Seasonal Differences In Disease Risk Are Not Reflected In Seasonal Variability In Immune Fitness

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KEYWORDS
Immune fitness; immunity; disease risk; infection; common cold, hay fever

ABSTRACT
There is seasonal variability in the incidence of immune-related diseases among the general population. Data from two studies was evaluated to determine whether or not this seasonal variability is also present for ratings of immune fitness, i.e., the capacity of the body to respond to health challenges (such as infections) by activating an appropriate immune response, essential to maintain health, prevent and resolve disease, and improve quality of life. The first study comprises a between group comparison of participants that rated their past month's immune fitness either in winter, spring or summer. The second longitudinal study comprised a within-subject comparison of participants that rated their momentary immune fitness two times in autumn, and subsequently in winter and summer. Both studies did not include any intervention. The analyses revealed no significant differences in immune fitness across the seasons. In conclusion, the impact of health challenges (e.g., the presence of rhinovirus or a greater pollen count) differs between seasons, and thereby can increase the chances of getting sick (e.g., common cold in winter or allergic rhinitis in spring). However, the data from the two studies presented here suggest that immune fitness does not vary across the seasons.

Conflicts of Interest: Over the past 3 years, J.V. has received research support from Danone and Inbiose and acted as a consultant/advisor for Eisai, KNMP, Med Solutions, Mozand, Red Bull, Sen-Jam Pharmaceutical, and Toast!. J.V. owns stock from Sen-Jam Pharmaceutical. J.V., E.I., and D.D. received travel support from Sen-Jam Pharmaceutical. P.K. is CEO of PanGenix. Over the past 36 months, A.S. has acted as a consultant/expert advisor to Bayer, Coca Cola, Danone, Delica Therapeutics, GlaxoSmithKline, Naturex, Nestlé, McCormick, Metavate Consultancy, PepsiCo, Pfizer, Pharmavite, REVIV, Sanofi, and Verdure Sciences and has held research grants from Abbott Nutrition, Arla Foods, the Australian Research Council, Bayer, DuPont, Fonterra, GlaxoSmithKline, the High Value Nutrition Fund, the National Health and Medical Research Council, Nutricia-Danone, Sanofi. A.S. is Chief Scientific Officer for Ārepa Nootropics and is on the Scientific Advisory Board of Sen-Jam Pharmaceutical. S.B. has received funding from Red Bull GmbH, Kemin Foods, Sanofi Aventis, Phoenix Pharmaceutical, BioRevive, Australian Government Innovations Scheme and GlaxoSmithKline. J.G. is part-time employee of Nutricia Danone and received research grants from Nutricia research foundation, Top Institute Pharma, Top Institute Food and Nutrition, GSK, STW, NWO, Friesland Campina, CCC, Raak-Pro, and EU. L.D. has nothing to declare.

Introduction

There is seasonal variability in the incidence of immune-related diseases among the general population (Dowell, 2001; Grassly and Fraser, 2006). For example, infection rates for the common cold and flu are usually higher in autumn and winter compared to the summer season (Berginc *et al*., 2024). Alternatively, seasonal allergic rhinitis is more commonly reported with higher temperatures in spring and summer compared to the winter months (Schreurs *et al*., 2022).

Thus, the seasonal variation in disease incidence is related to increased presence of related pathogens such as viruses (i.e., virulence). Seasonal factors impacting virulence include temperature, humidity, and sunlight exposure. In relation, human behavior can significantly contribute to the risk of acquiring a disease. For example, in winter people spend more time indoors in sometime poorly ventilated crowded areas (e.g., travel to work by bus instead of the bicycle). These seasonal behavioral adaptations increase the chances of acquiring communicable diseases such as the common cold or the 2019 coronavirus disease (Ahmadzadeh *et al*., 2021). Alternatively, when temperatures rise in spring and summer people spend more time outdoors. At the same time, pollen counts are increased, and in line the chances of experiencing allergic rhinitis are greater.

The question arises whether seasonal variations in disease prevalence are also related to a variation in immune fitness across the seasons. Immune fitness can be defined as the capacity of the body to respond to health challenges (such as infections) by activating an appropriate immune response, essential to maintain health, prevent and resolve disease, and improve quality of life (Verster *et al*., 2022). Becoming sick is associated with reporting reduced immune fitness. There are various factors that determine self-reported immune fitness, including the type and frequency of occurrence of immune related complaints, their duration and severity, and impact on daily activities (Verster *et al*., 2022, Verster *et al*., 2023a). To capture these different elements into one global measure of immune fitness, often a single-item immune fitness scale is used, ranging from 0 (very poor) to 10 (excellent) (Verster *et al*., 2022) (See Figure 1). The single-item assessment of immune fitness can be conducted for either momentary assessments (i.e., 'at this moment') or retrospectively (e.g., 'for the past month').

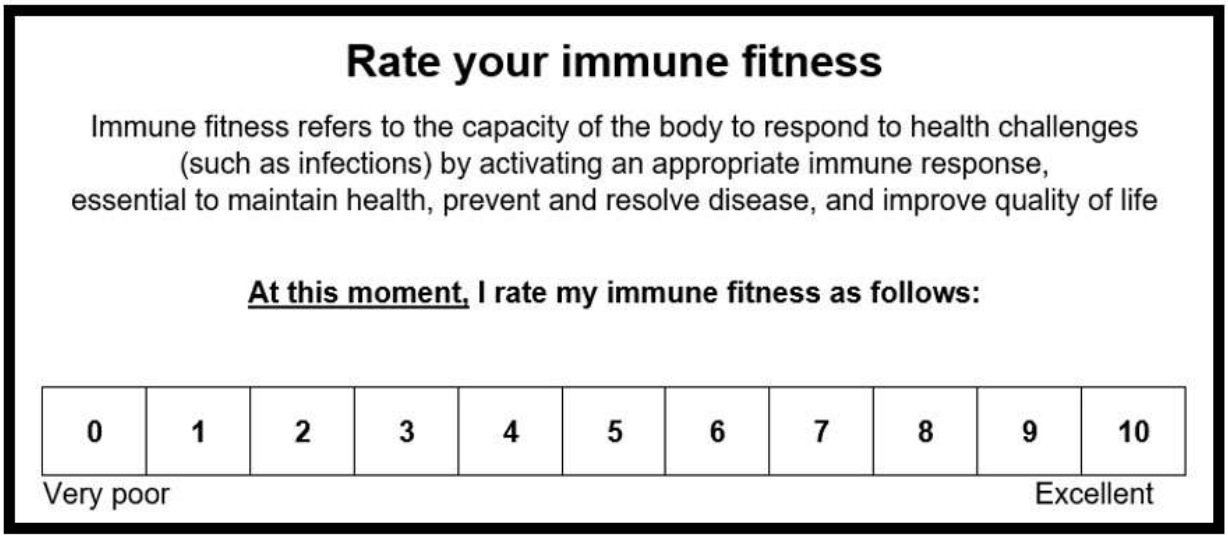

Figure 1. The single-item scale to assess immune fitness.

As the disease prevalence and virulence vary across seasons, it can be argued that this should also be the case for perceived health and immune fitness. Seasonal effects have been observed in the levels of immune function biomarkers in blood (Nelson and Demos, 1996; Fares, 2013) and hormone levels (Kuzmenko *et al*., 2021). In this context, research has suggested that the immune system is weakened during the cold seasons, i.e. winter (Maes *et al*., 1994; Altizer *et al*., 2006) and strengthened in warmer periods, i.e. summer (Dowell, 2001; Khoo *et al*. 2011). In a longitudinal study in 56 human subjects, Ter Horst *et al*., (2021) found significant seasonal effects in levels of immune biomarkers in blood, including higher concentrations in winter for IL-18, IL-18P, resistin, and $\alpha 1$ antitrypsin. Although not consistently, cytokine production capacity after stimulation with the influenza virus, Borrelia burgdorferi, and Escherichia coli also differed between the seasons. Of note, for several of the assessed biomarkers no seasonal effects were observed.

It is important to note that these studies based their conclusions on observed changes in blood concentrations of immune biomarkers of systemic inflammation (e.g., cytokines). However, although these biomarkers are important indicators of the immune system function, they do not fully cover the concept of immune fitness (Verster *et al*., 2022; Verster *et al*., 2023a). For example, biomarker changes may remain unnoticed by individuals and as such do not influence their perception of health and immune fitness. Further, reduced immune fitness can also be experienced when biomarkers of immune functioning remain within the normal range (Verster *et al*., 2022; Verster *et al*., 2023a). Previous research that directly compared saliva immune biomarker concentrations with immune fitness ratings found only modest correlations, and most of them did not reach statistical significance (Mulder *et al*., 2023). Therefore, while biomarkers assessments are important, they do not adequately represent the concept of immune fitness as perceived by individuals.
Immune fitness is thus a critical yet underexplored dimension that reflects an individual's subjective experience of their of their immune system's functioning and is influences how they cope with seasonal diseases (Verster *et al*., 2022). Higher self-reported immune fitness is linked to greater resistance to infections and faster recovery as individuals feel physically and mentally equipped to combat illness (Dhabhar, 2014; Nieman and Wentz, 2019). A positive perception may also encourage healthier behaviors—such as increased physical activity or better stress management, which further supports recovery (Walsh *et al*., 2011). Conversely, low perceived immune fitness can prolong symptoms by undermining confidence in recovery (Cohen *et al*., 2006). Up to now it remains to be determined whether or not immune fitness varies across the seasons.
Here we present data from two studies that investigated immune fitness across the different seasons. The first study comprises a between group comparison of participants that rated their past month's immune fitness either in winter, spring or summer. The second longitudinal study comprised a within-subject comparison of participants that rated their momentary immune fitness two times in autumn, and subsequently in winter and summer. As no interventions were included in the two studies, it was hypothesized that immune fitness scores remained stable across the seasons.

Methods

3.1. Study 1. UK and Ireland

A cross-sectional online survey was conducted among UK and Irish adults following a psychology course at the Open University. Participants were invited via the Open University's participant pool management software (SONA systems, https://www.sona-systems.com) and completed online via Qualtrics. The study was approved by The Open University Human Research Ethics Committee (HREC) (approval code: HREC/4628) and electronic informed consent was obtained from all participants.
As part of the survey, the past month's immune fitness was assessed with a single-item scale, ranging from 0 (very poor) to 10 (excellent) (Verster *et al*., 2022; Verster *et al*., 2023). In addition to demographics (sex, age, height, and weight), single item assessments were made for past month's quality of life (Verster *et al*. 2024) and past month's mood, including stress, anxiety, depression, worry, shyness, fatigue, loneliness, hostility, and happiness (Verster *et al*., 2021).
Statistical analyses were conducted with SPSS (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 30.0. Armonk, NY: IBM Corp.). Mean and standard deviation (SD) were computed for each variable. The survey was completed between February and July 2024, covering immune fitness ratings from January to June of 2024. According to the completion date, subjects were allocated to one of three groups: winter (January – February 2024), spring (March – May 2024), and summer (June 2024). Data from the three groups (winter, autumn, and summer) were compared with the Independent Samples Kruskal Wallis Test. Percentual data was compared with the Chi-Squared test. Differences between the groups were considered significant, after Bonferroni's correction, if $p < 0.025$.

3.2. Study 2: Australia

A prospective study was conducted among Australian adults aged 16 years and older. Participants were recruited via advertisement, and the survey was completed online via SurveyMonkey. The study was approved by the Swinburne's Human Research Ethics Committee (SUHREC) (Approval number: 2018/319), and conducted in line with the Australian National Statement on Ethical Conduct in Human Research.
In 2020, participants were invited to complete 4 online surveys assessing 'psychological health and well-being during the COVID-19 situation'. The first three surveys were four weeks apart, April 2020 (T1, Autumn), May 2020 (T2, Autumn), June 2020 (T3, Winter) of 2020, and December 2020 (T4, Summer).

As part of the survey, momentary immune fitness was assessed with a single-item scale, ranging from 0 (very bad) to 10 (very good) (Verster *et al*., 2022; Verster *et al*., 2023). A definition of immune fitness was provided to aid the understanding of participants. The 21-item Depression Anxiety Stress Scale (DASS-21) was completed to assess depression, anxiety, and stress (Henry *et al*. 2005). Each item is rated on a scale from 0 ("Did not apply to me at all") to 3 ("Applied to me very much or most of the time"). The sum scores for the subscales are calculated and multiplied by 2, with higher sum scores implying greater symptoms severity. The Brief Resilience Scale (BRS) (Smith *et al*., 2008) was completed to evaluate perceived ability to recover from stress or the ability to bounce back, i.e. mental resilience. The BRS comprises 6 items rated on a scale from 1 ("Strongly disagree") to 5 ("Strongly agree"), of which 3 items are reverse scored. Sum scores range from 0 to 30. A higher sum score of 6-items implies a higher level of mental resilience. Loneliness was assessed with the 3-item Loneliness Scale (Hughes *et al*., 2004), assessing the dimensions relational connectedness, social connectedness, and self-perceived isolation. Items are rated on 3-point scales: 1 = hardly ever; 2 = some of the time; and 3 = often. The loneliness sum score ranges from 0 to 9, with higher scores implying greater loneliness. Statistical analyses were conducted with SPSS (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 30.0. Armonk, NY: IBM Corp.). Within-subject comparisons of the four assessments over time were made with the related samples Friedman's two-way analysis of variance by rank test. A Bonferroni's correction was applied, and differences were considered significant if $p < 0.017$.

Results

3.1. UK and Ireland: between-group comparison

A total of n = 1178 subjects participated in the study (85.7% female). The mean (SD) immune fitness ratings for the winter, spring, and summer group were 6.7 (2.2), 6.4 (2.2), and 6.6 (2.1), respectively (See Figure 2). No significant differences were found between the immune fitness ratings ($p = 0.262$). Except for a small but significant lower age of the summer group compared to winter ($p < 0.001$) and spring ($p = 0.002$), the groups did not significantly differ on the assessments of other demographics, mood, or quality of life (See Table 1).

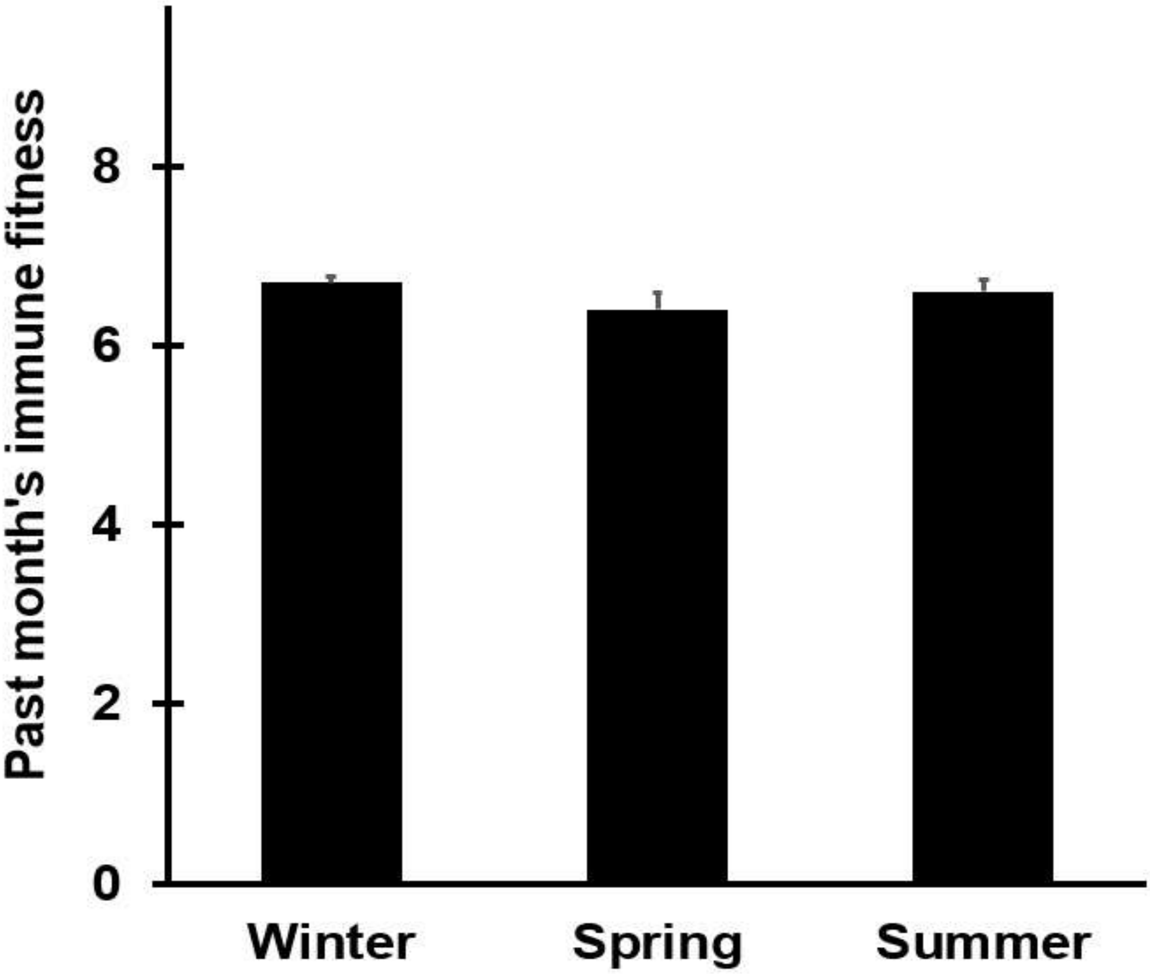

Figure 2. Past month's immune fitness across seasons (between groups).

	Winter	Spring	Summer	*p*-value
N	812	129	237	-
Male/female ratio	109/703	21/108	39/198	0.404
Age (years)	34.3 (11.0)	34.4 (10.5)	31.2 (10.4) *	< 0.001 *
Height (m)	1.66 (0.1)	1.67 (0.1)	1.66 (0.1)	0.715
Weight (kg)	75.8 (18.8)	77.1 (18.3)	75.7 (19.4)	0.531
Immune fitness	6.7 (2.2)	6.4 (2.2)	6.6 (2.1)	0.262
Stress	6.5 (2.2)	6.8 (2.4)	6.6 (2.2)	0.211
Anxiety	6.0 (2.7)	6.3 (3.0)	6.1 (2.8)	0.398
Depression	3.8 (3.1)	4.1 (3.3)	3.7 (3.1)	0.617
Worry	5.8 (2.8)	6.2 (2.9)	5.7 (2.9)	0.161
Shyness	3.2 (2.9)	3.6 (3.0)	3.3 (2.9)	0.512
Fatigue	5.9 (2.8)	6.3 (2.9)	5.9 (2.7)	0.173
Loneliness	3.4 (3.1)	3.6 (3.3)	3.7 (3.1)	0.456
Hostility	2.2 (2.4)	2.2 (2.4)	2.3 (2.4)	0.853
Happiness	5.8 (2.2)	5.6 (2.2)	6.1 (2.0)	0.146
Quality of life	6.5 (2.0)	6.4 (2.2)	6.6 (2.0)	0.895

Table 1. Study outcomes according to season.

Mean and Standard deviation (SD) are shown. Significant differences between the groups ($p < 0.025$ after Bonferroni's correction) are indicated by *.

3.2. Australia: within-subject comparison

A total of N = 325 participants completed the 4 assessments. Their mean (SD) age was 57.4 (14.3) years old (range 20 to 87 years old) and 72.0% of them were female. Their mean (SD) momentary immune fitness score remained stable over the 4 assessments (see Figure 3 and Table 2), with no significant differences between the test days ($p = 0.725$).

	T1 (Autumn)	T2 (Autumn)	T3 (Winter)	T4 (Summer)	*p*-value
Immune fitness	7.3 (2.4)	7.3 (2.3)	7.3 (2.3)	7.2 (2.6)	0.725
Mental resilience	21.5 (5.0)	21.4 (5.2)	21.0 (5.9)	21.4 (5.7)	0.097
Depression	7.2 (8.4)	6.9 (8.7)	7.0 (8.6)	6.1 (8.1) *	< 0.001 *
Anxiety	3.4 (5.1)	3.7 (6.4)	3.7 (5.9)	3.6 (5.6)	0.907
Stress	8.9 (8.3)	8.5 (8.4)	8.9 (8.3)	8.5 (8.4)	0.328
Loneliness	5.0 (1.9)	4.7 (1.8) *	4.7 (2.0)	4.4 (1.8) *	< 0.001 *

Table 2. Study outcomes according to season.

Mean and Standard deviation (SD) are shown. Significant differences between the assessments and T1 ($p < 0.017$ after Bonferroni's correction) are indicated by *.

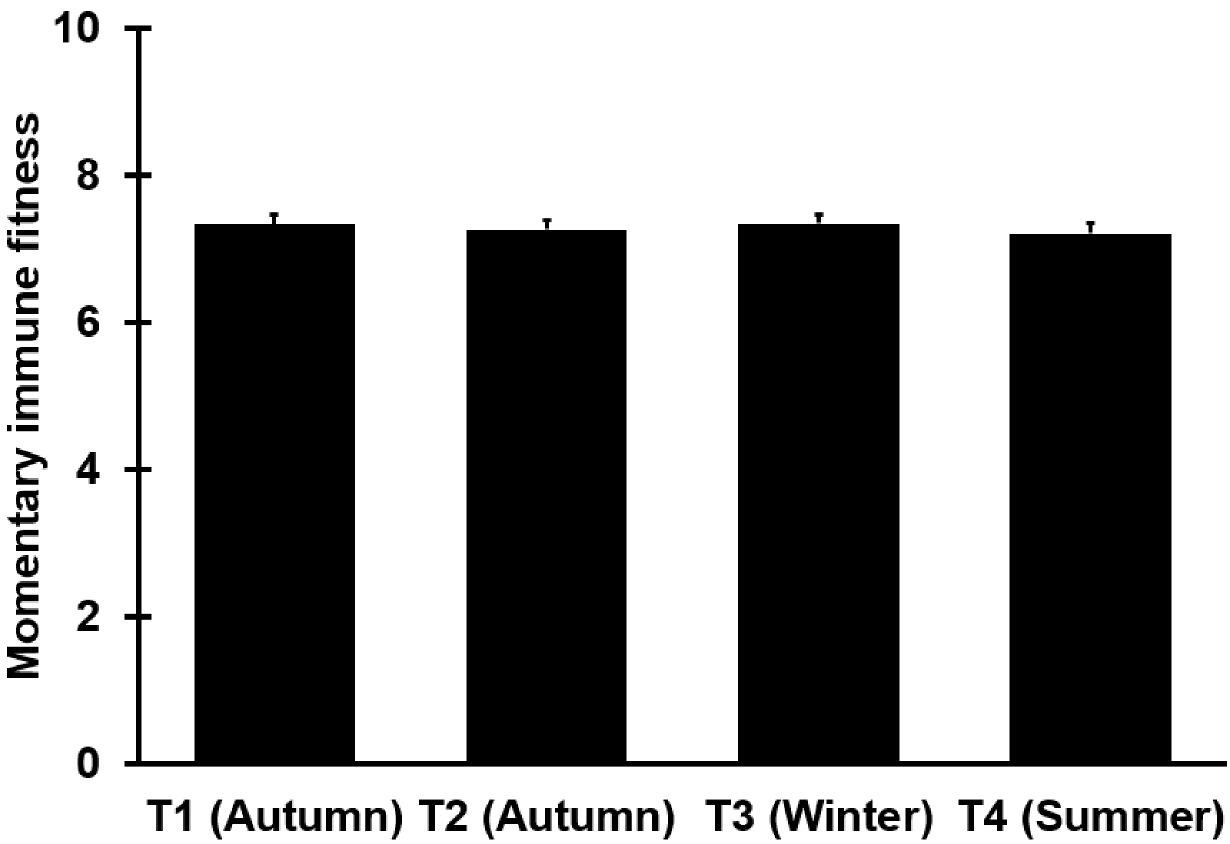

Figure 3. Momentary immune fitness across seasons (within subjects).

In contrast, significant differences between the test days were observed for other variables (See Table 2). The differences were statistically significant for depression ($p < 0.001$) and loneliness ($p < 0.001$), but not for mental resilience, anxiety, and stress (see Table 2). For depression a significant difference was found between T1 and T4 ($p < 0.001$). For loneliness, the T2 score was significantly lower than T1 ($p = 0.005$) and the T4 score was significantly lower than T1 ($p < 0.001$), T2 ($p = 0.006$), and T3 ($p < 0.001$).

Discussion

The between group comparisons of the UK and Irish sample revealed that, despite the known seasonal differences in the frequency of occurrence of immune-related complaints and diseases such as the common cold and hay fever, there were no significant seasonal differences in immune fitness, i.e., the capability to fight these health challenges. No significant differences were found in past month's immune fitness between winter, spring and summer. The three samples did not differ in demographics, except a slight age difference that can not be considered clinically relevant. Also, the groups did not differ on mood and quality of life. Taken together, the data suggest no seasonal differences in immune fitness.

The prospective Australian within-subject study confirmed the between-group comparisons observed in the UK and Irish survey. Notwithstanding the fact that the Australian study was conducted while progressing into the COVID-19 pandemic with different COVID-19 measures (e.g., stringent versus limited lockdown periods) were installed on the subsequent testing periods, at the group level no significant differences in momentary immune fitness were observed. Thus, no significant differences were found between the immune fitness assessments made in autumn, summer and winter.

Taken together, the impact of health challenges (e.g., the presence of rhinovirus or a greater pollen count) differs between seasons, and thereby can increase the chances of getting sick (e.g., common cold in winter or hay fever in spring). However, the data from the two studies presented here suggest that immune fitness does not vary across the seasons. In other words, the presence of health challenges differs between the seasons, whereas the perceived susceptibility to disease (i.e., the level of immune fitness) remains unaltered across the seasons.

These findings challenge the assumption that seasonal fluctuations in disease incidence or immune biomarker expression reflect corresponding changes in immune fitness. The findings indicate that individuals maintain a relative consistent baseline ability to cope with health challenges, regardless of seasonal pathogen exposure, possibly due to adaptive behavioral or physiological mechanisms not captured in our assessments.

A limitation of the UK and Irish study was the fact that a between-subject design was used. Three groups were compared. Although the groups were identical on many factors, theoretically they could differ on other variables that were not assessed. The latter could then mask a possible seasonal effect in immune fitness. However, in the within-subject Australian prospective, longitudinal study it was confirmed that immune fitness ratings remained stable over the different seasons that were assessed. In this study, the subjects were their own control, avoiding the possible impact of known and unknown between-group differences. Nevertheless, the progressing COVID-19 pandemic could have potentially impacted the immune fitness assessments. Therefore, this study should be replicated to confirm its findings.

A second limitation of the two studies was their relative small sample size. As a result, no sub-analyses were conducted to evaluate the impact of subject characteristics such as sex, age, and disease state on possible seasonal fluctuations in immune fitness ratings. The skewed sex ratio, with mostly female participants (85.7% in the UK/Irish study, 72.0% in the Australian study), may have influenced the study outcomes. Women often report lower immune fitness than men (Mulder *et al*., 2024), possibly due to stronger immune responses, differing health perceptions, or social biases (Boerma *et al*., 2016; Verster *et al*., 2023b; Klein and Flanagan, 2016). Therefore, future studies with larger sample sizes, balanced for sex and age are needed, including the assessment of potentially other relevant covariates. An important example of such a covariate that was not assessed in the current two studies is baseline health status. Individuals with underlying chronic health conditions such as diabetes or asthma might perceive their immune fitness differently across seasons compared to healthy individuals (Fares, 2013). Preferably, these studies should also take into account environmental data to directly explore the level of pathogen exposure in participants.

Finally, in both studies a global, single-item assessment was applied to assess immune fitness. In general, single-item assessments are often considered as a better approach than composite, multiple-item assessments, as the former are more likely to encompass all factors influencing immune fitness (US FDA, 2009). However, a disadvantage of a single item assessment is that this global rating does not provide any information on the type, duration, severity, frequency of occurrence, impact on daily life of immune-related complaints that may determine the overall immune fitness score. An alternative questionnaire to assess immune fitness is the 7-item Immune Fitness Questionnaire (ISQ) (Wilod Versprille *et al*. 2019). With the ISQ, the past 12 month's frequency of occurrence of sudden high fever, diarrhea, headache, skin problems (e.g., acne and eczema), muscle and joint pain, common cold, and coughing is assessed. Up to now, the ISQ is most often used in cross-sectional studies, but can also be implemented in clinical trials if the 12 month assessment period is adapted.

Future studies should determine if ISQ scores also remain stable across the seasons by adjusting the ISQ assessment period to shorter durations that align with seasonal changes.

In conclusion, the presented studies observed no seasonal differences in global immune fitness ratings. The data suggest that, despite the known seasonal differences in the presence and severity of health challenges, these do not appear to impact people's perceived level of immune fitness required to combat them.

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