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An ecological comparison to inspect the aftermath of post COVID-19 condition in Italy and the United States

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Post COVID-19 Condition (PCC) is a clinical syndrome following COVID-19 disease. PCC symptoms in adults entail significant productivity loss and reduced quality of life. This study aimed at estimating the epidemiological and economic burden of PCC among the working-age population of Italy and the US. This ecological analysis was conducted on data from January 2020 to April 2023, regarding population aged 18–64. PCC incidence for the US was retrieved from publicly reported estimates, while for Italy it was estimated from COVID-19 cases. Prevalence of factors associated with PCC and parameters to calculate temporary productivity losses (TPL) were retrieved. An estimated incidence rate ratio (eIRR) of PCC incidence in Italy and the US was calculated. TPL for reduced earnings and total quality-adjusted life years (QALYs) lost were also estimated. The ecological eIRR Italy/US was 0.842 [95%CI 0.672–1.015], suggesting that, holding COVID-19 cases constant, 15.8% fewer PCC cases have occurred in Italy compared to the US. Overall PCC cases were found to be 12.0 [95%CI 9.9–14.1] million in the US, with 1.9 [95%CI 1.6–2.3] million QALYs lost, and 2.4 [95%CI 1.8–3.0] million in Italy, with 0.4 [95%CI 0.3–0.5] million QALYs lost. Up to April 2023, the TPL was estimated to be Int$7.5 [95%CI 5.8–10.1] billion in Italy and $41.5 [95%CI 34.3–48.7] billion in the US. PCC has had a significant epidemiological and economic impact on the working-age population. The findings from this study may be of use for health planning and policy regarding PCC in working-age adults.

Keywords Post COVID-19 condition, Quality-adjusted life years loss, Productivity loss, Health policy, Epidemiological burden

Post COVID-19 condition (PCC), also known as long COVID or post-acute sequelae of SARS-CoV-2 infection, refers to the persistent signs, symptoms, and conditions experienced by individuals even after the acute phase of COVID-19 has resolved[1]. PCC is now defined by the World Health Organization (WHO) as "the continuation or development of new symptoms 3 months after the initial SARS-CoV-2 infection, with these symptoms lasting for at least 2 months with no other explanation"[2].

A significant proportion of individuals recovering from COVID-19 may experience prolonged symptoms. Woodrow et al. found a prevalence estimate of 42.1% in their systematic review, with values ranging from 0 to 93% in the various studies selected[3]. This result agrees with another meta-analysis estimating a global PCC prevalence of 43%[4], while another paper showed that 80% of individuals with a confirmed COVID-19 diagnosis presented at least one long-term symptom[5].

PCC encompasses a wide range of symptoms that could significantly impact the physical, mental, and functional well-being of affected individuals. While the acute phase of COVID-19 primarily affects the respiratory system[6], PCC affects various organ systems, such as the respiratory, cardiovascular, nervous, renal, endocrine

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and gastrointestinal systems[7]. The most common symptoms reported include fatigue, cognitive impairment, and dyspnea; other frequent symptoms include sleep disturbances, headache, joint pain, myalgia and mental health symptoms[4,5,8,9]. The severity and duration of PCC symptoms can vary considerably with some individuals experiencing mild symptoms that gradually improve over time, while others endure persistent and debilitating symptoms that significantly impact their daily lives[1].

The consequences of PCC might be challenging even for its socio-economic implications, that include: (i) reduced quality of life (QoL), due to the prolonged nature of the symptoms; (ii) reduced productivity, due to limitations in performing daily tasks and fulfilling work responsibilities, or directly attributable to increased absenteeism and reduced working hours; and (iii) substantial healthcare costs, as affected individuals may require ongoing medical consultations, diagnostic tests, therapeutic interventions and supportive services to manage their symptoms and address potential complications[10].

Despite the growing recognition of PCC and its multifaceted implications, there are still significant research gaps that need to be addressed, including the need for more comprehensive evidence on the epidemiological and economic burden of PCC and the identification of effective health policy interventions. The recognition of PCC varies between countries; in the US, the International Classification of Diseases 11th Revision (ICD-11) is utilized, which includes a specific diagnosis code for PCC. Conversely, Italy currently still lags behind without providing a specific diagnosis code for PCC and data on its incidence. The aim of this study is to estimate the magnitude of the epidemiological and economic burden, among working age individuals, posed by PCC in Italy and the US.

Results

Epidemiological considerations from the existing evidence

By combining proportions of risk factors in Italian and US population with corresponding effect sizes, on average, the ecologically estimated PCC incidence rate ratio (eIRR) between Italy and the US (see "Statistical analysis of epidemiological parameters" in the "Methods" section for the details about the computation of this metric) can be estimated at 0.842 [95% CI 0.672–1.015; 90% CI 0.705–0.992]. Therefore, according to this model, in the working age group, an equal number of COVID-19 cases has resulted in 15.8% fewer cases of PCC in Italy compared to the US. Table 1 reports all details about the impact of each single variable after considering both prevalence and effect size data.

Particularly, it could be estimated that the higher vaccination status in Italy may have brought to a reduction in PCC incidence by almost 10% for an equal number of COVID-19 cases, compared to the US (eIRR = 0.902 [95% CI 0.888–0.915]). Considering the period with available vaccines only (i.e., from December 2020 to April 2023), the reduction in PCC incidence would rise to roughly 16% (eIRR = 0.841 [95% CI 0.823–0.859]).

Starting from the available number of COVID-19 cases in the US and from the expected incidence of PCC, we could suppose the total number of PCC cases in the US to be 12.0 [95% CI 9.9–14.1] million, corresponding to 1.9 [95% CI 1.6–2.3] million QALYs lost. By applying the obtained eIRR, and considering both US figures and

Adjusting factor	Value	95% CI
Comorbidities		
Obesity	0.953	0.887–1.019
Type 2 diabetes	0.995	0.992–0.997
Hypertension	0.955	0.769–1.141
Asthma	0.989	0.979–0.998
COPD	0.995	0.986–1.003
IHD	1.001	1.000–1.001
CKD	0.997	0.991–1.003
Depressive disorders	0.997	0.989–1.004
Anxiety disorders	0.994	0.981–1.006
Risk factors		
Smoking	1.010	1.007–1.013
Sex	1.052	1.052–1.052
Vaccination status[§]		
Vaccines (I, II, III doses):		
Whole period (Jan 2020–Apr 2023)	0.902	0.888–0.915
Period with vaccines available (Dec 2020–Apr 2023)	0.841	0.823–0.859
Overall eIRR	0.842	0.672–1.015

Table 1. Adjusting factors for estimating PCC cases, obtained after combining epidemiological data with boundary conditions derived from the literature. *COPD* chronic obstructive pulmonary disease, *CKD* chronic kidney disease, *eIRR* estimated incidence rate ratio, *IHD* ischemic heart disease. [§]In order to consider the time in which vaccines were actually administered, this value was computed as the ratio between integral sums (per day) of the risk yielded by the proportions of people with 0, 1, 2 or 3 doses in Italy and in the US, weighted by the respective coefficients shown in Table 5.

the number of COVID-19 cases in Italy, we could estimate an occurrence of 2.4 [95% CI 1.8–3.0] million PCC cases in Italy, with 0.4 [95% CI 0.3–0.5] million QALYs lost.

The economic cost of PCC in Italy and US

Up to April 2023, the TPL was estimated to be Int$7.5 [95% CI: Int$5.8–Int$10.1] billion and $41.5 [95% CI $34.3–$48.7] billion in Italy and in the US, respectively. Table 2 lists the economic costs for each working age class. An age-wise distribution showed that in Italy people aged 50–64 years contributed to the highest loss in income, accounting for 44% of the total loss. In the US, those aged 30–39 years experienced the highest income loss, contributing to 29.7% of the total.

In the same period, the cost of reduced QoL was computed to be Int$14.7 [95% CI Int$10.9–Int$19] billion in Italy, corresponding to 0.47% of the national GDP. For the US, the same cost was estimated to attain $196.3 [95% CI $162.2–$230.3] billion, i.e. 0.94% of the country's GDP. Table 3 highlights the economic loss due to reduced health for each working age group.

Discussion

Our data suggest that PCC imposes a substantial epidemiological and economic burden both in Italy and in the US. These findings contribute to previous studies that examined the economic impact of long-term health complications of COVID-19 within the US population. In late 2020[11], Cutler forecast a loss of $2.6 trillion while in 2022 his estimate projected a net income loss of $1 trillion. When adding lost QALYs and increased medical spending, the total loss was $3.7 trillion[12]. Other studies have also estimated the populations unable to work or working reduced hours due to PCC[13–15]. Particularly, a recent report reckoned that up to 4 million Americans were out of work in 2022[16].

The joint reading of study findings suggests some main implications for decision-making in the healthcare sector. Firstly, almost two thirds of the positive effect estimated by the eIRR is attributable to the protective role of COVID-19 vaccination. As of January 2024, nearly 48 million people in Italy are fully vaccinated (81.2% of the total population)[17], whereas the same proportion attains just 69.5% in the USA. A recent study compared vaccinated (at least one dose) and unvaccinated people who contracted COVID-19 only after allocation: findings

Country	Age group	PCC cases, thousands [95% CI]	TPL [95% CI]	
			Overall, Int$ billions	Per capita, Int$
Italy				
	18–29	245 [183–317]	0.71 [0.53–0.91]	120 [90–154]
	30–39	526 [393–680]	1.74 [1.31–2.25]	264 [198–341]
	40–49	642 [479–830]	2.12 [1.59–2.75]	258 [194–335]
	50–64	938 [700–1212]	3.25 [2.42–4.19]	234 [174–301]
	Total	2351 [1755–3039]	7.81 [5.83–10.10]	226 [168–292]
United States of America				
	18–29	3,418 [2825–4012]	7.13 [5.89–8.37]	159 [131–186]
	30–39	3082 [2546–3616]	12.32 [10.18–14.45]	264 [218–310]
	40–49	2626 [2170–3082]	10.50 [8.67–12.32]	246 [203–289]
	50–64	2890 [2388–3392]	11.55 [9.55–13.56]	182 [150–213]
	Total	12,016 [9929–14,102]	41.50 [34.29–48.70]	210 [173–246]

Table 2. Temporary productivity loss due to PCC in Italy and USA. Temporary productivity loss values are expressed in international dollars (Int$). For the United States, US dollars reflect the same purchasing power parity of the international dollars. *CI* confidence intervals, *PCC* post COVID condition, *TPL* temporary productivity loss.

Country	QALYs lost, thousands [95% CI]	Economic loss [95% CI]	
		Overall, Int$ billions	Per capita, Int$
Italy			
	384 [287–496]	14.7 [11.0–19.0]	425 [316–550]
United States of America			
	1960 [1620–2300]	196.3 [162.1–230.3]	1033 [853–1212]

Table 3. Reduced quality of life and relative economic impact due to PCC. Economic loss values are expressed in international dollars (Int$) in billions. For the United States, US dollars reflect the same purchasing power parity of the international dollars. *CI* confidence intervals, *QALYs* quality-adjusted life years.

showed that vaccination significantly lessens the risk of developing PCC in adults and pointed at the protective effectiveness of vaccines against infection with SARS-CoV-2 as a key factor in population-level prevention of PCC[18]. Tsampasian et al. also suggested that two doses determined 40% lower risk of developing PCC[19]; Notarte et al. systematically gathered primary evidence regarding a protective role of vaccination against PCC[20].

The wide vaccine coverage achieved in Italy was obtained through mass vaccination and governmental policies to optimize adherence and compliance (e.g., Green Pass introduction, personal restrictions, gradually compulsory vaccination)[21–24]. In the US, vaccine hesitancy during the pandemic has proven to be a noteworthy, multifactorial phenomenon[25,26], since, despite substantial supplies and resources, the vaccination rate was low compared to other high-income countries[27], especially due to inequalities[28]. Therefore, in light of these findings, vaccination campaigns should be planned and strengthened by building confidence in public perceptions, empowering transparent and effective communication, and curbing vaccine hesitancy through tailored vaccine-promoting health policies that address and dismantle disparities[29].

Secondly, one third of the positive effect is due to a lower prevalence, in Italy, of underlying conditions likely associated with a higher risk of developing PCC, as widely supported in literature[30–33]. Interestingly, non-modifiable risk factors are unlikely to determine differences between the two nations, as both older age and female-male ratio are similar in both countries[34]. Of note, while severity of COVID-19 course puts at higher risk for more severe PCC, even mild cases are at risk for PCC[35,36], supporting the necessity for mitigation practices (e.g., mask wearing, physical distancing), since vaccines showed heterogeneous effects on lowering transmission rates of different strains[37].

As the demographic aging phenomenon has arisen in the last decades, along with a consistently heavier burden from chronic diseases, the Italian National Health Service (NHS) has focused on implementing and strengthening policies at a national (i.e., National Chronicity Plan and National Prevention Plan[38]), regional and local level, to meet the emerging, complex and multidisciplinary health needs that chronic diseases carry[39]. In the US, PCC was recognized as a disability under the Americans with Disabilities Act (ADA)[40] in July 2021. The Social Security Administration also acknowledges PCC as a disability that may qualify for Social Security Disability Insurance (SSDI) benefits. For workers experiencing significant mental or physical impairment, the US Department of Labor requests both work accommodations (e.g., working remotely, providing training to change the employee's job position, allowing flexible scheduling, etc.) and SSDI benefits to be offered by companies. Conversely, no workplace policies directly address adjustments for PCC patients in Italy. However, a recent multidisciplinary panel established good care practices targeted to patients with PCC, healthcare professionals and the healthcare system, mentioning performance reduction at work as an evaluation area to be addressed with a multidisciplinary team[41].

These findings lead to further implications related also to the prevention of similar phenomena concerning future epidemics, burdening economic productivity, and systemic actions required to manage the current population with PCC. For this first issue, epidemic plans fostering national preparedness policies in community settings and workplaces, supported by operational plans at subnational levels, should be issued, reviewed and revised according to evidence-based literature; lessons learnt from regional or global outbreaks; or evolution of national or international legislation about communicable disease prevention and control. In relation to a better management of PCC, access and continuity of care programs should be implemented to address the diverse needs of these patients, such as symptoms management and workplace adjustments, through integrated care pathways involving multi-disciplinary teams, facilitating the return to productive employment according to the perspective of workplace disability management[42]. In this view, healthcare professionals' training needs to be prioritized to ensure patients receive proper diagnosis and access care pathways.

The study's findings should be read considering its strengths and limitations. The PCC is topical and still underrepresented in scientific literature. Notwithstanding, the most updated evidence was used in the analyses. In the comparison between Italy and the US, heterogeneity of age class structure was noted among some parameters of interest (see, for instance, age group classifications for epidemiological data, employment and comorbidities in Table 4), as well as slight mismatches among time points when respective data were available, and possible collinearity between variables (e.g. different comorbidities could be related to one another). Nonetheless, these parameters were only used as adjusting factors, hence a slight mismatch between age groups or possible collinearity between variables are unlikely to bear any significant effect on final predictions. Moreover, technically, the impact of each variable might have been slightly overestimated, as the ORs were used as effect sizes instead of the RRs: however, all the adjustment variables had modest effect sizes (i.e., all ORs are close to 1) and the expected prevalence of the event (i.e. PCC) is around 20%, so we can assume that ORs can be considered as a good proxy without substantially biassing the analysis[43].

Although vaccine waning could impair the protective effect against PCC in the long term, the impact of booster doses is yet to be studied. Of note, differences between pre-Delta, Delta and Omicron variants in determining prolonged symptoms were no longer significant, after accounting for vaccination status[44].

Moreover, a sharp difference in the available estimates of economic loss per QALY was found between the US and Italy, which led to huge differences in the overall estimate for QoL-related losses that may affect this comparison. The main reasons for such differences in the monetary value of QALYs are to be sought by several factors, characterizing each country, related to the economic differences, cost of living and income levels, healthcare system structure, and cultural and societal values. Economically, compared to Italy, the United States has a higher GDP per capita[45] and spends more on healthcare per capita[46], which translates to a higher willingness and ability to pay for healthcare interventions. Additionally, the cost of living and income levels in the United States are generally higher, leading to a higher valuation of health benefits. The structure of the healthcare system also plays a significant role: the US system, with its reliance on private insurance and higher out-of-pocket payments, values health outcomes more monetarily to justify expensive treatments. In contrast, Italy's publicly funded healthcare system prioritizes cost-effectiveness and equitable resource distribution, resulting in a lower monetary

Parameter	Italy		United States		Source
	Age group	Estimate	Age group	Estimate	
Demographic data					
Female population (millions)	20–24	1.4	20–24	11.0	[50]
	25–29	1.4	25–29	11.1	
	30–34	1.6	30–34	11.8	
	35–39	1.7	35–39	11.3	
	40–44	1.9	40–44	11.0	
	45–49	2.2	45–49	10.2	
	50–54	2.4	50–54	10.6	
	55–59	2.5	55–59	10.7	
	60–64	2.2	60–64	11.0	
Male population (millions)	20–24	1.5	20–24	11.4	[50]
	25–29	1.6	25–29	11.4	
	30–34	1.6	30–34	12.0	
	35–39	1.7	35–39	11.5	
	40–44	1.9	40–44	11.2	
	45–49	2.2	45–49	10.2	
	50–54	2.4	50–54	10.6	
	55–59	2.4	55–59	10.3	
	60–64	2.0	60–64	10.4	
Epidemiological data					
COVID-19 cases (millions, % out of the age group population)	20–29	2.8 (47.5%)	18–29	19.8 (44.1%)	[54,55]
	30–39	3.4 (51.5%)	30–39	16.2 (34.8%)	
	40–49	4.1 (50.0%)	40–49	13.8 (32.4%)	
	50–59	4.3 (44.3%)	50–64	18.2 (28.6%)	
	60–69	2.9 (37.1%)			
COVID-19 vaccinations by number of doses up to April 30th, 2023 (millions, % out of the age group population)	20–29	No: 0.5 (8.4%) ≥ 1d: 5.4 (91.6%) ≥ 2d: 5.1 (86.5%) ≥ 3d: 4.1 (69.5%)	18–24	No: 5.4 (17.7%) ≥ 1d: 25.1 (82.3%) ≥ 2d: 20.4 (66.9%) ≥ 3d: 7.4 (24.3%)	[55,56]
	30–39	No: 0.8 (12.1%) ≥ 1d: 5.8 (87.9%) ≥ 2d: 5.5 (83.4%) ≥ 3d: 4.4 (66.7%)	25–39	No: 11.3 (16.5%) ≥ 1d: 57.1 (83.5%) ≥ 2d: 47.6 (69.6%) ≥ 3d: 19.1 (27.9%)	
	40–49	No: 0.8 (9.9%) ≥ 1d: 7.3 (90.1%) ≥ 2d: 7.0 (86.4%) ≥ 3d: 6.0 (74.1%)	40–49	No: 4.5 (11.1%) ≥ 1d: 36.2 (88.9%) ≥ 2d: 31.2 (76.6%) ≥ 3d: 15.0 (36.8%)	
	50–59	No: 1.2 (12.5%) ≥ 1d: 8.4 (87.5%) ≥ 2d: 7.9 (82.3%) ≥ 3d: 7.6 (79.2%)	50–64	No: 2.8 (4.4%) ≥ 1d: 60.9 (95.6%) ≥ 2d: 53.3 (83.7%) ≥ 3d: 31.0 (48.7%)	
Employment					
Continued					

Parameter	Italy		United States		Source
	Age group	Estimate	Age group	Estimate	
Hourly salary (α)	20–29	10.0 € (Int$ 16.6)	18–24	12.0 $	57,58
	30–39	11.4 € (Int$ 18.9)	25–64	23.0 $	
	40–49	11.4 € (Int$ 18.9)			
	50–59	12.0 € (Int$ 19.9)			
	60–69	12.0 € (Int$ 19.9)			
Labor force (β)	20–29	42.6%	18–24	071.0%	59,60
	30–49	75.7%	25–64	78.2%	
	50–69	64.1%			
Working hours/week (δ)	18–64	40	18–64	40	
Prevalence of comorbidities and other risk factors					
Obesity (w_1)	18–34	5.2%	20–39	39.8%	61,62
	35–49	9.5%	40–59	44.3%	
	50–69	14.2%	60 +	41.5%	
Type 2 diabetes (w_2)	18–34	1.0%	20–39	4.4%	61,63
	35–49	2.4%	40–59	16.4%	
	50–69	8.5%	60 +	30.0%	
Hypertension (w_3)	18–34	2.3%	20–39	23.4%	61,64
	35–49	9.5%	40–59	52.4%	
	50–69	34.8%	60 +	74.1%	
Asthma (w_4)	20–54	4.2%	20–54	8.0%	65
	55–59	4.5%	55–59	10.1%	
	60–64	4.8%	60–64	11.4%	
COPD (w_5)	20–54	1.2%	20–54	1.5%	65
	55–59	3.4%	55–59	7.0%	
	60–64	4.8%	60–64	10.0%	
IHD (w_6)	18–44	1.0%	18–24	0.3%	65
			25–44	1.2%	
	45–54	4.4%	45–54	3.6%	
	55–64	7.0%	55–64	9.0%	
CKD (w_7)	20–54	5.3%	20–54	6.7%	65
	55–59	9.1%	55–59	13.8%	
	60–64	11.4%	60–64	17.6%	
Depressive disorders (w_8)	20–54	5.0%	20–54	6.4%	65
	55–59	5.4%	55–59	4.8%	
	60–64	5.5%	60–64	4.4%	
Anxiety disorders (w_9)	20–54	6.6%	20–54	8.4%	65
	55–59	6.3%	55–59	7.2%	
	60–64	6.3%	60–64	6.5%	
Smoking (w_{10})	20–24	22.9%	18–24	5.3%	66,67
	25–34	25.7%	25–44	12.6%	
	35–44	24.8%			
	45–54	23.0%	45–64	14.9%	
	55–59	20.1%			
	60–64	20.5%			
PCC incidence (available for the US only)					
Estimated incidence of PCC among people who ever had COVID-19	–	–	All ages	24.1%	15
Quality of life					
Value for QALY (μ)	All ages	€23,074 (Int$ 38,202)	All ages	$100,000 (Int$ 100,000)	68,69

Table 4. List of retrieved parameters specific to Italy and the United States. For the United States, US dollars reflect the same purchasing power parity of the international dollars. *COPD* chronic obstructive pulmonary disease, *CKD* chronic kidney disease, *IHD* ischemic heart disease, *PCC* post-COVID condition, QALY quality-adjusted life year, *Int$* international dollar, *€* euro, *$* US dollar.

value for QALYs[47]. Cultural and societal values further influence these valuations, as the USA tends to emphasize extending life at higher costs, while Italy focuses on broader access to healthcare. In fact, the comparison between Italy and the US is subject to limitations arising from the aforementioned differences between these countries. However, the availability of incidence estimates for the US allowed applying a more robust methodology than would have been feasible by benchmarking countries more similar to Italy, such as the United Kingdom, where point or period prevalence data only were available[48]. Eventually, the potential limitation arising from the fact that the US incidence of PCC among COVID cases is estimated from a survey conducted as early as in 2021, i.e. without the knowledge from the most recent years, is unlikely to bear a significant impact on the calculation, as symptoms characterizing PCC were sufficiently clear from the beginning: indeed, the relative stability of the period prevalence estimates is suggestive of a sort of steady state of this phenomenon also in 2022–2023, at least from a diagnostic point of view[49].

Further studies should replicate the analyses in more countries, by employing more robust and updated data on epidemiology and disutility of PCC. Effects of PCC on society are not limited to loss of productivity in the employed population. Children and adolescents experiencing PCC symptoms that hinder learning in the school setting and force them to fall behind represent the future working class. Future research should focus on exploring potential consequences (i.e., psychophysical, social, cultural, economic) and preventing them.

In conclusion, PCC has been a consequence of an unexpected illness due to a novel virus, representing a significant public health issue. Our results are an example of how a healthier population, with fewer comorbidities, allows for a better preparedness for public health emergencies. These factors also come along with positive externalities in the socio-economic sphere consisting of lower losses of productivity and detriments in QoL.

Our research serves as a call to action for decision-makers to address PCC, steering the implementation of robust health policies and programs and the pursuit of adequate primary prevention strategies to pave the way towards a healthy and productive society.

Methods

The study used aggregated and anonymous data only, which ensured full conformity with the Helsinki Declaration of Ethical Principles and with Italian (Law 2003/196) and international (EC/2016/679) data protection regulations. No informed consent provisions were applicable for the same reason.

Study design and target population

This study was an ecological analysis based on data publicly available on scientific databases and institutional repositories. Data were searched for Italy and the US until March 26, 2024, in relation to the period from the beginning of the pandemic onwards. Owing to the lack of point data reported since May 2023, we restricted the analysis to the period between January 1, 2020 to April 30, 2023 (40 months overall). The entire analysis included working-age individuals, where working age was defined as between 18 and 64 years.

Data sources and model inputs

An overview of secondary scientific studies (i.e., systematic reviews with/without meta-analysis) was performed to assess possible factors associated with the development of PCC and collect effect sizes. Moreover, institutional websites were looked up for the respective demographic, epidemiological and socio-economic data for each country.

Data sources for all the parameters included in the analyses are summarized in Tables 4 and 5. Table 4 includes information specifically retrieved from institutional websites for Italy and the US, while Table 5 shows parameters that were derived from the literature and used as weights for country-level data, with the assumption of no difference in variables' impact between the two countries. According to the literature, individual conditions associated with developing PCC were smoking status and female sex. Diseases shown to be associated with a higher occurrence of PCC by the literature were obesity, type 2 diabetes mellitus (T2DM), hypertension, asthma, chronic obstructive pulmonary disease (COPD), ischemic heart disease (IHD), chronic kidney disease (CKD), depression and anxiety disorders (Table 5). Data published in journal studies or institutional repositories showed that the USA recorded higher prevalence of the major comorbidities such as obesity, T2DM, hypertension, asthma, COPD and CKD compared to Italy; on the contrary, Italy had a higher share of smokers, while prevalence rates for anxiety, depressive disorders and IHD were similar for the two countries. COVID-19 vaccination rates were also higher in Italy for all age groups, with more than 60–80% of the population fully covered with the booster dose, compared to corresponding rates below 30–50% in the US (Table 4).

Statistical analysis of epidemiological parameters

The statistical software R (version 4.2.2) was used for all statistical analyses. Given the absence of any institutional estimate for the occurrence of PCC cases in Italy, this number was estimated starting from US data[12] with a two-step approach: the first step involved considering factors associated with developing PCC after COVID-19 and analyzing them ecologically in order to provide an estimated Italy/US incidence rate ratio (eIRR) that could be applied to the sum of at-risk population-time yielded by cases that tested positive for COVID-19 at least once in each country. For each variable, analyses were stratified according to the age groups in turn provided by respective data sources, by keeping Italian and US demographic data[50] as population weight for each group. Specifically, for each parameter i assessed (i.e., 12 parameters), a ratio (w_i) was computed between the Italian and US population, each pooled weighting by the respective prevalence of the condition i and effect size of i in terms of odds ratios (ORs): the ORs were used as a proxy of risk ratios (RRs) given the presence of pooled estimates (i.e., meta-analyses), where the absence of prevalence data for relevant conditions prevented from converting ORs

Parameter	Value [95% CI if available]	Symbol	Source
Employment			
Disability due to PCC (%)	0.25	ε	[15]
Duration of PCC (weeks)	17.38	λ	[70]
Comorbidities (effect size on PCC incidence: OR)			
Obesity	1.15 [0.94–1.42]	w_1	[19]
Type 2 diabetes	1.06 [1.03–1.10]	w_2	[19]
Hypertension	1.30 [0.52–2.66]	w_3	[71]
Asthma	1.24 [1.05–1.48]	w_4	[19]
COPD	1.38 [0.70–2.74]	w_5	[19]
IHD	1.28 [1.13–1.45]	w_6	[19]
CKD	1.12 [0.85–1.48]	w_7	[19]
Depressive disorders	1.19 [0.60–2.37]	w_8	[19]
Anxiety disorders	1.19 [0.60–2.37]	w_9	[19]
Other risk factors (effect size on PCC incidence: OR)			
Smoking	1.10 [1.07–1.13]	w_{10}	[19]
Female sex	1.57 [0.94–2.62]	w_{11}	[19]
Vaccination status (effect size on PCC incidence: OR)			
One dose (all papers)	0.68 [0.55–0.83]	w_{12} (combined)	[72]
One dose (removing outliers)	0.99 [0.94–1.06]		[72]
Two doses (all papers)	0.57 [0.43–0.76]		[19]
Two doses (removing outliers)	0.72 [0.59–0.87]		[72]
Three or more doses	0.16 [0.03–0.85]		[72]
Quality of life			
Disutility due to PCC	0.49	γ	[73]

Table 5. Boundary conditions assumed and/or retrieved from the literature. *COPD* chronic obstructive pulmonary disease, *CKD* chronic kidney disease, *IHD* ischemic heart disease, *OR* odds ratio, *PCC* post-COVID condition, *DOL* U.S. Department of Labor, *INPS* National Institute for Social Security, *BLS* U.S. Bureau of Labor Statistics, *ISTAT* Italian National Institute of Statistics.

into RRs. This weighting was performed stratifying by each age group *j* provided by the respective data sources, according to the following formula:

$$w_i = \frac{\frac{\sum_j P_{ITA,j} \times (\pi_{ITA,j,not\_i} + \varphi_i \times \pi_{ITA,j,i})}{P_{ITA}}}{\frac{\sum_j P_{US,j} \times (\pi_{US,j,not\_i} + \varphi_i \times \pi_{US,j,i})}{P_{US}}}$$

where φ_i is the effect size (i.e., risk or odds ratio) connected to the factor *i* on PCC development, P_{ITA} is the overall working-age population in Italy, $P_{ITA,j}$ is the population in Italy for the age group *j*, π_{ITA,j,not_i} is the prevalence of individuals without the condition *i* in the age group *j* in Italy, $\pi_{ITA,j,i}$ is the prevalence of individuals with the condition *i* in the age group *j* in Italy. The same parameters are similarly defined for the US.

For each of these ratios, the uncertainty was computed considering the 95% confidence interval (CI) of the effect sizes. Hence, the final eIRR between Italy and the US was computed as:

$$eIRR = \prod_{i=1}^{12} w_i$$

by performing 10,000 simulations on the available uncertainty intervals; the median of the obtained distribution was chosen as eIRR, and the 90% and 95% CIs were computed.

The second step involved estimating the number of PCC cases in Italy by multiplying the obtained eIRR by the incidence rate of PCC cases in the US, and rescaling it to the number of COVID-19 cases in Italy. The evaluation of the 95% confidence interval followed the same approach described for the eIRR.

The number of PCC cases in the US was deduced from incidence estimates available on institutional websites and updated using analogous input parameters and methods as mentioned for Italy (Tables 4, 5).

Analysis of economic parameters

The human capital approach (HCA) was adopted to estimate the productivity loss of temporary work absenteeism (TPL) due to PCC[51,52]. The methodology suggested by Pearce et al.[53] was used to implement the HCA framework. Both for Italy and for the US, estimates of individual TPL (Δ) were calculated for each working age group *j* as the weekly median wage (τ) by the duration of the condition (i.e., length of absenteeism from work) (λ). τ was obtained by multiplying the wage per hour (α) by the weekly working hours (δ), adjusted for the effective reduction in labor supply due to significant impairment (ε) (Table 5).

$$\tau = \alpha \times \delta \times \varepsilon$$

$$\Delta = \tau \times \lambda$$

Δ was then multiplied by PCC cases (υ), in each working age group *j*, and summed over them to obtain the total cost of PCC-related reduced earnings (Ω).

$$\Omega = \sum_{j=1}^{4} \Delta \times \upsilon_j$$

Total lost QoL (Π) was calculated by multiplying the individual QALY loss (η) by the value of a year of good health (μ) and then by the PCC cases (υ) in Italy and in the US. η was estimated by multiplying the QALY disutility of PCC (γ) by the duration of PCC (λ) (Table 5).

$$\eta = \gamma \times \lambda$$

$$\Pi = \eta \times \mu \times \upsilon$$

Data availability

Datasets gathering the data collected from the different sources, and used for the analyses produced in this study, are available upon request to the corresponding author.

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Author contributions

All the authors participated in the conceptualization of the study; G.M.R., A.H.A. and H.S.M.A.E. were involved in data curation; M.C.N., G.M.R. and J.G. performed the formal analysis, and M.C.N. and J.G. developed software codes. M.C.N., G.M.R., A.H.A., J.G. and H.S.M.A.E. contributed to validation and visualisation of the results achieved. M.M.G. and G.D. supervised the work and co-ordinated the project. All the authors participated in the writing, both for the original drafting and for the review and editing. All the authors read and approved the final manuscript and agreed to the final submission.

Competing interests

The authors declare no competing interests.

Additional information

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