Health behaviors are largely not predictive of adverse events following influenza vaccination

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ABSTRACT

Background: Identifying health behaviors associated with adverse events following immunization (AEFI) could identify intervention targets for AEFI prevention.

Methods: University employees receiving an influenza vaccination (n = 1301) completed a series of online surveys for health behaviors including sleep, exercise, dietary intake, and smoking habits, and emotional state (baseline), and for indications of AEFI (three days post-vaccination) and influenza-like illness (ILI) symptoms (fortnightly follow-up for 4 months).

Results: 29.9% of participants reported an AEFI and 46.0% reported experiencing ILI during follow-up. Multivariate logistic regression revealed usual sleep duration was associated with AEFI (odds ratio 1.20, 95% confidence interval 1.03–1.41), increasing with each hour of sleep. ILI was associated with reporting AEFI (1.70, 1.24–2.33), increasing BMI (1.03, 1.00–1.06) and survey response frequency (1.13, 1.04–1.22), and decreased with better usual sleep quality (0.96, 0.92–1.00) and with increasing age (0.98, 0.96–1.00). Sex stratification revealed no significant predictors of AEFI for either sex; in women, experiencing AEFI increased likelihood of ILI (1.88, 1.25–2.85) and in men, survey completion frequency increased ILI likelihood (1.19, 1.05–1.36).

Conclusions: Our study suggests modifying health behaviors would not alter AEFI risk and reactivity may signal weaker immunogenicity but confirmation through objective measures is warranted.

1. Introduction

An adverse event following immunization (AEFI) is an unexpected or undesirable event after vaccination. Prior AEFI experience and even fears of experiencing non-severe AEFIs can hamper uptake [1,2]. Further, a poor vaccination experience can lead to needle fear and noncompliance with medical treatment which could negatively impact other medical care and treatment-seeking behavior [3].

Habitual health behaviors are associated with immune function: regular exercise, for example, can reduce chronic inflammation and infectious disease risk [4]. Health behaviors may also affect vaccination responses [5] and the likelihood of an AEFI. Exercise and regular physical activity, for example, can improve antibody response [6] and several studies have found a reduction in the risk of AEFI with exercise [7–10], although there are conflicting findings [11,12]. Other modifiable behaviors, such as attaining sufficient sleep or nutritional composition, have an impact on the immune system [13] and therefore the potential to impact AEFI risk, but this has yet to be examined. For example, numerous studies have evaluated nutrient intake and effect on antibody response [5] but only one study has examined AEFI risk and dietary intake. That study found people experiencing paresthesia following influenza vaccination were approximately half as likely to regularly consume alcohol [10]. Similarly, there is literature examining sleep and antibody response [5], but to our knowledge no study has evaluated sleep duration or quality as a determinant of AEFI.

The mechanisms leading to AEFI are poorly understood but may involve the stimulation of localized pro-inflammatory mediators and vasodilation, and the activation of nocioceptors and release of cytokines to induce systemic symptoms [14]. Risk factors for AEFI are also poorly understood. There is some evidence that rates of AEFI vary with vaccine formulation [15] and vaccine administration technique [16]. AEFI occurrence may be related to non-modifiable factors of the vaccinee such as sex [15–18], age [18,19] or a history of illness or allergy [10]. Psychological and emotional states have also been associated with vaccine reactogenicity [10] and immunogenicity [20].

A better understanding of who experiences AEFI is important not only in expanding mechanistic investigations but also in direct application by identifying patients potentially needing closer post-vaccination monitoring and could help to
identify who to target with interventions, such as prophylactic anti-pyrogenic administration, to reduce AEFI. Further, were modifiable predictors of AEFI known, then it would be possible to communicate and promote these so that AEFI risk might be reduced.

Therefore, this study explored the effect of health behaviors on the likelihood of experiencing an AEFI in a university employee population offered a free influenza vaccination. Demographics and psychological and emotional states were also considered. Finally, since little is known about the relationship between the initial vaccination response and its effectiveness, a secondary aim of this study was to identify whether experiencing an AEFI was associated with experiencing influenza-like illness (ILI), using ILI as an indicator of vaccine effectiveness.

2. Patients and methods

2.1. Setting and recruitment

Participants were recruited at an employee influenza vaccination clinic held on The University of Sydney main campus over eight workdays in May 2021. Any employee of 18 or more years of age who attended the clinic where the research team was located and who the clinic deemed medically eligible for the Afluria vaccine was eligible for study participation. The study was approved by the University of Sydney Human Research Ethics Committee (2019/711).

2.2. Study procedure

Participants provided written informed consent and then were asked to complete an online survey (baseline) during the clinic’s post-vaccination 15-minute observation window and to complete ten follow-up surveys online. For each follow-up survey, participants were sent a link to report behavior on the day of vaccination (day one post vaccination), experience of AEFI (day three post-vaccination or the first weekday thereafter), or experience of influenza-like illness (fortnightly for a total of 16 weeks’ follow-up). Survey responses were only considered if completed on the day of vaccination (baseline); within two days of vaccination (vaccination day behavior survey); within five days of vaccination (AEFI survey); and within two days of response solicitation (ILI survey). The procedural timeline is indicated in Figure 1 (timeline).

2.3. Measures

The baseline survey included questions on demographics, symptoms of depression and anxiety (using the Depression Anxiety Stress Scales (DASS-21) form) [21], influenza vaccination history, and usual behaviors of sleep duration and quality (six items from the Medical Outcomes Study) [22], physical activity (PA), alcohol, fruit and vegetable intake, and smoking. The survey also asked participants to identify their vaccine administrator (by color-coding administrators) and time of waking that morning and was time-stamped to allow for a circadian timing indicator. On the morning following vaccination, a survey (vaccination day behavior survey) measured three additional potential determinants: moderate to vigorous PA engagement on vaccination day, perceived stress on the day of vaccination (not at all/only a little/to some extent/somewhat/very much), and sleep quality on the night following vaccination (rated from 0 ‘much worse than normal’ to 100 ‘much better than normal’). The AEFI survey asked about experience of an AEFI and, for those reporting reactions, symptom type. The ILI survey was structured similarly, with reports of illness followed by questions around symptom types. Further, participants who reported ILI were also asked whether they had received a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination or been diagnosed with COVID-19 during that fortnight. Supplement 1 contains all survey questions.

2.4. Analysis

2.4.1. Data treatment

2.4.1.1. COVID-19 adjustments. This study began when the State of New South Wales (NSW), Australia had minimal pandemic restrictions (e.g. participants could work unmasked on-campus maintaining 2-m social distancing) and under 5400 confirmed COVID-19 cases had been reported since the pandemic start [23]. NSW was early into its SARS-CoV-2 vaccination rollout: at the time of study baseline less than 5% of the population had been vaccinated but 68% had at least one dose by study end [24]. The state entered a COVID-19 pandemic lockdown (i.e. stay-at-home orders) just after the third fortnightly observation period and this continued through the remainder of the study.

Figure 1. Study timeline. AEFI, adverse event following immunization; ILI, influenza-like illness.
A priori we decided to treat as missing any response of ILI occurring in the same fortnight as a SARS-CoV-2 vaccination due to the high reactogenicity of these vaccines and their AEFI often mimicking influenza symptoms [25], and to exclude as missing any response of COVID-19 diagnosis and further observation points for such an individual. Hence, we removed 514 observations (n = 391 individuals) for SARS-CoV-2 vaccination and two individuals due to COVID-19 diagnoses (one each beginning the fourth and sixth fortnightly observation periods).

2.4.1.2. Variable calculations and categorizations.
Reporting of experiences of AEFI and ILI were dichotomized. Free text responses for AEFI (n = 89) were independently coded by two investigators (KE, EG; 93% initial agreement), and all symptoms were categorized as local (i.e. swelling or pain at injection site) or systemic (e.g. nausea, headaches, or fever). For ILI, the outcome was defined as no ILI experience during the observation period vs at least one occurrence, an approach used elsewhere [26].

Two continuous variables were calculated. Body Mass Index (BMI) was calculated from participant-reported height and weight. The duration between waking up and receiving the vaccination (‘time lag’) was calculated in hours by subtracting waking time from the vaccination time.

Categorical variables were categorized or condensed as follows. Smoking behavior response categories ‘daily’ (1.2%), ‘occasionally’ (3.5%), or ‘have tried a few times’ (2.2%) were collapsed into current smokers; never (57.2%) and former (16.2%) smoking categories were not manipulated. Alcohol consumption frequency responses ‘never’ (11.5%) and ‘monthly or less’ (18.4%) were collapsed to seldom; response categories of monthly (2–4 times/month, 25.3%), weekly (2–3x/week, 28.7%) and frequently (≥4x/week, 15.9%) were not manipulated. Vaccination history was dichotomized according to receipt of previous year’s influenza vaccination (12.2% ‘last year only’ and 75.5% ‘last year and previously’, vs 3.2% ‘never before’ and 9.0%, ‘not in previous year’). Three nurses were identified as administering 80.3% of all vaccines; participants unable to recall which nurse (14.5%) or who identified one of two other nurses (5.3%) were collapsed into ‘other’ (n = 184, 19.8%). Experiencing stress on the day of vaccination was collapsed to some stress (‘only a little’ (34.1%), ‘to some extent’ (13.4%), ‘somewhat’ (7.2%) or ‘very much’ (3.9%)) vs ‘none at all’ (41.5%).

2.4.2. Data analysis
Of the 2403 clinic attendees, 1435 employees consented to participate (55% participation rate), with 1301 providing useable baseline surveys (54.1% overall clinic participation), as shown in Figure 2. Outcome analyses were based on complete cases, resulting in n = 926 for the AEFI analysis and n = 810 for the ILI analysis. Population characteristics for the full n = 1301 participants are presented in Supplement 2, Table S1 (which also includes sub-group comparisons).

[Figure 2, Recruitment and Participation Flow Chart, about here]

2.4.2.1. AEFI. A three-stage approach was used for assessing the relationships between the baseline variables and the outcome of AEFI (n = 926). First, proportional and means tests were conducted using chi-square, student-t-tests or Kruskal-Wallis tests, as appropriate. Second, each variable was independently evaluated using logistic regression on the outcome of interest. Third, any variable with p < 0.2 in the second stage was entered into a multivariate logistic regression model; an exception to this was that the day of vaccination measurements were excluded as these behaviors (exercise, stress, sleep) may have been affected by vaccination experience.

2.4.2.2. ILI. For ILI, there were 810 participants in the sample. A similar three-stage approach was used to address the secondary aim regarding the association between experiencing AEFI and ILI. Demographics were compared and then variables, including behaviors and AEFI, were entered into logistic regression models. Additional variables considered for the ILI outcome multivariate analysis included experiences on the day of vaccination (i.e. day 1 responses) as there is reason to believe these acute behaviors can affect the antibody response [27,28] and therefore could influence ILI experience. Multivariable logistic regression involved complete cases with n = 810. (Supplement 2, Table S1, compares characteristics of these complete cases to the n = 926 in the AEFI analysis and to n = 1301 baseline respondents as well as further sample comparisons.)

2.4.2.3. Sensitivity analyses. Since sex/gender differences in vaccination responses are well-documented [16,29], an a priori decision was made to also conduct sex-stratified analyses on both outcomes. A second analysis explored whether response frequency for the series of ILI surveys had an impact on the ILI outcome, due to the proportion of those either responding intermittently or counted as missing due to SARS-CoV-2 vaccination.

All analyses were conducted in R [30] with alpha set at 0.05; graphics were created with package ggplot2 [31] and time calculations with package lubridate [32].

3. Results
Most staff participating in the study (n = 1023) were women (60.2%), with a mean age of 43 years (range 18.7–73.1 years). A majority of participants abstained from ever smoking (57.2%) or had quit (16.2%). Most reported behaviors did not meet health guidelines: only 9.5% and 45.5% of participants met vegetable and fruit intake recommendations [33], respectively, and only 44.3% were active on most days of the week. However, most (68.4%) participants’ usual sleep duration (median interquartile range (IQR) 7.0 [6.50, 7.50] h/night) fell within recommended ranges for their age [34]. DASS-21 [21] responses were scored as ‘normal’ for depression, anxiety, and stress for a majority (73.8%, 78.5%, and 74.6%, respectively) of participants.

3.1. AEFI
For the AEFI survey, n = 926 (71.2%) respondents provided complete data. These participants are described in Table 1. Of the
complete cases, 29.9% (n = 277) experienced an AEFI, with 71.1% of those with AEFI experiencing local reactions and 61.0% of those with AEFI experiencing a systemic reaction. More women experienced local reactions (76.6% women vs 61.8% men, p = 0.013) but there was no sex difference in systemic reactions (59.4% vs 63.7%, p = 0.56) nor overall AEFI (63.2% vs 57.5%, p = 0.123). Symptoms of depression and anxiety as measured by the DASS-21 subscales were higher among those with AEFI, with higher proportions of those scoring above normal for either anxiety and depression reporting reactions (24.9% vs 18.8%, p = 0.044, and 31.0% vs 22.5%, p = 0.008, respectively); the proportions with symptoms of stress did not differ between AEFI and no AEFI groups (26.0% vs 22.7% p = 0.312).

Univariate modeling showed a positive association between AEFI and DASS-21 scores (odds ratio (OR) 1.02, 95% confidence interval (95%CI) 1.00–1.04) and an inverse one between AEFI and age (OR 0.99, 95%CI 0.97–1.00). Quality of sleep ratings on the night following vaccination were lower when AEFI was reported (OR 0.99, 95%CI 0.98–1.00) but being physically active on the day of vaccination (OR 1.05, 95%CI 0.75–1.48) and perceived stress on that day (OR 1.35, 95%CI 0.96–1.89) were not associated with experiencing AEFI, nor was the time lag (OR 1.01, 95%CI 0.95–1.07). (Univariate modeling is further reported in Supplement 3, Tables S2 and S3.) Multivariate analysis revealed the odds ratio for AEFI increased with increasing usual sleep duration (adjusted OR (aOR) 1.2 for each hour, 95%CI 1.03–1.41). Odds ratios varied between nurses, as shown in Figure 3, but none were significantly different from the reference nurse.

3.2. ILI

Of the 926 AEFI survey respondents, 902 (97.4%) completed at least one ILI survey, with 575 (63.7%) completing at least six usable ILI surveys (categorized as ‘high responders’). Of the 810 complete cases for ILI modeling, 46.0% (n = 373) of participants reported having ILI during the 16-week follow-up period. Age, usual sleep quality, and frequency of physical activity at baseline were lower among those who reported experiencing ILI while DASS-21 scores were higher, as shown in Table 2. Higher proportions of those experiencing ILI also reported experiencing any AEFI, a systemic or a local AEFI. Among those reporting ILI, the most common ILI symptoms were related to blocked or runny nose (n = 695 incidences), sore throat (n = 495 incidences) or tiredness (n = 425 incidences).

Univariate modeling showed positive associations between reporting ILI and DASS-21 scores (OR 1.02, 95%CI 1.00–1.04)
Table 1. Participant characteristics: AEFI analysis (n = 926).

|                              | no AEFI reported | AEFI reported | p     |
|------------------------------|------------------|---------------|-------|
| N (%)                        | 649 (70.1)       | 277 (29.9)    | 0.123 |
| Women, n (%)                 | 373 (57.5)       | 175 (63.2)    | 0.041 |
| Age in years, mean (SD)      | 43.0 (11.28)     | 41.3 (11.39)  | 0.429 |
| BMI (kg/m²), median [IQR]    | 24.4 [21.97, 27.64] | 23.7 [21.94, 27.14] | 0.221 |
| Physical activity frequency (d/w), mean (SD) | 3.4 (2.02) | 3.2 (1.97) | 0.351 |
| Fruit servings/d, median [IQR] | 1.0 [1.00, 2.00] | 1.0 [1.00, 2.00] | 0.0802 |
| Vegetable servings/d, median [IQR] | 2.0 [1.50, 3.00] | 2.0 [1.50, 3.00] | 0.006 |
| Frequency of alcohol consumption, n (%) | 0.802 |
| Seldom                       | 194 (29.9)       | 81 (29.2)     | 0.565 |
| Monthly                      | 156 (24.0)       | 75 (27.1)     |       |
| Weekly                       | 189 (29.1)       | 76 (27.4)     | 0.221 |
| Frequently                   | 110 (16.9)       | 45 (16.2)     | 0.497 |
| Smoking, n (%)               | 369 (56.9)       | 164 (59.2)    |       |
| Never                        | 112 (17.3)       | 40 (14.4)     |       |
| Former                       | 168 (25.9)       | 73 (26.4)     |       |
| Usual sleep quality, median [IQR] | 28.0 [25.00, 31.00] | 28.0 [25.00, 30.00] | 0.171 |
| Usual sleep duration, median [IQR] | 7.0 [6.50, 7.50] | 7.0 [6.50, 8.00] | 0.033 |
| DASS-21, median [IQR]        | 8.0 [4.00, 14.00] | 10.0 [5.00, 16.00] | 0.006 |
| Influenza vaccination received in prior year, n (%) | 0.746 |
| Day of vaccination           | 569 (87.7%)      | 240 (86.6%)   |       |
| Time lag (h) from waking until vaccination, mean (SD) | 5.8 (2.28) | 5.8 (2.31) | 0.739 |
| Nurse, n (%)                 | 112 (17.3)       | 40 (14.4)     | 0.180 |
| Nurse 1                      | 273 (42.1)       | 132 (47.7)    |       |
| Nurse 2                      | 73 (11.2)        | 25 (9.0)      |       |
| Nurse 3                      | 178 (27.4)       | 61 (22.0)     |       |
| Other                        | 125 (19.3)       | 59 (21.3)     |       |
| Physically active on the day, n (%) | 0.855 |
| Perceived some stress on the day, n (%) | 0.100 |
| Acute sleep quality (0–100 scale, mean (SD)) | 61.8 (20.39) | 58.5 (20.14) | 0.033 |

Square brackets indicate interquartile range (IQR) and parentheses indicate standard deviation (SD) or percentage. AEFI, adverse event following immunization; BMI, body mass index; DASS-21, depression, anxiety and stress scale.

Figure 3. Adjusted odds ratio for experiencing AEFI. Reference categories were nurse (1) and sex (male). N = 926, R² = 0.023. AEFI, adverse event following immunization; BMI, body mass index; DASS-21, depression, anxiety and stress scale; PA, physical activity.
and experiencingILI and AEFIs (OR 1.75, 95%CI 1.29–2.38). There were inverse relationships between AEFIs and age (OR 0.97, 95%CI 0.96–0.98), physical activity (OR 0.91, 95%CI 0.85–0.97) and usual sleep quality (OR 0.96, 95%CI 0.93–0.99). Other baseline factors were not associated, e.g. the time lag OR was 0.98, 95%CI 0.93–1.04. Experiencing either a systemic AEFI or a local AEFI was positively associated with ILI (OR 1.70, 95%CI 1.19–2.45 and OR 1.72, 95%CI 1.23–2.42, respectively). (Univariate modeling is further reported in Supplement 3, Tables S4 and S5.)

Multivariate modeling revealed several significant predictors, as shown in Figure 4. Odds ratios for experiencing ILI were lower with greater age (aOR 0.98 95%CI 0.96–1.00) and displayed an age × sex interaction effect (aOR 0.97 women relative to men, 95%CI 0.95–1.00) such that the age effect on lowering odds was more pronounced in women. Odds ratios for experiencing ILI also decreased with increasing usual sleep quality (aOR 0.96, 95%CI 0.92–1.00) and tended to do so with more frequent physical activity (aOR 0.93, 95%CI 0.86–1.00). Odds ratios for ILI were higher with increasing BMI (aOR 1.03, 95%CI 1.00–1.06), with experiencing an AEFI (aOR 1.7, 95%CI 1.24–2.33), and with the frequency of ILI survey responding (aOR 1.13, 95%CI 1.04–1.22).

### 3.3. Sensitivity analyses

#### 3.3.1. Sex stratification ILI survey response frequency

Stratification by sex revealed different potential predictors for AEFI in multivariate modeling. In women PA, alcohol consumption, sleep duration, nurse and age were entered into the model whereas in men DASS-21, usual sleep duration × usual sleep quality interaction and age were entered. However, no significant predictors emerged for either sex. Sex stratified analyses are shown in Supplement 3, Table S2.

Sex stratification for ILI revealed increasing age lowered odds for ILI in both sexes (aOR 0.96, 95%CI 0.94–0.98 and aOR 0.98, 95%CI 0.96–1.00 for women and men, respectively). In women, OR for ILI were also determined by AEFI experience relative to not experiencing an AEFI (aOR 1.88, 95%CI 1.25–2.85) while in men the OR increased with each ILI survey completed (aOR 1.19, 95%CI 1.05–1.36). Full results are shown in Supplement 3, Table S4.

#### 3.3.2. ILI survey response frequency

In a sensitivity analysis, we explored whether response frequency had an impact on predictors of ILI. This analysis was limited to n = 537 high responders who had completed at least six usable ILI surveys. This restricted model displayed two
predictors for experiencing ILI which also appeared in the main model: the sex × age interaction (aOR 0.97 95% CI 0.94–1.00) and experiencing an AEFI (aOR 1.67 95% CI 1.12–2.49). Predictors which did not reach statistical significance had the same direction of effect as in the main model (i.e. age, usual sleep quality, PA frequency, and alcohol consumption) or were not formerly present (i.e. fruit consumption and nurse). The restricted model further differed by not containing predictors BMI or stress on the day of vaccination. Full details of the sensitivity analysis are presented in Supplement 2, Table S4.

4. Discussion

This study explored the association of health behaviors with the likelihood of experiencing an AEFI and subsequent ILI. Understanding these relationships is important because experiencing an AEFI can negatively affect vaccine uptake [1,2], a problem particularly relevant during a pandemic. We found predictors of solicited AEFI and ILI were not the same. Experiencing an AEFI appears largely unmodifiable through behavior, with the exception of the positive association with longer usual sleep duration. Reporting experience of an AEFI was associated with subsequently experiencing ILI; higher BMI and poorer usual sleep quality were also associated with ILI. The majority of findings were the same when analyzed separately by sex, but we did find a strong association between solicited AEFI and ILI experiences in women and reporting frequency and ILI experience in men. While these sex-stratified results need to be interpreted with caution due to the reduced sample size in the analysis and may reflect gender differences in reporting, sex differences in vaccine responses have been demonstrated previously [29] and these results may provide avenues for further research.

Although we expected to find decreased AEFI risk with exercise and increased AEFI risk with stress and depressive symptoms given prior evidence has suggested these patterns [7–10], the only behavior we found associated with AEFI was usual sleep duration. The likelihood of experiencing AEFI, with control for both mental state and sleep quality, increased with each hour of sleep duration. We also tested and confirmed the sleep duration and AEFI risk relationship was linear and not U-shaped (Supplement 3), as a U-shaped relationship between sleep duration and health has been proposed [35]. Thus, although our results imply reducing sleep duration could reduce the risk of AEFI, we caution such interpretation. We did not use a validated measure of sleep duration and the difference between groups in sleep duration, while significant, may not be clinically meaningful. With no comparative evidence, it is difficult to determine whether our finding could be a Type 1 error. Finally, much literature supports negative health outcomes, including impaired immunity, from sleep deficits [13] and therefore the potential for increased likelihood of AEFI may be a preferred health outcome to other negative health effects from sleep deprivation.

Although there is evidence of improved antibody response with longer usual sleep duration [36], antibody maintenance does not appear linked to baseline sleep duration [37,38]. This could explain why we did not observe a relationship between
sleep duration and experiencing ILI. We did, however, observe that improved increasing sleep quality predicted lower odds for experiencing ILI, similar to previous findings [39,40]. Because sleep quality and duration are linked [41], we also tested whether a sleep quality \times duration interaction effect existed for either AEFI or ILI and found none (shown in Supplement 3, Tables S2 and S4).

We also used the time lag variable (hours between waking and vaccination) as an indicator of circadian timing. Despite expectations for increased reactogenicity with longer lags [42] and increased effectiveness with shorter lags as higher antibody responses have been demonstrated with morning vaccination [43], the time lag was not associated with either outcome (Supplement 3, Tables S2 and S4) in agreement with a recent study finding no time of day association with reactogenicity to influenza vaccination [18].

A secondary and novel aim of our study was to determine whether reporting AEFI experience was associated with ILI. Experiencing an AEFI increased the odds ratio for experiencing ILI, suggesting a reactogenic experience may indicate lower effectiveness. This association was confirmed in a sensitivity analysis restricted to the 537 respondents with at least six (of eight) usable ILI surveys. This may reflect a bias in that those experiencing AEFI are then also more likely to report ILI [44]. The literature demonstrates the reporting of drug reactions differs by sex, and these differences are both drug-specific and symptom-specific [45]; further, racial differences in reporting acute pain may be a reflection of socio-economic, and not biologic, factors [46]. Thus, it is possible that reporting biases could contribute to the observed association between AEFI and ILI. This potential reporting bias makes collection of objective data important to confirm the association between these vaccination responses. To our knowledge, only one other study has investigated reactogenicity as a predictor of either effectiveness or immunogenicity in influenza vaccines, finding older adults (>65 years) who reported fever had a higher H1N1 response than those who did not but reporting injection site redness was associated with lower H3N2 response [47]. Recent studies using SARS-CoV-2 vaccines do not reach consensus on the association between reactogenicity and immunogenicity but do suggest that certain systemic reactions could predict antibody response [48–50]. In contrast, we found experiencing either systemic or local reactions alone to predict ILI (Supplement 3, Table S5) which suggests reduced immunogenicity followed a reactogenic response. Currently, some public health messages addressing concerns around vaccine safety state that side effects indicate vaccine effectiveness (e.g. [51]). Our findings suggest the association between experiencing an AEFI and vaccine effectiveness may not necessarily be a positive one and public health messaging around influenza vaccination safety and effectiveness may need reexamining. Our findings also underscore the need for future exploration regarding the association between reactogenicity, immunogenicity, and effectiveness across the lifespan and with different vaccines; such exploration might first address reporting biases as these have been identified whereas biological mechanisms have not yet been proposed.

The observed tendencies for higher risk of AEFI and ILI in women compared to men are consistent with the literature [17,52] and together with the observed differences in behaviors and demographics associated with immune outcomes emphasize the need for sex- and gender- considerations in vaccination studies, as previously identified [16]. Our results suggest women may be more reactogenic yet experience less effectiveness, while other work has shown reactogenic men have higher immunogenicity [48]. A sex difference in contagion exposure could explain the difference in ILI but seems unlikely as numerous studies show women are more likely to practice handwashing and other hygiene measures [53,54]; however, women are predominant in people-facing jobs (e.g. child-care) which may increase exposure [55]. We observed an inverse association between age and ILI, with the same direction of effect for AEFI. This appears to contradict immunosenescence literature, but we note our sample is comparatively young, comprising only 10 participants ≥65 years old and a median age of 41. An age difference in contagion exposure could also contribute to the observed relationship between age and ILI; recent literature in similarly aged persons is not conclusive as to age as a factor in contagion prevention [56,57]. Other observed associations were consistent with the literature. For example, a positive association between BMI and ILI has been reported previously [58].

4.1. Strengths and limitations

This study encompasses a broad range of measures that smaller studies have implicated as having a potential role in vaccination immunogenicity and uses a large sample for analysis. It is novel in documenting an association between vaccine reactogenicity and effectiveness. However, some limitations need acknowledgment. First, the use of subjective measures, some of which were not validated, may bias the results, e.g. another study reported that the incidence of objectively measured fever was lower than that of feeling feverish following SARS-CoV-2 immunization [19]. Secondly, the generalizability may be limited due to differences in populations (for example, sleep duration was higher in the analyzed sample than among other baseline respondents) and reporting biases. The active surveillance of AEFI can yield higher rates than passive surveillance [59] and AEFI and behavior reporting may be subject to a number of biases [44,60]. Extensive analyses with sub-populations based on data availability generally observed the same direction of effect from predictors for both AEFI and ILI outcomes, but the potential for inflated effect sizes due to associations from healthier people responding to follow-up surveys remains. The ongoing pandemic also presents limitations: vaccine roll-out decreased the available follow-up data, while the associated lockdown likely decreased potential influenza exposure relative to other influenza seasons, thus again potentially reducing generalizability and introducing confounding. Repeating the experiment without pandemic conditions would likely increase exposure and therefore might increase ILI-predictor variable effects.

5. Conclusions

Our study suggests modifying health behaviors is not a potential avenue for decreasing the likelihood of influenza
vaccine AEFI: although we observed the likelihood of AEFI increases with each hour sleep duration, short sleep duration is associated with health risks and therefore at this stage, we cannot recommend restricting sleep duration in order to mitigate vaccine side-effects. The finding that most health behaviors do not alter likelihood of AEFI may be a positive finding as it suggests there is no need for behavior change prior to vaccination, removing what might have been a potential barrier to vaccination. We found reactogenicity predicted ILL in contradiction of current literature and supporting the need for future investigation in associations between reactogenicity and immunogenicity. Use of objective measures, such as thermometer-measured fever, antibody response and influenza diagnosis, could confirm our findings.

Funding
This paper was not funded.

Declaration of interest
The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or material discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures
A reviewer on this manuscript has disclosed that they have received/receive investigator initiated grant funding form Sanofi and Merck.

Data availability
The data that support the findings of this study are available on request from the corresponding author.

Author contributions
E Goldbaum and KM Edwards co-conceived and co-designed the study; E Goldbaum acquired data; E Goldbaum and YS Bin led the analysis and, with authors R Booy and KM Edwards, the interpretation of data. E Goldbaum drafted the article, and all authors critically revised it for intellectual content before approving the final version for submission.

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