1999	U	U	U	U	Y	U	Y	U	Y	Y	U	N	N	Mod	Mod	Low	4	7	2	13	0.31	0.54	0.15
3	Sellors, 2000	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Low	Low	Low	13	0	0	13	1.00	0.00	0.00
4	Wright, 2000	U	U	Y	Y	Y	Y	Y	N	N	Y	N	N	N	Mod	Low	Low	6	2	5	13	0.46	0.15	0.38
5	Belinson, 2001	Y	U	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Low	Low	Low	12	1	0	13	0.92	0.08	0.00
6	Lorenzat, 2002	Y	Y	Y	U	Y	U	Y	Y	Y	Y	Y	Y	N	Low	Low	Low	10	2	1	13	0.77	0.15	0.08
7	Nobbenh, 2002	Y	U	U	U	Y	U	Y	Y	Y	Y	Y	Y	Y	Low	Mod	Low	9	4	0	13	0.69	0.31	0.00
8	Garcia, 2003	Y	U	Y	U	Y	Y	Y	Y	Y	Y	N	Y	N	Low	Low	Low	9	2	2	13	0.69	0.15	0.15
9	Salmeron, 2003	U	U	Y	U	Y	N	Y	U	N	Y	Y	Y	Y	Mod	Low	Mod	7	4	2	13	0.54	0.31	0.15
10	Brink 2006	U	U	Y	Y	Y	Y	Y	Y	N	Y	N	Y	N	Mod	Low	Low	8	2	3	13	0.62	0.15	0.23
11	Daponte, 2006	Y	U	U	U	Y	U	Y	U	Y	Y	U	N	N	Low	Mod	Low	5	6	2	13	0.38	0.46	0.15
12	Girianelli, 2006	U	U	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Mod	Low	Low	11	2	0	13	0.85	0.15	0.00
13	Holanda, 2006	U	U	Y	U	Y	Y	Y	Y	Y	Y	Y	N	N	Mod	Low	Low	8	3	2	13	0.62	0.23	0.15
14	Seo, 2006	U	U	Y	U	Y	U	Y	Y	Y	Y	N	N	N	Mod	Low	Low	6	4	3	13	0.46	0.31	0.23
15	Szarewski, 2007	Y	U	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Low	Low	Low	12	1	0	13	0.92	0.08	0.00
16	Qiao, 2008	Y	U	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Low	Low	Low	12	1	0	13	0.92	0.08	0.00
17	Bhatla, 2009	Y	U	Y	U	Y	U	Y	Y	Y	Y	Y	N	Y	Low	Low	Low	9	3	1	13	0.69	0.23	0.08
18	Balasubra., 2010	Y	U	Y	U	Y	U	Y	Y	Y	Y	Y	Y	Y	Low	Low	Low	10	3	0	13	0.77	0.23	0.00
19	Gustavson, 2011	U	U	U	U	Y	Y	Y	Y	Y	Y	Y	N	N	Mod	Mod	Low	7	4	2	13	0.54	0.31	0.15
20	Taylor, 2011	Y	U	Y	Y	Y	Y	Y	Y	Y	Y	N	N	N	Low	Low	Low	9	1	3	13	0.69	0.08	0.23
21	Twu, 2011	U	U	Y	U	Y	U	Y	U	N	Y	N	Y	Y	Mod	Low	Low	6	5	2	13	0.46	0.38	0.15
22	Belinson, 2012	U	U	Y	U	Y	U	Y	Y	N	Y	Y	N	Y	Mod	Low	Low	7	4	2	13	0.54	0.31	0.15
23	Dijkstra, 2012	U	U	U	Y	Y	U	Y	Y	Y	Y	N	N	N	Mod	Low	Low	6	4	3	13	0.46	0.31	0.23
24	L.-Filho, 2012	Y	U	Y	Y	Y	N	Y	U	Y	Y	Y	U	U	Low	Low	Mod	8	4	1	13	0.62	0.31	0.08
25	van Baars, 2012	U	U	U	U	N†	U	U	Y	N	U	Y	N	N	Mod	Mod	High	2	7	4	13	0.15	0.54	0.31
26	Zhao, 2012a	Y	Y	Y	U	Y	U	Y	Y	Y	Y	Y	N	N	Low	Low	Low	9	2	2	13	0.69	0.15	0.15
27	Zhao, 2012b	Y	Y	Y	U	Y	U	Y	Y	Y	Y	Y	N	N	Low	Low	Low	9	2	2	13	0.69	0.15	0.15
28	Zhao, 2012c	Y	Y	Y	U	Y	U	Y	Y	Y	Y	Y	N	N	Low	Low	Low	9	2	2	13	0.69	0.15	0.15
29	Darlin, 2013	U	U	U	U	Y	U	Y	Y	Y	Y	Y	Y	N	Mod	Mod	Low	7	5	1	13	0.54	0.38	0.08
30	Geraets, 2013	Y	U	U	U	Y	U	Y	Y	Y	Y	N	N	N	Low	Mod	Low	6	4	3	13	0.46	0.31	0.23
31	Guan, 2013	N	U	U	U	Y	U	Y	Y	Y	Y	N	N	N	High	Mod	Low	5	4	4	13	0.38	0.31	0.31
32	Jentschke,2013a	U	U	U	U	Y	U	Y	U	Y	Y	Y	N	N	Mod	Mod	Low	5	6	2	13	0.38	0.46	0.15
33	Jentschke,2013b	U	U	Y	U	Y	U	Y	U	Y	Y	Y	N	N	Mod	Low	Low	6	5	2	13	0.46	0.38	0.15
34	Nieves, 2013	Y	Y	U	Y	Y	N	Y	U	Y	Y	Y	Y	Y	Low	Low	Mod	10	2	1	13	0.77	0.15	0.08

Table 8 (continued).

No	Author, year	Enrolment P1	Exclusions P2	Testcutoff T1	Tests blinded T2	Ref R1	Ref blinded R2	Incorp R3	delay reftest F1	part verif F2	diff verif F3	withdr explained F4	uninterpret tests F5	uninterpret ref F6	Patient selection	Test	Reference test	#Y	#U	#N	tot	%Y	%U	%N
35	Zhao, 2013	Y	Y	Y	Y	Y	U	Y	U	Y	Y	Y	U	U	Low	Low	Low	9	4	0	13	0.69	0.31	0.00
36	Chernesky, 2014	U	N	Y	U	Y	U	Y	Y	Y	Y	U	U	U	Mod	Low	Low	6	6	1	13	0.46	0.46	0.08
37	Hesselink, 2014	U	U	Y	Y	N	U	N	U	U	U	U	Y	U	Mod	Low	Mod	3	8	2	13	0.23	0.62	0.15
38	Jeronimo, 2014a	Y	Y	Y	U	Y	U	Y	U	N	Y	Y	N	N	Low	Low	Low	7	3	3	13	0.54	0.23	0.23
39	Jeronimo, 2014b	Y	Y	Y	U	Y	U	Y	U	N	Y	Y	N	N	Low	Low	Low	7	3	3	13	0.54	0.23	0.23
40	Jeronimo, 2014c	Y	Y	Y	U	Y	U	Y	U	N	Y	Y	N	N	Low	Low	Low	7	3	3	13	0.54	0.23	0.23
41	Jeronimo, 2014d	Y	Y	Y	U	Y	U	Y	U	N	Y	Y	N	N	Low	Low	Low	7	3	3	13	0.54	0.23	0.23
42	Wang, 2014	Y	Y	Y	N	Y	N	N	U	N	N	U	U	U	Low	Mod	High	4	4	5	13	0.31	0.31	0.38
43	Zhang, 2014	Y	Y	Y	U	Y	U	Y	U	Y	Y	Y	U	U	Low	Low	Low	8	5	0	13	0.62	0.38	0.00
44	Boggan, 2015	N	Y	Y	Y	Y	U	N	U	N	Y	Y	U	U	Mod	Low	Mod	6	4	3	13	0.46	0.31	0.23
45	Porras, 2015	Y	Y	Y	N	Y	Y	Y	U	U	N	Y	U	U	Low	Mod	Low	7	4	2	13	0.54	0.31	0.15
46	Chen, 2016 (a)	Y	U	U	U	U	U	U	U	U	U	Y	U	U	Low	Mod	Mod	2	11	0	13	0.15	0.85	0.00
47	Chen, 2016 (b)	U	Y	Y	U	Y	Y	Y	Y	Y	Y	U	Y	U	Low	Low	Low	9	4	0	13	0.69	0.31	0.00
48	Jentschke, 2016	U	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Low	Low	Low	11	1	1	13	0.85	0.08	0.08
49	Qin, 2016	Y	Y	U	U	Y	Y	Y	Y	Y	Y	Y	Y	U	Low	Mod	Low	10	3	0	13	0.77	0.23	0.00
50	Stanczuk, 2016	Y	U	Y	U	Y	U	N	U	N	N	Y	Y	Y	Low	Low	Mod	6	4	3	13	0.46	0.31	0.23
51	Aiko, 2017	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Low	Low	Low	12	1	0	13	0.92	0.08	0.00
52	Asciutto, 2017	U	U	Y	Y	Y	Y	Y	Y	Y	Y	N	U	U	Mod	Low	Low	8	4	1	13	0.62	0.31	0.08
53	Catarino, 2017	Y	Y	U	U	U	Y	Y	U	N	Y	Y	Y	Y	Low	Mod	Low	8	4	1	13	0.62	0.31	0.08
54	Leeman, 2017	U	U	U	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	Mod	Low	Low	9	4	0	13	0.69	0.31	0.00
55	Asciutto, 2017	U	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Low	Low	Low	12	1	0	13	0.92	0.08	0.00
56	Leinonen,2018	N	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	Mod	Low	Low	11	1	1	13	0.85	0.08	0.08
	#yes	30	22	39	20	52	20	50	34	39	50	39	25	19	33	41	47	**439**	**198**	**91**	**728**	**0.60**	**0.27**	**0.13**
	#unclear	23	33	17	34	2	32	2	21	3	3	7	9	12	22	15	7							
	#no	3	1	0	2	1	4	4	1	14	3	10	22	25	1	0	2							
	total	**56**	**56**	**56**	**56**	**56**	**56**	**56**	**56**	**56**	**56**	**56**	**56**	**56**	**56**	**56**	**56**							
	% yes	54	39	70	36	93	36	89	61	70	89	70	45	34	59	73	84							
	% unclear	41	59	30	61	4	57	4	38	5	5	13	16	21	39	27	13							
	% no	5	2	0	4	2	7	7	2	25	5	18	39	45	2	0	4							

* QUADAS=Quality Assessment of Diagnostic Accuracy Studies.
** QUADAS items[19]: (P1) acceptable enrolment method, (P2) inappropriate exclusions avoided, (T1) pre-specified test cut-off, (T2) results of index and comparator tests blinded towards each other and reference test, (R1) acceptable reference test, (R2) results of reference test blinded towards index and comparator tests, (R3) incorporation bias avoided, (F1) acceptable delay between triage tests and reference test, (F2) partial verification avoided, (F3) differential verification avoided, (F4) withdrawals explained, (F5) uninterpretable results reported for tests, (F6) uninterpretable results reported for reference test. Each quality item is judged with: Y (fulfilled, green), U (unclear, yellow), N (not fulfilled, red).

6. Assessment of risk of bias in randomized trials

Table 9. Summary of the quality of included studies, according to the Cochrane Tool for Risk of Bias[11].

Risk of Bias	Selection		Attrition	Reporting	
	Random sequence generation	Allocation concealment	Incomplete outcome data	Reporting of timelines	Selective reporting
Bais, 2007	Low	Medium	Low	Low	Low
Gok, 2010	Low	Medium	Low	Low	Low
Giorgi-Rossi, 2011	Low	Low	Low	Low	Low
Lazcano-Ponce, 2011	Medium$^{\bullet}$	Low	Low	Medium	Medium$^{¥}$
Piana, 2011	Low	Medium	Low	Medium	High$^{¥□}$
Szarewski, 2011	Medium$^{\Delta}$	Medium	Low	Low	Low
Virtanen, 2011	Low	Medium	Low	Low	Low
Wikstrom, 2011	Medium$^{\Delta}$	Medium	Low	Low	Low
Gok, 2012	Low	Medium	Low	Low	Medium$^{¥}$
Darlin, 2013	Medium$^{\Delta}$	Medium	Low	Medium	Medium$^{¥}$
Sancho-Garnier, 2013	Medium$^{\Delta}$	Medium	Low	Low	Medium$^{¥}$
Broberg, 2014	Medium$^{\Delta}$	Medium	Low	Medium	Low
Cadman, 2014	Low	Low	Low	Low	Low
Arrossi, 2015	Medium*	Low	Low	Low	Low
Cadman, 2015	Low	Low	Low	Low	Low
Giorgi Rossi, 2015	Low	Low	Low	Low	Low
Enerly, 2016	High$^{\delta}$	High	Low	Low	Medium
Moses, 2016	Low	Low	Low	Medium	Low
Racey, 2016	Low	Low	Low	Medium	Low
Sultana, 2016	Low	Low	Low	Low	Medium
Zehbe, 2016	Medium*	Medium	Low	Medium	Medium$^{\Omega}$
Kitchener, 2017	Medium	Medium	Low	Low	Low
Modibbo, 2017	High$^{\alpha}$	Medium	Low	Low	Medium$^{¥}$
Kellen, 2018	Low	High$^{\epsilon}$	Low	Low	Medium$^{\epsilon}$
Tranberg, 2018	Low	Low	Low	Low	Low

High=high risk of bias, Low=low risk of bias, Medium=intermediate risk of bias.

$^{\bullet}$ Non-random factor is included in design. Women assigned to the self-sampling arm who were found not at home, were reassigned to cytology.)

$^{\Delta}$ Details of the randomization process are not documented.

$^{¥}$ Intention-to-treat analysis was not reported. If there were women who went to the clinic for conventional screening, after being invited for self-sampling, it was not documented.

$^{□}$ Women in the self-sampling arm could opt-out, and those who did were excluded from the analysis (possibly leading to an artificially high participation rate in the self-sampling arm).

* Cluster-randomisation of community health workers to self-sampling and control arm.

$^{\Omega}$ Intention-to-treat analysis unclear (nbs < than per protocol analysis)

$^{\varphi}$ Non-randomised trial.

$^{\delta}$ Non-random factors in design. Investigators used randomisation to identify 800 screening non-attenders (300 each from age groups 26–34 and
35–49 years, and 200 from the age group 50–69 years). The remaining non-attenders in the study area screening programme were considered the control group.

$^{\beta}$ Concealment accomplished using distance between clusters.

$^{\alpha}$ Randomisation occurred after enrolment.

$^{\epsilon}$ Timing of invitation in experimental arms was different from invitation in the first control arm; compliance with cytology triage and detection rate of CIN2+ not reported.

7. Absolute accuracy of hrHPV DNA testing on self-samples

Table 10. Meta-analysis of the absolute sensitivity and specificity of hrHPV testing on self-samples, hrHPV testing on clinician samples to detect CIN2+ and CIN3+, by clinical setting (primary cervical cancer screening, testing of high-risk groups, follow-up of women because of previous cervical abnormalities and post-treatment follow-up).

Sample	**Test**	**Number of studies**		**Sensitivity**, in % (95% CI)		**Specificity**, in % (95% CI)	
		CIN2+	**CIN3+**	**CIN2+**	**CIN3+**	**CIN2+**	**CIN3+**
Primary routine screening							
Self-sample	SA-based‡	14	8	77 (69-82)	77 (67-85)	84 (77-88)	87 (85-89)
	PCR‡	4	2	96 (89-99)	95 (91-98)†	79 (65-89)	86 (86-87)†
Clinician-sample	SA-based	14	8	93 (89-96)	96 (94-97)	86 (81-90)	90 (88-92)
	PCR	4	2	96 (91-98)†	96 (93-98)†	79 (60-90) †	88 (88-89)*
Testing of high-risk groups							
Self-sample	SA-based	2	0	84 (78-90)†	-	77 (76-79)†	-
	PCR	1	0	100 (83-1.00)*	-	61 (55-67)*	-
Clinician-sample	SA-based	2	0	93 (89-97)†	-	83 (81-84)†	-
	PCR	1	0	100 (83-1.00)*	-	64 (58-70)*	-
Follow-up of previous cervical abnormalities/Colposcopy clinic							
Self-sample	SA-based	7	4	79 (69-87)	81 (52-95)	51 (33-68)	39 (22-61)
	PCR	13	7	88 (84-91)	90 (81-95)	51 (42-59)	46(35-57)
Clinician-sample	SA-based	7	4	94 (86-98)	90 (76-96)*	64 (42-82)	44 (27-63)*
	PCR	13	7	90 (86-93)	96 (90-98)	48 (40-56)	43 (30-56)
Post treatment follow-up							
Self-sample	SA-based	1	0	55 (36-72)	-	64 (60-67)	-
Clinician sample	SA-based	1	0	85 (68-95)	-	73 (69-76)	-

† Separate random effect models used for pooling of binomial data, ignoring correlation between sensitivity and specificity. * No pooling since only 1 study.
‡SA-based: signal-amplification based hrHPV DNA tests (Hybrid Capture II or Cervista). PCR: hrHPV DNA testing with clinically validated polymerase chain reaction.

8. Relative accuracy of hrHPV testing on self- compared to clinician-samples

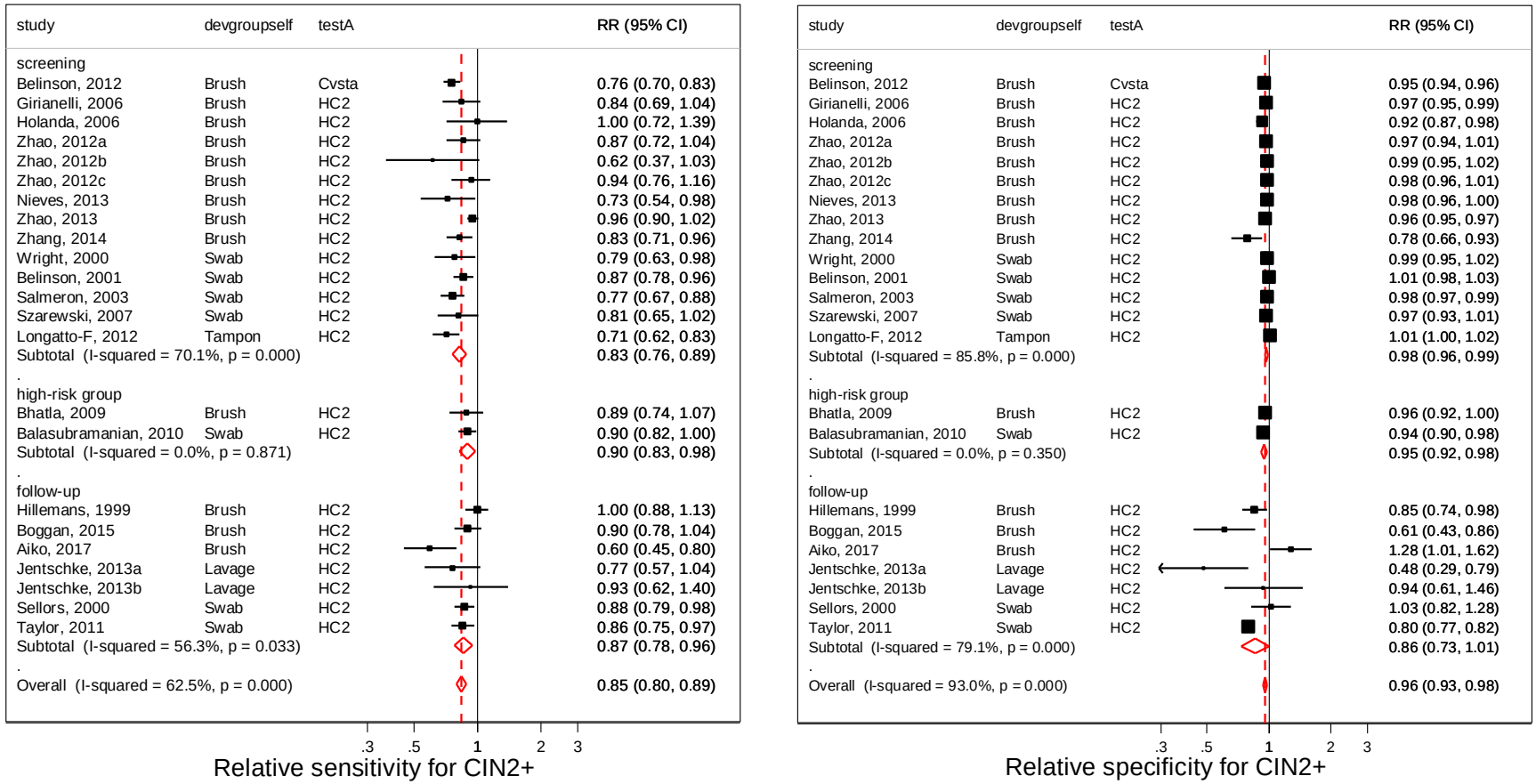


Figure 3. Relative sensitivity (left) and specificity (right) of hrHPV testing with signal-amplification based tests on self-samples compared to hrHPV testing on clinician samples to detect CIN2+, by clinical setting. p value for inter-setting heterogeneity = 0.394 for relative sensitivity and =<0.0001 for relative specificity.

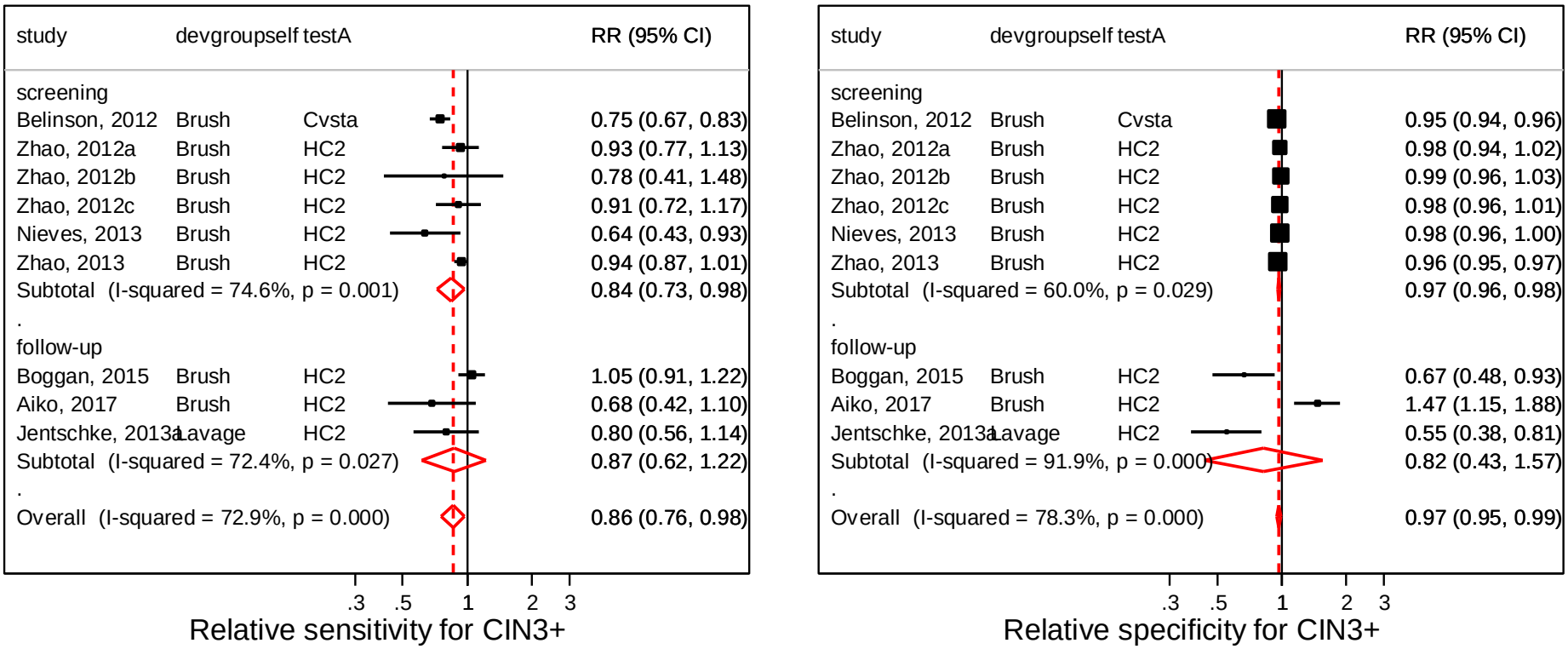


Figure 4. Relative sensitivity (left) and specificity (right) of hrHPV testing with signal-amplification based tests on self-samples compared to hrHPV testing on clinician samples to detect CIN3+, by clinical setting. p value for inter-setting heterogeneity = 0.109 for relative sensitivity and <0.0001 for relative specificity.

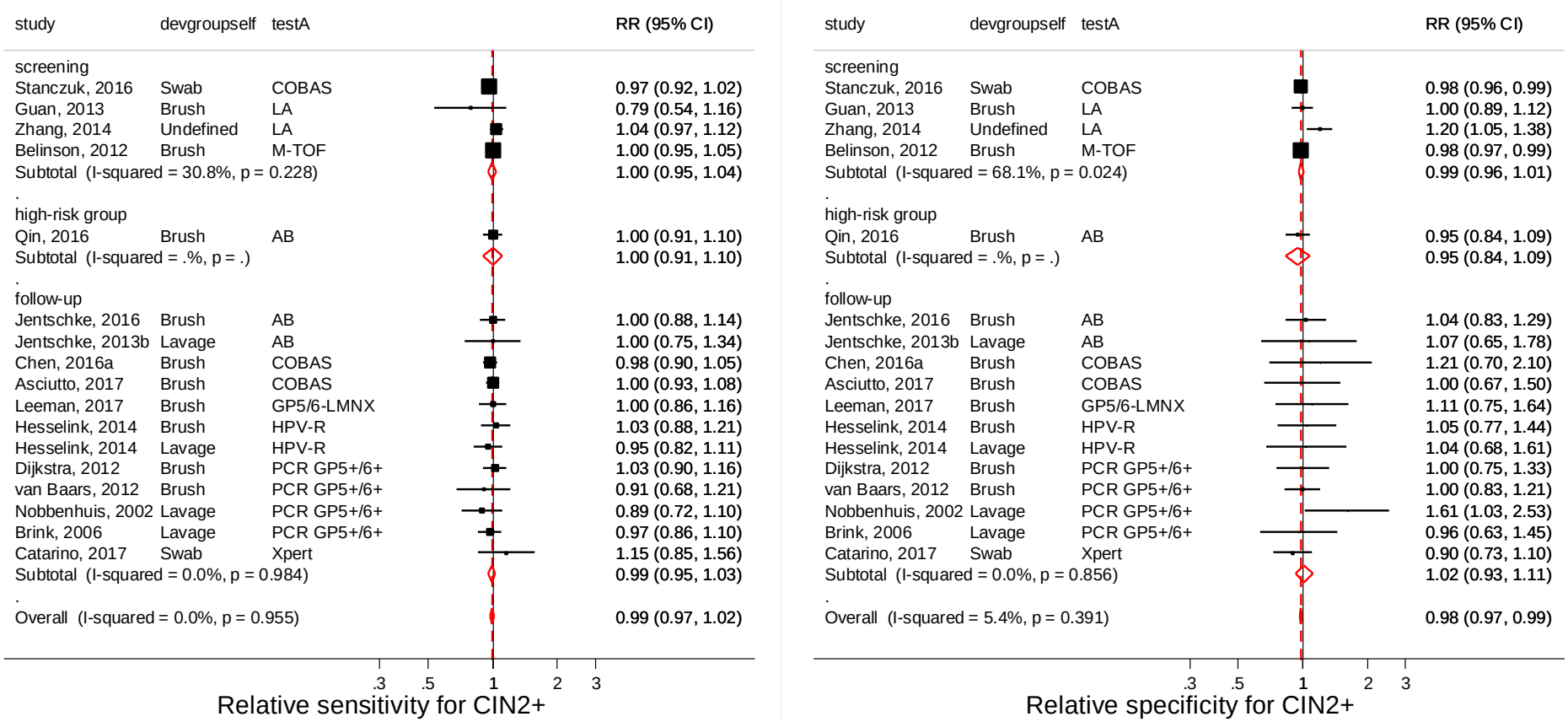
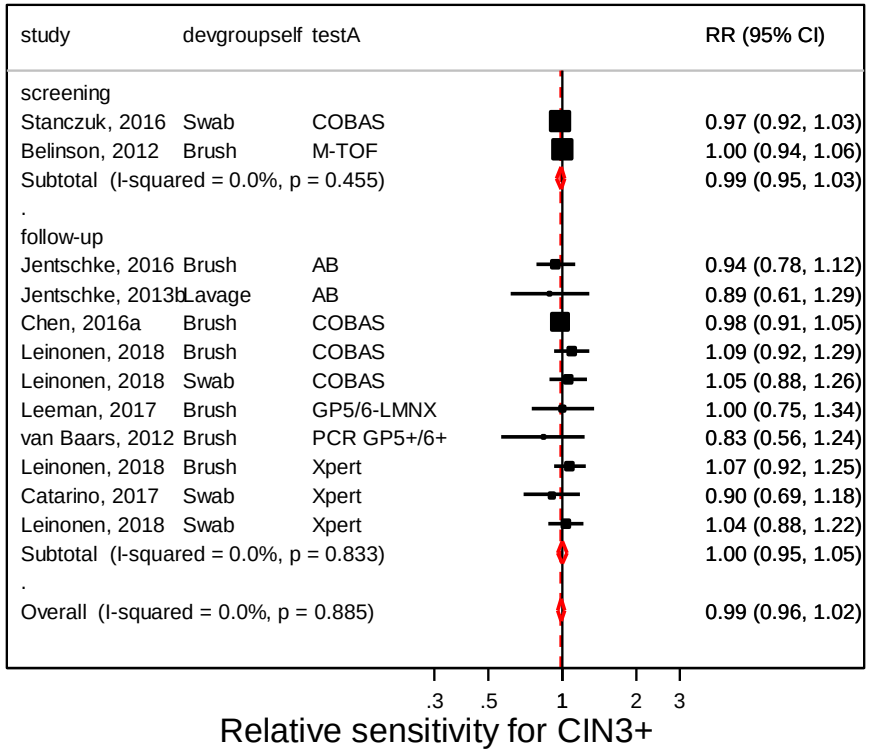


Figure 5. Relative sensitivity (left) and specificity (right) of hrHPV testing using clinically validated PCR based assays on self-samples compared to hrHPV testing on clinician samples to detect CIN2+, by clinical setting. p value for inter-setting heterogeneity = 0.989 for relative sensitivity and =0.616 for relative specificity.



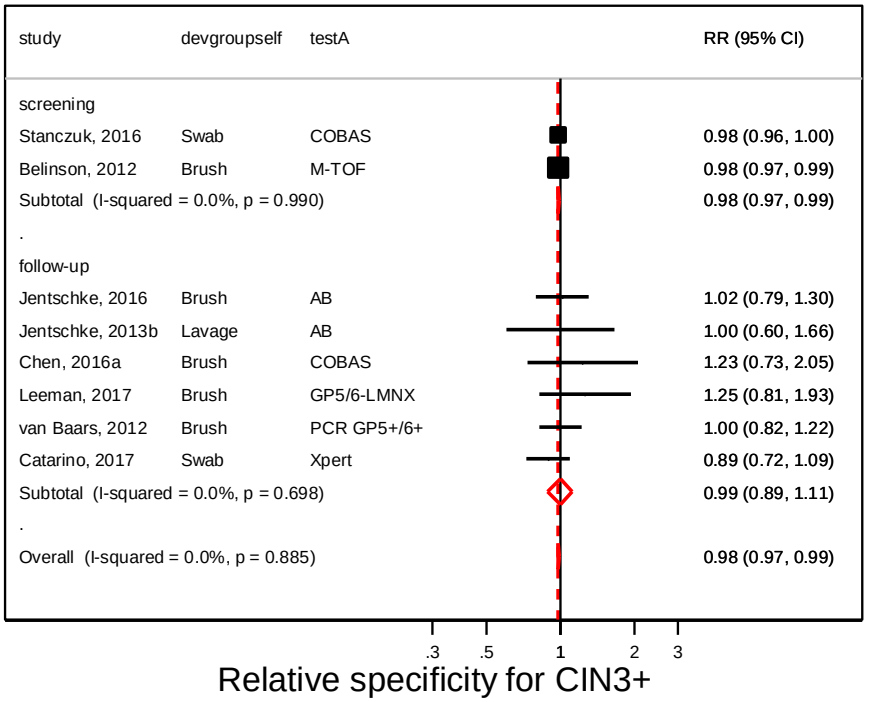


Figure 6. Relative sensitivity (left) and specificity (right) of hrHPV testing using clinically validated PCR-based assays on self-samples compared to hrHPV testing on clinician samples to detect CIN3+, by clinical setting. p value for inter-setting heterogeneity = 0.683 for relative sensitivity and = 0.799 for relative specificity.

9. Effect of covariates on the relative accuracy of hrHPV testing on self- vs to clinician samples

9.1. Test effects

Table 11. Variation in relative sensitivity and specificity (and 95% CI) of hrHPV testing on self-samples compared to clinician samples to detect CIN2+, according to the used hrHPV test. Relative values were computed using a bivariate normal model for the logits of sensitivity and specificity.

Covariate	Number of studies	Relative sensitivity	Relative specificity
Test			
SA-hrHPV Tests:			
HC2	22	0.85 (0.81-0.89)*	0.96 (0.94-0.97)*
Cervista	1	0.76 (0.70-0.83)*	0.95 (0.94-0.99)*
careHPV	7	0.84 (0.76-0.92)*	1.00 (0.99-1.00)
PCR-hrHPV Tests:			
GP5+/6+ PCR-EIA	6	0.94 (0.88-1.02)	1.09 (0.96-1.22)
Linear Array†	2	1.00 (0.93-1.07)	1.11 (1.00-1.23)
HPV DNA Chip	1	1.03 (0.89-1.19)	0.88 (0.55-1.42)
Abbott RealTime hrHPV test†	3	1.00 (0.93-1.08)	0.98 (0.88-1.09)
MALDI-TOF	1	1.00 (0.95-1.05)	0.98 (0.97-0.99)*
Cobas-4800†	3	0.98 (0.94-1.02)	0.93 (0.86-1.01)
SPF10-DEIA	4	0.97 (0.91-1.02)	0.97 (0.921.02)
Modified GP5+/6+-Luminex	1	0.96 (0.75-1.24)	0.94 (0.67-1.33)
HPV Risk	1	0.95 (0.82-1.11)	1.04 (0.68-1.61)
GP5+/6+-LMNX	1	1.00 (0.86-1.16)	1.11 (0.75-1.64)
Xpert HPV	1	1.15 (0.85-1.56)	0.90 (0.73-1.10)
hrHPV mRNA Test:			
APTIMA†	3	0.69 (0.52-0.92)*	0.97 (0.92-1.02)

* ratio statistically significantly different from 1. † Correlation between logit sensitivity and logit FPR were relaxed since the bivariate model with correlation did not converge.

9.2. Self-sampling device effects

Table 12. Relative sensitivity and specificity for CIN2+ of hrHPV testing on self- vs. clinician samples, stratified by self-sampling device.

Covariate	Number of studies	Relative sensitivity	Relative specificity
Self-sampling device, if SA-hrHPV DNA tests			
Cytobrush†	3	0.97 (0.92-1.02)	0.94 (0.89-0.98)*
Conical brush	7	0.85 (0.79-0.91)*	0.97 (0.95-0.99)*
POI/NIH self-sampler	2	0.74 (0.66-0.83)*	0.97 (0.95-0.99)
Evalyn Brush	1	0.66 (0.45-0.80)*	1.28 (1.01-1.62)*
Delphi Sampler	2	0.82 (0.65-1.05)	0.68 (0.35-1.33)
Dacron swab	6	0.86 (0.82-0.90)*	0.94 (0.88-1.02)
Cotton swab	1	0.81 (0.65-1.02)	0.97 (0.93-1.01)
Tampon	1	0.71 (0.62-0.83)*	0.96 (0.94-0.98)*
Self-sampling device, if validated hrHPV PCR			
Conical brush	4	1.02 (0.97-1.06)	0.98 (0.97-0.99)
POI/NIH self-sampler	1	0.96 (0.89-1.03)	0.98 (0.97-0.99)
Evalyn-Brush	3	0.99 (0.90-1.09)	1.03 (0.90-1.17)
Qvintip	1	0.93 (0.80-1.09)	1.07 (0.87-1.32)
Vibabrush	2	0.95 (0.83-1.09)	1.18 (0.98-1.42)
Lavage	2	0.95 (0.85-1.06)	1.23 (0.74-2.05)
Delphi Sampler	2	0.96 (0.84-1.10)	1.05 (0.76-1.47)
Dacron swab	1	0.97 (0.92-1.02)	0.98 (0.96-0.99)
Cotton swab	2	1.04 (0.85-1.28)	0.91 (0.76-1.09)
Cobas PCR Female Swab Sample Kit	1	1.00 (0.93-1.08)	1.00 (0.67-1.50)

† A continuity correction was applied to avoid exclusion of studies with 100% sensitivity on self and 100% specificity on the clinician samples: +0.5 for the TP self and FN self, + correction factor for the TPclin and the FNclin. The correction factor = (((TPself*TPclin+ 0.5*TPclin) / (TPself+1))-TPclin)*(TPself+1) /(-TPself).
* Statistically significant.
PS: Table is restricted to relevant well characterized devices.

9.3. Transport/storage medium effects

Table 13. Relative sensitivity and specificity for CIN2+ of hrHPV testing on self- vs. clinician samples, stratified by individual storage medium or transport recipients.

Covariate	Number of studies	Relative sensitivity	Relative specificity
Transport/storage Medium, if SA-hrHPV DNA tests			
Cell-preserving media			
PreservCyt	2	0.76 (0.70-0.83)*	0.96 (0.94-0.99)*
SurePath	0	-	-
CitoLiq	1	0.84 (0.69-1.04)	0.97 (0.95-0.99)*
Media allowing virological testing			
STM	12	0.85 (0.81-0.89)*	0.96 (0.92-0.99)*
PBS	1	0.77 (0.57-1.04)	0.48 (0.29-0.79)*
UCM	1	1.00 (0.72-1.39)	0.92 (0.87-0.98)*
CCM	1	0.96 (0.90-1.02)	0.96 (0.95-0.97)*
Transport/storage Medium, if validated PCR-hrHPV tests			
Cell-preserving media			
PreservCyt	4	1.00 (0.96-1.04)	0.98 (0.97-0.99)*
SurePath	2	0.99 (0.90-1.10)	1.02 (0.79-1.31)
CitoLiq	0	-	-
Media allowing virological testing			
PBS	1	0.89 (0.72-1.10)	1.61 (1.03-2.53)*
Roche PCR medium	1	0.97 (0.92-1.02)	0.98 (0.96-0.99)
Cobas collection kit	1	1.00 (0.93-1.08)	1.00 (0.67-1.50)
Dry collection			
Evalyn tube	3	0.99 (0.90-1.09)	1.03 (0.90-1.17)
Qvintip tube	1	0.93 (0.80-1.09)	1.07 (0.87-1.32)
FTA cartridge†	3	0.93 (0.83-1.05)	1.03 (0.91-1.17)

† a special continuity correction was applied to avoid exclusion of studies with 100% sensitivity on self and 100% sensitivity on the clinician samples: +0.5 for the TP self and FN self, + correction factor for the TPclin and the FNclin. The correction factor = (((TPself*TPclin+ 0.5*TPclin) / (TPself+1))-TPclin)*(TPself+1) /(-TPself).

PS: Table is restricted to relevant well characterised media used to store vaginal self-collected material.

9.4. Influence of study quality/design

In a bivariate random-effects meta-regression model, including sampling procedure (self- vs. clinician sampling) and the study setting (screening, high-risk group testing, or follow-up, and restricting to validated PCR-hrHPVs, the addition of QUADAS items did not contribute, in general, in a significantly better fit of the accuracy estimates for outcome CIN2+. There were only a few exceptions:

- The sensitivity of PCR-hrHPV testing for CIN2+, was significantly higher when the reference standard interpretation was blinded compared to when it was not blinded to the hrHPV tests (ratio: 1.07, 95% CI: 1.01-1.13, p=0.0268).
- The sensitivity was higher when avoidance of partial verification was unclear compared to when verification was partial (ratio: 1.10, 95% CI: 1.01-1.20, p=0.0360); in addition the specificity was lower when partial verification was unclear vs. clearly partial (0.54, 95% CI: 0.32-0.89, p=0.0162) and also when partial verification was avoided vs. clearly partial (ratio: 0.75, 95% CI: 0.60-0.93, p=0.0105).
- The sensitivity was lower when withdrawals of subjects were clearly explained vs. when not explained (ratio: 0.95, 95% CI: 0.90-0.99, p=0.0209).

- The sensitivity was higher when reporting of un-interpretable test results was unclear vs. when not reported (ratio: 1.08, 95% CI: 1.02-1.14, p=0.0109). The specificity was lower when reporting of un-interpretable test results was unclear vs. when clearly not reported (ratio: 0.41, 95% CI: 0.30-0.56, p=<0.0001).
- The sensitivity was higher when reporting of un-interpretable results of the reference standard was unclear vs. when not reported (ratio: 1.06, 95% CI: 1.01-1.12, p=0.0112). The specificity was lower when reporting of un-interpretable reference test results was unclear vs. when clearly not reported (ratio: 0.56, 95% CI: 0.40-0.77, p=0.0004)**.**
- When the significance level (α accepted at $p<0.05$) was adjusted by applying a Bonferroni correction ($\alpha/k=0.05/13=0.0038$) for multiple testing, only contrasts marked in bold above still were significant. The adjusted relative sensitivity and specificity of hrHPV DNA testing on self- vs. clinician sample was not affected by inclusion of the QUADAS items into the multivariate regression model.

9.5. Small study effects, publication bias

Absolute accuracy
The effect of study size on accuracy estimates of hrHPV tests performed on self- and clinician samples, in the context of screening was assessed from a regression of the effective study size against the logarithm of the diagnostic odds ratio as proposed by Deeks *et al.* (J Clin Epidemiol 2005;58: 882-93)[12], see Table 14.

Table 14. Small study effects in the absolute accuracy of hrHPV testing on self-samples and in the accuracy of hrHPV testing on clinician samples.

Collection type	Category hrHPV DNA test	Outcome	p value
Self-samples	SA	CIN2+	0.94
		CIN3+	0.49
	Validated PCR	CIN2+	0.26
		CIN3+	-
Clinician-samples	SA	CIN2+	0.64
		CIN3+	0.96
	Validated PCR	CIN2+	0.56
		CIN3+	-

No evidence of small study effects could be identified (p always >0.25).

Relative accuracy
p values in the relative sensitivity and specificity are assessed as proposed by Harbord *et al.* *(*Stat Med 2006; 20:641–54). The intercept and the slope of the regression of $Z/\sqrt{V}$ against $\sqrt{V}$ are shown when the p-values are significant (p<0.05).
Only for the relative sensitivity of PCR-hrHPV tests on self- vs. clinician samples, a significant small study effect could be identified.

Table 15. Small study effects in the relative accuracy of hrHPV testing on self-samples vs. clinician samples.

Test	Outcome	p (relative sensitivity)	Intercept (bias)	Slope	p (relative specificity)
SA-hrHPV tests	CIN2+	0.062	-	-	0.220
	CIN3+	0.286	-	-	0.775
Validated PCR-hrHPV test	CIN2+	0.428	-	-	0.051
	CIN3+	0.013	-0.98 (-1.64 to -0.31)	-0.01 (-0.02 to 0.04)	0.329

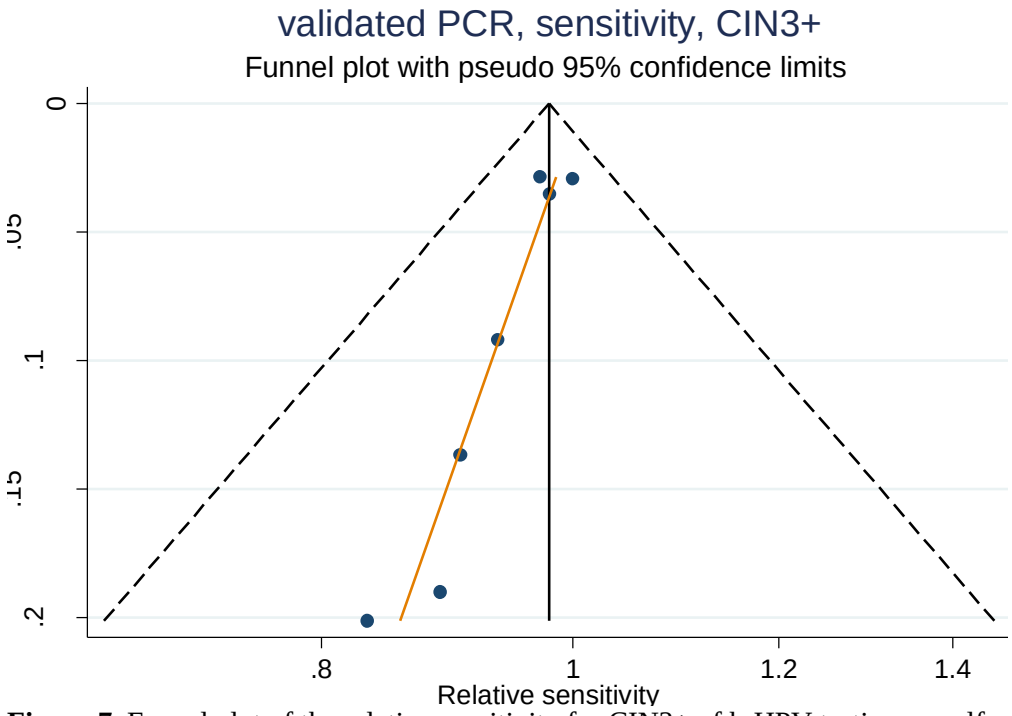


Figure 7. Funnel plot of the relative sensitivity for CIN3+ of hrHPV testing on self-samples versus clinician samples.

The effect size, on the X axis (log of the relative sensitivity, on an exponentiated scale) is plotted against a measure related to the study size measure on the Y axis (standard error of the relative sensitivity). Some asymmetry can be discerned, with more small studies (at the bottom, left) showing a low relative sensitivity for CIN3+.

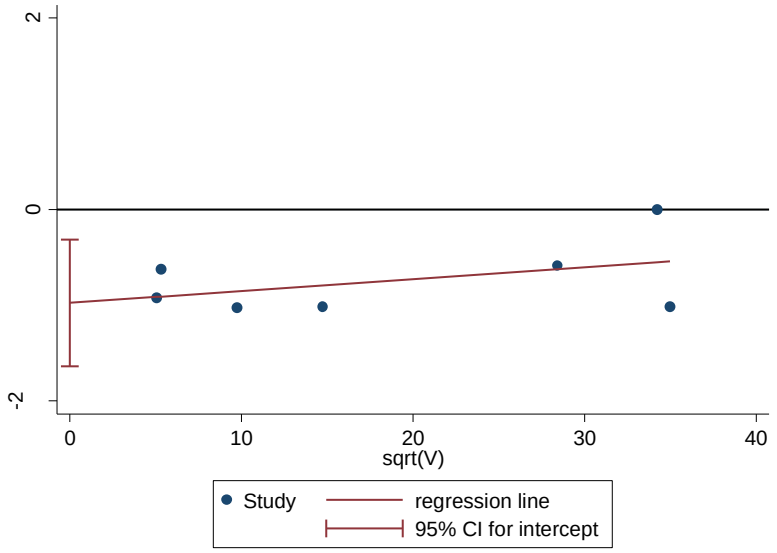


Figure 8. Small study effect in the relative sensitivity for CIN3+ of hrHPV testing with validated PCR-hrHPV tests on self- vs. clinician samples.

The Harbord's plot is based on the regression of $Z/\sqrt{V}$ against $\sqrt{V}$. *Z* is the efficient score and *V* is the variance of *Z* under the null hypothesis (Harbord *et al.*, Stat Med 2006; 20: 641–54). The intercept is statistically different from zero, whereas the slope is not significantly different from a horizontal line.

10. Participation in the self-sampling arm and control arm of RCTs

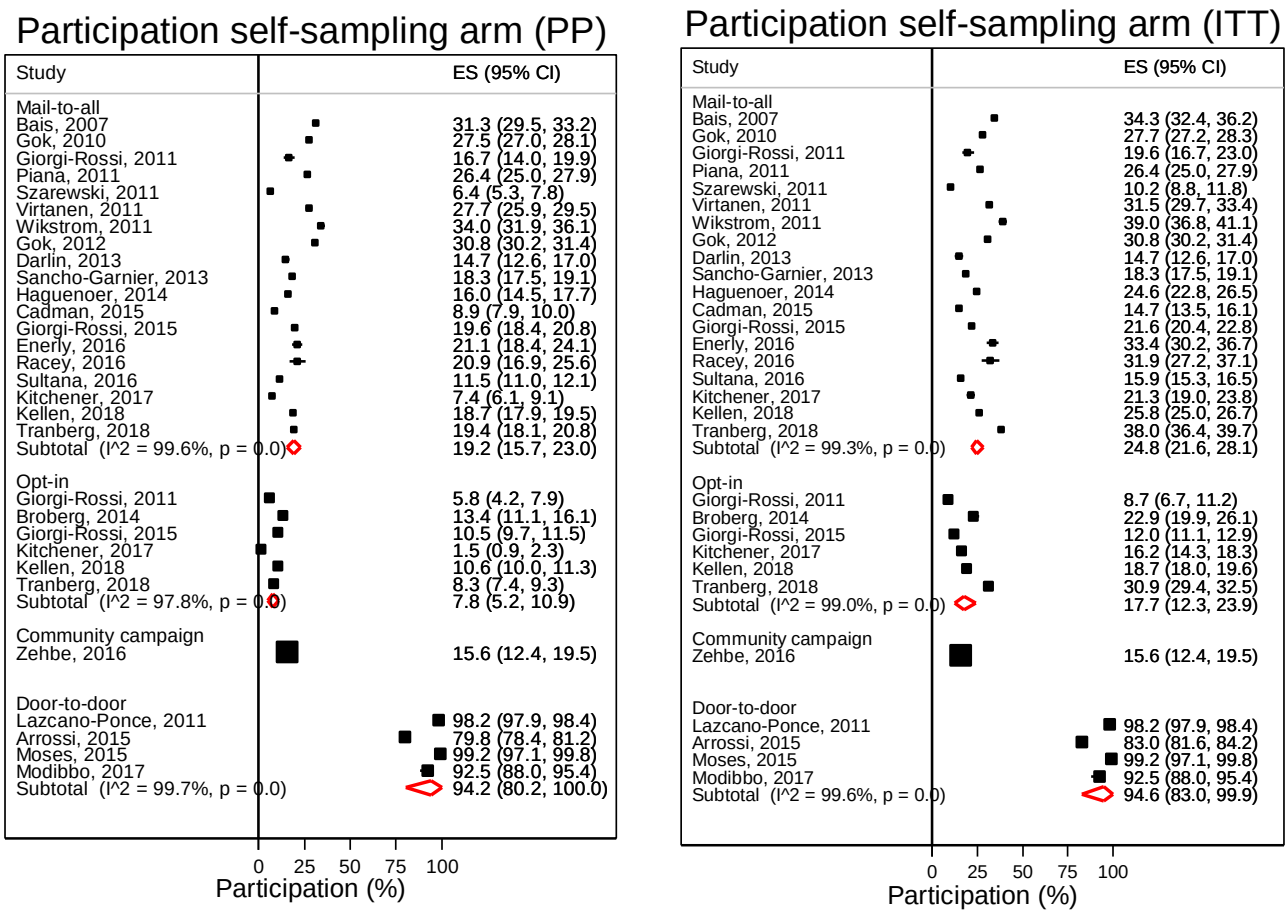


Figure 9. Participation rate in the self-sampling arm of randomized trials. Left: per-protocol (PP) analysis (only hrHPV tests on self-samples counted); right: intention-to-treat (ITT) analysis (also Pap smears counted).

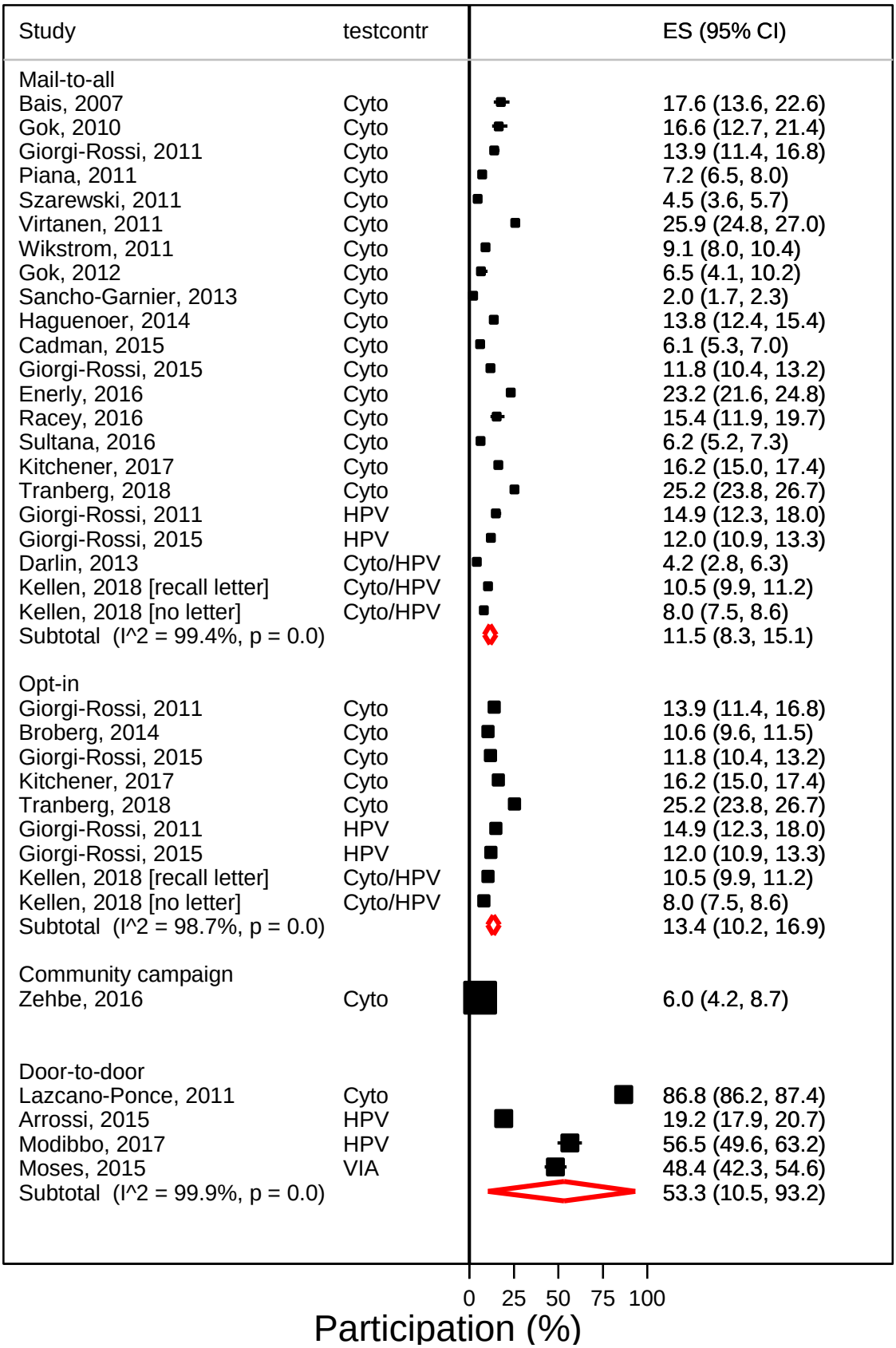


Figure 10. Participation in the control arm according to the invitation scenario applied in the self-sampling arm.

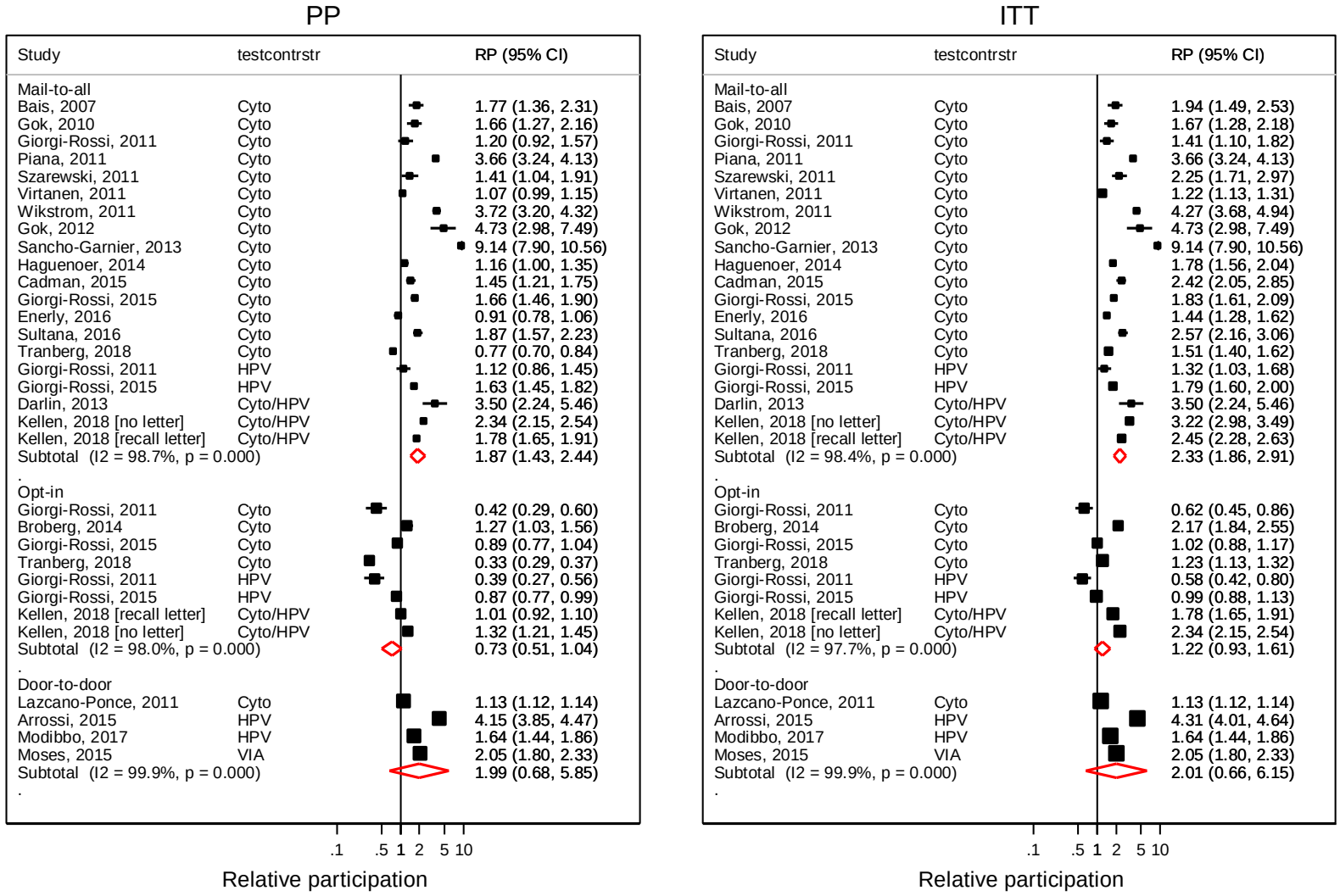


Figure 11. Relative participation (RP) in the self-arm vs. the control arm of randomized trials. Left: per-protocol (PP) analysis, right: intention-to-treat (ITT) analysis.

Table 16. Participation rate in the self-sampling arm and control arms and relative participation in randomized trials that reported data stratified by screening history status.

Study	Age (years)	Scenario	Screening history	Participation self-sample arm	Participation control arm	Relative participation (95% CI)	p†
Gok, 2010	30-60	Mail-to all	screened ≥ 5 y ago	27.7%	16.6%	1.67 (1.28-2.18)	0.8480
			screened >7 y ago	15.8%	9.0%	1.76 (1.09-2.86)	
Broberg, 2014	30-62	Opt-in	screened ≤ 10 y ago	39.7%	16.9%	2.35 (1.88- 2.931)	0.1708
			screened > 10 y ago	20.3%	7.0%	2.89 (2.14-3.89)	
			never screened	19.1%	9.7%	1.96 (1.50-2.56)	
Cadman, 2015	25-65	Mail-to all	screened 0-3y ago	29.5%	16.4%	1.81 (0.85- 3.83)	0.1776
			screened 3-5y ago	33.1%	15.1%	2.19 (1.71-2.81)	
			screened 5-10y ago	18.8%	7.5%	2.50 (1.85-3.37)	
			screened >10y ago	11.3%	2.3%	4.94 (2.60-9.39)	
			never screened	8.3%	3.1%	2.68 (1.81-3.96)	
Sultana, 2016	30-69	Mail-to all	screened >2.5 y ago	11.6%	6.4%	1.80 (1.41-2.29)	0.3934
			never screened	20.5%	9.4%	2.18 (1.51-3.15)	
Tranberg, 2018	30-64	Mail-to all	regularly screened*	29.7%	35.7%	0.83 (0.76-0.91)	<0.0001
			under-screened	25.3%	14.3%	1.78 (1.45-2.18)	
			never screened	19.9%	7.2%	2.75 (1.96- 3.84)	
		Opt-in	regularly screened	43.2%	35.7%	1.21 (0.76-0.91)	<0.0001
			under-screened	20.0%	14.3%	1.40 (1.45-2.18)	
			never screened	8.7%	7.2%	1.21 (1.96-3.84)	

* Definitions of categories of screening history in Tranberg, 2018

Regularly screened:

Age 30-34 y; 56-64y: =2 cervical cytology samples were registered

Age 35-55y: =3 cervical cytology samples were registered

Underscreened:

Age 30-34 y; 56-64y: only one cervical cytology sample registered

Age 35-55y: 1 or 2 cervical cytology samples were registered

Never screened: no cervical cytology sample was registered (registry covers 15 years of screening)

† p valued for heterogeneity by category of screening history (computed according the Mantel-Haenszel method)

Table 17. Test for publication bias (small sample effects) in the relative participation (self-sampling arm vs control arm).

Scenario	Analysis	Harbord's p value
Mail-to-all	Per protocol	0.409
	Intention-to-treat	0.360
Opt-in	Per protocol	0.094
	Intention-to-treat	0.133

11. Specimen adequacy, test positivity rate, follow-up adherence, detection of CIN2+

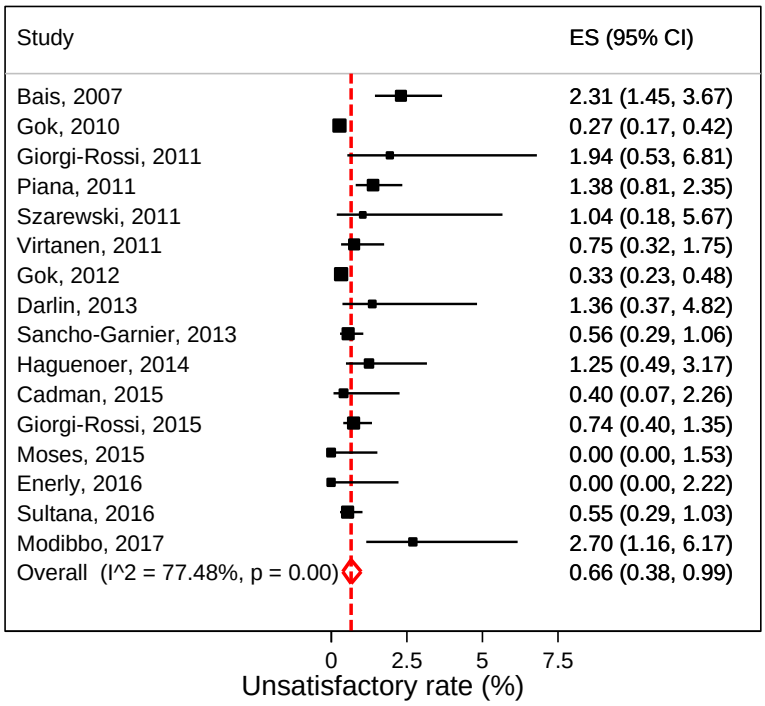


Figure 12. Proportion of self-samples that was unsatisfactory for hrHPV testing.

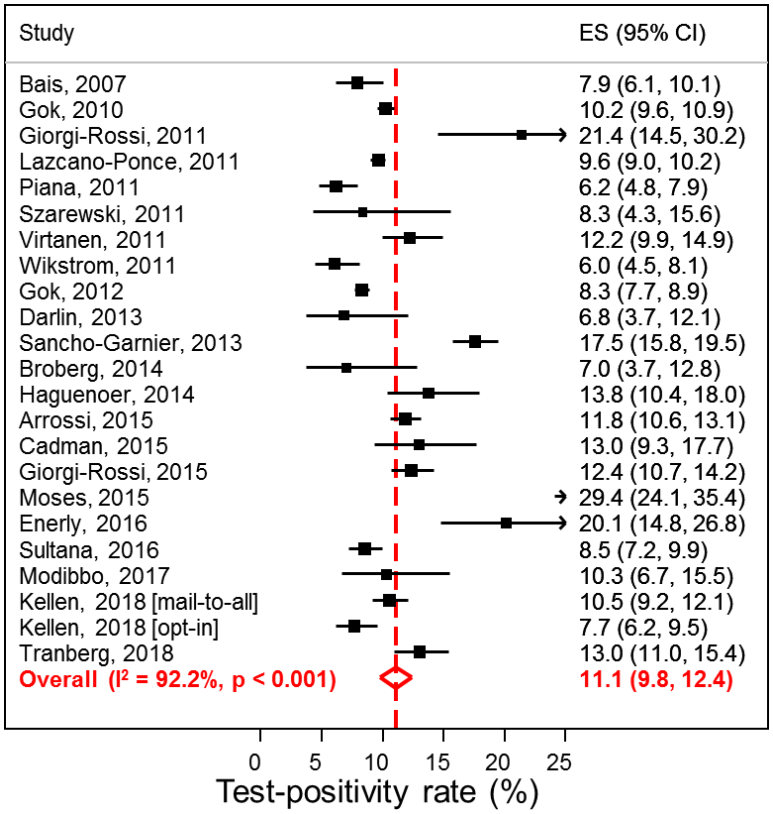


Figure 13. hrHPV test positivity in self-samples (experimental arm).

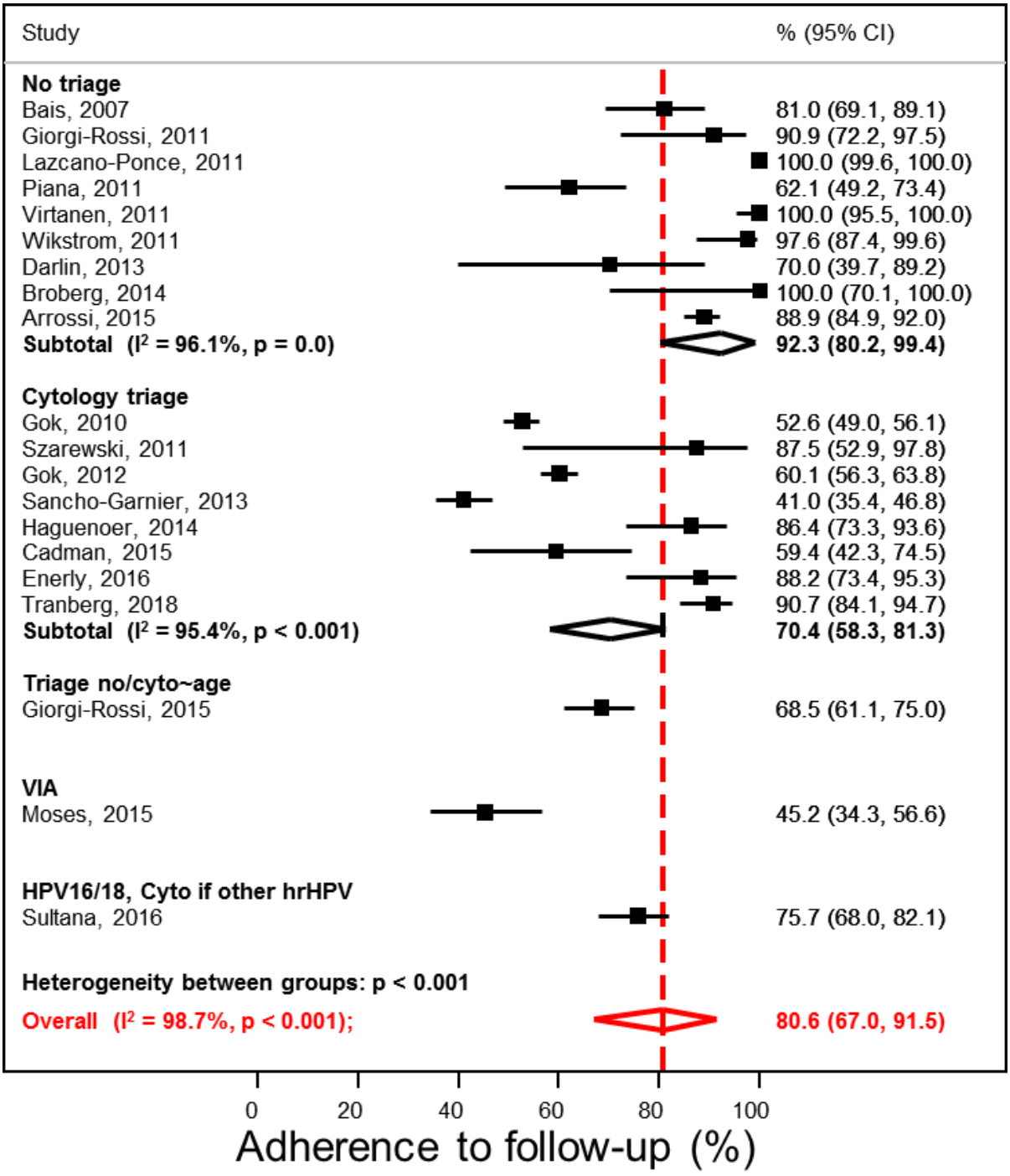


Figure 14. Follow-up adherence among women with a positive hrHPV test result on their self-sample, stratified by the applied triage policy (in the self-sampling arm of RCTs).

Abbreviations
VIA: visual inspection after application of acetic acid; HPV: hr: high-risk; HPV: human papilloma virus;

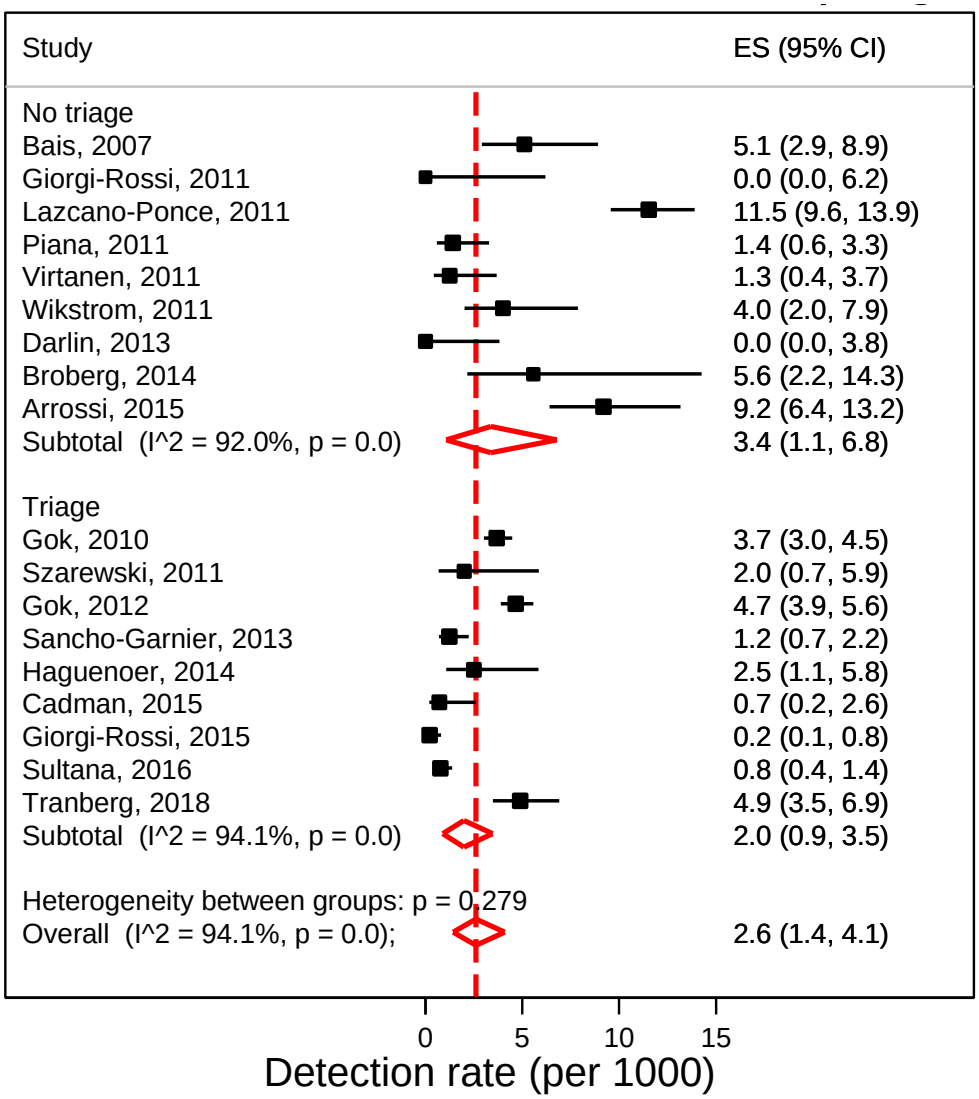


Figure 15. Detection of CIN2+ per 1000 invited women in the self-sampling arm, stratified by triage policy.

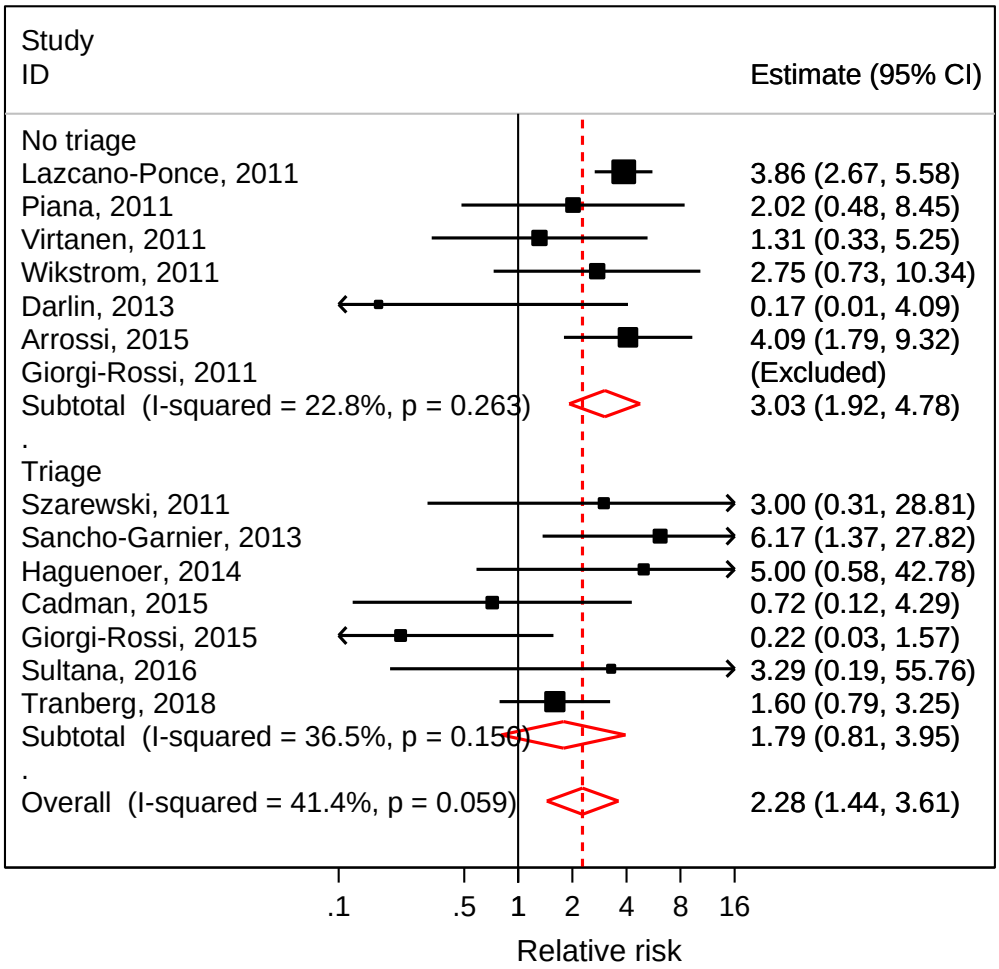


Figure 16. Relative detection of CIN2+ in the self- compared to the control arm among invited women, by triage policy in the self-sampling arm.

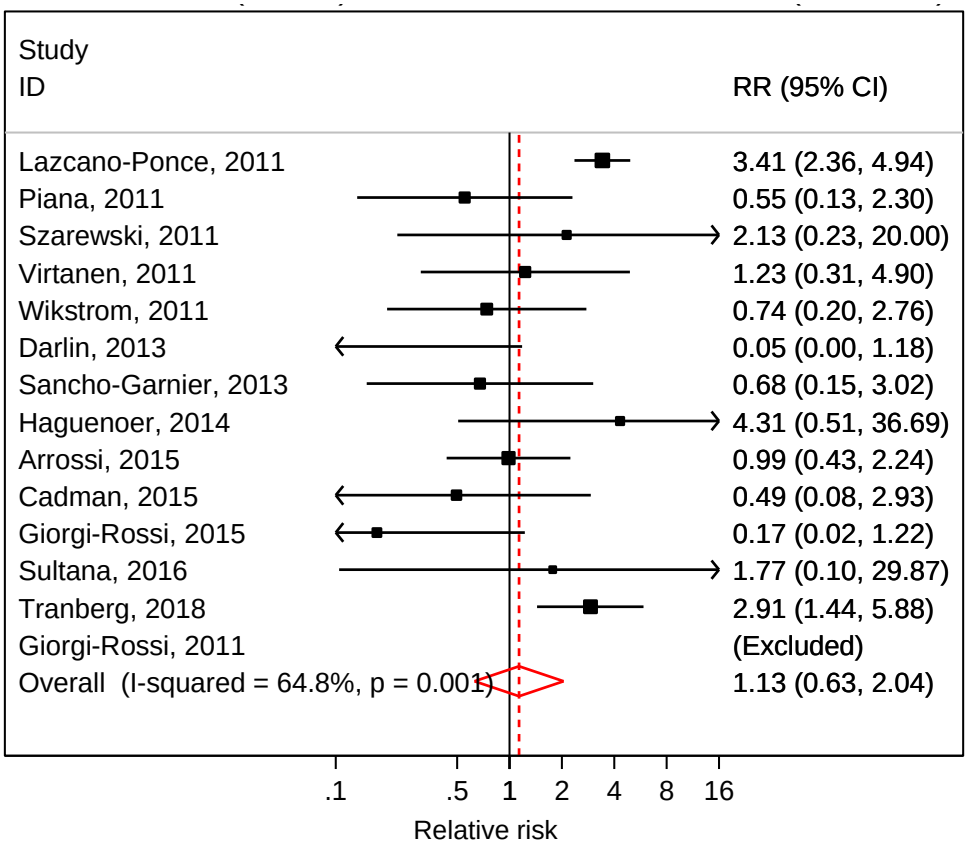


Figure 17. Relative detection of CIN2+ in the self-sampling compared to the control arm among screened women.

12. Research agenda

Table 18. Research agenda: propositions for studies involving HPV testing on self-samples.

Item	Proposition for new study/guideline development
1	Diagnostic test accuracy studies involving multiple device/HPV assay and storage medium/HPV assay combinations using accuracy the HPV assay test on a cervical clinician-taken sample as standard comparator test, with correlation between analytic outcomes and clinical outcomes (sensitivity, specificity for CIN2/3+), allowing for test cut-off optimisation.
2	Evaluation of the relative accuracy of HPV testing on urine vs vaginal self-samples vs cervical clinician collected samples.
3	Extension of the current meta-analysis including also HPV testing on urine specimens. specimen.
4	Continuous update of meta-analyses. An editor of a journal with good impact factor may be approached for online updates of important meta-analysis.
5	Definition of validation requirements for HPV testing on self-samples, similar to the international validation criteria for new HPV tests for primary cervical cancer screening on clinician samples.
6	Randomised participation trials or other controlled pilot studies in each country or region planning introduction of self-sampling.
7	Randomised participation trials involving general practitioners, with an intervention arm where under-screened women receive a self-sampling kit when they contact the practice for whatever reason. Preliminary small scale studies suggest substantially higher response rates than send-to-all or opt-in self-sampling strategies.
8	Individual-patient-data (IPD) meta-analysis of participation trials allowing for more precise assessment of the influence of population characteristics on study outcomes which is currently not assessable from aggregated data published in the peer-reviewed literature.
9	Participation trials in developing countries where other designs than home-visits are applied.
10	Evaluation of the diagnostic test accuracy of molecular markers applicable on self-specimen, which can be used to triage women with a hrHPV-positive self-sample avoiding the necessity of an additional visit for the collection of a cervical sample by a clinician.
11	Potential of self-sampling as a first option in primary cervical cancer screening as an alternative for the collection of a cervical sample by a clinician.

13. Reference List

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