Title: HPV Self-Sampling in Cervical Screening: a Rapid Review

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Sources
This rapid review was conducted by the Evidence Synthesis Group at the Complex Reviews Synthesis Unit (ESG @CRSU). Evidence relevant to the most recently published YouScreen study, which estimated the impact of offering HPV self-sampling to non-attenders within the cervical screening programme in England, was synthesised(1).

Funder
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Role of Funder
The protocol was developed independently of the funder of the study (NIHR). Feedback on the draft protocol and approval of the final protocol, were sought from the UK National Screening Committee (NSC).

Conflict of interest
No authors have known conflicts of interest to declare.

Abstract

Introduction
Cervical cancer is ranked the fourth most frequently diagnosed and the fourth leading cause of cancer deaths in women in the world. The WHO published a new guideline on using the human papillomavirus DNA (HPV DNA) test as primary screening in place of a Pap smear and visual inspection with acetic acid (VIA). HPV DNA tests can be done on both clinician and self-collected samples. Several countries, including France, Sweden and Australia, have incorporated self-sampling into their national screening programs, either as a primary screening approach or as a method targeted at under-screened individuals.

There is interest within the National Screening Committee to incorporate self-sampling into the cervical screening program in the UK, specifically for non-responders (≥6 months overdue for screening including never screeners). The YouScreen study was an implementation feasibility study that evaluated the impact of opportunistic and mail-to-all offering of HPV self-sampling at primary care encounters to people who did not attend for cervical screening in England. To contextualize and better understand the potential policy implications of the findings of the YouScreen study, this rapid review aimed to address questions on the accuracy, concordance, uptake and acceptability of self-sampling over clinician-collected samples. The first two questions focused on women eligible for cervical cancer screening, while the latter two questions focused on women who were under/never screeners.

Method
This is a rapid review that has primarily been developed based on recent recommendations and methodological guidance provided by the Cochrane Rapid Reviews Methods Group. To optimise the methodological rigour of this rapid review, preference was given to restriction, rather than omission, of systematic review components. Given the required expediency of the evidence synthesis, this pragmatic approach leverages multiple existing well-conducted systematic reviews which are aligned with the respective objectives of this rapid review. These reviews formed the basis of our data extraction, with limited searches overlapping those utilised in the reviews, intended to identify new publications with which analyses could updated. Narrative data synthesis was conducted to address the respective clinical questions. Where possible, meta-analysis was conducted on relevant outcomes related to accuracy, concordance, uptake, and acceptability.

Findings
The review included 180 studies. We have found that the self-sampling screening has similar accuracy as clinician-collected samples especially when PCR-based assays are used. Similarly, there is high concordance between the self-sampling and clinician-collected samples, in which the overall agreement was 87.1% (95% CI; 85.6 to 88.6) and the kappa value of 0.70 (95% CI; 0.67 to 0.73). The commonly used self-sampling strategies were opt-in and mail-to-all self-sampling strategies, with limited studies on opportunistic self-sampling done in the health care setting in which the self-sampling is done when a non-attendee visits the health facility for any other reasons. Mail-to-all all strategies had higher uptake with participation differences of 11.3% (95% CI: 8.4 to 14.2) in the intention-to-treat (ITT) analysis and 7.7% (95% CI: 4.7 to 10.8) in the per protocol (PP) analysis. However, opt-in had similar uptake with the clinician-collected sample in the PP analysis but with higher uptake in the ITT analysis (participation difference of 5.0% (95% CI; 1.4 to 8.6)). Although, self-sampling is highly acceptable to non-attendees (91% (95% CI; 85.3 to 94.6)) with less than 1% of unsatisfactory samples requiring retest and more than 80% adherence to self-sampling.

Conclusion and Recommendation

Self-sampling is a feasible strategy for reaching non-attendees and should be considered in the national screening program to reach the non-attendees, especially on using the PCR-based assay. However, before this is done, understanding the cost-effectiveness, logistics and compliance of the strategies is important to understand country-specific strategies for reaching the non-attendees.

Table of Content

Definition of Key Terms

Biopsy	*A medical procedure that involves taking a small sample of body tissue to be examined.*
Cervical intraepithelial neoplasia	*A precursor of cervical cancer which is classified according to the severity of dysplasia as CIN1 (low grade), CIN2+(high grade)*
Community mobilization and outreach	*Community campaigns with outreach supported by mass media in which attending women were offered a self-sampling kit at the end of a sensibilization session as well as, an individualized self-sampling kit delivery approach in which community healthcare workers directly contacted women at their homes or workplaces.*
Direct offer at a healthcare service	*Study participants were offered a self-sample at the end of an individual appointment (when they contacted a health service for whatever reason) and were given the choice to do it on-site in a private room or to take it home.*
Door to door	*A self-sampling where self-sampling kit are distributed and collected by a community health worker at home*
HPV DNA testing	*A laboratory test in which cells are scraped from the cervix to look for DNA of human papillomaviruses HPV.*
HPV DNA self-sampling (‘self-testing’; ‘home HPV testing’; ‘self HPV testing’)	*HPV DNA screening in which eligible women collect themselves the samples*
Intention-to-treat	*In the intention-to-treat (ITT) analyses, study participants who had been offered a self-sample but visited an HCP to have a sample taken instead were also counted as participants.*
Mailed to all	*Self-sampling kit sent without request.*
Non-attenders	*Individuals eligible to participate in the cervical screening programme that are under-screeend or have never participated.*
Opportunistic	*Request or on HCP recommendation for self-sampling, without organised invitation.*
Opt-in	*Offering study participants the possibility to obtain a self-sampling kit: women had to request the self-sampling kits to be received my mail or, alternatively, these could be collected from the local clinic/pharmacy.*
Per protocol	*Only study particiants who took a self-sample in the experimental groups were counted as participants.*
YouScreen	*An implementation feasibility study that evaluated the impact of opportunistically offering HPV self-sampling at primary care encounters to people who did not attend cervical screening in England.*

List of Abbreviations

CIN	Cervical intraepithelial neoplasia
COVID-19	Coronavirus disease-19
CRSU	Complex Reviews Synthesis Unit
DNA	Deoxyribonucleic acid
HC	Hybrid capture
HPV	Human papillomavirus
HPV-DNA	Human Papillomavirus-DNA
hrHPV	High-risk human papillomavirus
ITT	Intention to treat
LLETZ	Large loop excision of transformation zone
NSC	National Screening Committee
NHS	National Health Service
PCR	Polymerase chain reaction
PP	Per protocol
SA	Signal amplification
SES	Socioeconomic status
TA	Target amplification
UK	United Kingdom

Introduction

Rationale

Globally, cervical cancer is the fourth most frequent malignancy, and in the UK, has an approximate incidence of 3200 diagnoses annually(2). Persistent genital infection with Human Papillomavirus (HPV), one of the most common sexually transmitted infections, is estimated to be responsible for more than 90% cases of cervical cancer(3). There are greater than 200 HPV genotypes, which may be stratified into high-risk (hrHPV) and low-risk/non-oncogenic strains; the former includes types 16, 18, 31 and 33. Protracted HPV infection is associated with the development of cervical intraepithelial neoplasia (CIN), a precursor of cervical cancer which is classified according to the severity of dysplasia as CIN1 (low grade) and CIN2+ (high grade) (4). Owing to the considerable lag period often between 10 and 20 years, between HPV infection and the development of cervical cancer, there is substantial opportunity for early detection of precancerous lesions via screening and immediate treatment (5).

The NHS cervical screening programme was introduced in 1988. Currently, those with a cervix in England and Northern Ireland are invited for screening three-yearly between the ages of 25 and 49, and five-yearly between ages 50 and 64. In Scotland and Wales, eligible individuals are screened at intervals of five years(2). Owing to greater sensitivity in identifying CIN, hrHPV DNA detection has replaced cytological techniques as the preferred screening method. Those with a positive result are referred for cytology; individuals with abnormal cytology are invited for colposcopy. Clinical guidelines recommend monitoring of CIN1 lesions, whilst CIN2+ lesions should be managed by conservatively or by removing the abnormal cells, most frequently by large loop excision of the cervical transformation zone (LLETZ) depending on individual circumstances and preferences (4,6).

Whilst screening programmes have been demonstrated to mitigate the incidence of cervical cancer, coverage in many countries is suboptimal, and cervical cancer is most frequently diagnosed in those who are either underscreened or who have never participated in regular screening(6,7). Indeed, the reasons reported for non-participation are multifarious, but include insufficient time to attend a clinic, lack of awareness, anxiety regarding a gynaecological examination, or physical discomfort during specimen collection. Service issues may also present barriers to participation, such as a lack of suitable appointment times, or nearby clinics(9). Participation is often reduced in some patient populations, including those in minority ethnic groups, those of low socio-economic status, and transgender and non-binary people with a cervix(8,9). A range of diagnostic HPV-DNA tests and sampling methods are available, and samples may be self-collected from the vagina, as an alternative to collection from the cervix by a healthcare professional(10). Indeed, self-sampling has several advantages compared to clinician-based sampling, including reduced invasiveness, greater privacy, more convenient, and it has thus been proposed as a strategy to improve uptake of cervical screening. Furthermore, there is increasing evidence that self-sampling has good diagnostic accuracy is acceptable to screenees, and that it may improve cervical screening coverage(11). Several countries, including France, Sweden and Australia, have incorporated self-sampling into their national screening programmes, either as a primary screening approach, or as a method targeted at underscreened individuals.

There is interest within the National Screening Committee to incorporate self-sampling into the cervical screening programme in the UK, specifically for non-attenders(1). The YouScreen study was an implementation feasibility study which evaluated the impact of opportunistically and mail-to-all offering HPV self-sampling at primary care encounters to people that did not attend for cervical screening in England. To contextualize and better understand the potential policy implications of the findings of the YouScreen study, this rapid review aimed to address questions on the accuracy, concordance, uptake and acceptability of self-sampling over clinician-collected samples. The first two questions focused on women eligible for cervical cancer screening, while the latter two questions focused on women who were under/never screeners.

Aim

To contextualise and better understand the potential policy implications of the findings of the YouScreen study, the aim of this rapid review was to address the following clinical questions:

I. What is the accuracy of HPV testing in self-collected samples compared with health professional collected samples, and does this vary according to eligible women and test characteristics?
II. What is the level of concordance between HPV-DNA testing in self-collected samples and clinician/health professional collected samples, and does this vary according to eligible women and test characteristics?
III. What is the uptake of cervical screening by HPV self-sampling method when compared to health professional sampling method in non-attenders; i.e. women who are under-screened or have never participated in cervical screening, with those offered health professional sampling; and does this vary according to eligible women and test characteristics?
IV. Are HPV self-sampling screening strategies acceptable to those that have not attended the regular cervical screening programme, and does this vary according to eligible and test characteristics?

Objectives

The primary objectives of this rapid review are:

- To compare the diagnostic accuracy of HPV-DNA testing on self-collected samples with testing on samples collected by a healthcare professional, in eligible women for cervical screening programme
- To compare the uptake of cervical screening and adherence to follow-up, for self-sampling compared to sample collection by a healthcare professional, in eligible women who do not participate in a regular cervical screening programme
- To evaluate the acceptability of self-collection of samples for HPV-DNA testing in eligible women who do not participate in a regular cervical screening programme, and the factors which influence acceptability

The secondary objectives of this rapid review are:

- To determine if the diagnostic accuracy of HPV testing of self-collected samples varies according to eligible women characteristics, including socio-economic status, screening history, and clinical history, and test characteristics, including sampling device, storage medium, testing methodology, and setting
- To assess the variation in uptake of cervical screening and adherence to follow-up for self-sampling in eligible women who do not participate in a regular cervical screening programme, according to their characteristics, including socio-economic status and clinical history, and test characteristics, including sampling device, storage medium, testing methodology, and setting

Methods

The approach to this rapid review has primarily been developed based on recent recommendations and methodological guidance provided by the Cochrane Rapid Reviews Methods Group(12–16). However, it also accounts for the specific challenges of rapid reviews on diagnostic tests, namely the particular statistical methods for diagnostic accuracy and methodologies explicitly designed to evaluate the conduct of studies of diagnostic tests(17). To optimise the methodological rigour of this rapid review, preference is given to restriction, rather than omission, of systematic review components(12). Indeed, given the required expediency of the evidence synthesis, this pragmatic approach leverages multiple existing well-conducted systematic reviews which are aligned with the respective objectives of this rapid review. Where applicable, these form the basis of our data extraction, with limited searches overlapping those utilised in the reviews, intended to identify new publications with which analyses can be updated. The quality of the reference reviews was assessed using AMSTAR 2. The accuracy studies were assessed using the QUADAS tool for both studies included in the review and post review studies. The Cochrane Risk of Bias (RoB) was used by the uptake reference review and post review studies. The risk of bias of the studies in the acceptability study were assessed using Nudelman and Otto, 2020 tool Risk of Bias Utilized for Surveys Tool (ROBUST)(18). The RoB for concordance studies was not assessed since there is not a validated tool for assessing concordance studies. Furthermore, we engaged regularly with the NSC throughout the rapid review process to ensure that outputs are aligned with their requirements. Patient and public involvement activities were embedded within the YouScreen study, so are not included within this rapid review.

Eligibility Criteria

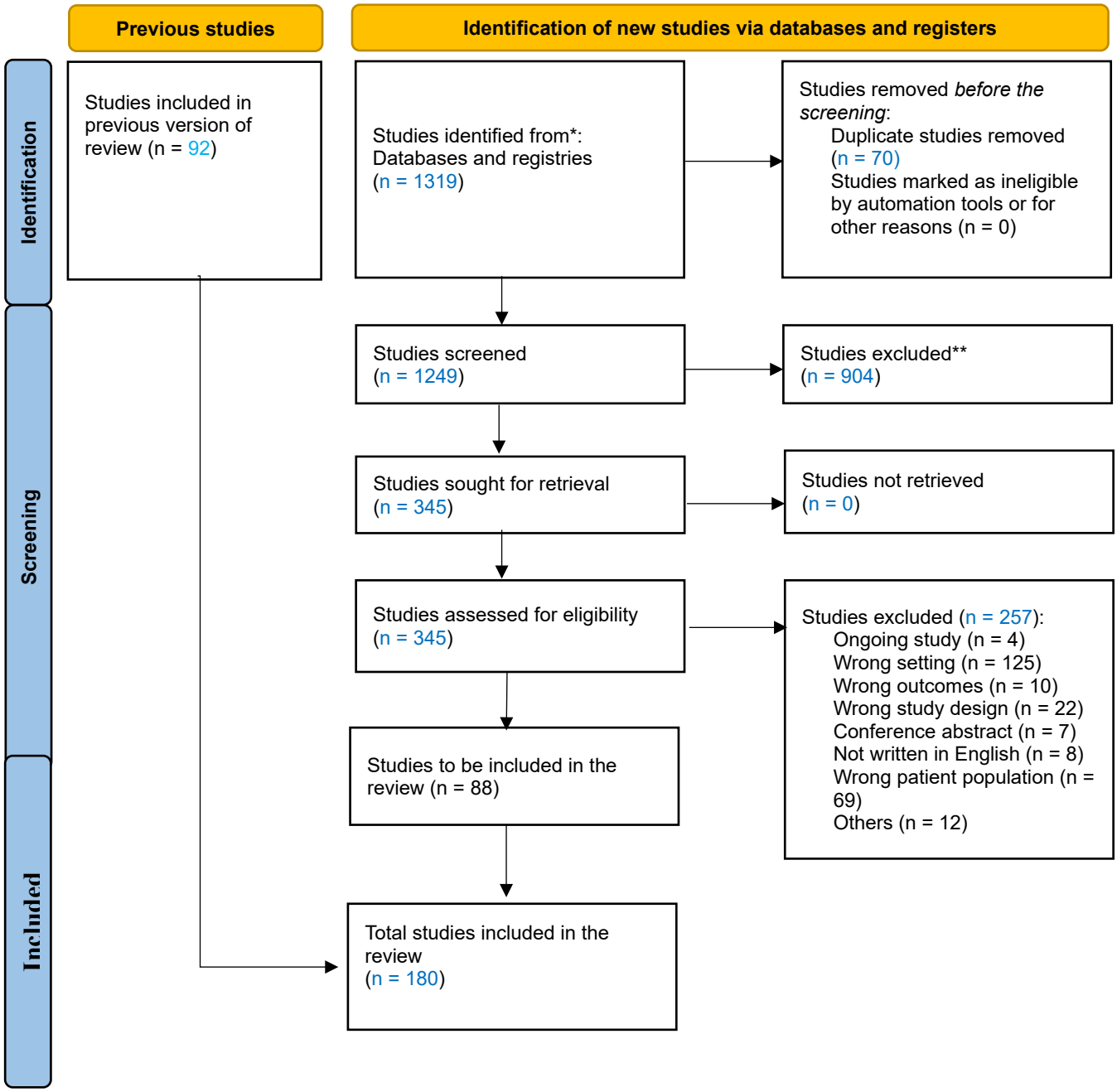
The eligibility criteria and search methods for each respective clinical question are outlined separately below. The respective systematic reviews upon which each search strategy is based are reported, with the search strategies detailed in the Appendix. The start dates for the searches have been selected to allow for three months of overlap with the end date of the search in the prior review, to ensure that all relevant new publications are captured. The identification of ongoing studies is limited in this review to ClinicalTrials.gov, for instances in which a more comprehensive search of multiple trial registries has been conducted in the primary review(s).

Screening Process

All studies fulfilling the eligibility criteria were included in the review. Abstracts, conference proceedings and non-English language studies were excluded from the review. Screening of abstracts were conducted by two independent reviewers (NT and RM). Full text records were screened by one reviewer and validation of excluded records (20%) was undertaken by a second reviewer. All discrepancies were resolved by consensus and/or a third reviewer.

Overall, 180 studies are included in this review – 92 studies from the systematic reviews and 88 from the top-up search. From the search, 1319 studies were identified from databases and registries; 70 studies were duplicates; 904 studies were excluded based on title and abstract screening; 345 studies were assessed by full article screening in which 257 studies were excluded (*Figure 1*).

Figure 1: PRISMA Flow Chart for the Included Studies



Data Extraction

Data extraction from individual reviews and studies were carried out by a single reviewer. Where feasible, data were extracted from existing systematic reviews. Co-variate data were extracted from the original studies in instances where this has not been recorded in a prior review. Data extraction was then completed for additional studies identified in the searches that have not been captured in prior reviews.

Synthesis

Narrative data synthesis was conducted to address the respective clinical questions. The following was carried out for all meta-analyses conducted:

- Meta-analyses were primarily conducted in R(19) using the {meta}(20)or {metafor} package(21). Where necessary, the variance for each study could be estimated from the reported confidence intervals using the conv.wald command in {metafor}.
- Forest plots were produced to investigate potential heterogeneity in meta-analyses. For each forest plot, studies were ordered by year to assess any temporal patterns.
- Outcomes were pooled separately by characteristics that were known to give inherently different results.
- Meta-regressions were conducted to assess whether certain characteristics had an (unknown) effect on outcomes and whether they explain any potential heterogeneity. Characteristics were added alone to the meta-regression with a significant effect being defined as a p-value for testing its inclusion of less than 0.05. For characteristics that have a significant effect on the outcome, a respective subgroup forest plot was produced. Characteristics were only tested if there was sufficient data and the data was in a quantitively analysable format.

In addition, approaches to tailored quantitative analyses for each respective clinical question, results and discussions are outlined separately below.

Quality of the Included Studies

Most of the studies had low risks on items assessed on the concordance expect on the patient selection- applicability concerns only one study had low risk of bias with the rest of studies having having risk (Appendix Table II). The quality of included studies considering uptake of self-sampling was assessed using ROBINS-I and RoB-2, as applicable, and as appropriate; two studies were evaluated using the former, and six studies using the latter tool. All of the assessed studies had a serious/high risk of bias. (Appendix Table III). On the acceptability, out of 48 studies accessed for quality, 46 studies scores 4 points or below. Most of the studies did not report on the items in the assessment tool (Appendix Table IV).

Tailored Methodological Approaches, Result and Discussion for Individual Review Questions

[I] Accuracy of HPV testing in self-collected samples compared with health professional-collected samples

Methodological Approaches

A prior review by Arbyn et al was used as a basis in addressing this question(22)

Population	Individuals eligible for cervical screening*
Index Test	HPV testing on self-collected sample
Comparator Test	HPV testing on healthcare professional-collected sample
Co-variates (where available)	• Background risk of population • Screening history of population (e.g under-screened, never screened) • Clinical history of population (e.g HIV positive) • Testing methodology • Sampling method/kit • Storage medium • Home-based vs in-clinic self-sampling • Age; Socioeconomic status; Ethnicity
Outcomes (where available)	• Absolute sensitivity and specificity of HPV self-sampling for the detection of CIN2+ and CIN3+ of index and comparator tests • Relative sensitivity and specificity of HPV self-sampling for CIN2+ and CIN3+ of HPV self-sampling versus clinician-based sampling

	• False-positive and false-negative rates of HPV self-sampling versus clinician-based sampling • PPV and NPV of HPV self-sampling • Proportion of self-selected samples in which HPV status cannot be determined (e.g. insufficient sample, failed lab tests) • Proportion of women with a 'failed' test/sample who are asked to provide a second sample • Proportion of women with a positive test result who attend clinic for diagnostic investigations and treatment (including cytology follow-up)		
Study designs	Cross-sectional studies, cohort studies, randomised controlled trials (RCTs), systematic reviews.		
Electronic databases	Database: ☒ MEDLINE ☒ CENTRAL ☒ EMBASE ☒ Clinical Trial Registry (ClinicalTrials.gov)	From: 1st January 2018 (overlap with Arbyn et al. 2018)	To: March 2024

**These include "women who were irregularly screened, never screened, or did not respond to invitation or reminder letters for conventional screening for cervical cancer", as defined in the Abryn review.*

Analyses were conducted according to the methods recommended in the Cochrane Handbook for Systematic Review of Diagnostic Test Accuracy (utilising the supplementary material in Chapter 10)(23). For each study, 2x2 tables for self-sampling (self) and healthcare professional sampling (health) were either extracted or back-calculated from the absolute sensitivities and specificities (with variance calculated from 95% confidence intervals) for self and health. Using the {lme4}(24) package, a single model was defined that included both sensitivity and specificity for self and health, together, with separate variances for self and health. This model gave pooled estimates of absolute sensitivity and specificity for self and health. Using the {msm}(25) package, the pooled absolute and relative difference between self and health for sensitivity and specificity could be calculated using the delta method(26) for calculating the confidence intervals. Absolute and relative differences were estimated separately for screening and colposcopy referral populations, and CIN2+ and CIN3+. Assay testing methodology and self-sampling device and setting were tested regarding affecting the outcome. These were tested by adding them to the model and then comparing models using the likelihood ratio test.

Results

The accuracy question included 39 studies – 18 studies from the referenced reviews and 21 from the top-up search (*Table 1*). The studies were conducted in 13 different high-income countries. 7 studies included women who were attending primary screening, 30 studies included women who were referred for colposcopy and 2 studies included other populations. The number of participants in the studies ranged from 42 to 7,643. The self-sampling devices reported in these studies were brush (15), swab (13), and lavage (4). The relative sensitivity/specificity reported in the detection of CIN2+ was reported in all studies (39). The assay used in these studies included PCR (28), HC2 (5) and some studies used more than one assays (5). The most frequently used storage medium was cell preserving (26).

In order to calculate the pooled estimates appropriately (as per the Cochrane Handbook), the raw 2x2 data table are required. The reference reviews only reported relative sensitivity and specificity for each study, which was not sufficient to back-calculate the requisite data. Furthermore, of all studies identified from the top-up search, eight did not have the necessary data (e.g. no comparator; no standard error). This has reduced the number of studies available for meta-analysis to 13 studies.

Pooled analysis showed that the sensitivity of self-sampling was lower than for healthcare professional sampling; however, it was not statistically significant (*Table 2*). Self-sampling device and setting did not give a significant effect on the absolute difference for colposcopy referral CIN2+ (LR test p-value = 0.143 and 0.984, respectively). Assay methods were all target-amplification methods regarding colposcopy referral CIN2+. Other groupings were not tested for test characteristic effects due to the small number of studies.

None of the 39 studies identified had data regarding numbers of samples that could not be determined/needed a second sample or data regarding the number of women with a positive test result attending clinics for further investigation.

Table 1: Characteristics of Studies on Test Accuracy of HPV Testing in Self-selected Samples

Author, Year and Country	Population	Sample Size	Age (years)	Ethnicity	Device used	Setting	hrHPV Assay	Storage Medium	Outcomes Assessed
Hillemanns 1999 Germany(27)	Colposcopy referral	247	Not specified	No reported	Brush	Not specified	HC2	"placed into a specimen collection tube"	CIN2+
Sellors 2000 Canada(28)	Colposcopy referral	200	Mean 31.5 Range not given	Not reported	Swab	Not specified	HC2, PCR (L1 consensus)	Self: STM Clin brush: STM Clin swab: sterile phosphate buffered saline	CIN2+
Nobbenhuis 2002 The Netherlands(29)	Colposcopy referral	71	Mean 35 Range not given	Not reported	Lavage	Not specified	PCR	PBS	CIN2+
Brink 2006 The Netherlands(30)	Colposcopy referral	96	Median 35 Range 18-59	Not reported	Lavage	Not specified	PCR	SurePath	CIN2+
Szarewski 2007 UK(31)	Primary screening	920	Median 29 (population 1) Median 41 (population 2)	Not reported	Swab	Not specified	Not specified		CIN2+
Balasubramanian 2010 USA(32)	Primary screening (high risk)	1665	Median 23 Range 18-50	Not reported	Swab	Not specified	HC2	STM	CIN2+

Dijkstra 2012 The Netherlands(33)	Colposcopy referral	135	Median 34 Range not given	Not reported	Brush	Not specified	PCR	Cell preserving	CIN2+
van Baars 2012 The Netherlands(34)	Colposcopy referral	134	Mean 40 Range 21-66	Not reported	Brush	Not specified	PCR	Self: FTA cartridge Clin: ThinPrep, SurePath	CIN2+ CIN3+
Jentschke 2013a Germany(35)	Colposcopy referral	72	Mean 37 Range 16-68	Not reported	Lavage	Not specified	HC2	Self: buffered saline Clin: PreservCyt, Cervatec	CIN2+ CIN3+
Jentschke 2013b Germany(36)	Colposcopy referral	42	Mean: 36 Range: 18-68	No reported	Lavage	Not specified	hrHPV: HC2 P16: p16INK4a ELISA	Self: buffered saline Clin: PreservCyt, Cervatec	CIN2+ CIN3+
Stanczuk 2016 UK(37)	Primary Screening	5318	Mean 41 Range 18–76	Not reported	Swab	Not specified	PCR	Cell preserving	CIN2+ CIN3+
Jentschke 2016 Germany(38)	Colposcopy referral	136	Mean 36 Range 17–78	Not reported	Brush	Not specified	PCR	Cell preserving	CIN2+ CIN3+
Aiko 2017 Japan(39)	Colposcopy referral	136	Mean not given Range 20-69	Not reported	Brush	Not specified	HC2		CIN2+ CIN3+
Asciutto 2017 Sweden(40)	Colposcopy referral	218	Mean 35 Range 19-71	Not reported	Swab	Not specified	PCR	Cell preserving	CIN2+
Leeman 2017 The Netherlands(41)	Colposcopy referral	91	Mean not reported Range 18-60	Not reported	Brush	Not specified	PCR	Cell preserving	CIN2+ CIN3+

Catarino 2017 Switzerland(42)	Colposcopy referral	150	Median 32 Range 18-69	Not reported	Swab	Not specified	PCR	Cell preserving	CIN2+ CIN3+
Leinonen 2018 Norway(43)	Other	240	Mean 38 Range 21-80	Not reported	Brush and Swab	Not specified	PCR	Cell preserving	CIN3+
Leinonen 2018 Norway(43)	Colposcopy referral	Self sampling: Evalyn Brush=287; FLOQ swabs=286 Health professional sampling: 259	Not reported	Not reported	Swab and Brush	Home	PCR	Cell preserving	CIN3+
Igidbashian 2014 Italy(44)	Primary screening	700	Mean 44.3 Range. Not reported	Not reported	Brush	Clinical setting	The Hybrid Capture II (HC2) microplate method	Cell preserving	CIN2+
Mangold 2019 Germany(45)	Colposcopy referral	208	Not reported	Not reported	Swab	Not specified	Signal amplification and PCR	Cell preserving	CIN2+
Edbald-Svensson 2018 Sweden(46)*	Colposcopy referral	63	Mean 42 Range 24–64	Not reported	Swab	Not specified	PCR	Cell preserving	CIN2+
El-Zein 2018 Canada(47)*	Colposcopy referral	1217	Not reported	Not reported	Swab	Clinical setting	PCR	Cell preserving	CIN2+ CIN3+
El-Zein 2019 Canada(48)	Colposcopy referral	700	Mean 37.7 Range not reported	Not reported	Swab	Clinical setting	PCR	Cell preserving	CIN2+ CIN3+

Polman 2019 The Netherlands(49)*	Primary screening	Self sampling: 7643 Health professional sampling: 6282	Self sampling mean= 45·5 Clinician based sampling mean = 45·7 Range not given	No reported	Brush	Home	PCR	Cell preserving	CIN2+ CIN3+
Onuma 2020 Japan(50)*	(1) Outpatients with abnormal cytology and requiring colposcopy and biopsy and (2) NILM/HPV-positive patients in the Fukui Cervical Cancer Study	100	Mean 41.8 Range not given	Not reported	Brush	Clinical setting	Cobas 4800 system (PCR)	Cell preserving	CIN2+
Ørnskov 2020 Denmark(51)*	Colposcopy referral	305	Median 34 Range 17-85	Not reported	Brush	Clinical setting	PCR	Cell preserving	CIN2+ CIN3+
Cho 2020 South Korea(52)*	Colposcopy referral	314	Median 40 Range not reported	Not reported	Brush	Clinical setting	PCR	Cell preserving	CIN2+
Rohner 2020a USA(53)	Colposcopy referral	314	Median 36 Range not given	Non-Hispanic white: 38% Hispanic: 29%	Brush	Clinical setting	PCR	Cell preserving	CIN2+

				non-Hispanic Black: 26% Other racial identities: 6%					
Rohner 2020b USA(54)*	Colposcopy referral	307	Median 36 Range not given	Hispanic: 29% Non-Hispanic white:38% Non-Hispanic black: 26%; Other: 7%	Brush	Clinical setting	PCR	Cell preserving	CIN2+
Ertik 2021 Germany(27)*	Colposcopy referral	65	Median age 36 Range 24–76	Not reported	Swab and Brush	Home	PCR	Cell preserving	CIN2+
Klischke 2021 Germany(55)*	Colposcopy referral	70	Mean 37	Not reported	Brush	Clinical setting	PCR	Cell preserving	CIN2+ CIN3+
Latsuzbaia 2022a Belgium(56)*	Colposcopy referral	485	Median 40 Range not reported	No reported	Brush	Clinical setting	PCR	Cell preserving	CIN2+ CIN3+
Avian 2022 Italy(57)*	Primary screening	889	Mean not reported 30-39: 190 (21.4%); 40-49: 303 (34.1%); 50-59: 299 (33.6%); ≥ 60: 97 (10.9%)	Not reported	Swab	Clinical setting	PCR	Cell preserving	CIN2+

Latsuzbaia 2022b Belgium(58)	Colposcopy referral	486	Median 40 Range not reported	Not reported	Swab and Brush	Clinical setting	PCR	Cell preserving	CIN2+ CIN3+
Stanczuk 2022 UK(59)	Primary screening	4617	Mean 41.3 Range not given	Not reported	Not specified	Not specified	Cobas 4800 PCR-based DNA test	ThinPrep (PreservCyt Solution Hologic, UK)	CIN2+CIN3+
Latsuzbaia 2023a Belgium(60)	Colposcopy referral	483	Median 40 Range not reported	Not reported	Swab and Brush	Clinical setting	PCR and signal amplification	Cell preserving	CIN2+ CIN3+
Latsuzbaia 2023b Belgium(61)	Colposcopy referral	493	Not reported	Not reported	Swab and Brush	Clinical setting	PCR	Cell preserving	CIN2+ CIN3+
Martinelli 2023 Italy(62)*	Colposcopy referral	245	Median 38 Range not reported	Not reported	Swab	Clinical setting	PCR	Cell preserving	CIN2+
Martinelli 2024 Italy(63)*	Colposcopy referral	290	Median 40 Range not reported	Not reported	Swab	Clinical setting	PCR	BD HPV Self Collection Diluent	CIN2+ CIN3+

Coloured red: From the top up search

* Indicate studies included in meta-analysis

Table 2: Pooled Estimates for Absolute Accuracy Measures

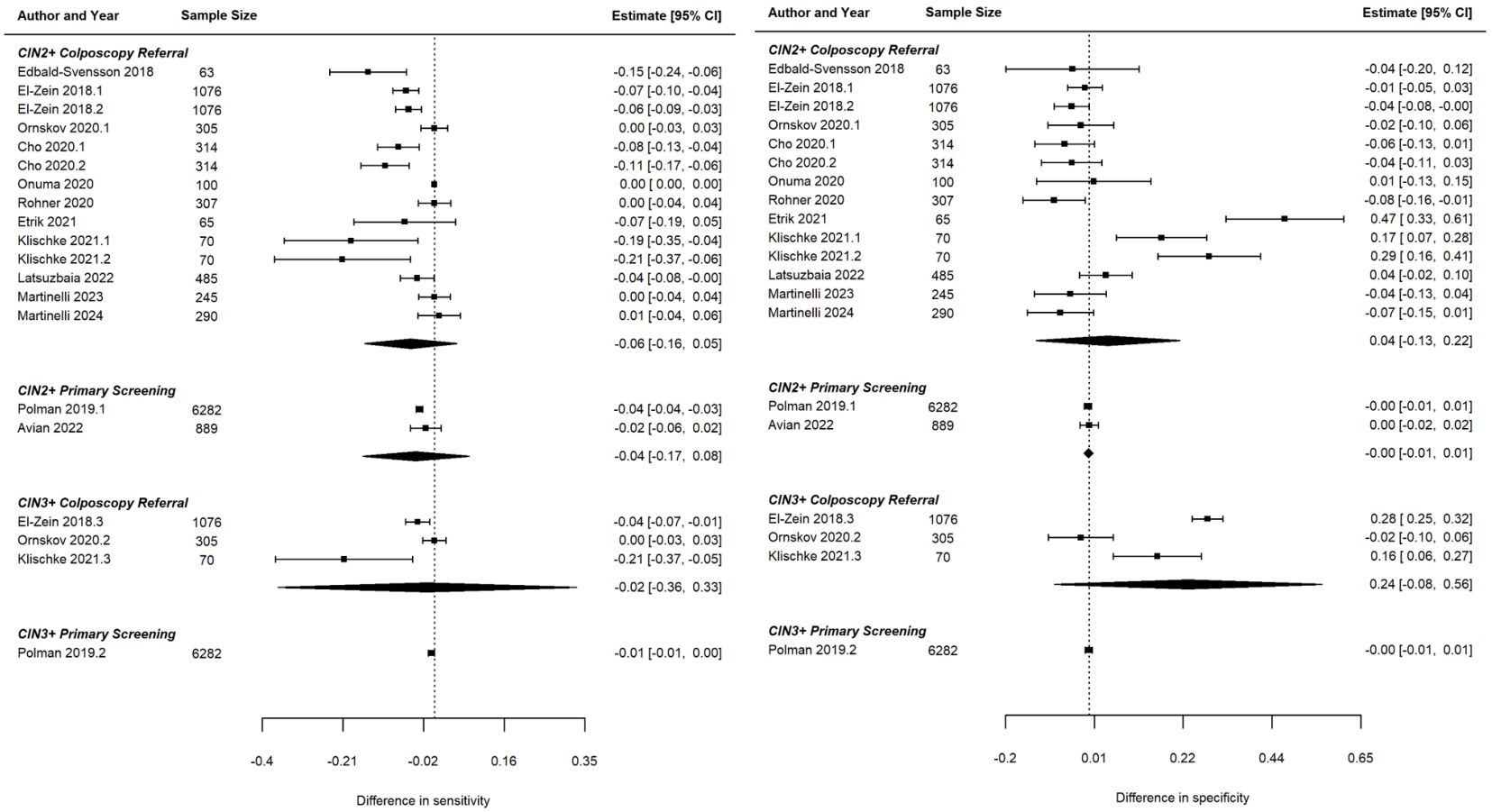
Group	No. of studies[a]	Sensitivity (95% CI)				Specificity (95% CI)			
		Self	Health	Absolute Difference	Relative Difference	Self	Health	Absolute Difference	Relative Difference
Colposcopy referral & CIN2+	11[b]	81.7 (70.9 to 89.0)	87.2 (80.3 to 91.9)	-5.5 (-16.2 to 5.2)	0.94 (0.82 to 1.07)	56.7 (41.3 to 70.9)	52.2 (44.2 to 60.1)	4.5 (-12.7 to 21.7)	1.09 (0.80 to 1.48)
Colposcopy referral & CIN3+	3	84.4 (37.0 to 98.0)	86.1 (56.3 to 96.7)	-1.7 (-36.4 to 33.1)	0.98 (0.65 to 1.48)	82.8 (43.1 to 96.8)	59.1 (40.5 to 75.4)	23.7 (-8.3 to 55.7)	1.40 (0.90 to 2.18)
Primary screening & CIN2+	2	87.4 (76.1 to 93.8)	91.6 (77.4 to 97.2)	-4.3 (-16.6 to 8.1)	0.95 (0.83 to 1.09)	93.9 (93.2 to 94.6)	94.1 (93.3 to 94.8)	-0.2 (-1.2 to 0.9)	1.00 (0.99 to 1.01)
Primary screening & CIN3+	1	95.1 (88.5 to 100.0)	95.8 (91.2 to 100.0)	N/A	N/A	93.4 (92.9 to 94)	93.5 (92.9 to 94.1)	N/A	N/A

Self = self-sampling; Health = health-professional sampling

[a] Studies may contribute to multiple outcome groups; total of 13 studies across all groups

[b] Cho (2022) and Klischke (2021) had separate results for two different assays, El-Zein (2018) had separate results for two different swabs.

Figure 2: Forest plot of absolute difference in sensitivity and specificity



Cho (2022) and Klischke (2021) had separate results for two different assays, El-Zein (2018) had separate results for two different swabs
Study-level estimates were calculated in isolation for the purpose of creating a forest plot; the pooled results were calculated as per the Cochrane handbook

Discussion

The pooled absolute sensitivity of hrHPV assays for CIN2+ and CIN3+ were lower for self-sampling than for health professional sampling, for both colposcopy referral and primary screening. In contrast, the pooled absolute specificity of hrHPV assays for CIN2+ was greater for self-sampling than for health professional sampling for colposcopy referral, but not for primary screening. However, there were a limited number of studies on the primary (7) screening compared to referral to colposcopy (30); the differences observed were not statistically significant. The relative sensitivity and specificity of self-sampling and clinician-collected samples were high. These findings are consistent with those reported in the source review. In high income countries, the interest in HPV DNA self-sampling has been for non/under screeners attendees (22). However, our review has included women of the general population with majority of studies including women who were referred for colposcopy or those attending the primary screening.

[II] The level of concordance between HPV-DNA testing in self-collected samples and health professional collected samples in cervical screening non-attenders

Methodology Approach

A prior review by Arbyn et al was used as a basis in addressing this question, with specific additional consideration of an updated review and meta-analysis on concordance between self-collected and clinician-collected samples for HPV testing(22,64).

Population	Individuals eligible for cervical screening		
Index test	HPV testing on self-collected specimens		
Comparator/reference standard	HPV testing on healthcare professional-collected specimens in index test subject		
Co-variates (where available)	• Background risk of population • Clinical history of population • Testing methodology • Sampling method/kit • Storage medium • Home-based vs in-clinic self-sampling • Age; Socioeconomic status; Ethnicity • Comorbidities captured by clinical history		
Outcomes (where available)	• HPV status • Test positivity ratio • Percent positive agreement • Percent negative agreement • Cohen's Kappa statistic • Positive concordance • Negative concordance		
Study designs	RCTs, cohort studies, systematic reviews		
Electronic databases	Database: ☒ MEDLINE ☒ CENTRAL ☒ EMBASE ☒ Clinical Trial Registry (ClinicalTrials.gov)	From: 1st January 2018 (overlap with Arbyn et al. 2018)	To: March 2024

Test positivity rate ratio, overall agreement, positive agreement, negative agreement, kappa, positive concordance, and negative concordance were meta-analysed – note that all of these measures were extracted concordant outcomes from the studies and were comparing self-samples vs healthcare professional collected results. Test positivity rate ratio was meta-analysed with {metafor} using a log transformation. Kappa was meta-analysed with {metafor} and utilised the measure of overall agreement to estimate variance when applicable(65). The remaining outcomes were meta-analyses of proportions using the metaprop command in {meta}. Assay testing methodology, self-sampling setting, and self-sampling device were tested regarding influencing the outcomes.

Results

The concordance question included 50 studies – 26 from reference review (12 studies had no outcome and hence not included in this study- *Appendix V*) and 24 from the top-up search. The studies were conducted in 15 different countries, and the number of participants in the studies ranged from 25 to 4,617. The ages of the included participants ranged from 18 to 76 years involving women referral for colposcopy clinic (26). The self-sampling devices which were used included brush (14), swab (9), and lavage (4). The self-sampling was reported done mostly in the clinical setting (27), followed by at home (5). The most used assay was PCR (22) (*Table 3*)

There were ten studies not included in the meta-analysis due to the lack of information (e.g. only gave kappa without respective variance, or only gave number of participants with a positive/negative result by self-sampling or healthcare professional, but not how many were agreed upon). This resulted in 28 studies with at least one concordance outcome that were included in the meta-analysis.

Table 3 Characteristics of Included Studies on Concordance between HPV-DNA Testing in Self and Health Professional Collected Samples

Author, Year, Country	Population	Sample Size	Age (years)	Ethnicity	Device	Setting	hrHPV Assay	Storage medium
Morrison 1992 USA(66)*	Colposcopy referral	25	Not specified	Not specified	Lavage	Clinical setting	PCR	Ethanol carbowax
Hillemann 1999 Germany(67)*^[1]	Colposcopy referral	247	Not specified	Not specified	Lavage	Clinical setting	PCR	Ethanol carbowax
Nobbenhuis 2002 The Netherlands(29)*^[1]	Colposcopy referral	71	Mean 35 Range not given	Not specified	Brush	Clinical setting	PCR	PBS
Brink 2006 The Netherlands(30)*^[1]	Colposcopy referral	96	Median 35 Range 18-59	Not specified	Brush	Clinical setting	PCR	STM
Seo 2006 South Korea(68)*^[1]	Colposcopy referral	118	Mean 46.2	Not specified	Swab	Clinical setting	hrHPV DNA Chip	Not specified
van Baars 2012 The Netherlands(34)*^[1]	Colposcopy referral	134	Mean 40 Range not given	Not specified	Brush	Clinical setting	PCR	FTA cartridge
Darlin 2013 Sweden(69)*^[1]	Colposcopy referral	108	Mean 34 Range not given	Not specified	Brush	Clinical setting	PCR	PreservCyt

Author, Year, Country	Population	Sample Size	Age (years)	Ethnicity	Device	Setting	hrHPV Assay	Storage medium
Jentschke 2013a Germany (35)	Colposcopy referral	72	Mean 37 Range not given	Not specified	Lavage	Clinical setting	HC2 P16: p16INK4a ELISA	Buffered saline
Jentschke 2013b Germany(36)	Colposcopy referral	49	Mean 36 Range not given	Not specified	Lavage	Clinical setting	HC2 P16: p16INK4a ELISA	Buffered saline
Chernesky 2014 Canada(70)*^[1]	Colposcopy referral	580	Mean 39 Range not given	Not specified	Brush	Clinical setting	APTIMA HPV	APTIMA SCT
Jentschke 2016 Germany(38)*^[1]	Colposcopy referral	136	Mean 36 Range not given	Not specified	Brush	Clinical setting	Abbott RealTime and hrHPV PCR	Dry, then transferred to PreservCyt
Aiko 2017 Japan(39)*^[1]	Colposcopy referral	136	Not specified	Not specified	Brush	Clinical setting	HC2	Not reported
Asciutto 2017 Sweden(40)*^[1]	Colposcopy referral	218	Mean 35 Range not given	Not specified	Swab	Clinical setting	Cobas 4800	Cobas PCR Female Swab Sample Kit
Catarino 2017 Switzerland(42)*^[1]	Colposcopy referral	150	Mean 32 Range not given	Not specified	Swab	Clinical setting	Xpert HPV; part of clin sample also cobas 4800.	Dry samples
Leinonen 2018 Norway(43)*^[1]	Not reported	240	Mean 38 Range not given	Not specified	Brush	Home	Anyplex II HPV28; cobas	Dry transport of self-collection devices to lab

Author, Year, Country	Population	Sample Size	Age (years)	Ethnicity	Device	Setting	hrHPV Assay	Storage medium
							4800, Xpert HPV	
Igidbashian 2014 Italy (44)	Not reported	700	Mean: 44.3 Range not given	Not specified	Not reported	Clinical setting	Hybrid Capture (HC)	Not reported
Des Marais 2018 USA (71)*^[1]	Low income	193	Mean 45 Range 30–63	Black (25.7%), White (44.5%), Hispanic (25.7%), Others (4.2%)	Brush	Home	Aptima HPV assay (Hologic, Inc.)	Aptima sample transport media
Svensson 2018 Sweden (46)*^[1]		63	Mean 42 Range 24-64	Not specified	Qvintip	Clinical setting	PCR	Not reported
El-Zein 2018 Canada (47)^[1]	Women referred for colposcopy	1076	Mean not Reported Range 21-74	Not specified	Swab	Clinical setting	PCR	PreservCyt
Onuma 2020 Japan(50)*^[1]	(1) Outpatients with abnormal cytology and requiring colposcopy and biopsy and (2) NILM/HPV-positive patients in the Fukui Cervical Cancer Study	100	Mean 41.8 Range not given	Not specified	Brush	Clinical setting	PCR	ThinPrep vials
Woong Cho 2020 South Korea(52)*	Women referred to colposcopy for abnormal cytology	314	40±15.4 years (Reported this a		Swab	Clinical Setting	PCR	PreservCyt Solution (ThinPrep)

Author, Year, Country	Population	Sample Size	Age (years)	Ethnicity	Device	Setting	hrHPV Assay	Storage medium
			median age)					
Rohner 2020b USA(54)*^[1]	Women who were attending colposcopy clinics	307	Median 36 Range not given	Non-Hispanic white 38%; Hispanic white 29%; Non-Hispanic 26%; other (7%)	Not reported	Not reported	PCR (Urine sample)	Becton Dickinson (BD) molecular tube containing 0.2 ml of a proprietary preservative
Satake 2020 Japan(72)*	No details provided	300	Mean not reported Range 20-59	Not specified	Home Smear Set (ISK Co., Ltd., Tokyo, Japan)	Clinical setting	PCR	Cell fixation container (principal component is ethanol)
Saville 2020 Australia(73)*^[1]	Referral for colposcopy	292-296	Not reported	Not specified	Swab	Clinical setting	Cobas 4800; Cobas; Onclarity; GeneXpert; Anyplex II; Abbott	Not reported
Tranberg 2020 Denmark(74)*^[1]	Women diagnosed with ASC-US.	150	Median 45 Range not given	Not specified	Not specified	Home	GENOMICA CLART® Cobas	Transportation tube with preservative media (Genelock, ASSAY ASSURE, Sierra Molecular, CA
Ertik 2021 Germany(75)	Patients referred to colposcopy clinics with abnormal results	65	Mean 36 Range, 24–76	Not specified	Swab, Brush	Home	PCR	ThinPrep PreservCyt

Author, Year, Country	Population	Sample Size	Age (years)	Ethnicity	Device	Setting	hrHPV Assay	Storage medium
Hong Kim 2021 South Korea(76)	Women who had abnormal cervical smears or who were HPV-positive	151	Median 50 Range 21–65	Not specified	G+Kit®; DocTool	Clinical setting	PCR	Not reported
Klischke 2021 Germany(55)	Patients from the colposcopy clinic	70	Mean 37 Range not given	Not specified	Brush	Clinical setting	PCR	ThinPrep PreservCyt Solution
Rohner 2021 USA(77)*^[1]	Women attending colposcopy clinics with i) abnormal cytology results, ii) infection with HPV-16 or 18, iii) persistent infection with other hr-HPV genotypes, or iv) treatment for CIN2+	314	Median 36 Range not given	Non-Hispanic white 38%; Hispanic 29%; non-Hispanic black 26% and others 6%	Brush	Not reported	PCR	ThinPrep
Avian 2022 Italy(57)		889	Not specified	Not specified	Swab	Clinical setting	PCR	ThinPrep
Giubbi 2022 Italy(78)	Women, referred to colposcopy	30	Mean 36.5 Range not given	Not specified	Swab	Clinical setting	PCR (Anyplex™II HPV28 (Seegene); HPV28 (Seegene)); Papilloplex® High Risk HPV; (GeneFirst); HPV	ThinPrep®PreservCyt® ; eNat®

Author, Year, Country	Population	Sample Size	Age (years)	Ethnicity	Device	Setting	hrHPV Assay	Storage medium
							OncoPredict (Hiantis)	
Martinelli 2022 Italy(79)*^[2]	Women referred to colposcopy	64	Mean 38.4 Range not given	Not specified	Swab Colli-pee®- for first-void urine (FVU) sample	Not specified	BD Onclarity™ HPV Assay	PreservCyt Preservative urine conservation medium (UCM)
Naseri 2022 USA(80)*^[2]	Women with and without a history of high-risk HPV infection and with regular menses	106	Mean 31.0 Range not given	Asian 35.8%; Black 1.9%; Native Hawaiian/Other Pacific Islander 1.9%; White 48.1%, others 11.3%	Swab Q-Pad (QvinTM, Menlo Park, CA)	Clinical setting Home	Roche Cobas 4,800	Cobas media solution. Dry samples
Ngu 2022 Hong Kong(81)*^[1]	History of sexual activity and underserved population	121	Mean not reported Range 30-65	Not specified	Swab	Not reported	PCR	PreservCyt media
Terada 2022 Japan(82)	Women attending hospital for abnormal cervical cytology	300	Mean not reported Range 21-50	Not specified	Brush Colli-pee®- for urine (FVU) sample	Not reported	PCR	PreservCyt

Author, Year, Country	Population	Sample Size	Age (years)	Ethnicity	Device	Setting	hrHPV Assay	Storage medium
Stanczuk 2022 UK(59)	Women eligible for cervical screening	4617	Mean 41.3 Range not given	Not specified	Not specified		Cobas 4800 PCR-based DNA test	ThinPrep (PreservCyt Solution, Holgic UK)
Gibert 2023 Spain(83)^[1]	Women recruited from a colposcopy clinic	120	Median 46 Range 40–51	Spain 62.5%; Central and South America 21.7%; European and United Kingdom 7.5%, Others (8.3%)	Swab, Iune HPV sterile test cannula, brush, Mia by XytoTest	Clinical setting	PCR	PreservCyt, reTect TM Preservation and Transport Media
Martinelli 2024 Italy(63)^[1]	Women who were referred to colposcopy	286	Median 40 Range not given	Not specified	Swab	Clinical sampling	Ist sample on VIPER; Second vaginal sample with VIPER; Second vaginal sample with COR	Dry samples

* and ^ indicate studies that were included in the meta-analysis for overall agreement and kappa respectively. ^[1] and ^[2] indicate that the variance for kappa was directly taken from the study or calculated from other data respectively.
Coloured red: studies from top-up search

Table No 4: Pooled Estimates for Concordant Outcomes

Outcome	Subgroup**	No. of studies*	All results
Overall agreement (%)	All	25	87.1 (85.6 to 88.6)
	Clinical setting	18	86.1 (84.0 to 88.0)
	Home setting	4	90.0 (88.0 to 91.6)
Kappa	All	25	0.70 (0.67 to 0.73)
	Clinical setting	18	0.73 (0.70 to 0.76)
	Home setting	4	0.62 (0.57 to 0.67)
Test positivity rate ratio	All	12	0.97 (0.89 to 1.04)
	Swab & TA assay	3	1.03 (0.99 to 1.06)
	Lavage & TA assay	1	1.24 (1.10 to 1.40)
	Brush & TA assay	6	0.95 (0.90 to 1.00)
	Brush & SA assay	1	0.66 (0.56 to 0.77)
	Brush & RNA assay	1	0.98 (0.90 to 1.06)
Positive agreement (%)		17	85.5 (81.6 to 88.7)
Negative agreement (%)	All	17	82.3 (74.9 to 87.9)
	Clinical setting	13	86.8 (83.6 to 89.5)
	Home setting	1	52.3 (47.1 to 57.5)
Positive concordance (%)		13	77.0 (70.7 to 82.1)
Negative concordance (%)		13	74.6 (70.8 to 78.1)

* Many studies gave multiple results (e.g. different assays, devices)
** Only reported where the inclusion of the respective variable gave a significant (<0.05) result

Figure 3 and *Figure 4* show the results for overall agreement and kappa respectively. The included studies reported overall agreement ranging from 77% to 96% and kappa value ranging from 0.47 to 0.86. There was substantial heterogeneity amongst the studies.

Regarding overall agreement, test assay gave no significant effect ($p = 0.292$), while self-sampling device gave a borderline significant effect ($p = 0.046$). However, the only device that gave a significant result was 'tampon' which was only informed by one study. There was a statistically significant effect regarding clinical setting ($p = 0.008$) where overall agreement was higher for tests taken in a home setting (*Figure 5*). Regarding kappa, self-sampling device and test assay gave no significant effect ($p = 0.948$ and $p = 0.139$, respectively). There was a statistically significant effect regarding clinical setting ($p <0.001$) where kappa was higher for tests taken in a clinical setting (*Figure 6)*, which was in direct contrast to the result found for overall agreement.

Negative agreement was also affected by setting of the test ($p <0.001$) and the test positivity rate ratio was jointly affected by self-sampling device and assay method ($p <0.001$) (*Table 4)*. Other outcomes were not affected by the other characteristics tested.

Figure 3 Overall Agreement

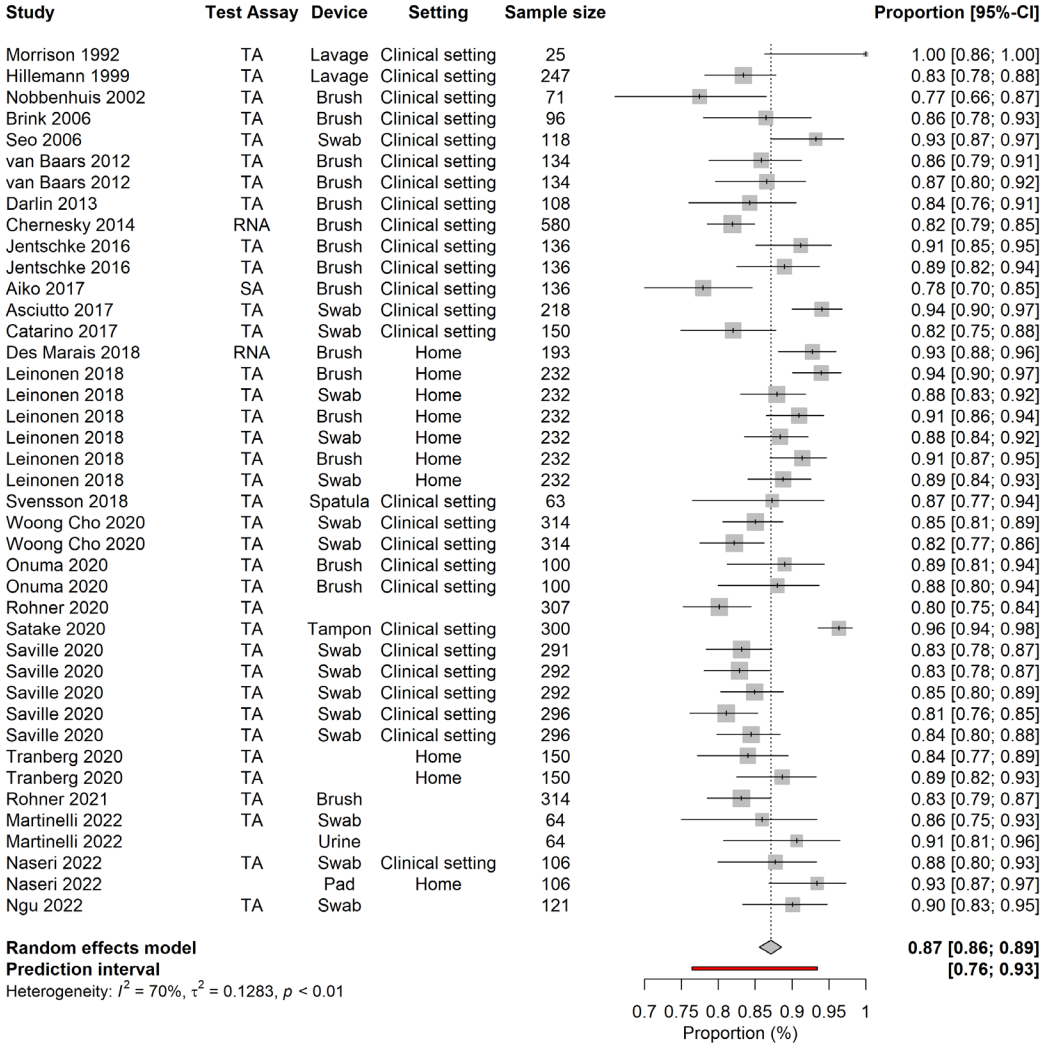


Figure 4 Forest plot for kappa

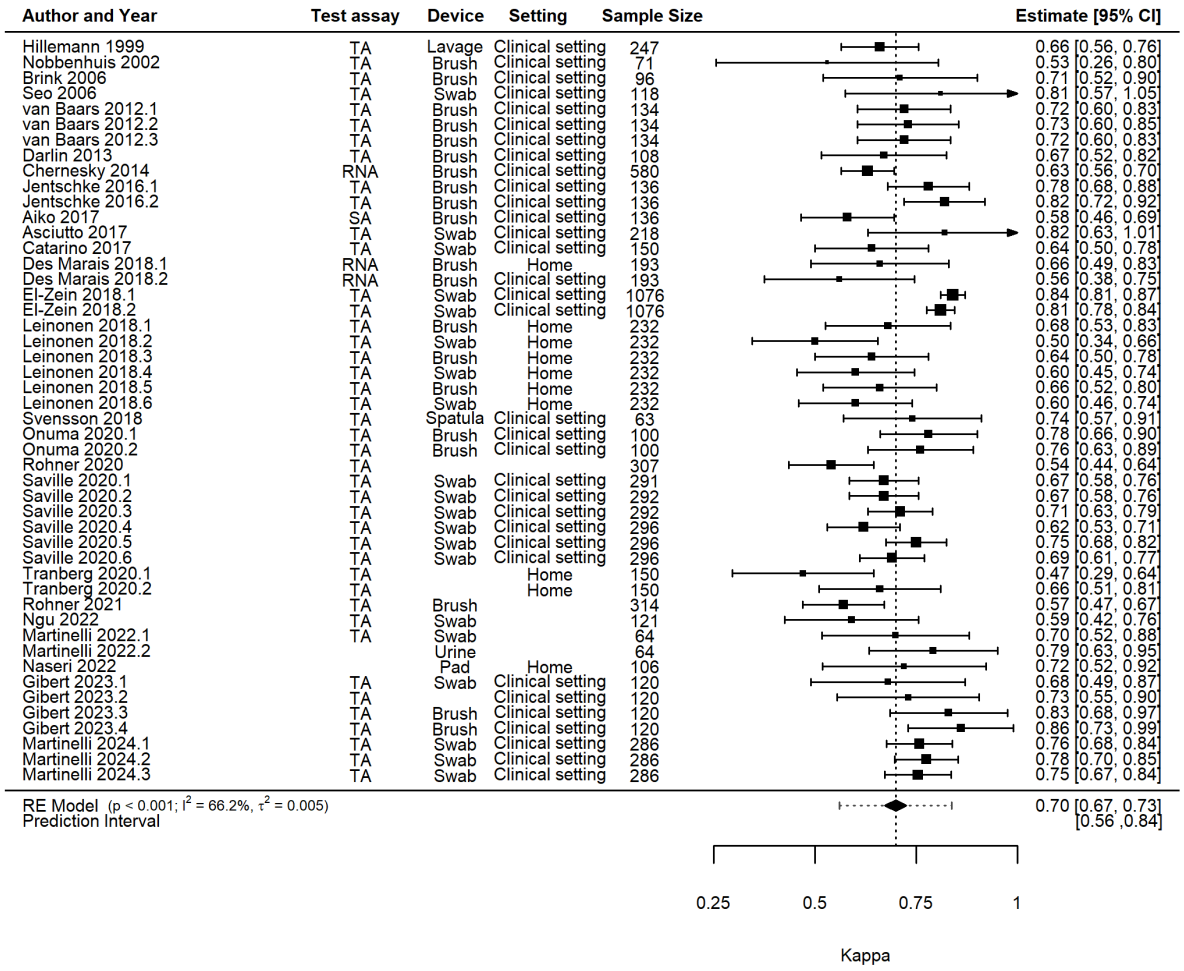


Figure 5 Overall Agreement across Settings

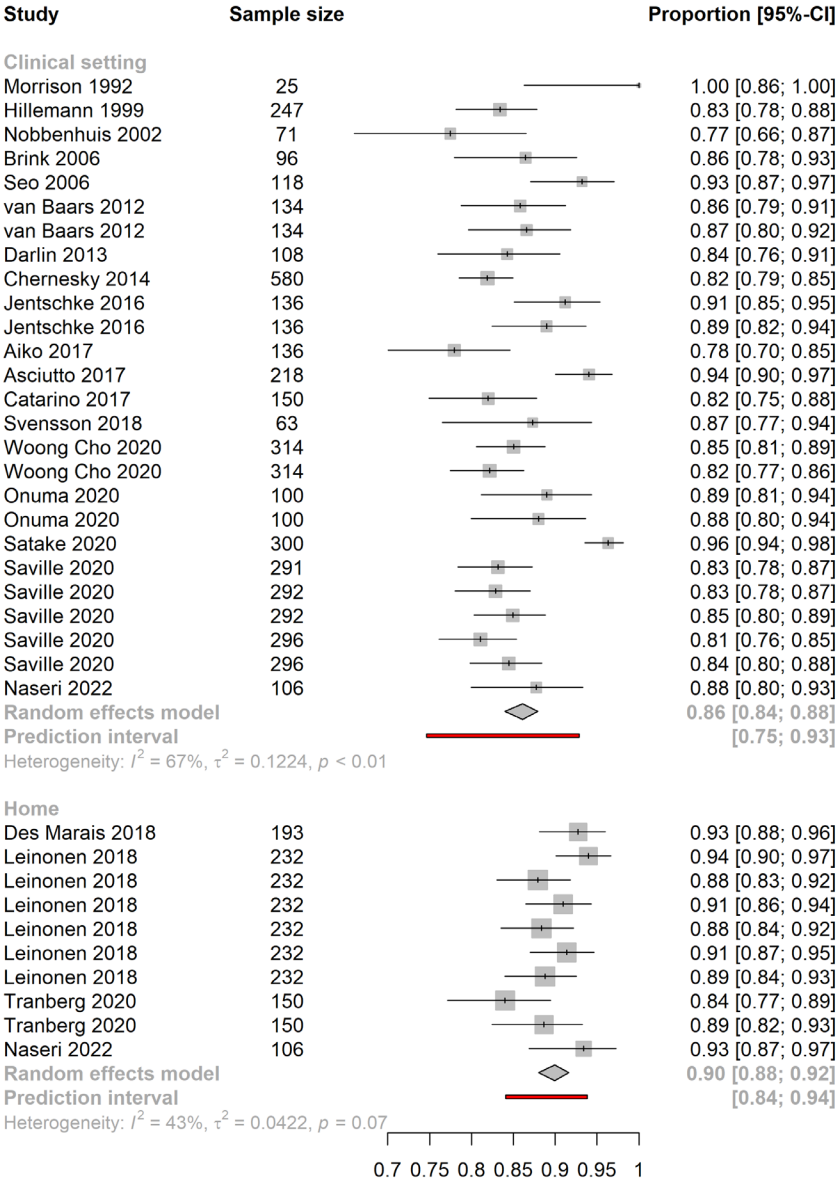
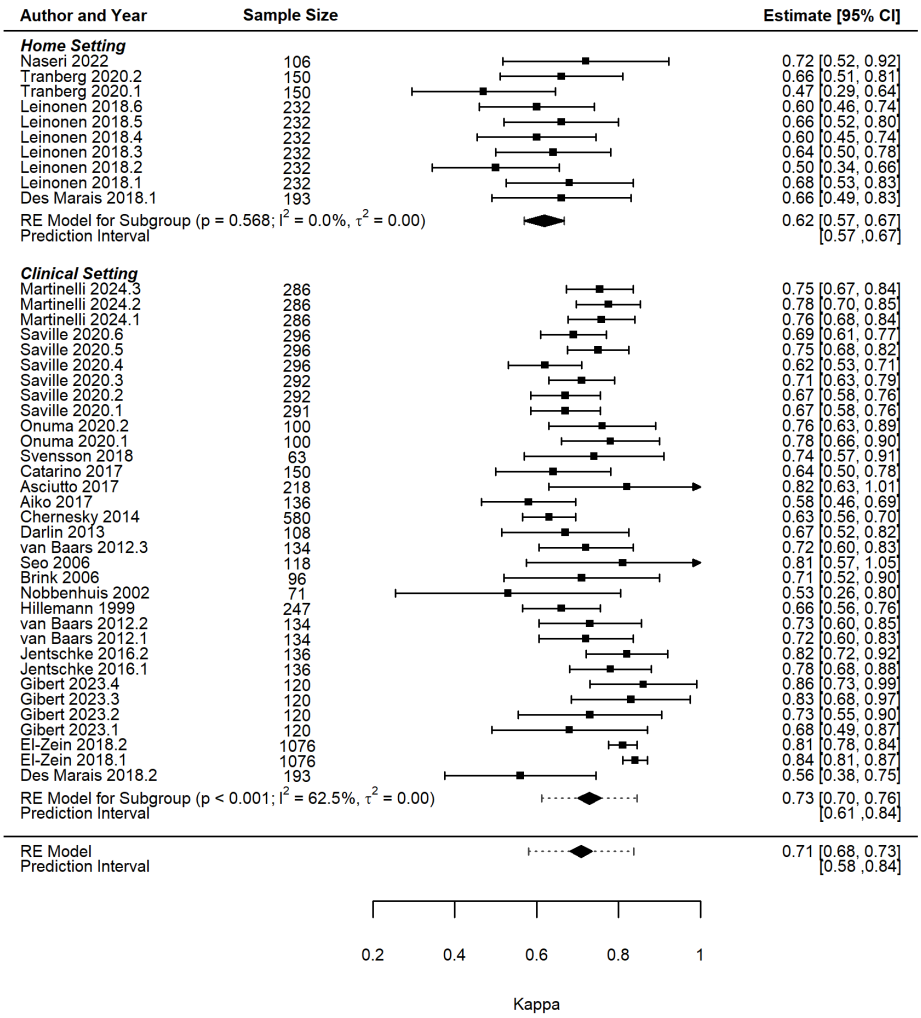


Figure 6 Kappa by setting



Discussion

Our meta-analysis showed 87.1% agreement and a kappa value of 0.70 between self-sampling and healthcare professionals. The level of overall agreement was found to be higher among home setting than clinical setting; however, this was in direct contrast to that was observed with the kappa measure. The negative agreement and test positivity ratio differed across the self-sampling devices. The negative agreement also differed on the self-sampling settings and test positivity ratio differed across the self-sampling test assay. These findings are consistent with the findings from Arbyn et al 2022 which reported pooled estimates of agreement of 88.7% and the kappa of 0.72 (84). In our subgroup analysis, the overall agreement was higher in the target amplification-based DNA assay compared to other assays. In Arbyn's analysis, the test positivity ratio did not change between the signal amplification assay and target amplification assay(84). However, in this analysis, it was recommended that test positivity ratios may not be appropriate for predicting the clinical sensitivity of SA tests of self -vs clinician-collected samples(84). This is because the specificity of SA is lower

with self-sampling and the higher test sensitivity of the SA is associated with false positive results instead of true positive. The possible biological explanation of this is the lower load of HPV in the vagina and cross-reactions with low-risk HPV types with SA(84)

[III] Uptake of cervical screening by HPV self-sampling method when compared to health professional sampling method in non-attenders with those offered health professional sampling

Methodological Approach

A prior review by Arbyn et al was used as a basis in addressing this question(22).

Population	Individuals who were invited to participate in standard cervical screening programme but did not respond to invitation or did not participate in the screening programme		
Intervention	Invitation to HPV based cervical screening - self sampling: opt-in, mailed, door-to-door, opportunistic		
Comparator	Invitation to HPV based cervical screening - clinician/health professional sampling		
Co-variates (where available)	• Invitation strategy (including opt-in; opt-out; opportunistic) • Screening history • Time from invitation for clinician/health professional sampling • Clinical history of population • Sampling method (brush, swab, lavage) • Location of test (home vs clinic/primary care) • Use of reminders (e.g. SMS) • Age; Socioeconomic status; Ethnicity • Comorbidities		
Outcomes (where available)	• Uptake of HPV based cervical screening (absolute participation) • Relative participation • Participation difference • Adherence to follow-up among those with a positive test result • PPV for CIN2+ among those with a positive test that attended for follow-up • Proportion of self-sampling individuals with unsatisfactory test results, i.e HPV status cannot be determined (e.g. insufficient sample, failed lab tests) • Proportion of women with a 'failed' test/sample who are asked to provide a second sample • CIN2+ detection rate • Frequency of screening across rounds		
Study designs	RCTs, cohort studies, systematic reviews		
Electronic databases	Database: ☒ MEDLINE ☒ CENTRAL ☒ EMBASE ☒ Clinical Trial Registry (ClinicalTrials.gov)	From: 1st January 2018 (overlap with Arbyn et al. 2018)	To: March 2024

Within each study, absolute participation was defined as the number of responders divided by the total number of individuals invited for the respective screening technique. Participation difference was then defined as the difference between these absolute percentages (i.e. self-sampling – control), and relative participation was calculated by dividing the absolute percentage of responders in the self-sampling group by the absolute percentage of responders in the control group. Absolute participation (self-sampling and control), unsatisfactory sample, adherence to follow-up, and CIN2+ detection were pooled using the metaprop command in {meta}. Participation difference and relative participation were meta-analysed using the metabin command in {meta}. Absolute and relative participation outcomes were meta-analysed separately for per protocol/intention-to-treat analysis results and invitation scenario. Per protocol analysis included women who participated in the cervical cancer screening through an HPV DNA self-sampling arm only. Intention-to-treat analysis included also those who were invited for self-sampling but chose to have a clinician-collected sample instead. Self-sampling device, whether reminders were used, and time between invitation and healthcare professional sampling were tested regarding influencing the outcomes.

Results

The uptake question included 38 studies – 26 articles from the existing review (One had no outcome - *Appendix VI*) and 12 studies from the top-up articles. These studies were from 17 High-Income Countries. All studies included were for individuals who were non-attendees of the regular screening which included those who had never screened. Due to the rapid nature of this review, we included only the studies that had a population of a sum of more than 1000 in both arms. The number of participants ranged from 529 to 57,717 in the self-sampling arm and 261 to 23,632 in the control arm. The age of the participants ranged from 20 to 69 years. Almost all studies used either opt-in (7), mail-to-all all (20), or a combination of these two self-sampling strategies (10). One study, in addition to mail-to-all and opt-in, also studied opportunistic offering of self-sampling. Thirteen studies evaluated the use of reminders for those overdue for screening. The sampling devices included brush (11), swab (13), lavage (4); four studies assessed more than one device. Most of the studies reported both per protocol (PP) and intention to treat (ITT) analyses (30) (*Table 5*).

Table 5 Characteristics of Included Studies for Uptake Question

Author, Year, Country	Population	Sample Size	Age (years)	Invitation Strategy	Reminder	Time from Invitation to collected sample	Self-sampling device	Per protocol (PP) or Intention to Treat (ITT) Analysis	Outcomes Reported
Bais 2007 New Zealand(85)	Under screened	Intervention 2,352 Comparator 272	Range 30-50	Mail to all	No	6 months	Brush	PP &ITT	Response rates; adherence to follow-up; insufficient sample; CIN+ 2 detection
Gok 2010 The Netherlands (86)	Under screened	Intervention 26,886 Comparator 277	Range 30-60	Mail-to-all		12months	Lavage	PP &ITT	Response rates; adherence to follow-up; insufficient sample; CIN+ 2 detection
Giorgi-Rossi 2011 Italy(87)		Intervention Mail-to-all: 616; Opt-in: 622 Comparator Mail-to-all: 619; Opt-in: 616	Range 35-65	Mail-to-all; Opt-in	No	3 months	Brush	PP &ITT	Response rates; adherence to follow-up; insufficient sample; CIN+ 2 detection
Piana, 2011 France(88)	Under screened	Intervention 4,400 Comparator 4,934	Range 35-69	Mail-to-all	No	Not documented	Not documented	PP &ITT	Response rates; adherence to follow-up; insufficient sample; CIN+ 2 detection

Author, Year, Country	Population	Sample Size	Age (years)	Invitation Strategy	Reminder	Time from Invitation to collected sample	Self-sampling device	Per protocol (PP) or Intention to Treat (ITT) Analysis	Outcomes Reported
Szarewski 2011 UK(89)	Under screened	1,500 in both intervention and comparator	Range 25-64	Mail-to-all	No	6 months	Swab	PP &ITT	Response rates; adherence to follow-up; insufficient sample; CIN+ 2 detection
Virtanen 2011 Finland(90)	Under screened	Intervention 2,397 Comparator 6,302	Range 30-60	Mail-to-all	No	Not documented	Lavage	PP &ITT	Response rates; adherence to follow-up; insufficient sample; CIN+ 2 detection
Wikstrom 2011 Sweden(91)	Under screened	Intervention 2,000 Comparator 2,060	Range 39-60	Mail-to-all	Yes	12 months	Swab	PP &ITT	Response rates; adherence to follow-up; CIN+ 2 detection
Gok 2012 The Netherlands (92)	Under screened	Intervention 25,561 Comparator 261	Range 30-60	Mail-to-all	No	12 months	Brush	PP &ITT	Response rates; adherence to follow-up; insufficient sample; CIN+ 2 detection
Darlin 2013 Sweden(93)	Under screened	Intervention 1000 Comparator 500	Range 32-65	Mail-to-all	Yes	Not documented	Not documented	PP &ITT	Response rates; adherence to follow-up; insufficient

Author, Year, Country	Population	Sample Size	Age (years)	Invitation Strategy	Reminder	Time from Invitation to collected sample	Self-sampling device	Per protocol (PP) or Intention to Treat (ITT) Analysis	Outcomes Reported
									sample; CIN+ 2 detection
Sancho-Garnier 2013(94) France(94)	Under screened	Intervention 8,829 Comparator 9,901	Range 35-69	Mail-to-all	No	Not documented	Swab	PP &ITT	Response rates; adherence to follow-up; insufficient sample; CIN+ 2 detection
Broberg 2014 Sweden(95)	Never screened; Under screened	Intervention 800 Comparator 4000	Range 30-62	Opt-in	Yes	Not documented	Swab	PP &ITT	Response rates; adherence to follow-up; CIN+ 2 detection
Haguenoer 2014 France(96)	Under screened	Intervention 1,999 Comparator Cytology 2,000 No intervention 1,999	Range 30-65	Mail-to-all	No	9m; 12m	Swab	PP &ITT	Response rates; adherence to follow-up; insufficient sample; CIN+ 2 detection
Cadman 2015 UK(97)	Under screened	3000 in both arm	Range 25-65	Mail-to-all	No	3 months	Swab	PP &ITT	Response rates; adherence to follow-up; insufficient sample; CIN+ 2 detection

Author, Year, Country	Population	Sample Size	Age (years)	Invitation Strategy	Reminder	Time from Invitation to collected sample	Self-sampling device	Per protocol (PP) or Intention to Treat (ITT) Analysis	Outcomes Reported
Giorgi-Rossi 2015 Italy(98)	Under screened	Intervention Mail-to-all: 4,516; Opt-in: 4,513 Comparator Mail-to-all: 1,998; Opt-in: 3,014	Range 30-64	Mail-to-all; Opt-in	No	3 months	Lavage	PP &ITT	Response rates; adherence to follow-up; insufficient sample; CIN+ 2 detection
Enerly 2016 Norway(99)	Under screened	Intervention 800 Comparator 2,593	Range 26-69	Mail-to-all	No	Not documented	Lavage (Delphi screener) / Evalyn brush (randomized)	PP &ITT	Response rates; adherence to follow-up; insufficient sample
Sultana 2016 Australia(100)	Never screened; Under screened	Intervention 14,153 (7,075 un-screened; 7,078 under-screened) Comparator 2,025 (1,014 un-screened; 1,011 under- screened)	Range 30-69	Mail-to-all	No	6 months	Swab	PP &ITT	Response rates; adherence to follow-up; insufficient sample; CIN+ 2 detection
Kitchener 2017 UK(101)	Under screened	Intervention Mail-to-all: 1,141 (32 GPs);	Mean 20 (Grampian)	Mail-to-all; Opt-in	No	3m, 6m, 12m, 18m	Lavage (Delphi Screener)/	PP &ITT	Response rates.

Author, Year, Country	Population	Sample Size	Age (years)	Invitation Strategy	Reminder	Time from Invitation to collected sample	Self-sampling device	Per protocol (PP) or Intention to Treat (ITT) Analysis	Outcomes Reported
		Opt-in: 1,290 (66 GPs) Comparator 3,782 (101 GPs)	Mean 25 (Manchester))				Evalyn Brush		
Kellen 2018 Belgium(102)	Under screened	Intervention Mail-to-all: 9,118; Opt-in: 9,098. Comparator Reminder letter: 8,830; No reminder: 8,849	Range 30-64	Mail-to-all; Opt-in	Yes	12m	Qvintip	PP &ITT	Response rates.
Tranberg 2018 Denmark(103)	Never screened; Under screened	Intervention Mail-to-all: 3,265; Opt-in: 3,264. Comparator 3,262	Range 30-64	Mail-to-all; Opt-in	Yes	6 months	Brush	PP &ITT	Response rates; adherence to follow; CIN+ detection
Ivanus 2018 Slovenia(104)	Under screened	Intervention Mail-to-all: 9,556; Opt-in: 14,400 Comparator 2600	Range 34-64	Mail-to-all; Opt-in	No	12 months	Mail-to-all: Qvintip (Swab), HerSwab (Swab) and Delphi Screener	PP &ITT	Response rates; adherence to follow-up

Author, Year, Country	Population	Sample Size	Age (years)	Invitation Strategy	Reminder	Time from Invitation to collected sample	Self-sampling device	Per protocol (PP) or Intention to Treat (ITT) Analysis	Outcomes Reported
							(Lavage). Opt-in: Qvintip		
Elfström 2019 Sweden(105)	Under screened	Intervention Mail-to-all: 2,000; Opt-in: 2,000 Comparator 2000	Range 33 - 60	Mail-to-all; Opt-in	No	3 months	Swab	PP &ITT	Response rates; CIN+ detection
Jalili 2019 Canada(106)	Under screened	Intervention 529 Comparator 523	Range 30 - 65	Mail-to-all	Yes	6 months	Swab	PP &ITT	Response rates
Winer 2019 USA(107)	Under screened	Intervention 9,960 Comparator 9,891	30 - 64	Mail-to-all	No	6months	Not documented	PP &ITT	Response rates; adherence to follow-up; insufficient sample; CIN+ 2 detection
Lilliecreutz 2020 Sweden(108)	Under screened	Intervention 3,068 Comparator 3,538	Range 30 - 64	Mail-to-all	Yes	6 months	Swab	PP &ITT	Response rates; adherence to follow-up; CIN+ detection

Author, Year, Country	Population	Sample Size	Age (years)	Invitation Strategy	Reminder	Time from Invitation to collected sample	Self-sampling device	Per protocol (PP) or Intention to Treat (ITT) Analysis	Outcomes Reported
Brewer 2021 New Zealand(109)	Never screened; Under screened	Intervention Mail-to-all: 1467: Opt-in: 1574 Comparator 512	Range 30-69	Mail-to-all; Opt-in, and Opportunistic	Yes	3 months	Swab	PP &ITT	Response rates; follow up; insufficient sample
Virtanen 2014 Finland(90)	Under screened, never screened	Intervention 4536 Comparator Not reported	Range 25-67	Mail-to-all	Not reported	Not documented	Lavage	Not reported	Response rates; adherence to follow-up; CIN2+
Lam 2017 Denmark(110)	Under-screened, never screened	Intervention 23,632	Range 27 - 65	Opt-in	Yes	8 weeks	Brush	PP and ITT	Response rates
Gunvor Aasbø 2022 Norway(111)	Never screened; Under screened	2000 in both arms	Mean 54.3	Mail-to-all; Opt-in	Yes	Not documented	Brush	PP &TT	Response rates; adherence to follow-up; CIN2+ detection
Fujita 2022	Never screened;	Intervention 7,340	Range 30-59	Opt-in	Yes	Not documented	Brush	Not reported	Response rates; insufficient sample

Author, Year, Country	Population	Sample Size	Age (years)	Invitation Strategy	Reminder	Time from Invitation to collected sample	Self-sampling device	Per protocol (PP) or Intention to Treat (ITT) Analysis	Outcomes Reported
Japan(112)	Under screened	Comparator 7,782							
Ejegod 2022 Denmark(113)	Never screened; Under screened	Intervention 57,717 Comparator Not reported	Range 27-65	Opt-in	Yes	Not documented	Brush	PP & ITT	Response rates; adherence to follow-up
Sultana 2022 Australia(114)	Never screened; Under screened	Intervention 12,572 Comparator Not reported	Range 30-69	Mail-to-all	No	2 years	Swab	Not reported	Response rates; adherence to follow-up; insufficient sample; CIN+ 2 detection
Winer 2022 USA(115)	Never screened; Under screened. White 71.6%, did not specify others' percentage	Intervention 9843 Comparator 9891	Mean 50.1	Mail-to-all	Not reported	Enrolled for 3 years and 5 months or more, and with no Papanicolaou test within 3 years and 5 months	Not reported	ITT	Response rates
Auvinen 2022 Finland(116)		Intervention 5350 Comparator Not reported	Range 25-69	Opt-in.	Not reported	No documented	Aptima Multitest sampling kit	Not documented	Response rates; adherence to follow-up; insufficient

Author, Year, Country	Population	Sample Size	Age (years)	Invitation Strategy	Reminder	Time from Invitation to collected sample	Self-sampling device	Per protocol (PP) or Intention to Treat (ITT) Analysis	Outcomes Reported
									sample; CIN+ 2 detection
Nishimura 2023 Japan(117)	Never screened; Under screened	Intervention 7,653 No Comparator	Range 20-50	Opt in	Not reported	Not documented	Brush	ITT	Response rates' adherence to follow-up; CIN2+
Winer 2023 USA(118)	Never screened; Under screened; Routinely screened Due for screening: White 73.4%; Asian 12.4%; Black or African American 4.9%; others 9.3% Overdue: White 73.6%; Asian	Intervention Due for screening 12,928; Overdue for screening 8279; Unknown screening history 9942 Comparator 12,142	Mean 45.9	Opt in; Mail-to-all	Yes	Due for screening ≤3 months; Overdue for screening (co-testing >5.25years ago, Papanicolaou testing alone >3.25 years ago, or no Papanicolaou testing with continuous enrolment ≥3.25 years, unknown enrolment ≥6 months and <3.25 years,	Swab	ITT	Response rates; adherence to follow-up

Author, Year, Country	Population	Sample Size	Age (years)	Invitation Strategy	Reminder	Time from Invitation to collected sample	Self-sampling device	Per protocol (PP) or Intention to Treat (ITT) Analysis	Outcomes Reported
	11.5%; Black or African American 5.2%; others 9.7%					no recorded screening)			
Taro2024 Japan(119)	Never screened; Under screened	Intervention 3489 Comparator Not reported	30-39	Opt-in	Not reported	Not documented	Brush	PP & ITT	Response rates, Adherence to follow-up; CIN2+
Ngo2024 Czech Republic(120)	Never screened; Under screened	Intervention 800 Comparator 764	Range 50–65	Mail-to-all	Yes	Not documented	Brush	PP & ITT	Response rates' insufficient sample; dherence to follow-up

NB: Response rates: if the study reported any of the following absolute response rate, relative response rate, response difference. Adherence to follow-up: if the study reported on adherence to follow-up of individuals who receive positive screening results. Insufficient sample: proportion of individuals with unsatisfactory test results i.e HPV status could not be determined.

Colored red: studies from top-up search.

Eight studies were not included in the meta-analysis as, for fairer comparisons, only those that reported uptake for both the self-sampling and control arms were included leaving 29 studies. *Table 6* shows the percentage of women having a hrHPV test done with a self-sample, separately for those who received a self-sampling kit mailed to their home (mail-to-all) and those having to request a self-sampling kit (opt-in). Overall, the participation rate is higher amongst self-sampling compared with controls.

Table 6 Absolute and Relative participation in self-sampling and/versus control arms

Invitation scenario	**No. of studies**	**Absolute participation**		**Participation difference % (95% CI)**	**Relative participation (95% CI)**
		Self-sampling % (95% CI)	**Control % (95% CI)**		
Per protocol					
Mail-to-all	26*	17.7 (15.0 to 20.8)	9.1 (6.9 to 12.0)	7.7 (4.7 to 10.8)	1.94 (1.48 to 2.55)
Opt-in	10*	8.5 (6.3 to 11.4)	9.8 (6.5 to 14.4)	-2.3 (-6.5 to 2.0)	0.88 (0.51 to 1.52)
Intention-to-treat					
Mail-to-all	28*	23.0 (20.2 to 26.0)	10.0 (7.4 to 13.2)	11.3 (8.4 to 14.2)	2.34 (1.87 to 2.93)
Opt-in	10*	15.2 (11.5 to 19.8)	9.8 (6.5 to 14.4)	5.0 (1.4 to 8.6)	1.56 (1.09 to 2.24)

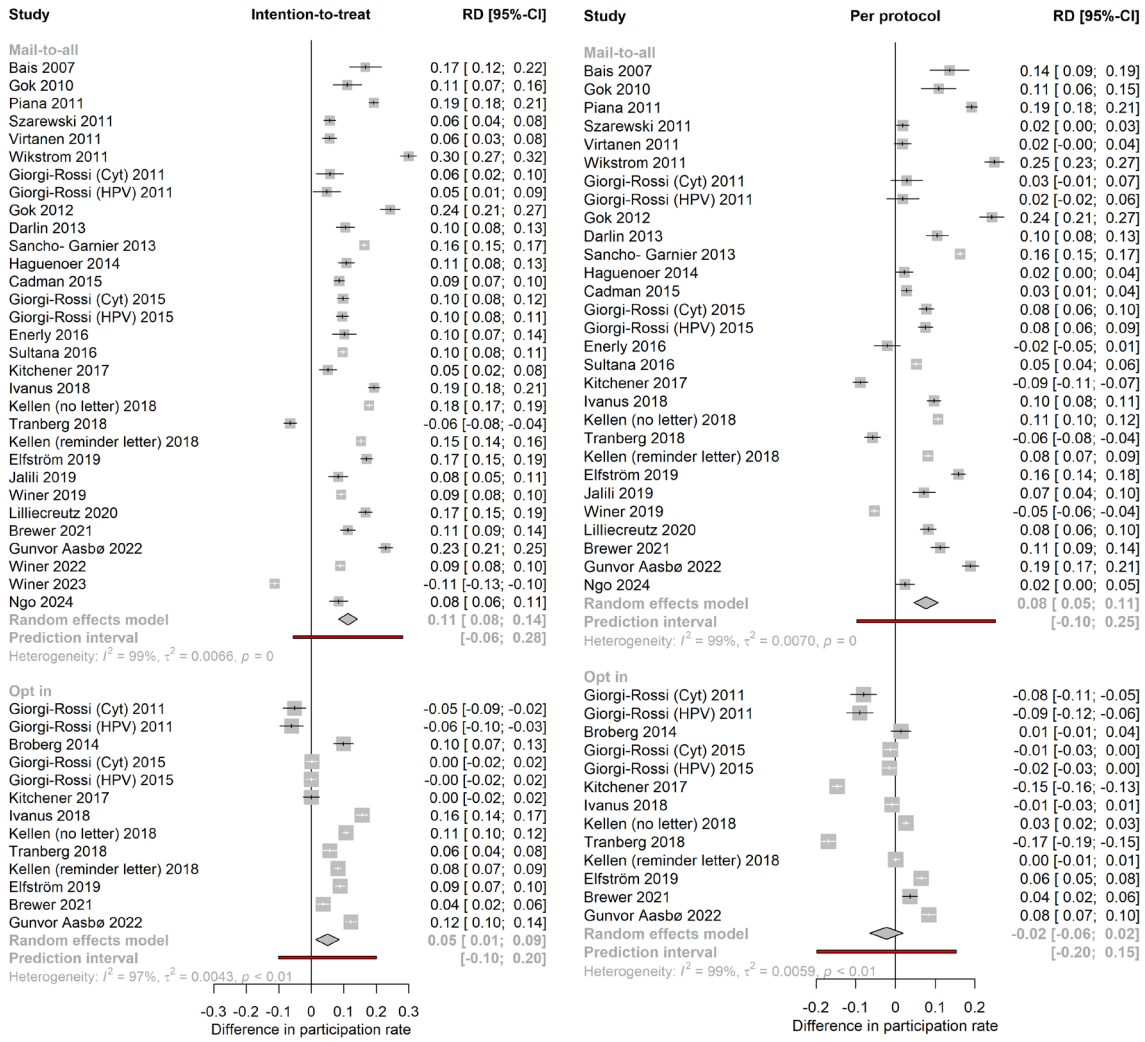
*Giorgi-Rossi (2011) & Giorgi-Rossi (2015) had two control groups (one with cytology, and another with HPV testing). Kellen (2018) also had two control groups (with and without recall letters).
Absolute participation is the number of responders divided by the total number of individuals in the respective group. Participation difference is the difference between these absolute percentages (i.e. self-sampling – control), and relative participation is the absolute percentage of responders in the self-sampling group divided by the absolute percentage of responders in the control group.

The difference in participation rates of each study included in meta-analysis is shown in *Figure 7*. For the mail-to-all invitation strategy, the time between the invite and a health professional taking the sample affected the participation difference (difference increased by 1.0% (95% CI: 0.1% to 1.8%) and 1.2% (95% CI: 0.4% to 2.0%) per month under the per protocol and intention-to-treat analysis respectively (both estimated from 20 study data points)). No other tested characteristics gave a significant effect for both per protocol and intention-to-treat analyses.

For the opt-in invitation strategy, the use of reminders and time between invite and a health professional taking the sample increased the participation difference by 7.1% (95% CI: 0.5% to 13.6%) and 1.2% (95% CI: 0.5% to 2.0%) (per month, estimated from 10 study data points) respectively under the intention-to-treat analysis. No other tested characteristics gave a significant effect. None of the tested characteristics gave a significant effect for the opt-in invitation strategy under the per protocol analysis.

When incorporating the above characteristics, the heterogeneity did not significantly improve (i.e. I^2 remained above 96% for all groups.

Figure 7 Difference in Participation Rate between Self-sampling and Control



The pooled proportion of unsatisfactory samples taken by the self-sampling group, their adherence to follow-up, and the CIN2+ detection per 1000 women invited are show in *Table 7*. Due to only two studies reporting such information for control arms, pooled relative rates could not be estimated.

Table 7 Sample adequacy, adherence, and CIN2+ detection rates

Parameter	No. of studies	Absolute proportion self-sampling (% unless other specified) (95% CI)
Unsatisfactory sample	20	0.9 (0.6 to 1.2)
Adherence to follow-up	29	80.5 (72.2 to 86.7)
CIN2+ detection (per thousand women screened)	25	11.6 (8.4 to 16.0)

Discussion

The pooled participation was higher in the mail-to-all self-sampling strategies compared to control. This was also observed when comparing opt-in strategy with control in the intention-to-treat analysis; however, no statistically significant difference was observed in the per protocol analysis. Overall, the absolute participation rate was greater in the intention-to-treat analysis than in the per protocol analysis. These findings are consistent with the reference review(7).

However, mail-to-all may not be the optimal strategy when implementing self-sampling into clinical practice. Whilst mail-to-all screening strategies increased uptake for non-attendees, it is costly and may result in significant wasted resoureces,, as the majority do not return the kit; the pooled participation rate was only 17.7% in our per protocol analysis. Furthrrmore, the YouScreen study reported that the opportunistic offering of self-sampling kits by healthcare providers was associated with a five times (65.5%) greater uptake compared to a mail-to-all self-sampling strategy (12.9%)(1). Furthermore, although self sampling improves screening uptake, the diagnostic accuracy of screening for high risk HPV may not be increased.

The percentage of unsatisfactory samples was very low 0.9 (95%CI; 0.6 to 1.2) while adherence to follow-up was 80.5 (95%CI; 72.2 to 86.7) which encourages the applicability of this method. Whilst the small percentage of the unsatisfactory sample may be reassuring for those whom doubts regarding their self-efficacy in performing self-sampling is a barrier to participation, this is likely an under-estimate and may vary according to the device utilised (123). One of the challenges of self-sampling is loss of follow-up, however, this level of adherence assures the linkage of those with positive results to further assessment for identification of precancer and cancer.

[IV] Acceptability of HPV self-sampling screening strategies to those that have not attended the regular cervical screening programme

Methodological Approach

A prior review by Nelson et al was utilised as the basis for addressing this question, with particular consideration of additional reviews by Yeh et al and Nishimura et al(121,122)

Population	Individuals eligible for cervical screening who do not attend for health professional testing (non-attenders)
Intervention	Invitation to HPV-based cervical screening - self-sampling
Comparator	Invitation to HPV-based cervical screening - health professional sampling
Co-variates (where available)	• Invitation strategy • Sampling method (brush, swab, lavage) • Screening history • Clinical history of population • Population subgroup (eg SES, ethnicity, LGBT+)
Outcomes (where available)	Overall: • Stated overall acceptability • Stated preference in compared with clinician-based screening • Stated preference for the setting of self-collection of sample • Stated willingness to repeat screening Individual characteristics of acceptability/experience including: • Logistic measures of acceptability (e.g convenience, accessibility)

	• Procedure-related measures of acceptability (e.g pain/physical discomfort, ease of use, confidence in result, self-efficacy to do the test) • Psychosocial measures of acceptability (e.g stigma, embarrassment, anxiety, fit with values)		
Study designs	RCTs, cohort studies, feasibility studies, mixed methods studies, surveys and systematic reviews.		
Electronic databases	Database: ☒ MEDLINE ☐ CENTRAL ☒ EMBASE ☒ Other (CINAHL, LILACS, SCOPUS, OpenGrey, ProQuest, Cochrane Library) ☒ Clinical Trial Registry (ClinicalTrials.gov)	From: 1st December 2014 (overlap with Nelson et al. 2015)	To: March 2024

All outcomes were meta-analysed using the metaprop command in {meta}. Due to data availability, only self-sampling devices were tested regarding influencing the outcomes.

Results

The acceptability question had 53 articles: 22 from the review (5 studies had no outcome *Appendix VII*) and 31 from the post-review top-up search. The studies were from 19 different countries. The participants ranged from 31 – 9,484 with the age range from 14 – 69. The basic review did not include population details such as screening history, ethnicity and SES. Some of the post-review studies included this population details. The review also did not include the self-sampling invitation strategy. Some of the studies included invitation strategies. Two studies included a combination of opt-in and mail to all strategy and one study had a combination of community mobilization and opt-in strategy. Three studies (3) used a mail-to-all strategy, two (2) self-sampling offered at the clinical setting and two (2) studies reported using community outreach and mobilization strategies. The self-sampling devices included in the studies are brush (11), swab (17), lavage (3), tampon (1) and more than one device in 3 studies. The basic review also did not include the outcomes of individual characteristics of acceptability (logistics, procedural and physiological). The acceptability was reported for overall acceptability and stated preference for self-sampling over healthcare professionals. However, some of the top-up studies include the individual characteristics of acceptability and overall acceptability (*Table 8*)

Table 8 Characteristics of Included Studies for Acceptability of HPV Self-sampling Screening Strategies

Author, Year, Country	Population	Sample size	Age (years)	Invitation Strategy	Self-sampling device used	Outcomes	
						Acceptability	Individual characteristics of acceptability
Dannecker 2004 Germany(123)		333	Mean 45		Brush	Overall acceptability; preference	
Kahn 2005 USA(124)		120	Mean 17.8 Range 14-21		Swab	Preference	
Anhang 2005 USA(125)		172	25%: 25-35; 10%: >55	Not specified	Swab	Preferences	
Waller 2006 UK(126)		902	Mean 34.2		Swab	Preference	
Wikstrom 2007 Sweden(127)		94	Range 35-55		Qvintip	Preference	
Barbee 2010 USA(128)		245	6%:18-25; 94%: ≥25		Tampon	Preference	
Cerigo 2011		92	Mean 33.2		Swab	Preference	

Author, Year, Country	Population	Sample size	Age (years)	Invitation Strategy	Self-sampling device used	Outcomes	
						Acceptability	Individual characteristics of acceptability
Canada(129)			Range 18-69				
Delere 2011 Germany (130)		156	Range 20-30		Lavage		
Igidbashian 2011 Italy(131)		194	Mean 39.6 Range 19-72		Brush and Delphi screener (Lavage)	Overall acceptability; preference	
Rossi 2011 Italy(87)		147	Range 25-64		Not reported	Preference	
Ortiz 2012 Puerto Rico(132)		100	Mean 26.4 Range 18-34		Dacron Swab, CytoBrush	Preference	
Van Baars 2012 The Netherlands(34)		127	Median 40		Brush	Overall acceptability; preference	
Castell 2014 Germany(133)		108	Range 20-69		Lavage	Overall acceptability; preference	
Catarino Jr 2014 Switzerland(134)		158	Mean 43.6		Swab	Overall acceptability; preference	
Montealegre 2014 USA(135)		100	Median 38		Cytology Broom	Acceptability	
Nelson 2014 USA(136)		67	Median 24 Range 21-30		Swab	Preference	
Virtanen 2014	Finish 93%; Swedish 2.2%; Other 4.8%	909	Range 30-64		Lavage		Procedural and psychosocial

Author, Year, Country	Population	Sample size	Age (years)	Invitation Strategy	Self-sampling device used	Outcomes	
						Acceptability	Individual characteristics of acceptability
Finland(137)							
Vanderpool 2014 USA (Appalachian)(138)	Low income Caucasian (100%)	31	Mean 38.5		Brush	Overall acceptability	
Galbraith 2014 USA(139)	Low-income status women: Non-Hispanic Black (55%), White (33%), Other (13%)	199	Range 30-65		Brush	Overall acceptability; preference	Procedural
Bosgraaf 2014 The Netherlands(140)		9484	Range 29-63		Lavage and brush	Preference	Logistic and psychosocial
Catarino 2015 Switzerland(141)	European (39.8%), Swiss (17.7%), Asian (7.0%), African (9.5%), Latin American (36.7%), Others (7.0%)	158	Mean 43.6		Swab	Overall acceptability; preference	Procedural
Chou 2015 Taiwan(142)		282	Mean 48.1	Mail-to-all	Brush	Overall acceptability	Procedural
Crosby 2015 USA (rural Appalachian)(143)	Rural, economically disadvantaged area: White (93.8%), Black (2.8%), and others (3.4)	400	Mean 40.2	Community outreach and mobilization	Swab	Preference	procedural
Sultana 2015 Australia(144)		746	30-69 (inclusion criteria)		Swab	Preference	Logistic, procedural and psychosocial
Crosby 2016 USA(145)	A highly impoverished and geographically isolated population of medically underserved	88	Mean 46.5	Community outreach and mobilization	Swab	Preference	Procedural

Author, Year, Country	Population	Sample size	Age (years)	Invitation Strategy	Self-sampling device used	Outcomes	
						Acceptability	Individual characteristics of acceptability
	Black women residing in the Mississippi Delta						
Ilangovan 2016 USA(146)	Women in Safety Net institutions: Latinas (74.4%), Haitian (25.6%)	180 (those who completed the questionnaire for self-sampling were 121)	Mean 52	Offered in the healthcare setting	Preventive Oncology International/ National Institute of Health self-sampler	Preference	Logistic, procedural, and psychosocial
Racey 2016 Canada(147)		70	Mean 53.6 Range 51.2-56.0		Swab	Overall acceptability; preference	
Levinson 2016 USA(148)	White (59%), Black (41%)	35	Median 38			Preference	
Anderson 2017 USA(149)	Low income: Black (55%), White (35%), Other (10%)	227	Median 44 Range 30-64		Brush	Overall acceptability; preference	Logistic and procedural
Karjalainen 2016 Finland(150)		67 (39 lavage, 28 Brush)			Lavage and Brush		Logistic, procedural, and psychosocial
Kilfoyle 2018 USA(151)	Low-income women: White (35%), Black (56%), and others (9%)	221 (the acceptance was reported for 100)	Median 44 Range 30–64			Overall acceptability; preference	Procedural, and psychosocial
Des Marais 2018 USA(71)	Low-income women: White (45%), Black (26%), Hispanic (26%), Other races (4%)	193	Median age 45 Range 30-63		Brush	Overall acceptability; preference	Procedural
Molokwu 2018 USA(152)		202	Mean 46.4	Community outreach and mobilization		Preference	

Author, Year, Country	Population	Sample size	Age (years)	Invitation Strategy	Self-sampling device used	Outcomes	
						Acceptability	Individual characteristics of acceptability
Smith 2018 USA(111)	Low income	227	Median 42 Range 30-65		Brush	Overall acceptability	
Brewer 2019 New Zealand(153)	Pacific (55.4), Maori (21.4), Asian (16.1), other (7.1)	56 (herSwab N=51, Delphi Screener 8, Cobas CT/NG Swab 7)	Median 39.5 Range 20-61	Opt-in; Mail-to-all	Swabs and Delphi Screener (Rovers Medical Devices)	Overall acceptability; preference	Logistic, procedural and psychosocial
Adcock 2019 New Zealand(154)	Maori (100%)	397	≥25			Overall acceptability; preference	Procedural and psychosocial
Reiter 2019 USA (Appalachain)(155)	White, non-Hispanic (98%) and others (2%)	79	Mean 46.4		Brush	Preference	Logistic and psychosocial
Datta 2020 Canada(156)	Never screeners: Canada (62%), United States/Europe (9%), other countries (28%); Under screeners: Canada (90%), United States/Europe (4%), other countries (6%)	Never 53, Under screeners 89	21 -65 (Inclusion criteria)			Overall acceptability	
Malone 2020 USA(157)	White (88.8%), Black/African American (0.9%), Asian/Pacific Islander (5.2%), others (4.3%), and unknown (0.9%)	120	Range 30-64	Mail-to-all	Swab	Preference	Logistic, procedural, and psychosocial
Andersson 2021		43 cases, 479 control (controls	Case Mean 44.5		Swab	Overall acceptability	Logistic and procedural

Author, Year, Country	Population	Sample size	Age (years)	Invitation Strategy	Self-sampling device used	Outcomes	
						Acceptability	Individual characteristics of acceptability
Sweden(158)		are not long-term non-attenders hence results are only reported for cases)					
Bromhead 2021(159)	Māori, Pacific and Asian	58	Median 45 Range 30-68		Swab	Preference	Logistic, procedural and psychosocial
Veerus 2021 Estonia(160)		1857	Range 37-62 range	Opt-in; Mail-to-all	Qvintip and Evalyn brush	Preference	procedural and psychosocial
Chaw 2022 Brunei(161)	Malay 93.0%, Chinese 4.1%, Other 0.31%	97	Median 41	Offer in the healthcare setting	Brush	Preference	Logistic, procedural and psychosocial
Ngu 2022 Hong Kong(81)	Chinese (52.3%), Philippine (38.9%), Asian-not specified (4.4%), and unknown (5%)	321	Range 30-65 range	Community outreach and mobilization and opt-in	Swab	Overall acceptability; preference	Logistic, procedural, and psychosocial
Parker 2022 USA(162)	Low income enrolled in the safety net: Mexico (39.5%), United States (20.6%), Central America (20.6%), South America (1.7%), Asia (0.9%), Europe (1.3%) and other (0.9%)	153	Mean 47.2	Mail-to-all	Swab		Logistic and psychosocial
Sherman 2022 New Zealand(163)	Maori (28.7%), Pasifika (27.9%), and Asian (43.4%)	376	Mean 46.5		Swab	Preference	Logistic, procedural and psychosocial
Zhu 2022	North American Aboriginal (2.5%), Other	524	Mean 47.9			Overall acceptability	

Author, Year, Country	Population	Sample size	Age (years)	Invitation Strategy	Self-sampling device used	Outcomes	
						Acceptability	Individual characteristics of acceptability
Canada(164)	North American (43.9%), European (31.3%), Asian (17.6%), and other (4.8%)						
Fujita 2023 Japan(165)		1,192	Mean 44.1		Brush		Logistic and psychosocial

All 48 studies were included across the meta-analyses, but studies rarely had data for all the outcomes presented (e.g. some only presented data regarding reasons for (dis)liking self-sampling). The pooled estimates for the acceptability outcomes are shown in *Table 9*. It found that 91% of women are generally accepting of self-sampling, with 74.4% and 59.5% stating preference of doing it at home and doing it themselves rather than a healthcare setting/professional respectively.

Table 9 Pooled Analysis for Acceptability Outcomes

Outcome	Subgroup[$]	No. of studies	Pooled proportion (%) (95% CI)
General acceptability of self-sampling		21[*%]	91.0% (85.3% to 94.6%)
Preference for self-sampling over healthcare professional sampling		25	59.5% (46.0% to 71.7%)
Preference for self-sampling at home over healthcare setting	All	7	74.4% (63.8% to 82.7%)
	Swab	3	83.3% (74.7% to 89.4%)
	Brush	2	68.2% (62.9% to 73.0%)
	Multiple	1	50.2% (49.2% to 51.2%)
Stated willingness to repeat cervical screening	All	15	91.3% (87.2% to 94.2%)
	Swab	5	87.0% (82.4% to 90.5%)
	Brush	5	95.0% (90.5% to 97.5%)
	Tampon	1	96.7% (91.5% to 98.8%)
	Multiple	2	79.7% (52.4% to 93.3%)
Stated that self-sampling is convenient		15[*£]	87.0% (77.9% to 92.7%)
Stated that self-sampling is accessible		1	19.5% (10.5% to 33.9%)
Screened individuals felt confident in the result of self-sampling	All	7[£]	74.1% (57.3% to 85.8%)
	Brush	3	84.0% (69.6% to 92.3%)
	Lavage	2	86.3% (73.9% to 93.3%)
	Swab	2	51.3% (35.5% to 66.7%)
Screened individuals reported self-efficacy in conducting self-sampling themselves		11[£]	88.4% (78.7% to 94.0%)
Stated that self-sampling led to pain or discomfort		22[*£]	18.5% (11.7% to 28.0%)
Stated that self-sampling caused embarrassment		13[£]	12.1% (3.8% to 32.5%)
Stated that self-sampling caused anxiety		4[£]	35.2% (2.8% to 91.1%)
Stated that self-sampling did not fit with values		2[*]	59.9% (8.1% to 96.2%)

'Multiple' refers to studies where multiple devices were considered with results aggregated together

[$] Only reported where the inclusion of the respective variable gave a significant (<0.05) result

[*] Brewer (2019) had separate results for swab and lavage

[%] Datta (2020) had separate results for those never screened and those under-screened

[£] Karjalainen (2016) had separate results for lavage and brush

Figure 8 and *Figure 9* illustrate high heterogeneity regarding the general acceptability of self-sampling and its preference over healthcare professionals respectively. *Figure 8* shows consistently high proportions of general acceptability in earlier years, with wide variation in later years. Sampling device was not found to affect general acceptability or preference for self-sampling (p = 0.118 and 0.799, respectively).

High heterogeneity was also observed among the lesser reported acceptability outcomes. Self-sampling device was tested for potential effects, for which only preferences for home setting, willingness to repeat, and individuals feeling confident of the results gave a significant result (*Table 9)*. There were insufficient data in a consistent format for ethnicity or age to be considered in a quantitative manner.

Figure 8 General Acceptability of Self-sampling

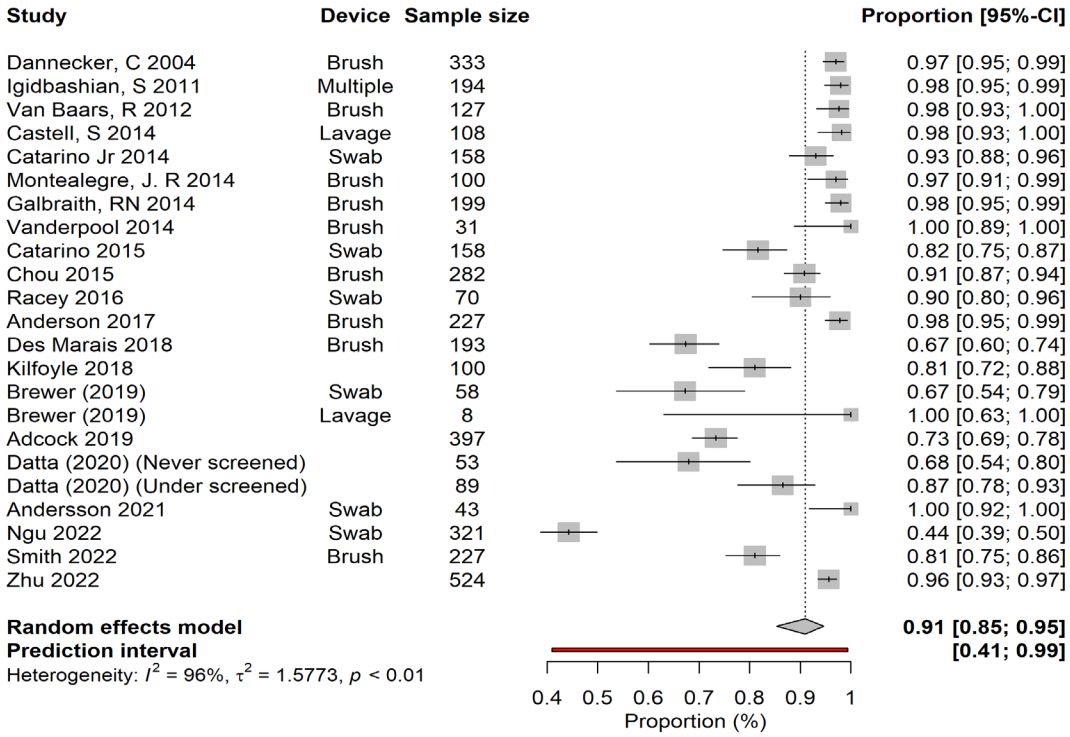
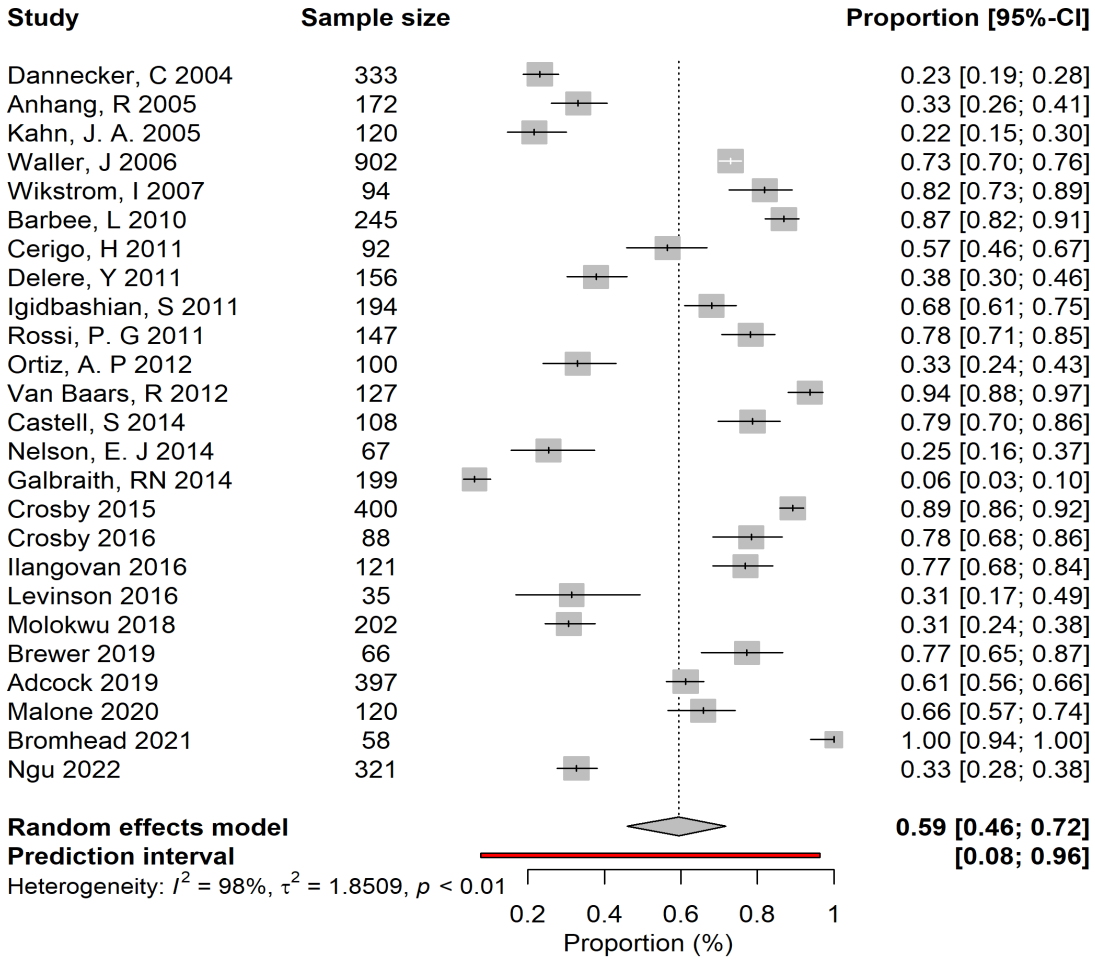


Figure 9 Women Preferring Self-sampling to Healthcare Professional Sampling



Preference for self-sampling at home over healthcare setting differed across self-sampling device and invitation strategy. *Figure 10* and *Figure 11* shows that the preference for a home setting was higher for swabs and higher when offered in a healthcare setting respectively (p <0.001 and p=0.020 respectively). It was not possible to analyse device and invitation strategy together due to the lack of data.

Figure 10 Stated Preference for Self-sampling at Home versus Healthcare Setting According to Sample Device

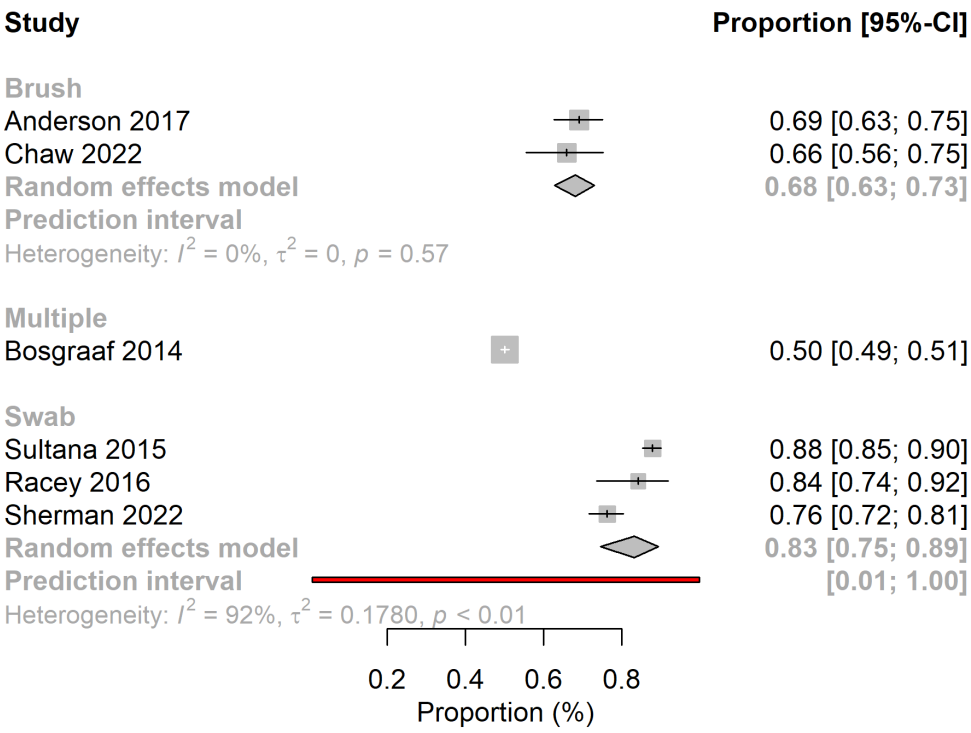
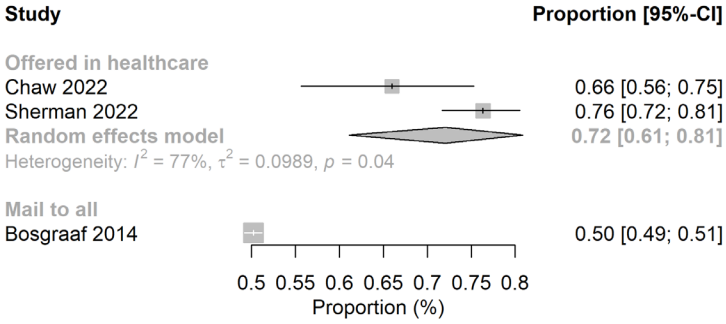
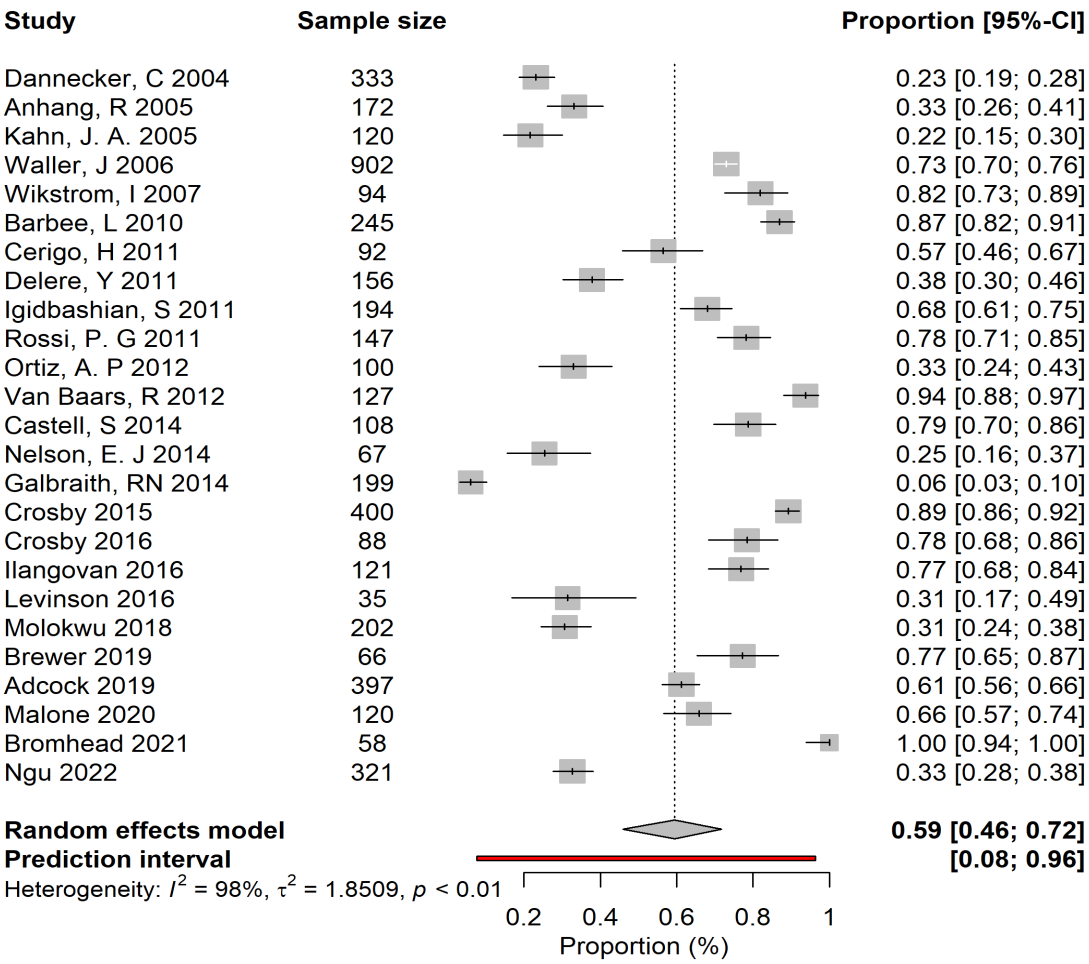

Study
Proportion [95%-CI]
Brush
Anderson 2017
0.69 [0.63; 0.75]
Chaw 2022
0.66 [0.56; 0.75]
Random effects model
0.68 [0.63; 0.73]
Prediction interval
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.57
Multiple
Bosgraaf 2014
0.50 [0.49; 0.51]
Swab
Sultana 2015
0.88 [0.85; 0.90]
Racey 2016
0.84 [0.74; 0.92]
Sherman 2022
0.76 [0.72; 0.81]
Random effects model
0.83 [0.75; 0.89]
Prediction interval
[0.01; 1.00]
Heterogeneity: I^2 = 92%, τ^2 = 0.1780, p < 0.01
0.2
0.4
0.6
0.8
Proportion (%)

Figure 11 Stated Preference for Self-sampling at Home versus Healthcare Setting According to Invitation Strategy



Willingness to repeat cervical screened differed across the self-sampling device. *Figure 12* shows that the willingness was higher for brushes and tampons compared with swabs (p = 0.007 for inclusion of sampling deviance as covariate). There was not sufficient data, or in a consistent format, for ethnicity or age to be considered in a quantitative manner.

Figure 12 Stated Willingness to Repeat Cervical Screening



Discussion

Our review found that cervical cancer screening non-attendees generally accept self-sampling (91%) with a high proportion willing to repeat cervical screening (91%). While 74% expressed preference for self-sampling at home over healthcare setting, a lower proportion (59%) stated a preference for self-sampling over healthcare professional sampling. Overall, 87% found self-sampling to be convenient. The reference review reported pooled reasons for preferring self-sampling were ease of use (91%), not embarrassing (91%), privacy (88%), comfort performing self-sampling (88%), ability to do it oneself (69%) and convenience (65%) (121). The most reported pooled reason for disliking was the uncertainty of doing it correctly (21%), pain or physical uncomfortable (10%), anxiety (15%) and not wanting to touch themselves (6%) (121). Our meta-analysis found that self-sampling led to pain or discomfort (18%), caused embarrassment (12%), caused anxiety (35%) and did not fit with their values (60%). Despite these reported advantages of self-sampling, the strategy may exclude those with disabilities which limit their ability to self sample such as people with visual impairments, motor dysfunction, or mental health issues.

Data was limited regarding reasons for liking or disliking self-sampling for non-attenders. Indeed, the data is available for studies that were newly extracted but were not available for the studies in the existing review.

Strength and Limitations

This is a comprehensive rapid review of the existing literature in HPV self-sampling for cervical cancer screening. However, there are limitations to this analysis. Firstly, the amount of data available for this analysis was limited. Due to the rapid nature of the review, many study results were extracted from existing reviews. Unfortunately, only the relative sensitivity and specificities were reported in the review(s) we utilized for the accuracy question, which could not be used to back-calculate the necessary 2x2 tables. Secondly, the statistical methods used to calculate the pooled estimate for the accuracy question do not consider the 'paired' nature of the studies (i.e. the fact that it was the same women in the 'self' and the 'health' arms for each study). However, we believe that the consequence, if there is any, of not taking this into account means the estimates above (95% CI) may be slightly conservative. Finally, the assessment of subgroups was not possible due to limited data from the studies from the reference review and the study not analysing the outcome at the subgroup level. There was not sufficient data, or a consistent format, for ethnicity or age to be considered quantitatively. Participation is often reduced in some patient populations, including those in minority ethnic groups, those of low socio-economic status, and transgender and non-binary people with a cervix, but there were insufficient data to explore the possible impact of self-sampling in these populations in our review.

In Context of the YouScreen Study

The YouScreen study was a feasibility clinical trial embedded within the Cervical Screening Programme in England Programme to estimate the impact of offering self-sampling to non-attenders in practice. Self-sampling kits were offered opportunistically in-person in GP primary care and offered systematically via direct mailout. In the opportunistic offering of sampling arm, 65.5% returned self-samples compared with 12.9% in the systematically direct mailout arm(1). Our rapid review found one study that offered opportunistic self-sampling kit in GP primary care which it uptake was 6.9%(109), but our data on mail-to-all self-sampling reported similar participation rates (17.7% to 23%). YouScreen showed self-sampling resulted in a 22% increase and 12% increase in non-attenders screened per month from the per protocol and intention-to-treat analysis, respectively(1). Our meta-analysis of the literature also reported an increase in uptake, but the effect was more modest.

Conclusion

Self-sampling is a feasible strategy for reaching non-attendees in and should be considered in the national screening program to reach the non-attendees, especially on using the PCR-based assay.

However, before this is done, understanding the cost-effectiveness, logistics and compliance of the strategies is important to understand country-specific strategies for reaching the non-attendees.

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Appendix I: Search Strategies

Clinical Accuracy (per Arbyn et al.)(22)

Database	Search
PubMed	#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 from January 2018 to March 2024. #9: #7 AND #8
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)
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

Strategies to increase population coverage of cervical screening (Albyn et al.)(22)

Database	**Search**
PubMed	(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)

Acceptability
(per Nelson et al)(121)

Database	**Search**
ProQuest Dissertations and Theses	(Prefer* OR feasib* OR accept* OR barrier OR cost OR attitude) AND (HPV OR "Human papillomavirus") AND (self-collect* OR self-sampl* OR self-screen*)
PubMed	(("human papillomavirus"[All Fields] OR HPV[All Fields]) AND (accept[All Fields] OR prefer[All Fields] OR ("attitude"[MeSH Terms] OR "attitude"[All Fields]) OR barrier[All Fields] OR fesi[All Fields] OR ("economics"[Subheading] OR "economics"[All Fields] OR "cost"[All Fields] OR "costs and cost analysis"[MeSH Terms] OR ("costs"[All Fields] AND "cost"[All Fields] AND "analysis"[All Fields]) OR "costs and cost analysis"[All Fields]))) AND (self-collection[All Fields] OR self-collect[All Fields] OR self- sampling[All Fields] OR self-sample[All Fields] OR self-screen[All Fields])
SCOPUS	(TITLE-ABS-KEY ("human papillomavirus" OR hpv) AND TITLE-ABS-KEY (accept OR prefer OR attitude OR barrier OR feasib OR cost) AND TITLE- ABS-KEY (self-collection OR self-collect OR self-sampling OR self-sample OR self-screen))
Web of Science	TOPIC: ("human papillomavirus" OR HPV) AND TOPIC: (accept OR prefer OR attitude OR barrier OR cost OR feasib) AND TOPIC: (self-collection OR self-collect OR self-sampling OR self-sample OR self-screen)

	Timespan: All years. Indexes: SCI-EXPANDED, SSCI, A&HCI.
OpenGrey	(HPV OR "Human papillomavirus") AND (collect* OR Sampl* OR screen*) HPV OR "Human papillomavirus"
Cochrane Database of Systematic Reviews	HPV OR "Human papillomavirus"

(per Yeh et al. and Nishimura et al)(122,166)

Database	**Search**
PubMed	("human papillomavirus"[tiab] OR HPV[tiab] OR "cervical"[tiab] OR "cervix"[tiab]) AND ("self-test" [tiab] OR "self-testing" [tiab] OR "home-based test"[tiab] OR "home-based testing"[tiab] OR "home test"[tiab] OR "home testing"[tiab] OR "clinic-based test"[tiab] OR "clinic-based testing"[tiab] OR "community-based test"[tiab] OR "pharmacy-based test"[tiab] OR "self-administer"[tiab] OR "self-sampling"[tiab] OR "self-collecting"[tiab] OR "self-collected"[tiab] OR "self-collection"[tiab] OR "self- versus provider-collected"[tiab] OR "self- and provider-collected"[tiab] OR "self-versus physician- collected"[tiab] OR "self- and physician-collected"[tiab] OR "self care"[Mesh] OR self- administration[Mesh] OR "self assessment"[Mesh])
CINAHL	(TI "human papillomavirus" OR TI HPV OR TI cervical OR TI cervix OR AB "human papillomavirus" OR AB HPV OR AB cervical OR AB cervix) AND (TI “self-test” OR AB “self-test” OR TI "self-testing" OR AB “self-testing” OR TI “home-based test" OR AB “home-based test” OR TI "home-based testing" OR AB “home-based testing” OR TI "home test" OR AB “home test” OR TI "home testing" OR AB “home testing” OR TI "clinic-based test" OR AB “clinic-based test” OR TI "clinic-based testing" OR AB “clinic-based testing” OR TI "community-based test" OR AB “community-based test” OR TI "pharmacy-based test" OR AB “pharmacy-based test” OR TI "self- administer" OR AB “self-administer” OR TI "self-sampled" OR AB “self-sampled” OR TI "self-sample" OR AB “self-sample” OR TI "self-sampling" OR AB “self-sampling” OR TI "self-collecting" OR AB “self- collecting” OR TI "self-collected" OR AB “self-collected” OR TI "self-collection" OR AB “self-collection” OR TI "self- versus provider-collected" OR AB “self- versus provider-

	collected" OR TI "self- and provider- collected" OR AB "self- and provider-collected" OR TI "self- versus physician-collected" OR AB "self- versus physician-collected" OR TI "self- and physician-collected" OR AB "self- and physician-collected")
Embase	('human papillomavirus':ab,ti OR HPV:ab,ti OR cervical:ab,ti OR cervix:ab,ti) AND ('self-test':ab,ti OR 'self-testing':ab,ti OR 'home-based test':ab,ti OR 'home-based testing':ab,ti OR 'home test':ab,ti OR 'home testing':ab,ti OR 'clinic-based test':ab,ti OR 'clinic-based testing':ab,ti OR 'community-based test':ab,ti OR 'pharmacy-based test':ab,ti OR 'self-administer':ab,ti OR 'self- sampled':ab,ti OR 'self-sample':ab,ti OR 'self-sampling':ab,ti OR 'self-collecting':ab,ti OR 'self- collected':ab,ti OR 'self-collection':ab,ti OR 'self- versus provider-collected':ab,ti OR 'self- and provider-collected':ab,ti OR 'self- versus physician-collected':ab,ti OR 'self- and physician-collected':ab,ti)
LILACS	("human papillomavirus" OR HPV OR cervical OR cervix) [words] AND ("self-test" OR "self-testing" OR "home-based test" OR "home-based testing" OR "home test" OR "home testing" OR "clinic-based test" OR "clinic-based testing" OR "community-based test" OR "pharmacy-based test" OR "self-administer" OR "self-sampling" OR "self-collecting" OR "self-collected" OR "self-collection" OR "self- versus provider-collected" OR "self- and provider-collected" OR "self-versus physician-collected" OR "self- and physician-collected") [words]

Appendix Table II: Quality of Included Studies: Accuracy of HPV testing in self-collected samples compared with health professional-collected samples

	Patient selection		Index test		Reference standard		Flow and Timing
Study	Risk of bias	Applicability concern	Risk of bias	Applicability concern	Risk of bias	Applicability concern	Risk of bias
Aiko 2017	Low	High	High	Low	Low	Low	Low
Avian 2022	Low	High	Low	Low	Low	Low	Unclear
Cho 2020	Low	High	Low	Low	Low	Low	High
Edblad-Svensson 2018	Low	High	High	Low	Low	Low	High
El-Zein 2018	Low	High	Low	Low	Low	Low	Unclear
El-Zein 2019	Low	High	Low	Low	Low	Low	Unclear
Ertik 2021	Low	High	Low	Low	Low	Low	Low
Igidbashian 2014	Low	High	Low	Low	Low	Low	High
Klischke 2021	Unclear	High	Low	Low	Low	Low	High
Latsuzbaia 2022a	Low	High	Low	Low	Low	Low	Low
Latsuzbaia 2023a	Low	High	Low	Low	Low	Low	Low
Latsuzbaia 2022b	Low	High	Low	Low	Low	Low	Low
Latsuzbaia 2023b	Low	High	Low	Low	Low	Low	Low
Leinonen 2018	Unclear	High	Low	Low	Low	Low	High
Mangold 2019	Unclear	High	Low	Low	Low	Low	Low
Martinelli 2023	Unclear	High	Unclear	Unclear	Low	Low	Low
Martinelli 2024	Low	High	Low	Low	Low	Low	Low
Naseri 2022	Low	High	Low	High	Low	Low	Low
Onuma 2020	High	High	Low	Low	Low	Low	Low
Ornskov 2021	Low	High	Low	Low	Low	Low	Low
Pasquier 2023	Unclear	High	Low	Low	Low	Low	Low
Polman 2019	Low	Low	Low	Low	Low	Low	High
Rohner 2020a	Low	High	Low	Low	Low	Low	High
Rohner 2020b	Low	High	Low	Low	Low	Low	High

Table III: Quality of Included Studies

RoB Tool	Author, Year of Publication	Bias due to confounding	Bias in classification of interventions	Bias from randomisation process	Bias in. selection of participants into study	Bias due to deviations from intended interventions	Bias due to missing data	Bias arising from measurement of outcome	Risk of bias in selection of reported result	Overall
ROBINS-I v2	Ngo 2024	Serious	Low		Low	Low	Low	Serious	Low	Serious
	Vitanen 2014	Serious	Low		Low	Serious	Low	Serious	Low	Serious
RoB-2	**Winer 2023**			Some concerns		Low	Low	High	Low	High
	Auvinen 2022			Low		Some concerns	Low	High	Some concerns	High
	Fujita 2022			Low		High	Low	High	Low	High
	Winer 2022			Low		Some concerns	Low	High	Low	High
	Gunvor Aasbø 2022			Low		Low	Low	High	Low	High
	Sultana 2021			Low		Low	Low	High	Low	High

Table IV: Quality of Included Studies Acceptability of HPV Self-sampling Screening Included in reference review without outcomes

Authors	Years of Publications	Country	Is the sampling frame largely representative?	Were appropriate participant recruitment methods utilized?	Is the exclusion rate acceptable?	Is the final sample size sufficient?	Are demographic variables reported?	Do the measures have adequate reliability?	Was the study conducted in a controlled setting?	Was management of data acceptable?	Overall score

Dannecker	2004	Germany	No	No	No	Yes	Yes	No	No	No	2
Kahn	2005	USA	No	No	No	Yes	Yes	Yes	No	No	3
Anhang	2005	USA	No	No	No	Yes	Yes	No	No	No	2
Waller	2006	UK	Yes	No	No	Yes	Yes	No	No	No	2
Wikstrom	2007	Sweeden	Yes	No	No	Yes	Yes	No	No	No	3
Barbee	2010	USA	No	No	No	Yes	Yes	No	No	No	2
Delere	2011	Germany	No	No	No	Yes	Yes	No	No	No	2
Cerigo	2011	Canada	No	No	No	Yes	Yes	No	No	No	2
Igidbashian	2011	Italy	No	No	No	Yes	Yes	No	No	No	2
Rossi	2011	Italy	Yes	Yes	No	Yes	Yes	No	No	No	4
Ortiz	2012	Puerto Rico	No	No	No	Yes	Yes	No	No	No	2
Van Baars	2012	The Netherlands	No	No	No	Yes	Yes	Yes	No	No	2
Bosgraaf	2014	The Netherlands	Yes	No	No	Yes	Yes	No	No	No	3
Galbraith	2014	USA	No	No	No	Yes	Yes	No	No	No	2
Virtanen	2014	Finland	Yes	No	No	Yes	Yes	No	No	No	2
Vanderpool	2014	USA	No	No	No	Yes	Yes	No	No	No	2
Castell	2014	Germany	Yes	Yes	No	Yes	Yes	No	No	Yes	5
Montealegre	2014	USA	No	No	No	Yes	Yes	No	No	No	2
Nelson	2014	USA	No	Yes	No	Yes	Yes	No	No	No	3
Catarino,Jr	2014	Switzerland	No	No	No	Yes	Yes	No	No	No	2
Chou	2015	Taiwan	Yes	Yes	No	Yes	Yes	No	No	Yes	5
Sultana	2015	Australia	No	No	No	Yes	Yes	No	No	Yes	3
Crosby	2015	USA	No	No	No	Yes	Yes	Yes	No	No	2
Crosby	2016	USA	No	No	No	Yes	Yes	Yes	No	No	3
Racey	2016	Canada	No	No	No	Yes	Yes	Yes	No	Yes	4
Ilangovan	2016	USA	No	No	No	Yes	Yes	No	No	No	2
Karjalainen	2016	Finland	Yes	Yes	No	Yes	Yes	No	No	No	4
Crosby	2016	USA	No	No	No	Yes	Yes	No	No	No	2

Levinson	2016	USA	No	No	No	Yes	Yes	No	No	No	2
Anderson	2017	USA	No	No	No	Yes	Yes	No	No	No	2
Des Marais	2018	USA	No	No	No	Yes	Yes	No	No	Yes	3
Molokwu	2018	USA	No	Yes	No	Yes	Yes	No	No	Yes	4
Kilfoyle	2018	USA	No	No	No	Yes	Yes	No	No	Yes	3
Adcock	2019	New Zealand	No	No	No	Yes	Yes	No	No	No	2
Brewer	2019	New Zealand	No	No	No	Yes	Yes	No	No	No	2
Reiter	2019	USA	No	Yes	No	Yes	Yes	No	No	No	3
Malone	2020	USA	Yes	Yes	No	Yes	Yes	Yes	No	Yes	6
Datta	2020	Canada	No	No	No	Yes	Yes	No	No	Yes	3
Andersson	2021	Sweden	No	No	No	Yes	Yes	No	No	No	3
Bromhead	2021	New Zealand	No	No	No	Yes	Yes	Ni	No	Yes	4
Veerus	2021	Estonia	Yes	Yes	No	Yes	Yes	No	No	No	4
Smith	2022	USA	No	No	No	Yes	Yes	No	No	Yes	3
Chaw	2022	Brunei	No	No	No	Yes	Yes	No	No	No	2
Ngu	2022	Hong Kong	No	No	No	Yes	Yes	No	No	No	2
Sherman	2022	New Zealand	Yes	No	No	Yes	Yes	No	No	No	3
Parker	2022	USA	No	Yes	No	Yes	Yes	No	No	No	3
Zhu	2022	Canada	No	No	No	Yes	Yes	No	No	Yes	3
Fujita	2023	Japan	No	No	No	Yes	Yes	No	No	Yes	3

Appendix V: Studies with no outcome on Concordance between HPV-DNA Testing in Self and Health Professional Collected Samples from the review

Author, Year, Country	Population	Sample Size	Age (years)	Ethnicity	Device	Setting	hrHPV Assay	Storage medium
Sellors 2000 Canada(28)	Not reported	200	Mean 31.5 Range not given	Not specified	Swab	Clinical setting	Both HC2, PCR (L1 consensus)	Self: STM Clin brush: STM Clin swab: sterile phosphate-buffered saline
Daponte 2006 Greece(167)	Not reported	98	Not specified	Not specified	Brush	Clinical setting	PCR	PBS
Szarewski 2007 UK(31)	Not reported	920	Median 29 (pop 1) Median 41 (pop 2)	Not specified	Swab	Not specified	HC2	Not specified
Balasubramanian 2010 USA(32)	High risk	1665	Median 23 Range 18-50	Not specified	Swab	Not specified	HC2	STM
Gustavsson 2011 Sweden(168)	Not reported	50	Mean not reported Range 39-60	Not specified	Brush	Clinical setting	PCR	FTA cartridge

Twu 2011 Taiwan(169)	Unscreened for ≥3years	252	Median 42 Range 26-79	Not specified	Brush	Clinical setting	PCR	STM
Dijkstra 2012 The Netherlands(33)	Not reported	135	Median 34 Range not given	Not specified	Brush	Clinical setting	PCR	PreservCyt
Geraets 2013 Spain(170)	Not reported	182	Median 34 Range: 16-76	Not specified	Brush	Clinical setting	PCR	FTA cartridge
Stanczuk 2016 UK(37)	Not reported	5,318	Mean 41 Range not given	Not specified	Swab	Not reported	Cobas 4800	PreservCyt
Leeman 2017 The Netherlands(41)	Not reported	91	Not specified	Not specified	Brush	Clinical setting	SPF10-DEIA-LIPA25 & GP5+/6+-EIA- LMNX	Dry up to 3 months, then placed in vial with PreservCyt for shipment
Asciutto 2018 Sweden(32)	Not reported	176	Mean 34 Range not given	Not specified	Swab	Clinical setting	APTIMA	APTIMA vaginal specimen collection kit
Leinonen 2018 Norway(43)	Not reported	240	Mean 38 Range not given	Not specified	Brush	Home	Anyplex II HPV28; cobas 4800, Xpert HPV	Dry transport of self-collection devices to lab

Appendix VI: Characteristics of Studies Included Studies for Uptake of HPV DNA Self Sampling that had no outcome in the reference review

Author, Year, Country	Population	Sample Size	Age (years)	Invitation Strategy	Reminder	Time from Invitation to collected sample	Self-sampling device	Per protocol (PP) or Intention to Treat (ITT) Analysis	Outcomes Reported
Veerus 2021 Estonia(171)	Never screened; Under screened	Intervention Mail-to-all: 4000 Opt-in: 8000 Comparator Not started	Range 37-62	Mail-to-all; Opt-in	No	Not documented	Qvintip and Evalyn brush	Not reported	Not reported

Appendix: VII:Characteristics of Included Studies for Acceptability of HPV Self-sampling Screening Included in reference review without outcomes

Author, Year, Country	Population	Sample size	Age (years)	Invitation Strategy	Self-sampling device used	Outcomes	
						Acceptability	Individual characteristics of acceptability
Harper 2002 USA(172)		67	Mean 37.7		Dacron Swab and Tampon		
Jones 2012 USA(173)		197	Median 45		Lavage		
Litton 2013 USA(174)		516	≥30		Not reported		
Chen 2014 Taiwan(175)		297	Range 18-65		Unable to determine		
Haguenoer 2014 France(96)		722	Range 20-65		Swab		