https://doi.org/10.1186/s12879-026-12907-5

BMC Infectious Diseases

RESEARCH

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The role of vaccination, underlying health conditions, and working in healthcare in the socioeconomic disparities in COVID-19 hospitalization: a mediation analysis using interventional effect models

Lisa Cavillot[1,2*], Beatrijs Moerkerke[3], Brecht Devleesschauwer[1,4], Jinane Ghattas[1,2], Joris A. F. van Loenhout[1], Laura Van den Borre[1], Niko Speybroeck[2], Tom Loeys[3] and Robby De Pauw[1,5]

Abstract

Background Prior research has established an association between socioeconomic determinants and COVID-19 hospitalization rates. This study explores the potential mediation of this association by vaccination status, underlying health conditions, and working in healthcare.

Methods We conducted a retrospective cohort study including 111,159 and 337,232 adults living in the Walloon or Brussels regions in Belgium with a confirmed SARS-CoV-2 infection during the Delta-predominant period (1 September 2021 to 22 December 2021) and the Omicron-predominant period (4 January 2022 to 1 September 2022), respectively. Data on COVID-19-related hospital admissions, education, vaccination, underlying health conditions, and individuals working in healthcare were retrieved from multiple national registers, linked at an individual level using the Belgian social security number. Mediation analyses using interventional effect models were used to assess the mediation role of vaccination, underlying health conditions, and working in healthcare in the relationship between education and COVID-19 hospitalization.

Results Shifting from moderate or high education to low education increased the probability of COVID-19 hospitalization by 0.694% points (95% CI 0.561–0.819) during the Delta period and 0.547% points (95% CI 0.491–0.603) during the Omicron period. Most of this increase was due to the direct effect of education, accounting for 84.6% of the total effect during Delta and 93.1% during Omicron. During the Delta period, education disparities in COVID-19 hospitalization were partially mediated by vaccination (10.1%) and underlying health conditions (6.3%). During the Omicron period, education disparities in COVID-19 hospitalization were partially mediated by underlying health conditions (4.8%), vaccination (1.4%), and working in healthcare (0.7%).

*Correspondence:
Lisa Cavillot
lisa.cavillot@uclouvain.be

Full list of author information is available at the end of the article

Conclusions This study demonstrates that socioeconomic disparities in COVID-19 hospitalization rates are partially mediated by vaccination and underlying health conditions. This suggests that public health interventions aimed at increasing vaccination rates and preventing underlying health conditions could mitigate some of the effects of socioeconomic disparities in COVID-19 hospitalization outcomes. However, future research is needed to investigate additional mediating factors of education in COVID-19 hospitalization, such as living and working conditions, to better elucidate the causal pathways of social inequalities in severe COVID-19.

Clinical trial number Not applicable.

Keywords COVID-19 hospitalization, Education, Vaccination, Mediation analyses

Introduction

The coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread rapidly across the world. This resulted in a pandemic, as announced by the World Health Organization (WHO) in March 2020 [1].

Rapidly, a large body of literature highlighted a clear social gradient in both SARS-CoV-2 infection and the development of subsequent severe COVID-19 outcomes (e.g. hospitalization, ICU admission, death), disproportionately affecting individuals from lower socioeconomic (SE) groups (e.g. low levels of income or education, living in overcrowded households, poor housing conditions) [2–7]. As a result, the COVID-19 pandemic was very quickly described as a *syndemic*, emphasizing the interaction between the purely biological nature of the virus and the social determinants of health (e.g., education, housing, employment), exacerbating social inequalities already deeply rooted in our society [2, 8, 9].

Within the *syndemic* framework of the pandemic, four key pathways explain how the social determinants of health shape inequalities in COVID-19 health outcomes [10, 11]. First of all, **unequal exposure** indicates that disadvantaged SE groups are overrepresented in essential and in person occupations with limited opportunities for remote work [12, 13], and rely heavily on public transportation during the pandemic [14–17], increasing their risk of exposure. Secondly, **unequal transmission**, whereby disadvantaged SE groups are more likely to live in densely populated urban areas [18–20] or in overcrowded households [21–23], increasing the risk of viral transmission. Thirdly, **unequal susceptibility** with disadvantaged SE groups presenting poorer baseline health conditions with a higher rate of non-communicable diseases (e.g., obesity, cardiovascular diseases, diabetes) [24], which has been shown to increase the risk of developing severe COVID-19 outcomes [25, 26]. Lastly, **unequal treatment and preventive services** with SE inequalities observed in access to preventive health behaviors during the COVID-19 pandemic, including vaccination [27–29]. Although vaccination effectively reduce the risk of severe COVID-19 [30–32], the spread of such preventive measures is accompanied by an increase in social health inequalities, particularly in its early stages [33]. In Belgium, the largest SE disparity in vaccination coverage was observed among individuals with lower education, who were 37% less likely to receive the first vaccine dose compared to those with higher education [27]. Part of this association can be linked to health literacy, which plays an important role in the adoption of preventive health behaviors [34, 35]. Consequently, individuals from lower SE groups have a higher risk of severe COVID-19 outcomes due to lower adoption of preventive behaviors linked to lower levels of health literacy [36].

Within the third and fourth pathways of the syndemic framework of the pandemic, i.e., unequal susceptibility and unequal access to treatment and preventive services, we hypothesized that vaccination, underlying health conditions, and health literacy may mediate the association between SE determinants and severe COVID-19 outcomes.

To our knowledge, no research has examined the extent to which vaccination, underlying health conditions, and health literacy could mediate social inequalities in severe COVID-19 outcomes. To address this gap, the objective of the present study was to identify the mediating effect of vaccination, underlying health conditions, and health literacy, the latter being proxied by having a degree in healthcare, on the association between education and COVID-19 hospitalization among infected Belgian adults.

Materials & methods

Causal framework and study design

We conducted a retrospective cohort study using data from the LINK-VACC project, a population data linkage set up by Sciensano, the Belgian Institute of Health. LINKVACC contains selected variables from multiple existing national health and social sector registries. The data are stored in a pseudonymized environment and linked at the individual level using the Belgian social security number [37]. For the present study, six registers were used:

1) The COVID-19 Healthdata test database containing exhaustive data from COVID-19 laboratory tests

(polymerase chain reaction or antigenic tests) performed in Belgium (date of sampling, test result) as well as demographical data on the tested person [38];

2) The Clinical Hospital Surveillance (CHS) database containing non-exhaustive patient-level data from admission and discharge forms on approximately 50% of the patients admitted with a confirmed COVID-19 diagnosis across all 103 Belgian hospitals [39];
3) The Belgian Vaccine register for COVID-19 (Vaccinnet+) containing exhaustive data on COVID-19 vaccine doses administered to Belgian residents (brand of the vaccine, lot number, date of administration, date of registration) as well as demographical data on the vaccinated person (sex, age, postal code of residence);
4) The DEMOBEL database provided by Statistics Belgium (Statbel) containing data on sociodemographic (SD) and SE characteristics on everyone tested and/or vaccinated for COVID-19;
5) The InterMutualistic Agency (IMA) database containing data on reimbursed healthcare and medicines of Belgian residents insured in the country tested and/or vaccinated for COVID-19 and;
6) The Common Base Registry for HealthCare Actors (CoBRHA) allowing the identification of individuals who have been licensed to practice a healthcare profession in Belgium.

Belgium is composed of three regions: Brussels, Flanders, and Wallonia. This research focused only on data from the Walloon and Brussels regions from the six data sources mentioned above, as permission to use the data was not granted for the Flemish region. As of 1 January 2021, the Walloon and Brussels regions covered 42% of the total Belgian population [40].

Study population and study period

A flowchart demonstrating the selection of the study population is available in Fig. 1. All laboratory-confirmed SARS-CoV-2 infections recorded in the COVID-19

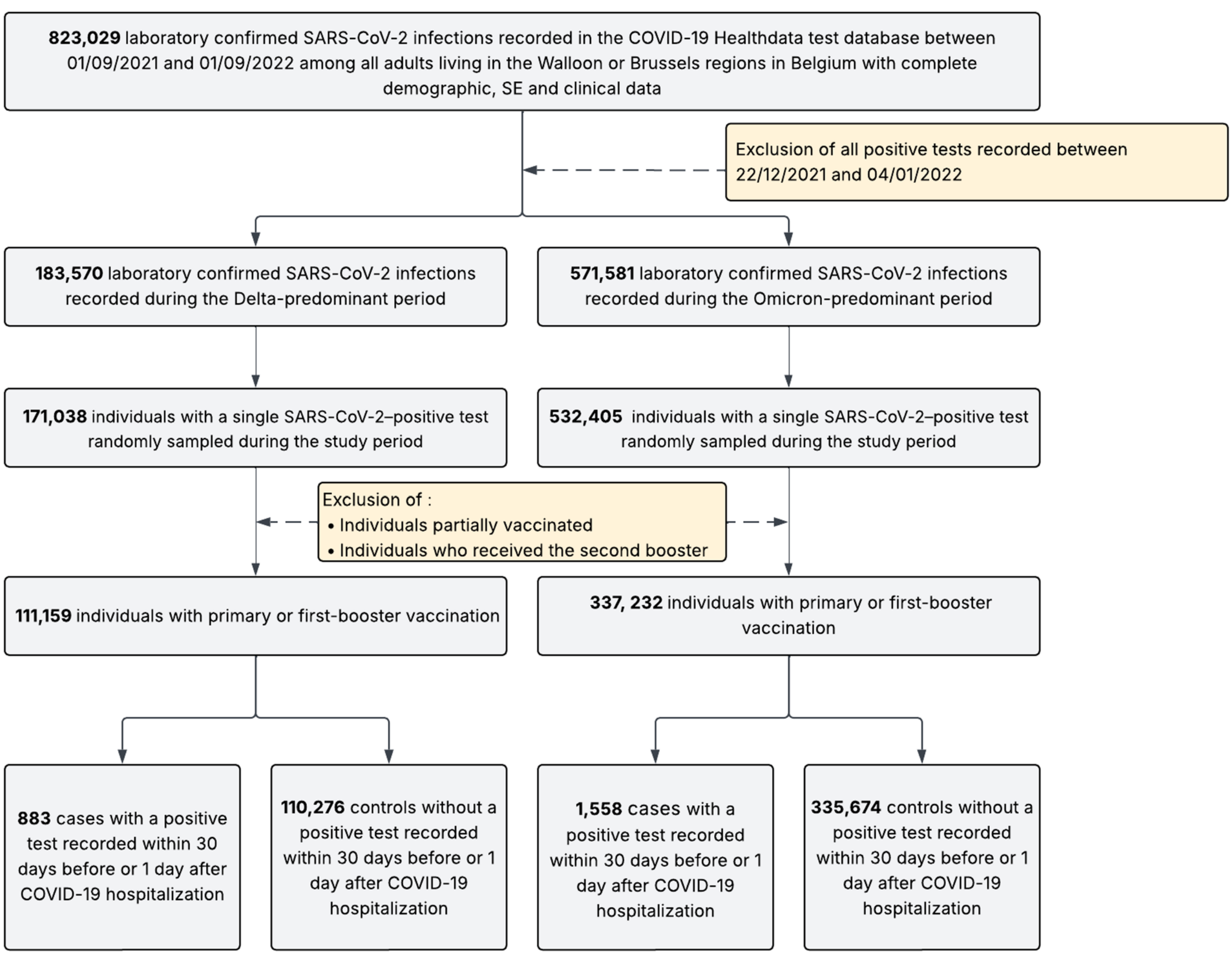


Fig. 1 Flowchart of the study population

Healthdata test database between 1 September 2021 and 1 September 2022 among adults (≥ 18 years) living in the Walloon or Brussels regions in Belgium with complete demographic, SE, and clinical data were included. By September 2021, all adults were eligible for the primary vaccination course, with 71% of the total Belgian adult population having completed their primary vaccination course at that date [41, 42]. This date also marked the start of the vaccination campaign for the first booster in Belgium [42].

Given the differential impact of SARS-CoV-2 variants on disease severity and vaccine effectiveness [43, 44], the study period was stratified by variant of concern (VOC) of predominance. A VOC was considered dominant when it accounted for at least 80% of sequenced samples recorded over a given period, a threshold chosen due to limited sequencing coverage (< 10%) in Belgium's baseline genomic surveillance [45]. The Delta-predominant period included all positive tests sampled between 1 September 2021 (start of the study period) until 22 December 2021. The Omicron-predominant period included all positive tests sampled between 4 January 2022 until 1 September 2022 (end of the study period). All positive tests sampled between 22 December 2021 and 4 January 2022 were dropped.

For each VOC period, only one positive test per individual was kept. For individuals with multiple positive tests recorded during the study period, infection periods were defined. An infection period included all positive tests counted over a 21-day period. For each infection period, only the first test of each period was kept, as the other tests probably reflected the same infection. When several infection periods were recorded for the same individual, only one was chosen at random.

The vaccination rollout for the second booster had begun at the end of the study period with only 5.34% of the Belgian population vaccinated with a second booster by 1 September 2022 [42]. Therefore, we excluded individuals who received a second booster, as well as individuals with incomplete vaccination course (i.e., a single dose of a two-dose primary schedule).

Cases were identified thanks to a link with the CHS database and defined as individuals who were hospitalized for COVID-19 either (a) within 30 days after their positive test date; (b) or one day before their positive test date, to avoid misclassifying nosocomial infections as community cases.

Outcome

The study outcome consisted of a COVID-19-related hospital admission defined by a hospital admission with a confirmed COVID-19 diagnosis by means of a positive RT-PCR or RAT and symptoms at admission. Based on the classification of SARS-CoV-2 infections established by the European Center for prevention and Disease Control (ECDC) [46], only community-acquired, nursing-home acquired, and infections of unknown origin in healthcare workers were kept. Indeterminate COVID-19 cases, and healthcare-associated or probable healthcare-associated nosocomial infections were excluded.

Exposure

As SE exposure, we used the educational level provided by the DEMOBEL database and classified in eight categories using the International Standard Classification of Education (ISCED) (see Supplementary Table 1). We merged these eight categories into two main educational levels: 'Low' (ISCED 0 to ISCED 2) and 'Moderate or high' (ISCED 3 to ISCED 8). 'Moderate or high education' was considered as the reference category.

Mediators

In the causal inference framework for observational studies, an exposure can be associated with an outcome through both direct and indirect pathways [47]. The indirect pathway involves a mediator, an intermediate variable that lies in the causal pathway between the exposure and the outcome, partially or fully explaining their association and making the unraveling of causal mechanisms feasible [47, 48]. A mediator can be distinguished from a confounder which is a third variable with a direct causal effect on the outcome and the exposure of interest [49]. As mediator variables, we selected vaccination status, underlying health conditions, and working in healthcare.

The vaccination status was taken 14 days before the date of infection with SARS-CoV-2 and was distinguished between 'No vaccination' and 'Primary or first-booster vaccination'. A primary-vaccination was defined as receiving two doses of BNT162b2, mRNA-1273, or ChAdOx1 (mRNA vaccines), or one dose of Ad26.COV2.S (viral vector vaccine). 'Primary or first-booster vaccination' was considered as the reference category.

Underlying health conditions (e.g. cardiovascular diseases, thrombosis, type 2 diabetes, chronic obstructive pulmonary disease) were deduced from data on reimbursed healthcare and medicine of Belgian residents ensured in the country available in IMA. Within the LINKVACC project, only underlying health conditions associated with an increased risk of severe COVID-19 were selected from IMA, this is therefore not a complete overview of all underlying health conditions. The overview of underlying health conditions included in IMA can be found in a report by Stouten et al. [50]. Two categories based on the number of underlying health conditions were distinguished: 'No underlying health condition' and 'At least one underlying health condition'. 'No underlying health condition' was considered as the reference category.

To identify individuals working in healthcare, we used a proxy variable available in CoBRHA allowing to identify all individuals who have been licensed to practice a healthcare profession in Belgium. 'Working in healthcare' was considered as the reference category.

Confounders

Age (at the beginning of the study period), gender, province of residence, and migration background were included as potential confounders. Age and gender were available in Vaccinnet + and the COVID-19 Healthdata test database, registers re-using demographic information from the Belgian national register. The province of residence was based on the postal code of residence available in the national register. Concerning the Walloon region, the five provinces were included: Walloon-Brabant, Hainaut, Liege, Luxemburg, and Namur. The Brussels region is not branched into provinces, and has therefore been directly included alongside the five provinces of the Walloon region. CHS hospital coverage during the study period varied by province, with the highest coverage for the province of Hainaut (70%) and the lowest for the province of Liege (15%). Assuming that the province of residence was equivalent to the province of the hospital where the individual was admitted, we used the province of residence as confounder to counter the bias induced by the difference in hospitalization coverage by province. Indeed, province has been considered as confounder in the statistical analyses given the known association between SE status and province in Belgium [51–53]. Migration background was available in STATBEL and based on a combination of the first nationality and the parent's country of origin. Four groups were distinguished: 'Belgian natives', 'Second-generation migrants', 'First-generation migrants', and 'First-generation non-European migrants'.

Statistical analyses

The study population was first described with the frequency rates and percentages for categorical variables and the median and the interquartile range (IQR) for continuous variables.

To assess the role of multiple mediators in the association between education and COVID-19 hospitalization, we applied causal mediation analysis within the interventional effects framework. Causal mediation analysis are usually applied within the potential outcomes framework, defining the causal effect for a given unit as the difference in its outcome under exposure versus control conditions, measured at the same time point [54–56]. However, this approach requires strong assumptions when multiple mediators are involved. Specifically, it assumes a known causal ordering of mediators and no unmeasured confounding, conditions that are rarely satisfied in practice [57].

To address this limitation, we applied causal mediation analysis within the interventional effects framework, an extension of the potential outcomes framework, which offers more flexibility when the true causal structure among the mediators is unknown [58–60].This approach estimates indirect effects through simulated interventions on mediator distributions and decomposes the total effect into direct and indirect effects. Thanks to this method, each indirect effect passing through each distinct mediator can be assessed separately [61]. Interventional effects are perfectly suited to assess effects of non-manipulable exposures such as SE determinants and have to be interpreted on the population level rather than the individual level [61]. Our proposed causal diagram for mediation analyses within the interventional effects framework is presented in Fig. 2.

The total effect was estimated by regressing COVID-19 hospitalization (Y) on education (A) conditional on covariates (C) (Eq. 1).

$$E(Y|A,C) = \beta_0 + \beta_A A + \beta_{C1} Age + \beta_{C2} Gender + \beta_{C3} Province + \beta_{C4} Migration\ background \quad (1)$$

Although both the exposure and mediators are binary and generalized linear models can be used to estimate risk differences within the interventional effects framework, we chose to use linear models for their analysis, hence assuming a linear probability model. This approach offered a number of advantages. First, for binary outcomes, linear regression is often preferred for estimating causal effects of an exposure [62]. Indeed, when computing linear regression coefficients, the effects estimated are directly interpretable as probabilities and the decomposition of the total effect into direct and indirect effects is more straightforward [62, 63]. Linear models are also more robust when interaction terms are included [62]. Additionally, our proposed method for mediation analysis was computationally more efficient with linear models. Empirically, predicted probabilities remained within the [0,1] range and diagnostic checks did not indicate substantial model misspecification.

To estimate the interventional (in)direct effects, two sets of linear regression models were used. The first model (Eq. 2) was estimated by regressing COVID-19 hospitalization (Y) on education (A) and mediators (Ms) conditional on covariates (C).

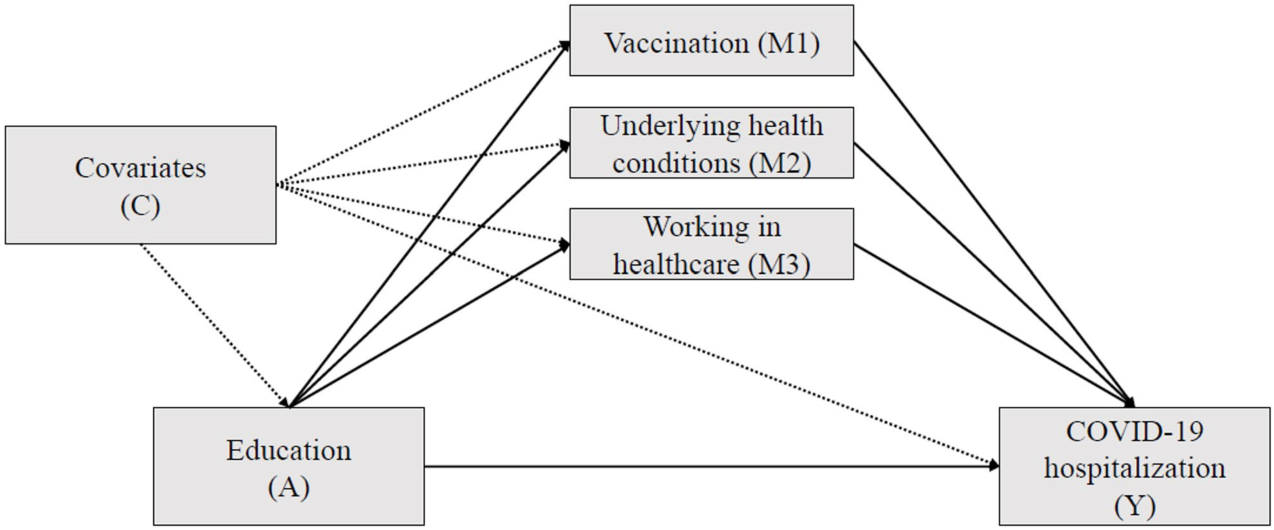


Fig. 2 Proposed causal diagram for the mediating effect of vaccination (M1), underlying health conditions (M2), and working in healthcare (M3) on the association between education (A) and COVID-19 hospitalization (Y) conditional on covariates (C). M1, M2, and M3 are assumed to be independent and not affect each other causally

$$E\left(Y|A,Ms,C\right)=\beta_{0}+\beta_{A}A+\sum_{s=1}^{3}\beta_{s}M_{s} + \beta_{C1}Age + \beta_{C2}Gender + \beta_{C3}Province + \beta_{C4} Migration\ background \quad (2)$$

The second set of models (Eq. 3) was estimated by regressing each mediator (*Ms*) separately on education (*A*) conditional on covariates (*C*). The effect of education (*A*) transmitted through each distinct mediator (*Ms*) along the causal pathway between *A* and *Ms* was captured in the regression coefficient δ_{s} (Eq. 3).

$$E\left(Ms|\,A,C\right)=\delta_{0s}+\delta_{s}A+\delta_{C1s}Age + \delta_{C2s}Gender+\delta_{C3s}Province + \delta_{C4s}Migration\ background \quad (3)$$

The statistical methodology used in this paper was based on Loh. et al. [61] and the code used in this study can be found on GitHub [64]. All statistical analyses were performed in R version 4.0.5 [65]. The package "lavaan" [66] was used to estimate interventional (in)direct effect models.

Sensitivity analyses

Education, vaccination, underlying health conditions, and working in healthcare are interrelated factors that may jointly influence COVID-19 hospitalization. Indeed, interactions between the three mediators can be expected. The effect of vaccination may vary for different levels of underlying health conditions, as individuals with comorbidities were prioritized during Belgium's vaccination campaign [41]. The effect of vaccination may also vary by healthcare worker status, as healthcare workers were also prioritized during Belgium's vaccination campaign and reported higher vaccination rates [41, 42]. The effect of education on COVID-19 hospitalization may also depend on mediator values, as variation in vaccination coverage, number of underlying health conditions, and working in healthcare can be expected according to the level of education [27, 36, 67].

To account for these potential interactions, sensitivity analyses were performed by including three types of interactions in the outcome model: exposure-mediator, mediator-mediator, and exposure-mediator-mediator interactions. The outcome model was therefore specified as shown in Eq. 4, where $(A:M_k)$ represents the exposure-mediator interactions, $(M_i:M_j)$ represents the mediator-mediator interactions, and $(A:M_i:M_j)$ represents the exposure-mediator-mediator interactions.

$$E\left(Y|\,A,Ms,C\right)=\beta_{0}+\beta_{A}A+\sum_{s=1}^{3}\beta_{s}M_{s} + \sum_{k=1}^{3}\left(\beta_{A:M_k}\left(A:M_k\right)\right)+\sum_{i,j=1}^{3}\left(\beta_{M_i:M_j}\left(M_i:M_j\right)\right) + \sum_{m,i,j=1}^{3}\left(\beta_{A:M_i:M_j}\left(A:M_i:M_j\right)\right)+\beta_{C1}Age+\beta_{C2}Gender + \beta_{C3}Province+\beta_{C4}Migration\ background \quad (4)$$

The interventional indirect effect for a single mediator *Ms* represents the change in the expected outcome when the distribution of *Ms* is shifted from what it would be under one exposure level (e.g., *A* = 0) to what it would be under another exposure level (e.g., *A* = 1), while holding *A* fixed. This effect is estimated by simulating interventions that replace the observed distribution of Ms with the distribution it would have under an alternative exposure level, it therefore captures both the direct contribution of Ms to the outcome but also its interaction with the exposure and with the other mediators, as specified in the outcome model (Eq. 4). When mediators are correlated and their covariance structure differs across exposure levels, an additional component, referred to as the mutual indirect effect, arises. This component reflects the portion of the indirect effect transmitted jointly through the interdependence among mediators and is captured by the interaction terms involving the three mediators and the exposure [61].

When mediator–mediator interactions are included, the indirect effect attributed to each mediator depends on how the mediators are labeled (e.g., M1, M2, M3). Because this labeling is arbitrary and does not imply a causal order, the estimated effects can vary purely due to labeling choices [61]. To account for this, an additional sensitivity analysis was conducted by examining all possible combinations of labeling the mediators, which involves considering different permutations.

Results

Characterization of the study population

The characterization of the study population stratified by VOC period is available in Table 1. The final study population included 111,159 and 337,232 individuals with a confirmed SARS-CoV-2 infection during Delta and Omicron periods, respectively. During both VOC-periods, the study population had a median age of 41

Table 1 Characterization of the study population, including all Belgian adults living in the Walloon or Brussel regions in Belgium with a SARS-CoV-2 positive test, stratified between the Delta-predominant period (1 September 2021 to 22 December 2021) and the Omicron-predominant period (4 January 2022 to 1 September 2022)

	Delta-predominant period		**Omicron-predominant period**	
	Total study population (*N* = 111 159)	**Hospitalized COVID-19 patients (*N* = 883)**	**Total study population (*N* = 337 232)**	**Hospitalized COVID-19 patients (*N* = 1 558)**
Covariates				
Age (in years), median[IQR]	41 [31–54]	65 [51.5–76]	41 [30–55]	75 [65–83]
Gender, n(%)				
Females	62 113 (55.9)	397 (45)	195 809 (58.1)	745 (47.8)
Males	49 046 (44.1)	486 (55)	141 423 (41.9)	813 (52.2)
Migration background, n(%)				
Belgian natives	70 858 (63.7)	497 (56.3)	295 218 (70.4)	1 136 (72.9)
Second-generation migrants	12 258 (11)	39 (4.4)	39 809 (9.5)	63 (4)
First-generation European migrants	13 041 (11.7)	172 (19.5)	40 137 (9.6)	247 (15.9)
First-generation non-European migrants	15 002 (13.5)	175 (19.8)	44 423 (10.6)	112 (7.2)
Province, n(%)				
Walloon-Brabant	15 073 (13.6)	90 (10.2)	43 771 (13)	167 (10.7)
Hainaut	38 894 (35)	420 (47.6)	128 922 (38.2)	938 (60.2)
Liege	458 (0.4)	5 (0.6)	1 485 (0.4)	5 (0.3)
Luxemburg	8 553 (7.7)	45 (5.1)	23 712 (7)	56 (3.6)
Namur	18 281 (16.4)	92 (10.4)	50 505 (15)	139 (8.9)
Brussels	29 900 (26.9)	231 (26.2)	88 837 (26.3)	253 (16.2)
Exposure				
Education, n(%)				
Moderate or high	75 707 (68.1)	401 (45.5)	222 155 (65.9)	543 (34.8)
Low	35 452 (31.9)	482 (54.5)	115 077 (34.1)	1 015 (65.2)
Mediators				
Vaccination status, n(%)				
No vaccination	32 219 (29)	486 (55)	65 235 (19.3)	231 (14.8)
Primary or first-booster vaccination	78 940 (71)	397 (45)	271 997 (80.7)	1 327 (85.2)
Underlying health conditions, n(%)				
No underlying health condition	79 226 (71.3)	292 (33.1)	232 458 (69)	247 (15.9)
At least one underlying health condition	31 933 (28.7)	591 (66.9)	104 774 (31)	1 311 (84.1)
Working in healthcare, n(%)				
No	101 540 (91.4)	847 (95.9)	307 217 (91.2)	1 530 (98.2)
Yes	9 619 (8.6)	36 (4.1)	30 015 (8.9)	28 (1.8)

years. During both VOC-periods, most participants were females, Belgian natives, moderately or highly educated, had a primary or first-booster vaccination, had no underlying health condition, and did not work in healthcare.

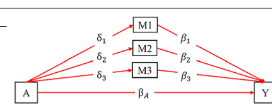
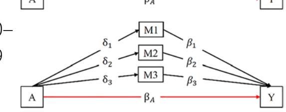
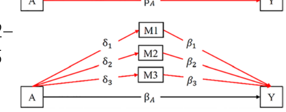
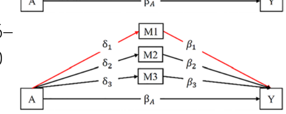
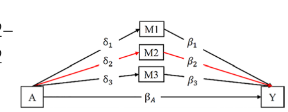
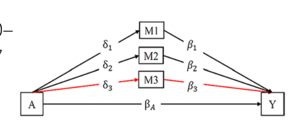
Table 1 also provides the characterization of individuals with recorded hospitalizations for COVID-19 in the CHS database by VOC period. During Delta and Omicron periods, 883 (0.79%) and 1,558 (0.46%) individuals were recorded as hospitalized for COVID-19, respectively. The median age of COVID-19 hospitalized patients during the Delta period (65 IQR 51.5–76) was lower compared than that of patients hospitalized during the Omicron period (75 IQR 65–83). During both VOC-periods, most COVID-19 hospitalized patients were males, Belgian natives, had low education, were not vaccinated, had at least one underlying health condition and did not work in healthcare.

Mediation analyses using interventional (in)direct effect models

Table 2 shows the interventional (in)direct effect estimates, bootstrap standard errors (SE), and 95% confidence intervals (CI) for the mediating effect of vaccination (M1), underlying health conditions (M2), and working in healthcare (M3) on the association between education and COVID-19 hospitalization stratified by VOC-predominant period, along with mediation path diagrams and interventional effects definitions.

During both VOC periods, the total effect (TE) indicates that shifting from moderate or high education to low education increased the probability of being hospitalized for COVID-19 by 0.694% points (95% CI 0.561% – 0.819%) during Delta and 0.547% points (95% CI 0.491% – 0.603%) during Omicron. Most of this increase was attributable to the direct effect (DE) of education, which accounted for 84.6% of the TE during Delta and 93.1% during Omicron. The remaining proportion was explained by the joint indirect effect (JIE) of all

Table 2 Interventional (in)direct effect estimates, bootstrap standard error (SE), and 95% confidence intervals (CI) for the mediating effect of vaccination, underlying health conditions, and working in healthcare on the association between education and COVID-19 hospitalization stratified by VOC-predominant period, along with mediation path diagrams and interventional effects definition

Interventional effects	Delta-predominant period			Omicron-predominant period			Mediation path analyses	
	Estimate	Bootstrap SE	95% CI	Estimate	Bootstrap SE	95% CI	Mediation path diagram	Interventional effects definition
Total effect (*TE*)	0.00694	0.00066	0.00561–0.00819	0.00547	0.00028	0.00491–0.00603		$TE = \beta_A + \sum_{s=1}^{3} \delta_s \beta_s$
Direct effect (*DE*)	0.00587	0.00068	0.00452–0.00722	0.00509	0.00029	0.00450–0.00529		$DE = \beta_A = TE - \sum_{s=1}^{3} \delta_s \beta_s$
Joint indirect effect (*JIE*)	0.00109	0.00009	0.00090–0.00128	0.00038	0.00003	0.00032–0.00045		$JIE = \sum_{s=1}^{3} \delta_s \beta_s = TE - \beta_A$
Indirect effect via M1 (vaccination) (IE_{M1})	0.00070	0.00006	0.00059–0.00081	0.00008	0.00001	0.00006–0.00010		$IE_{M1} = \delta_1 \beta_1$
Indirect effect via M2 (underlying health conditions) (IE_{M2})	0.00044	0.00006	0.00032–0.00057	0.00027	0.00002	0.00022–0.00032		$IE_{M2} = \delta_2 \beta_2$
Indirect effect via M3 (working in healthcare) (IE_{M3})	-0.00005	0.00005	-0.00015–0.00090	0.00004	0.00002	0.00000–0.00007		$IE_{M3} = \delta_3 \beta_3$

Interventional (in)direct effect models are adjusted for age, gender, province, and migration background. The numbering of the mediators is arbitrary and does not imply an order of causality between the multiple mediators. Standard error and 95% CI were constructed using 500 non-parametric bootstrap samples. 'A' denotes the exposure (i.e. education). 'Y' denotes the outcome (i.e. COVID-19 hospitalization). Red lines denote causal paths through which (in)direct interventional effects pass.

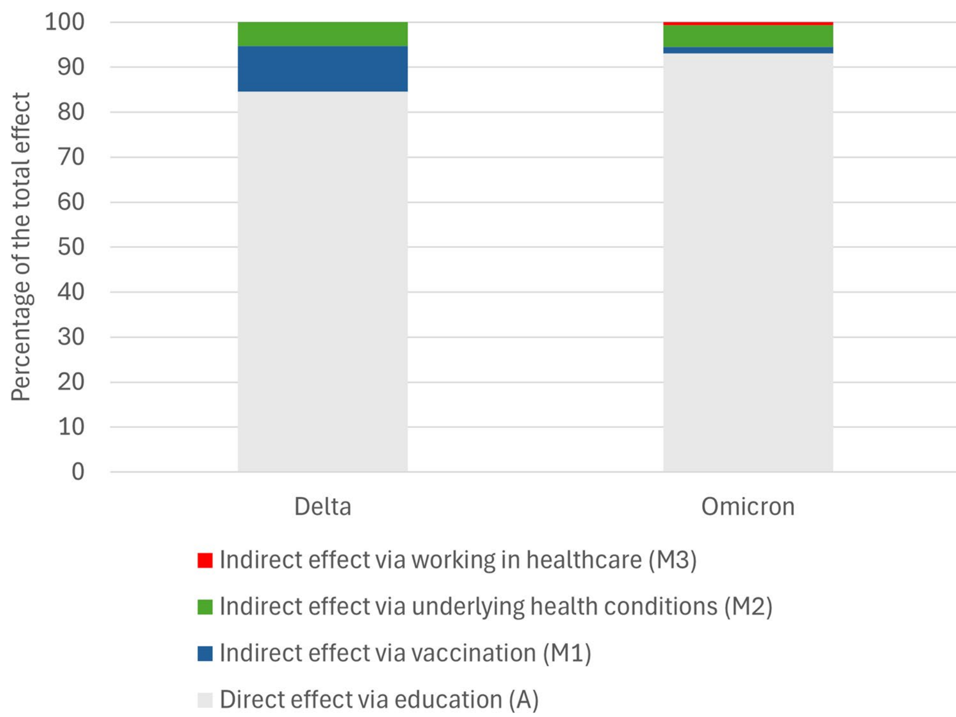


Fig. 3 Distribution of the direct effect, indirect effect via vaccination (M1), indirect effect via underlying health conditions (M2), and indirect effect via working in healthcare (M3) relative to the total effect during the Delta- and Omicron-predominant periods

mediators, accounting for 15.4% of the TE during Delta and 6.9% during Omicron (Fig. 3).

When looking at the indirect effect of each mediator separately, shifting the vaccination distribution from that observed among individuals with moderate or high education to that of individuals with low education increased the probability of being hospitalized for COVID-19 by 0.070% points (95% CI 0.059% – 0.081%) during Delta and 0.008% points (95% CI 0.006% – 0.010%) during Omicron. Regarding underlying health conditions, shifting its distribution from that observed among individuals with moderate or high education to that of individuals with low education increased the probability of being hospitalized for COVID-19 by 0.044% points (95% CI 0.032% – 0.057%) during Delta and 0.027% points (95% CI 0.022% – 0.032%) during Omicron. Regarding working in healthcare, shifting its distribution from that observed among individuals with moderate or high education to that of individuals with low education did not significantly increase the probability of being hospitalized for COVID-19 during Delta, but increased this probability by 0.004% points (95% CI 0.000% – 0.007%) during Omicron.

Proportionally, this means that during the Delta period, vaccination and underlying health conditions accounted for 10.1% and 6.3% of the TE, respectively. During the Omicron period, underlying health conditions, vaccination, and working in healthcare accounted for 4.8%, 1.4%, and 0.7% of the TE. Our mediators therefore explained a limited portion of the relationship between education and COVID-19 hospitalization (Fig. 3).

Sensitivity analyses

A first sensitivity analysis was computed by including exposure-mediator, mediator-mediator, and exposure-mediator-mediator interactions in the outcome model. The resulting estimated interventional (in)direct effects and 95% CI showed similar trends compared to the main analysis, except for the estimated interventional indirect effect via working in healthcare during the Omicron period which is no longer significant (Supplementary Table 2). Figure 4 illustrates the proportional contributions of the direct effect of education on COVID-19 hospitalization and of each indirect effect, accounting for the three types of interactions.

A second sensitivity analysis was computed accounting for the variation of the indirect effect through each mediator due to the labelling assigned to the mediators, presumed to be arbitrary. The results obtained from analyzing each of all possible permutations of mediator indices (3!=6) yielded similar estimates for both the maximum and minimum values of the (in)direct interventional effects (Supplementary Table 3), indicating that the results are robust to mediator ordering and not driven by an arbitrary labelling choice.

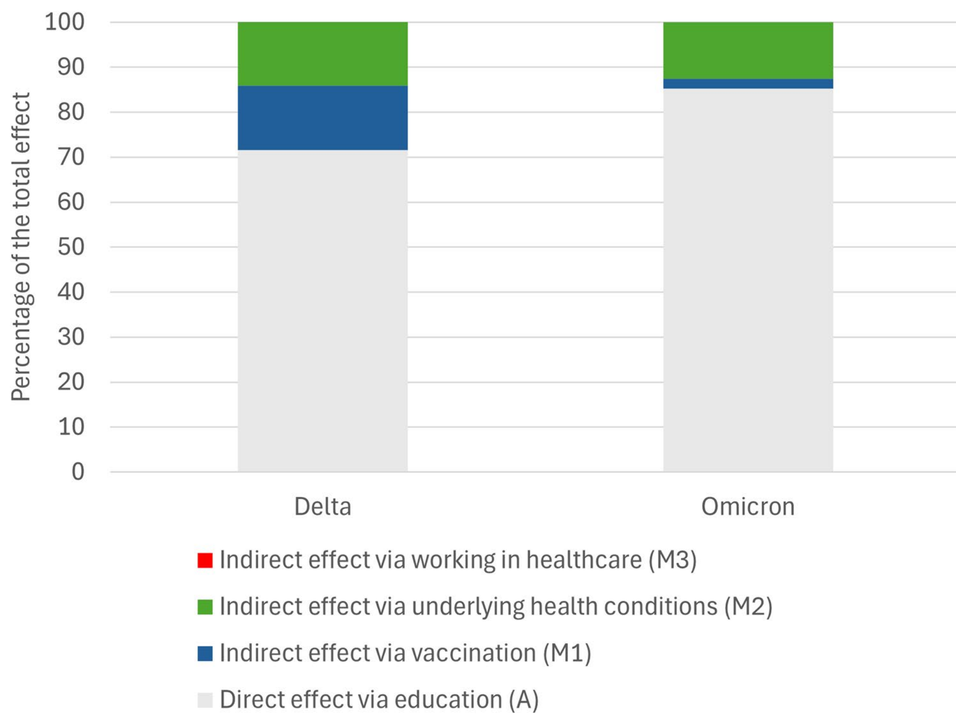


Fig. 4 Distribution of the direct effect, indirect effect via vaccination (M1), indirect effect via underlying health conditions (M2), and indirect effect via working in healthcare (M3) relative to the total effect accounting for exposure-mediator, mediator-mediator, and exposure-mediator-mediator interactions during the Delta- and Omicron-predominant periods, respectively

Discussion

In the CHS database a non-exhaustive reporting system in Belgium, 0.79% and 0.46% of individuals with a confirmed SARS-CoV-2 infection were hospitalized for COVID-19 during the Delta and Omicron periods, respectively. During both VOC periods, the majority of hospitalized COVID-19 patients had low education (54.5% and 65.2% for Delta and Omicron periods, respectively). In comparison, 32% of Belgian adults aged 25 years and older had a low educational level (up to lower secondary education) in 2021 [53]. This highlights the overrepresentation of adults with a low educational level among COVID-19 hospitalized patients compared to the general adult population in Belgium.

Using interventional (in)direct effect models, we found that shifting from a high to a low level of education increased the probability of COVID-19 hospitalization by 0.7% points during the Delta period and by 0.5% points during the Omicron period. These modest increases likely reflect the low prevalence of COVID-19 hospitalization during both VOC periods. During both VOC periods, the association between education and COVID-19 hospitalization was only partially mediated by vaccination and underlying health conditions, with all mediators jointly accounting for approximately 16% of the total effect during the Delta period and 10% during the Omicron period.

Our findings, showing a slightly higher increase in COVID-19 hospitalization rates among individuals with lower education levels, are consistent with several international studies, although those studies generally reported larger effect sizes [68–74]. Among all confirmed COVID-19 cases in Sweden by mid-September 2020, Bergman et al. found that, compared to individuals with primary education, the probability of hospitalization decreased by 13% for those with secondary education, 21% for those with post-secondary education (< 3 years), and 27% for those with post-secondary education (≥ 3 years) [72]. Similarly, in Switzerland, individuals residing in neighborhoods with the highest SE position had a 44% lower risk of COVID-19 hospitalization compared to those in the lowest SE position [73]. At the European level, a two-sample Mendelian randomization study showed a 0.540 higher odds of severe COVID-19 per one standard deviation increase in years of schooling [74].

The mediation role of chronic comorbidities in the association between SE status and respiratory infectious diseases has been previously shown by Ye et al., who reported that cardiovascular diseases and diabetes mediated 6.8% and 2.2% of this association, respectively [75]. This aligns with our findings showing a significant mediating effect of underlying health conditions on the association between education and COVID-19 hospitalization. To our knowledge, the extent to which comorbidities mediate this association has not been investigated yet.

However, the association of comorbidities with both SE status and COVID-19 hospitalization is well known, making this mediating role plausible. Indeed, individuals from lower SE groups present higher rates of comorbidities [67], due to factors such as decreased access to healthcare resources and unhealthy lifestyle habits (e.g. smoking, alcohol consumption, lower physical activity) [76]. Having comorbidities has also been shown to increase the risk of COVID-19 hospitalization [70–72] through several biological mechanisms including excessive pro-inflammatory responses and decreased tolerance to respiratory failure [25].

Similar mediation mechanisms may apply to vaccination, given its known association with both SE status and COVID-19 hospitalization [27–79]. SE disadvantaged groups showed lower vaccine uptake [27, 77, 79]. This may stem from reduced confidence in vaccine efficacy or concerns about side effects [80], limited access to healthcare and resources [77], or lower health literacy exacerbating fear and negative preconceptions about the vaccine [81]. However, the vaccine has been shown to be effective against COVID-19 hospitalization across both Delta and Omicron variants [32, 79, 82]. For instance, in Belgium, Braeye et al. showed a VE against COVID-19 hospitalization up to 50 days since the last vaccination of 93% and 94% for primary and booster vaccination, respectively. For the Omicron variant, the VE was 59% and 87% for primary and booster vaccination, respectively [32]. While the specific outcome may vary, a previous study conducted in the United States has also shown evidence of the mediating effect of vaccination on the association between SE status and severe COVID-19 outcomes by demonstrating that 37.6% of the impact of SE status on COVID-19 mortality was mediated by the vaccination coverage rate [83]. This highlights the importance of variations in vaccination coverage in exacerbating social inequalities in COVID-19 severe outcomes, and advocates achieving the most equitable vaccination coverage possible.

Our results showed a lower mediating effect of vaccination on the association between education and COVID-19 hospitalization during the Delta period compared to the Omicron period (10% vs. 1.4%, respectively). This difference in mediating effect across VOC periods could be due to variations in VE, disease severity, and population immunity. Indeed, VE against severe SARS-CoV-2 infection is higher for Delta compared to Omicron, and Omicron infections generally led to less severe clinical symptoms than Delta [32, 43, 84–87]. In addition, waning vaccine-induced immunity over time, along with natural immunity from prior SARS-CoV-2 infections, could also explain the reduced VE against hospitalization during the Omicron period compared to the Delta period [88, 89].

The three mediators included in our study only partly explained the association between education and COVID-19 hospitalization, with approximately 85% and 93% of this association unexplained by the mediators during the Delta and Omicron periods, respectively. A study conducted in England found that inequalities in SARS-CoV-2 transmission factors (e.g., overcrowded households, air quality, rurality, care homes) explained 73% of the effect of deprivation on COVID-19 mortality, followed by inequalities in vulnerability factors (i.e., chronic baseline conditions), accounting for 49% [90]. In our analysis, vaccine uptake and baseline chronic conditions, reflecting unequal access to preventive services and vulnerability, respectively, played only a moderate mediating role in social disparities in COVID-19 hospitalization. This is in line with a previous systematic review examining factors mediating disparities in infection and poor outcomes during the 2009 H1N1 Influenza pandemic in the United States [91]. In this study, the authors showed that social disparities in 2009 H1N1 outcomes were mainly driven by differential exposure to the virus rather than by susceptibility or access to care, with individual-level factors such as health behaviors and comorbidities contributing less. In our study, the lack of data on exposure and transmission factors may explain why a substantial portion of the association between education and COVID-19 hospitalization remains unexplained.

To the best of our knowledge, this is the first study investigating the mediation role of vaccination, underlying health conditions, and working in healthcare in the association between education and COVID-19 hospitalization using interventional effect models allowing to consider multiple mediators without assuming any causal structure between them. However, our study has four main limitations:

1) First, our study lack on data on unequal exposure and transmission pathways, which are key drivers of social health inequalities in EID's health outcomes. The availability of mediating factors accounting for unequal transmission and exposure pathways would likely have provided a more comprehensive explanation of social disparities in severe COVID-19, and helped identify the most critical factors to target in order to reduce them. Therefore, by including mediating factors that account for the four pathways driving social inequalities in EIDs within the syndemic framework, more comprehensive and effective policy recommendations could have been developed.
2) Second, the CHS database is not exhaustive and recorded only 59.3% and 42.3% of the total COVID-19 hospital admissions during the Delta and Omicron periods, respectively, leading to a sampling bias and significant underestimations of hospitalization

rates. In addition to the non-exhaustive nationwide hospital coverage, variations in hospital reporting rate were found by province. To counter this latter sampling bias, we used the province of residence as a confounder but an additional limitation lies under the assumption that an individual was hospitalized in her or his province of residence which may not be true. However, we have assumed that the variation in the hospital reporting rate did not depend on the SE status of the province, which would have further increased the sampling bias. Indeed, during our study period, the province of Hainaut had the highest reporting rate (± 70%) while the province of Liege had the lowest (± 15%). Average annual tax income per capita in 2020 was higher in the province of Liege (18,233 euros) compared to the province of Hainaut (17,118 euros) [51] and the unemployment rate in 2022 was 10.6% for the province of Hainaut and 8.4% for the province of Liege [52].

3) Third, a proxy based on the date of diagnosis was used to determine whether the infection was due to the Delta or the Omicron variant due to the few sequenced-laboratory confirmed infections during the study period. As such, certain infections will undoubtedly have been misclassified, but as we assume the required proportion to consider a period as dominant for a certain variant to be 80%, we expect the impact of this to be limited.
4) Fourth, to define the mediator 'Working in healthcare', we used a proxy variable identifying individuals with a degree in health, the rationale being that individuals working in healthcare are expected to have a higher level of health literacy that we hypothesized to lie on the causal pathway between education and COVID-19 hospitalization. However, having a healthcare degree does not necessarily imply working in the healthcare sector or applying the health knowledge acquired during training. This is therefore a crude measure which may have impacted our results. In addition, other factors than the possession of a degree in healthcare contribute to health knowledge.
5) Finally, the interventional effect framework is more robust than traditional natural effects as it does not rely on cross-world independence assumptions (i.e., assumptions about counterfactual outcomes under one exposure level combined with mediators set to values from another) and defines effects under well specified stochastic interventions on the mediators. Nevertheless, although our models were adjusted for measured covariates, concerns about unmeasured exposure–outcome, exposure–mediator, and mediator–outcome confounding may persist, and our findings should therefore be interpreted with caution.

Conclusion

Our findings hold implications for crisis management, indicating that, to partly reduce socioeconomic disparities in COVID-19-related hospitalizations, public health strategies should focus on preventing underlying health conditions and enhancing vaccination rates by promoting health education, especially within the lowest socioeconomic groups, to increase vaccine knowledge and confidence. Nevertheless, further research is needed to identify additional factors within the syndemic framework of the pandemic, especially transmission and exposure factors, that could further mediate social disparities in severe COVID-19.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12879-026-12907-5.

Supplementary Material 1

Acknowledgements

We would like to thanks the Walloon and Brussels regions who gave us the authorization to use the LINKVACC data to perform this study.

Author contributions

LC reviewed the literature; LC, BD, JG, J A.F. L, LB, NS, and RP conceived the study; LC, BD, JG, J A.F. L, LB, NS, and RP selected the study population; LC, BM, TL, and RP designed the statistical methodology; LC and RP conducted the statistical analyses; LC, BM, TL, and RP interpret the findings; LC wrote the first draft of the paper. All authors revised the text. All authors approved the final version of this manuscript and accepted responsibility for its submission for publication.

Funding

This study was supported by the FOD/SPF Public Health of Belgium and the Belgian federated entities through funding for the LINK-VACC project on vaccine surveillance. In addition, Belgian Science Policy Office (BELSPO) funded this research within the BRAIN-be 2.0 framework supporting pillar 3 Federal societal challenges (grant number B2/202/P3/HELICON). The sponsors did not have a role in the conduction of the study, the writing of the manuscript, or in the decision to submit it for publication.

Data availability

The data used in this study are pseudonymized individual data obtained from several national registers hosted by Healthdata.be, an independent institution within Sciensano aiming to bring together all the data currently stored in multiple health registers on a single web-based platform. Due to the General Data Protection Regulation (GDPR) legislations in Belgium, these data are not publicly available. Data request must be addressed to the Information Security Committee (ISC).

Declarations

Ethics approval and consent to participate

The protocol of the LINK-VACC project was approved by the Medical Ethics Committee from the Vrije Universiteit of Brussels on 3 February 2021 (B.U.N 1432020000371) and obtained authorization from the Information Security Committee (ISC) Social Security and Health (reference number: IVC/KSZG/21/034). As confirmed by Sects. 23 and 24 of the *Guidelines 03/2020 on the processing of data concerning health for the purpose of scientific research in the context of the COVID-19 outbreak* of the European Data Protection Board (V1.0 of 21 April 2020), this survey falls under Article 6 § 1(e) and Article 9 § 2(i) of the General Data Protection Regulation (GDPR). In appliance with these GDPR legal grounds of data processing, no informed consent had to be signed by the patients.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Epidemiology and Public Health, Sciensano, Sciensano Rue Ernest Blerot 1, Brussels 1070, Belgium
[2]Research Institute of Health and Society, University of Louvain, Brussels, Belgium
[3]Department of Data Analysis, Ghent University, Gent, Belgium
[4]Department of Translational Physiology, Infectiology and Public health, Ghent University, Merelbeke, Belgium
[5]Department of Rehabilitation Sciences, Ghent University, Ghent, Belgium

Received: 20 August 2024 / Accepted: 12 February 2026
Published online: 19 February 2026

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