Health Psychology

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Optimizing Mood Prior to Influenza Vaccination in Older Adults: A Three-Arm Randomized Controlled Trial

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Objective: This trial explored the psychological and immunological effects of two brief interventions, targeting improving positive mood, administered to older adults immediately prior to influenza vaccination. The primary aim was to examine whether the interventions resulted in greater positive mood compared to usual care, and if so, which was superior. Secondary outcomes included antibody responses to vaccination and feasibility of collecting clinical outcome data (e.g., respiratory infections). ***Method:*** Six hundred and fifty-four older adults (65–85 years) participated in a three-arm, parallel, randomized controlled trial between September 2019 and May 2020. Immediately prior to receiving an adjuvanted trivalent influenza vaccine (Fluad, Seqirus UK Ltd), participants viewed one of two brief (15-min) video-based positive mood interventions (one fixed content, one allowing participant choice) or received usual care. State affect was measured

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Kieran Ayling served as lead for data curation, formal analysis, and visualization. Michaela Brown served in a supporting role for conceptualization and formal analysis. Sophie Carlisle served in a supporting role for conceptualization and formal analysis. Robert Bennett served in a supporting role for data curation and funding acquisition. Heather Buchanan served in a supporting role for funding acquisition and methodology. Jennifer Dumbleton served in a supporting role for methodology. Christopher Hawkey served in a supporting role for methodology. Katja Hoschler served in a supporting role for data curation, investigation, and methodology. Ruth H. Jack served in a supporting role for data curation and formal analysis. Jonathan Nguyen-Van-Tam served in a supporting role for conceptualization, methodology, and supervision. Simon Royal served in a supporting role for funding acquisition. David Turner served in a supporting role for funding acquisition. Maria Zambon served in a supporting role for investigation and methodology. Lucy Fairclough served in a supporting role for data curation, funding acquisition, investigation, and methodology. Kavita Vedhara served as lead for supervision. Kieran Ayling, Lucy Fairclough, and Kavita Vedhara contributed equally to conceptualization. Kieran Ayling, Michaela Brown, Sophie Carlisle, and Kavita Vedhara contributed equally to investigation and methodology. Kieran Ayling, Michaela Brown, and Sophie Carlisle contributed to project administration and writing–original draft. Kieran Ayling, Robert Bennett, Heather Buchanan, Simon Royal, David Turner, and Lucy Fairclough contributed equally to supervision. Kieran Ayling, Michaela Brown, Sophie Carlisle, Robert Bennett, Heather Buchanan, Jennifer Dumbleton, Christopher Hawkey, Katja Hoschler, Ruth H. Jack, Jonathan Nguyen-Van-Tam, Simon Royal, David Turner, Maria Zambon, Lucy Fairclough, and Kavita Vedhara contributed equally to writing–review and editing. Michaela Brown and Sophie Carlisle contributed equally to data curation. Kieran Ayling, Michaela Brown, Sophie Carlisle, Jonathan Nguyen-Van-Tam, and Kavita Vedhara contributed equally to funding acquisition. Katja Hoschler, Maria Zambon, and Lucy Fairclough contributed equally to resources.

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immediately prior to, and following, intervention exposure or usual care. Antibody responses were measured prevaccination and 4 weeks postvaccination. Clinical outcomes were extracted from primary care records for 6 months following vaccination. ***Results:*** Both interventions were equally effective at improving mood prior to vaccination compared to usual care. Antibody responses were highly robust with postvaccination seroprotection rates of >88% observed for all vaccine strains. Antibody responses did not significantly differ between groups. Clinical outcome data were feasible to collect. ***Conclusions:*** Brief psychological interventions can improve mood prior to vaccination. However, altering antibody responses to highly immunogenic adjuvanted vaccines may require more targeted or prolonged interventions. The provision of choice did not notably enhance the interventions impact on mood or antibody outcomes.

Public Significance Statement
This randomized controlled trial demonstrates that brief psychological interventions can improve mood in a clinical setting prior to vaccination. Providing choice over intervention content does not seem to significantly improve the effectiveness of these interventions. Where vaccines are already highly immunogenic, improving mood may not meaningfully impact on subsequent antibody responses.

Keywords: positive affect, positive mood, randomized controlled trial, vaccination, psychoneuroimmunology

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Background

Preventative vaccines, such as for influenza, are often less effective in older adults compared to their younger counterparts due to age-related immunological changes (Chen et al., 2009). Pharmacological solutions to this issue have had some, limited success—but vaccine efficacy is still suboptimal in this population. Nonpharmacological approaches, such as the use of psychological and behavioral interventions have shown promise (Pascoe et al., 2014; Vedhara et al., 2019) with approaches as diverse as cognitive-behavioral stress management to long-term moderate exercise interventions being found to impact on immune responses to a range of vaccines (Kohut et al., 2004; Vedhara et al., 2003). While these findings are informative, many of these interventions are likely of limited real-world utility, due to their length, burden on patients, cost, and resource demands. There is a need therefore to develop effective, brief nonpharmacological vaccine adjuvants that can be delivered at scale and at low-cost to realize public health benefit. Here, we describe a three-armed randomized controlled trial, evaluating the potential utility of two brief digital positive mood interventions delivered at the point of vaccination during the 2019–2020 U.K. annual influenza vaccination program. Our primary focus was on exploring whether these interventions could be successfully implemented into a primary care vaccination schedule and comparing their impact on positive mood outcomes. We also collected secondary outcomes relating to antibody responses and health care utilization outcomes to inform future clinical effectiveness trials.

The Challenge of Influenza and Influenza Vaccines in Older Adults

Older adults produce lower levels of protective antibodies following influenza vaccination (Goodwin et al., 2006) and are less likely to be prevented from contracting severe influenza illness (Rondy et al., 2017) than younger adults. This is particularly problematic because older adults are at the greatest risk of the most severe complications of influenza infection (Centres for Disease Control and Prevention, 2021; Cromer et al., 2014; Matias et al., 2016; Office for National Statistics, 2021; Thompson et al., 2003).

The Case for Nonpharmacological Adjuvants and How They Might Work

A range of psychological and behavioral factors—including sleep, physical activity, nutrition, stress, and mood—have been associated with immune function and vaccination responses (Calder, 2020; Pressman et al., 2019; Segerstrom & Miller, 2004; Spiegel et al., 2002; Woods et al., 2009). Unlike many predictors of vaccine response (e.g., age, genetics, prior exposures), such factors have the benefit of being potentially modifiable via targeted interventions. As such, psychological and behavioral interventions may provide an avenue by which improvements to vaccine responses in older adults could be realized, acting as a so-called nonpharmacological vaccine adjuvant (Vedhara et al., 2019).

To explore how nonpharmacological adjuvants might work, it is worth first considering the mechanisms of action for chemical adjuvants. Chemical adjuvants, such as aluminum salts and MF59 (an oil-in-water emulsion), are added to some vaccines to elicit an enhanced immune response to the vaccine antigens. While different chemical adjuvants exert differing effects, generally they are thought to work by creating a more "immunocompetent local environment" at the injection site, by influencing innate immune activity and function such as cytokine production and cell recruitment (Awate et al., 2013; De Gregorio et al., 2013). These early influences in the first stages of the immune cascade following vaccination ultimately lead to enhanced antibody production several weeks postvaccination, even though these chemical adjuvants have been long cleared.

Turning to nonpharmacological adjuvants, experimental studies demonstrate that brief mood inductions and experimentally induced stressors can have measurable, causal effects on some of these same innate immunological parameters, including on cytokine production (such as IL-6) and innate immune cell counts in sera (Ayling et al., 2020; Pressman & Black, 2012; Segerstrom & Miller, 2004). This therefore represents a plausible mechanistic pathway by which brief psychological interventions could influence immune responses to vaccination: by optimizing the host immune environment for antigenic challenge at the point of vaccination, much like a chemical adjuvant works. Indeed, real-world

evidence from naturalistic diary studies demonstrates changes to immunological parameters, including antibody secretion, in response to changing psychological states (e.g., Stone et al., 1994), and multiple observational studies have shown associations between trait psychological states and immune responses to multiple vaccinations in a range of populations (e.g., Marsland et al., 2001, 2006; Wright et al., 2005).

Background to the Present Trial

As part of a program of work investigating the potential of nonpharmacological vaccine adjuvants, we previously reported a prospective longitudinal cohort study investigating multiple behavioral and psychological factors and their relationship with influenza vaccine responses in older adults (Ayling et al., 2018). This found that older adults who reported greater positive affect on the day of vaccination had greater antibody responses to influenza vaccination at 4 and 16 weeks postvaccination. We subsequently developed, and piloted, a brief positive mood intervention administered on the day of influenza vaccination in older adults. This pilot trial showed that, compared to a neutral mood intervention, the positive mood intervention significantly improved mood, and point estimates favored the intervention group in terms of antigen-specific immunoglobulin G (IgG) responses to the influenza vaccine (Ayling et al., 2019).

While these, and other, findings point to the potential for positive mood to act as a vaccine adjuvant in older adults (e.g., Marsland et al., 2007), to adequately test this hypothesis, we need effective interventions that induce positive mood that are pragmatically designed to have utility in primary care settings where vaccines are administered. While our previously developed intervention successfully induced positive mood in this context (Ayling et al., 2019), there remained a need to examine intervention effects in comparison to usual care and determine if intervention effects on mood could be enhanced further. Qualitative feedback from the pilot trial of a fixed-content intervention (Ayling et al., 2019) indicated that providing participants with a degree of choice around intervention content would be welcomed, given individual variations in taste and humor. Indeed, systematic review evidence indicates that participants who are able to choose their intervention(s)/treatment(s) (or elements of them) may have increased intervention satisfaction and clinical outcomes in terms of physical and mental health (Lindhiem et al., 2014).

Thus, we report here a three-arm randomized controlled trial designed to examine the impact of two brief positive mood interventions (one fixed content and one allowing participant choice) compared to usual care, in older adults on the day of influenza vaccination. The primary aim was to examine whether the two interventions resulted in greater positive mood compared to usual care, and if so, which was superior. Secondary aims related to collecting evidence to inform the design of a future clinical effectiveness trial. Specifically, we sought to quantify between-groups differences in IgG and hemagglutination–inhibition antibody (HAI) responses to influenza vaccination and explore the feasibility of collecting routine healthcare outcome data on influenza-related clinical outcomes. As such this study should only be considered a preliminary study in relation to the impact of brief positive mood interventions on vaccination responses as it was powered based on the primary (mood) outcomes.

Method

Transparency and Openness Statement

In this article, we report how we determined our sample size, all data exclusions, all manipulations, and all measures that were included in the study, and we follow the CONSORT guideline for reporting parallel group randomized trials. Analysis code and research materials are available at https://bit.ly/3tGPWl4. Data are available upon reasonable request from the corresponding author. Analyses plans were not preregistered, although unplanned exploratory analyses are indicated as such in the text. Statistical analyses were performed using R (packages used can be found in the online supplemental materials). The trial was preregistered on clinicaltrials.gov (NCT03956329).

Study Design

A three-arm, parallel, randomized control trial was conducted alongside the 2019/2020 annual influenza vaccination schedule in the United Kingdom. Participants were invited between August and October 2019, with study appointments and vaccination completed between September and December 2019, with trial involvement continuing to May 2020. Ethical approval for the research was given by the Health Research Authority and East Midlands-Nottingham Research Ethics Committee 1 (19/EM/0081) prior to study commencement.

Sample Size Calculation

The study was powered to detect differences in mood outcomes. Based on a 2:2:1 allocation ratio, a priori power calculations indicated a sample of 253 participants in each experimental arm and 108 participants in the control arm would be required to detect a medium-sized ($d = 0.4$) difference between experimental arms and control with 90% power in separate one-tailed t tests. One-tailed tests were used for this primary power analysis because of a high degree of confidence of the expected direction of effect given previous piloting (Ayling et al., 2019). Additionally, this would provide 80% power to detect a smaller ($d = 0.25$) difference between experimental arms in a two-tailed t test. Therefore, a recruitment target of 650 participants was set to allow for reasonable levels of attrition in line with prior studies in this population.

Participants

Participants who fully consented into the trial included 654 older adults aged between 65 and 85 years at the point of invitation. Participants were recruited from 13 GP practices in the East Midlands, United Kingdom. Practices were selected to cover both inner-city and more rural areas, as well as a range of indices of deprivation (based on postal code). To minimize differences in prior exposure between participants, inclusion was limited to those who had received an influenza vaccination in the previous year (2018/2019). To maximize generalizability, all other exclusion criteria were kept to a minimum. Participants were excluded if: they had a diagnosis of a cognitive condition that would make participation difficult; had insufficient English language skills to participate in study activities; were deemed by a healthcare provider to be too physically frail to participate; had insufficient hearing and/or vision such that engagement with the intervention would be comprised; or had

a contraindication for influenza vaccination or venepuncture. Participants received a £20 inconvenience payment for taking part in the study.

Randomization

Participants were individually randomized on a 2:2:1 ratio to the standardized (fixed-content) positive mood intervention, choice-based positive mood intervention, or usual care arms, respectively, at the point participants agreed to participate. Randomization was done using an online generated block randomization sequence (block size = 10) initiated by a third party. This randomly generated sequence was paired to participant ID numbers in such a manner that touchscreen computer tablets were programmed to run the appropriate intervention/control program without the researchers being aware of participant assignment. To avoid contamination, participants randomized into the usual care arm were booked into separate sessions to those receiving one of the two interventions. As a result, the study team was unblinded to the usual care allocation but remained blinded to which of the two intervention arms participants were assigned. Participants were made aware that they would be randomly allocated to either view a video or wait for a short period prior to vaccination. However, they were not told that the interventions were designed to improve mood or about the differing nature of the two positive mood interventions (standardized and choice) to minimize possible demand characteristics.

Procedure

Eligible potential participants were invited via letter from their GP practices, with interested patients asked to return a reply slip to researchers. Researchers (Kieran Ayling, Michaela Brown, and Sophie Carlisle) then contacted the potential participants to explain the trial in more detail, answer any questions, and complete initial enrollment. Participants were then sent a baseline questionnaire via post which captured demographic information, health status, and trait psychological factors (see below for details). Participants were asked to return this questionnaire in a freepost envelope, prior to their scheduled study/vaccination appointment. Participants then attended a scheduled study appointment at their GP practice, at which they completed written informed consent. Participants were booked into these study appointments in groups of typically five to seven people. Some participants ($n = 51$) did not attend this session, or did not provide written consent, and thus were removed from the trial. While these participants had already been randomized, they did not know their allocation prior to withdrawal.

Participants who fully consented into the trial ($n = 654$) had their height and weight measured to determine body mass index and provided a venous blood sample to determine prevaccination antibody status. Participants were then given a brief demonstration on how to use the computer tablet devices (model: ASUS-T101HA, AsusTek Computer Inc.) and completed measures of preintervention state affect on the device. Participants then received their intervention or usual care exposure (see below). Immediately after this, participants completed postintervention state affect measures and were vaccinated with the 2019/2020 season northern hemisphere Fluad (Sequirus UK Ltd) Adjuvanted Trivalent Influenza Vaccine (Surface Antigen, Inactivated). Typically, the vaccine was administered less than 5 min following the end of the intervention or usual care exposure. Participants reattended their GP practice on a second occasion 4 weeks following this initial study appointment to provide postvaccination blood samples for the determination of antibody responses to the vaccination. Materials and stimuli used in the study can be accessed at https://bit.ly/3tGPWl4.

Study Conditions

Standardized Positive Mood Intervention

Participants in the standardized (fixed-content) positive mood condition viewed a video-based intervention previously described by Ayling et al. (2019). In brief, the video lasted approximately 15 min and included three "classic" comedy clips, uplifting music, and images. The intervention was codeveloped with older adult public contributors and has previously been shown to induce positive mood in older adults (Ayling et al., 2019). Participants viewed the intervention video on individual tablet devices, wearing over-ear headphones.

Choice Positive Mood Intervention

Participants in the choice positive mood intervention were asked to choose, via the tablet device, three different videos from the following categories: "stand-up comedy," "sit-coms," "music," and "variety." There were three video options in each category (12 overall) and participants could browse between categories before choosing each option. Some of this content overlapped with the clips used in the standardized intervention and the others were chosen in collaboration with a patient advisory group for this research. The frequency with which each option was chosen is presented in the online supplemental materials. Each video was approximately 5 min in length, meaning the overall intervention was time-matched to the standardized positive mood intervention. Participants viewed the intervention videos on individual tablet devices, wearing over-ear headphones.

Usual Care Control

Participants in the control condition were asked to wait in the study room or practice waiting room for 15 min. A countdown timer was displayed on the participants' tablet screen to indicate how long remained. Participants were not prevented from talking to each other if they wished during this time.

Measures

Primary Outcome Measures—State Affect

Prior to, and immediately following intervention or usual care exposure, all participants completed the Affective Slider Scale (Betella & Verschure, 2016), the Scale of Positive and Negative Experience (SPANE—Diener et al., 2009), and two visual analog scales from the Dynamic Visual Analog Mood Scales (DVAMS—Barrows & Thomas, 2018). The Affective Slider—Valence subscale was selected a priori to be the primary outcome measure. Further details are given in the online supplemental materials.

Secondary Outcome Measures

Baseline/Trait Mood Measures. Positive and negative trait affect were measured using the Positive and Negative Affect Schedule Short Form (PANAS-SF—Watson et al., 1988). Perceived stress over the previous month was measured using

the Perceived Stress Scale (PSS-10—Cohen, 1988). Health status was measured using the 12-item Short-Form Health Survey (SF-12 v1—Ware et al., 1995, 1996). Further details are given in the online supplemental materials.

Immune Measures. Venous blood samples (8 ml) were obtained prevaccination and 4 weeks postvaccination to measure vaccine-specific antibody responses. On the day of collection, after being allowed to clot at room temperature, samples were centrifuged at 2,000*g* for 10 min, after which sera were separated and stored at −80°C until analysis. Researchers conducting immune analyses were blinded to intervention allocation at the point immune analyses were conducted. Samples were analyzed for strain-specific IgG via enzyme-linked immunoassay, and strain-specific HAI antibodies via hemagglutination inhibition assay (for details see the online supplemental materials).

Medical Record Data Collection. As part of a feasibility exercise for planning potential future trials, patients' medical records were extracted by GP practice staff for the 6 months following vaccination (up to March 2020–May 2020). Primary Care records were searched for instances of respiratory infections, antibiotic prescriptions, and hospital attendance that occurred during this period using a range of Read codes (developed with and reviewed by clinicians). Due to resource constraints, data extraction was only attempted for 12 of the 13 sites that used the same medical record system. Findings for these outcomes are reported in the online supplemental materials.

Statistical Analysis

Statistical analyses were performed using R (packages used can be found in the online supplemental materials). All analyses presented reflect an intention-to-treat population, where all participants who fully consented into the study ($n = 654$) are included where data were available. In the case of missing data (e.g., missing scale items, nonattendance at follow-up, failed venepuncture), no imputation was performed. Per-protocol analyses were also conducted excluding 18 participants who were deemed to have had significant protocol deviations (standardized: $n = 6$; choice: $n = 8$; usual care: $n = 4$, see the online supplemental materials). Per-protocol analyses did not result in any differing interpretations from intention-to-treat analyses so are not presented here.

Postintervention mood outcomes (primary) and postvaccination continuous antibody outcomes (secondary; IgG and HAI geometric mean titers) were compared across arms using analyses of covariance (ANCOVA) with the corresponding preintervention or prevaccination measure included as a covariate in each analysis. Planned Bonferroni-adjusted comparisons were then used to compare between pairs of trial arms. IgG antibody outcomes were $\log_2$--transformed to improve normality, however, for psychological outcomes transformations did not substantially improve normality and thus were analyzed in their untransformed state. While the sample size is relatively large and parametric tests are reasonably robust, some parametric test assumptions were violated for some ANCOVA analyses. Therefore, we conducted sensitivity analyses using nonparametric equivalents (Quade's) where appropriate. These resulted in no substantive differences in interpretation of results and therefore are not reported here. Seroprotection (titer $\geq$ 1:40) and seroconversion (fourfold increase or titer $\geq$ 1:40 if undetectable prevaccination) proportions between trial arms were examined using chi-squared tests. To examine changes in antibody levels from pre- to postvaccination across groups, paired *t* tests were used. Clinical outcome data are presented descriptively in the online supplemental materials.

Results

Participant Recruitment and Randomization

Figure 1 shows the flow of participants through the study. A total of 7,025 eligible participants were invited between August 2019 and October 2019, 848 (12.1%) of which returned a reply slip. Of these positive responses, 705 agreed to participate and were randomized, with 654 attending the required study visit and providing written consent. Table 1 shows participant demographics by group and overall. Some drop-out between randomization and consent occurred ($n = 51$, 7.2%) due to randomization taking place at the point of recruitment, often days or weeks prior to the first visit to the GP practice where written consent was obtained. This process was necessary to book participants into separate sessions for usual care and intervention participants, due to concerns relating to contamination observed in an earlier pilot trial (Ayling et al., 2019). Attrition was low, with 617 participants of the 654 who fully consented (94.3%) attending their GP practice for 4 weeks postvaccination blood sampling. Table S1 in the online supplemental materials shows baseline/trait measures for psychological factors and health status by group.

Mood Outcomes (Primary)

Pre- and Postintervention state affect scores can be seen in Table S2 in the online supplemental materials. ANCOVA results for the primary outcome showed significant differences between groups on Affective Slider—Valence subscale, $F(2, 631) = 9.53$, $p < .001$, $\eta^2_G = .029$. All other state mood outcomes were consistent with these findings, showing significant between-group differences, affective slider—alertness, $F(2, 631) = 5.46$, $p = .004$, $\eta^2_G = .017$; DVAMS—happy/sad, $F(2, 619) = 20.96$, $p < .001$, $\eta^2_G = .063$; DVAMS—alert/sleepy, $F(2, 619) = 8.69$, $p < .001$, $\eta^2_G = .027$; SPANE-Positive, $F(2, 629) = 11.02$, $p < .001$, $\eta^2_G = .034$; SPANE-Negative, $F(2, 627) = 5.39$, $p = .005$, $\eta^2_G = .017$.

Bonferroni-adjusted planned comparisons revealed significantly greater improvements in state affect for participants who viewed either standardized or choice interventions compared to usual care for all mood outcome measures (except for affective slider—alertness, for which only the choice arm showed significantly greater increases compared to usual care), but no significant differences on mood outcomes were observed between the interventions (see Figure 2).

Antibody Outcomes (Secondary)

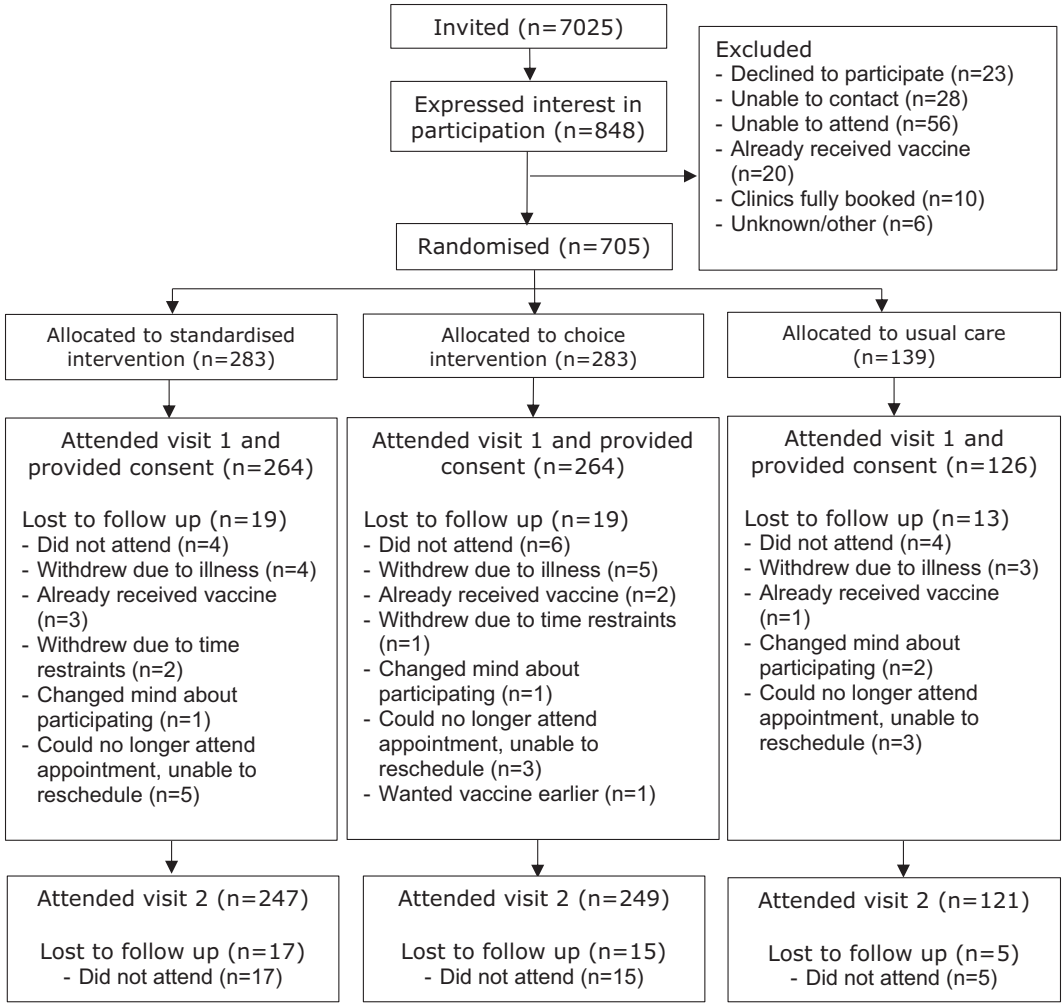
Blood samples were successfully obtained for 650 of 654 participants (99.4%) at baseline, with 602 samples collected at 4 weeks postvaccination (92.0% of all participants, 97.6% of those attending at 4 weeks postvaccination).

IgG

Across groups, for all strains, paired *t* tests showed significant increases in $\log_2$-transformed IgG antibody levels following vaccination (all *p*s $< .001$).

ANCOVA results showed no significant differences between groups on IgG antibody levels following vaccination (see Table S3 in the online supplemental materials), for all strains, H1N1,

Figure 1
CONSORT Flow Diagram of Participants in the Trial



$F(2, 584) = 1.08$, $p = .339$, $\eta^2_G = .004$; H3N2, $F(2, 584) = 1.12$, $p = .326$, $\eta^2_G = .004$; B, $F(2, 584) = 0.30$, $p = .743$, $\eta^2_G = .001$. Bonferroni-adjusted planned comparisons showed no statistically significant differences between intervention arms and usual care, or between intervention arms.

HAI

Considering the whole cohort, prevaccination rates of seroprotection (titer $\geq$ 1:40) were 63.7% for H1N1, 29.5% for H3N2, and 79.9% for B strains. These increased postvaccination to 89.9% for H1N1, 88.5% for H3N2, and 95.8% for B strains. Seroconversion rates ($\geq$ fourfold increase or $\geq$1:40 with undetectable prevaccination titer) were 41.5% for H1N1, 77.0% for H3N2, and 18.5% for B strains. Geometric mean HAI antibody titers across the cohort significantly increased for all strains following vaccination (all $ps < .001$).

ANCOVA results showed no significant differences between groups on HAI antibody levels following vaccination in terms of geometric mean HAI titers, H1N1, $F(2, 584) = 0.04$, $p = .961$, $\eta^2_G < .001$; H3N2, $F(2, 584) = 0.03$, $p = .968$, $\eta^2_G < .001$; B, $F(2, 584) = 0.13$, $p = .874$, $\eta^2_G < .001$ (see Figure 3). Chi-squared analyses also found no significant differences between arms on postvaccination seroprotection or seroconversion rates (see Table 2).

Discussion

The primary aim of this trial was to examine whether two brief (15 min) positive mood interventions (one standardized/fixed-content, one involving participant choice) improved older adults' positive mood prior to vaccination when compared with usual care, and if so, which was superior. We observed that participants in both intervention arms showed significantly greater improvements in mood from pre- to postintervention compared to those in the usual care arm. This was seen for the primary outcome (Affective Slider—Valence subscale), as well as for four of the five other state affect measures, with the only deviation being the Affective Slider—Alertness subscale for which only the choice arm resulted in significantly improved mood compared to usual care. One explanation for this increase in alertness being only seen in the choice intervention arm may reflect the comparatively active versus passive

Table 1
Participant Demographics

Demographic	Usual care ($N = 126$)	Standardized intervention ($N = 264$)	Choice intervention ($N = 264$)	Overall ($N = 654$)
Sex				
Male	59 (46.8%)	127 (48.1%)	117 (44.3%)	303 (46.3%)
Female	67 (53.2%)	137 (51.9%)	147 (55.7%)	351 (53.7%)
Age in years (at randomization)				
Mean (*SD*)	74.0 (5.43)	73.2 (5.11)	73.3 (4.91)	73.4 (5.10)
Ethnicity				
White	121 (96.0%)	254 (96.2%)	255 (96.6%)	630 (96.3%)
Mixed	0 (0%)	1 (0.4%)	0 (0%)	1 (0.2%)
Asian	2 (1.6%)	1 (0.4%)	0 (0%)	3 (0.5%)
Black	0 (0%)	2 (0.8%)	0 (0%)	2 (0.3%)
Other	0 (0%)	1 (0.4%)	0 (0%)	1 (0.2%)
Missing	3 (2.4%)	5 (1.9%)	9 (3.4%)	17 (2.6%)
Marital status				
Married	79 (62.7%)	173 (65.5%)	170 (64.4%)	422 (64.5%)
Single, never married	9 (7.1%)	8 (3.0%)	11 (4.2%)	28 (4.3%)
Separated/divorced	10 (7.9%)	35 (13.3%)	29 (11.0%)	74 (11.3%)
Widowed	19 (15.1%)	36 (13.6%)	39 (14.8%)	94 (14.4%)
Cohabiting	6 (4.8%)	8 (3.0%)	7 (2.7%)	21 (3.2%)
Missing	3 (2.4%)	4 (1.5%)	8 (3.0%)	15 (2.3%)
Lives independently				
No	6 (4.8%)	13 (4.9%)	10 (3.8%)	29 (4.4%)
Yes	117 (92.9%)	247 (93.6%)	247 (93.6%)	611 (93.4%)
Missing	3 (2.4%)	4 (1.5%)	7 (2.7%)	14 (2.1%)
Education				
School	67 (53.2%)	119 (45.1%)	127 (48.1%)	313 (47.9%)
University (undergraduate)	17 (13.5%)	27 (10.2%)	25 (9.5%)	69 (10.6%)
University (postgraduate)	20 (15.9%)	45 (17.0%)	50 (18.9%)	115 (17.6%)
Other	19 (15.1%)	68 (25.8%)	54 (20.5%)	141 (21.6%)
Missing	3 (2.4%)	5 (1.9%)	8 (3.0%)	16 (2.4%)
Smoker				
No	117 (92.9%)	251 (95.1%)	240 (90.9%)	608 (93.0%)
Yes	6 (4.8%)	9 (3.4%)	17 (6.4%)	32 (4.9%)
Missing	3 (2.4%)	4 (1.5%)	7 (2.7%)	14 (2.1%)
Body mass index				
Mean (*SD*)	28.1 (5.76)	27.2 (4.95)	27.9 (5.08)	27.7 (5.17)
Missing	1 (0.8%)	1 (0.4%)	1 (0.4%)	3 (0.5%)

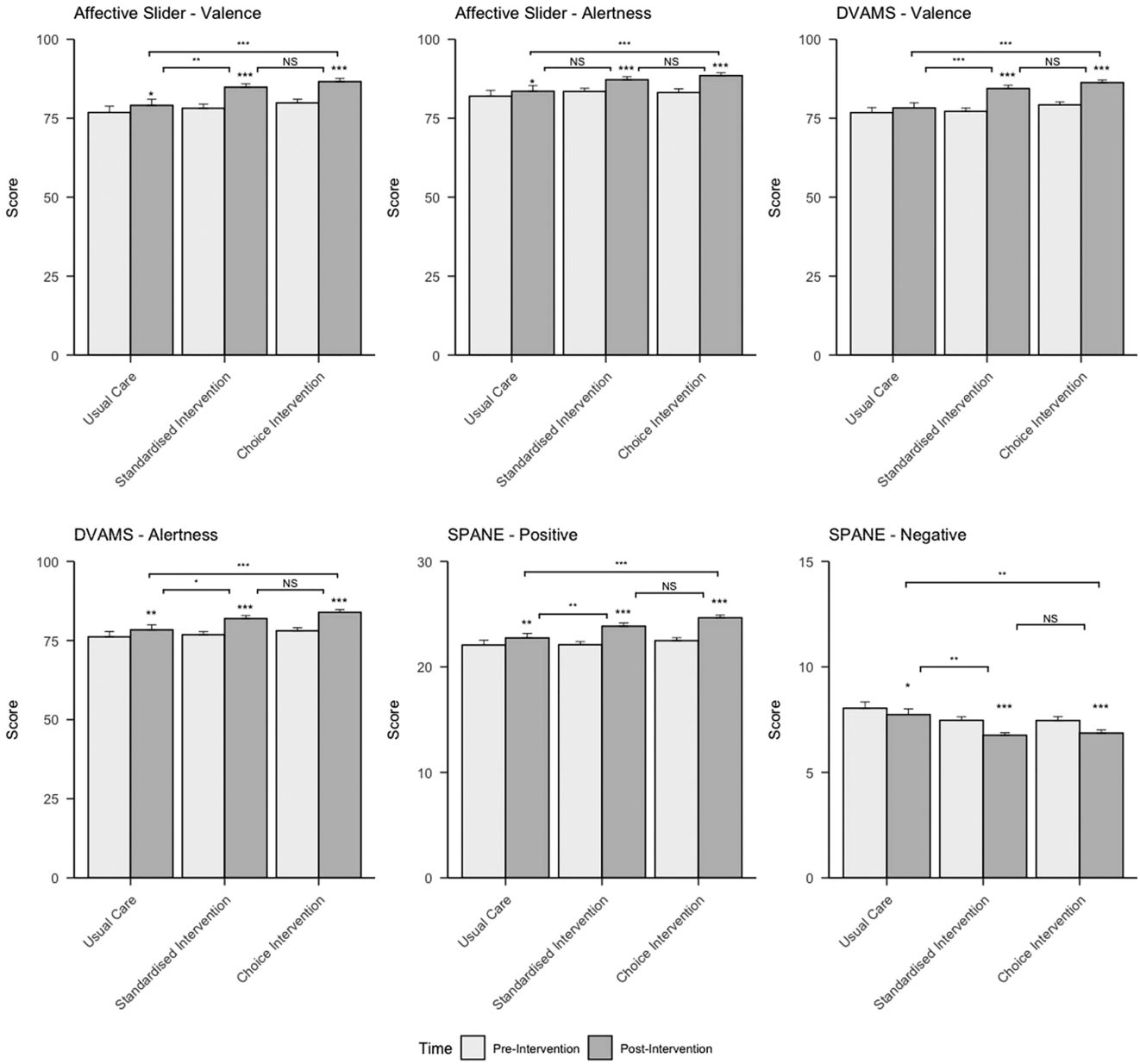
natures of the two interventions. The choice intervention required participants to remain actively engaged with the intervention (via selecting intervention components throughout), whereas the standardized intervention was one continuous exposure that did not require participants to do anything other than passively view the content. However, when comparing the two interventions directly with each other, no significant differences were observed in the primary mood outcome or the other state affect measures, suggesting both interventions were equally effective at inducing positive mood.

The finding that the provision of choice within the positive mood intervention did not result in notably improved mood outcomes contrasts with prior review evidence that found allowing participants to exercise choice/personal preferences in relation to their intervention or treatment leads to better satisfaction and clinical outcomes—including those relating to mental health (Lindhiem et al., 2014). However, the focus of that review was primarily on patient/practitioner shared decision making and clinical outcomes did not solely include mood-related outcomes. Results from the present trial suggest that in the context of brief positive mood interventions, while the provision of choice may be desirable, it does not necessarily lead to improved intervention potency. It is noteworthy that others have similarly reported that when given a choice of positive mood interventions, self-selection is no more effective than random assignment (Silberman, 2007). Indeed, in a recent systematic review and meta-analysis comparing choice-based interventions to matched nonchoice interventions (across a range of contexts) the authors found that while providing participants choice reduced attrition and increased satisfaction with the intervention, there was only weak (nonsignificant evidence) that this influenced mood-related outcomes (Carlisle et al., 2021).

A further consideration, however, is that preintervention positive mood levels were high across all three arms for all measures (see Figure 2). This raises the issue of whether ceiling effects could have limited the potential impact of the interventions. Indeed, in exploratory analyses, we found that in both intervention arms, participants with the lowest preintervention mood had larger mood improvements than those who scored the highest preintervention, potentially indicative of ceiling effects (see the online supplemental materials). It may be that brief positive mood interventions such as these would be more effective in participants prescreened for low mood or in populations where low mood is particularly prevalent, with potential implications for possible immune effects. However, further evidence is needed as to whether mood and immunological effects of acute psychological mood induction are similar in low-mood and typical older adult populations, and whether the acute effects of a brief psychological intervention are sufficient to overcome the well-documented deleterious

Figure 2

State Affect Measures Pre- and Postintervention



Note. Brackets indicate differences between arms controlling for preintervention score, other comparisons are within arms. Error bars reflect 95% confidence interval.

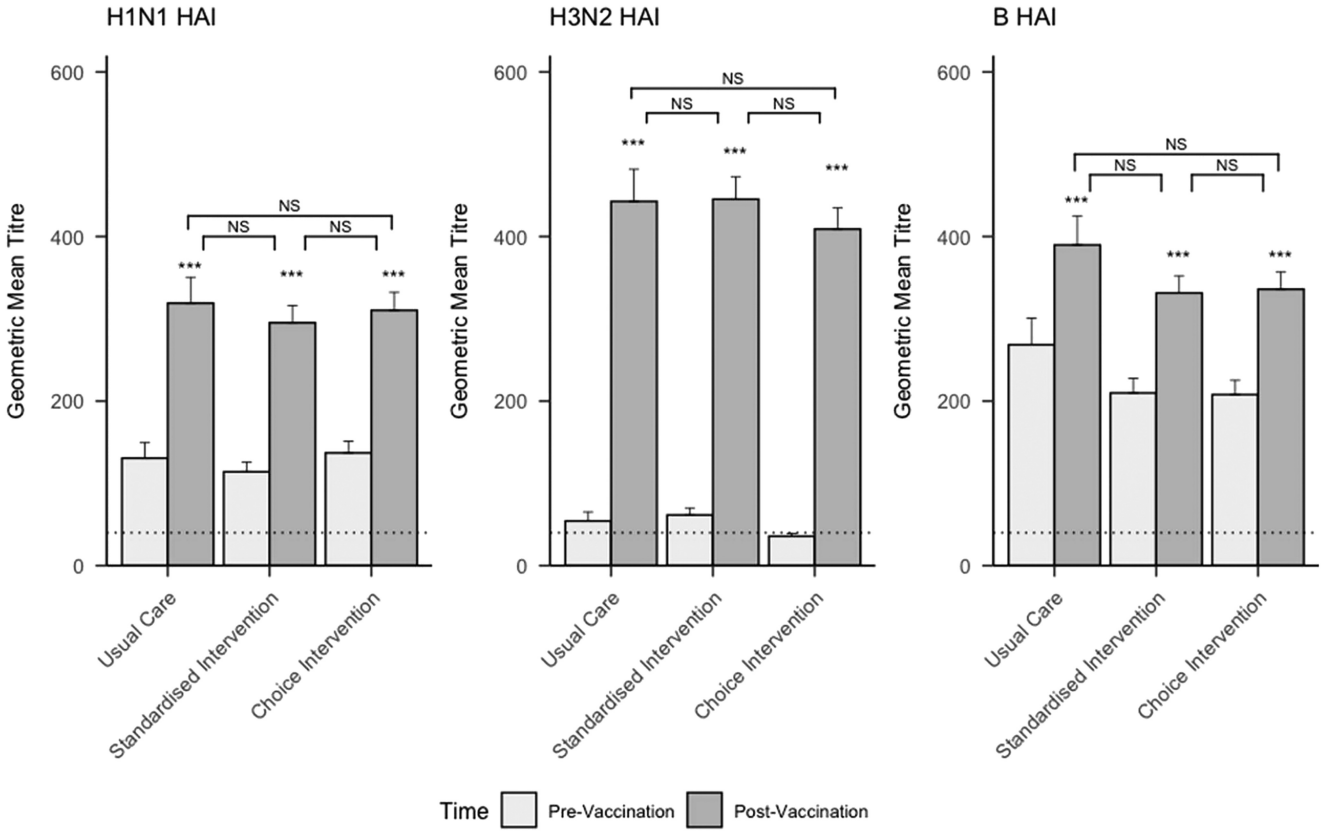
* $p < .05$. ** $p < .01$. *** $p < .001$. $NS = p \geq .05$.

effects of prolonged negative psychological states on immunity (Marsland et al., 2001; Segerstrom & Miller, 2004).

The secondary aims of this trial focused on collecting data to inform a future clinical effectiveness trial of a brief positive mood intervention on immune and clinical outcomes. We found it was feasible to collect blood samples (92.0% of recruited participants successfully sampled at all timepoints) and clinical outcome data (92.1% of participants with complete data) with low attrition. This indicates a larger effectiveness trial would be feasible to conduct alongside the routine influenza vaccine schedules. The present trial was only powered to assess between arm differences on mood outcomes and was not specifically powered for secondary outcomes such as antibody levels. Thus, as expected, we found no evidence of statistically significant differences between those receiving either intervention or usual care, in terms of vaccine-specific antibody responses. It is important to note that the size of the present trial means there was only sufficient power to reliably detect medium-to-large between-group differences, and thus these findings should be treated with due caution. Future trials may need to consider the likelihood that potential effects of brief nonpharmacological adjuvants could be small, even if clinically

Figure 3

HAI Geometric Mean Titers Pre- and Postvaccination



Note. Dotted line indicates seroprotection threshold (≥40). Brackets indicate differences between arms controlling for preintervention mean titers, other comparisons are within arms. Error bars reflect 95% confidence interval. HAI = hemagglutination–inhibition antibody.
* $p < .05$. ** $p < .01$. *** $p < .001$. *NS* = $p \geq .05$.

significant given the large number of people vaccinated annually.[1] Further, given antibody levels are only an imperfect proxy measure for protection, future trials may choose to focus on more clinically relevant measures such as healthcare utilization, where resources allow. It is noteworthy, however, that healthcare utilization as captured by medical records likely only captures the most severe infections, as many people will opt to self-manage any infection at home without seeking treatment.

Given our interest in the future application of brief psychological interventions to enhance the effectiveness of vaccines, and the mechanisms by which this might occur, some further consideration is warranted here. It is worth observing that the differences in antibody outcomes between groups were attenuated in comparison to those reported in our previous pilot trial (Ayling et al., 2019). One plausible explanation for this is the use of an adjuvanted vaccine in the present work. Adjuvanted influenza vaccines are necessarily more immunogenic than nonadjuvanted vaccines (Coleman et al., 2021) and have been approved for use in U.K. older adults from 2018/2019 precisely to deal with issues of poor vaccine immunogenicity in this population. Indeed, consistent with this, we observed very high rates of postvaccination seroprotection with 79% of participants achieving HAI titers ≥ 40 for all three vaccine strains 4 weeks following receiving an adjuvanted influenza vaccine. This was considerably higher than 4-week postvaccination seroprotection rates observed an earlier study, in older adult participants with similar demographics who received an unadjuvanted influenza vaccine (33%, Ayling et al., 2018).

To our knowledge, this is the first trial to examine the effects of a psychological vaccine adjuvant on an already adjuvanted vaccination and these findings suggest that the potential for a psychological adjuvant to further enhance a pharmacologically adjuvanted vaccination may be limited. Indeed, if we hypothesize that psychological adjuvants could work through similar mechanisms of action to chemical adjuvants, by optimizing the immune environment for antigenic challenge at the point of vaccination, then with hindsight we could say that expecting to observe additive benefits may have been unrealistic. The reliance on an adjuvanted influenza vaccine in this trial was necessitated due to the purchasing decisions of participating GP practices not known until late in the trial planning process. Most vaccinations, for most populations, remain unadjuvanted—as such future research in nonadjuvanted vaccines, or populations at greater risk of impaired

[1] We note that to detect a small ($d = 0.1$) effect size with 80% power in a two-tailed between groups t test (1:1 allocation) would need a sample size of 3,142 participants.

Table 2
HAI Seroprotection and Seroconversion Rates by Group

Immune outcome	Usual care	Standardized intervention	Choice intervention	Chi-squared test
H1N1 Seroprotection prevaccination	75 (62.0%)	169 (65.8%)	162 (62.5%)	$\chi^2 = 0.77$, $p = .679$
H1N1 Seroprotection postvaccination	109 (90.8%)	218 (90.5%)	214 (88.8%)	$\chi^2 = 0.52$, $p = .772$
H3N2 Seroprotection prevaccination	30 (24.8%)	86 (33.5%)	72 (27.8%)	$\chi^2 = 3.59$, $p = .166$
H3N2 Seroprotection postvaccination	106 (88.3%)	213 (88.4%)	214 (88.8%)	$\chi^2 = 0.03$, $p = .987$
B Seroprotection prevaccination	94 (77.7%)	211 (82.1%)	204 (78.8%)	$\chi^2 = 1.35$, $p = .508$
B Seroprotection postvaccination	116 (96.7%)	229 (95.0%)	232 (96.3%)	$\chi^2 = 0.72$, $p = .697$
H1N1 Seroconverted	48 (41.4%)	95 (40.3%)	101 (42.8%)	$\chi^2 = 0.31$, $p = .854$
H3N2 Seroconverted	88 (75.9%)	176 (74.6%)	189 (80.1%)	$\chi^2 = 2.14$, $p = .343$
B Seroconverted	19 (16.4%)	42 (17.8%)	48 (20.3%)	$\chi^2 = 0.95$, $p = .622$

Note. Prevaccination usual care $n = 121$; standardized intervention $n = 257$, choice intervention $n = 259$. Postvaccination usual care $n = 120$; standardized intervention $n = 241$, choice intervention $n = 241$. HAI = hemagglutination–inhibition antibody.

responses to vaccination (e.g., informal caregivers), may be a better model and provide greater insight to the effectiveness of brief positive mood interventions as vaccine adjuvants.

Beyond the issue of effectiveness, many questions remain to be answered in relation to understanding the optimal design of a nonpharmacological vaccine adjuvant that go beyond the scope of the present trial. In particular, we note there is a lack of robust evidence relating to the ideal timing of such interventions, their length, and the impact these factors have on immune function. For example, careful mechanistic work could explore where there may be timepoints, in the cascade of immune responses that follow vaccination, where interventions (pharmacological or nonpharmacological) that optimize the functioning of the host immune environment may be particularly biologically relevant. Further, future research should explore whether there is a "minimum" length of such an intervention and/or whether longer interventions could potentially be more potent if they result in longer-lasting effects on immunity. With all these possibilities, it will be important for researchers to remember to balance any effects with the practical restraints of delivering such an intervention around vaccinations administered in primary care which may necessitate innovative and novel approaches.

Limitations and Strengths

The present study is the largest randomized controlled trial to date examining the effects of a potential psychological adjuvant administered at the point of influenza vaccination, or indeed any vaccination. We employed multiple measures of state affect and immune assays for measuring antibody responses, to give greater confidence in our findings. The study design was rigorous and controlled, and attrition across the study was low.

We acknowledge several limitations in this study, which should be considered when interpreting the findings. First, while the comparator group in this trial was as close an approximation of usual care as was feasible, the experiences of control participants did differ in some significant ways from true usual care, such as in the completion of questionnaires and interaction with researchers and other participants in their group. This is underlined by the fact we saw increases in positive mood in the usual care arm, albeit significantly less so than in control arms, despite receiving no intervention. Next, while attempts were made to ensure participants were representative of a typical older adult cohort by minimizing exclusion criteria, it is important to note our sample was self-selected, and therefore may not be entirely representative of this population. One stark example of this is that despite recruiting from several sites with high levels of ethnic diversity, participants who agreed to participate in the trial almost exclusively identified their ethnicity as White-British. Further, it is reasonable to assume that our sample is more representative of "healthy ambulatory older adults" than all older adults as requirements for the study to attend their local GP practice for vaccination may have prevented the frailest and/or housebound patients from participating. As such, extrapolation of these results beyond this population should be treated with due caution.

It is also important to highlight that the present trial only focused on antibody responses at 4 weeks postvaccination—reflecting the peak for serum antibody response to influenza vaccination in older adults (Gross et al., 1996). It therefore cannot contribute to the existing evidence base relating to the impact of psychobehavioral factors (and/or psychological adjuvants) on cellular immunity (Kohut et al., 2002) or indeed waning vaccine immunity (e.g., Ayling et al., 2018; Phillips et al., 2005; Pressman et al., 2005), a topic that may be of increasing interest in the wake of the COVID-19 pandemic.

In sum, this trial has demonstrated that a brief digital intervention delivered prior to vaccination is effective in enhancing positive mood and feasible to deliver within routine care. Beyond the current context of vaccinations, there may be other clinical or nonclinical environments in which such mood improvements may be desirable (e.g., for patients about to undergo surgery or other research studies), and we have, therefore, made our materials freely available for other researchers to use (https://bit.ly/3tGPWl4). Future directions should include examining intervention effects on populations screened for low mood (e.g., informal caregivers) or at particular risk of impaired responses to vaccination (e.g., people on immunosuppressant therapies) and include a focus on mechanistic pathways as well as impacts on both short and long-term antibody and cellular immunity.

References

Awate, S., Babiuk, L. A., & Mutwiri, G. (2013). Mechanisms of action of adjuvants. *Frontiers in Immunology*, *4*, Article 114. https://doi.org/10.3389/fimmu.2013.00114

Ayling, K., Fairclough, L., Buchanan, H., Wetherell, M. A., & Vedhara, K. (2019). Mood and influenza vaccination in older adults: A randomized controlled trial. *Health Psychology: Official Journal of the Division of Health Psychology, American Psychological Association*, *38*(11), 984–996. https://doi.org/10.1037/hea0000786

Ayling, K., Fairclough, L., Tighe, P., Todd, I., Halliday, V., Garibaldi, J., & Royal, S. (2018). Positive mood on the day of influenza vaccination predicts vaccine effectiveness: A prospective observational cohort study.

Brain, Behavior, and Immunity, *67*, 314–323. https://doi.org/10.1016/j.bbi.2017.09.008

Ayling, K., Sunger, K., & Vedhara, K. (2020). Effects of brief mood-improving interventions on immunity: A systematic review and meta-analysis. *Psychosomatic Medicine*, *82*(1), 10–28. https://doi.org/10.1097/PSY.0000000000000760

Barrows, P. D., & Thomas, S. A. (2018). Assessment of mood in aphasia following stroke: Validation of the Dynamic Visual Analogue Mood Scales (D-VAMS). *Clinical Rehabilitation*, *32*(1), 94–102. https://doi.org/10.1177/0269215517714590

Betella, A., & Verschure, P. F. M. J. (2016). The Affective Slider: A Digital Self-Assessment Scale for the measurement of human emotions. *PLoS One*, *11*(2), Article e0148037. https://doi.org/10.1371/journal.pone.0148037

Calder, P. C. (2020). Nutrition, immunity and COVID-19. *BMJ Nutrition, Prevention & Health*, *3*(1), 74–92. https://doi.org/10.1136/bmjnph-2020-000085

Carlisle, S., Ayling, K., Jia, R., Buchanan, H., & Vedhara, K. (2021). The effect of choice interventions on retention-related, behavioural and mood outcomes: A systematic review with meta-analysis. *Health Psychology Review*, *16*(2), 220–256. https://doi.org/10.1080/17437199.2021.1962386

Centres for Disease Control and Prevention. (2021, October 4). *Estimated flu-related illnesses, medical visits, hospitalizations, and deaths in the United States—2017–2018 flu season*. www.cdc.gov/flu/about/burden/2017-2018.htm

Chen, W. H., Kozlovsky, B. F., Effros, R. B., Grubeck-Loebenstein, B., Edelman, R., & Sztein, M. B. (2009). Vaccination in the elderly: An immunological perspective. *Trends in Immunology*, *30*(7), 351–359. https://doi.org/10.1016/j.it.2009.05.002

Cohen, S. (1988). Perceived stress in a probability sample of the United States. In S. Spacapan, & S. Oskamp (Eds.), *The social psychology of health* (pp. 31–67). Sage Publications.

Coleman, B. L., Sanderson, R., Haag, M. D. M., & McGovern, I. (2021). Effectiveness of the MF59-adjuvanted trivalent or quadrivalent seasonal influenza vaccine among adults 65 years of age or older, a systematic review and meta-analysis. *Influenza and Other Respiratory Viruses*, *15*(6), 813–823. https://doi.org/10.1111/irv.12871

Cromer, D., van Hoek, A. J., Jit, M., Edmunds, W. J., Fleming, D., & Miller, E. (2014). The burden of influenza in England by age and clinical risk group: A statistical analysis to inform vaccine policy. *Journal of Infection*, *68*(4), 363–371. https://doi.org/10.1016/j.jinf.2013.11.013

De Gregorio, E., Caproni, E., & Ulmer, J. (2013). Vaccine adjuvants: Mode of action. *Frontiers in Immunology*, *4*, Article 214. https://doi.org/10.3389/fimmu.2013.00214

Diener, E., Wirtz, D., Biswas-Diener, R., Tov, W., Kim-Prieto, C., Choi, D., & Oishi, S. (2009). New measures of well-being. In E. Diener (Ed.), *Assessing well-being: The collected works of Ed Diener* (pp. 247–266). Springer Netherlands. https://doi.org/10.1007/978-90-481-2354-4_12

Goodwin, K., Viboud, C., & Simonsen, L. (2006). Antibody response to influenza vaccination in the elderly: A quantitative review. *Vaccine*, *24*(8), 1159–1169. https://doi.org/10.1016/j.vaccine.2005.08.105

Gross, P. A., Russo, C., Teplitzky, M., Dran, S., Cataruozolo, P., & Munk, G. (1996). Time to peak serum antibody response to influenza vaccine in the elderly. *Clinical Diagnostic Laboratory Immunology*, *3*(3), 361–362. https://doi.org/10.1128/cdli.3.3.361-362.1996

Kohut, M. L., Arntson, B. A., Lee, W., Rozeboom, K., Yoon, K.-J., Cunnick, J. E., & McElhaney, J. (2004). Moderate exercise improves antibody response to influenza immunization in older adults. *Vaccine*, *22*(17–18), 2298–2306. https://doi.org/10.1016/j.vaccine.2003.11.023

Kohut, M. L., Cooper, M. M., Nickolaus, M. S., Russell, D. R., & Cunnick, J. E. (2002). Exercise and psychosocial factors modulate immunity to influenza vaccine in elderly individuals. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, *57*(9), M557–M562. https://doi.org/10.1093/gerona/57.9.M557

Lindhiem, O., Bennett, C. B., Trentacosta, C. J., & McLear, C. (2014). Client preferences affect treatment satisfaction, completion, and clinical outcome: A meta-analysis. *Clinical Psychology Review*, *34*(6), 506–517. https://doi.org/10.1016/j.cpr.2014.06.002

Marsland, A., Cohen, S., Rabin, B. S., & Manuck, S. B. (2001). Associations between stress, trait negative affect, acute immune reactivity, and antibody response to hepatitis B injection in healthy young adults. *Health Psychology*, *20*(1), 4–11. https://doi.org/10.1037/0278-6133.20.1.4

Marsland, A., Cohen, S., Rabin, B. S., & Manuck, S. B. (2006). Trait positive affect and antibody response to hepatitis B vaccination. *Brain, Behavior, and Immunity*, *20*(3), 261–269. https://doi.org/10.1016/j.bbi.2005.08.009

Marsland, A., Pressman, S., & Cohen, S. (2007). Positive affect and immune function. In M. Lewis, J. M. Haviland-Jones, & L. F. Barrett (Eds.), *Handbook of positive emotions* (pp. 761–779). Guilford Publications.

Matias, G., Taylor, R. J., Haguinet, F., Schuck-Paim, C., Lustig, R. L., & Fleming, D. M. (2016). Modelling estimates of age-specific influenza-related hospitalisation and mortality in the United Kingdom. *BMC Public Health*, *16*(1), Article 481. https://doi.org/10.1186/s12889-016-3128-4

Office for National Statistics. (2021). *Deaths from influenza only in 2019 and 2020 in the UK—Office for National Statistics*. www.ons.gov.uk/aboutus/transparencyandgovernance/freedomofinformationfoi/deathsfrominfluenzaonlyin2019and2020intheuk

Pascoe, A. R., Fiatarone Singh, M. A., & Edwards, K. M. (2014). The effects of exercise on vaccination responses: A review of chronic and acute exercise interventions in humans. *Brain, Behavior, and Immunity*, *39*, 33–41. https://doi.org/10.1016/j.bbi.2013.10.003

Phillips, A. C., Burns, V. E., Carroll, D., Ring, C., & Drayson, M. (2005). The association between life events, social support, and antibody status following thymus-dependent and thymus-independent vaccinations in healthy young adults. *Brain, Behavior, and Immunity*, *19*(4), 325–333. https://doi.org/10.1016/j.bbi.2004.10.004

Pressman, S. D., & Black, L. L. (2012). Positive emotions and immunity. In S. C. Segerstrom (Ed.), *The Oxford handbook of psychoneuroimmunology* (pp. 92–104). Oxford University Press. https://doi.org/10.1093/oxfordhb/9780195394399.013.0006

Pressman, S. D., Cohen, S., Miller, G. E., Barkin, A., Rabin, B. S., & Treanor, J. J. (2005). Loneliness, social network size, and immune response to influenza vaccination in college freshmen. *Health Psychology*, *24*(3), 297–306. https://doi.org/10.1037/0278-6133.24.3.297

Pressman, S. D., Jenkins, B. N., & Moskowitz, J. T. (2019). Positive affect and health: What do we know and where next should we go? *Annual Review of Psychology*, *70*(1), 627–650. https://doi.org/10.1146/annurev-psych-010418-102955

Rondy, M., El Omeiri, N., Thompson, M. G., Levêque, A., Moren, A., & Sullivan, S. G. (2017). Effectiveness of influenza vaccines in preventing severe influenza illness among adults: A systematic review and meta-analysis of test-negative design case-control studies. *The Journal of Infection*, *75*(5), 381–394. https://doi.org/10.1016/j.jinf.2017.09.010

Segerstrom, S. C., & Miller, G. E. (2004). Psychological stress and the human immune system: A meta-analytic study of 30 years of inquiry. *Psychological Bulletin*, *130*(4), 601–630. https://doi.org/10.1037/0033-2909.130.4.601

Silberman, J. (2007). Positive intervention self-selection: Developing models of what works for whom. *International Coaching Psychology Review*, *2*(1), 70–77. https://doi.org/10.53841/bpsicpr.2007.2.1.70

Spiegel, K., Sheridan, J., & Van Cauter, E. (2002). Effect of sleep deprivation on response to immunization. *JAMA*, *288*(12), 1471–1472. https://doi.org/10.1001/jama.288.12.1469

Stone, A. A., Neale, J. M., Cox, D. S., Napoli, A., Valdimarsdottir, H., & Kennedy-Moore, E. (1994). Daily events are associated with a secretory immune response to an oral antigen in men. *Health Psychology*, *13*(5), 440–446. https://doi.org/10.1037/0278-6133.13.5.440

Thompson, W. W., Shay, D. K., Weintraub, E., Brammer, L., Cox, N., Anderson, L. J., & Fukuda, K. (2003). Mortality associated with influenza

and respiratory syncytial virus in the United States. *JAMA*, *289*(2), 179–186. https://doi.org/10.1001/jama.289.2.179

Vedhara, K., Ayling, K., Sunger, K., Caldwell, D. M., Halliday, V., Fairclough, L., Avery, A., Robles, L., Garibaldi, J., Welton, N. J., & Royal, S. (2019). Psychological interventions as vaccine adjuvants: A systematic review. *Vaccine*, *37*(25), 3255–3266. https://doi.org/10.1016/j.vaccine.2019.04.091

Vedhara, K., Bennett, P. D., Clark, S., Lightman, S. L., Shaw, S., Perks, P., Hunt, M. A., Philip, J. M. D., Tallon, D., Murphy, P. J., Jones, R. W., Wilcock, G. K., & Shanks, N. M. (2003). Enhancement of antibody responses to influenza vaccination in the elderly following a cognitive-behavioural stress management intervention. *Psychotherapy and Psychosomatics*, *72*(5), 245–252. https://doi.org/10.1159/000071895

Ware, J., Keller, S. D., & Kosinski, M. (1995). *SF-12: How to score the SF-12 physical and mental health summary scales*. The Health Institute, New England Medical Center.

Ware, J., Kosinski, M., & Keller, S. D. (1996). A 12-Item Short-Form Health Survey: Construction of scales and preliminary tests of reliability and validity. *Medical Care*, *34*(3), 220–233. https://doi.org/10.1097/00005650-199603000-00003

Watson, D., Clark, L. A., & Tellegen, A. (1988). Development and validation of brief measures of positive and negative affect: The PANAS scales. *Journal of Personality and Social Psychology*, *54*(6), 1063–1070. https://doi.org/10.1037/0022-3514.54.6.1063

Woods, J. A., Keylock, K. T., Lowder, T., Vieira, V. J., Zelkovich, W., Dumich, S., Colantuano, K., Lyons, K., Leifheit, K., Cook, M., Chapman-Novakofski, K., & McAuley, E. (2009). Cardiovascular exercise training extends influenza vaccine seroprotection in sedentary older adults: The immune function intervention trial. *Journal of the American Geriatrics Society*, *57*(12), 2183–2191. https://doi.org/10.1111/j.1532-5415.2009.02563.x

Wright, C. E., Strike, P. C., Brydon, L., & Steptoe, A. (2005). Acute inflammation and negative mood: Mediation by cytokine activation. *Brain, Behavior, and Immunity*, *19*(4), 345–350. https://doi.org/10.1016/j.bbi.2004.10.003

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