research

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ORIGINAL RESEARCH Cohort study of UK Biobank participants

Genetic risk, incident stroke, and the benefits of adhering to a healthy lifestyle

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Study question Does adherence to a healthy lifestyle attenuate the risk of stroke associated with genetic factors?

Methods The present study included 306 473 men and women, aged 40-73 years, recruited between 2006 and 2010 into UK Biobank, a prospective population based cohort study in the UK. Cox regression was used to estimate hazard ratios for a first stroke. The authors constructed a polygenic risk score of 90 single nucleotide polymorphisms previously associated with stroke at $P<1\times10^{-5}$ and tested this score for an association with incident stroke. Adherence to a healthy lifestyle was determined using four factors: no current smoking, healthy diet, body mass index <30, and regular physical exercise.

Study answer and limitations Genetic and lifestyle factors were independently associated with risk of incident stroke. Weaknesses of the study include the possibility that lifestyle changed between time of recruitment and end of follow-up, restriction to only four lifestyle factors, and limited generalisability to populations of non-European ancestry.

What this study adds The study findings highlight the potential of lifestyle interventions to reduce risk of stroke in entire populations, even in those at high genetic risk of stroke.

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Relative and absolute risk of incident stroke according to genetic and lifestyle profiles

	Lifestyle		
Genetic risk	Favourable	Intermediate	Unfavourable
Low			
Hazard ratio* (95% CI)	1 (reference)	1.36 (1.14 to 1.63), $P=7.3\times10^{-04}$	1.84 (1.44 to 2.35), $P=8.0\times10^{-07}$
8 year cumulative incidence† (%) (95% CI)	0.54 (0.47 to 0.60)	0.74 (0.63 to 0.85)	0.95 (0.74 to 1.17)
Intermediate			
Hazard ratio* (95% CI)	1.26 (1.09 to 1.46), P=0.002	1.62 (1.37 to 1.92), $P=3.2\times10^{-08}$	1.85 (1.46 to 2.37), $P=5.4\times10^{-07}$
8 year cumulative incidence† (%) (95% CI)	0.67 (0.60 to 0.74)	0.82 (0.71 to 0.93)	0.92 (0.72 to 1.12)
High			
Hazard ratio* (95% CI)	1.44 (1.25 to 1.66), $P=7.0\times10^{-07}$	1.70 (1.44 to 2.01), $P=8.1\times10^{-10}$	2.30 (1.84 to 2.87), $P=3.3\times10^{-13}$
8 year cumulative incidence† (%) (95% CI)	0.78 (0.70 to 0.86)	0.91 (0.78 to 1.04)	1.11 (0.89 to 1.33)

*Calculated using Cox proportional hazards models, adjusted for age, sex, first 10 principal components of ancestry, and genotyping batch.
†Calculated using the cumulative incidence function as implemented in the "cmprsk" R package.

Which shingles vaccine for older adults?

ORIGINAL RESEARCH Systematic review and network meta-analysis

Efficacy, effectiveness, and safety of herpes zoster vaccines in adults aged 50 and older

Tricco AC, Zarin W, Cardoso R, et al

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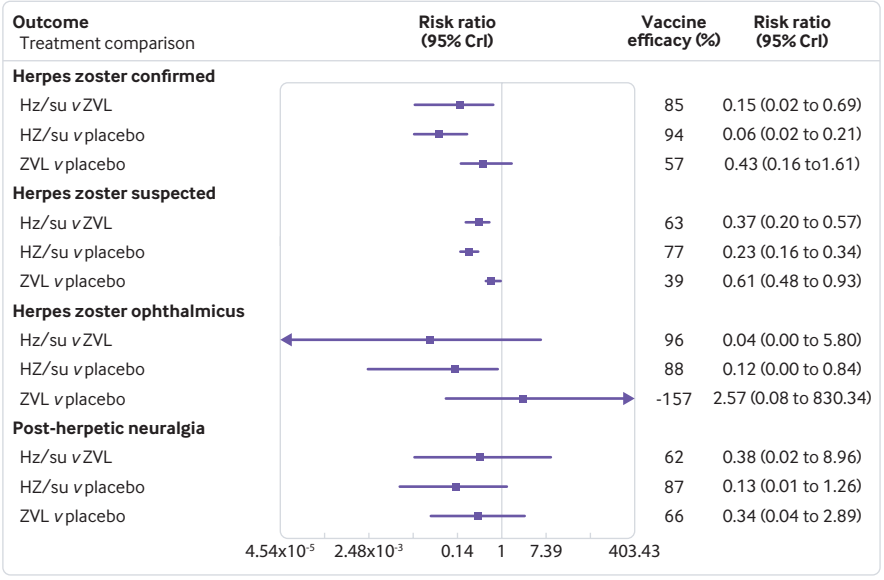
Study question What is the efficacy, effectiveness, and safety of the live attenuated vaccine against herpes zoster compared with the herpes zoster adjuvant recombinant subunit vaccine or placebo for adults aged 50 years and older?

Methods The authors carried out a systematic review with Bayesian meta-analysis and network meta-analysis of studies identified through a search of Medline, Embase, and the Cochrane Library from inception to January



Forest plot of estimated results from meta-analysis and network meta-analysis of vaccine efficacy outcomes in reducing cases of herpes zoster, herpes zoster ophthalmicus, and post-herpetic neuralgia. CrI=credible interval; Hz/su=herpes zoster adjuvant recombinant subunit vaccine; ZVL=live attenuated vaccine

COMMENTARY The new vaccine is more effective, but causes more (non-serious) ADVERSE EVENTS

The prevention of shingles in older adults has been augmented with a new option. In addition to the live attenuated herpes zoster vaccine, an adjuvant recombinant subunit vaccine was recently approved by drug regulators in the US,[1] Canada,[2] Europe, and Japan.[3] In their study, Tricco and colleagues addressed the important question of which vaccine is safer and more effective in older adults.[4] The authors conducted a comprehensive systematic review of both scientific and grey literature and used network meta-analysis techniques to compare the two vaccines indirectly, in the absence of any head-to-head trials.

Compared with the live attenuated vaccine, the subunit vaccine reduced doctor or laboratory confirmed cases of shingles by 85% (risk ratio 0.15, 95% confidence interval 0.02 to 0.69) and reduced suspected cases by 63% (0.37, 0.20 to 0.57) in adults aged 50 years or older. This increased efficacy comes with a short term cost—participants given the subunit vaccine had a significantly greater risk of adverse events at the injection site than those given the live attenuated vaccine.

Given the newer vaccine's trade-off between higher efficacy, adverse effects, and cost, a question mark remains over its likely uptake

Tricco and colleagues should be applauded for their rigorous methods and extensive literature search, but included studies were heterogenous, varying substantially in sample size (54-704 312 patients) and duration (3-102 months). The combination of both immunocompromised and immunocompetent patients in the main analysis made the live attenuated vaccine not statistically different from placebo in preventing confirmed shingles. Nevertheless, the analysis highlighted an important point: the subunit vaccine is more effective and more reactogenic than the live attenuated vaccine.

Preferred vaccine

So, which vaccine should be offered to patients? The US Advisory Committee on Immunization Practices recommends the subunit vaccine for people aged 50 years and older, including for those who received the live attenuated vaccine more than two months previously.[5] While the live attenuated vaccine is still a recommended option for people aged 60 years or more, the updated guidelines now state explicitly that the subunit vaccine is preferred.[5] The National Advisory Committee on Immunization of Canada also prefers the subunit vaccine, and it recommends the live attenuated vaccine only for patients who have a contraindication to the subunit vaccine or when the subunit vaccine is not available.[6]

Although these guidelines harmonise, several points deserve emphasis. First, the subunit vaccine requires two doses unlike the live attenuated vaccine, which requires only one, potentially reducing adherence. Patients who experience adverse events after a first dose are particularly likely to default on the second. The recent shortage of subunit vaccine could make adherence even more problematic.[8]

Second, the comparative effectiveness of the two vaccines is influenced by both efficacy at vaccination and duration of

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2017. Additionally, they searched for studies that were difficult to locate or unpublished and scanned the reference lists of identified studies. Experimental (eg, randomised controlled trials), quasi-experimental (eg, interrupted time series), and observational (eg, cohort) studies comparing the live attenuated vaccine with the subunit vaccine, placebo, or no vaccine in adults aged 50 years and older were included. Relevant outcomes were incidence of herpes zoster (primary outcome), herpes zoster ophthalmicus, post-herpetic neuralgia, quality of life, adverse events, and death. Two reviewers independently performed screening, data abstraction, and risk of bias appraisal.

Study answers and limitations The subunit vaccine was found to be 85% more effective in preventing herpes zoster cases than the live attenuated vaccine. However, the subunit vaccine led to 30% more injection site adverse events, such as redness or swelling. No statistically significant differences were identified between the two vaccines for serious adverse events and deaths. Several of the planned subgroup analyses (eg, age, immune competence) could not be performed owing to insufficient data.

What this study adds The adjuvant recombinant subunit vaccine might prevent more cases of herpes zoster than the live attenuated vaccine. Compared with the live attenuated vaccine, however, the subunit vaccine might carry a greater risk of adverse events at injection sites.

Competing interests, funding, and data sharing
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Study registration Prospero CRD42017056389.

protection. But long term duration of protection after vaccination with the subunit vaccine is unknown. Yearly data from randomised trials showed a decline in protection after four years.[10 11] Although efficacy in year 4 was still 85% compared with that for placebo we should be careful to not make overly optimistic assumptions about the durability of the subunit vaccine until more follow-up data are available.

Caveats

Third, it is critical that adverse reactions associated with the subunit vaccine continue to be monitored post-marketing. Because the AS01B adjuvant system can help boost a strong immune response, improving vaccine efficacy, it tends to cause more local and systemic reactions, a fact confirmed by Tricco and colleagues.[7 12] The need to mix two vaccine components combined with different storage requirements and a different route of administration from the live attenuated vaccine leads to a higher risk of errors when administering the subunit vaccine.[13] Fourthly, clinical trial data suggest that the subunit vaccine could be more effective than the live attenuated vaccine among people in their 70s,[10-15] when shingles is more prevalent. Unfortunately, Tricco and colleagues were unable to explore comparative effectiveness further by age group.

Finally, they did not have enough data to compare the efficacy of the vaccines against post-herpetic neuralgia—the main reason for vaccinating people against shingles.

The live attenuated vaccine has been on the market for more than a decade but coverage is suboptimal: 33% in the US,[16] 41% in England,[17] and 8% in Canada.[18] Given the newer vaccine's trade-off between higher efficacy, adverse effects, and cost,[19] a question mark remains over its likely uptake. When prescribing the subunit vaccine, doctors may want to focus on people aged 70 years or older who are most vulnerable to shingles and emphasise the importance of completing both doses and monitoring adverse effects.

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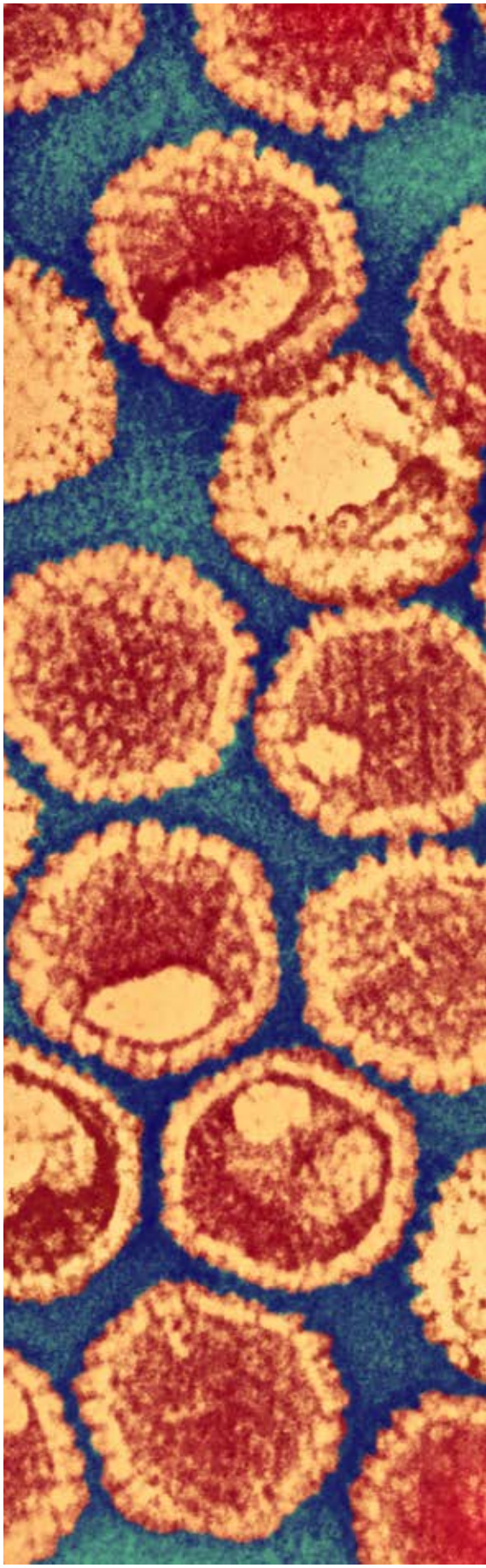

Angiotensin converting enzyme inhibitors and risk of lung cancer

Hicks BM, Filion KB, Yin H, Sakr L, Udell JA, Azoulay L

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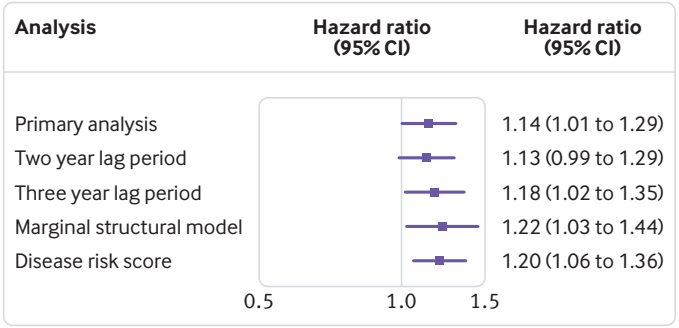
Study question Is the use of angiotensin converting enzyme inhibitors (ACEIs), compared with use of angiotensin receptor blockers, associated with an increased risk of lung cancer?

Methods This study used data from the UK Clinical Practice Research Datalink to identify a cohort of patients (aged 18 years or over) who started taking antihypertensive drugs between 1 January 1995 and 31 December 2015, with follow-up until 31 December 2016. Use of ACEIs was modelled as a time varying variable and compared with use of angiotensin receptor blockers, with exposures lagged by one year to account for cancer latency. Hazard ratios with 95% confidence intervals of incident lung cancer were estimated for use of ACEIs overall, by cumulative duration of use, and by time since initiation.



Forest plot summarising results of primary and sensitivity analyses assessing association between angiotensin converting enzyme inhibitor use and lung cancer incidence

Study answer and limitations 92 061 patients generated 6 350 584 years of follow-up and 7952 incident lung cancer events (crude incidence rate 1.3 (95% confidence interval 1.2 to 1.3) per 1000 person years). Overall, use of ACEIs was associated with an increased risk of lung cancer (1.6 *v* 1.2 per 1000 person years; hazard ratio 1.14, 95% confidence interval 1.01 to 1.29). Hazard ratios gradually increased with longer durations of use, with an association evident after five years of use (hazard ratio 1.22, 1.06 to 1.40) and peaking after more than 10 years of use (1.31, 1.08 to 1.59). Similar findings were observed with time since initiation. Given the observational nature of this study, residual confounding remains possible.

What this study adds Use of ACEIs was associated with an increased risk of lung cancer, compared with use of angiotensin receptor blockers. The association was particularly elevated among patients using these drugs for more than five years.

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