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Relationship between multimorbidity, SARS-COV-2 infection and long COVID: a cross-sectional population-based French survey

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Abstract

Background Understanding the risks of COVID-19-related consequences for vulnerable groups such as people with multimorbidity is crucial to better tailor health care and public health measures. The main objective of this study was to explore the association between multimorbidity and WHO-defined post-COVID condition (PCC), while also considering the association with SARS-COV-2 infection given that the infection is a prerequisite of PCC.

Methods This population-representative cross-sectional study was conducted in the general adult population in mainland France between 29 August and 31 December 2022 ($N=1813$). The analyses of the association between multimorbidity (defined as disease count and most prevalent dyads/triads) and PCC or SAR-COV-2 infection were adjusted for age, sex, socioeconomic variables and number of infections (for PCC only) using adjusted Poisson regression with robust variance.

Results The study population had a mean age (SD) of 53 (± 18.5) years, while 53.6% were women. The likelihood of SARS-COV-2 infection increased with disease count but was only significant for ≥ 4 diseases. Five dyads and one triad presented a higher risk; almost all included anxiety. The likelihood of PCC increased with disease count, prevalence ratios (PRs) (95% CI) for 1, 2–3 and ≥ 4 diseases versus 0 were 1.90 (1.16–3.13), 3.32 (2.07–5.35) and 5.65 (3.41–9.38), respectively, and for 19 of 26 most prevalent dyads and the triad. The association was strongest for cardiac rhythm disorder and either low back pain (PR (95%CI) 4.17 (2.03–8.53)) or anxiety (PR (95%CI) 3.73 (1.98–7.01)).

Conclusions Multimorbidity, most frequently in combination with anxiety or low back pain, presented a significant association with PCC beyond that of SARS-CoV-2 infection underscoring the importance of implementing strategies to prevent and manage persistent symptoms in vulnerable groups.

Keywords Multimorbidity, Multiple conditions, SARS-COV-2, Long COVID, Post COVID-19 condition, France

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Background

Understanding high-risk groups during the COVID-19 pandemic has driven major public health decisions such as isolating during outbreaks or prioritising vaccination. Clinical decisions like hospital admission or mechanical ventilation for COVID-19 patients were also guided by preexisting health issues [1]. Although the role of individual diseases such as diabetes, cardiovascular or respiratory illnesses in COVID-19-related risks and consequences was explored in the earlier pandemic years [2], the risks for individuals with multiple diseases or multimorbidity were seldom assessed [3]. Recently, more studies have explored this issue [4–7], although they remain focused on short-term outcomes such as mortality, hospitalisation or intensive care unit (ICU) admission, while evidence on the long-term effects of SARS-COV-2 infection among patients with multimorbidity is absent [3]. Given that multimorbidity has become 'the rule rather than the exception' in clinical practice due to increased life expectancy and disease accumulation with age [8, 9], data regarding the risks for this vulnerable population group in the context of changing epidemiological situations are extremely relevant.

Individuals with more diseases or a higher comorbidity index score such as Elixhauser or Charlson comorbidity indices have consistently shown a higher likelihood of hospitalisation, ICU admission or mortality [4–7, 10]. The relationship with SARS-COV-2 infection is less often investigated and with less conclusive findings: some evidence indicates a higher infection probability for a greater morbidity burden, while the opposite effect is also observed, potentially due to the better compliance with protective measures during the pandemic [6, 11].

Long COVID refers to prolonged symptoms after SARS-CoV-2 infection. Depending on the duration of symptoms, the time of their appearance and other criteria, this pathology has received several designations. The National Institute for Care and Excellence (NICE) describes ongoing symptomatic COVID-19 in which the signs and symptoms of COVID-19 last from 4 to 12 weeks and post-COVID-19 syndrome in which the signs and symptoms consistent with COVID-19 appear during or after infection and last for over 12 weeks with no alternative diagnosis [12]. In addition, the World Health Organisation (WHO) refers to post-COVID-19 condition (PCC) [13] (with the four criteria detailed later in the manuscript), while Thaweethai et al. describe post-acute COVID-19 sequelae (PASC) involving ongoing, relapsing, or new symptoms or conditions lasting for at least 30 days after infection [14]. All the definitions acknowledge a diversity of symptoms such as chronic fatigue, cognitive dysfunction, altered smell and taste, dyspnea and anxiety [15, 16]. Many potential causes of long COVID have been suggested, including (but not limited to) immune dysregulation, persisting deposits of SARS-COV-2 virus and dysfunctional signalling in the nervous system [17]. Risk factors include socioeconomic characteristics such as larger household size and low financial security, number of SARS-COV-2 infections, vaccination status, work-related factors such as negative effects of the COVID-19 pandemic on occupation (loss or change of profession) and work conditions, overall perception of COVID-19 severity and long COVID awareness [18]. A recent meta-analysis highlighted the higher risk of long COVID for individuals with existing chronic conditions such as mental health issues, ischemic heart diseases, diabetes, chronic obstructive pulmonary disease and immunosuppression [19]. Only a few studies accounted for the number of diseases or Charlson comorbidity index when analysing the risks of prolonged symptoms after SARS-COV-2 infection [20–23] or treated multimorbidity as a binary variable, which limits our understanding of the association between more granular multimorbidity groups and long COVID [24]. A clearer and more focused approach to the risks of long COVID is thus required for individuals with multimorbidity.

This study investigates the association between multimorbidity, operationalised as disease count and disease combinations, and WHO PCC in a representative sample of adults in mainland France. As SARS-COV-2 infection is a prerequisite for PCC, we also analysed the relationship between multimorbidity and SARS-COV-2 infection.

Methods

Study design

This cross-sectional study was conducted among the adult population (≥ 18 years) in mainland France. Participants were randomly selected using landline (two-stage sampling design; one person per household was selected following the Kish model) and mobile phone numbers (the owner of the number was selected) [25]. Data were collected by a specialised market research provider IPSOS [26] between 29 August and 31 December 2022 in two phases: computer-assisted telephone interview (CATI) and computer-assisted web interview (CAWI). The first part inquired about the number and date of SARS-COV-2 infection(s) (year/month/day), acute infection symptoms and the confirmed or probable status of infection. Data also included COVID-19-related hospitalisations and ICU admissions, workplace contaminations, every PCC symptom appearance (year/month/day), their link with SARS-COV-2 infection (confirmed by a physician) and impact on daily functioning (participant's rating as no, low, moderate, strong and very strong impact for each PCC symptom). This part also

collected socioeconomic data as well as brief information about health care usage and general and mental health. All participants whose symptoms complied with WHO PCC criteria (PCC participants) were directed to an online platform to complete CAWI, as were sub-samples of non-infected participants (sampling ratio 1/5.7) and infected participants without PCC (sampling ratio 1/2.0). The mentioned sampling ratios were chosen to ensure the minimum sample size for each sample group (> 150 participants) [18]. CAWI collected detailed information about health care use in the past 12 months (specialist consultations, medical exams), COVID-19-related work absence, vaccination, chronic conditions, health behaviour, mental health, quality of life, social support, impact of COVID-19 crisis on income as well as professional and social life. The full interview (CATI and CAWI) lasted for around 45 min.

Ascertainment of SARS-CoV-2 infections and post-COVID-19 condition

SARS-CoV-2 infections were regarded as confirmed cases when the infection was confirmed by a test or physician and probable cases when participants declared that infection was most likely due to COVID-19 even if no testing was performed or when the test was negative. Multiple infections were separately recorded when occurring more than 2 months apart. For each infection (up to five infections), the same procedure was repeated, including specifying the date of infection (day/month/year) and inquiring whether the infection was confirmed or probable.

We used the WHO PCC definition to select PCC patients: confirmed or probable infected subjects with at least one symptom appearing within 3 months of infection and lasting for at least 2 months, which could not be explained by an alternative diagnosis and had an impact on daily functioning [27, 28]. The date of infection and appearance of symptoms allowed us to estimate the duration of symptoms and exclude those predating SARS-CoV-2 infection. The list of PCC symptoms is available in Supplementary Table 1.

Definition and operationalisation of multimorbidity

Multimorbidity was defined as the coexistence of ≥ 2 chronic conditions in an individual [29, 30] and operationalised through disease groups (0, 1, 2–3, 4 + diseases) and disease combinations (most frequent dyads and triads). Participants selected chronic conditions from a list of 21 + conditions if they were present in the past 12 months and had been diagnosed by a physician (Table 1). All diseases were combined into dyads and triads, which were then tested for prevalence in the total population. Dyads and triads with > 30 subjects were considered the most prevalent.

Statistical analyses

The likelihood of SARS-COV-2 infection was estimated among all study participants who answered CAWI. The likelihood of developing PCC was estimated among infected CAWI subjects.

Study characteristics were presented as crude numbers and weighted percentages using sex, age, region of residence, urbanisation unit, household size and education level for standardisation based on data from the French National Institute for Statistics and Economic Studies (Insee).

All covariates were tested for association with multimorbidity, SARS-COV-2 infection and PCC using age- and sex-adjusted Poisson regression [31]. Associated variables and those identified in the literature as relevant were included in the final models as adjustment factors.

Final models were hence adjusted for age, sex, socioeconomic variables and number of infections (for the risk of PCC) using adjusted Poisson regression with robust variance to estimate prevalence ratios (PRs) and 95% confidence intervals (CI) for the association between multimorbidity (as a disease count [four categories] or disease combinations [dyads and triads]) and SARS-CoV-2 infection and PCC, respectively [31]. Reference categories were 0 diseases (for the analyses with disease count) and the population without the dyad/triad in question (including individuals with other disease combinations and 0 or 1 disease) (for the analysis with disease combinations).

Multicollinearity was tested among the adjustment factors such as socioeconomic variables and number of infections using the Spearman correlation coefficient.

To conduct a more detailed analysis of the associations, we tested for age- and sex-based interactions with multimorbidity in relation to SARS-COV-2 infection and PCC.

To estimate a possible departure from a multiplicative effect of diseases on the likelihood of PCC and infection, we tested the interactions between diseases constituting the dyads in the fully adjusted models [32].

All analyses were performed in SAS, version 9.2 software (SAS Institute, Cary, NC).

Funding source and ethics approval

This study did not receive any specific funding from public or private agencies or from non-profit entities. The study was approved by the local Ethics and Deontology Committee on 19 August 2022.

Data and codes can be made available upon reasonable request and approval from the ethics committee.

Table 1 Study characteristics of the total study sample, infected participants and participants with post-COVID-19 condition

		Total study sample (*N* = 1813)		**Infected participants (*N* = 1448)**		**Infected participants with post-COVID-19 condition (*N* = 178)**	
		N	**%[a]**	***N***	**%[a]**	***N***	**%[a]**
Sex	Male	779	46.4	624	46.6	48	29.5
	Female	1034	53.6	824	53.4	130	70.5
Age	18-29	219	12.2	198	15.8	23	14.2
	30-39	257	13.7	225	16.7	25	16.5
	40-49	356	17.5	299	18.6	51	26.0
	50-59	373	16.6	323	20.1	43	22.7
	60-69	330	18.3	238	15.1	28	15.8
	70+	278	21.7	165	13.7	8	4.9
Living alone	Yes	428	28.2	302	22.0	27	15.5
	No	1385	71.8	1146	78.0	151	84.5
Education	Less than secondary	506	37.9	373	30.5	43	30.3
	Secondary	616	31.4	503	34.5	60	33.6
	Tertiary	691	30.7	572	35.0	75	36.1
Employment status	Paid employment	1062	50.6	920	60.4	124	67.0
	Unemployed	69	4.0	56	3.7	8	5.4
	Retired	508	35.0	326	24.4	25	14.1
	Other inactive	174	10.4	146	11.6	21	13.5
Household income	First tertile	320	22.0	236	18.0	29	18.9
	Second tertile	659	36.8	515	36.0	65	37.0
	Third tertile	759	36.6	637	41.9	76	40.1
	Not reported	75	4.6	60	4.2	8	4.0
Household financially at ease	Yes	1194	66.4	938	65.0	87	47.4
	No	619	33.6	510	35.0	91	52.6
Smoking every day	Yes	271	16.5	213	14.9	39	22.8
	No	1542	83.5	1235	85.1	139	77.2
Moderate physical activity	Almost never or never	107	7.3	73	5.2	10	5.7
	Max 3 times a month	602	31.3	495	33.6	64	35.6
	Several times a week	1104	61.5	880	61.2	104	58.7
Alcohol consumption	No consumption in the last 12 months to 3 times a month	938	52.1	747	51.4	107	61.1
	1 to 6 days a week	741	40.1	604	42.0	60	33.6
	Every day or almost every day	134	7.7	97	6.6	11	5.3
COVID-19 vaccination status	0 or 1 doses	174	8.3	155	10.5	22	13.0
	2	378	17.6	350	24.3	45	27.1
	3 or 4	1261	74.1	943	65.2	111	59.9
Number of infections	0	365	45.2	NA	NA	NA	NA
	1	1159	45.0	1159	82.1	117	63.5
	≥2	289	9.8	289	17.9	61	36.5
Hospitalisation due to COVID-19	Yes	20	0.6	20	1.0	4	2.7
	No	1793	99.4	1428	99.0	174	97.3
ICU admission due to COVID-19	Yes	5	0.2	5	0.3	1	0.6
	No	1808	99.8	1443	99.7	177	99.4

Table 1 (continued)

		Total study sample (*N* = 1813)		Infected participants (*N* = 1448)		Infected participants with post-COVID-19 condition (*N* = 178)	
		N	%[a]	*N*	%[a]	*N*	%[a]
Multimorbidity (number of diseases)	0	637	36.5	513	38.1	28	15.6
	1	491	27.8	384	26.7	41	22.2
	2 or 3	470	24.1	380	24.7	66	37.1
	≥4	215	11.7	171	10.6	43	25.1
Individual diseases							
Hypertension		215	13.4	150	10.2	19	11.3
Angina pectoris or myocardial infarction		11	0.4	10	0.6	3	1.6
Stroke or cerebrovascular accident (with or without sequelae)		6	0.3	5	0.4	1	0.6
Lower limb arteritis (arterial disease)		6	0.7	3	0.2	0	0.0
Cardiac rhythm disorder		111	5.6	93	6.1	19	11.7
Organ or blood cancer		36	2.0	27	2.1	2	1.0
Chronic bronchitis, emphysema, COPD		43	1.7	37	1.9	8	4.6
Asthma		76	3.6	66	4.1	13	7.1
Hearing impairment		133	8.0	101	7.0	17	9.9
Uncorrected eyesight problems		98	4.8	82	4.8	24	13.7
Liver cirrhosis		3	0.2	2	0.1	0	0.0
Thyroid disorders (goiter, hyper- or hypothyroidism)		104	5.3	83	5.1	14	6.7
Depression		127	5.6	114	6.8	36	21.8
Anxiety		316	14.0	278	17.5	68	39.8
Low back pain		373	19.6	297	18.5	57	31.7
Peripheral osteoarthritis		229	14.3	166	11.2	31	18.3
Osteoporosis		60	3.0	47	3.1	7	3.9
Renal insufficienc		27	2.3	17	1.3	2	1.3
Physical disability due to accident or illness		73	4.1	57	4.0	10	5.3
Diabetes		90	5.0	67	4.5	10	6.5
Obesity		311	17.9	249	17.2	35	21.5
Other		194	9.3	160	9.7	32	16.1

COPD Chronic obstructive pulmonary disease

[a] weighted percentages

Results

Study population characteristics

The CAWI response rate was 43% with 1813 participants completing the interview; this was similar across all groups. The mean age (SD) was 53 (± 18.5) and 53.6% were women.

Over one-third (35.8%) of the population had two or more chronic conditions (multimorbidity). The most frequent conditions were low back pain, obesity, peripheral osteoarthritis and anxiety (Table 1).

Twenty-six dyads were identified. The most frequent were low back pain and peripheral osteoarthritis (5.6%), anxiety and low back pain (5.4%), and hypertension and obesity (4.6%). Only one triad was observed in over 30 subjects, combining anxiety, depression and low back pain (1.2%) (Supplementary Table 2). Descriptive statistics showed that individuals with multimorbidity were more frequently older, women and lived alone; they more often had less than secondary education, were less financially at ease, more frequently vaccinated for COVID-19 with three or four doses and, despite being less infected overall, were slightly more infected two or more times, as opposed to people without multimorbidity (Table 2). However, the age- and sex-adjusted Poisson regression model showed no association between multimorbidity and vaccination, suggesting

Table 2 Sample characteristics of total CAWI study sample with and without multimorbidity

		With multimorbidity (*N*=685)		Without multimorbidity (*N* = 1128)	
		N	%[a]	*N*	%[a]
Sex	Male	236	37.6	543	51.4
	Female	449	62.4	585	48.6
Age	18-29	53	6.9	166	15.2
	30-39	72	8.5	185	16.6
	40-49	108	12.2	248	20.4
	50-59	155	17.0	218	16.3
	60-69	130	20.0	200	17.4
	70+	167	35.5	111	14.0
Living alone	Yes	192	35.2	236	24.2
	No	493	64.8	892	75.8
Education	Less than secondary	234	46.0	272	33.4
	Secondary	219	27.2	397	33.7
	Tertiary	232	26.8	459	32.9
Employment status	Paid employment	323	35.3	739	59.1
	Unemployed	31	3.7	38	4.1
	Retired	262	51.3	246	25.9
	Other inactive	69	9.7	105	10.8
Household income	First tertile	128	23.5	192	21.1
	Second tertile	269	40.4	390	34.9
	Third tertile	256	31.5	503	39.4
	Not reported	32	4.6	43	4.6
Household financially at ease	Yes	405	61.4	789	69.1
	No	280	38.6	339	30.9
Smoking every day	Yes	104	15.3	167	17.2
	No	581	84.7	961	82.8
Moderate physical activity	Almost never or never	44	7.5	63	7.1
	Max 3 times a month	237	32.2	365	30.8
	Several times a week	404	60.4	700	62.1
Alcohol consumption	No consumption in the last 12 months to 3 times a month	385	56.1	553	49.9
	1 to 6 days a week	246	34.6	495	43.2
	Every day or almost every day	54	9.3	80	6.9
COVID-19 vaccination status	0 or 1 doses	65	6.9	109	9.1
	2	114	13.0	264	20.1
	3 or 4	506	80.1	755	70.7
Number of infections	0	134	46.0	231	44.8
	1	427	43.7	732	45.7
	≥2	124	10.2	165	9.5
Hospitalisation due to COVID-19	Yes	15	1.1	5	0.2
	No	670	98.9	1123	99.8
ICU admission due to COVID-19	Yes	4	0.4	1	0.1
	No	681	99.6	1127	99.9
Multimorbidity (number of diseases)	0	NA	NA	637	56.8
	1	NA	NA	491	43.2
	2 or 3	470	67.3	NA	NA
	≥4	215	32.7	NA	NA

Table 2 (continued)

	With multimorbidity (*N*=685)		Without multimorbidity (*N* = 1128)	
	N	%[a]	*N*	%[a]
Individual diseases				
Hypertension	178	31.8	37	3.2
Angina pectoris or myocardial infarction	11	1.2	NA	NA
Stroke or cerebrovascular accident (with or without sequelae)	5	0.8	1	0.1
Lower limb arteritis (arterial disease)	6	1.9	NA	NA
Cardiac rhythm disorder	98	13.7	13	1.1
Organ or blood cancer	29	4.6	7	0.6
Chronic bronchitis, emphysema, COPD	39	4.2	4	0.3
Asthma	63	7.5	13	1.4
Hearing impairment	112	18.2	21	2.3
Uncorrected eyesight problems	86	11.4	12	1.2
Liver cirrhosis	3	0.5	NA	NA
Thyroid disorders (goiter, hyper- or hypothyroidism)	85	11.5	19	1.8
Depression	118	14.5	9	0.6
Anxiety	260	32.9	56	3.5
Low back pain	298	43.8	75	6.1
Peripheral osteoarthritis	197	32.5	32	4.2
Osteoporosis	53	7.0	7	0.8
Renal insufficiency	24	5.6	3	0.4
Physical disability due to accident or illness	66	10.2	7	0.7
Diabetes	79	12.2	11	1.0
Obesity	209	32.6	102	9.8
Other	132	18.2	62	4.4

CAWI Computer-assisted web interview, *COPD* Chronic obstructive pulmonary disease

[a] weighted precentages

that vaccination status was associated with age; the association between multimorbidity and vaccination status (0 or 1 vaccine) was PR (95%CI) 0.92 (0.69–1.23) $p=0.583$, while it was 0.89 (0.72–1.14) $p=0.320$ with vaccination status (two vaccinations) compared with three or four vaccinations.

Overall, 1448 individuals were infected (or 54.8%, weighted percentage), with a mean age (± SD) of 49 (± 14.4) and 53.4% women. Among infected participants, 87.7% had a positive test. Similar to the total sample, 35.2% of infected participants had ≥ 2 chronic conditions and 10.6% had ≥ 4. The most frequent diseases were similar as in the overall CAWI sample (Table 1). Anxiety and low back pain (5.6%), anxiety and depression (4.9%), low back pain and peripheral osteoarthritis (4.6%), low back pain and obesity (3.5%), and anxiety and obesity (3.5%) were the most frequent dyads, whereas the anxiety, depression and low back pain triad had a prevalence of 1.9% (Supplementary Table 3). Characteristics of the sample with multimorbidity were similar to those described above (Supplementary Table 4).

Among infected individuals, 178 had PCC (or 7.0%, weighted percentage); PCC was more frequent among women and the 40–49 age group (Table 1). PCC was more frequent among infected individuals with multimorbidity, being 12.5% versus. 4.1% for the non-multimorbidity group (Supplementary Table 4).

Associations with multimorbidity

The model adjusted for age, sex, education and income presented an increasing risk of SARS-COV-2 with an increasing number of diseases, although the association was only significant for the last multimorbidity group (≥ 4 diseases), PR (95%CI): 1.22 (1.01–1.48), $p=0.037$ (Supplementary Table 5). There was no between-sex difference. Individuals aged ≥ 60 years and those with the lowest household income had the lowest risk of infection (Supplementary Table 6).

Five dyads and the triad were associated with an increased risk of infection and almost all included anxiety (Supplementary Table 5). Certain individual diseases were significantly associated with SARS-COV-2 infection

Table 3 Association between disease groups and disease combinations with post-COVID-19 condition (PCC) among infected individuals adjusted for age, sex, household financially at ease and number of infections

Number of chronic conditions (ref. 0)	PR[a]	95%	CI[a]	*p*-value
1 disease	1.90	1.16	3.13	0.011
2-3 diseases	3.32	2.07	5.35	<.000
≥4 diseases	5.65	3.41	9.38	<.000
Disease combinations (dyads and triad)				
Any ≥2 diseases	2.78	2.01	3.86	<.000
Hypertension + low back pain	2.48	1.26	4.89	0.009
Hypertension + peripheral osteoarthritis	1.55	0.65	3.67	0.322
Hypertension + obesity	1.80	0.87	3.75	0.113
Anxiety + depression	2.75	1.81	4.19	<.000
Anxiety + low back pain	2.29	1.50	3.50	0.000
Anxiety + obesity	1.99	1.15	3.44	0.015
Low back pain + peripheral osteoarthritis	2.80	1.67	4.69	<.000
Low back pain + obesity	0.90	0.43	1.90	0.786
Hypertension + cardiac rhythm disorder	2.61	1.05	6.50	0.039
Hypertension + hearing impairment	2.56	1.03	6.34	0.043
Hypertension + anxiety	2.12	0.93	4.83	0.073
Hypertension + diabetes	2.62	1.02	6.76	0.046
Cardiac rhythm disorder + anxiety	3.73	1.98	7.01	<.000
Cardiac rhythm disorder + low back pain	4.17	2.03	8.53	<.000
Cardiac rhythm disorder + peripheral osteoarthritis	2.82	1.14	6.95	0.024
Hearing impairment + anxiety	2.35	1.17	4.74	0.017
Hearing impairment + low back pain	2.66	1.26	5.62	0.010
Hearing impairment + peripheral osteoarthritis	2.32	1.07	5.04	0.033
Uncorrected eyesight problems + anxiety	2.90	1.70	4.92	<.000
Uncorrected eyesight problems + low back pain	2.34	1.27	4.30	0.006
Uncorrected eyesight problems + peripheral osteoarthritis	3.70	2.15	6.37	<.000
Thyroid disorders (goiter, hyper- or hypothyroidism) + low back pain	1.67	0.76	3.65	0.204
Depression + low back pain	2.72	1.56	4.75	0.000
Anxiety + peripheral osteoarthritis	3.30	2.02	5.38	<.0001
Peripheral osteoarthritis + obesity	1.01	0.41	2.47	0.981
Diabetes + obesity	1.44	0.66	3.16	0.365
Anxity + depression + low back pain	2.73	1.54	4.84	0.001

PR Prevalence ratio, *95% CI* 95% Confidence interval

[a] PR and 95% CI estimated with Poisson regression with robust variance

in the adjusted models such as angina pectoris or myocardial infarction, cardiac rhythm disorder, anxiety and depression (Supplementary Table 7).

The model adjusted for age, sex, household financial ease and number of infections presented an increased likelihood of PCC for an increasing number of diseases. PRs (95%CIs) and p values for 1, 2–3 and ≥4 diseases versus 0 were 1.90 (1.16–3.13), $p=0.011$; 3.32 (2.07–5.35), $p=<0.000$ and 5.65 (3.41–9.38), $p\leq0.000$, respectively (Table 3). The likelihood of PCC was higher for women and those infected at least twice, while the risk was lower for the oldest age group (≥70 years) and financially better-off households (Supplementary Table 8).

Using the Spearman correlation coefficient, no collinearity was found between independent variables. Sex- and age-based interactions with multimorbidity in relation to PCC did not present significant results, nor did the sex and multimorbidity interaction with SARS-COV-2 infection. Age (10-year intervals) and multimorbidity interaction in relation to SARS-COV-2 infection was significant for the multimorbidity groups with 2–3 and ≥4 conditions, PRs (95%CIs) 0.92 (0.85–1.00) $p=0.046$ and 0.89 (0.81–0.98) $p=0.018$, respectively. This indicates the weakening strength of the association between multimorbidity and infection with age; for example, for the multimorbidity group with two to three conditions, the

strength of the association between multimorbidity and infection decreased by 8% with every 10 years of age compared with 11% for the group with ≥ 4 conditions.

The triad and 19 dyads were associated with PCC. PRs (95%CI) were the highest for cardiac rhythm disorder and low back pain 4.17 (2.03–8.53), $p \leq 0.000$ and for cardiac rhythm disorder and anxiety 3.73 (1.98–7.01), $p \leq 0.000$ compared with individuals without those dyads (including individuals with 0 and 1 disease). For the triad, the PR was 2.73 (1.54–4.84), $p = 0.001$ (Table 3). Angina pectoris or myocardial infarction, cardiac rhythm disorder, hearing impairment, uncorrected eyesight problems, depression, anxiety, low back pain and peripheral osteoarthritis were individually associated with PCC in the adjusted models (Supplementary Table 9).

The interaction between the dyad diseases showed no significant results, suggesting that the hypothesis of multiplicative effects of disease combinations on the likelihood of PCC and SARS-COV-2 infection should not be rejected, except for the dyads of anxiety and depression and of low back pain and obesity, which presented significant sub-multiplicative effects for the likelihood of PCC (Supplementary Tables 10 and 11).

Discussion

This representative population-based study conducted in autumn 2022 in France assessed the likelihood of SARS-COV-2 infection and PCC for individuals with multimorbidity. Only the group with ≥ 4 diseases presented a significantly higher likelihood of SARS-COV-2 infection; the likelihood of infection was also higher for several disease combinations, almost all of which included anxiety. Earlier findings about SARS-COV-2 risks for people with multimorbidity have been inconsistent, indicating either elevated risks [33–35] or lower likelihood of infection or no association [6, 36]. These discrepancies may be methodological (e.g. different multimorbidity measurements) or depend on the study sample characteristics or country-specific contexts (e.g., different protective measures, SARS-COV-2 testing policies, availability of tests in the early months after their release) [37]. Our study may not be fully comparable, as it was conducted during the Omicron strain, which was more contagious but less harmful compared with previous ones, also reflected in the high infection rate in our population [25, 38]. Furthermore, the vast majority of our sample was vaccinated, which can increase the number of asymptomatic cases. The recent concepts of 'immunosenescence' and 'inflammaging' acknowledge age-related changes in the immune system, leading to deteriorated immune response and lasting silent inflammation due to the overstimulated but inefficient immune system. Older people may therefore have higher susceptibility to infections and more severe outcomes [39, 40]. Although our regression analysis showed a lower infection risk in older people, this may result from better adherence to non-pharmaceutical (such as masks use and social distancing) [41] and pharmaceutical (such as vaccination) interventions. In addition, the healthy survivor effect, which is a type of selection bias that may diminish the strength of the association due to the survival of healthier individuals [42], cannot be excluded, especially since over one-third of our population had multiple conditions, which is associated with higher mortality [43]. However, given the low hospitalisation rate and even lower ICU admission rate of our study sample, we do not believe that this effect had a significant impact on our findings. In our study, given the lack of association between multimorbidity and vaccination status, our models were not adjusted for vaccination. This is not surprising considering the very high vaccination rate in France during the COVID-19 pandemic, particularly during the advanced stages of the Omicron wave [44]. Interactions between biological changes associated with advanced age and elevated morbidity burden may have resulted in significant results in the group with the highest disease count. The interaction between multimorbidity and age presented a decreasing strength of association between multimorbidity and SARS-COV-2 infection with age in our study. This phenomenon is not exceptional, as the strength of the association for other outcomes, e.g. quality of life, has been observed to weaken with age among people with multimorbidity [45].

Huang et al. observed almost a doubled risk of infection for individuals with cardiovascular and complex comorbidities (hypertension, arthritis, retinopathy/eye diseases and hyperlipidaemia) [46]. Our method focused on the most prevalent dyads and triads, which may have generated different combinations compared with the cluster analysis of Huang et al. Both studies nevertheless included a long list of chronic conditions and adjusted for several potential confounders, although our study had vaccinated population. None of our combinations associated with a higher infection risk included cardiovascular disease, while eyesight problems formed part of two patterns with significant associations.

One of our strongest findings was that four out of five dyads and the triad involved anxiety. Mental health issues, included in a heterogeneous cluster in Huang et al. [46], also showed a stronger association with infection. This may be because anxious people report more symptoms or engage in more frequent testing or more frequent visits to general practitioners because SARS-COV-2 infection causes mental stress and anxiety [47] or because chronic psychological stress makes people more susceptible to infection by triggering unregulated immune responses, as previously suggested for several

upper respiratory infections [48]. Specifying the date of symptom occurrence (including anxiety) in our study aimed to exclude symptoms predating the SARS-COV-2 infection. However, it is possible that anxiety, like other symptoms, that occurred after the infection may not have had a direct link with PCC.

The likelihood of PCC was higher for people with more diseases and for dyads combining cardiac rhythm disorder and low back pain or anxiety and for dyads combining peripheral osteoarthritis with eyesight problems or anxiety. Only one identified triad, combining anxiety, depression and low back pain, was associated with an elevated risk of PCC and, to a much lower extent, SARS-COV-2 infection.

Our results confirm previous findings about the higher likelihood of long COVID in people with greater disease burden [20–23]. Several studies did not observe a higher risk of long COVID but rather more long COVID symptoms in individuals with multimorbidity [24, 49]. Higher risk of PCC was linked to a wide range of individual chronic conditions [28, 50], as was the case in our study. We nevertheless could not identify studies exploring the effect of disease combinations on long COVID. In our sample, 19 of the 26 most prevalent dyads were significantly associated with PCC. In addition, our results suggest a probable multiplication effect of certain disease combinations. However, the combinations of anxiety and depression, and low back pain and obesity presented sub-multiplicative effects on PCC, probably due to the frequent overlapping of these conditions. Similar studies using comparable lists of diseases and analytical methods would elucidate this disease coupling and their joint effects on PCC.

Strengths and limitations

This large representative population-based study was conducted on a random sample of the general population residing in France. The questionnaire was based on the WHO PCC criteria (Coste J. Under revision: Prevalence of long COVID in the general adult population according to different definitions and sociodemographic and infection characteristics. A nationwide random sampling survey in France after the Omicron waves in autumn 2022.) and included a large list of chronic conditions to explore multimorbidity. Operationalising multimorbidity as the number and pattern of diseases allowed a more detailed examination of the associations. Nevertheless, the cross-sectional study design did not allow for the causal interpretation of findings, and longitudinal observations are required to understand temporal trajectories of this condition. This is particularly relevant for chronic conditions, which may show the same symptoms as PCC. However, in the study questionnaire, the date of symptom onset allowed us to identify their occurrence before or after infection. It cannot be excluded that some new symptoms were linked to pre-existing chronic conditions, triggered or not by the infection, and not linked to PCC, as also mentioned above. The study was self-reported, which may have led to recall and social desirability biases, even though for certain information such as SARS-COV-2 infection, PCC symptoms and chronic conditions, other means of validation were sought such as infection confirmed by a test or physician (for confirmed infections), exclusion of other diagnoses (for PCC symptoms) and medical diagnoses for chronic diseases. This study did not collect biomedical data, which would provide additional information about the physiological vulnerability of different multimorbidity groups. It was not possible to distinguish cases with different virus variants, which would be informative when investigating the risks associated with different variants. Certain PCC cases may have been omitted due to recovery over time. Using a comprehensive database, the analyses were adjusted for different variables, although some factors like hospitalisation or ICU admission, which are potential risk factors for PCC [50], were not considered due to their small prevalence.

Research and policy recommendations

Despite recent advances that consider multimorbidity alongside individual diseases, evidence is still lacking regarding its impact on COVID-19 outcomes [3]. Although it may be expected that more diseases combined with advanced age are associated with poorer COVID-19 outcomes, our results provide precise estimates of the risk associated with different multimorbidity groups. Certain disease combinations significantly affect outcomes like functionality, quality of life, health care management and costs due to their additive or multiplicative interactions [51]. Similar considerations emerge in the context of COVID-19 where certain disease clusters present stronger associations with COVID-19 outcomes. Efforts should focus on identifying the most common and most impactful disease combinations to improve overall care for patients with multimorbidity. Potential mechanisms of disease pairing were described over a decade ago through pathways of direct causation between diseases, associated risk factors, and interacting risk factors where each can cause either disease, independent mechanisms or chance [52]. A better understanding of these mechanisms would help explain the logic of disease clustering and predict the impact on various health outcomes. This goes beyond understanding mere physiological processes and includes interactions with socioeconomic circumstances, health behaviours and environmental factors. Considering a particular vulnerability of the population

with multimorbidity to a number of health outcomes, including COVID-19 and perhaps other potential health threats should they emerge, further understanding and surveying multimorbidity remains one of the major health and population health priorities.

Conclusions

Multimorbidity, most frequently in combination with anxiety or low back pain, presented a significant association with PCC beyond that of SARS-CoV-2 infection underscoring the importance of implementing strategies to prevent and manage persistent symptoms in vulnerable groups. COVID-19 and especially long COVID are yet to be understood, but evidence points to their long-lasting consequences requiring comprehensive and multisectoral management. This is already the case for people with multimorbidity who often navigate through single-disease-oriented health care systems to manage their multiple needs. Integrated care, which is often recommended for people with multimorbidity, might therefore be valuable for individuals with long COVID. This may be another incentive to move toward a more integrated and multidisciplinary approach to health care.

Abbreviations

COVID-19	COronaVIrus Disease of 2019
WHO	World Health Organisation
PCC	Post-COVID-19 condition
SARS-COV-2	Severe acute respiratory syndrome coronavirus 2
PR	Prevalence ratio
CI	Confidence interval
ICU	Intensive care unit
NICE	The National Institute for Care and Excellence
PASC	Post-acute COVID-19 sequelae
CATI	Computer-assisted telephone interview
CAWI	Computer-assisted web interview
INSEE	French National Institute for Statistics and Economic Studies
SD	Standard deviation

Supplementary Information

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Supplementary Material 1.

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Authors' contributions

TM and JC designed the study. TM conducted the analyses. OS, MvdA, MR, JC and TM participated in the data interpretation. TM wrote the first draft of the article. All authors read and approved the final manuscript.

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Data availability

Data are available upon reasonable request and approval from the ethics committee.

Declarations

Ethics approval and consent to participate

The planning, conduct and reporting of the survey was in line with the Declaration of Helsinki and French laws. The study was approved by the local Ethics and Deontology Committee on 19 August 2022. This study relies only on the analysis of anonymously collected data. In accordance with the guidelines of the French Data Protection Authority (Commission Nationale de l'Informatique et des Libertées); all subjects included in this study were informed and gave oral consent to participate before the telephone interview.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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