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Assessing the association of physical distancing to avoid COVID-19 with health-related quality of life in immunocompromised adults: results from the cross-sectional observational EAGLE study

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ABSTRACT

Introduction Immunocompromised individuals have suboptimal COVID-19 vaccine responses and may continue physically distancing to avoid COVID-19. The EAGLE Study aimed to quantify physical distancing behaviours and associations with health-related quality of life (HRQoL) and related measures in immunocompromised adults.

Methods EAGLE was a cross-sectional, observational online survey study of US and UK immunocompromised adults, children and those children's caregivers, with adult analyses reported here. Multichannel enrolment and self-reported data collection occurred from December 2022 to June 2023. Immunocompromising diagnosis confirmation using medical records was requested from a randomly selected subset. Physical distancing (in past 4 weeks) was measured using the Physical Distancing Scale for COVID-19 Avoidance (PDS-C19). HRQoL and related measures were the 12-item Short Form Health Survey version 2 (SF-12v2) (includes Short-Form 6-Dimensions), Quality of Life Disease Impact Scale-7-item (QDIS-7), Direct Measure of Loneliness, EQ-5D-5L, Hospital Anxiety and Depression Scale and Work Productivity and Activity Impairment plus Classroom Impairment Questions: Specific Health Problem (WPAI+CIQ:SHP). Associations between PDS-C19 and HRQoL and related measures were assessed using Pearson correlation, linear regression (potential confounders-adjusted) and preliminary structural equation modelling (SEM).

Results 2320 immunocompromised adults fully completed the survey. Confirmation of diagnosis was requested from 27% and confirmed for 90% of responders. 68% of participants reported moderate to high physical distancing. Physical distancing had low correlations with SF-12v2-measured HRQoL domains (range |r|=0.18 to 0.39) and medium correlations with QDIS-7 (r=0.78) and WPAI+CIQ:SHP-measured activity impairment (r=0.68) and presenteeism (r=0.51). In SEM, direct PDS-C19 relationships explained most activity correlations: QDIS,

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ COVID-19-related societal restrictions were lifted globally by 2022 due to successful vaccination programmes; however, immunocompromised individuals are still advised to take individual-level infection risk-reducing behaviours due to suboptimal vaccine responses. Limited evidence exists on the association between physical distancing and health-related quality of life (HRQoL) in the post-lockdown period, particularly for immunocompromised individuals.

WHAT THIS STUDY ADDS

⇒ This large cross-sectional survey (n=2320 immunocompromised adults) quantified physical distancing behaviours using the newly developed Physical Distancing Scale for COVID-19 Avoidance (PDS-C19).

⇒ Approximately two-thirds (68%) of immunocompromised adults were still practicing physical distancing behaviours in the post-lockdown era, and higher intensities of physical distancing were associated with greater HRQoL impairments, even after adjusting for confounding variables.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These findings highlight the concurrent challenges faced by immunocompromised populations and point to potential health inequalities. Such observations may inform public health strategies, policies and guidelines that aim to provide support in the COVID-19 endemic era through consideration of both preventive measures against COVID-19 and HRQoL concerns.

β=0.46 (SE=0.02); activity impairment, β=0.40 (0.02); presenteeism, β=0.29 (0.04). Unstandardised PDS-C19 confounder-adjusted linear regression coefficients were similar to those of SEM.

Conclusions Over 3 years after COVID-19 emergence, a disproportionate number of immunocompromised adults reported substantially physically distancing to avoid COVID-19. Higher physical distancing intensities were associated with greater HRQoL impairments, suggesting such challenges coexist as ongoing concerns for immunocompromised adults.

INTRODUCTION

Following the success of global COVID-19 vaccination programmes, most health authorities lifted COVID-19-related societal restrictions by 2022,[1 2] and in May 2023, the WHO declared that COVID-19 was no longer an international public health emergency. This prompted the reallocation of funds and attention from COVID-19 pandemic relief towards long-term economic recovery.[3] However, this transition is concerning to immunocompromised individuals who have suboptimal responses to COVID-19 vaccinations, and therefore remain at high risk of severe COVID-19 outcomes.[4–8] Following UK government and US Centers for Disease Control and Prevention (CDC) guidelines,[9–11] immunocompromised patients include, for example, those with certain cancers, solid organ transplants, primary immunodeficiency disorders and patients receiving immunosuppressive treatments. This vulnerable population comprises an estimated 3.9% of the adult and adolescent population in the UK[4] and 2.7–6.6% of adults and 2.6% of children in the USA.[12–14] Health authorities globally, including in the USA and UK, recognise the continued vulnerability of immunocompromised individuals and advise continuing individual-level, risk-reducing behaviours to protect against infection,[10 15] including physical distancing strategies such as avoiding or reducing time spent in crowded places and increasing space between oneself and others.[15 16] As of April 2022, UK data collected after COVID-19-related societal restrictions ('lockdowns') were lifted have indicated that two-thirds of people at high risk of severe COVID-19 continued to take additional risk-reduction precautions, either voluntarily or as recommended by clinical guidelines or their physician. Additionally, 13% were still following the government 'shielding' advice.[17] While these measures are important for COVID-19 prevention, real-world studies of immunocompromised individuals throughout lockdown periods have shown detrimental impacts on various aspects of health-related quality of life (HRQoL) and work productivity.[18–23] In a national UK survey conducted in July 2023, immunocompromised individuals facing a fourth year of practising physical distancing reported reduced HRQoL compared with the general population.[24] However, no large-scale studies have been conducted in the COVID-19 post-lockdown setting to comprehensively quantify the intensity of these behaviours in immunocompromised populations or to investigate the association of these behaviours with HRQoL or work impairment measures.[25 26] Here, we present the results of the EAGLE Study, in which the primary objectives were to describe the associations between physical distancing for COVID-19 avoidance with HRQoL and health state utilities in immunocompromised adults. Secondary objectives were to describe associations between physical distancing for COVID-19 avoidance with levels of anxiety, depression and work impairment and productivity in immunocompromised adults. The cross-sectional associations of these behaviours with HRQoL measures were assessed during the transition of the COVID-19 pandemic to an endemic state, which was dominated by SARS-CoV-2 omicron variants.[27]

MATERIALS AND METHODS

Study design

The EAGLE Study was a noninterventional, observational, cross-sectional survey in immunocompromised adults, adolescents and children and their caregivers residing in the USA and UK, conducted in the post-lockdown period from December 2022 through June 2023 (AstraZeneca study code: D8850R00013). Non-immunocompromised individuals were included for informal benchmarking, not formal comparison. A summary of the EAGLE Study protocol has been published.[9] In brief, the survey was a one-time, web-based, self-administered or proxy-administered set of online questions in English (USA/UK) and Spanish (USA) and was designed to be completed on an electronic device in 30–45 min. Physical distancing behaviours to avoid COVID-19 were captured using the Physical Distancing Scale for COVID-19 Avoidance (PDS-C19).[28 29] HRQoL and health state utilities were assessed using well-established, previously validated instruments. Contextual data and potential confounders were captured using study-specific survey questions, including risk factors for severe COVID-19, which are listed in the online supplemental materials.

Patient and public involvement

Patients were involved in the design of the study protocol. Their role is described in detail in the EAGLE Study protocol.[9]

Eligibility criteria

Full inclusion and exclusion criteria are reported in the EAGLE Study protocol.[9] All enrolled adults were aged ≥18 years and resided in the USA or UK. Immunocompromised participants were defined based on the UK government and US CDC guidelines,[9–11] as those who self-reported as having one or more of the following conditions or treatments in the period 2 months before enrolment: haematologic malignancies, solid tumours (on active treatment), solid organ or stem cell transplant, end-stage kidney disease, primary immunodeficiency disorders, immunosuppressant treatment, HIV infection (uncontrolled) or other immunocompromising condition. We also included individuals with contraindications to the COVID-19 vaccine, who were considered immunocompromised for this study because they may remain

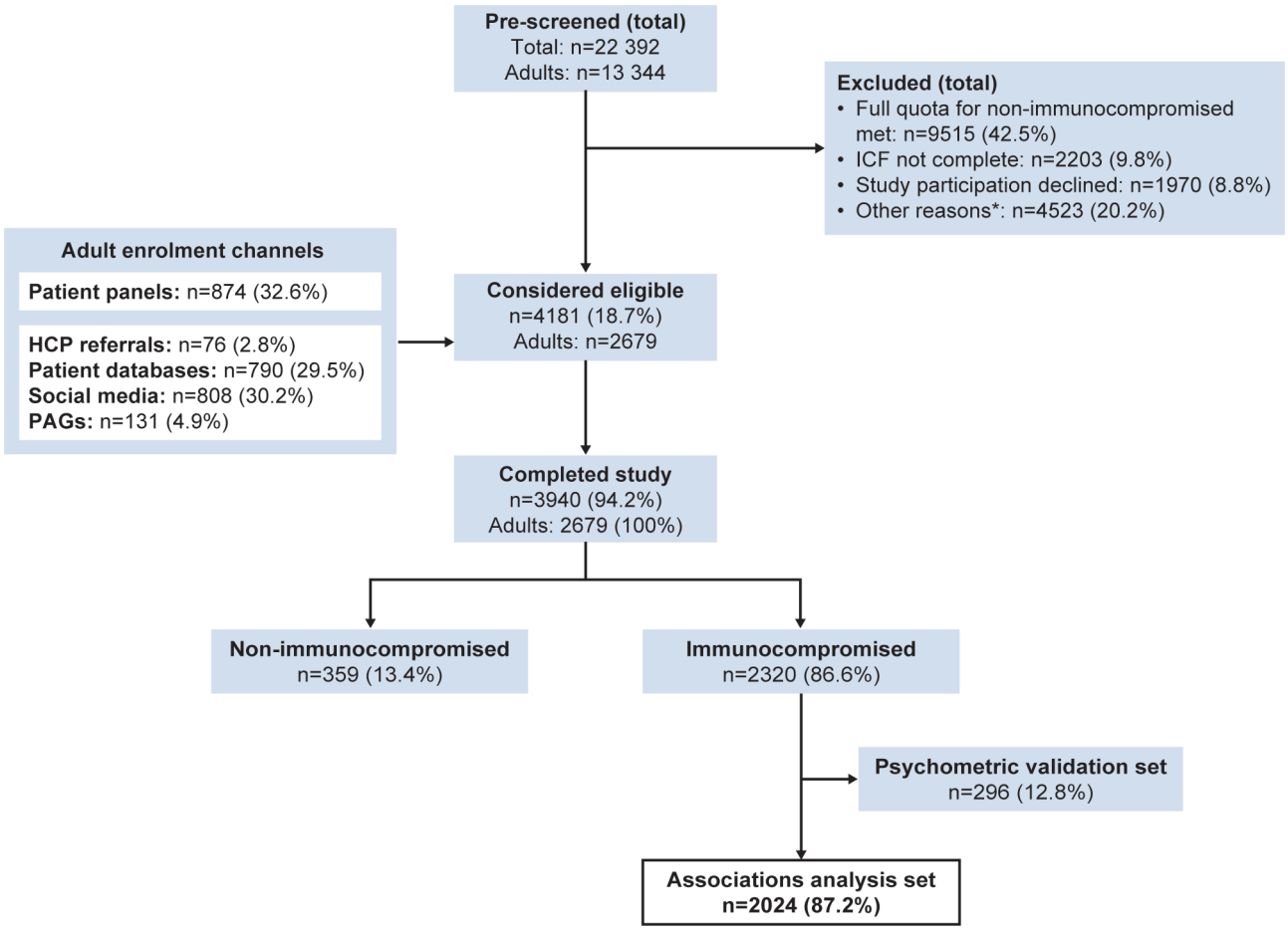

Figure 1 Flow chart of participant selection. Interested participants recruited through patient panels were prescreened and preconsented online; those recruited via other methods were prescreened by phone. Eligible participants were then sent a link to the survey via email. *Other reasons included: currently participating in clinical trial (n=708), immunocompromised status <2 months (n=259), taking prophylaxis medication (n=573), consent declined (n=152), below age of consent (n=150), no immunocompromised condition reported in prescreening (n=232), currently hospitalised (n=71), child does not live in same household (n=22), location outside of USA or UK (n=13), not comfortable completing questionnaires (n=555), child did not provide verbal consent (n=3), not wanting to participate (n=37), survey expired (n=1199), screen-failed by Global Perspectives because of not meeting inclusion/exclusion criteria (n=293), information not available (n=256). HCP, healthcare professional; ICF, informed consent form; PAG, patient advocacy group.

susceptible to severe COVID-19 outcomes. Complete exclusion criteria are listed in the online supplemental materials.

Recruitment

Participants were identified and recruited by Global Perspectives, an IQVIA company. Multiple direct-to-patient channels of recruitment were employed to allow broad representation of participants, including patient panels and networks, clinician referral, social media and patient advocacy groups (figure 1). Participants who completed the survey were sent an honorarium at fair market value, per local country guidance.

Given that immunocompromising status was also self-reported, a medical document showing proof of immunocompromising diagnosis or treatment was requested from a randomly selected sample of about 25% of participants to confirm their diagnosis.

Measures

Physical distancing intensity was measured using the PDS-C19, a novel self- and observer-reported behavioural scale. It includes seven items to measure the intensity of physical distancing behaviours to avoid COVID-19 in the past 4 weeks, from the highest (eg, avoiding people in own home and avoiding essential travel) to the lowest levels (eg, avoiding places where many people are expected). A five-point Likert scale is used: never, rarely, sometimes, often and always. Psychometric validation has shown adequate reliability and validity of the PDS-C19 for measuring intensity of physical distancing among both immunocompromised and non-immunocompromised individuals.[28–30] The PDS-C19 is scored via a table (T-score map) that provides, for each raw score (0–28), the mean latent trait scores (derived using a generalised partial credit model) on a T-score metric (mean 50; SD 10) of a centring sample from the psychometric validation subset

consisting of respondents who did not answer 'never' to all seven PDS-C19 items. PDS-C19 scores were sorted into the following SD-based ordinal categories to indicate the intensity of physical distancing: very low (<30), low (30–39.99), moderate (40–59.99) and high/very high (≥60).[28 30]

Primary HRQoL measures used were the 12-item Short Form Health Survey version 2 (SF-12v2®)[31] and Quality of Life Disease Impact Scale-7 item scale (QDIS-7®).[32] Loneliness was captured through the Direct Measure of Loneliness (DMOL) instrument.[33] Health state utilities were estimated using the EQ-5D-5L and Short Form 6-Dimensions (SF-6D®, based on the SF-12).[34 35] Secondary measures were the Work Productivity and Activity Impairment plus Classroom Impairment Questions: Specific Health Problem (WPAI+CIQ:SHP®)[36] and the Hospital Anxiety and Depression Scale (HADS).[37] For both the QDIS-7 and the WPAI+CIQ:SHP, items included the specific attribution to the following condition or health problem: 'avoiding COVID-19'.

Scoring of the HRQoL, utilities and related measures followed that of the respective instruments' licenseholders' instructions. For the SF-12, norm-based scores had been derived from the general US[38] and UK populations.[39] For the EQ-5D, utility scores were estimated using UK[40] and US country-specific value sets. For the HADS, scores of 15–21 indicate severe cases of anxiety or depression (clinically significant disorder), 11–14 indicate moderate cases (clinically significant disorder), 8–10 indicate mild disorder and 0–7 indicate non-cases (nondiagnosable).[37]

Statistical analysis

The EAGLE Study participant flow is shown in figure 1. Data from immunocompromised adults were analysed via Pearson correlation to assess associations between PDS-C19 and HRQoL measures (including utilities). Score-level descriptive statistics were provided for the domains of all HRQoL-related measures in the full analysis set (FAS, the set of participants who completed the entire battery of measures in the study). Descriptive analyses were also conducted across the physical distancing groups (very low, low, moderate, high/very high), as so-defined from the PDS-C19 score. Linear regression and preliminary structural equation modelling (SEM) were used to assess direct and indirect associations between physical distancing and HRQoL. The SEMs were fit via Mplus (V.8.8).[41] All other statistical analyses were performed in SAS V.9.4. A formal power calculation was not conducted, and p values were not adjusted for multiplicity. Any p values reported as ≤0.05 must only be interpreted as being nominally statistically significant.

Pearson correlation coefficients

Strength of association was characterised using the following thresholds: negligible ($|r|<0.2$), low ($0.2\leq|r|<0.5$), medium ($0.5\leq|r|<0.8$) and high ($|r|\geq0.8$). Furthermore, in social science studies, $|r|=0.2$ represents a recommended minimum effect size for 'practically' significant effects,[42] and $|r|=0.5$ represents the largest magnitude effect typically observed (ie, $|r|\geq0.5$ is quite substantial).[43]

Linear regression analysis

Separate multiple linear regression models were fitted for each HRQoL-related measure, with the PDS-C19 score as the main independent variable, along with potential confounding variables selected across three domains (see online supplemental methods): other available risk mitigation behaviour variables (mask wearing, others isolating to protect you, number of COVID-19 vaccine doses), worry-related variables (perception of infection risk, perceived potential severity of COVID-19, knowledge of family/friend deaths due to COVID-19) and other demographic or clinical characteristics (sex, age, ethnicity, type of health insurance (US participants), number of people living in household, education and immunocompromising category). A worry-related variable, risk to others, was excluded because of its high correlation with level of worry about being seriously ill from COVID-19. The models included the given HRQoL-related measure as a univariate dependent variable. The list of potential confounding variables included in the models were specified *a priori* and were identified based on literature and experts' recommendations. These results were reported in terms of unstandardised regression coefficients (B).

Preliminary SEM

The ability of the PDS-C19 and other items collected in the survey to predict responses to HRQoL-related outcomes was investigated using the Health Belief Model (HBM)[44] (online supplemental information: HBM), whereby beliefs predict behaviours, which in turn predict outcomes. In this study, the central belief of interest was the perceived threat of COVID-19. This latent construct was assessed through specific survey questions. The hypothesised relationships from the HBM were tested via preliminary SEM analyses that modelled the direct and indirect relationships between PDS-C19 and other HRQoL-related measures simultaneously (see online supplemental figure 1). SEM analyses were conducted to support the regression analyses. Unstandardised SEM results were reported in terms of regression coefficients (B) while standardised results were reported in terms of betas (βs). For further details on the SEM methods, please refer to the online supplemental information: Preliminary SEM.

RESULTS

Participants

In total, 2679 adults were enrolled in the USA (n=2020) and UK (n=659) from December 2022 to June 2023 (figure 1). All adult enrolees completed the survey (100% response). Of these, 2320 were immunocompromised, and 296 were included in the psychometric validation set,

leaving 2024 immunocompromised adults in the associations analysis set (this is the FAS, excluding the subset of patients who were included in the psychometric validation subset). Unless explicitly stated otherwise, all results in this manuscript are for immunocompromised adults. Select results for non-immunocompromised adults, including demographics and clinical characteristics, are in online supplemental tables 1,2.

There was a diverse spread of immunocompromising categories self-reported by adult participants (n=2320), with a large proportion of self-reported 'other immunocompromising conditions' (n=1025; 44.2%; table 1). A total of 618 of 2335 (26.5%) adult immunocompromised participants were randomly selected to provide confirmation of diagnosis (15 participants were initially identified as immunocompromised during prescreening and later responded during screening that they were unsure if a doctor had told them that they had a reduced immune system—thus, we reclassified those participants as non-immunocompromised for analyses). Of 618 randomly selected participants, 360 (58.3%) provided confirmation of diagnosis evidence; 320 (89.9%) of which were confirmed (online supplemental table 3).

Most immunocompromised adults (n=2320) were female (76.3%), White (78.4%), 45–64 years of age (45.8%), from the USA (73.8%), employed full-time or part-time (52.2%) and had completed some higher-level/university education (76.4%; table 1). Most immunocompromised adults (76.4%) reported having at least one of the listed additional risk factors for severe COVID-19, and 65.5% had received three or more COVID-19 vaccine doses.

Table 1 Demographic and clinical characteristics of the immunocompromised adult participants of the EAGLE Study, USA and UK, 2022–2023 (n=2320)

Category	Characteristic	n (%)
Immuno-compromising category*	Immunosuppressant treatment	733 (31.6)
	Solid tumours (on active treatment)	418 (18.0)
	Haematological malignancies	249 (10.7)
	Primary immunodeficiency disorder	219 (9.4)
	COVID-19 vaccine contraindication†	98 (4.2)
	Solid organ transplant	84 (3.6)
	End-stage kidney disease	74 (3.2)
	Stem cell transplant or other bone-marrow transplant	71 (3.1)
	HIV infection (uncontrolled)	58 (2.5)
	Other immunocompromising conditions	1025 (44.2)
Sex	Female	1769 (76.3)
Age group, years	18–24	55 (2.4)
	25–44	811 (35.0)
	45–64	1062 (45.8)
	≥65	392 (16.9)
Marital status	Single and never married or in a civil partnership	446 (19.2)
	Married, partnership, long-term relationship or cohabitation	1454 (62.7)
	Divorced/separated or widowed	405 (17.5)
	Prefer not to say	15 (0.6)
Education level	High school or less	527 (22.7)
	Less than a 4-year degree	598 (25.8)
	4-year degree	730 (31.5)
	Advanced degree	445 (19.2)
	Prefer not to say	18 (0.8)
	Missing	2 (0.1)
Country of residence	USA	1712 (73.8)
	UK	608 (26.2)
Race/ethnicity (USA, n=1712)*	White	1299 (75.9)
	Black	286 (16.7)
	Asian	42 (2.5)
	Other‡	158 (9.2)
	Prefer not to say	11 (0.6)
Race/ethnicity (UK, n=608)*	White	519 (85.4)
	Asian or Asian British	34 (5.6)
	Black, Black British, Caribbean or African	29 (4.8)
	Other§	26 (4.3)
	Prefer not to say	1 (0.2)

Continued

Physical distancing intensity

Immunocompromised adults showed moderate levels of physical distancing over the past 4 weeks (mean PDS-C19 T-score 46.4; table 2). The distribution among distancing intensity categories was as follows: very low (n=412; 17.8%), low (n=333; 14.4%), moderate (n=1228; 52.9%) and high/very high (n=347; 15.0%); thus, more than two-thirds (67.9%) of these adults showed moderate or high/very high physical distancing intensity. Descriptive statistics for PDS-C19 and HRQoL measures for non-immunocompromised adults are available in online supplemental table 2.

HRQoL and other measures, by physical distancing intensity

The mean SF-12 summary scores were 45.4 for the mental component and 40.9 for the physical component (table 2). Individual domains within this measure ranged from 41.0 to 45.2. Lower (worse) SF-12 scores were observed with increased physical distancing intensity (table 2). The mean QDIS-7 score for immunocompromised adults was 54.6. DMOL results indicated that 15.4% of immunocompromised adults felt lonely often/always.

Mean health state utilities were 0.68 (SD: 0.3) and 0.65 (SD: 0.1) as measured by the EQ-5D-5L and SF-6D,

Table 1 Continued

Category	Characteristic	n (%)
Health insurance coverage (US only, n=1712)*	Employment based	811 (47.4)
	Direct purchase, retail	103 (6.0)
	Medicare/Medicaid	929 (54.3)
	Military/Veterans Association	39 (2.3)
	Uninsured	15 (0.9)
	Other	55 (3.2)
	Prefer not to say	12 (0.7)
Employment status (n=2024)*	Employed full-time/part-time/self-employed	1056 (52.2)
	Disabled/unable to work	533 (26.3)
	Stay at home to look after my family	143 (7.1)
	Retired	367 (18.1)
	Unemployed	109 (5.4)
	Prefer not to say	14 (0.7)
Work setting in past 4 weeks (n=1016)	Work from home	326 (32.1)
	Work outside home in an indoor environment	651 (64.1)
	Work outside home in an outdoor environment	39 (3.8)
School university setting in the past 4 weeks (n=104)	I study from home only	55 (52.9)
	I study from a school/university or other place of study	29 (27.9)
	Both of the above	20 (19.2)
Ever tested positive for SARS-CoV-2	Yes	864 (37.2)
	No	1186 (51.1)
	Do not know	270 (11.6)
Hospitalised due to COVID-19	Yes	125 (5.4)
	No	2195 (94.6)
Number of other risk factors for severe COVID-19¶	None	524 (22.6)
	1	727 (31.3)
	2	521 (22.5)
	3	277 (11.9)
	≥4	248 (10.7)
	Missing	23 (1.0)
Number of SARS-CoV-2 vaccine doses	None	313 (13.5)
	1–2	488 (21.0)
	≥3	1519 (65.5)

*Multiple selections allowed, counts and percentages are not mutually exclusive.
†While those with COVID-19 vaccination contraindications are not generally considered 'immunocompromised', they were considered as immunocompromised for the purposes of the EAGLE Study because they are not adequately protected by such vaccination and therefore may remain susceptible to severe COVID-19 outcomes.
‡Other includes American Indican, Alaska Native, Native Hawaiian, other Pacific Islander, Hispanic and some other race.
§Other includes mixed or multiple ethnic groups and other ethnic group.
¶Other risk factors for severe COVID-19 included living in a nursing home or aged-care facility, hypertension, diabetes, cardiovascular disease, problems related to being overweight, current respiratory illness, currently smoke, formerly smoked, pregnant, health-care worker, asthma, cerebrovascular disease, chronic lung disease, chronic heart disease, chronic liver disease, cystic fibrosis, had tuberculosis, had cancer that is now in remission.

respectively (table 2). Lower utility values were observed with increasing physical distancing intensity; adults practising high/very high physical distancing had mean utility values of 0.51 (SD: 0.3) and 0.56 (SD: 0.1) as measured by the EQ-5D-5L and SF-6D, respectively.

The HADS indicated that 473 (23.4%) immunocompromised adults met the threshold for mild (though clinically relevant) anxiety, 450 (22.2%) for moderate anxiety and 246 (12.2%) for severe anxiety; 403 (19.9%) attained the level for mild (though clinically relevant) depression, while 287 (14.2%) and 84 (4.2%) met the threshold for moderate and severe depression, respectively.

Of the immunocompromised adults who were employed during the study (n=1056; 52.2%), WPAI+CIQ:SHP scores indicated that these individuals reported reductions in their work productivity due to avoiding COVID-19. Immunocompromised adults missed a mean of 7.2% of their work hours (absenteeism) and had a 17.3% impairment in working ability (presenteeism). Participants' overall work impairment (ie, work productivity loss, the linear combination of absenteeism and presenteeism) was calculated as 20.4%, and activity impairment due to avoiding COVID-19 was 25.9%. Individuals who physically distanced at high/very high intensity experienced the highest levels of impairment (table 2).

Among subgroups, those with COVID-19 vaccine contraindication practised the greatest intensity of physical distancing behaviours (mean=51.4), while individuals on immunosuppressant treatments had slightly lower SF-12 scores across nearly all domains compared with the other immunocompromising categories (online supplemental table 4).

Association between physical distancing and HRQoL and other measures

The correlations showing the association between physical distancing and the potential predictors are shown in online supplemental table 5, and the association between physical distancing and the outcome measures is shown in table 3. Higher intensities of physical distancing for COVID-19 avoidance showed 'medium' magnitudes of correlation with greater activity impairment measures that specified COVID-19 avoidance: QDIS-7 (r=0.78) and WPAI+CIQ:SHP-measured activity impairment (r=0.68) and presenteeism (r=0.51). Higher intensities of physical distancing for COVID-19 avoidance showed 'negligible' to 'low' magnitudes of correlation with worsening HRQoL when COVID-19 avoidance was not specified (SF-12v2, HADS, EQ-5D-5L and SF-6D; these correlations ranged from |r|=0.18 to 0.39; online supplemental figure 2). The lowest magnitude correlation (|r|=0.18) was with the energy and vitality domain of the SF-12, while the highest magnitude correlation (|r|=0.78) was observed with the QDIS-7.

Table 2 Physical distancing and HRQoL measures of immunocompromised adult participants of the EAGLE Study, USA and UK, 2022–2023

Measures	Subcategories	Measure score range	Overall (n=2024)	Physical distancing level (FAS, n=2320)			
				Very low	Low	Moderate	High/very high
PDS-C19, mean (SD)		T-score (M=50, SD=10)	46.4 (12.0)	–	–	–	–
SF-12, mean (SD)	Physical functioning*	T-score (M=50, SD=10)	41.0 (10.1)	–	–	–	–
	Role limitations (physical)*		41.3 (9.2)	–	–	–	–
	Bodily pain*		43.4 (10.4)	–	–	–	–
	General health perceptions*		41.4 (10.3)	–	–	–	–
	Energy and vitality*		42.8 (9.6)	–	–	–	–
	Social functioning*		42.6 (10.6)	–	–	–	–
	Role limitations (emotional)*		44.3 (10.7)	–	–	–	–
	Mental health*		45.2 (10.4)	–	–	–	–
	Mental component summary scale		45.4 (10.6)	48.7 (10.0)	48.6 (9.9)	44.7 (10.1)	40.0 (11.0)
	Physical component summary scale		40.9 (10.0)	45.2 (10.4)	42.9 (10.0)	40.5 (9.3)	35.4 (9.3)
QDIS-7, mean (SD)		T-score (M=50, SD=10)	54.6 (12.8)	–	–	–	–
DMOL felt lonely often/always, n (%)		NA	312 (15.4)	–	–	–	–
EQ-5D-5L index value, mean (SD)		0.0–1.0†	0.68 (0.3)	0.78 (0.2)	0.74 (0.2)	0.67 (0.2)	0.51 (0.3)
EQ-5D-VAS, mean (SD)		0.0–100.0	65.2 (19.5)	70.4 (18.0)	69.5 (17.7)	64.8 (18.5)	54.7 (22.8)
SF-6D, mean (SD)		0.0–1.0	0.65 (0.1)	0.71 (0.1)	0.69 (0.1)	0.64 (0.1)	0.56 (0.1)
HADS, mean (SD)	Anxiety	0.0–21.0	8.7 (4.7)	6.4 (4.4)	7.2 (4.4)	9.1 (4.4)	11.7 (5.0)
	Depression		6.4 (4.4)	4.2 (3.9)	4.8 (3.8)	6.8 (4.0)	9.5 (4.6)
WPAI+CIQ: SHP, mean (SD)‡	Absenteeism, % hours missed§	0.0–100.0	7.2 (18.7)¶	2.03 (11.8)	1.67 (11.4)	8.23 (19.4)	23.7 (29.3)
	Presenteeism, % impairment§		17.3 (23.1)**	4.2 (11.4)	6.6 (11.7)	21.4 (22.7)	39.8 (30.0)
	Overall work impairment, %§		20.4 (26.9)**	5 (13.3)	7.5 (14.1)	25.4 (26.7)	48.1 (33.9)
	Activity impairment due to avoiding COVID-19, % impairment		25.9 (27.2)	3.8 (9.1)	8.5 (10.9)	29.1 (24.1)	57.8 (28.2)

'–' indicates not calculated.
*Part of the SF-12v2 8 domains.
†Values can potentially go below zero.
‡Class productivity impairment not shown.
§Physical distancing level computed out of employed adults: very low 237/412 (57.5%); low 170/333 (51.1%); moderate 613/1228 (49.9%); high/very high 121/347 (34.9%).
¶n=936.
**n=926.
DMOL, Direct Measure of Loneliness; FAS, full analysis set; HADS, Hospital Anxiety and Depression Scale; HRQoL, health-related quality of life; M, mean; NA, not applicable; PDS-C19, Physical Distancing Scale for COVID-19 Avoidance; QDIS-7, Quality of Life Disease Impact Scale-7-item scale; SD, standard deviation; SF-12, 12-item Short Form Health Survey; SF-6D, Short Form 6-Dimensions; VAS, Visual Analogue Scale; WPAI+CIQ:SHP, Work Productivity and Activity Impairment Plus Classroom Impairment Questions: Specific Health Problem.

Health-related quality of life

Regression models for each of the HRQoL measures showed statistically significant associations with physical distancing intensity (PDS-C19) after confounder adjustment (table 4). PDS-C19 had the strongest relationship with QDIS-7 (also on a T-score metric), where a one-unit change in the PDS-C19 T-score corresponded to a 0.54 (SE=0.02) change in QDIS. Other notable relations included EQ-5D VAS (0–100 metric) and SF-12 Social Functioning (T-score) where a one-unit change in

Table 3 Summary of associations between PDS-C19 and HRQoL and other measures via bivariate Pearson correlations (r), standardised (β) and unstandardised (B) preliminary SEM regression coefficients and Bs from separate multivariable linear regression models for each outcome (n=2024)

Type	Measure	r	SEM		Regression
			β	B	B
HRQoL	QDIS-7	0.78	0.46*	0.49*	0.54
	SF12v2 physical component summary scale	−0.32	−0.17*	−0.14*	−0.16
	SF12v2 mental component summary scale	−0.27	−0.07*	−0.06*	−0.15
	EQ-5D-VAS	−0.26	−0.12*	−0.20*	−0.27
Utility	EQ-5D Index	−0.33	−0.18*	−0.00*	−0.005
	SF-6D	−0.37	−0.15*	−0.00*	−0.003
Mental health	HADS anxiety	0.34	0.05	0.02	0.07
	HADS depression	0.39	0.10*	0.04*	0.08
Roles and activities	WPAI activity impairment	0.68	0.40*	0.91*	0.97
	WPAI presenteeism	0.51	0.29*	0.59*	0.5
	WPAI absenteeism	0.33	0.15*	0.24*	0.2

*p<0.01.
HADS, Hospital Anxiety and Depression Scale; HRQoL, health-related quality of life; PDS-C19, Physical Distancing Scale for COVID-19 Avoidance; QDIS-7, Quality of Life Disease Impact Scale-7-item scale; SEM, structural equation model; SF-6D, Short Form 6-Dimensions; SF-12v2, 12-item Short Form Health Survey version 2; VAS, Visual Analogue Scale; WAPI, Work Productivity and Activity Impairment.

PDS-C19 corresponded to a −0.27 (SE=0.05) and −0.26 (SE=0.03) change in those measures, respectively.

Consistent with the regression models, the preliminary SEM identified statistically significant associations between HRQoL and PDS-C19 measures for QDIS-7, EQ-5D-VAS (Visual Analogue Scale), SF-12 (physical component score) and DMOL, which was included as a predicted mediator in all models. Partitioning of the effect showed that most of the standardised associations between HRQoL and PDS-C19 measures could be mainly attributed to direct but not indirect associations, with total (direct+indirect) effect size ranging from |β|=0.12 to 0.48 (indirect associations of PDS-C19 with outcomes mediated by DMOL ranged from |β|=0.01 to 0.07). Further SEM results are shown in online supplemental table 6.

Utilities

Regression models for both utility measures (EQ-5D-5L and SF-6D) showed statistically significant associations with PDS-C19 after confounder adjustment. Given these measures' 0–1 metric, however, the relationship of the PDS-C19 with them was negligible (table 4). SEM showed similar results (online supplemental table 7).

Other measures

Regression models for HADS anxiety and depression (0–21 metric) were both statistically significantly associated with PDS-C19, with a one-unit change in PDS-C19 score corresponding with a 0.07 (SE=0.01) change in the anxiety score and a 0.08 (SE=0.01) change in the depression score (table 4). Activity impairment (WPAI+CIQ:SHP; 0–100 metric) was also statistically significantly associated with PDS-C19, where a one-unit change in the PDS-C19 T-score corresponded to a 0.97 (SE=0.06) change in WPAI+CIQ:SHP (table 4). SEM results are shown in online supplemental table 8.

Regression models for WPAI+CIQ:SHP measures (all 0–100 metrics) of absenteeism, presenteeism and overall work impairment (ie, work productivity loss) were conducted in employed immunocompromised adults (table 4). All three scales were statistically significantly associated with PDS-C19, with a one-unit change in PDS-C19 score corresponding with a 0.20 (SE=0.08) change in the absenteeism score, a 0.50 (SE=0.09) change in the presenteeism score and a 0.63 (SE=0.10) change in the overall work impairment score (table 4). SEM results are shown in online supplemental table 9.

DISCUSSION

EAGLE is the first study to robustly and comprehensively measure the intensity of physical distancing to avoid COVID-19 and its association with HRQoL and related measures using a novel physical distancing scale and several previously validated HRQoL and related instruments. The study demonstrated that greater levels of physical distancing for COVID-19 avoidance had moderate to strong nominally statistically significant associations with worsening HRQoL and mental health and greater activity impairment.

HRQoL of immunocompromised adults from the EAGLE Study is lower than existing general population country norms measured pre-COVID-19 across all items/domains. It was notable that EQ-5D-derived utility values from immunocompromised adults in the US/UK cross-sectional EAGLE Study (0.68) were around 20% lower than UK norms (approximately 0.80–0.85).[45 46]

For the SF-12, the US general population norm in 2009 was 50,[47] while mean values for immunocompromised individuals in EAGLE ranged from 41.0 to 45.2 across the eight domains. These findings imply that immunocompromised adults in the COVID-19 post-lockdown period had lower HRQoL than the pre-COVID-19 general population. For the QDIS-7, in which higher scores indicate greater limitations, the US norm in 2011 for the chronically ill population was 50,[48] which was similar to the

Table 4 PDS-C19 regression coefficients from multiple linear models estimating single outcomes from the QDIS-7, EQ-5D, SF-12v2, DMOL, SF-6D, WPAI+CIQ:SHP and HADS instruments

Measures		Regression models (individual outcomes)*		
		Unstandardised PDS-C19 direct association		
		B (SE)		95% CI
QDIS-7†		0.54 (0.02)‡		0.50 to 0.58
EQ-5D-VAS†		–0.27 (0.05)‡		–0.37 to –0.17
	Physical functioning§	–0.20 (0.03)‡		–0.25 to –0.15
	Role limitations (physical)§	–0.19 (0.02)‡		–0.24 to –0.15
	Bodily pain§	–0.19 (0.03)‡		–0.25 to –0.14
	General health perceptions§	–0.08 (0.03)**		–0.13 to –0.03
	Energy and vitality§	–0.08 (0.03)**		–0.14 to –0.03
	Social functioning§	–0.26 (0.03)**		–0.31 to –0.21
	Role limitations (emotional)§	–0.21 (0.03)‡		–0.26 to –0.16
	Mental health§	–0.13 (0.03)‡		–0.18 to –0.07
	Mental component summary scale	–0.15 (0.03)‡		–0.21 to –0.10
SF-12†	Physical component summary scale	–0.16 (0.03)‡		–0.22 to –0.12
DMOL¶†		0.01 (<0.01)‡		0.007 to 0.016
	EQ-5D-5L index value¶	–0.005 (0.001)‡		–0.006 to –0.004
Utilities†	SF-6D¶	–0.003 (<0.001)‡		–0.003 to –0.002
Population		**FAS (n=2320)**	**Employed adults**	
	Activity impairment	0.97 (0.06)**		0.87 to 1.08
	Absenteeism††	–	0.20 (0.08)	0.04 to 0.35
	Presenteeism‡‡	–	0.50 (0.09)**	0.33 to 0.68
WPAI+CIQ:SHP	Overall work impairment‡‡	–	0.63 (0.10)**	0.43 to 0.83
	Anxiety	0.07 (0.01)**	§§	0.05 to 0.09
HADS	Depression	0.08 (0.01)**	§§	0.06 to 0.10

*Covariates included mask wearing, number of COVID-19 vaccine doses, frequency of others isolating to protect you in the past 4 weeks, perception of infection risk, perceived potential severity of COVID-19, knowledge of family/friend deaths due to COVID, sex, age, ethnicity, type of health insurance (US participants), number of people living in household, education and immunocompromising category.
†Excludes psychometric validation set, n=2024.
‡p<0.01.
§Part of the SF-12v2 eight domains.
¶Reported to three decimal places due to small effect sizes.
**p<0.001.
††n=927.
‡‡n=917.
§§Not conducted in employed-only group.
DMOL, Direct Measure of Loneliness; EQ-5D-5L, 5-level EQ-5D; FAS, full analysis set; HADS, Hospital Anxiety and Depression Scale; HRQoL, health-related quality of life; PDS-C19, Physical Distancing Scale for COVID-19 Avoidance; QDIS-7, Quality of Life Disease Impact Scale-7-item scale; SF-6D, Short Form 6-Dimensions; SF-12v2, 12-item Short Form Health Survey version 2; VAS, Visual Analogue Scale; WPAI+CIQ:SHP, Work Productivity and Activity Impairment Plus Classroom Impairment Questions: Specific Health Problem.

QDIS-7 mean score found in the EAGLE Study for immunocompromised adults (54.6).

The EAGLE Study builds on prior studies that found that public health social restrictions were associated with lower observed HRQoL.[18–23 30] Our results showed that the highest levels of physical distancing were associated with the greatest levels of anxiety and depression, indicated by HADS scores that crossed the threshold into mild disorders. This is consistent with the Spring 2025 Harvard Youth Poll, conducted in young US adults, including some who had been adults during the public health emergency phase of the COVID-19 pandemic, which found that those who became socially isolated during that phase reported higher rates of depression.[49] Our results also correspond with a survey conducted in February 2021, which found that, compared with the first COVID-19 pandemic wave (March 2020), generalised anxiety of the broader population was lower. However, in the shielding population, levels of generalised and health anxiety increased, with a positive correlation between the

length of time shielding and health anxiety.[50] Similarly, another survey found that physical and mental health of clinically extremely vulnerable survey responders had worsened by 35% and 42%, respectively, since shielding against COVID-19 had begun.[18] Furthermore, in a survey conducted in the UK at a similar time to the EAGLE Study, immunocompromised individuals reported higher levels of worry due to COVID-19 and poorer mental health compared with the general population.[24] Collectively, these cross-sectional observations align with emerging evidence suggesting relationships between mental health indicators among immunocompromised individuals, SARS-CoV-2 infection concerns and adherence to preventative behaviours. While physical distancing remains an important protective strategy for this vulnerable population, physical distancing appears to be associated with psychological challenges—an important clinical consideration as COVID-19 transitions to endemicity.

Further, using the DMOL, the UK Office for National Statistics survey conducted from April to May 2020 reported that the proportion of adults who often or always felt lonely was 5.0% compared with 7.2% when the survey was repeated from October 2020 to February 2021.[33] However, in the EAGLE Study, 15.4% of immunocompromised adults reported that they often or always felt lonely. Previous studies reported that loneliness can be predictive of depression,[51] and workplace loneliness is likely to impact work productivity.[52] As such, loneliness (as measured by the DMOL) should mediate the relationship between avoidance behaviours and other HRQoL-related outcomes.[51–54] This aligns with our findings showing an association between the DMOL and PDS-C19 measures. Clinicians should consider screening immunocompromised individuals for loneliness, as the higher prevalence of loneliness in this population may serve as an early indicator of depression and reduced productivity, potentially guiding earlier psychological interventions and supporting more comprehensive care approaches that address both physical vulnerability and psychosocial well-being.

Limitations

The design of the EAGLE Study was cross-sectional and noninterventional; thus, a causal association between physical distancing behaviours and HRQoL, mental health and work impairment cannot necessarily be inferred, nor can we rule out the possibilities of reverse causation or no causation. Hence, lower HRQoL among immunocompromised individuals could be due to existing impairments from underlying immunocompromising conditions or underlying comorbidities. While interventional studies could demonstrate whether increased physical distancing for COVID-19 avoidance causes poorer HRQoL in immunocompromised adults, it may not be feasible or ethical to design such studies without effective pharmaceutical options for prevention of COVID-19 in immunocompromised individuals. Analyses from the EAGLE Study data revealed graded associations between physical distancing intensity levels (PDS-C19) and HRQoL measures specific to avoiding COVID-19 (QDIS-7, WPAI+CIQ:SHP), with higher physical distancing scores corresponding to lower HRQoL scores. These associations persisted after adjustment for potential confounding factors in the regression models, suggesting a robust association between these variables, though the direction and nature of this relationship cannot be definitively established in this cross-sectional analysis. While our study population included a high proportion of females and individuals with higher educational qualifications, which potentially suggests selection bias, the findings remained consistent even after adjusting for 'sex' and 'educational qualification' as confounding factors in both regression model and SEMs.

In the EAGLE Study, participants were not asked to comment on their level of worry related to their underlying immunocompromising condition, nor was there a formal assessment of immunocompromising category severity. Both factors may play a role in HRQoL. Though most immunocompromised participants had at least one additional risk factor for severe COVID-19, it is possible that additional risk factors are likely missing, given the non-exhaustive closed list with no options for study participants to add additional items. Additionally, though these risk factors for severe COVID-19 may have contributed to reducing HRQoL, they were not included as confounders in the regression and SEM models; thus, they were only indirectly controlled for in the models via the perceived threat item, 'Are you worried about getting seriously ill from COVID-19?' Another limitation lies in the high percentage of individuals who reported 'other immunocompromising category'; we did not further classify their immunocompromised conditions or treatments. Furthermore, most data in the study were self-reported and therefore subject to reporting and recall bias, except for the confirmation of diagnosis for immunocompromised condition or treatment using medical records provided by participants. The data in this study were also geographically restricted to UK and US participants, but the EAGLE Study protocol has since been adapted for use in a wider subsequent study including non-Western countries (AstraZeneca study in progress) and in the Netherlands.[55]

Finally, the p values presented only denote nominal statistical significance and should be interpreted with caution as no formal power calculation with correction for multiple comparisons was performed.

Strengths

Strengths of the EAGLE Study included the large sample (2320 immunocompromised adults), enrolment in the UK and the USA with a wide age range and a reasonable number of participants distributed across the immunocompromised categories targeted for recruitment. Importantly, self-reported immunocompromising conditions were validated in a randomly selected subpopulation (21% of participants recruited outside of patient panels) using medical documentation, with most

immunocompromising diagnoses confirmed. Multiple participant recruitment methods were used, including a virtual approach; thus, the study was not limited to site-based or clinic-based recruitment, which is important for a population that is physically distancing. Furthermore, the study participant recruitment, enrolment and data collection period encompassed several months and included two peaks of the SARS-CoV-2 omicron era (ie, omicron BQ.1 and XBB.1.5) and their respective off-peak periods,[56] providing good coverage of the COVID-19 pandemic when it was still considered a public health emergency. Moreover, an explicit risk assessment of worry related to COVID-19 was included in the questionnaire and in the SEM. Additionally, all measures used in the study were valid for use in the EAGLE Study population, including the PDS-C19, which was validated within the study using a partitioned sample.[28 29] HRQoL-related instruments had published reference values for comparison and evidence of their appropriateness in a wide range of indications, allowing comparison of our study to published values. Finally, the analyses were conducted in immunocompromised people who had lived with their condition for at least 2 months, thereby reducing the impact that a new diagnosis or treatment would have on HRQoL but allowing enough time for an earlier diagnosis or treatment to potentially affect HRQoL.

CONCLUSIONS

In this large cross-sectional, noninterventional study conducted approximately 1 year after COVID-19 societal lockdowns were lifted in the USA and UK, physical distancing behaviours were reported by most of the immunocompromised adults. A higher physical distancing intensity was nominally statistically significantly associated with decreased HRQoL outcomes, increased anxiety and depression, lower health utility scores and reduced work productivity among immunocompromised adults, with these associations persisting after adjustment for potential confounding factors. These findings highlight that COVID-19 avoidance behaviours and quality-of-life challenges coexist as ongoing concerns in this vulnerable population.

Given their suboptimal responses to COVID-19 vaccines, immunocompromised individuals are likely to continue practising physical distancing as COVID-19 transitions to endemicity, unless more effective medical interventions become available. The EAGLE Study has identified important health disparities by quantifying physical distancing behaviours and their association with health outcomes, providing valuable utility data for health economists to more accurately estimate disease burden in health technology assessments. From a methodological standpoint, our study provides a feasible and robust framework to measure risk-reduction behaviours.

Lastly, the findings of the EAGLE Study suggest that healthcare providers and policymakers might consider routine mental health screenings for immunocompromised patients, telehealth services, workplace accommodations and public health messaging that address both protective behaviours and psychological well-being. Such approaches could help address quality-of-life concerns in immunocompromised individuals during ongoing and future public health challenges.

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Competing interests AstraZeneca was involved in the study design, data collection, analysis and interpretation. PW is a former AstraZeneca employee (at the time of study conduct) and is a current IQVIA employee and may hold stock and/or stock options in AZ and/or IQVIA. JCM, SP, SB and MK are employees of IQVIA and may hold stock and/or stock options. JMR and TM were IQVIA employees at the time of the study. SV and SA are employees of AstraZeneca and may hold stock and/or stock options in that company. TAH and ST were AstraZeneca employees at the time of the study. RTCY is an employee of P95 and was under contract with AZ at the time of the study. JLS is an employee of Severens HTA Consultancy and may hold stock and/or stock options. Severens HTA Consultancy was contracted by IQVIA to consult on the design and results interpretation for the EAGLE Study. Outside of the EAGLE Study, JLS received advisory fees from IQVIA. PAP was contracted by IQVIA to consult on the design and results interpretation for the EAGLE Study. JEWJ is an employee of John Ware Research Group and may hold stock and/or stock options. He also holds the copyright for the QDIS. John Ware Research Group was contracted by IQVIA to consult on the design and results interpretation for the EAGLE Study. At the time of the study design and inception, Global Perspectives was an independent company, but they were acquired officially by IQVIA in October 2022. EAGLE Study participants recruitment opened in December 2022 and was completed in June 2023.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Ethics approval This study was performed in accordance with ethical principles consistent with the Declaration of Helsinki, Good Pharmacoepidemiology Practices (GPP) and the applicable legislation and/or regulations on noninterventional studies and/or observational studies. The study received institutional review board (IRB) approval in the USA (WCG IRB. Letter of approval of EAGLE Study Protocol v1.0 and related material. IRB tracking number: 20226100, 15 November 2022), and IRB approval was not required in or obtained from the UK. In accordance with local regulations and the ethical principles that have their origin in the principles of the Declaration of Helsinki, all participants provided informed consent electronically before entering into the study.

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