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Incidence determinants and serological correlates of reactive symptoms following SARS-CoV-2 vaccination

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Prospective population-based studies investigating associations between reactive symptoms following SARS-CoV-2 vaccination and serologic responses to vaccination are lacking. We therefore conducted a study in 9003 adults from the UK general population receiving SARS-CoV-2 vaccines as part of the national vaccination programme. Titres of combined IgG/IgA/IgM responses to SARS-CoV-2 spike (S) glycoprotein were determined in eluates of dried blood spots collected from all participants before and after vaccination. 4262 (47.3%) participants experienced systemic reactive symptoms after a first vaccine dose. Factors associating with lower risk of such symptoms included older age (aOR per additional 10 years of age 0.85, 95% CI: 0.81–0.90), male vs. female sex (0.59, 0.53–0.65) and receipt of an mRNA vaccine vs. ChAdOx1 nCoV-19 (0.29, 0.26–0.32 for BNT162b2; 0.06, 0.01–0.26 for mRNA-1273). Higher risk of such symptoms was associated with SARS-CoV-2 seropositivity and COVID-19 symptoms prior to vaccination (2.23, 1.78–2.81), but not with SARS-CoV-2 seropositivity in the absence of COVID-19 symptoms (0.94, 0.81–1.09). Presence vs. absence of self-reported anxiety or depression at enrolment associated with higher risk of such symptoms (1.24, 1.12–1.39). Post-vaccination anti-S titres were higher among participants who experienced reactive symptoms after vaccination vs. those who did not ($P < 0.001$). We conclude that factors influencing risk of systemic symptoms after SARS-CoV-2 vaccination include demographic characteristics, pre-vaccination SARS-CoV-2 serostatus and vaccine type. Participants experiencing reactive symptoms following SARS-CoV-2 vaccination had higher post-vaccination titres of IgG/A/M anti-S antibodies. Improved public understanding of the frequency of reactogenic symptoms and their positive association with vaccine immunogenicity could potentially increase vaccine uptake.

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INTRODUCTION

The COVID-19 pandemic is the greatest threat in a generation to global health, having caused more than 6.1 million deaths to date[1]. SARS-CoV-2 vaccination represents the mainstay of disease control, but uptake is suboptimal, largely owing to vaccine hesitancy[2]. Fear of experiencing post-vaccination reactogenic symptoms - the physical manifestation of the inflammatory response to vaccination[3]—is often a contributing factor to such hesitancy[4]. Investigating the frequency with which post-vaccination reactogenic symptoms are experienced, risk factors for experiencing them and associations with vaccine immunogenicity has potential to yield information that will allow potential vaccinees to assess their risk of experiencing such symptoms, and to understand the significance of their presence or absence.

Existing studies investigating reactogenicity to first and second doses of SARS-CoV-2 vaccination have reported that post-vaccination symptoms are more commonly reported by women vs. men, in younger vs. older people, and in those who have had previous SARS-CoV-2 infection vs. those who have not[5–9]. However, the range of potential determinants explored by these studies has been limited: none have explored the potential impact of pre-vaccination anxiety or depression, specific comorbidities, medications or socio-economic factors which may either directly influence risk of reactogenic symptoms, or confound associations with age and sex. Additionally, there is controversy regarding the relationship between post-vaccination symptoms from a full course of vaccination and SARS-CoV-2 vaccine immunogenicity, with some studies showing no relationship between post-vaccination symptoms and titres of antibodies to the SARS-CoV-2 spike (S) glycoprotein[7,10], one reporting a positive association overall[8], and another reporting a positive association in men, but not in women[11]. These studies were relatively small and were not population based, limiting both power and generalisability of their findings.

To address these limitations, we conducted a large, population-based study in United Kingdom (UK) adults receiving SARS-CoV-2 vaccines, capturing detailed information on multiple potential determinants of reactogenic symptoms, and assaying combined IgG, IgA and IgM responses to SARS-CoV-2 spike protein before and after vaccination.

RESULTS

Participant flow and characteristics

Of the 17,796 participants who completed the COVIDENCE UK baseline questionnaire by September 2021, we excluded those

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who had no pre-vaccination serology ($n = 6343$) or who had not completed a full vaccination regimen ($n = 2273$). We also excluded those with missing data for independent variables required for minimal adjustment in the regression models ($n = 177$), resulting in 9003 participants being eligible for this analysis (Supplementary Fig. 1, Supplementary Material). Selected baseline characteristics of participants included in the analysis are presented in Table 1. The mean age of those contributing data to analyses was 61.3 years (range: 16.6–88.0), 70.7% were female, 96.4% identified their ethnic origin as White, and 88.4% were living in England. A total of 6322 (70.2%) participants experienced at least one post-vaccination symptom. The mean number of days from the date of second vaccine dose to date of dried blood spot was 58.2 (s.d. 22.4). This differed slightly for participants who did vs. did not report systemic symptoms after vaccination (56.2 vs. 61.2 days, $P < 0.001$), but was no different for those who did vs. did not report local symptoms after vaccination (57.9 vs. 58.6 days, $P = 0.23$).

Table 1. Participant characteristics at baseline ($n = 9003$).

	Characteristic	*N* (%)
Age, years	16–29.99	120 (1.3)
	30–39.99	341 (3.8)
	40–49.99	800 (8.9)
	50–59.99	2192 (24.4)
	60–69.99	3617 (40.2)
	≥70.00	1933 (21.5)
Sex	Female	6367 (70.7)
	Male	2363 (29.3)
Ethnicity	White	8676 (96.4)
	Mixed/multiple/other ethnic groups	197 (2.2)
	Asian/Asian British	94 (1.0)
	Black/African/Caribbean/Black British	36 (0.4)
Country of residence	England	7961 (88.4)
	Northern Ireland	139 (1.5)
	Scotland	563 (6.3)
	Wales	340 (3.8)
Highest educational level attained	Primary/Secondary	978 (10.9)
	Higher/further (A levels)	1265 (14.1)
	College	3991 (44.4)
	Post-graduate	2762 (30.7)
Body mass index[a]	<25, kg/m^2	4369 (48.6)
	25–30, kg/m^2	2907 (32.4)
	>30, kg/m^2	1709 (19.0)
Self-reported general health	Excellent	1878 (20.9)
	Very good	3590 (39.88)
	Good	2326 (25.8)
	Fair	949 (10.5)
	Poor	260 (2.9)
Tobacco smoking status	Not a current smoker	8633 (95.9)
	Current smoker	370 (4.1)
E-cigarette status[b]	Not a current vaper	8778 (97.7)
	Current smoker	207 (2.3))
Alcohol consumption	None	2349 (26.1)
	1–7 units	3189 (35.4)
	8–14 units	1853 (20.6)
	15–21 units	901 (10.0)
	22–28 units	403 (4.5)
	>28 units	308 (3.4)
Vaccine type	2 doses ChAdOx1	5988 (66.5)
	2 doses BNT162b2	2864 (31.8)
	2 doses MRNA-1273	59 (0.66)
	2 doses Other[c]	92 (1.02)
Month of dose for first dose	Q1 (Jan–Mar)	8262 (91.8)
	Q2 (Apr–Jun)	625 (6.9)
	Q3 (Jul–Sep)	1 (0.01)
	Q4 (Oct–Dec)	115 (1.3)
Month of dose for second dose	Q1 (Jan–Mar)	751 (8.3)
	Q2 (Apr–Jun)	7975 (88.6)
	Q3 (Jul–Sep)	274 (3.0)
	Q4 (Oct–Dec)	3 (0.03)

[a]Body mass index missing for 18 participants.
[b]Vape status missing for 18 participants.
[c]Single dose Janssen ($n = 12$), 2 doses Novavax ($n = 6$), 2 doses Valneva ($n = 3$), Comcov2 trial ($n = 1$), Not sure/do not know.

Incidence of reactive symptoms by dose order and vaccine type

Figure 1 presents the proportions of participants reporting systemic and local symptoms by dose order and vaccine type. Systemic symptoms following first dose were most commonly reported by participants who received ChAdOx1 (57.1%), followed by BNT162b2 (28.3%) and mRNA-1273 (3.4%; $P < 0.001$). Following the second dose, the proportion of participants experiencing systemic symptoms was similar for ChAdOx1 (27.9%) vs BNT162b2 (28.9%), but lower for mRNA-1273 (8.5%; $P = 0.002$). Local symptoms following first dose were most common for BNT162b2 (51.3%), followed by ChAdOx1 (40.3%) and mRNA-1273 (10.2%; $P < 0.001$). Local symptoms after the second dose were reported less frequently than after the first dose, with a similar distribution according to vaccine type as seen with the first dose (BNT162b2 43.7% vs. ChAdOx1 27.4% vs. mRNA-1273 8.5%; $P < 0.001$).

Determinants of systemic reactive symptoms following first vaccine dose

After adjustment for age and sex only, 23 variables were found to associate with risk of experiencing systemic symptoms following a first vaccine dose with $P < 0.10$ (Table 2), and 14 did not (Supplementary Table 3, Supplementary Material). After inclusion of the former group of factors in a multivariable model, the following variables were independently associated with higher risk

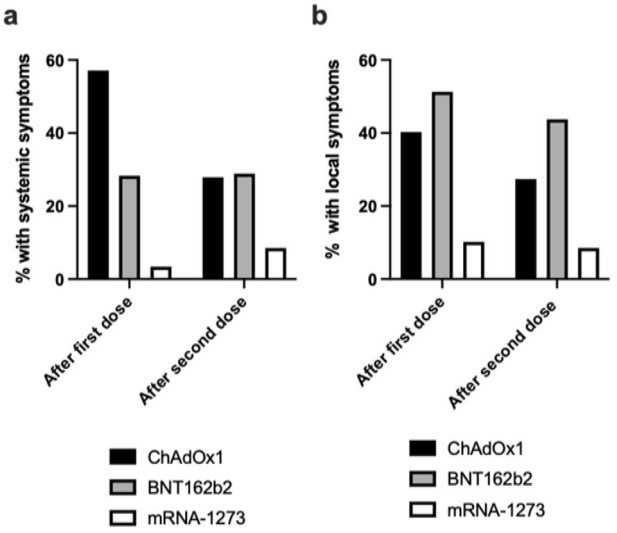

Fig. 1 Proportions of participants experiencing systemic or local reactive symptoms after receiving first and second doses of ChAdOx1, BNT162b2, and mRNA-1273 vaccines. Panel **a** shows systemic symptoms are more common with ChAdOx1 vaccine following first dose. Panel **b** shows local symptoms are more common with BNT162b2 vaccine following second dose.

Table 2. Incidence and determinants of systemic reactive symptoms after a first dose of SARS-CoV-2 vaccine.

			Minimally adjusted		Fully adjusted	
		N (%) symptomatic	aOR (95% CI)	*P*	aOR (95% CI)	*P*
Vaccine type	ChAdOx1	3420/5988 (57.0)	1.00		1.00	
	BNT162b2	810/2864 (28.3)	0.31 (0.28–0.34)	<0.001	0.29 (0.26–0.32)	<0.001
	MRNA-1273	2/59 (3.4)	0.03 (0.01–0.11)	<0.001	0.06 (0.01–0.26)	<0.001
	Other	30/92 (43.6)	0.34 (0.22–0.54)	<0.001	0.39 (0.4–0.62)	<0.001
Month of dose	Q1 (Jan–Mar)	4080/8262 (49.4)	4.14 (3.33–5.14)	<0.001	3.79 (3.01–4.76)	<0.001
	Q2 (Apr–Jun)	144/625 (23.0)	1.00		1.00	
	Q3 (Jul–Sep)	0/1 (0.00)	N/A		N/A[a]	
	Q4 (Oct–Dec)	38/1125 (31.3)	1.94 (1.24–3.02)	0.003	4.28 (2.69–6.80)	<0.001
Age, years	16–29.99	45/120 (37.5)	1.00		1.00	
	30–39.99	121/341 (35.5)	0.92 (0.59–1.42)	0.69	0.82 (0.49–1.33)	0.44
	40–49.99	373/800 (46.6)	1.42 (0.96–2.12)	0.08	0.90 (0.57–1.42)	0.65
	50–59.99	1286/2192 (58.7)	2.36 (1.61–3.45)	<0.001	1.03 (0.66–1.61)	0.90
	60–69.99	1716/3617 (47.4)	1.56 (1.07–2.28)	0.021	0.72 (0.46–1.12)	0.14
	≥70.00	721/1933 (37.3)	1.10 (0.75–1.61)	0.64	0.58 (0.37–0.92)	0.020
	P for trend				0.85 (0.81–0.90)	<0.001
Sex	Female	3297/6367 (51.8)	1.00		–	–
	Male	965/2636 (36.6)	0.57 (0.52–0.63)	<0.001	0.59 (0.53–0.65)	<0.001
IMD rank, quartile	Q1 (most deprived)	906/2030 (44.7)	0.84 (0.75–0.95)	0.006	0.90 (0.79–1.02)	0.10
	Q2	1020/2160 (47.2)	0.95 (0.84–1.07)	0.39	0.95 (0.84–1.08)	0.44
	Q3	1129/2343 (48.2)	1.00 (0.89–1.12)	0.96	1.00 (0.89–1.13)	0.97
	Q4 (least deprived)	1182/2430 (48.7)	1.00		–	–
	P for trend				0.96 (0.92–1.00)	0.070
Tobacco smoking status	Not current smoker	4097/8633 (47.5)	1.00		1.00	
	Current smoker	165/370 (44.7)	0.83 (0.67–1.03)	0.09	0.80 (0.64–1.01)	0.06
Alcohol, units/wk	0	1170/2349 (49.8)	1.00		1.00	
	1–7	1530/3189 (48.0)	0.95 (0.85–1.05)	0.31	1.01 (0.90–1.13)	0.91
	8–14	861/1853 (46.5)	0.93 (0.82–1.05)	0.25	1.02 (0.90–1.18)	0.68
	15–21	398/901 (44.2)	0.86 (0.73–1.01)	0.06	0.91 (0.77–1.08)	0.30
	22–28	178/403 (44.3)	0.91 (0.73–1.14)	0.42	0.98 (0.78–1.24)	0.89
	>28	125/308 (40.6)	0.80 (0.62–1.03)	0.08	0.84 (0.65–1.10)	0.21
	P for trend				0.98 (0.94–1.02)	0.26
Self-rated general health	Excellent	801/18,758 (42.7)	1.00		1.00	
	Very good	1620/3590 (45.1)	1.15 (1.02–1.29)	0.019	1.13 (1.00–1.28)	0.05
	Good	1162/2326 (50.0)	1.37 (1.21–1.56)	<0.001	1.38 (1.20–1.58)	<0.001
	Fair	530/949 (55.9)	1.67 (1.42–1.96)	<0.001	1.53 (1.28–1.83)	<0.001
	Poor	149/260 (57.3)	1.74 (1.33–2.27)	<0.001	1.54 (1.14–2.07)	0.005
	P for trend				1.15 (1.10–1.21)	<0.001
Pre-vaccination SARS-CoV-2 status	Seronegative	3560/7640 (46.6)	1.00		1.00	
	Seropositive asymptomatic	439/958 (45.8)	0.99 (0.86–1.13)	0.83	0.94 (0.81–1.09)	0.42
	Seropositive symptomatic	263/405 (64.9)	2.01 (1.62–2.48)	<0.001	2.23 (1.78–2.81)	<0.001
	P for trend				1.26 (1.15–1.38)	<0.001
Self-rated anxiety or depression	No	3040/6744 (45.1)	1.00		1.00	
	Yes	1220/2253 (54.2)	1.35 (1.23–1.49)	<0.001	1.24 (1.12–1.39)	<0.001
Asthma	No	3489/7552 (46.2)	1.00		1.00	
	Yes	773/1451 (53.3)	1.29 (1.15–1.45)	<0.001	1.12 (0.95–1.32)	0.18
Atopic disease[b]	No	3041/6684 (45.5)	1.00		1.00	
	Yes	1221/2319 (52.7)	1.28 (1.16–1.41)	<0.001	1.20 (1.08–1.34)	0.001
Arterial disease	No	4040/8514 (47.5)	1.00		1.00	
	Yes	222/489 (45.4)	1.21 (1.00–1.47)	0.049	1.31 (1.06–1.63)	0.014
Kidney disease	No	4164/8821 (47.2)	1.00		1.00	
	Yes	98/182 (53.9)	1.47 (1.09–1.99)	0.012	1.40 (1.01–1.93)	0.043

Table 2 continued

			Minimally adjusted		Fully adjusted	
		N (%) symptomatic	aOR (95% CI)	*P*	aOR (95% CI)	*P*
Cancer	Never	3891/8117 (47.9)	1.00		1.00	
	Previous	346/809 (42.8)	0.84 (0.72–0.97)	0.021	0.83 (0.71–0.97)	0.019
	Active	25/77 (32.5)	0.64 (0.39–1.05)	0.078	0.62 (0.37-1.05)	0.076
Statins	No	3620/7,377 (49.1)	1.00		1.00	
	Yes	642/1626 (39.5)	0.87 (0.77–0.98)	0.022	0.84 (0.74–0.97)	0.014
ACE inhibitors	No	3903/8101 (48.2)	1.00		1.00	
	Yes	359/902 (39.8)	0.82 (0.7–0.95)	0.008	0.80 (0.69–0.94)	0.007
Inhaled corticosteroids	No	3951/8415 (47.0)	1.00		1.00	
	Yes	311/588 (52.9)	1.24 (1.04–1.47)	0.015	0.98 (0.78–1.25)	0.89
Systemic immunosuppressants	No	4051/8607 (47.1)	1.00		1.00	
	Yes	211/396 (53.3)	1.29 (1.05–1.59)	0.014	1.10 (0.87–1.38)	0.423
Inhaled bronchodilators	No	3807/8160 (46.6)	1.00		1.00	
	Yes	453/837 (54.1)	1.31 (1.14–1.52)	<0.001	1.49 (0.63–3.50)	0.37
Beta-2 adrenergic agonists	No	3,822/8,192 (46.7)	1.00		1.00	
	Yes	440/811 (54.3)	1.31 (1.13–1.51)	<0.001	0.66 (0.27–1.60)	0.36
Multivitamin supplement	No	3258/7168 (45.5)	1.00		1.00	
	Yes	1004/1835 (54.7)	1.42 (1.28–1.58)	<0.001	1.41 (1.26–1.58)	<0.001
Vitamin D supplement	No	3213/6690 (48.1)	1.00		1.00	
	Yes	1049/2133 (45.3)	1.81 (0.97–3.38)	0.06	0.92 (0.83–1.02)	0.12

[a]ORs were not calculated where fewer than 5 participants experienced an event.
[b]Atopic disease defined by atopic eczema/dermatitis and/or hayfever/allergic rhinitis.

of reporting systemic symptoms after first vaccine dose: time of year (aOR 3.79, 95% CI: 3.01–4.76, for Q1 vs. Q2; aOR 4.28, 95% CI: 2.69–6.80, for Q4 vs. Q2), poorer self-rated general health (aOR per category of worsening health 1.15, 95% CI: 1.10–1.21), pre-vaccination SARS-CoV-2 seropositivity with symptoms vs. pre-vaccination SARS-CoV-2 seronegativity (aOR 2.23, 95% CI: 1.78–2.81), presence vs. absence of self-rated anxiety or depression (aOR 1.24, 95% CI: 1.12–1.39), presence vs. absence of atopic disease (aOR 1.20, 95% CI: 1.08–1.34), presence vs. absence of arterial disease (aOR 1.31, 95% CI: 1.06–1.63), presence vs. absence of kidney disease (aOR 1.40, 95% CI: 1.01–1.93), and use vs. no use of multivitamin supplements (aOR 1.41, 95% CI: 1.26–1.58). Lower risk of developing systemic post-vaccination symptoms following first dose was independently associated with administration of mRNA vaccines vs. ChAdOx1 (aOR 0.29, 95% CI: 0.26–0.32 for BNT162b2 vs. ChAdOx1; aOR 0.06, 95% CI: 0.01–0.26 for mRNA-1273 vs. ChAdOx1), greater age (aOR per additional 10 years of age 0.85, 95% CI: 0.81–0.90), male vs. female sex at birth (aOR 0.59, 95% CI: 0.53–0.65), presence vs. absence of previous cancer (aOR 0.83, 95% CI: 0.71–0.97), use vs. no use of statins (aOR 0.84, 95% CI: 0.74–0.97), and use vs. no use of ACE inhibitors (aOR 0.80, 95% CI: 0.69–0.94).

Given that we showed no association between asymptomatic pre-vaccination SARS-CoV-2 infection and risk of systemic symptoms after a first vaccine dose (aOR 0.94, 95% CI: 0.81–1.09, Table 2), we conducted an exploratory analysis to compare pre-vaccination anti-S titres between participants who experienced symptomatic vs. asymptomatic SARS-CoV-2 infection prior to vaccination: the former group had higher anti-S titres than the latter ($P < 0.001$, Supplementary Fig. 2).

In another exploratory analysis, we investigated whether these factors also associated independently with the mean total number of different systemic symptoms reported by the subset of participants reporting at least one such symptom. Results are displayed in Supplementary Table 4, Supplementary Material. Higher mean number of systemic symptoms reported associated independently with younger age (*P* for trend 0.01), female vs. male sex (1.62 vs. 1.54, $P = 0.028$), symptomatic SARS-CoV-2 infection vs. no SARS-CoV-2 infection pre-vaccination (1.76 vs. 1.58, $P = 0.013$), administration of ChAdOx1 vs. BNT162b2 (1.69 vs. 1.20, $P < 0.001$) and presence vs. absence of atopic disease (1.66 vs. 1.58, $P = 0.019$).

Determinants of systemic symptoms following a second dose of vaccine were broadly similar, in that administration of BNT162b2 vs. ChAdOx1, vaccination in Q1 vs. Q2, poorer vs. better self-rated general health, pre-vaccination SARS-CoV-2 seropositivity with symptoms vs. pre-vaccination SARS-CoV-2 seronegativity, presence vs. absence of self-rated anxiety or depression, presence vs. absence of atopic disease, and use vs. no use of multivitamin supplements associated with higher risk of reporting symptoms and greater age, and male vs. female sex at birth all associated with lower risk. Additionally, a shorter inter-dose interval associated with reduced risk of systemic symptoms after the second vaccine dose (aOR 0.61, 95% CI: 0.46–0.83 for <6 weeks vs. >10 weeks; aOR 0.86, 95% CI: 0.76–0.96 for 6–10 weeks vs. >10 weeks), as did higher alcohol intake (aOR per increasing category 0.93, 95% CI: 0.89–0.96) and use vs. no use of anticholinergic medication (aOR 0.73, 95% CI: 0.53–0.99; Supplementary Table 5, Supplementary Material).

Determinants of local reactive symptoms following first vaccine dose

After adjustment for age and sex only, 33 variables were found to associate with risk of experiencing local symptoms following a first vaccine dose with $P < 0.10$ (Table 3) and 8 were not (Supplementary Table 6, Supplementary Material). After inclusion of all of these factors in a multivariable model, the following variables were independently associated with higher risk of reporting local symptoms after first dose: administration of BNT162b2 vs. ChAdOx1 (aOR 1.95 95% CI: 1.74–2.18), administration of vaccine

Table 3. Incidence and determinants of local reactive symptoms after a first dose of SARS-CoV-2 vaccine.

			Minimally adjusted		Fully adjusted	
		N (%) symptomatic	aOR (95% CI)	*P*	aOR (95% CI)	*P*
Vaccine type	ChAdOx1	2414/5988 (40.3)	1.00		1.00	
	BNT162b2	1470/2864 (51.3)	1.78 (1.62–1.96)	<0.001	1.95 (1.74–2.18)	<0.001
	MRNA-1273	6/59 (10.2)	0.16 (0.07–0.38)	<0.001	N/A	N/A
	Other	24/92 (26.1)	0.50 (0.31–0.81)	0.005	0.47 (0.27–0.82)	0.008
Timing	Before 12:00	1520/3193 (47.6)	1.00			1.00
	12:00–14:00	745/1425 (52.3)	1.23 (1.08–1.41)	0.002	1.23 (1.07–1.41)	0.004
	14:00–17:00	1097/2200 (49.9)	1.09 (0.98–1.22)	0.123	1.05 (0.93–1.18)	0.45
	After 17:00	509/1030 (49.4)	1.03 (0.89–1.19)	0.720	1.00 (0.85–1.17)	0.99
Month of dose	Q1 (Jan–Mar)	3722/8262 (45.1)	5.07 (4.04–6.35)	<0.001	1.11 (0.81–1.52)	0.51
	Q2 (Apr–Jun)	129/625 (20.6)	1.00		1.00	
	Q3 (Jul–Sep)	0/1 (0.00)	N/A		N/A	
	Q4 (Oct–Dec)	63/115 (54.8)	6.90 (4.46–10.7)	<0.001	0.89 (0.52–1.53)	0.68
Age, years	16–29.99	50/120 (41.7)	1.00		1.00	
	30–39.99	128/341 (37.5)	0.84 (0.55–1.29)	0.43	0.51 (0.21–1.28)	0.15
	40–49.99	389/800 (48.6)	1.29 (0.87–1.91)	0.20	0.46 (0.20–1.09)	0.08
	50–59.99	1164/2192 (53.1)	1.57 (1.08–2.29)	0.019	0.26 (0.11–0.60)	0.002
	60–69.99	1546/3617 (42.7)	1.09 (0.75–1.58)	0.66	0.17 (0.07–0.38)	<0.001
	≥70.00	637/1933 (33.0)	0.77 (0.53-1.13)	0.18	0.10 (0.04–0.23)	<0.001
	P for trend				0.62 (0.59–0.66)	<0.001
Sex	Female	3104/6367 (48.8)	1.00		1.00	
	Male	810/2636 (30.7)	0.50 (0.46–0.55)	<0.001	0.48 (0.43–0.54)	<0.001
Education	Primary/Secondary	381/978 (39.0)	0.82 (0.71–0.96)	0.012	0.78 (0.66–0.94)	0.009
	Higher/Further	553/1265 (43.7)	0.95 (0.83–1.09)	0.48	0.97 (0.82–1.34)	0.68
	College	1728/3991 (43.3)	0.94 (0.85–1.04)	0.24	0.96 (0.85–1.08)	0.50
	Post-graduate	1248/2762 (45.2)	1.00		1.00 (ref)	
	P for trend				0.94 (0.89–0.99)	0.024
Vigorous physical exercise, hr/wk	0	1529/3359 (45.5)	1.19 (1.06–1.32)	0.002	1.02 (0.89–1.17)	0.74
	1–3	1450/3323 (43.6)	1.09 (0.97–1.21)	0.15	1.05 (0.92–1.19)	0.49
	≥4	926/2301 (40.3)	1.00		1.00	
	P for trend				0.99 (0.92–1.06)	0.78
Light physical exercise, hr/wk	0–4	1305/2832 (46.1)	1.16 (1.04–1.29)	0.006	1.05 (0.92–1.19)	0.49
	5–9	1311/2983 (44.0)	1.07 (0.96–1.18)	0.24	1.07 (0.95–1.21)	0.27
	≥10	1293/3172 (40.8)	1.00		1.00	
	P for trend				0.98 (0.91–1.04)	0.46
Dietary restrictions	None	3679/8500 (43.3)	1.00			1.00
	Vegetarian	196/397 (49.4)	1.16 (0.95–1.43)	0.15	1.36 (1.05–1.76)	0.019
	Vegan	3679/8500 (43.3)	0.70 (0.47–1.04)	0.080	0.64 (0.40–1.03)	0.067
Self-rated general health	Excellent	711/1878 (37.8)	1.00		1.00	
	Very good	1491/3590 (41.5)	1.21 (1.08–1.36)	0.001	1.19 (1.04–1.36)	0.013
	Good	1099/2326 (47.3)	1.50 (1.32–1.70)	<0.001	1.43 (1.23–1.68)	<0.001
	Fair	481/949 (50.7)	1.64 (1.40–1.93)	<0.001	1.49 (1.21–1.83)	<0.001
	Poor	132/260 (50.8)	1.60 (1.23–2.09)	0.001	1.41(1.00–1.99)	0.048
	P for trend				1.14 (1.08–1.21)	<0.001
Body mass index, kg/m^2	<25	1882/4369 (43.1)	1.00		1.00	
	25–30	1226/2907 (42.2)	1.04 (0.94–1.14)	0.38	0.95 (0.85–1.07)	0.38
	>30	799/1709 (46.8)	1.12 (1.00–1.27)	0.05	0.88 (0.76–1.02)	0.08
Pre-vaccination SARS-CoV-2 status	Seronegative	3270/7640 (42.8)	1.00			1.00
	Seropositive asymptomatic	407/958 (42.5)	1.00 (0.87–1.15)	0.96	0.96 (0.81–1.12)	0.58
	Seropositive symptomatic	237/405 (58.5)	1.74 (1.41–2.14)	<0.001	1.84 (1.43–2.38)	<0.001
	P for trend				1.19 (1.08–1.32)	0.001

Table 3 continued

			Minimally adjusted		Fully adjusted	
		N (%) symptomatic	aOR (95% CI)	*P*	aOR (95% CI)	*P*
Self-rated anxiety or depression	No	2806/6744 (41.6)	1.00		1.00	
	Yes	1106/2253 (49.1)	1.23 (1.11–1.35)	<0.001	1.17 (1.03–1.32)	0.018
Asthma	No	3206/7552 (42.5)	1.00		1.00	
	Yes	708/1451 (48.8)	1.23 (1.10–1.38)	<0.001	1.17 (0.97–1.41)	0.10
Atopic disease[a]	No	2781/6684 (41.6)	1.00		1.00	
	Yes	1133/2319 (48.8)	1.27 (1.15–1.40)	<0.001	1.15 (1.02–1.30)	0.019
Diabetic status	No diabetes	3612/8278 (43.6)	1.00		1.00	
	Pre-diabetes	120/291 (41.0)	1.03 (0.81–1.32)	0.79	0.88 (0.67–1.17)	0.38
	Type 1 diabetes	35/61 (57.4)	1.84 (1.09–3.09)	0.022	1.02 (0.57–1.84)	0.94
	Type 2 diabetes	141/363 (38.6)	0.99 (0.79–1.24)	0.95	0.94 (0.71–1.25)	0.68
Heart disease	No	3769/8642 (43.6)	1.00		1.00	
	Yes	145/361 (40.2)	1.23 (0.99–1.54)	0.07	0.78 (0.49–1.22)	0.27
Arterial disease	No	3708/8514 (43.5)	1.00		1.00	
	Yes	206/489 (42.1)	1.33 (1.10–1.62)	0.004	1.43 (0.90–2.28)	0.13
Major neurological condition	No	3802/8752 (43.4)	1.00		1.00	
	Yes	112/251 (44.6)	1.29 (1.00–1.68)	0.05	1.00 (0.66–1.51)	1.00
Immunodeficiency	No	3883/8950 (43.4)	1.00		1.00	
	Yes	31/53 (58.5)	2.03 (1.16–3.55)	0.013	1.80 (0.92-3.47)	0.09
Statins	No	3272/7377 (44.4)	1.00		1.00	
	Yes	642/1626 (39.5)	1.18 (1.04–1.33)	0.008	1.09 (0.94–1.28)	0.26
Proton pump inhibitors	No	3354/7752 (43.3)	1.00		1.00	
	Yes	560/1251 (44.8)	1.20 (1.06–1.35)	0.005	0.98 (0.84–1.14)	0.77
Inhaled corticosteroids	No	3622/8415 (43.0)	1.00		1.00	
	Yes	292/588 (49.7)	1.27 (1.07–1.51)	0.006	1.02 (0.79–1.32)	0.89
SSRIs	No	3619/8430 (42.9)	1.00		1.00	
	Yes	295/573 (51.5)	1.22 (1.03–1.46)	0.022	1.06 (0.86–1.32)	0.57
Thiazides	No	3782/8708 (43.4)	1.00		1.00	
	Yes	132/295 (44.8)	1.25 (0.98–1.59)	0.07	1.24 (0.94–1.63)	0.14
Inhaled bronchodilators	No	3807/8160 (46.6)	1.00		1.00	
	Yes	453/837 (54.1)	1.31 (1.14–1.52)	<0.001	1.49 (0.63–3.50)	0.37
Sodium-glucose co-transporter-2 (SGLT2) inhibitors	No	3901/8955 (43.6)	1.00		1.00	
	Yes	13/48 (27.1)	0.57 (0.30–1.09)	0.09	0.48 (0.22–1.05)	0.07
Anti-platelet drugs	No	3666/8404 (43.6)	1.00		1.00	
	Yes	248/599 (41.4)	1.26 (1.06–1.50)	0.011	0.88 (0.54–1.44)	0.61
Beta-2 adrenergic agonists	No	3822/8192 (46.7)	1.00		1.00	
	Yes	440/811 (54.3)	1.31 (1.13–1.51)	<0.001	0.66 (0.27–1.60)	0.36
Aspirin	No	3716/8531 (43.6)	1.00		1.00	
	Yes	198/472 (42.0)	1.29 (1.06-1.56)	0.012	1.22 (0.74–2.02)	0.44
BCG vaccinated	No	414/1087 (38.1)	1.00		1.00	
	Yes	3197/7084 (45.1)	1.25 (1.09–1.43)	0.001	1.21 (1.04–1.41)	0.013
Multivitamin supplement	No	3258/7168 (45.5)	1.00		1.00	
	Yes	1004/1835 (54.7)	1.42 (1.28–1.58)	<0.001	1.41 (1.26–1.58)	<0.001
Vitamin D supplement	No	3213/6690 (48.1)	1.00		1.00	
	Yes	1049/2133 (45.3)	1.81 (0.97–3.38)	0.06	0.92 (0.83–1.02)	0.12

[a]Atopic disease defined by atopic eczema/dermatitis and/or hayfever/allergic rhinitis.

at lunchtime (i.e. 12:00–14:00) vs. morning (i.e. before 12:00; aOR 1.23, 95% CI: 1.07–1.41), vegetarian vs. unrestricted diet (aOR 1.36, 95% CI: 1.05–1.76), poorer vs. better self-rated general health (aOR per worsening health category 1.14, 95% CI: 1.08–1.21), pre-vaccination SARS-CoV-2 seropositivity with symptoms vs. pre-vaccination SARS-CoV-2 seronegativity (aOR 1.84, 95% CI: 1.43–2.38), presence vs. absence of self-rated anxiety or depression (aOR 1.17, 95% CI: 1.03–1.32), presence vs. absence of atopic disease (aOR 1.15, 95% CI: 1.02–1.30), BCG vaccinated vs. not (aOR 1.21, 95% CI: 1.04–1.41), and use vs. no use of multivitamin