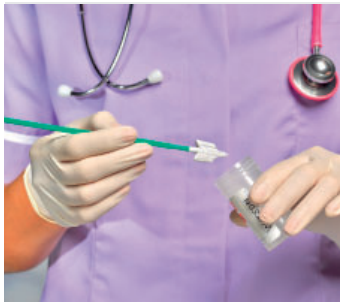
research

Behavioural weight management interventions in primary care p 353



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ORIGINAL RESEARCH Systematic review and meta-analysis of RCTs

Effectiveness of weight management interventions for adults delivered in primary care

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Study question How effective are behavioural weight management interventions for adults delivered in primary care?

Methods A systematic review and meta-analysis of randomised controlled trials investigating behavioural weight management interventions delivered in primary care versus comparator groups. Studies must have measured weight change at ≥12 month follow-up in adults with a body mass index ≥25. Trials from a previous systematic review were extracted and a search was completed in the Cochrane Central Register of Controlled Trials, Medline, PubMed, and PsychINFO from 1 January 2018 to 19 August 2021. Meta-analyses were conducted with random effects models, and the pooled mean difference for weight and waist circumference was calculated at 12 months.

Study answer and limitations 34 trials were included. Weight management interventions delivered in primary care were found to be effective for weight loss (mean difference −2.3 kg, 95% confidence interval −3.0 to −1.6 kg) and reducing waist circumference (−2.5 cm, 95% confidence interval −3.2 to −1.8 cm) at 12 months. At ≥24 months there was still a significant weight loss of −1.8 kg (95% confidence interval −2.8 to −0.8 kg) favouring the intervention. The trials were mainly conducted in socially economic developed countries, and heterogeneity in the meta-analyses was statistically significant. Prespecified subgroup analyses explained some, but not all, of the variance.

What this study adds Weight management interventions delivered in primary care were shown to be effective and can be used to help adults better manage their weight.

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Systematic review registration PROSPERO CRD42021275529.

Summary of main and secondary outcomes

Outcome	Mean difference (95% CI)	Heterogeneity, I^2 (%)
Weight change (kg):		
12 months	−2.3 (−3.0 to −1.6)	88
≥24 months	−1.8 (−2.8 to −0.8)	88
Last follow up	−1.9 (−2.5 to −1.3)	81
>12 intervention contacts	−2.4 (−3.0 to −1.7)	82
≤11 contacts	−0.7 (−1.2 to −0.08)	25
Waist circumference change at 12 months (cm)	−2.5 (−3.2 to −1.8)	69

HPV screening for cervical cancer is reaching maturity

ORIGINAL RESEARCH Observational study of English screening pilot data

Extension of cervical screening intervals with primary human papillomavirus testing

Rebolj M, Cuschieri K, Mathews CS, Pesola F, Denton K, Kitchener H; on behalf of the HPV pilot steering group

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Study question What is the risk of high grade cervical intraepithelial neoplasia or worse (CIN3+) and cervical cancer after a negative human papillomavirus (HPV) screening test result, compared with a negative, liquid based cytology (smear) test result?

Methods The English HPV pilot represented a real world, early implementation of HPV based primary cervical screening in six NHS laboratories including 1 341 584 women. The first round, where women followed routine screening protocols for either HPV or cytology tests, took place during 2013-16. Follow-up data were available until the end of 2019. Screening tests were compared according to the relative detection of CIN3+ and cervical cancer after a negative screening test result in the pilot's first round, adjusted for age, deprivation, and laboratory site.

Study answer and limitations Among women aged 25-49 years, a negative HPV test roughly halved the risk of interval cancer compared with a negative cytology test result (adjusted hazard ratio 0.44, 95% confidence interval 0.23 to 0.84). The detection of CIN3+ at the second screening round in three years decreased by about three quarters (adjusted odds ratio 0.26, 95% confidence interval 0.23 to 0.30), with almost no detection of cancer (0.02, 0.00 to 0.17). Among women aged 50-59 years in the first screening round, the corresponding risk of CIN3+ detection in five years compared with women aged 25-49 years was even lower (adjusted odds ratio 0.46, 0.27 to 0.79). Allocation of the screening tests was not randomised.

What this study adds This real life study provides evidence that supports the extension of routine recall intervals from three to five years for HPV negative women younger than 50 years planned within the English Cervical Screening Programme, and longer for women aged 50 years and older.

COMMENTARY Programmes will continue to evolve as the risk landscape changes

Several countries have transitioned from cytology based to primary HPV based cervical screening, including the Netherlands, Australia, England, Scotland, and Wales. Increased detection of cervical precancerous cells was seen in the first screening round after the more sensitive HPV test was introduced in populations previously screened only with cytology.[1-3]

In this issue, Rebolj and colleagues[4] report on the second screening round in the English HPV pilot, involving 1 341 584 women initially screened in 2013-16 and followed up until the end of 2019. The authors found that women younger than 50 years with a negative first round HPV test result were at much lower risk of cervical intraepithelial neoplasia grade 3 or worse (CIN3+) in the second round or interval cancers than women testing negative on the basis of cytology. Risk of second round CIN3+ for women who were HPV negative in the first round were even lower in individuals older than 50 years. These findings provide important data on the effectiveness of HPV screening in relation to incident CIN3+.

In the English Cervical Screening Programme, screening intervals are age dependent, with routine invitations sent at three years for women aged 25-49 years and at five years for women aged 50-64 years. However, a negative HPV test result is associated with a very low risk of CIN3+ over six or more years in trials,[7] which has led to a recommended screening interval of at least five years in most policy contexts.

Safely increasing the screening interval is an important contributor to the cost effectiveness of HPV screening.[8] Recent World Health Organization guidelines, for example, recommend an interval of five or 10 years for the general population (without HIV infection).[9] England's shorter intervals in younger women are a legacy from traditional cytology based screening, so the English pilot provides welcome additional local information to support a planned extension of the interval for those aged 25-49 years.

Changes to the interval, triage approach, or threshold for colposcopy referral might be required in the future

Triage

HPV screening is sensitive for infection, therefore appropriate triaging of HPV positive women and appropriate management of women who are triage positive or triage negative is critical.[10] In the English HPV pilot, women who were HPV positive were initially referred for colposcopy only if they had at least borderline cytological abnormalities. Women who were HPV positive and had no cytological abnormalities and then were HPV negative at early recall had an increased rate of CIN3+ at the second round of screening. The authors conclude that the screening interval for this group of women should be kept at three years.

This conclusion is not necessarily generalisable to other settings, however, because the determination of who is assigned to early recall depends on the triaging approach. Alternatives to the English pilot's approach (cytology) include direct referral for women with some of the highest risk HPV types (HPV 16 and 18), selective use of cytology to inform the referral decision only for women with other oncogenic HPV types , and use of emerging technologies

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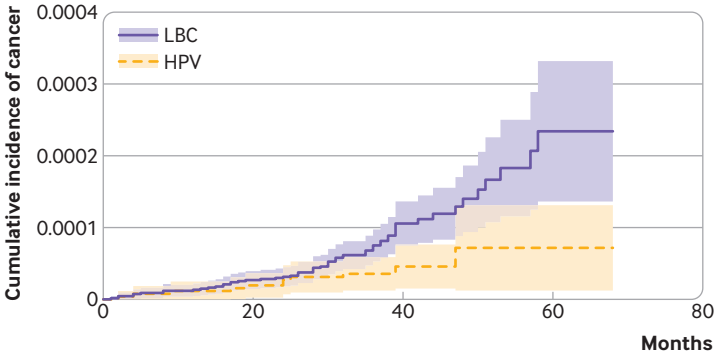

Cumulative incidence of interval cervical cancer after a negative screening test result in the first round for women aged 24-49 years. Interval cancers are those diagnosed between the first and second screening rounds. Shaded areas denote 95% confidence intervals. LBC=liquid based cytology; HPV=human papillomavirus

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Major challenges include managing the higher referral rates in the first round

such as dual stained cytology or methylation markers.[11 12]

In the context of HPV vaccination, which protects against infection with (at least) HPV types 16 or 18, direct referral of women with these infections in the first HPV screening round of the Australian National Cervical Screening Program did not greatly increase referrals. This strategy resulted in immediate detection of a large proportion (>80%) of the invasive cervical cancers seen in that screening round; of these, 20% had negative cytology and these women would not have been referred with cytology only triage.[2] Emerging data for longer term outcomes from programmes with alternative triaging approaches will therefore be important.

HPV screening programmes have had challenges around the choice of DNA or mRNA screening tests. A major systematic review recently concluded that, compared with validated DNA assays, APTIMA mRNA was similarly sensitive, but more specific, for CIN2+.[11-13] Rebolj and colleagues' findings broadly accord with, and add to, this body of evidence. However, self-collection of samples for HPV testing is an increasingly important tool for improving the equity and coverage of cervical screening programmes,[14 15] and some loss of sensitivity is reported in this context for mRNA, but not DNA, tests.[13]

The transition to HPV screening has been driven by its considerable advantages, including a very low risk of CIN3+ in women who were HPV negative, and the possibility of self-collection.

However, major challenges include managing the higher referral rates in the first round.[2] Because of the high detection of prevalent disease in the first round, detection rates of cervical precancerous cells will likely stabilise at lower levels in mature screening programmes, reflecting mainly incident disease. Ultimately, this lower rate of detected disease is expected to influence the balance of benefits and harms of screening: changes to the interval, triage approach, or threshold for colposcopy referral might be required in the future.

For women older than 50 years, for example, screening intervals longer than five years could be considered and discharging women in this age group altogether after two or more rounds of consistently negative screening results might be possible. Screening programmes will also need to adapt to the much lower lifetime risks associated with HPV vaccination.[17]

Ongoing information from the experiences of national programmes remain critical to support the safety of such risk based approaches. For now, however, findings from the English pilot show the enhanced benefits as HPV screening programmes mature: greater protection from invasive cervical cancer for those participating in screening.

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ORIGINAL RESEARCH Living systematic review with network meta-analysis

Effectiveness of heterologous and homologous covid-19 vaccine regimens

Au WY, Cheung PP-H

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Study question What is the effectiveness of heterologous and homologous covid-19 vaccine regimens with and without boosters in preventing covid-19 related infection, hospital admission, and death?

Methods A living systematic review and network meta-analysis were performed. 38 World Health Organization covid-19 databases were searched on a weekly basis from 8 March 2022. Studies that assessed the effectiveness of heterologous and homologous covid-19 vaccine regimens with or without a booster were identified. Eligible studies reported the number of documented, symptomatic, severe covid-19 infections, covid-19 related hospital admissions, or covid-19 related deaths among vaccinated and unvaccinated populations. The primary measure was vaccine effectiveness (calculated as 1−odds ratio).

Odds ratios and vaccine effectiveness of vaccine regimens by platform with only low risk of bias studies

Outcome and vaccine regimen	Odds ratio (95% credible interval)	Vaccine effectiveness (%)	GRADE
Documented covid-19 infection			
Three dose mRNA	0.04 (0.01 to 0.28)	96 (72 to 99)	High
Two dose adenovirus with one dose mRNA	0.12 (0.03 to 0.41)	88 (59 to 97)	High
Two dose mRNA	0.23 (0.12 to 0.42)	77 (58 to 88)	Moderate
Two dose adenovirus	0.26 (0.11 to 0.58)	74 (42 to 89)	High
One dose adenovirus	0.39 (0.18 to 0.84)	61 (16 to 82)	Moderate
One dose mRNA	0.41 (0.18 to 0.95)	59 (5 to 82)	High
Two dose inactivated	0.43 (0.09 to 2.02)	57 (−102 to 91)	High
Symptomatic covid-19 infection			
Three dose mRNA	0.02 (0.01 to 0.08)	98 (92 to 99)	High
Two dose mRNA	0.09 (0.03 to 0.28)	91 (72 to 97)	High
Two dose inactivated	0.28 (0.08 to 1.06)	72 (−6 to 92)	Moderate
One dose mRNA	0.45 (0.14 to 1.38)	55 (−38 to 86)	High
One dose inactivated	0.52 (0.07 to 3.83)	48 (−283 to 93)	Moderate
One dose adenovirus	0.57 (0.17 to 1.89)	43 (−89 to 83)	High
Severe covid-19 infection			
Two dose mRNA	0.01 (0 to 0.21)	99 (79 to 100)	High
Two dose adenovirus	0.04 (0 to 0.77)	96 (23 to 100)	High
One dose mRNA	0.04 (0 to 0.89)	96 (11 to 100)	High
Two dose inactivated	0.12 (0.02 to 0.67)	88 (33 to 98)	Moderate
One dose adenovirus	0.38 (0.07 to 2)	62 (−100 to 93)	High
Covid-19 related hospital admission			
Three dose mRNA	0.05 (0.03 to 0.1)	95 (90 to 97)	Moderate
Two dose mRNA	0.19 (0.13 to 0.28)	81 (72 to 87)	Moderate
Two dose adenovirus	0.19 (0.06 to 0.62)	81 (38 to 94)	Moderate
One dose adenovirus	0.2 (0.07 to 0.58)	80 (42 to 93)	Moderate

No vaccine group was used as a reference.
GRADE=grading of recommendations assessment, development, and evaluation.

Study answer and limitations The first round of the analysis comprised 53 studies. 24 combinations of covid-19 vaccine regimens were identified, of which a three dose mRNA vaccine regimen was found to be the most effective against asymptomatic and symptomatic covid-19 infections (vaccine effectiveness 96%, 95% credible interval 72% to 99%). Heterologous boosting using two dose adenovirus vector vaccines with one mRNA vaccine has a satisfactory vaccine effectiveness of 88% (59% to 97%). A homologous two dose mRNA vaccine regimen has a vaccine effectiveness of 99% (79% to 100%) in preventing severe covid-19 infections. Three dose mRNA vaccination is the most effective in reducing covid-19 related hospital admissions (95%, 90% to 97%). The vaccine effectiveness against death in people who received three doses of mRNA vaccine remains uncertain owing to confounders. Homologous and heterologous three dose regimens are effective in preventing infection by covid-19 variants (alpha, delta, and omicron strains). The optimum time interval between doses was not evaluated owing to limited information.

What this study adds The findings suggest a booster dose is needed to prevent covid-19 infections. Heterologous and homologous three dose regimens work comparably well in preventing covid-19 infections, even against different variants.

Funding, competing interests, and data sharing
Supported by the Chinese University of Hong Kong. No competing interests declared. Raw data were extracted from published and preprint studies available on the internet.