

Mapping COVID-19 Impact:
Cross-border Mobility, Social Networks, Vaccination, and Post-COVID Condition

Céline Johanna Angelique van Bilsen

Stellingen behorende bij het proefschrift:

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1. Zelfgerapporteerde gezondheidsdata zijn, ondanks methodologische beperkingen, een onmisbare bron van informatie voor epidemiologisch en volksgezondheidsonderzoek (dit proefschrift).
2. Vrije grensoverschrijdende mobiliteit is een essentiële determinant van sociale en mentale gezondheid in grensregio's, en verdient daarom expliciete bescherming binnen crisismaatregelen (dit proefschrift).
3. Vaccinatiegedrag wordt niet uitsluitend bepaald door individuele attitudes, maar in belangrijke mate door sociale context en leefomgeving (dit proefschrift).
4. Post-COVID-19 conditie heeft substantiële gevolgen voor duurzame arbeidsparticipatie en productiviteit en verdient daarom structurele aandacht binnen gezondheids- en arbeidsmarktbeleid (dit proefschrift).
5. De impact van COVID-19 is multidimensionaal en kan niet volledig worden begrepen vanuit één discipline (impact).
6. Human lives are caught in a precarious equilibrium between microparasitism and macroparasitism (Plagues and Peoples, William McNeill).
7. Health inequalities and the social determinants of health are not a footnote to the determinants of health. They are the main issue (Michael Marmot).
8. Human beings are members of a whole, in creation of one essence and soul (Saadi Shirazi).
9. Life shrinks or expands in proportion to one's courage (Anaïs Nin).
10. To awaken quite alone in a strange town is one of the pleasantest sensations in the world (Freya Stark).

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Céline Johanna Angelique van Bilsen
Academische Werkplaats Publieke Gezondheid Mosa

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TABLE OF CONTENTS

Chapter 1 General introduction 10

Section 1: Data collection during the COVID-19 pandemic

Chapter 2 COVID-19 pandemic response in the Meuse-Rhine 32
33 Euroregion: methods, participation and recommendations of a longitudinal cross-border study.
Archives of Public Health. 2023 May 13;81(1):91.
doi: 10.1186/s13690-023-01102-6.

Chapter 3 Design and recruitment of a large-scale cohort study 78
on prevalence, risk factors and impact evaluation of post-COVID-19 condition and its wider long-term social, mental, and physical health impact: The PRIME post-COVID study.
Frontiers in Public Health. 2022 Dec 15:10:1032955.
doi: 10.3389/fpubh.2022.1032955.

Section 2: Cross-border mobility, vaccination, and social networks

Chapter 4 Cross-border mobility in the Meuse-Rhine Euroregion: 104
Impact of COVID-19 border restrictions on everyday activities and visiting social network members.
Frontiers in Public Health. 2024 Apr:12:1281072.
doi: 10.3389/fpubh.2024.1281072.

Chapter 5 Differences in non-positive intention to accept the 152
COVID-19 booster vaccine between three countries in the cross-border region Meuse-Rhine Euroregion: The Netherlands, Belgium, and Germany.
Vaccine X. 2023 Aug:14:100306.
doi: 10.1016/j.jvacx.2023.100306.

Chapter 6 Social networks and COVID-19 vaccination 176
intention in Dutch middle-aged and older adults in 2020: Insights into individual, interpersonal, community, and societal determinants - The SaNAE study.
Vaccine X. 2024 Sep 24:20:100562.
doi: 10.1016/j.jvacx.2024.100562.

Chapter 7 Social networks, environmental, and individual factors associated with COVID-19 vaccination and booster uptake– the prospective PRIME cohort study. *Vaccine X. 2025 Feb:23:100626. doi:10.1016/j.jvacx.2025.100626.* 214

Section 3: Post-COVID-19 condition 260

Chapter 8 Workforce exit and work productivity loss in adults with and without post-COVID-19 condition: the PRIME post-COVID cohort study. *Submitted.* 262

Chapter 9 Recovery from post-COVID-19 condition and associated factors: the PRIME post-COVID study. *Submitted* 292

Chapter 10 General discussion 326

Summary 344

Nederlandse samenvatting 352

Impact 360

Dankwoord 366

Portfolio 370

List of Publications 374



Chapter 1

General introduction

SARS-CoV-2 PANDEMIC

From first detection to long-term consequences, the pandemic redrew the boundaries of health, society, and science. Viruses are not merely pathogens; they are evolutionary forces that expose the vulnerabilities of our biological and social networks. By exploiting transmission opportunities – from households to international mobility networks – they map our connectivity and reveal how behaviour, inequity, and policy shape epidemic trajectories. Their rapid mutation and selection pressures uncover the dynamics of host immunity, vaccination, and viral adaptation, creating shifting patterns of population immunity. In this dissertation, viruses are seen as system-level catalysts: agents that reconfigure institutions, accelerate scientific approaches, and leave measurable marks on bodies, data streams, and social structures.

Viruses are nucleic acid packages of DNA or RNA that rely entirely on host cells to replicate, using the host's replication and protein synthesis systems (1). Many human infectious diseases, such as influenza, HIV, and dengue, originated in animals before being transmitted to humans, referred to as host-switching or spillover events. Such events are driven by social and environmental factors—urbanization, crowding, mobility, inequity, deforestation, land-use change, wildlife trade, and climate variability—and by biological factors including cross-species contact, shared cellular traits, and the high adaptability of RNA viruses (1, 2). Coronaviruses are a family of RNA viruses found in various species, including humans (1). They are characterized by their distinctive crown-like spike proteins when viewed under a microscope (derived from the Latin word "corona") and primarily spread through respiratory droplets and aerosols (3). Coronaviruses were first linked to the common cold in the 1960s. Later, new strains caused more severe outbreaks, including SARS in 2002–2003 and MERS in 2012 (1, 3).

In late 2019, a novel coronavirus emerged in Wuhan, China, and rapidly spread globally. This virus, known as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), causes coronavirus disease 2019 (COVID-19) (4). The incubation period (the time between infection and the onset of symptoms) is typically between 5 and 7 days (5). Acute COVID-19 can manifest with various symptoms such as fever, cough, shortness of breath (dyspnea), fatigue, muscle aches, sore throat, loss of taste and smell, and gastrointestinal disturbances (6). The risk of

severe disease increases with age and is higher among individuals with underlying health conditions (7).

Testing was foundational to COVID-19 control: by identifying infections early, it enabled isolation of contagious individuals and activated contact tracing and quarantine to interrupt transmission chains (8). Laboratory polymerase chain reaction (PCR) and later rapid antigen tests supported targeted screening in high-risk settings (healthcare, long-term care, workplaces, schools) and informed community surveillance, including wastewater monitoring, to detect infection waves and emerging variants. Combined with non-pharmaceutical interventions (NPIs) such as mask use, improved ventilation, physical distancing, limits on gatherings, and remote work and schooling, test-trace-isolate-quarantine (TTIQ) strategies reduced effective contact rates and bought time for health systems to adapt. Their impact depended on speed, coverage, and equity. Timely access to tests, paid sick leave, and clear risk communication increased adherence, while delays and barriers impaired effectiveness (9, 10). As vaccines became available, the strategy shifted from suppression by NPIs alone to layered protection in which vaccination, including the primary series, boosters, and targeted campaigns for vulnerable groups, reduced severe disease, hospital burden, and onward transmission. Testing retained a complementary role in the vaccine era by informing isolation, outbreak control, and therapeutic eligibility, and by generating data to adjust policies as immunity waned and new variants appeared. Together, evolving combinations of testing, prevention, and vaccination formed an adaptive toolkit that balanced epidemic control with societal functioning (8).

Antibody (serological) testing played a limited role in population-level control but proved valuable in hospitals and research. Because IgM/IgG typically become detectable only 6–12 days after symptom onset and then wane over months, serology was not suitable for acute case finding, isolation decisions, or contact-tracing. Instead, its strengths lay elsewhere: in clinical care, to support diagnosis in late or post-acute presentations (e.g., when PCR was negative, yet suspicion remained), to assess vaccine or infection-induced responses in immunocompromised patients, and to inform therapeutic decisions. In research and surveillance, serology underpinned seroprevalence studies that estimated cumulative infections, infection fatality ratios, and immunity gaps, distinguishing infection-induced (anti-nucleocapsid) from vaccine-induced (anti-spike) antibodies where assays allowed (11–13).

COVID-19 was declared a Public Health Emergency of International Concern by the World Health Organization (WHO) on January 30, 2020, and declared a pandemic on March 11, 2020 (14).
Successive variants—Alpha, Beta, Gamma, Delta, and Omicron—emerged with greater transmissibility and virulence (the ability of a virus to cause severe disease) (15). By April 2023, global confirmed COVID-19 deaths were close to 7 million (16).

COVID-19 IN THE NETHERLANDS

The Netherlands confirmed its first COVID-19 case on February 27, 2020, in Noord-Brabant. Early clusters, likely linked to carnival events, quickly spread nationwide, heavily straining healthcare (17). PCR tests were initially available through public health services for symptomatic individuals with an epidemiological link and later expanded to broader groups. From May 2021, antigen-based self-tests became widely available for home use (8). The Netherlands experienced a significant impact from the COVID-19 pandemic, with over 8 million confirmed cases, more than 50,000 hospitalizations, and at least 40,000 reported deaths in the first two years (18). The province of Limburg was disproportionately affected, recording the third-highest hospitalization rate and the highest mortality rate nationally, as recorded by the national COVID dashboard. Several factors may have contributed to this, including early mass gatherings like the February 2020 carnival and a relatively older population.

TYPES OF MEASURES

Governments worldwide, including in the Netherlands, started implementing containment measures, including travel restrictions, quarantine measures, and lockdowns to prevent spread of the virus. The primary aim of these measures was to flatten the pandemic curve, reducing further transmission to keep infections within healthcare capacity. Containment strategies generally combine non-pharmaceutical and pharmaceutical interventions. Non-pharmaceutical measures include sanitation, mask-wearing, hand hygiene, isolation, contact tracing, quarantine, and risk communication, while pharmaceutical measures include vaccination and medications that reduce infectiousness (19, 20). The specific choice and design of the measures depend on the pathogen's mode of

transmission and is tailored to the characteristics of the infectious agent (20). Developing effective containment measures requires governments to balance social, economic, and political factors while accounting for unpredictable public responses, virus mutations, and evolving vaccination or treatment options (21).

TIMELINE OF MEASURES IN THE NETHERLANDS

In the Netherlands, measures started with the introduction of an 'intelligent' lockdown from March 15, 2020, including distancing, closures, travel limits, and hygiene measures (22). Between April and July 2020 COVID-19 cases declined, and restrictions were eased. Primary schools reopened in June, community and drive-through testing expanded, and face masks became mandatory in some settings. Non-essential businesses and public venues reopened with capacity limits. In August 2020 cases rose again, marking the second wave. Bars and restaurants closed in October, and stricter lockdowns, including a curfew, were imposed due to the Alpha variant. Mass vaccination started in January 2021, initially targeting healthcare workers and vulnerable groups, leading to gradual easing of restrictions. Between February and October 2021, social distancing and capacity limits were relaxed. The "corona entry ticket" system was introduced for nightlife in June, boosting vaccine uptake among young adults. The Delta variant caused a surge in cases, leading to temporary closures of bars and nightclubs, followed by gradual reopening. The Omicron variant prompted new restrictions in November 2021, but healthcare impact remained manageable. Restrictions were gradually lifted, including ending physical distancing and entry ticket requirements by February–April 2022 (Figure 1). Subsequent waves occurred but without new restrictions.

On May 5, 2023, the WHO declared that COVID-19 was no longer a Public Health Emergency of International Concern, marking its shift from a global emergency to a long-term challenge (23) and marking a major step in downscaling pandemic response.

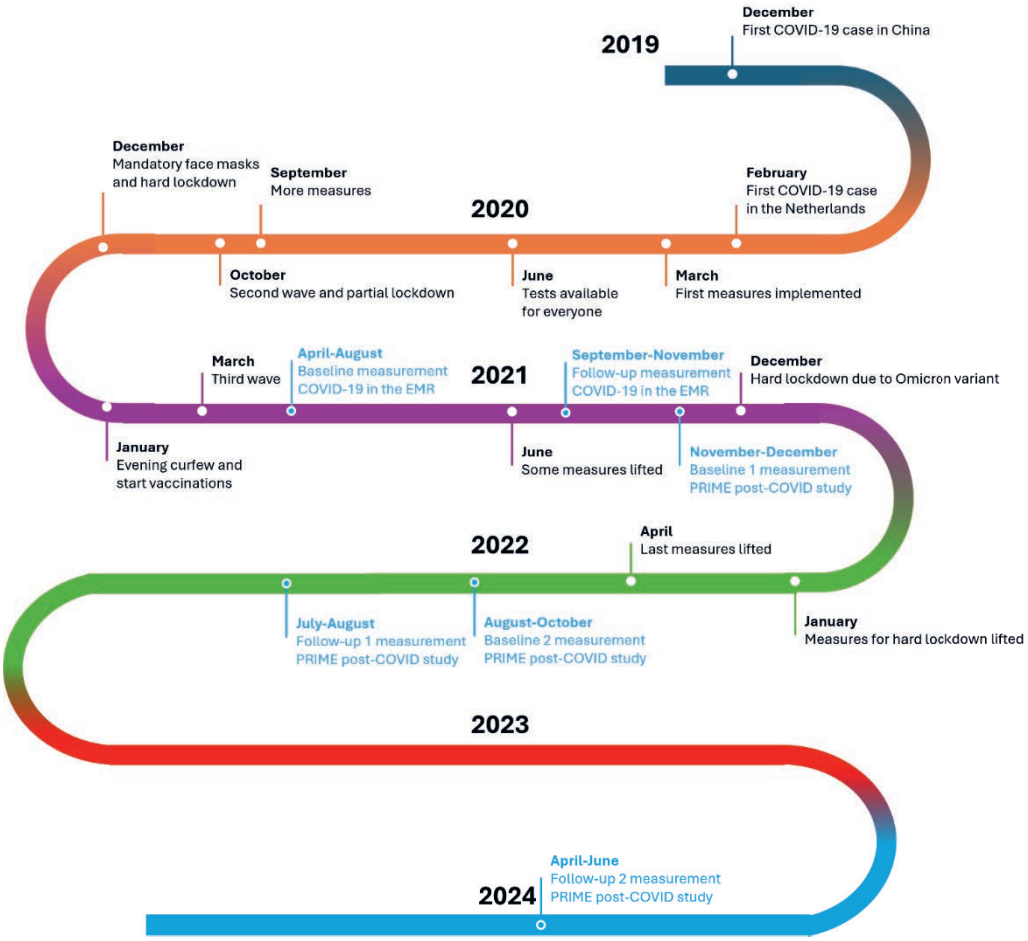

Figure 1. Timeline of COVID-19 in the Netherlands from 2019-2024, including the studies in this thesis conducted by the Public Health Service and Living Lab Public Health Mosa (AWPG Mosa).

COVID-19 IN THE MEUSE-RHINE EUROREGION

During the COVID-19 pandemic, the World Health Organization (WHO) advised against the implementation of travel restrictions (24). Nevertheless, many countries introduced such measures, restricting air travel and travel from specific high-risk regions with high infection risk (25). The enforcement of border closures within the European Union (EU) marked a historical event, as such restrictions had not occurred in decades since the signing of the Schengen Agreement in 1985

(26). These restrictions profoundly affected citizens whose daily lives are transnational, involving work, shopping, leisure, and family or social ties across borders. Given that 40% of EU-territory comprises cross-border region and 38% of EU-population lives in a cross-border region (27, 28), this highlights the relevance of assessing the impact of border measures.

The Meuse-Rhine Euroregion (EMR) is a border area encompassing three countries (Belgium, Germany, and the Netherlands) with a combined population of approximately four million people. The EMR includes the middle and southern parts of Limburg in the Netherlands; the provinces of Limburg, Liège, and the German-speaking Community in Belgium; and the Zweckverband Aachen region in Germany, which comprises the Städteregion Aachen and the districts of Düren, Heinsberg, and Euskirchen (Figure 2). In the EMR, cross-border dynamics complicated the early response. A large cluster emerged in Germany's Heinsberg district, bordering Limburg, but the area was not yet classified as a 'high-risk region' in the Dutch case definition. This meant exposures linked to Heinsberg did not initially meet the criteria for suspect cases (29). Nevertheless, the Regional Public Health Service (GGD), together with local mayors and the RIVM, implemented precautionary cross-border measures, including cancelling several post-carnival mass-gathering events, showing how local coordination could act faster than formal classifications.
Later, Belgium closed its borders and temporarily reinforced border controls with both the Netherlands and Germany from March 20 until June 15, 2020, while Germany strongly discouraged non-essential travel. Commuting to Germany for work purposes remained possible only with a commuting certificate (30). Consequently, these restrictions also affected the Netherlands, particularly the province of Limburg, which is geographically and socially embedded in a cross-border region.

The EMR functions as an integrated socio-economic space where cross-border mobility (CBM) is part of everyday life. Residents frequently cross borders for work, healthcare, leisure, and social interaction, often perceiving national boundaries as largely symbolic (30, 31). The introduction of border restrictions during the pandemic abruptly disrupted this interconnectedness, restricting social contact across the region (30, 31). Belgium, Germany, and the Netherlands adopted largely divergent and uncoordinated policy responses to COVID-19 (30). Evidence suggests that border closures were not highly effective in containing

the virus, and despite initial concerns, cross-border mobility within the Meuse-Rhine Euroregion did not significantly contribute to its spread (13, 32).



Figure 2. Map of the Meuse-Rhine Euroregion.

COVID-19 VACCINATION BEHAVIOR

Immunization is one of the most effective public health strategies (33). Vaccination helps build immunity against viruses, reducing the severity of symptoms or preventing illness altogether (34). The development and rollout of vaccines in 2021 marked a new phase of the pandemic. By December 8, 2021, 56% of people worldwide had been vaccinated with at least one COVID-19 dose and it is estimated that COVID-19 vaccines have averted nearly 20 million deaths worldwide (35). As new variants of the virus appeared, booster vaccines became necessary to maintain immunity. The Netherlands started its booster vaccination campaigns in early 2022. Vaccination rates among adults in South Limburg reached 81%, while booster uptake reached 63% by September 2022 (36). Mass vaccination aims to protect most of the population, slowing transmission and shielding those who cannot be vaccinated. This is called herd immunity and can only be achieved when a substantial proportion of the population is vaccinated (37).

Vaccine hesitancy is defined as a "delay in acceptance or refusal of vaccination despite availability of vaccination services" (38). The WHO identified vaccine

hesitancy as one of the top 10 threats to global health in 2019, responding to a global increase in vaccine-preventable diseases (39). The COVID-19 pandemic intensified debates around vaccinations, while social media rapidly spread misinformation, making reliable information harder to access. The WHO Director-General referred to this as an "infodemic." The pandemic may have decreased trust in vaccine safety and efficacy, including the COVID-19 vaccine but also other types such as childhood vaccinations (40, 41).

Vaccine intention is important for predicting uptake, but it does not always lead to actual vaccination, as individuals may either follow through or change their minds toward acceptance or refusal, based on evolving beliefs, social norms, and contextual factors (42, 43). Identified factors associated with COVID-19 vaccine uptake include older age, male sex, absence of pregnancy, higher education and socio-economic status, presence of chronic diseases, and beliefs such as higher perceived risk of infection, lower perceived risk of vaccine harm, and higher trust in vaccine safety and effectiveness (44, 45). Understanding factors associated with vaccination behavior is key to designing effective public health interventions, improving vaccine communication strategies, and addressing barriers to uptake.

SOCIAL NETWORKS

Health and health behaviors are shaped by a socio-ecological system involving individual, interpersonal, community, and societal levels (46). The interpersonal and community level includes social networks, which can be defined as the web of all social relationships of an individual. Aspects of social networks can be divided into structural, functional, and quality (47). Structural aspects include the size (number of persons) and diversity of a person's network, geographic proximity of contacts, and modes of interaction (in-person or remote). Relationships may involve family, friends, colleagues, neighbors, acquaintances, or caregivers. Functional aspects refer to dynamic processes like behavioral exchanges and types of social support (informational, emotional, practical) (47, 48). These reflect how individuals engage with society and access resources or health benefits. The type of social relationships can shape the type of support provided, with close ties (family and friends) typically offering emotional support, while weaker ties often supply informational support, particularly new information (49).

Social networks are powerful drivers of transmission, behavior, and resilience, yet they are inherently hard to capture because ties are dynamic, context-dependent, and only partially observable. Over the past two decades, however, methods to measure networks have matured, yielding tools for public health. Broadly, two designs are used: egocentric networks, which center on one individual (the ego) and their connected alters, and sociocentric networks, which map all ties within a bounded group (e.g., a classroom, ward, or village). Egocentric designs scale well to large populations and are especially useful in public health research (50). One common method to assess egocentric networks is the name-generator questionnaire, which asks individuals to list important people in their lives. Additional questions (name-interpreter items) gather details about these relationships, such as type, frequency, proximity, and support—along with attributes of the alters (e.g., age, gender, behavior) (51). These data help describe the network's structure, function, and quality.

Social networks play a vital role in emotional well-being, physical health, and longevity. Social networks influence health through multiple pathways, including social support, social influence and engagement, person-to-person interactions, and access to resources (47, 48). Strong social connections are associated with lower mortality, while social isolation and having fewer relationships are linked to chronic conditions such as type 2 diabetes, cardiovascular disease, and mental health problems (52-56). Loneliness, defined as a deficiency in meaningful social connections, is distinct from simply having few relationships but is similarly linked to negative health outcomes, including higher mortality risk (57). Emotional support from close contacts can reduce disease risk, help with coping, and improve access to healthcare resources (58, 59). Social networks also influence health behaviors, including vaccination and non-pharmaceutical infection prevention behavior (60-63). For example, social support from the network is linked to higher influenza vaccination uptake (64) and higher COVID-19 intention and uptake (65, 66). Understanding the social network and community factors that are associated with vaccination intentions and uptake can help guide effective public health responses.

POST-COVID-19 CONDITION

Post-COVID-19 condition (PCC), also known as long COVID, refers to symptoms that continue for at least three months following a SARS-CoV-2 infection. Global

estimates suggest that 6% of people with COVID-19 develop PCC. In total, around 400 million individuals have experienced this condition, with an estimated annual economic impact of approximately one trillion dollars, highlighting its substantial burden as a global public health concern (67, 68).

Long-term symptoms following acute infections are well-documented, including bacterial infections like Q-fever and Lyme disease, and viral infections such as encephalitis (69, 70). In mid-2020, reports began to emerge of persistent symptoms after SARS-CoV-2 infection, lasting for months after initial onset. These symptoms, such as fatigue, dyspnea, chest pain, cognitive disturbances, and joint pain, were collectively referred to by patients as "long COVID" (71, 72).

Due to the lack of a standardized clinical definition, various terms and criteria have been used to describe this condition. In October 2021, the World Health Organization (WHO) introduced the term "post-COVID-19 condition" (PCC), defining it as a condition occurring in individuals with a history of probable or confirmed SARS-CoV-2 infection, typically three months after onset, with symptoms lasting at least two months and not explained by another diagnosis (73).

Despite this definition, clinical practice often uses simplified criteria, such as the presence of one or more symptoms since infection (74). The inconsistency in definitions complicates accurate estimation of prevalence and incidence. Many studies lacked control groups or data on pre-infection symptoms, making it difficult to distinguish direct effects of the virus from indirect effects of the pandemic and

its measures (75, 76). There is substantial variation in prevalence estimates depending on the definition of post-COVID-19 condition used, with limited overlap between definitions, suggesting that the core criteria for PCC remain unclear. Including individuals without prior infection is essential to identify symptoms truly attributable to COVID-19. In 2021, at least one out of six people in South Limburg experience persisting symptoms after a SARS-CoV-2 infection (77).

The full scope of health complications from SARS-CoV-2 is still not fully understood. Symptoms of PCC are heterogeneous, including fatigue, dyspnea, and cognitive dysfunction (78). Different sub-phenotypes of PCC have been proposed: joint pain, dyspnea, chronic malaise and fatigue, chest pain, neurological deficits, dyspepsia, and cognitive changes (79). PCC has been linked to myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) due to overlapping symptoms like disabling fatigue, cognitive difficulties, pain, and

exercise intolerance. These symptoms may tremendously affect daily life and functioning, and thereby also have societal implications (80-82). Besides, factors related to recovery remain largely unknown. There is an urgent need for further research to clarify the condition and its broader impact, to develop effective care and treatment strategies.

AWPG MOSA

In the Netherlands, Public Health Services (PHS) play a central role in infectious disease surveillance by collecting and registering data on notifiable diseases and outbreaks reported by institutions and laboratories. These pseudonymized data are shared with the National Institute for Public Health and Environment (RIVM) to support national monitoring efforts, placing significant responsibility on the PHS in managing infection control. In South Limburg, the PHS collaborates closely with Maastricht University through the Living Lab Public Health Mosa (Academische Werkplaats Publieke Gezondheid Mosa), a partnership that bridges public health policy, research, and practice. This collaboration facilitated the rapid initiation of several regional studies during the COVID-19 pandemic.

euPrevent COVID-19

In 2021, a cross-border research initiative was launched with nearly one million euros in funding from Interreg V-A Euregio Meuse-Rhine. This longitudinal study examined pandemic response and infectious disease control across the Netherlands, Belgium, and Germany. The project involved extensive international collaboration between euPrevent, the Public Health Service South Limburg, Sciensano (Belgium), Care and Public Health Research Institute (CAPHRI), Maastricht University Medical Center + (MUMC+), the German-speaking community of Belgium, Gesundheitsamt des Kreises Düren, Gesundheitsamt des Kreises Heinsberg, and Gesundheitsamt der Städteregion Aachen. Letters and packages including a link to online questionnaires and at-home finger prick kits to test COVID-19 antibodies were distributed amongst selected citizens. Preparations faced challenges due to differing national regulations, highlighting the complexity of cross-border public health research. Besides quantitative data collection, citizen summits were organized to further elucidate the impact of COVID-19 on citizens in the EMR.

SaNAE

The SaNAE study (Social Network Assessment among Adults and Elderly) was established in 2018 in the Dutch province of Limburg, funded by ZonMw Netherlands. It investigates social networks and their relation to infectious diseases in adults aged 40 and older living independently. Participants were drawn from the 2016 Dutch Health Monitor, a national survey, which selects a random sample from the Basisregistratie Personen (BRP), and invited to complete the SaNAE baseline questionnaire in 2019. Follow-up questionnaires were conducted in August 2020 (early COVID-19 pandemic) and in 2022 (near the end of the pandemic). SaNAE is the only Dutch study providing detailed longitudinal data on social networks and infection prevention.

PRIME POST-COVID STUDY

To better understand the still ongoing long-term effects of COVID-19, the Prevalence, Risk factors, and Impact Evaluation (PRIME) post-COVID study was set up in late 2021. This large-scale, longitudinal cohort study investigates the prevalence and risk factors of post-COVID condition (PCC), as well as its broader impact on physical health, mental and emotional well-being, and socioeconomic circumstances. The Public Health Service of South Limburg was responsible for organizing regional COVID-19 testing and maintaining the associated registry. Leveraging this position, and following careful legal and ethical review, the Public Health Service was able to invite all adults in the region who had tested positive for SARS-CoV-2, using fully anonymized data for public health research purposes. Legally, the Public Health Service is authorized to use the registry data (fully de-identified) to perform research in public health.

AIM AND OULTINE OF THIS THESIS

The aim of this dissertation was to map the impact of COVID-19, providing perspectives on data collection during the pandemic, changes in cross-border mobility, cross-border booster intentions, vaccination behavior and social networks, the impact of post-COVID-19 condition on work participation, and factors associated with recovery from post-COVID-19 condition. By using quantitative longitudinal cohort data, this research aimed to provide a comprehensive understanding of the multifaceted impact of COVID-19, leading

to recommendations for policymakers and healthcare professionals to address these consequences in practice.

Section 1. Data collection during the COVID-19 pandemic

The first section covers longitudinal data collection during the COVID-19 pandemic. In **Chapter 2**, we describe comparable cross-border data collection and recommendations of a Euregional study in the EMR. In **Chapter 3**, the design and recruitment process of a prospective, observational, open cohort study – the Prevalence, Risk factors, and Impact Evaluation (PRIME) post-COVID study – are described. The PRIME post-COVID study aims to provide insights into various health-related aspects of post-COVID-19 condition (PCC), with its findings intended to support practical guidance for society as well as for clinical and public health practice.

Section 2. Cross-border mobility, vaccination, and social networks

Chapter 4 investigates the prevalence of cross-border mobility for social visits and for daily activities in the Dutch, Belgian, and German subregions of the EMR, how this changed during the pandemic, and how citizens experienced border restrictions, including associated factors. **Chapter 5** describes differences in non-positive intention to accept the COVID-19 booster vaccine between the Dutch, Belgian, and German subregions of the EMR, and associated factors. **Chapter 6** investigates COVID-19 vaccination intentions in middle-aged and older adults in 2020 and associations with interpersonal determinants, including a comprehensive description of social networks, and individual, community, and societal determinants using data from the SaNAE study (Social Network Assessment among Adults and Elderly). **Chapter 7** uses data from the PRIME study to assess COVID-19 vaccination and booster uptake and associated individual, interpersonal, community, and societal determinants, including a broad overview of social network aspects.

Section 3. Post-COVID-19 Condition

Chapter 8 investigates workforce exit in patients with post-COVID-19 condition (PCC) and in those recovered and with never PCC, and associated factors. Besides, work productivity loss and work incapacity are compared between groups. **Chapter 9** examines the proportion of patients with post-COVID-19 condition (PCC) who recover over time, including variations in daily functioning.

Factors associated with recovery are identified to provide insights and guidance for the future management of patients with PCC.

In **Chapter 10**, the main findings of this thesis are presented and contextualized through comparison with existing literature, leading to recommendations for future practice, policy, and research.

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Section 1

Data collection during the COVID-19 pandemic



Chapter 2

COVID-19 pandemic response in the Meuse-Rhine Euroregion: methods, participation and recommendations of a longitudinal cross-border study.

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ABSTRACT

Background

Comparative data collection in transborder areas can contribute to informed decision-making processes when dealing with borderless health threats such as pandemics and thus help minimize the negative health effects for its citizens. To examine the pandemic response over time and the impact of infectious disease control in a cross-border setting, a prospective longitudinal study was conducted in the border area between Germany, Belgium and the Netherlands.

Methods

In the spring of 2021, a random sample of 26,925 adult citizens selected from governmental registries was invited to collect a blood sample at home for SARS-CoV-2 antibody testing and to fill in an online questionnaire on attitudes and behaviour towards infection prevention measures, cross-border mobility, social network and support, COVID-19 self-reported infection(s) and symptoms, vaccination, general self-reported health and socio-demographics. In autumn 2021, participants were invited for a follow-up round. An online tool was developed to coordinate fieldwork procedures, real-time monitoring of participation and consultation of antibody test results. Furthermore, a helpdesk in all three languages for participants' support was set up.

Results

In the first round, 6,006 citizens in the Meuse-Rhine Euroregion participated. 15.3% of the invited citizens on the Belgian side of the border participated. In the Netherlands and Germany this was respectively 27% and 23.7%. In the follow-up round 4,286 (71.4%) citizens participated for the second time. The participation rate was highest in the age group 50–69 years and lowest in > 80 in all sub regions of the Meuse-Rhine Euroregion. More women participated than men. Overall, more blood samples were returned than completed questionnaires. In total, 3,344 citizens in the Meuse-Rhine Euroregion completed all components of participation in both rounds.

Conclusions

The collection of comparative data can help better assess the pandemic response and the impact of infectious disease control in a cross-border area.

Recommendations for a longitudinal cross-border study include a centralized online environment, mapping out potential challenges related to national regulations in the preparation phase and organizing regional coordination centres to create more familiarity and trust towards the involved organisations.

BACKGROUND

In December 2019, the first cases of the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) were reported in Wuhan, China (1). A month later, the novel pathogen was detected in Europe, causing an increased alertness among EU Member States (2). The European Centre for Disease Prevention and Control (ECDC) urged a rapid, proactive and comprehensive approach from policy makers to delay transmission and to reinforce the capacity of healthcare systems in March 2020 (3). The outbreak of SARS-CoV-2 marked the start of the implementation of a range of infection prevention measures such as lockdowns, school closures, travel restrictions, restrictions on leisure activities and postponement of regular healthcare. Infectious disease control in the EU was - and still is at the time of writing - dominantly tackled on a national level.

Borders arise through a socio-political process which does not always correspond to the borders perceived from a social, cultural and historical perspective. Up to 37% of the European population lives in a European internal border region (4). Taking into account the interconnectedness and mobility of populations in Europe, it is vital to assess the impact of infectious disease control in border regions in order to deal with current and future public health threats.

In the Meuse-Rhine Euroregion (EMR) citizens were confronted with a large number of open and unresolved questions in connection with the constantly changing crisis measures due to divergent national policies (5). The EMR covers the border area between Belgium, the Netherlands and Germany. A Euroregion can be described as a cross-border organization or institution that declared 'will of cooperation being reinforced by public institutionalisation via political agreement; and clearly shows signs of joint activities as well as consolidation of public cross-border policies, particularly when developing a common strategy' (6).

Comparative data– that includes cross-border aspects - enables policy makers, health care providers, and other stakeholders to better assess infectious disease control and the pandemic response in border regions. Up to this date such data remains limited, thus hindering representative and adequate health analyses.

In August 2020 'Impact of COVID-19 on the Meuse-Rhine Euroregion' was launched by foundation euPrevent (7). Citizens were invited to collect a blood

sample at home using a self-finger prick test and fill in an online questionnaire. To facilitate a uniform approach on all sides of the borders, an interregional partnership was set up. An online tool was developed to coordinate fieldwork procedures and the data collection process.
This paper presents the methods, participation and recommendations of an interregional cross-border study.

METHODS

Design

'Impact of COVID-19 on the Meuse-Rhine Euroregion' is a prospective longitudinal study that collected serological- and survey data to examine the impact of infectious disease control on citizens in the border region. Data collection took place twice, from April to July 2021 and September to November 2021 in each sub region in the EMR within the same cohort.

Setting

The regions involved in this study are the Belgian provinces Limburg and Liège (including the German-speaking Community), South Limburg (NL), and the German City Region Aachen and Districts of Düren and Heinsberg. In 2021 the EMR counted around four million inhabitants (8).

Project consortium

The project consortium consists of the Public Health Service South Limburg (NL), Sciensano (Belgian institute of public health, BE), Maastricht University Medical Centre (NL) and foundation euPrevent (NL). The associate partners are the Public Health Service Düren (DE), Public Health Service City Region Aachen (DE), Public Health Service Heinsberg (DE) and the German-speaking Community of Belgium (BE).

Sampling for baseline participation

Study population
The sampling frame consisted of all persons registered in the latest version of the National Register (NR) in Belgium, the Basic Registration of Persons (BRP) in The Netherlands and the Registration Offices (Einwohnermeldeämter) in Germany. Included in the study were the registered general adult population living in private

households. Individuals living in institutionalized settings such as prisons, psychiatric institutions and elderly homes were excluded from the sample. For Germany it was not possible to identify the living condition.

Sample size

The sample size was set at 3,500 in each country, that in turn was distributed among the sub regions according to the size of the adult population. The included adult population was ranked according to age group and sex. After ranking, the study population was divided into eight age groups: 18–29, 30–39, 40–49, 50–59, 60–69, 70–79, 80–89 and ≥ 90 and a stepwise selection was applied. The step size in each sub region was based on the total eligible population of that sub region divided by its sample size, starting from a random number. In Germany, the citizens of District Heinsberg and City Region Aachen were only classified by sex and a randomized sample was taken.

Substitution

Participation in this study implied performing a self-fingerpick test and completing an online questionnaire. Given the uncertainty of the response rate, the project consortium opted for substitution. In every region, an initial sample, with the same size and composition as the predefined net-sample, was selected by applying a stepwise selection of individuals after ranking the sampling frame by age-group and gender. Each time an individual was selected for participation, the next three individuals in the ordered list were selected as potential substitutes. Substitution of non-participants can help achieve the predetermined net sample, both in size as in composition (8). The selection probability of the substitute cases is conditional. This contradicts the idea of equal selection chances. Nevertheless, the probability of being an initial selected case is equal of being selected as a substitute case.

Opt-out and substitution

In South Limburg (NL), an opt-out procedure was required by the Dutch Ethical Committee. This procedure entailed that an announcement letter about the study was sent to each individual from the sample, informing them on the study and giving the option to disclose refusal of participation. To anticipate a high opt-out rate and potential delays in data collection the initial sample size of 3,500 was doubled in South Limburg, resulting in an initial sample of 7,000. For each opt-

out, 2 persons from the same age group and sex were selected from the reserve sample. By substituting twice, the probability of obtaining at least one participant increased. Those who did not wish to participate, had 12 days to opt-out online: via the link in the information letter, by mailing the enclosed return card, or by calling the call center set up for this project. The invitees that did not opt-out received the invitation to participate.
For the Belgian and German sub regions, this opt-out procedure was not required and for cost-effective motives therefore not applied.

Follow-up

Between 3 to 5 months after receiving an invitation to participate in the study, all invitees that participated – filling in the questionnaire and/or sending a blood sample and/or signing the informed consent - were invited for a follow-up round of data collection.

Measurements at baseline and at follow-up

SARS-CoV-2 antibody testing

To determine antibody responses to SARS-CoV-2 the Euroimmun Anti-SARS-CoV-2 QuantiVac ELISA (IgG) test and Euroimmun Anti-SARS-CoV-2 N CP ELISA (IgG) test (EUROIMMUN Medizinische Labordiagnostika AG, Lübeck, Germany) were used (9, 10). The Euroimmun Anti-SARS-CoV-2 QuantiVac ELISA (IgG) detects IgG antibodies binding the S1 antigen of SARS-CoV-2 in a quantitative manner using a 6-point calibration curve. The S1 antigen contains the immunologically crucial receptor binding domain (RBD), which is a key target antigen for virus neutralisation. The total amount of IgG antibodies is expressed as relative units per milliliter (RU/ml). The Euroimmun Anti-SARS-CoV-2 NCP ELISA (IgG) is a semi quantitative test which detects IgG antibodies directed against the nucleocapsid protein. Whereas S-directed assays detect both post natural infection and vaccine-induced antibodies, nucleoprotein assays only detect antibodies post natural infection.

According to the manufacturer's instructions, both the Euroimmun Anti-SARS-CoV-2 QuantiVac ELISA (IgG) and the Euroimmun Anti-SARS-CoV-2 NCP ELISA (IgG), human serum, plasma or dried capillary blood (dried blood spots) can be used as sample material. Data generated by Euroimmun, and by other institutions indicate high agreement between results obtained with venous serum samples

and small-volume samples such as dry blood spots (8–10). Both tests were performed using the manufacturers' instructions. The resulting extinction is calculated to a ratio (extinction of sample/extinction of calibrator) in case of the Euroimmun Anti-SARS-CoV-2 NCP ELISA (IgG) or is plotted against a 6-point calibration curve in case of the Euroimmun Anti-SARS-CoV-2 QuantiVac ELISA (IgG) in order to determine the relative units per milliliter (RU/ml).

For the Euroimmun Anti-SARS-CoV-2 QuantiVac ELISA (IgG) results were interpreted as followed:

Value (RU/ml)	*Interpretation*
< 8 RU/ml	negative
≥ 8 to < 11 RU/ml	borderline
≥ 11 RU/ml	positive

For the Euroimmun Anti-SARS-CoV-2 NCP ELISA (IgG) results were interpreted as followed:

Ratio	*Interpretation*
< 0.8	negative
≥ 0.8 to < 1.1	borderline
≥ 1.1	positive

In this study, borderline results were considered positive.

Home-sampling with a self-finger prick

Serological data were collected twice with the same cohort to assess the prevalence of SARS-CoV-2 (infection- and vaccine induced) antibodies and the changes over time in the EMR. Using a collection kit distributed by mail, participants collected circa 20 drops of capillary blood by self-finger pricking with a safety lancet into a BD Microtainer® K2EDTA collection tube. The addition of ethylenediaminetetraacetic acid in the test tube prevents clotting of blood, thereby enabling the analysis of the sample even days after collection.

Home-sampling increases participation and is a cost-effective alternative for clinical testing (11). Furthermore, the self-finger prick method offers the advantage of minimizing unnecessary movements of individuals to central blood

collection locations, thus not overburdening health care staff for whom workload is already high due to the continuing pandemic (12). Nevertheless, self-finger pricking might be difficult for motoric impaired participants or participants who find it difficult to collect a blood sample from themselves.

A small pilot including the self-finger prick method and the SARS-CoV-2 antibody tests was conducted at the Maastricht University Medical Centre among employees. The self-finger prick method showed to be feasible for the Anti-SARS-CoV-2 QuantiVac ELISA (IgG). The pilot sample included 11 SARS-CoV-2 IgG negative and 5 SARS-CoV-2 IgG positive individuals. Overall agreement between venous serum sampling and self-finger prick sampling in SARS-CoV-2 IgG negative individuals was 100% (11/11). One out of 5 SARS-CoV-2 IgG positives retrieved a borderline result in the self-finger prick sample. In a second pilot focusing on the Anti-SARS-CoV-2 NCP ELISA (IgG), 6/7 known PCR positive SARS-CoV-2 individuals were also identified as NCP positive when using small-volume (10 µl) samples.

Questionnaires

In addition to the serological data of two timeframes within the same cohort, participants were asked to fill in accompanying online questionnaires. Survey data enabled to examine associated factors of SARS-CoV-2 antibodies, determinants of non-positive intention for booster vaccination, changes in cross-border mobility over time, attitudes and behavior towards infection prevention measures and risk factors of loneliness during the pandemic. Both questionnaires were available in Dutch, German and French. Seven topics were included in both questionnaires: infection prevention measures (compliance, support, opinion on usefulness and level of difficulty to adhere), mobility (changes in mobility and cross border visits), social network, COVID-19 self-reported infection(s) and symptoms, vaccination, general health and socio-demographics. In the second questionnaire one topic on traveling during the summer was added (see Additional file 1: Table S1 for complete content of the questionnaires).

Ethical assessment

In the Netherlands, the study was submitted to the medical ethics review committee of Maastricht University Hospital and Maastricht University (METC azM/UM) and was assessed as not requiring a WMO. For Germany, no ethical assessment of the project was needed. The project had to be approved by the

heads of Gesundheitsamt Heinsberg, Düren and Aachen, and the in-house lawyers of Kreisverwaltung Heinsberg, Düren and Städteregion Aachen. In Belgium, the study was approved by the Medical Ethics Committee of the University Hospital Ghent and the University of Ghent (BC-09754).

Consent

An informed consent was to be filled in and signed by participants of this study. Participants in all participating countries were asked to consent: to participate in the study, for keeping personal data for a longer period of time to use for future research in the field of infectious diseases. In the Netherlands and Germany participants were asked consent to be contacted for future research. In Belgium participants were asked to be re-contacted for the follow-up round of the study.

Mailing procedure

A unique identification code was allocated to every invitee. From the 10-digit identification number, the following could be identified: sub region, sex, age group, ranking; initial sample, first or second substitute. Invitees were sent an invitation letter in the official language of the sub region with an information brochure, the personal ID-code, a link for filling in the online questionnaire, an informed consent form and a home-sampling kit. The home-sampling kit included illustrated instructions, two finger prick lancets, a micro tube (BD Microtainer® K2EDTA collection tube), plaster, gauze bandage, plastic safety bag and a pre-stamped envelope for return to the laboratory.
In both rounds and in all sub regions, 1 week after sending the invitation a general reminder letter was sent whether or not invitees participated.

Technical and logistical requirements developed to conduct the study

Online tool

An online tool was developed by an external software company and functioned as an intersection where all components of the cross-border study could be connected.
Employees who composed the test kits used the online tool to scan and connect unique ID-numbers to an empty blood tube containing a random 4-digit number. The result of the SARS-CoV-2 antibody tests were determined by the lab and noted in an Excel file together with the blood tube code. This file was periodically

delivered to the software developer to be imported and consulted by the researchers and participants in the online tool.

To process the informed consents, employees scanned the ID-number in the online tool, together with the items of consent given by the participant.

Invitees received the announcement letter or invitation letter with their personal ID-number and the link to the online tool where multiple actions could be taken: filling in the questionnaire, consulting the blood results, retrieving information on the study, and interpretation of test results. Dutch invitees could fill in their ID-number to opt-out for the study and the researchers processed the return cards in the online tool to register the opt-outs.

Via a helpdesk page, employees could assist participants with no computer (skills) or difficulties filling in the questionnaire. At the end of filling in the questionnaire, participants choose a pin code to consult the antibody test result 3 weeks after sending the blood sample. If participants forgot this code, employees could reset the pin code.

At any moment, the researchers could download a file with an overview of the ID-numbers and information about opt-out, completion of questionnaire, availability of blood results, and informed consents. At the end of the study, the anonymized dataset combining data from the questionnaire and the antibody test could be downloaded by the researchers and used for analysis.

Call center

For the data collection phase, a call center was set up by Public Health Service South Limburg (NL) in all three languages. Invitees to the study could call the call center for more information, to request the antibody result, to solve technical problems or to assist with the online questionnaire.

Call center employees logged the questions in a logbook anonymously, only mentioning the ID-number of invitees to ensure privacy. This way, the researchers could monitor the number and type of questions. Alternatively, participants could send an email to the researchers via the email address mentioned in the letters or on the website. Researchers answered the emails in the appropriate language.

Collection points

All blood samples for the antibody testing were analyzed in the laboratory of the MUMC+ in the Netherlands. Participants of Belgium and Germany sent their blood samples together with the signed consent form to a collection point in the respective countries instead of the laboratory, since personal information could not cross the border. The Ministry of the German-speaking Community in Belgium served as collection point for Belgian participants: informed consents were scanned in the online tool by employees of the Ministry of the German-speaking Community and sent to Sciensano, while the blood samples were transported to the laboratory by a courier. In Germany, a similar procedure was followed where the Public Health Service Düren was used as the collection point.

Ethics approval and consent to participate

This study was submitted to the medical ethics review committee of Maastricht University Hospital and Maastricht University (METC azM/UM) and was assessed as not requiring a WMO.

For Germany, no ethical assessment of the project was needed. The project had to be approved by the heads of Gesundheitsamt Heinsberg, Düren and Aachen, and the in-house lawyers of Kreisverwaltung Heinsberg, Düren and Städteregion Aachen.

In Belgium, the study was approved by the Medical Ethics Committee of the University Hospital Ghent and the University of Ghent (BC-09754).

RESULTS

Table 1 presents the population - versus sample distribution per age group in the Meuse-Rhine Euroregion.

Table 1. Population - versus sample distribution in the Meuse-Rhine Euroregion in 2020.

Age group	Population Dutch sub region (%)	Sample (%)	Population Belgian sub regions (%)	Sample (%)	Population German sub regions (%)	Sample (%)
18–29	89,284 (17.5)	594 (17.0)	270,465 (17.4)	609 (17.4)	172,521 (19.1)	674 (19.3)
30–39	64,406 (12.7)	455 (13.0)	247,132 (15.9)	556 (15.9)	132,566 (14.7)	540 (15.4)
40–49	66,997 (13.2)	441 (12.6)	250,223 (16.1)	564 (16.1)	122,024 (13.5)	488 (13.9)
50–59	94,382 (18.5)	619 (17.7)	276,557 (17.8)	622 (17.8)	172,218 (19.1)	673 (19.2)
60–69	88,646 (17.4)	645 (18.4)	248,819 (16.0)	560 (16.0)	140,051 (15.5)	538 (15.4)
70–79	67,089 (13.2)	475 (13.6)	165,326 (10.6)	372 (10.6)	92,120 (10.2)	334 (9.5)
> 80	38,189 (7.5)	271 (7.7)	96,032 (6.2)	215 (6.1)	72,194 (8.0)	252 (7.2)
Total	508,993	3500	1,554,554	3498	903,694	3499

Participation in round 1

In total, 26,925 citizens in the EMR received an invitation to participate in the study. Three hundred twenty invitations never arrived at their destination: 250 in Germany, 46 in Belgium and 24 in the Netherlands. The opt-out rate in South Limburg (NL) was 33.7% (2,358 opt-outs) in the initial sample and 38.2% (1,638 opt-outs) in the reserve sample. This implies that 35% from the invitees actively refused participation in the study. Opt-out rates increased with age group, and ranged from 18% in the group of 18–29 years to 64% in the group of ≥ 90 years. For the German and Belgian citizens active refusal could not be monitored since the opt-out procedure was not applied here. However, during the fieldwork monitoring, general low participation could be observed in the online environment. Substitutes were invited to achieve a higher net sample.

15.3% of the invited citizens in the Belgian sub regions participated in the study. In the Netherlands and Germany this was respectively 27% and 23.7%. 14% of the participants in the EMR have only sent blood but did not fill in the questionnaire. 3,7% completed the questionnaire without sending a blood sample. Survey data of these participants can still be used if serological data is not included in a particular analysis.

In total, 6,006 citizens in the EMR responded to the invitation by starting the questionnaire and/or sending blood and/or filling in the informed consent. In the overview below (Fig. 1) one can notice that of the 6,006 participants, not all completed all components of participation in this study. From 79,6% of the participants there was a completed questionnaire, valid blood sample and correctly filled in informed consent form.

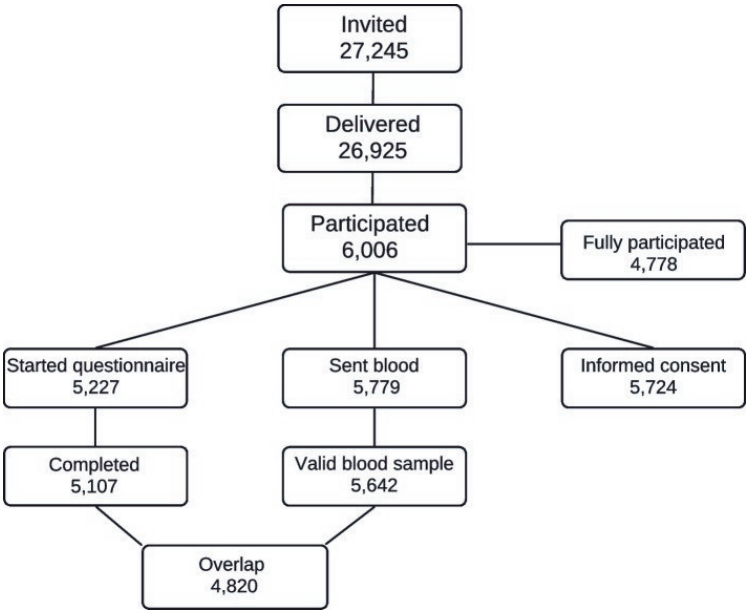

Figure 1. Flow diagram: Participation in round 1 between April and July 2021 of 'Impact of COVID-19 on the Meuse-Rhine Euroregion'

Participation in the follow-up round

In round 2, all participants who had filled in the questionnaire and/or sent in a blood sample plus informed consent form received a new invitation with a link to

the questionnaire and material for the at-home self-finger prick ($N = 6{,}006$). Between 21 September-30 September 2021 all invitations to participate in round 2 were sent. Three thousand forty-two in South Limburg (NL), 1,366 in the Belgian sub regions and 1,598 in the German sub regions.

71.4% (4,286) responded in round 2 and 55.7% (3,344) completed all components of participation in both rounds. The flow diagram of participation in the second round is presented in Fig. 2.

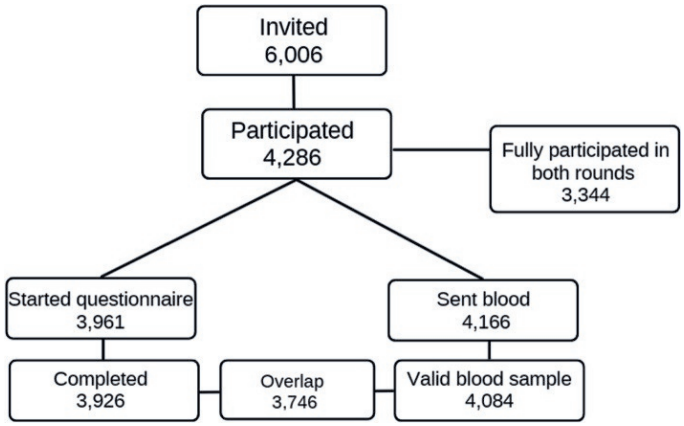

Figure 2. Flow diagram: Participation in round 2 between September and November 2021 of 'Impact of COVID-19 on the Meuse-Rhine Euroregion'.

Main requests/issues reported

During the period of data collection 1,306 questions through email and phone calls from invitees were received. 22% of the questions were related to the online environment: unable to find the webpage or consult the blood test results. 11% of the questions were related to problems with the self-finger prick test. Participants were offered a new collection kit when the self-finger prick blood collection had failed. Invitees also reached the call center or email with questions about resetting the pin code or forgetting the ID-number (9%), reporting of missing material or documents to fulfill participation (6%).

Characteristics of participants

The participation rate in round 1 was highest in the age group 50–69 years and lowest from > 80 in all sub regions of the EMR. In terms of gender, women participated more often than men. 20% from all invited women completed all

components of participation in the first round, compared to 15% of men. In round 2, these same determinants were found to be associated with participation. Table 2 presents participation in both rounds of the study, for age group.

Table 2. Age groups of participants from the study 'Impact of COVID-19 on the Meuse-Rhine Euroregion'

	First round		Follow-up: second round	
	Invited	Participants who responded in round 1	Participants who responded in round 2	Participants who completed both rounds
	n = 27,245	*n* = 6006	*n* = 4286	*n* = 3344
Age groups, n (%)				
18–29	4669 (17.1)	1046 (22.4)	390 (37.4)	282 (74.2)
30–39	3809 (14.0)	685 (18)	443 (64.7)	330 (74.5)
40–49	3699 (13.6)	806 (22)	663 (82.3)	472 (71.2)
50–59	4864 (17.9)	1255 (25.8)	933 (74.3)	797 (85.4)
60–69	4711 (17.3)	1311 (27.8)	1018 (77.7)	909 (89.3)
70–79	3402 (12.5)	705 (20.7)	669 (94.9)	462 (69.1)
80 +	2091 (7.7)	198 (9.5)	170 (85.9)	92 (54.1)

To correct for the discrepancies in the composition of the final sample in terms of age group and gender, weights will be added in the future analysis of study results.

Effect timing fieldwork round 1

Data collection occurred in different – though overlapping – periods in the different regions in the EMR due to logistic reasons. In what follows we illustrate the effect of timing differences on the collection of survey data and timing of analysis performed on the blood samples, by week. Figure 3 presents the timeline in which data collection took place.

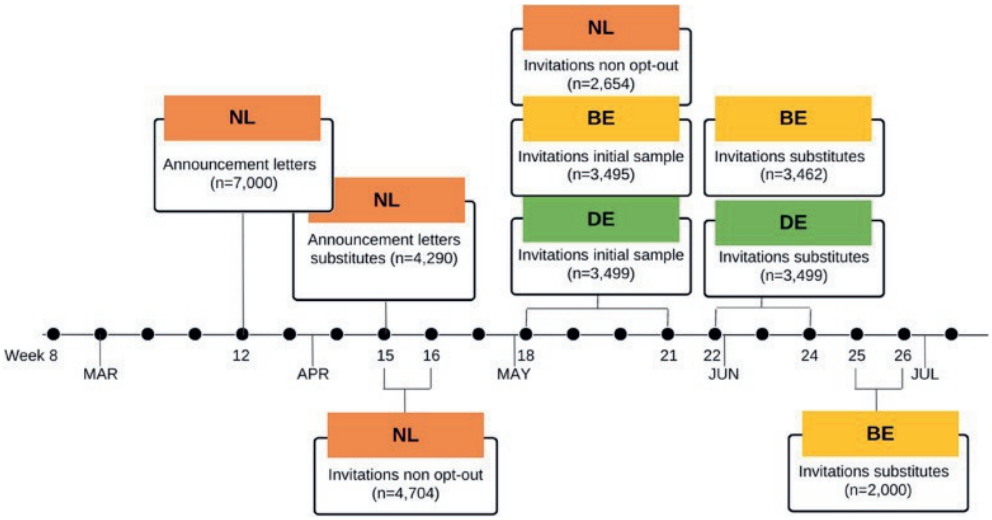

Figure 3. Timing fieldwork per country in round 1 of 'Impact of COVID-19 on the Meuse-Rhine Euroregion'.

Invitations with accompanying materials were sent starting from week 15 on the Dutch side of the EMR. Belgium and Germany started on week 18. By week 21 all invitations were sent out in the Netherlands, whereas in Belgium this was week 26.

Figure 4 visualizes the cumulative percentage of completion of the questionnaire in round 1. On June 6, 2021 (week 22), 95% of the Dutch participants had completed the questionnaire. On the same day 50% of the German and 42% of the Belgian participants had completed the questionnaire.

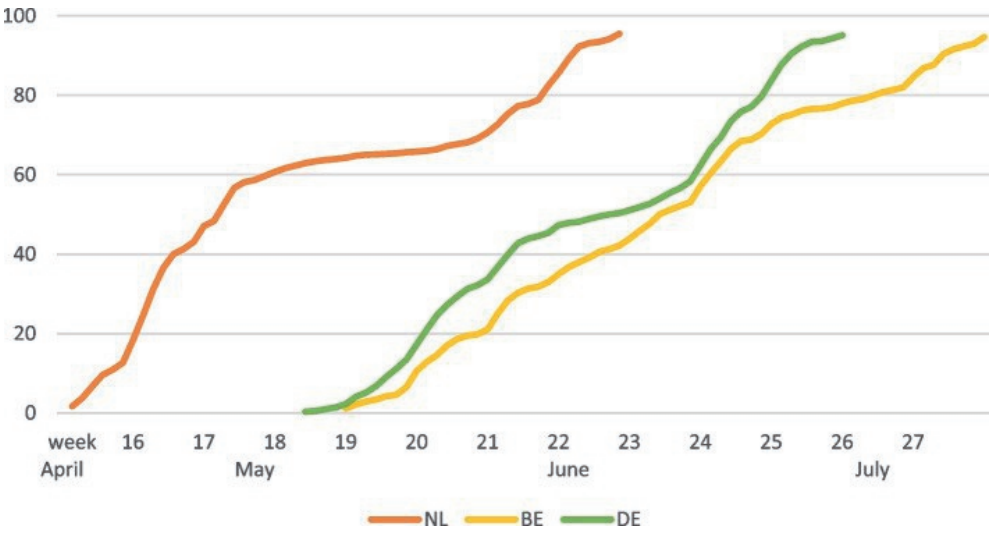

Figure 4. Cumulative percentage of questionnaire completion per country in round 1 (95%) of 'Impact of COVID-19 on the Meuse-Rhine Euroregion'.

DISCUSSION

Main results

In the first round, 6.006 citizens in the EMR participated. 15.3% of the invited citizens in Belgium participated. In the Netherlands and Germany this was respectively 27% and 26.7%. In the follow-up round 71.4% participated again. The participation rate was highest in the age group 50–69 years and lowest from > 80 in all sub regions of the EMR. In terms of gender, women participated more than men. Three thousand three hundred forty-four citizens in the EMR participated fully in both rounds.

Strengths

To conduct this cross-border study, an interregional partnership was formed with actors on all three sides of the border. The study took place in exceptional circumstances due to the COVID-19 pandemic. All the developments, negotiations, consultations and decisions had to be made online. The centralized online environment facilitated cross-border collaboration on equal footing where transparency and real-time monitoring of participation rates was possible for all actors involved, while respecting GDPR regulations.

Several initiatives were installed to minimize expected hurdles to participate. The borderless concept of the Meuse-Rhine Euroregion was taken into consideration by enabling participants contact the call center or project consortium through phone or email - or fill in the online questionnaire in one of the three official languages of the Euroregion. Furthermore, invitees had access to the online environment where the online questionnaires could be filled in and the antibody results and other resources such as 'Frequently Asked Questions' could be consulted. The helpdesk was available during regular office hours for personal assistance with participation if needed.

The initial scheme foresaw a consecutive substitution in case of non-participation. Given the low participation rates, this scheme was altered. As it was presumed that the matching criteria, age group and gender, were associated with the outcomes of the study, applying substitution was expected to lower possible bias compared to other techniques to cope with non-participation (e.g. simple sample inflation).

One might assume that providing personal information via a questionnaire is less invasive than providing a blood sample using a self-finger prick test at home. In both rounds, we received however more blood samples than questionnaires. This suggests that the self-finger prick method in combination with the incentive of receiving the antibody results afterwards is a cost-effective way to collect serological data on a large scale.

Limitations

Participation rates were relatively low, especially in the Belgian sub regions. The project in Belgium was hosted by Sciensano, the Belgian Institute for Health. The overall coordination was however done by the Public Health Service South Limburg (NL), which was also responsible for the organization of the call center while the Maastricht University Medical Centre (NL) was responsible for the blood analysis. For practical reasons, blood samples of participants in Belgium had to be sent to the Ministry of the German-speaking Community. Although the role of this Ministry was merely to serve as a collection point for the transfer of the sample to the Maastricht University Medical Centre (NL), it might have suggested that the Ministry as such was inclined in the project, something that might have hindered participation.

Low participation in this study can be assigned to difficulties concerning the hurdle of conducting a self-finger prick test and/or filling in the online questionnaire. Alternatives to detect SARS-CoV-2 antibodies could be offered, such as adding the option to conduct a serological test taken by health care providers. People not having access to internet or not having the needed skills to complete the questionnaire were met with the option to call or email the project consortium or the call center. A written questionnaire could be added to the invitation, for example in the reminder when the invitee has not participated yet. The mentioned alternatives however come with an extra cost and usage of resources.

While the shared methodology and research protocol was implemented as much as possible in all participating countries, aligning the project's objectives with national legislations and obtaining ethical approvals proved to be challenging and distorted simultaneous data collection in the first round. Hence, analysis of time-sensitive indicators could be done by using a sub sample for which data is available in every participating region.

Implications in public health

Most research projects enquire about geographical contexts that consist within the national border. Cross-border data collection in a border region however expands the geographical context by taking into consideration the movement of people across borders as a potential determinant on health-related outcomes. The shared methodology and research protocol facilitated the collection of comparative data in a highly interconnected transborder area. Furthermore, comparative cross-border data can contribute to informed decision-making processes when dealing with borderless health threats such as pandemics, and thus help minimize the negative health effects for its citizens.

Recommendations

1. Map out potential (local) challenges in the preparation phase of the data collection period to better schedule the timing of fieldwork procedures and data collection in all participating countries.
2. Develop a centralized online environment accessible to all involved actors to facilitate decision making and monitor participation rates during the data collection period.

3. Provide uniform communication towards invited citizens – available in all official languages –to acknowledge the interconnectedness across the border and to strengthen the concept of a cross-border research project.
4. Install systems for offering adequate support to anticipate potential hurdles for participation (e.g. helpdesk, call center, project website).
5. Establish interregional partnerships to help manage infectious disease control in transborder areas.

Conclusions

In the border area between Germany, Belgium and the Netherlands a cross-border study was conducted to assess the impact of the SARS-CoV-2 pandemic. This paper presented the methods and participation and formulated recommendations for longitudinal cross-border research.

An interregional partnership was formed to conduct the study on all sides of the borders. The centralized online environment led to cross-border collaboration on equal footing where transparency and real-time monitoring of participation rates was possible for all actors involved, while respecting GDPR regulations. The tool facilitated informed decision-making processes such as correcting for lower participation by inviting reserve invitees. The self-finger prick method in combination with the incentive of receiving the antibody result can be a cost-effective way to collect serological data on a larger scale.

However, the study also faced limitations, such as low participation rates in certain sub-regions and difficulties in obtaining ethical approvals and aligning the project's objectives with national legislation. Mitigating potential hurdles for participation and mapping out potential challenges in the preparation phase of the data collection period can help improve participation rates and ensure better coordination of the processes involved.

Overall, this study highlights the potential of sustainable cross-border collaborative practices in dealing with borderless issues such as pandemics. By disseminating further analysis in the future, the project outcomes will be able to inform important stakeholders in tackling borderless issues. Moving forward, it is important to continue to strengthen cross-border collaboration and implement best practices for data collection and coordination to better respond to future pandemics and other health crises.

ACKNOWLEDGEMENTS

The project consortium thanks the participants in this study and associate partners Public Health Service Düren (DE), Public Health Service City Region Aachen (DE), Public Health Service Heinsberg (DE) and German-speaking Community of Belgium (BE).

FUNDING

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SUPPLEMENTARY MATERIALS

Supplementary table 1: Items of the online questionnaires in 'Impact of COVID-19 on the Meuse-Rhine Euroregion'

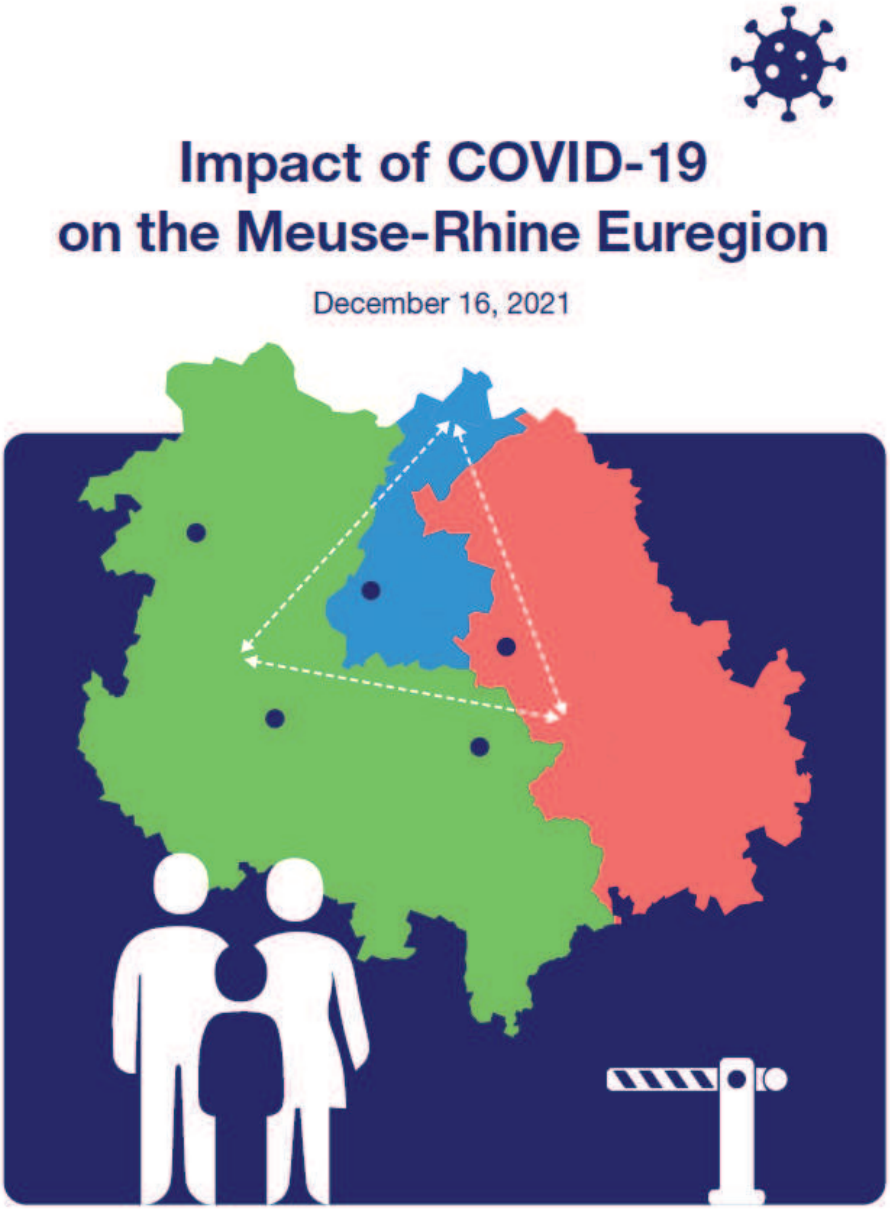
Topic	Questions	First round	Follow-up
Adherence to infection prevention measures during last 2 months	Social distancing (1.5m)	x	
	Washing hands with water and soap	x	
	Sneeze and cough in elbow	x	
	Wear a mask	x	
	Limit group size	x	
	Minimalize travel	x	
	Work from home	x	
Usefulness infection prevention measures against spread of COVID-19	Social distancing (1.5m)	x	x
	Washing hands with water and soap	x	x
	Sneeze and cough in elbow	x	x
	Wear a mask	x	x
	Limit group size	x	x
	Minimalize travel	x	x
	Work from home	x	x
	QR code		x
	Stay home and test in case of symptoms		x
Difficulty infection prevention measures	Social distancing (1.5m)	x	
	Washing hands with water and soap	x	
	Sneeze and cough in elbow	x	
	Wear a mask	x	
	Limit group size	x	
	Minimalize travel	x	
	Work from home	x	
Importance to maintain measures	Social distancing (1.5m)		x

	Washing hands with water and soap		x
	Sneeze and cough in elbow		x
	Wear a mask		
	Limit group size		x
	Minimalize travel		x
	Work from home		x
	QR code		x
	Stay home and test in case of symptoms		x
On what level should measures be decided?			x
Opinion on communication of measures			x
Mobility	Mobility experienced as limited during pandemic:		
	Between Netherlands and Belgium	x	
	Between Belgium and Germany	x	
	Between Germany and Netherlands	x	
	Did you experience the closing of borders as negative?		x
	Did you receive the healthcare you needed during the pandemic?		x
Social network	Number of housemates	x	x
	Age of housemates	x	x
	Membership association	x	x
	Personal contact with family members:		
	before covid	x	
	since covid	x	
	last month	x	x
	Personal contact with friends:		
	before covid	x	
	since covid	x	
	last month	x	x
	Personal contact with colleagues:		
	before covid	x	
	since covid	x	

	last month	x	x
	Family, friends, or acquaintances in neighbouring country	x	x
	Visiting family in neighbouring country:		
	before covid	x	
	since covid	x	
	last month	x	x
	Crossing the border for a short visit:		
	before covid	x	
	since covid	x	
	last month	x	x
	Loneliness [13]	x	x
	Multidimensional Scale of Perceived Social Support [14]	x	x
Travelling	Travelled/holiday during summer 2021?		x
	Reason to not travel during summer 2021		x
COVID-19 infection and symptoms	Do you think you have had COVID-19?	x	x
	Tested positive on COVID-19?	x	x
	How often tested positive? (including antibody test)	x	x
	Date positive test(s)	x	x
	Hospitalization because of COVID-19 infection	x	x
	Severity COVID-19 infection	x	x
	Symptoms at least 3 days	x	x
	Symptoms after 3 months	x	x
	Professional or informal help because of symptoms	x	x
	Effect on daily functioning	x	x
	Effect on work	x	x
Vaccination	Vaccination status	x	x
	Vaccination date	x	x

	Vaccine brand	x	x
	Intention to vaccinate	x	x
	Reasons to vaccinate	x	x
	Reasons for doubt	x	x
	Reasons to not vaccinate	x	x
	Booster willingness		x
General health	General health	x	x
	Happiness now	x	x
	Happiness pre-covid	x	x
	Height and weight	x	x
	Comorbidities	x	x
	Medication that suppresses immune system		x
	Flu vaccine in 2020	x	
	Other vaccines in adult life	x	
Socio-demographics	Age	x	x
	Gender	x	x
	Country of residence	x	x
	Level of education	x	x
	Work status	x	x
	Work sector		x
	Work abroad	x	x
	Study abroad	x	x
Did you expect the result of the first antibody test?			x

FACTSHEET: Impact of COVID-19 on the Meuse-Rhine Euregion



Background

This fact sheet describes the results of the project 'The impact of COVID-19 on the Meuse-Rhine Euregion (EMR)'. The EMR is the cross-border region between the Netherlands, Belgium and Germany. The aim of the project was to assess the impact of COVID-19 on this area.
The outcomes of this project could serve as an example of effects of COVID-19 for other border regions in the European Union, or even more broadly.

Citizens of the EMR were selected for the survey by means of drawing a sample from the Dutch region of South Limburg, the German regions of Heinsberg, Düren and Aachen, and the Belgian regions of Limburg, Liège and the German-speaking community. The study consisted of two rounds in which participants were asked to complete an online questionnaire and to draw blood by finger prick, from which antibodies against COVID-19 were measured. A total of 30,000 test kits were sent out. In the first round of this study, 4,766 people from the Netherlands, Germany and Belgium participated. Of these, 3,339 people (70%) also participated in the second round.

The partner organisations involved are GGD Zuid Limburg, euPrevent Foundation, Maastricht UMC+, Gesundheitsamt des Kreises Düren (Health Department of Düren District), Gesundheitsamt des Kreises Heinsberg (Health Department of Heinsberg District), Gesundheitsamt der Städte-Region Aachen (Health Department of the Aachen Municipality), Sciensano and the German-speaking Community of Belgium. The project was subsidised by the Interreg V-A EMR programme.

Study



Study population

Blood tests and completed questionnaires

Round 1: April-June 2021

- 6,018 people responded
- 4,766 complete participations (completed questionnaire + successful blood collection)

Round 2: September - October 2021

- 3,708 people responded
- 3,339 full participations in rounds 1 and 2 (completed questionnaire + successful blood collection)

Number of participants per country

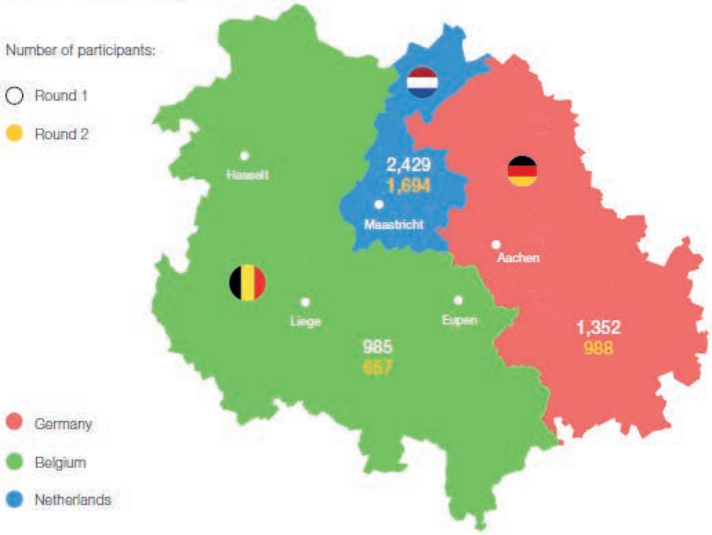
Round 1:

- Netherlands: 2,429 participants
- Germany: 1,352 participants
- Belgium: 985 participants

Round 2:

- Netherlands: 1,694 participants
- Germany: 988 participants
- Belgium: 657 participants.

The different numbers of participants were corrected with a weighting factor in order to obtain results that are as representative as possible of the population of the three EMR countries in terms of gender and age.



Study population

Gender

In round 1, 2,742 women (58%) and 2,022 men (42%) participated. Of the participants in round 1, 1,963 women (59%) and 1,374 men (41%) also participated in round 2.



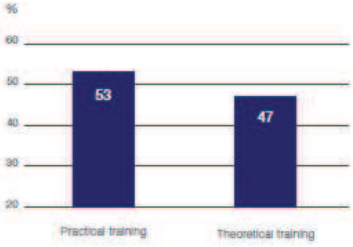
Age

The average age of the participants in the first round was 52 years and in the second round 55 years.



Education

Of the participants in both rounds, 53% had received a practical education (e.g., Mavo, MBO) and 47% had received a theoretical education (e.g., HBO, college or university).





COVID-19 measures

Investigated measures

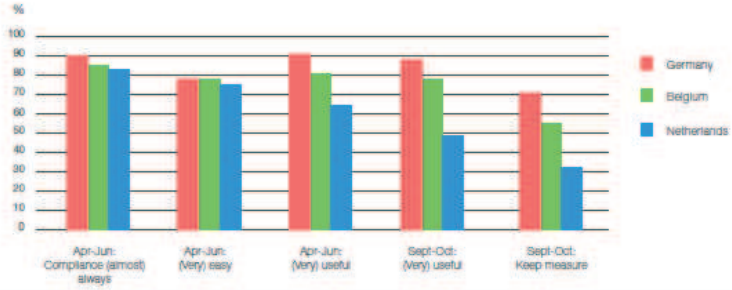
- Wearing a face mask
- Maintaining social distance (1.5 metres)
- Limiting group size
- Reducing travel
- Requiring a QR code (entry pass) for certain activities (only in round 2)
- Staying at home and testing in case of symptoms (only in round 2)



In April-June 2021, the citizens were asked to what extent they complied with the measures during the two months prior to the study and whether they found compliance with the measures easy. In both April-June and September-October 2021, the participants were asked whether they found the measures useful. In addition, in September-October 2021, they were asked to what extent they thought it was important to maintain the measures. The results are discussed for each measure.

Wearing a face mask

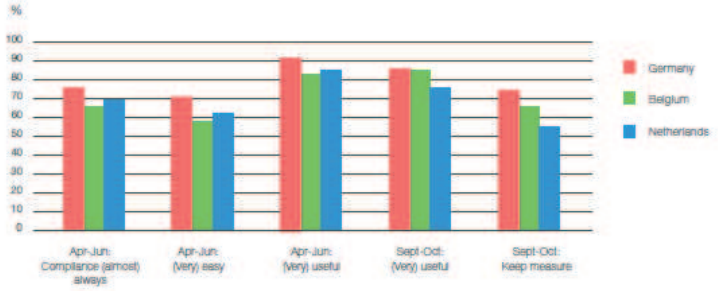
More than 80% of citizens indicated in April-June that they (almost) always comply with wearing a face mask, and the vast majority also found it easy and useful. The percentage of citizens in the Netherlands who find wearing a face mask useful decreased from 65% in April-June to 49% in September-October. Although the results of the EMR countries were largely similar in the first round, we could see a difference in how important citizens in the EMR countries think it is to keep this measure. For example, the Netherlands was least supportive (32%) of keeping the face mask and Germany the most (71%).



COVID-19 measures

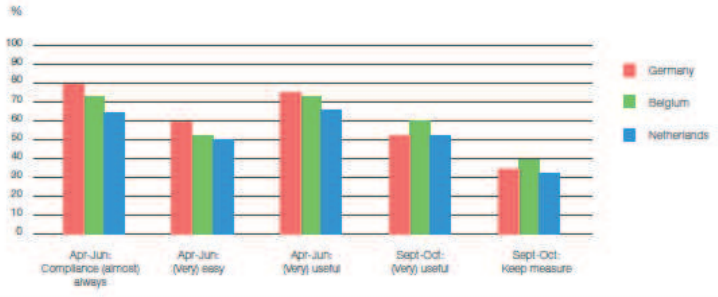
Maintaining social distance (1.5 metres)

In April-June, more than 80% of the citizens found maintaining 1.5 metres distance (very) useful. In September-October, this was still over 75% in all EMR countries. More than half of the citizens indicated that they found it (very) important to maintain this measure. This percentage was higher in Germany and Belgium, compared to the Netherlands.



Limiting group size

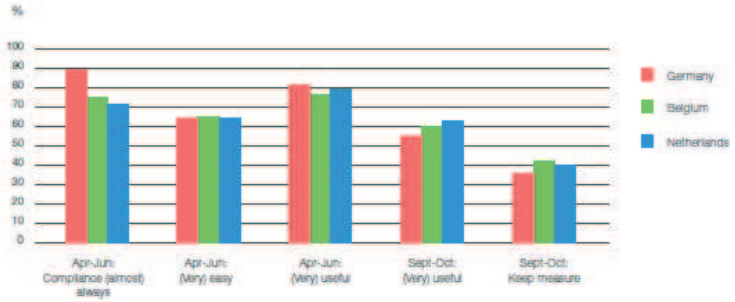
Compared to the other measures, limiting the group size was less frequently perceived as easy. In September-October, citizens were less likely to perceive this measure as (very) useful. Across the EMR, less than 40% of citizens indicated that they felt it was important to keep this measure. Compared to the other measures, maintaining a restriction on group size had the least support in EMR countries.



COVID-19 measures

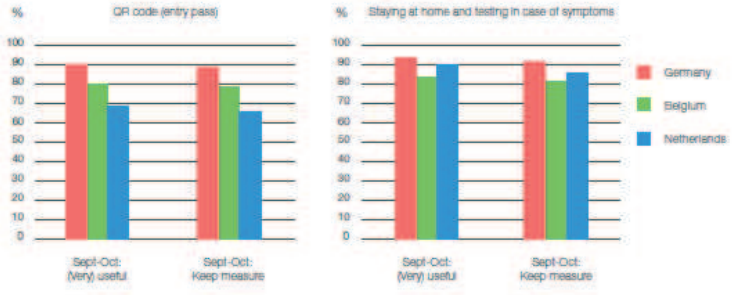
Restricting travel

In April-June, German citizens were most likely to report reduced travel. This measure was considered less useful in all EMR countries in September-October, compared to April-June. Less than 45% of citizens indicated that it was important to keep this measure. Citizens in the EMR countries are the most like-minded regarding the maintenance of travel restrictions.



Requiring a QR code and staying at home and testing in case of symptoms

The majority of citizens indicated that they found both the QR code (entry pass) and staying at home and testing in case of symptoms useful and considered it important to keep these measures. Support for the QR code was highest among German citizens and lowest among Dutch citizens. The citizens in all three EMR countries found the measure staying at home and testing in case of symptoms most important to keep compared to the other measures.



Mobility between EMR countries

Crossing the border for a short visit

The number of times per month that citizens crossed the border into a neighbouring EMR country for a short visit changed during the corona pandemic. Examples of reasons for a short visit are shopping, visiting a restaurant and refuelling.

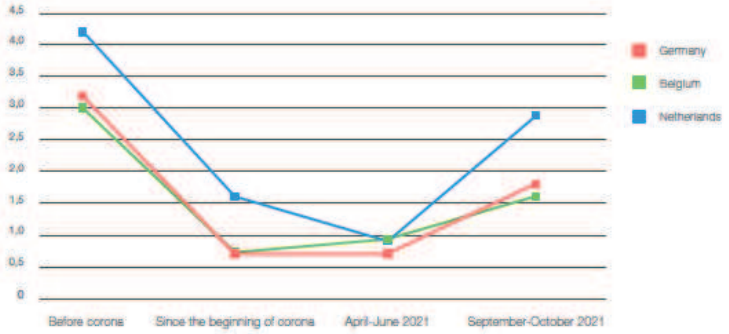


Before corona, this was on average **3.0 (Belgium)** to **4.2 (Netherlands)** times per month. **Since the beginning of corona,** this decreased to an average of **0.69 (Belgium)** to **1.6 (Netherlands)** times per month. Citizens reported crossing the border for a short visit on average **0.72 (Germany)** to **0.97 (Belgium)** times per month in **April-June**.

In **September-October,** this had increased again to an average of **1.6 (Belgium)** to **2.9 (Netherlands)** times per month. The results are in line with the measures in place at the time. Dutch citizens engaged in most cross-border traffic during the periods studied.



Crossing the border for a short visit (average per month)

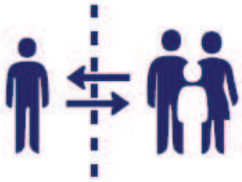


Mobility between EMR countries

Visiting family, friends and acquaintances across the border

The number of times that citizens visited family, friends or acquaintances across the border changed during the corona pandemic.

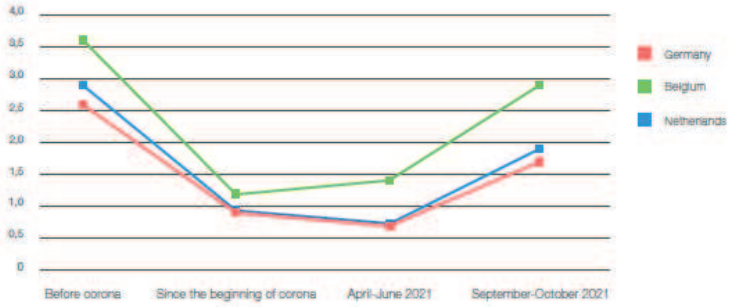




Before corona, this was on average **2.6 (Germany)** to **3.6 (Belgium)** times per month. **Since the start of corona,** this dropped to an average of **0.87 (Germany)** to **1.1 (Belgium)** times per month. Citizens reported in **April-June** that they visited family, friends or acquaintances across the border an average of **0.74 (Germany)** to **1.4 (Belgium)** times and in **September- October** this had increased to an average of **1.8 (Germany)** to **2.9 (Belgium)** times per month.

These results are in line with the measures in place at the time. The number of cross-border visits to family, friends or acquaintances has doubled in all three countries since the summer of 2021, but is still significantly lower than before corona. Belgian citizens visited family, friends or acquaintances the most during the periods studied.

Crossing the border to visit family, friends or acquaintances (average per month)



Mobility between EMR countries

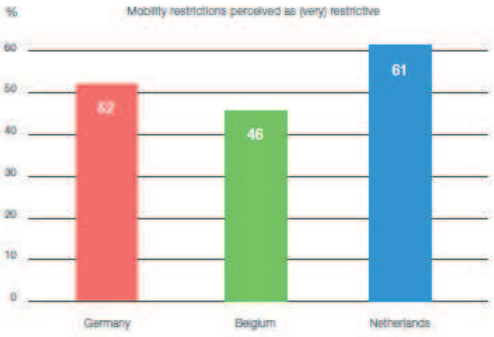
Working and studying abroad

2% of participants reported **working in a country other than their country** of residence. Less than **1%** of participants reported **studying in a country other than their country** of residence.



Mobility Limitations

In **April-June**, about half of the citizens experienced the mobility restrictions between EMR countries during the corona pandemic as (very) restrictive. In the **Netherlands** this was **61%** of citizens, in **Belgium 46%** and in **Germany 52%**.





This percentage was even higher within the group of people with family, friends or acquaintances living in a neighbouring EMR country. Two-thirds of the group of citizens with family, friends or acquaintances living across the border experienced the mobility restrictions between the countries as (very) restrictive.

Vaccination against COVID-19



Reasons for vaccination

The three most frequently cited reasons for vaccination against corona were similar in all three EMR countries: to prevent serious illness due to corona infection, protection of family and to return to the old normal. In all three countries, the reason 'return to the old normal' shifted from first place in April-June to third place in September-October.

Vaccination Rate

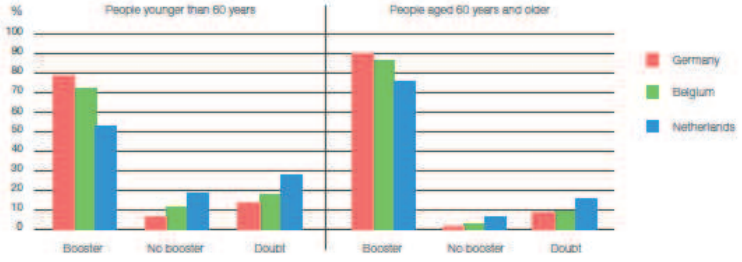
In **September-October**, **87%** of **Dutch** citizens, **96%** of **Belgian** citizens and **94%** of **German** citizens were fully vaccinated against COVID-19. Full vaccination means two vaccinations, one vaccination with the Janssen vaccine, or a combination of having undergone a corona infection and one vaccination. Vaccination rates in this study are slightly higher than those of the general adult population in South Limburg (84%), Belgium (86%), and North Rhine-Westphalia (81%).

Vaccination rate in this study	NL	BE	DE
Fully vaccinated	87%	96%	94%
Partially vaccinated	5%	1%	3%
Not vaccinated	8%	3%	3%

On average, 2% of citizens were still unsure about getting vaccinated and 3% said they did not want to get vaccinated.

Booster

In September-October, the majority of citizens indicated that they would take a booster vaccination against COVID-19 as soon as the opportunity presented itself. This percentage was higher among citizens aged 60 years and older, and among German citizens. In the Netherlands a higher proportion of citizens were hesitant compared to Belgium and Germany.

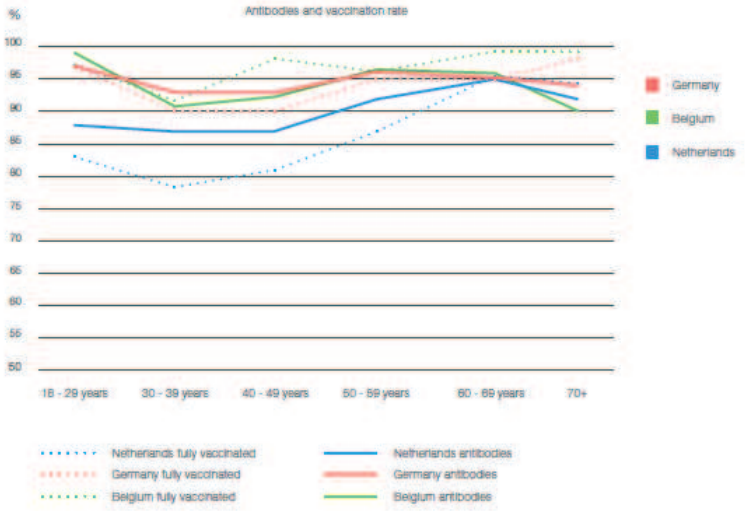


Antibodies against COVID-19

Analysis of blood samples

On average, **93%** of citizens in this study had **antibodies against COVID-19** at the time of blood collection (September-October). In the **Netherlands** this was on average **90%**, in **Belgium 94%,** and in **Germany 95%**. Citizens in the Netherlands were slightly less likely to have antibodies than citizens in Belgium and Germany.

The results refer to the (IgG) antibodies against the spike protein of the SARS-CoV-2 virus at the time of blood collection. The number of citizens with antibodies is generally high in all countries.



Summary

The study consisted of two rounds, in April–June and in September-October 2021. In **both rounds**, participants were asked to complete an online **questionnaire** and take a blood sample by finger prick, from which **antibodies** against COVID-19 were measured.

Measures

- In April–June, the vast majority (~60-80%) of citizens in the Netherlands, Belgium, and Germany indicated that they had (almost) always complied with the applicable **corona measures** and that they found these measures **easy and useful**. These percentages were highest among the German citizens.
- Maintaining **social distance (1.5 meters)** was consistently considered (very) useful by more than three-quarters of citizens. Therefore, more than half of citizens indicated that they found it (very) important to keep this measure.
- In Germany and Belgium, citizens still considered wearing a **face mask** useful, while this proportion dropped markedly in the Netherlands. Therefore, support for maintaining the face mask requirement was lowest among the Dutch citizens.
- **Restrictions on group size** and **travel** were considered less useful by citizens in the three EMR countries, compared to April–June. Support for maintaining these measures was low in all three EMR countries.
- The majority of citizens indicated that they found both the **QR code** (entry pass) and **staying at home and testing** in case of symptoms useful and considered it important to keep these measures. Support for the QR code was highest among German citizens and lowest among Dutch citizens.

Mobility

- A large proportion of the citizens experienced the **mobility restrictions** between countries during the corona pandemic as (very) **restrictive**. Crossing the border into an EMR neighbouring country to visit family, friends or acquaintances or for any other reason decreased during the corona pandemic.
- As measures related to border closure were lifted, the number of visits across the border increased. Though border crossings have doubled in all three countries since the summer of 2021, there were still significantly fewer than before corona.

Vaccination and antibodies in September-October

- On average, **93%** of all citizens were fully **vaccinated** against COVID-19. The most frequently cited reasons for vaccination were similar in all three EMR countries: to prevent illness, protect family and return to normal. The willingness to take a **booster vaccination** was highest among citizens aged 60 years and older.
- Analysis of the blood samples showed that on average 93% of citizens had **antibodies** against COVID-19.

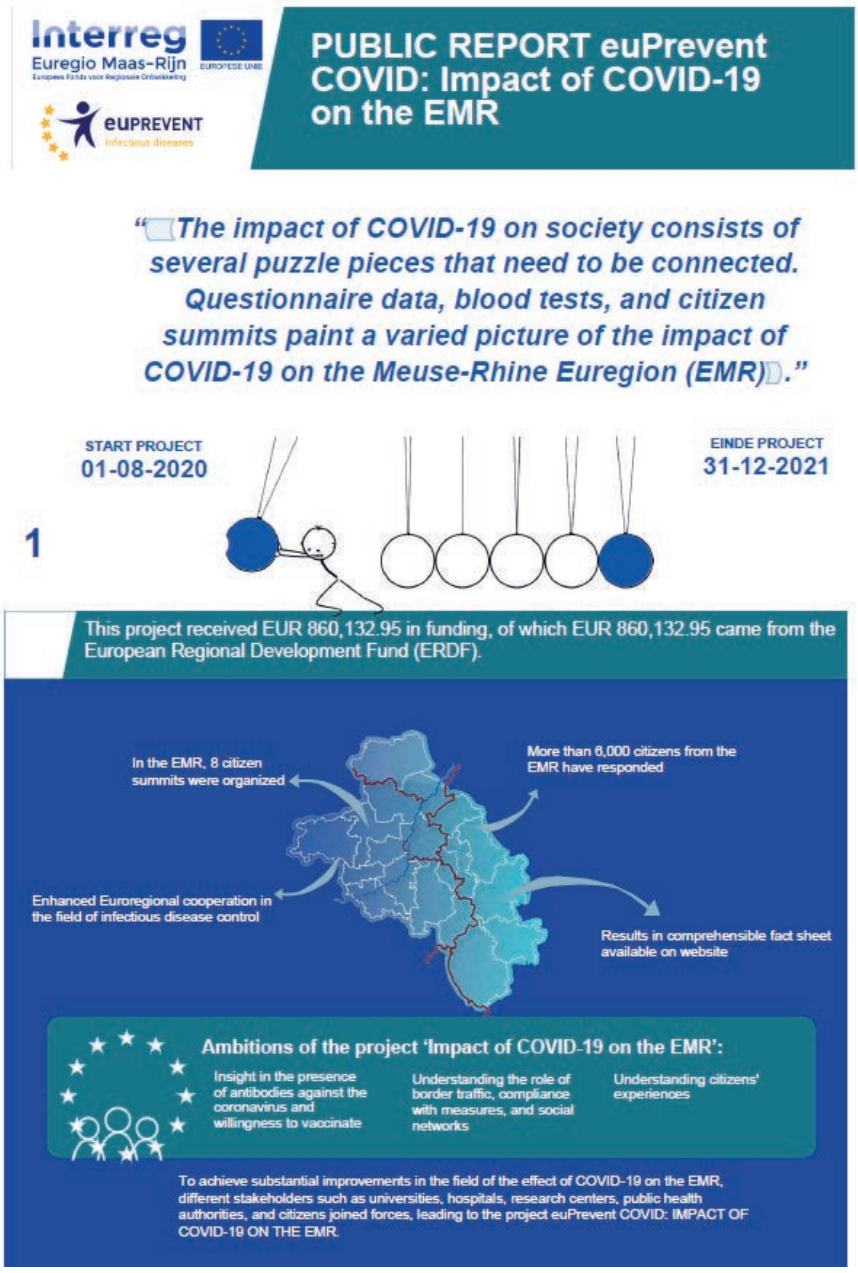
Points of interest from the study

- Because the number of participants varied per round, the study results were corrected with a weighting factor. As a result, the study is representative of the population in the three EMR countries in terms of gender and age.
- Blood collection via finger prick was not successful for all participants. This may have resulted in bias.
- More people were vaccinated in this study, compared to the general population.

Websites

https://euprevent-covid-tool.eu/
https://euprevent.eu/nl/covid-19/
https://www.ggdzl.nl/professionals/projecten-en-onderzoeken/impact-van-covid-19-op-de-euregio-maas-rijn/

PUBLIC REPORT 'Impact of COVID-19 on the EMR'



2 OUR ROUTE TO RESULTS



1 Questionnaire

- Two **online** questionnaires on infection prevention measures, social network, coronavirus infection and symptoms, vaccination readiness, general health, and socio-demographics
- **High willingness** corona vaccination and **booster**
- **Mobility restrictions** between EMR countries during the corona pandemic were perceived as **(very) restrictive**. Since summer 2021, the number of visits across the border has doubled, but is still significantly lower than before corona
- **Measures**: compliance high in April-June 2021. Support for some measures was lower in round 2

2 Antibody tests

-Blood tests taken at home via **finger prick** to measure antibodies against the coronavirus

- Round 1 (Apr-Jun 2021): 4766 full participations (questionnaire and antibody test)
- Round 2 (Sept-Oct 2021): 3339 full participations
- September-October 2021: on average 93% of the citizens have **antibodies** against the coronavirus



3 Citizen Summits



- Talking with citizens about their experiences with COVID-19
- 8 online citizens' summits in Maastricht (2x), Heinsberg, Düren, Aachen, Eupen, Hasselt and Liège
- **More attention** for citizens in **border regions** from national authorities
- Greater awareness of borders due to pandemic
- Improved **communication and cooperation** between countries in the EMR

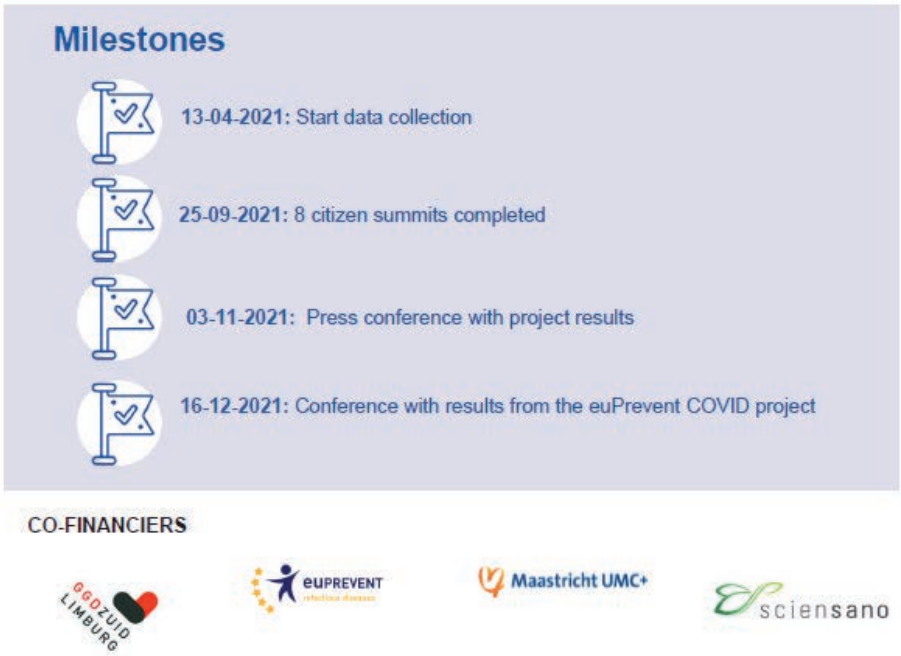
3 RESULTS AND DELIVERABLES

3 main results:

1. **Majority complies with applicable corona measures, has been vaccinated, and has antibodies:**
   The measures were considered easy and useful, especially among German citizens. Support for the face mask declined in the Netherlands. High support for QR code and staying home and testing in case of symptoms. In September-October, 93% of citizens had antibodies against the coronavirus. 93% of citizens had been vaccinated and willingness for booster vaccination was high.
2. **Mobility restrictions between EMR countries were perceived as (very) restrictive:**
   Crossing the border with an EMR neighboring country to visit family, friends, acquaintances, or for any other reason decreased during the corona pandemic. As measures related to border closure eased, the number of visits across the border increased.
3. **Citizens call for improved coordination, strategy and leadership in border region:**
   At the time of a pandemic, attention should be paid to clear communication and Euregional cooperation.

Supporting promotional and informational materials

1. Content fact sheet on questionnaires and antibody tests
2. Results of citizens' summits in fact sheet
3. COVID statistics available on the euregional health atlas: http://euregionalhealthatlas.eu/covid19.html



https://euprevent.eu/covid-19/





Chapter 3

Design and recruitment of a large-scale cohort study on prevalence, risk factors and impact evaluation of post-COVID-19 condition and its wider long-term social, mental, and physical health impact: The PRIME post-COVID study.

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Frontiers in Public Health. 2022; 10: 1032955
doi: 10.3389/fpubh.2022.1032955.

ABSTRACT

Background

Persistent symptoms, described as long COVID or post-COVID-19 condition, pose a potential public health problem. Here, the design and recruitment of the PRIME post-COVID study is described. PRIME post-COVID is a large-scale population-based observational study that aims to improve understanding of the occurrence, risk factors, social, physical, mental, emotional, and socioeconomic impact of post-COVID-19 condition.

Methods

An observational open cohort study was set up, with retrospective and prospective assessments on various health-conditions and health-factors (medical, demographic, social, and behavioral) based on a public health COVID-19 test and by self-report (using online questionnaires in Dutch language). Invited for participation were, as recorded in a public health registry, adults (18 years and older) who were tested for COVID-19 and had a valid Polymerase Chain Reaction (PCR) positive or negative test result, and email address. In November 2021, 61,655 individuals were invited by email to participate, these included all eligible adults who tested PCR positive between 1 June 2020 and 1 November 2021, and a sample of adults who tested negative (2:1), comparable in distribution of age, sex, municipality of residence and year-quarter of testing. New recruitment periods are planned as well. Participants are followed over time by regular follow-up measurements. Data are analyzed using the appropriate data-analyses methods.

Discussion

The PRIME post-COVID study will provide insights into various health-related aspects of post-COVID-19 condition in the context of various stages of the COVID-19 pandemic. Results will inform practical guidance for society, clinical and public health practice for the prevention and care for long-term impact of COVID-19.

INTRODUCTION

Since 2020, the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), causing coronavirus disease 2019 (COVID-19), has been disruptive to societies, globally. By August 2022, over 596 million confirmed cases were counted, accompanied by ~6 million deaths worldwide (1). An acute infection can be diagnosed using Polymerase Chain Reaction (PCR) testing and often presents with symptoms such as fever, cough, tiredness, and loss of taste or smell (2). The majority of the infections progress with mild symptoms and only few (up to a maximum of 20% in elderly) infected individuals require hospitalization (3, 4). Overall, men, people with more comorbidities, older age, and higher body mass index more frequently suffer a severe course of infection, resulting in a higher risk of hospitalization and dying as a consequence of COVID-19 (5, 6).

After great efforts to cope with new waves of SARS-CoV-2 infections globally, the Omicron wave had initially pointed to some hope of ending the pandemic (7), although situations may change quickly. Of an emerging concern are persistent symptoms after a SARS-CoV-2 infection (8–10). These persistent symptoms after COVID-19 are referred to as the patient-initiated term "long COVID" (11), "a condition whereby affected individuals do not recover for several weeks or months following the onset of symptoms suggestive of COVID-19" (12). As a global and standardized clinical case definition is lacking and various terminology is used to describe the same condition (13), the World Health Organization (WHO) released the term "post-COVID-19 condition" and a corresponding case definition. The WHO defined "post-COVID-19 condition" in October 2021 as "a condition that occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms, that last for at least 2 months, and cannot be explained by an alternative diagnosis" (14). Due to the high numbers of SARS-CoV-2 infections worldwide, post-COVID-19 condition poses a potential public health problem with a substantial impact on the socio-economic, emotional, and physical functioning of many individuals.

Currently, the impact of health problems after a SARS-CoV-2 infection are not fully understood, also the prevalence and incidence of post-COVID-19 condition are still unclear. Reasons for this unclarity include difficulties encountered in studying post-COVID-19 condition. In previous scientific studies, this translated

into the inclusion of participants without a formal diagnosis of an acute infection, due to the lack of PCR test capacity in the first wave (15), and long-term symptoms after an acute infection (13), due to the lack of a globally accepted case definition at that time before the release of the recent WHO definition. Furthermore, study participants were followed at different time points since infection, participants represented a selected population instead of a population-based population, being included from hospital-based settings (16), medical records (17), peer support groups (9), or social media platforms (18). Furthermore, in many studies, a control or reference group of negatives was lacking (19). Including specific study populations may lead to selection bias and alongside with the lack of harmonization of measures, these limitations hamper the comparison between studies, for instance regarding prevalence, incidence, and impact on health or socioeconomics (20). Furthermore, established risk factors for post-COVID-19 condition are, for example, female sex and pre-existing co-morbidities (21–23), but there are still knowledge gaps on risk factor coherence and possible protecting factors (for example vaccination) for post-COVID-19 condition.

The current study, called Prevalence, Risk factors and Impact Evaluation of post-COVID-19 condition (PRIME post-COVID) study, was set up to gain more insight into the occurrence and impact of post-COVID-19 condition in the community, by including a large-scale population-based PCR positive sample, a negative control group, and follow-up measures for prospective assessment. The findings of this study will contribute to the development of holistic social and health care pathways and support systems. Here, the design and recruitment are described.

METHODS AND ANALYSIS

The aim of our study is to understand the prevalence, incidence, risk factors and impact of post-COVID-19 condition.

The following study questions will be addressed:

1. What is the prevalence and incidence of post-COVID-19 condition in PCR confirmed SARS-CoV-2 positive adults, by various definitions, accounting for occurrence of symptoms in negative tested adults?
2. What are sociodemographic and medical risk factors (for example vaccination status and virus variant) for having, preserving, and recovering from post-COVID-19 condition?

3. What is the impact of having post-COVID-19 condition on negative health outcomes and socioeconomic aspects, including social, labor, and educational participation?
4. What is the role of having post-COVID-19 condition in maintaining positive health, including social, mental, emotional, and physical health?
5. How can health be promoted in relation to post-COVID-19 condition, using tools from medical and other types of care, in recovery and coping with post-COVID-19 condition?

Design and setting

An observational cohort study in positive and negative COVID-19 PCR-tested adults, including a retrospective and prospective element, was conducted to reach the study aims (Figure 1). The design is an open cohort study, meaning that new participants will be included over time. The first inclusion was in November/December 2021.

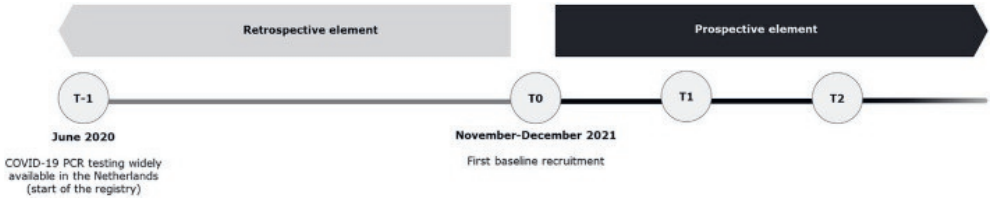

Figure 1. Overview of the prospective and retrospective elements of the PRIME post-COVID study design.

The study region has ~500,000 adult inhabitants (24) in a mixed urban area. Until now, the South Limburg region presents a comparable number of COVID-19 cases per 100,000 inhabitants compared to the Dutch average (46,115 vs. 45,735, respectively), but the highest national mortality rate of 209 deaths per 100,000 inhabitants, compared to 128 deaths per 100,000 inhabitants nationally (not age-standardized) (25).

The Public Health Service (GGD) South Limburg is the main responsible organizer for regional COVID-19 testing in the study region. Testing was free of charge for all inhabitants in the region from 1 June 2020 onward. Tested persons are standardly registered in the Dutch COVID-19 database CoronIT. The study population was approached to participate from this registry.

The Strengthening the Reporting of Observational studies (STROBE) checklist was used in reporting this study (Supplementary Table 1).

Study population

The target population consisted of adults tested for COVID-19 at the GGD South Limburg with a valid PCR test result (positive/negative). We here describe the recruitment of people tested between 1 June 2020 and 1 November 2021. The GGD South Limburg tested 472,982 adults in this period. Eligible for participation were tested adults (18+ years) with a registered email address available. Of eligible adults, all people with a positive COVID-19 PCR test, and a sample of people with a negative COVID-19 PCR test were selected. All positives who met the inclusion criteria were invited to obtain a representative sample of all positives in the test registry. A reasonable sample of ~20,000 negatives were additionally included (ratio 2:1). Regarding the positives, when a person had tested positive multiple times, the record of the first positive COVID-19 test was used in the analyses, as we intended to include data on the first exposure. Regarding the negatives, a sample of people with a negative PCR test were randomly selected in each strata with a distribution that matched (1:2) positives; strata included combinations of age (18–20, 20–30, 30–40, 40–50, 50–60, 60–70, 70–80, and 80+ years), sex (man, woman), year-quarter of 2020 and 2021 in which PCR test was performed, and municipality of residence (n = 16) (Table 1). When tested negative multiple times, the information regarding the last negative COVID-19 test was used to have the greatest assurance that an invited control was not infected up to the point of inclusion. This procedure allowed to include a group of negatives, similar to the positives regarding sociodemographic and timing of testing.

Table 1. Descriptives of invitees of the Prevalence, Risk factors and Impact Evaluation of post-COVID-19 condition (PRIME post-COVID) study

	Invitees n=61,655	
Test result, n (%)	Negative	Positive
	19,875 (32.2)	41,780 (67.8)
Sex, n(%)		
Men	9,917 (49.9)	18,794 (45.0)
Women	9,958 (50.1)	22,986 (55.0)
Age, n(%)		
18-20 years	1,211 (6.1)	3,519 (8.4)
20-30 years	3,719 (18.7)	9,367 (22.4)
30-40 years	3,202 (16.1)	6,823 (16.3)
40-50 years	2,991 (15.1)	6,560 (15.7)
50-60 years	3,678 (18.5)	7,816 (18.7)
60-70 years	3,098 (15.6)	4,697 (11.2)
70-80 years	1,525 (7.7)	2,252 (5.4)
80+ years	451 (2.3)	746 (1.8)
Year-quarter of test, n(%)		
2nd 2020*	361 (1.8)	49 (0.1)
3rd 2020	2,267 (11.4)	716 (1.7)
4th 2020	5,718 (28.8)	12,060 (28.9)
1st 2021	4,255 (21.4)	9,341 (22.4)
2nd 2021	3,635 (18.3)	9,561 (22.9)
3rd 2021	2,483 (12.5)	6,106 (14.6)
4th 2021**	1,156 (5.8)	3,947 (9.4)

* from June 2020
** until November 2021

Recruitment

Emails to invitees were sent between 17 and 25 November 2021. Invited for participation were 41,780 PCR COVID-19 positives and 19,875 negatives from test records registered in the registry. Invitees received an email containing the invitation for participation, study information with a link to the website (containing the participant information and email address in case of questions), and a weblink to the online questionnaire.

Participants needed to be able to understand, read and write the Dutch language, as all materials were provided in Dutch.

Digital informed consent was asked before the questionnaire started. Further digital informed consent was asked to link data from the questionnaire to the registry data (age, sex, municipality, date of test, and test result).

A reminder was sent 1 and 3 weeks after the invitation to invitees who did not respond to the invitation or started but did not complete the questionnaire. The

questionnaire was made available using the MWM2 application of market research platform Crowdtech (ISO 27001 certified).

Inclusion

Participation started after informed consent was obtained online. Filling out the baseline questionnaire took ~30–45 min. To motivate completion of the questionnaire, participants could stop interim and complete the questionnaire at a later time.

Data collection

Data are collected by online self-administered questionnaires. The baseline questionnaire could be filled in between 17 November 2021 until 9 January 2022. The questionnaire contained a range of factors, including health-factors and health-conditions (Table 2). At baseline, information on the current situation as well as historical information (such as symptoms between the test and the current date) was collected from the participants. Several in-depth questions were only deemed relevant for positives or negatives, and thus not asked to all participants to minimize unnecessary load.

Table 2. Topics and questions implemented in the questionnaires during different data collection time points of the Prevalence, Risk factors and Impact Evaluation of post-COVID-19 condition (PRIME post-COVID) study

Topic	Questions	Baseline
Demographics	Sex	X
	Year of birth	X
	Postal code	X
	Residential situation	X
	Relationship status	X
	Level of education	X
	Country of birth	X
COVID-19 test data	Test result	X
	Test date	X
	Vaccination status	X
	Vaccination date(s)	X
	Vaccination type(s)	X
	Presence of antibodies	-
Experienced symptoms	Symptoms when tested/previous questionnaire	X
	Symptoms now	X
	Severity of symptoms	X
	Duration of symptoms	X
	Course of symptoms	+
	Subjective assessment of degree of recovery	+
	Subjective assessment of having post-COVID-19 condition	+

Use of professional medical care	Treatment when tested (hospitalization, duration, and oxygen use)	+
	Received care since test/pervious questionnaire	X
	Reason for received care	+
Lifestyle	Smoking and substance	X
	Physical activity (International Physical Activity Questionnaire; IPAQ [22])	X
Experienced physical and mental health	Underlying disease	X
	Origination of underlying disease	X
	Overall general health	X
	Quality of life (EQ-5D-5L [23])	X
	Dyspnea (modified Medical Research Council; mMRC [24])	X
	Fatigue (Checklist Individual Strength – subscale subjective fatigue; CIS [25])	X
	Mental fatigue (self-constructed based on CIS-Fatigue [26])	X
	Coping (Cognitive Emotion Regulation Questionnaire; CERQ [27])	X
	Trauma (PTSD checklist for the DSM-5; PCL-5 [28])	+
	Depression (Patient Health Questionnaire-9; PHQ-9 [29])	X
	Loneliness (De Jong-Gierveld [30])	X
Labor participation	Labor participation (Work Productivity and Activity Impairment; WPAI [31])	X
Social participation	Membership to clubs	X
Structural and functional social network characteristics assessed with name generator method [32]	Type and number of network members (family, friends, acquaintances, neighbors, colleagues, clubmates, caregivers, others)	X
	Social support of each member	X
	Type of relation with each member	X
	Social strain	X
	Age of each member	X
	Gender of each member	X
	Residential distance of each member	X
	Type of contact with each member	X

X question asked to all participants
+ question asked to participants tested positive for COVID-19 only (using referral based on self-reported test result in questionnaire)
- question asked to participants tested negative for COVID-19 only (using referral based on self-reported test result in questionnaire)

Linkage of questionnaire and registry was done by unique email address, by the data manager. For data storage and analyses, each participant has a unique study code under which all data (questionnaires and registration data) are handled.

Prospective element: Follow-up

Follow-up measures are planned roughly each 6 months, with the option of in-between measures to assess emerging topics. All questionnaires include topics on demographics, COVID-19 test data, experienced symptoms, use of care, lifestyle, experienced physical and mental health, and labor and social network and social participation (Table 2). Additions will be made to the follow-up questionnaires, based on new insights in literature and emerging findings of data analyses.

Data analysis

Primary outcomes in analysis

The time frame for collecting the primary outcomes (summarized below) runs from the baseline questionnaire up to at least 2 years thereafter, assessed at regular intervals.

The main primary outcome:

- Post-COVID-19 condition: the symptoms that are defined by the WHO-definition of post-COVID-19 condition, as well as other types of definition. These include a range of symptoms measured at various time points, for example, the presence of at least one symptom 3 months after testing or when filling in the questionnaire, and experiencing of dyspnea (modified Medical Research Council; mMRC) or fatigue (Checklist Individual Strength—subscale subjective fatigue; CIS).

Other primary outcomes include:

- Mental health: negative health outcomes related to mental health such as depression (assessed by PHQ-9 scale) and trauma.
- Social health: negative health outcomes related to social health, such as loneliness (assessed by De Jong-Gierveld scale).
- Physical health: negative health outcomes related to physical health such as non-communicable chronic diseases (assessed upon self-report on a checklist of conditions present), health index/quality of life (assessed by EQ-5D-5L) and physical activity (assessed by IPAQ).

- Positive health: experienced general health (assessed by 5-point scale ECHI).

Certainty assessment

Data on age, sex, and test result provided in the questionnaire was linked back to this data as recorded in the registry from the corresponding email address, for purposes of certainty assignment, i.e., the likelihood that the respondent indeed was the intended invitee (Figure 2). Respondents were assigned a certainty score 0 (most likely the intended invitee) when respondents consented to link questionnaire and registry data on age, sex, and test result, and this data was the same. Score 1 was given when only the test result was discrepant. Participants who did not consent to link questionnaire and registry data were assigned with score 2. Score 3 was assigned to respondents who did not match on sex or age, representing probably another person than the intended invitee.

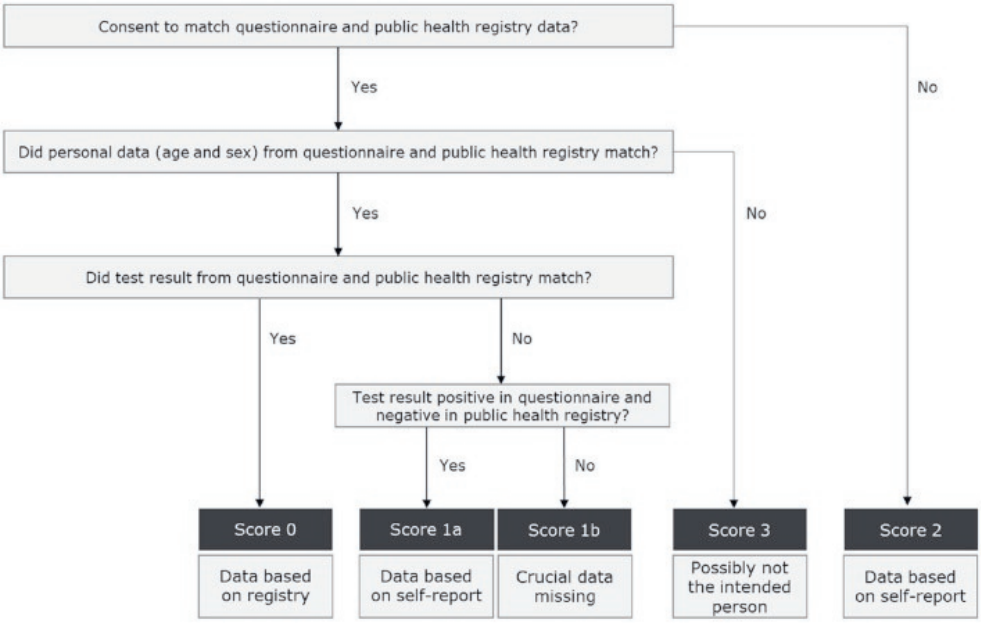

Figure 2. Decision tree to ascertain certainty assessment scores based on self-reported and public health registry data.

Furthermore, it cannot be formally ruled out that the negative PCR-tested participants, who also did not report COVID-19 antibodies pre-vaccination, might include some COVID-19 positive cases. The absence of SARS-CoV-2 antibodies does not guarantee that an infection did not take place since some people (often

mild cases) do not show sero-conversion and also sero-reconversion occurs over time (37–40). We will take reported antibody status in PCR negatives into account when estimating the prevalence of experienced symptoms.

Missing data and data cleaning

The questionnaire started with collection of clinical and demographical data. Participants who did not fill in these topics had insufficient data for any of the planned analyses. The remaining participants were categorized based on extent to which they completed the rest of the questionnaire. All questions were mandatory, therefore no missing data had to be handled and no imputation methods were used.

Statistical analysis

The obtained data will be analyzed using descriptive statistics, such as on prevalence of post-COVID-19 condition including 95% confidence intervals. To assess prevalence, participants tested negative are also presented, providing some insight of "background risk," as symptoms of post-COVID-19 condition may be nonspecific and present in the general population (41, 42). Prevalence of reported symptoms in post-COVID-19 condition participants will be compared to the prevalence in PCR negatives. Post-COVID-19 incidence will be estimated when follow-up data is available, by determining the proportion of newly diagnosed participants (since baseline) meeting the post-COVID-19 condition criteria. Multivariable models are used to test for the likelihood of (long-term) symptoms in positive vs. negative participants, adjusted for possible confounders. Possible confounders include age, sex, underling disease, severity of COVID-19, and year-quarter when tested. Risk factor analyses, with post-COVID-19 condition as outcome, will be performed using multivariable logistic regression models. Various sensitivity analyses will be performed, e.g., by only including participants with highest certainty score 0. These are examples of analyses to answer a main study question. Appropriate statistical analyses will be performed to answer all study questions.

DISCUSSION

The current paper outlined the design and recruitment of an observational population-based open cohort study in positive and negative COVID-19 PCR-tested adults. The cohort includes a retrospective and prospective element, to understand the prevalence, risk factors, and impact of post-COVID-19 condition.

The findings of this study will contribute to the further characterization of post-COVID-19 condition and provide new insights into the occurrence, recovery, and physical, emotional, social, and economic impact of post-COVID-19 condition. Furthermore, it will help increase awareness and recognition of post-COVID-19 condition and contribute to the development of holistic social and health care pathways and support systems.

Strengths and limitations

A major strength of this cohort study is the design comprising of a retrospective and prospective element. In general, including a large population-based sample is a strength, as large sample sizes promote precision and reliability of prevalence estimates and associations between post-COVID-19 condition and risk factors (43). By including a population-based sample we were able to minimize selection bias toward the inclusion of specific groups, such as hospital-based populations. Moreover, including PCR test-negative individuals to determine long-term symptoms and impact of the COVID-19 pandemic in general, made it possible to identify symptoms and impact accountable to a SARS-CoV-2 infection. Matching test-negatives to test-positives on key characteristics (i.e., sex, age, and year-quarter of testing) when sampling limits possible confounding by accounting for the distribution of these characteristics. Finally, a wide range of physical, emotional, social, and behavioral aspects will be mapped using extensive questionnaires, including multiple standardized and validated questions on diverse topics. Doing so enables us to approach post-COVID-19 condition holistically, and to correct future analysis for several confounding factors. By the comprehensive assessment in the current study, post-COVID-19 condition will be classified by several definitions put forward in the literature. These definitions will be compared with each other, and with the established case definition provided by the WHO as well.

The main limitation resides in the use of self-reported online questionnaire data. No additional clinical assessment or investigations on symptoms and physical fitness could be performed. This method of data collection (i.e., using self-administered questionnaires) is always susceptible to information bias. As expected with large-scale population-based studies, a number of the invitees might not respond. Invitees being less digitally skilled are hindered to participate without assistance, which might result in selection (non-response) bias and reduced external validity. The same holds for invitees who were unable to read or understand the Dutch language, as all materials were provided in Dutch. Differential selection bias might occur when the chance of participation is higher in test-positives vs. test-negatives, when positives believe to suffer from long-term symptoms since their infection. Possible over- and under representations of specific subgroups in the eventual study population will be considered when estimating post-COVID-19 condition prevalence, for example by weighing these subgroups according to the distribution in the invited population to enhance representativeness and thereby external validity. Overrepresentations may affect internal validity when non-participation of specified subgroups is related to both exposure and outcome. We will therefore study whether the association between risk factors and post-COVID-19 condition differs (i.e., heterogeneity of the effect) in different subgroups. Lastly, we acknowledge the possible limited generalizability of our results, due to the focus on the southern region of the Netherlands.

Despite these general strengths and limitations of the design, the retrospective and prospective elements both have their own strengths and limitations to be discussed.

Retrospective element

The retrospective aspect of the study design allows us to obtain crucial data on health status and required professional care when tested and the months thereafter, until filling out the questionnaire.

In this respect, the main limitation to be mentioned is the possibility of recall bias, which mainly occurs when participants were tested a long time ago. Recall bias might be differential, for example when positives recall experienced symptoms different compared to negatives. Nevertheless, the risk of misclassification bias in the test result (i.e., the exposure data) and possible confounders (i.e., sex, age,

and year-quarter of testing) was diminished by linking the data from the questionnaire and public health registry data for the majority of the participants.

Prospective element

The major strength of the prospective assessments is the opportunity to study changes in outcomes and determinants before, during, and after (re)infection. Causal hypotheses can be considered, as the order of observations is equal to the natural course of events over time. Besides, overall PCR test data (from June 2020 onwards) can be accessed from the public health registry as well, to gain a reliable estimation of total exposure (i.e., the total number of positive tests/re-infections). Furthermore, the inclusion of new participants tested in later calendar periods (open cohort design) is of great value to study the prevalence of post-COVID-19 condition in the context of new emerging virus variants. In addition, it is predicted that the proportion of test-negative controls declines over time, due to acquired infection. The prospective aspect enables us to include supplemental controls to maintain a sufficient number of test-controls.

Attrition bias is the major limitation of the prospective element to be acknowledged. Selective withdrawal might occur when participants are physically unable to complete follow-up questionnaires, due to severe illness for example. This disproportional attrition threats the internal validity and might lead to underestimation or overestimation of prevalence estimates or associations (43). In general, we will consider the described limitations in the interpretation of our results, and when possible, take them into account in analysis.

To conclude, the PRIME post-COVID longitudinal study design holds several considerable strengths, such as the mapping of a wide variety of physical, emotional, social, and behavioral aspects, and including a population-based sample additionally comprising PCR negatives. Results of our study will contribute to the further characterization of post-COVID-19 condition and thereby inform practical guidance for society, and clinical and public health practice for the prevention and care for long-term impact of COVID-19.

ETHICS AND DISEMMINATION

Ethical considerations

The Medical Ethical Committee of Maastricht University Medical Center+, Maastricht Netherlands waived this study (METC2021-2884), as the Medical Research Involving Human Subjects Act (WMO) did not apply to this study. The study is additionally registered at ClinicalTrials.gov Protocol Registration and Results System (NCT05128695).

Invitee contact details were retrieved from regular infectious disease control test activities from our medical records. Invitees received an email containing the invitation for participation and a link to the online questionnaire. Information about the study was provided, including the link to the study website, containing the participant information. Voluntary digital informed consent was asked before the questionnaire started.

After participation, data were fully de-identified for further analysis. The study protocol was exempt from formal medical-ethical approval under prevailing laws in the Netherlands, as it concerns an observational study using anonymous questionnaire data only (as stated by the National Central Committee for Human Studies: www.ccmo.nl and in the conduct of good behavior in research). As such, no additional administrative permissions were compulsory to use the required data, as it was owned by our own public health service. Additionally, a Data Protection Impact Assessment (DPIA) was conducted as determined in the General Data Protection Regulation (GDPR), to take appropriate precautionary measures to limit privacy risks of data processing.

Dissemination

Key results of the study will be communicated to the participants using a comprehensible report written for a lay audience. The findings of our study will be published in peer-reviewed journals and presented in scientific meetings and conferences as well.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

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FACTSHEET: Results of the PRIME study

1e vragenlijst

- 12.453 deelnemers
- Zowel deelnemers **met longCOVID** als **zonder longCOVID**
- **58%** vrouwen en **42%** mannen
- Gemiddeld **52 jaar** (van **18 tot 95 jaar**)

2e vragenlijst

- **4.036** deelnemers
- Zowel deelnemers **met longCOVID** als **zonder longCOVID**
- **55%** vrouwen en **45%** mannen

Prevalentie & symptomen

- Tenminste **1 op de 6** volwassenen in Zuid-Limburg die corona hebben gehad, had longCOVID eind 2021.
- De volgende **6 symptomen** kwamen het vaakst voor bij deelnemers met longCOVID:









Verergering klachten na inspanning (PEM)

- Lichamelijk of geestelijk moe, pijn of ziek na kleine inspanning.
- Aanzienlijk deel van de deelnemers met longCOVID heeft PEM (post-exertionele malaise):

48% 41%



Intolerantie voor staan (OI)

- Na het staan last van snelle hartslag, wazig zien, licht gevoel in hoofd of flauwvallen.
- Aanzienlijk deel van de deelnemers met longCOVID heeft OI (orthostatische intolerantie):

29% 28%



Aanbeveling:
Screen mensen met longCOVID op PEM en OI om geschikte behandeling te bieden en klachten niet te verergeren.

Ervaren gezondheid

Van de deelnemers **met longCOVID** heeft



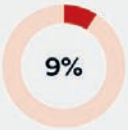
Pijn of ongemak



Angstige of sombere gevoelens



Problemen met lopen



Problemen met zichzelf wassen of aankleden

Invloed op dagelijkse activiteiten

Volwassen deelnemers **met longCOVID** (zonder andere aandoeningen) voelden zich tenminste

2x **zoveel beperkt in het uitvoeren van dagelijkse activiteiten door gezondheidsproblemen,** vergeleken met deelnemers zonder longCOVID.





Section 2

Cross-border mobility, vaccination, and social networks



Chapter 4

Cross-border mobility in the Meuse-Rhine Euroregion: Impact of COVID-19 border restrictions on everyday activities and visiting social network members.

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ABSTRACT

Introduction

Cross-border mobility (CBM) to visit social network members or for everyday activities is an important part of daily life for citizens in border regions, including the Meuse-Rhine Euroregion (EMR: neighboring regions from the Netherlands, Belgium, and Germany). We assessed changes in CBM during the COVID-19 pandemic and how participants experienced border restrictions.

Methods

'Impact of COVID-19 on the EMR' is a longitudinal study using comparative cross-border data collection. In 2021, a random sample of the EMR-population was invited for participation in online surveys to assess current and pre-pandemic CBM. Changes in CBM, experience of border restrictions, and associated factors were analyzed using multinomial and multivariable logistic regression analysis.

Results

Pre-pandemic, 82% of all 3,543 participants reported any CBM: 31% for social contacts and 79% for everyday activities. Among these, 26% decreased social CBM and 35% decreased CBM for everyday activities by autumn 2021. Negative experience of border restrictions was reported by 45% of participants with pre-pandemic CBM, and was higher ($p < 0.05$) in Dutch participants (compared to Belgian; aOR= 1.4), cross-border [work] commuters (aOR= 2.2), participants with cross-border social networks of friends, family or acquaintances (aOR= 1.3), and those finding the measures 'limit group size' (aOR= 1.5) and 'minimalize travel' (aOR= 2.0) difficult to adhere to and finding 'minimalize travel' (aOR= 1.6) useless.

Discussion

CBM for social contacts and everyday activities was substantial in EMR-citizens, but decreased during the pandemic. Border restrictions were valued as negative by a considerable portion of EMR-citizens, especially when having family or friends across the border. When designing future pandemic control strategies, policy makers should account for the negative impact of CBM restrictions on their citizens.

INTRODUCTION

The European Union (EU) comprises 360 internal land border regions, encompassing 40% of the territory and 38% of the EU population (1, 2). Until March 2020, there was complete border permeability among the signatories of the Schengen Agreement (3). The coronavirus disease 2019 (COVID-19) pandemic, which started in 2020, presented an unprecedented situation. The temporary reintroduction of border control resulted in a sudden restriction of free movement in the EU and had far-reaching health, social, and economic consequences (3). This situation also affected the border region Meuse-Rhine Euroregion (EMR), covering the border area of the Netherlands, Belgium, and Germany.

Mobility in the EMR is synonymous with cross-border mobility (CBM) due to the population living in close proximity to a national border. Mobility is crucial for accessing facilities and engaging in social interactions, and thereby various aspects of wellbeing and health. For example, in the EMR, CBM encompasses essential medical activities such as visiting healthcare professionals. Within the EMR there is a high degree of patient mobility and citizens tend to be highly willing to travel to neighboring member states to receive medical treatments (4). Border control measures during the pandemic hindered cross-border healthcare, resulting in challenges in cross-border communication and collaboration among EMR public health professionals (5).

Furthermore, CBM has various transport modes. Those that require physical activity, such as walking and cycling, have been shown to positively impact self-perceived health, mental health including perceived stress, loneliness, social health, and reduced mortality (6, 7). Additionally, car use and use of public transportation have been associated with health outcomes such as increased physical activity, reduced social frailty in elderly, and reduced loneliness in European adults (6, 8, 9). Limited mobility during the COVID-19 pandemic has been linked to reduced happiness, also referred to as subjective wellbeing (10, 11). Finally, mobility is associated with increased social participation (12). Maintaining CBM is thus important in health.

With a population of 4 million, the inhabitants of the EMR have extensive cross-border connections, including social contacts, work, study, leisure, and healthcare

(3, 5, 13–16). Therefore, CBM is an important part of daily life for EMR-citizens and borders are generally perceived as non-existent (17). Citizens cross borders for several reasons which are interconnected, such as cross-border commuting, social visits, and leisure activities (18). This includes everyday activities such as grocery shopping and visiting restaurants, and in-person contact with social network members with visits to family, friends, and acquaintances living across the border (social visits). Social connections play a crucial role in promoting physical and mental well-being, including happiness (19, 20). Social isolation is associated with health risks, chronic illness, and all-cause mortality (21, 22). Social networks can serve as a buffer by providing social support during stressful events, including the COVID-19 pandemic (23). However, social interactions have been shown to be significantly decreased during the pandemic, with fewer in-person contacts and reduced social network interactions (23).

The efficacy of border restrictions in controlling the transmission of SARS-CoV-2 has been debated. The effectiveness of border restrictions depends highly on timing, the stage of the epidemic, interconnectedness of countries, local measures undertaken, extent of implementation, and adherence (24, 25). A study among 10,0001 citizens in the Dutch EMR subregion indicated that CBM was not associated with seroprevalence of SARS-CoV-2, which may suggest a limited role of border traffic in the virus spread (16).

By our knowledge, there are no existing reports on CBM for visiting social network members and everyday activities in the EMR. Whilst it is known that CBM decreased during the pandemic (15), it is not clear to which extent, and how citizens experienced CBM restrictions.

This study aimed to assess changes in cross-border visits during the pandemic and the impact of border restrictions on citizens in the EMR, focusing on differences between the three regions. Therefore, we assessed factors associated with changes in CBM for social contacts and everyday activities in autumn of 2021, compared to before the COVID-19 pandemic, and which factors are associated with experienced negative impact of border restrictions.

METHODS

Context of border restrictions in the EMR during the COVID-19 pandemic

Belgium closed its borders with neighboring countries between March 2020 and June 2020 and restricted all entry to the country. Border checks were enforced and border crossings had to be justified via forms. Cross-border workers were allowed to cross borders, but only with a declaration from the employer, which posed challenges for independent workers. Germany never introduced border controls with Belgium or the Netherlands, but health checks were enforced from March 2020. The Netherlands never closed its borders (15). However, all three EMR-countries advised citizens to stay within their own country (26). Between January and April 2021 Belgium again closed its borders for non-essential travel (16) (Figure 1).

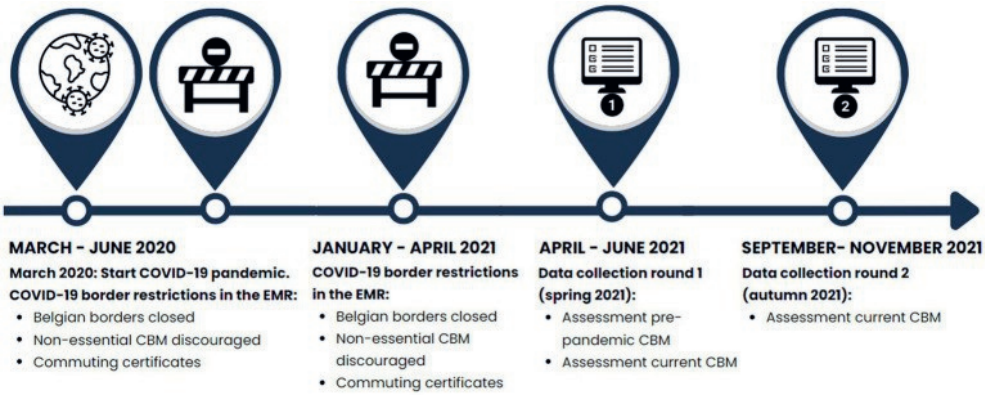

Figure 1. Timeline of data collection and border restrictions in the EMR.

Study design and participants

'Impact of COVID-19 on the EMR' is a longitudinal study of EMR residents, using a comparative cross-border data collection (27). A survey was conducted in EMR-subregions, including the Belgian provinces Limburg (Dutch-speaking), Liège (French-speaking), and the German-speaking community of Belgium (Ostbelgien as a part of Liège). Apart from that, South Limburg (the Netherlands; Dutch-speaking) and the German City of Aachen and Districts of Düren and Heinsberg (German-speaking) were included (Figure 2).

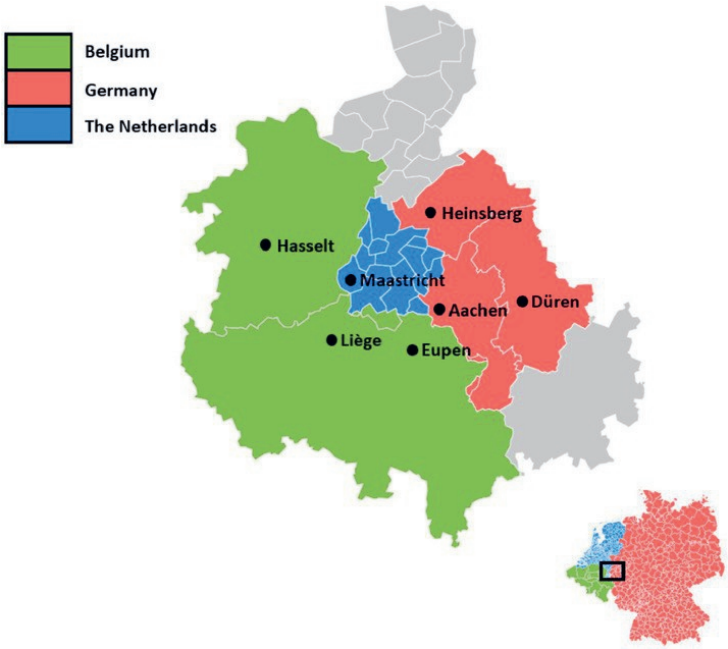

Figure 2. The parts of the Meuse-Rhine Euroregion (EMR) included in this study.

Participants were recruited through written invitations, including a letter and questionnaire link, based on national resident registers. In spring 2021, a random sample of in total 26,925 citizens aged 18 years and older, residing in private households in the EMR, was selected from the national registers in each country and invited to participate. Further details about the sampling methods applied in each country, stepwise selection, and opt-out procedures has been described previously (27). Participation rates ranged from 15.3% in the Belgian subregions (8,911 invitees and 1,366 participants) to 27% (11,266 invitees and 3,042 participants) and 26.7% (6,748 invitees and 1,598 participants) in the Dutch and German subregions, respectively. All 6,006 initial participants (round one) were subsequently invited for follow-up (round two).

Questionnaire data on CBM were collected between April 13 and June 29, 2021 (round one) and between September 21 and November 20, 2021 (round two; Figure 1).

A total of 3,557 participants completed the questionnaires from both rounds. In the current study, CBM behavior and impact of border restrictions are described

for the 3,543 participants who had no missing data for variables included in the analysis.

Measurements

CBM pre-pandemic (outcome 1)

Participants reported whether they have family, friends or acquaintances in another EMR-country and how many times per month on average they crossed the border to either visit social network members or for everyday activities before the pandemic. Based on the distribution of the data, the number of total cross-border visits before the pandemic was grouped into 0 times per month, 1–2 times per month, 3–5 times per month, and ≥ 6 times per month.

We distinguished between different types of CBM:

- Cross-border visits for visiting social network members: this was the average (as reported by the participant) number of times a month participants visited family, friends or acquaintances living across the border before the pandemic (measured in round one) and in the last month (round two).
- Cross-border visits for everyday activities: this was the average (as reported by the participant) number of times a month a participant had crossed the border for a short visit (for example grocery shopping or visiting a restaurant), before the COVID-19 pandemic, i.e., before February 2020 (measured in round one) and in the last month (when filling in the round 2 questionnaire in September to November 2021).
- Total visits were assessed by combining information on cross-border visits for social contacts or everyday activities.

Work-related CBM was not included as an outcome since changes herein were not evaluated and the number of participants working across the border was low.

Changes in CBM during the pandemic (outcome 2)

For CBM for social contacts (outcome 2a), everyday activities (outcome 2b), and total visits (outcome 2), participants were categorized into three groups based on their reported number of cross-border visits per month in autumn 2021 compared to before the COVID-19 pandemic: those with a decrease of more than one, those with an increase of more than one, and those with no change (a change of one or zero).

Experience of border restrictions (outcome 3)

Experienced impact of border restrictions was assessed by a question on whether the experience of border restrictions during the pandemic was negative for the participant themselves (five-point scale; from totally disagree to totally agree). For analyses, this outcome was grouped into 'neutral/no negative experience' (answers: neutral, disagree or totally disagree) and 'negative experience' (answers: totally agree or agree).

CBM and happiness (sub analysis)

Given that mobility and wellbeing are closely linked, we conducted a sub analysis to explore potential associations between happiness and cross-border visits. Data on happiness ('All things considered, how happy would you say you are?'), measured on a scale from 0 (unhappy) to 10 (happy), were collected for the pre-pandemic time point (assessed retrospectively in spring 2021) and in autumn 2021. A score < 8 was classified as indicative of unhappiness.

Covariates

Various socio-demographic factors were included: country (the Netherlands, Belgium or Germany), sex (male or female), age group (18–29, 30–39, 40–49, 50–59, 60–69 or ≥ 70 years), and level of education (theoretical or practical). Employment status was categorized into working in own country, working in another country, and not working. Apart from that, presence of comorbidities (yes/no) and having family, friends or acquaintances across the border (yes/no) were assessed.

Several measures that were taken in response to the COVID-19 pandemic were included in the questionnaire, such as 'limit group size', 'minimalize travel', and 'work from home'. We assessed perceived usefulness and perceived difficulty of these measures as measured in round one (at time when the measures were implemented). For perceived usefulness of measures, options were '(very) useful or neutral' and 'not useful (at all)'. Perceived difficulty was divided into '(very) easy or neutral' and '(very) difficult'.

Analytical approach and methodology

Data on CBM were measured for three different countries with seven different regions. In analyses, the focus was on countries (not regions) due to the low

number of participants in some regions. In all analyses, we evaluated CBM for social contacts, everyday activities, and total visits.

CBM pre-pandemic (outcome 1)

CBM for total visits, visiting social network members, and for everyday activities was described. Subsequently, we described the characteristics of participants who had CBM for social visits or everyday activities compared to those who did not have CBM before the pandemic. Characteristics of participants with or without CBM before the pandemic were described in a table of N and proportions. Univariate and multivariable logistic regression analyses were used to determine whether differences between country of residence and other covariates were statistically significant.
Subsequently, we restricted further analyses to those participants who reported CBM pre-pandemic.

Changes in CBM during the pandemic (outcome 2)

Changes in total CBM, social CBM (outcome 2a), and CBM for everyday activities (outcome 2b) were examined using descriptive analyses.
To determine factors associated with changes in total CBM since baseline (decrease, increase or no change [+/- 1]), univariate and multivariable multinomial regression analyses were used. The main determinant was country. Covariates evaluated were the number of cross-border visits pre-pandemic, sex, age group, level of education, work situation, presence of comorbidities, having family, friends or acquaintances across the border, and perceived usefulness and perceived efficacy for the measures 'limit group size', 'minimalize travel', and 'work from home'.

Changes in CBM and associated factors were assessed for social visits (outcome 2a) and visits for everyday activities (outcome 2b) separately, restricted to the subpopulations who those who reported pre-pandemic social CBM or CBM for everyday activities. For these two outcomes, the number of pre-pandemic cross-border visits was included as a continuous variable, since participant numbers were smaller.

Experience of border restrictions (outcome 3)

To examine experience of border restrictions, univariate and multivariable logistic regression analyses were performed. Main determinants were country and

changes in CBM (also defined as outcome 2). Other factors included were the number cross-border visits pre-pandemic, sex, age group, level of education, work situation, presence of comorbidities, having family, friends or acquaintances across the border, and perceived usefulness and perceived efficacy for the measures 'limit group size', 'minimalize travel', and 'work from home'.

CBM and happiness (sub analysis)

We used descriptive statistics, chi-square tests, and logistic regression analysis to assess the proportions of participants classified as unhappy, comparing different groups based on the average number of cross-border visits per month (0 [reference], 1 to 2, 3 to 5, or > 5). We performed univariate analysis, followed by adjusted analysis taking into account country, age, sex, and having social contacts across the border.

Statistical procedures and model building

For all main outcomes, univariate and multivariable models were adjusted for country and number of pre-pandemic cross-border visits. Apart from that, we corrected for changes in CBM for outcome 3. There was no multicollinearity between the included variables since Variance Inflation Factor (VIF) values were < 3. For pre-pandemic CBM, interactions between country and sex, as well as country and age, were tested and showed no statistically significant interaction. For model building, variables with a p-value of <0.10 in the univariate analysis were included in the multivariable models by backwards selection. A p-value of <0.05 was considered statistically significant to be retained in the final models. Data were analyzed with IBM Statistical Package for the Social Sciences (SPSS) version 27.

Ethics statement

The studies involving human participants were reviewed and approved by the Medical Ethical Committee of the MUMC+ (2020-2463-A-1). In Belgium, the study was approved by the Medical Ethical Committee of the University Hospital Ghent and the University of Ghent (BC-09754). In Germany, no ethical assessment of the project was required. Written informed consent was obtained from the individual(s) for participation and for the publication of any potentially identifiable images or data included in this article.

RESULTS

Study population

A total of 3,543 participants completed both questionnaires and had no missing data for the variables included in the analysis. Participants were on average 55 ± 15.5 years old and 59% was female. The majority of included participants was Dutch (N = 1791; 51%), followed by German (N = 1,030; 29%), and Belgian (N = 722; 20%).

Pre-pandemic CBM (outcome 1)

Of all 3,543 participants, 82% reported pre-pandemic CBM: 31% had at least one visit per month to cross-border social network members and 79% for everyday activities (Table 1). Differences in pre-pandemic CBM between the three countries were statistically significant in adjusted models (Supplementary Table 1). CBM was highest in the Netherlands (90% of participants; aOR = 4.4; 95%CI: 3.5–5.5), followed by Germany (81% of participants; aOR = 2.4; 95%CI 1.9–3.0), and Belgium (63% of participants; reference). CBM was >75% for all age groups. Participants who were employed more often reported CBM, with the highest proportion (96%) among participants working in another country. Most participants with pre-pandemic CBM had 1–2 cross-border visits per month (Table 1).

Table 1.Proportions for pre-pandemic CBM in participants living in the EMR (*N* = 3,543).

	CBM at baseline N=2,900	%	No CBM at baseline N=643	%	Total
Country					
Belgium	457	63.3	265	36.7	722
Netherlands	1,610	89.9	181	10.1	1791
Germany	833	80.9	197	19.1	1,030
Sex					
Female	1,698	82.0	373	18.0	2071
Male	1,202	81.7	270	18.3	1,472
Age group					
18–29	244	77.2	72	22.8	316
30–39	296	81.5	67	18.5	363
40–49	420	84.3	78	15.7	498
50–59	710	83.1	144	16.9	854
60–69	788	83.6	155	16.4	943
≥70	442	77.7	127	22.3	569
Level of education					
Theoretical	1,377	82.5	292	17.5	1,669
Practical	1,523	81.3	351	18.7	1874
Work situation					
Working in own country	1,595	84.2	299	15.8	1894
Working in other country	68	95.8	3	4.2	71
Not working	1,237	78.4	341	21.6	1,578
Presence of comorbidities					
No comorbidities	1,160	82.2	252	17.8	1,412
Comorbidities	1740	81.7	391	18.3	2,131
Having family/friends/acquaintances across the border					
Yes	1,277	94.0	82	6.0	1,359
No	1,623	74.3	561	25.7	2,184

Mobility at baseline (before the pandemic)					
Yes, social visits and visits for everyday activities	1,001	100	0	0	1,001
Yes, only visits for everyday activities	1806	100	0	0	1806
Yes, only social visits	93	100	0	0	93
No	0	0	643	100	643
Mobility in round 1 (spring 2021)					
Yes, social visits and visits for everyday activities	218	98.6	3	1.4	221
Yes, only visits for everyday activities	717	95.7	32	4.3	749
Yes, only social visits	130	98.5	2	1.5	132
No	1835	75.2	606	24.8	2,441
Mobility in round 2 (autumn 2021)					
Yes, social visits and visits for everyday activities	525	98.5	8	1.5	533
Yes, only visits for everyday activities	1,522	89.9	171	10.1	1,693
Yes, only social visits	108	90.8	11	9.2	119
No	745	62.2	453	37.8	1,198
Number of pre-pandemic border crossings per month					
0	0	0	643	100	643
1–2	1,318	100	0	0	1,318
3–5	882	100	0	0	882
≥6	700	100	0	0	700

Changes in CBM (outcome 2)

Pre-pandemic CBM was reported by 2,900 participants (82%). Of those, 37% reported CBM in spring 2021 (round 1) and 74% reported CBM in autumn 2022 (round 2; Figure 3; Supplementary Table 2).

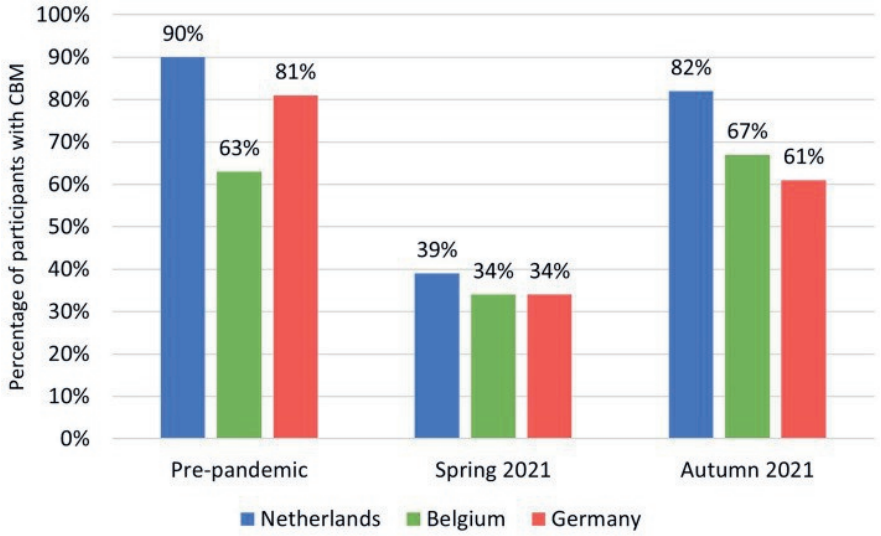

Figure 3. Proportion of CBM per EMR-country before the pandemic and in spring and autumn 2021 for participants with pre-pandemic CBM (N = 2900).

A decrease in cross-border visits (assessed at round 2) was observed in 40% of participants with pre-pandemic CBM, whereas 49% had no change or a change of one, and 11% had an increase of more than one (Table 2). The majority of participants (>90%) had a change between 2 and 5.

Table 2. Proportions and multinomial regression analysis for changes in cross-border visits in participants with pre-pandemic CBM (*N* = 2,900).

	Proportions				Univariate-corrected for country and number of pre-pandemic cross-border visits per month						Multivariable					
	Decrease>1 N=1,146		Increase>1 N=324		Decrease>1			Increase>1			Decrease>1			Increase>1		
	N	%	N	%	OR	95%CI	p	OR	95%CI	p	OR	95%CI	p	OR	95%CI	p
Country							**0.001**			**0.001**			**<0.001**			**<0.001**
Belgium	146	31.9	37	8.1	Ref			Ref			Ref			Ref		
Netherlands	680	42.2	209	13.0	0.92	0.69–1.23	0.58	1.62	1.10–2.39	**0.014**	0.89	0.67–1.18	0.41	1.79	1.20–2.66	**0.004**
Germany	320	38.4	78	9.4	1.20	0.88–1.63	0.24	1.25	0.82–1.92	0.30	1.15	0.85–1.57	0.37	1.35	0.87–2.08	0.18
Number of pre-pandemic border crossings per month							**<0.001**			**<0.001**			**<0.001**			**<0.001**
1–2	160	12.1	140	10.6	Ref			Ref			Ref			Ref		
3–5	445	50.5	107	12.1	8.83	7.06–11.04	**<0.001**	2.20	1.66–2.93	**<0.001**	9.04	7.22–11.32	**<0.001**	2.12	1.59–2.83	**<0.001**
≥6	541	77.3	77	11.0	44.08	32.93–59.01	**<0.001**	6.26	4.36–9.00	**<0.001**	47.28	35.02–63.82	**<0.001**	5.31	3.65–7.73	**<0.001**
Sex							**<0.001**			**<0.001**			**<0.001**			**<0.001**
Female	677	39.9	158	9.3	Ref			Ref			Ref			Ref		
Male	469	39.0	166	13.8	0.78	0.64–0.94	**0.011**	1.40	1.09–1.80	**0.008**	0.78	0.64–0.95	**0.014**	1.39	1.08–1.79	**0.010**

Age group							0.41			0.41						
18–29	78	32.0	33	13.5	0.92	0.61–1.39	0.68	1.66	0.98–2.81	0.059						
30–39	108	36.5	31	10.5	1.14	0.78–1.68	0.50	1.37	0.81–2.32	0.25						
40–49	166	39.5	37	8.8	1.10	0.77–1.56	0.61	1.11	0.67–1.84	0.68						
50–59	278	39.2	85	12.0	0.99	0.72–1.34	0.92	1.45	0.95–2.22	0.089						
60–69	325	41.2	99	12.6	1.12	0.83–1.52	0.46	1.57	1.04–2.39	**0.033**						
≥70	191	43.2	39	8.8	Ref			Ref								
Level of education							0.11			0.11						
Theoretical	518	37.6	159	11.5	Ref			Ref								
Practical	628	41.2	165	10.8	1.21	1.00–1.47	**0.049**	1.01	0.78–1.29	0.97						
Work situation							**<0.001**			**<0.001**			**<0.001**			**<0.001**
Working in own country	606	38.0	189	11.8	Ref			Ref			Ref			Ref		
Working in other country	35	51.5	18	26.5	0.75	0.36–1.55	0.43	2.90	1.35–6.23	**0.007**	0.74	0.36–1.55	0.43	2.84	1.32–6.13	**0.008**
Not working	505	40.8	117	9.5	0.94	0.78–1.15	0.56	0.74	0.57–0.97	**0.026**	0.94	0.77–1.14	0.54	0.76	0.58–0.98	**0.035**

Presence of comorbidities							0.25			0.25
No comorbidities	440	37.9	142	12.2	Ref			Ref		
Comorbidities	706	40.6	182	10.5	1.09	0.90–1.32	0.40	0.87	0.68–1.12	0.29
Having family/friends across the border							0.31			0.31
No	506	31.2	166	10.2	Ref			Ref		
Yes	640	50.1	158	12.4	1.00	0.82–1.23	1.00	1.22	0.93–1.58	0.15
Perceived difficulty (R1)										
Limit group size							**0.033**			**0.033**
(very) easy/neutral	945	40.1	249	10.6	Ref			Ref		
(very) difficult	201	36.9	75	13.8	0.79	0.62–1.01	0.063	1.17	0.87–1.58	0.30
Minimalize travel							0.11			0.11
(very) easy/neutral	968	39.0	265	10.7	Ref			Ref		
(very) difficult	178	42.7	59	14.1	0.98	0.75–1.29	0.90	1.39	0.99–1.94	0.055
Work from home [A]							**0.023**			**0.023**
(very) easy/neutral/ not applicable	843	40.0	215	10.2	Ref			Ref		

(very) difficult	303	38.2	109	13.7	1.04	0.84–1.28	0.75	1.44	1.11–1.88	**0.007**					
Perceived usefulness (R1)															
Limit group size							**<0.001**			**<0.001**			**0.003**		**0.003**
(very) useful/neutral	1,049	40.1	272	10.4	Ref			Ref			Ref			Ref	
(very) useless	97	33.8	52	18.1	0.74	0.54–1.03	0.076	1.61	1.13–2.30	**0.009**	0.76	0.55–1.06	0.11	1.51	1.05–2.16	**0.027**
Minimalize travel							**0.002**			**0.002**					
(very) useful/neutral	1,074	39.8	287	10.6	Ref			Ref							
(very) useless	72	35.3	37	18.1	0.72	0.49–1.06	0.098	1.63	1.07–2.48	**0.022**					
Work from home [A]							**0.014**			**0.014**					
(very) useful/neutral/not applicable	1,082	39.8	292	10.7	Ref			Ref							
(very) useless	64	35.4	32	17.7	0.76	0.51–1.14	0.19	1.54	0.99–2.40	0.056					

Reference = no change in short cross-border visits. OR, odds ratio; 95%CI = 95% confidence interval. Nagelkerke pseudo-R^2 value of the multivariable model = 0.38. Decrease > 1 indicates a decrease of 1 or more cross-border visits per month in autumn 2021, compared to before the COVID-19 pandemic. Increase > 1 indicates an increase of 1 or more cross-border visits per month in autumn 2021, compared to before the COVID-19 pandemic. R1 = round 1 questionnaire. [A]For 'work from home', all participants who were not working (e.g., retired, students) were grouped 'not applicable'. This group was then included in the categories of '(very) useful or neutral' for perceived usefulness, and '(very) easy or neutral' for perceived efficacy of working from home.

Factors associated with changes in CBM (outcome 2)

Around 40% of participants from the Netherlands and Germany experienced a decrease in CBM, compared to 32% in Belgium. Dutch participants most often had an increase in CBM (13%), followed by Belgian (8%) and German (9%) participants (Table 2).

Factors independently associated with a decrease of >1 in cross-border visits in autumn 2021, compared to baseline were having 3–5 (aOR = 9.0; 95%CI 7.2–11.3) or ≥ 6 (aOR = 47.3; 95%CI 35.0–63.8) baseline border crossings per month and female sex.

Factors independently associated with an increase of >1 in cross-border visits were Dutch residency (aOR = 1.8; 95%CI 1.2–2.7) as opposed to Belgian, male sex (aOR = 1.4; 95%CI 1.1–1.8), working across the border (aOR = 2.8; 95%CI 1.3–6.1), and low perceived usefulness of the measure 'limit group size' (aOR = 1.5; 95%CI 1.1–2.2). A higher number of pre-pandemic cross-border visits was also a significant factor for an increase in CBM (3–5 visits: aOR = 2.1; 95%CI 1.6–2.8; ≥6 visits: aOR = 5.3; 95%CI = 3.7–7.7; Table 2).

Factors associated with changes in CBM to visit social network members (outcome 2a)

Participants in the Netherlands and Germany presented similar proportions of around 25% for a decrease in social CBM in autumn 2021, compared to pre-pandemic. Those with a decrease of >1 in social CBM had an average number of pre-pandemic border crossings of 12.46, whereas it was 10.09 for those with an increase. This was the only factor associated with a decrease in social CBM between autumn 2021 and baseline (aOR = 1.2; 95%CI 1.1–1.2). Factors independently associated with an increase of >1 in cross-border visits were working across the border (aOR = 4.1; 95%CI 1.6–10.4), low perceived usefulness of 'minimalize travel' (aOR = 2.1; 95%CI 1.1–3.8) and a higher number of pre-pandemic border crossings per month (aOR = 1.1; 95%CI 1.1–1.2; Table 3).

Table 3. Proportions and multinomial regression analysis for changes in cross-border visits to visit social network members in participants with pre-pandemic CBM for visiting social network members (*N* = 1,094).

	Proportions				**Univariate-corrected for country and number of pre-pandemic cross-border visits per month**						**Multivariable**					
	Decrease>1 N=287		**Increase>1 N=68**		**Decrease>1**			**Increase>1**			**Decrease>1**			**Increase>1**		
	N	**%**	**N**	**%**	**OR**	**95%CI**	**p**	**OR**	**95%CI**	**p**	**OR**	**95%CI**	**p**	**OR**	**95%CI**	**p**
Country							0.54			0.54			0.95			0.95
Belgium	32	25.0	12	9.4	Ref			Ref			Ref			Ref		
Netherlands	187	26.7	40	5.7	1.35	0.81–2.24	0.25	0.70	0.35–1.43	0.33	1.18	0.70–2.00	0.53	1.08	0.48–2.45	0.85
Germany	68	25.7	16	6.0	1.35	0.77–2.37	0.30	0.78	0.34–1.75	0.54	1.19	0.67–2.12	0.56	1.27	0.51–3.18	0.61
Number of pre-pandemic border crossings per month (continuous)	12.46 (10.51)		10.09 (9.94)				**<0.001**			**<0.001**			**<0.001**			**<0.001**
					1.17	1.14–1.21	**<0.001**	1.14	1.10–1.19	**<0.001**	1.18	1.14–1.21	**<0.001**	1.12	1.08–1.17	**<0.001**
Sex							0.92			0.92						
Female	130	27.7	31	6.6	Ref			Ref								
Male	157	25.1	37	5.9	0.94	0.69–1.28	0.69	0.99	0.60–1.66	0.98						

Age group															
18–29	14	21.5	4	6.2	0.76	0.36–1.62	0.48	1.15	0.33–4.05	0.83					
30–39	15	15.0	10	10.0	0.56	0.28–1.12	**0.099**	2.03	0.77–5.32	0.15					
40–49	46	28.7	10	6.3	1.05	0.62–1.77	0.85	1.29	0.50–3.34	0.60					
50–59	75	28.1	12	4.5	0.96	0.60–1.53	0.86	0.87	0.35–2.16	0.76					
60–69	87	28.4	23	7.5	1.11	0.71–1.74	0.64	1.72	0.76–3.89	0.19					
≥70	50	25.5	9	4.6	Ref			Ref							
Level of education							0.43			0.43					
Theoretical	127	23.6	34	6.3	Ref			Ref							
Practical	160	28.8	34	6.1	1.22	0.90–1.66	0.20	1.05	0.63–1.75	0.85					
Work situation (R1)							**0.005**			**0.005**			**0.004**		**0.004**
Working in own country	134	24.2	29	5.2	Ref			Ref			Ref		Ref		
Working in other country	18	31.6	14	24.6	0.66	0.29–1.50	0.32	3.73	1.49–9.31	**0.005**	0.64	0.28–1.46	0.29	4.10	1.62–10.38	**0.003**
Not working	135	28.0	25	5.2	1.16	0.85–1.58	0.35	1.04	0.59–1.82	0.90	1.14	0.83–1.56	0.42	1.14	0.64–2.02	0.65

Presence of comorbidities							0.31			0.31						
No comorbidities	98	23.8	28	6.8	Ref			Ref								
Comorbidities	189	27.7	40	5.9	1.27	0.92–1.74	0.14	0.98	0.58–1.64	0.92						
Perceived difficulty (R1)																
Limit group size							0.31			0.31						
(very) easy/neutral	241	27.1	55	6.2	Ref			Ref								
(very) difficult	46	22.5	13	6.4	0.73	0.49–1.10	0.13	0.93	0.49–1.79	0.83						
Minimalize travel							**0.027**			**0.027**			**0.021**			**0.021**
(very) easy/neutral	242	26.5	48	5.3	Ref			Ref			Ref			Ref		
(very) difficult	45	25.0	20	11.1	0.80	0.53–1.22	0.31	1.94	1.08–3.45	**0.025**	0.81	0.53–1.25	0.35	2.07	1.14–3.75	**0.016**
Work from home [A]							0.91			0.91						
(very) easy/neutral/not applicable	207	25.6	50	6.2	Ref			Ref								
(very) difficult	80	28.2	18	6.3	0.94	0.66–1.32	0.71	0.91	0.51–1.62	0.75						
Perceived usefulness (R1)																
Limit group size							0.45			0.45						

(very) useful/neutral	263	26.5	59	5.9	Ref			Ref		
(very) useless	24	23.5	9	8.8	0.84	0.49–1.43	0.52	1.45	0.67–3.11	0.35
Minimalize travel							0.16			0.16
(very) useful/neutral	263	25.8	58	5.7	Ref			Ref		
(very) useless	24	31.6	10	13.2	1.09	0.61–1.97	0.77	2.21	1.02–4.78	**0.045**
Work from home [A]							0.16			0.16
(very) useful/neutral/ not applicable	269	26.5	59	5.8	Ref			Ref		
(very) useless	18	22.8	9	11.4	0.73	0.39–1.37	0.32	1.74	0.79–3.83	0.17

Reference = no change in long cross-border visits for visiting social network members. OR, odds ratio; 95%CI = 95% confidence interval. Nagelkerke pseudo-R^2 value of the multivariable model = 0.24. Decrease > 1 indicates a decrease of 1 or more long cross-border visits to visit family, friends or acquaintances per month in autumn 2021, compared to before the COVID-19 pandemic. Increase > 1 indicates an increase of 1 or more long cross-border visits to visit family, friends or acquaintances per month in autumn 2021, compared to before the COVID-19 pandemic. R1 = round 1 questionnaire. [A]For 'work from home', all participants who were not working (e.g., retired, students) were grouped 'not applicable'. This group was then included in the categories of '(very) useful or neutral' for perceived usefulness, and '(very) easy or neutral' for perceived efficacy of working from home

Factors associated with changes in CBM for everyday activities (outcome 2b)

In autumn 2021, around 35% of Dutch and German participants and 28% of Belgian participants showed a decrease in CBM for everyday activities, compared to pre-pandemic. Dutch participants most often had an increase in CBM (11%; Table 4).

Table 4. Proportions and multinomial regression analysis for changes in short cross-border visits for everyday activities in participants with pre-pandemic CBM for everyday activities (*N* = 2,789).

	Proportions				**Univariate-corrected for country and number of pre-pandemic cross-border visits for everyday activities per month**						**Multivariable**					
	Decrease>1 N=967		**Increase>1 N=261**		**Decrease>1**			**Increase>1**			**Decrease>1**			**Increase>1**		
	N	**%**	**N**	**%**	**OR**	**95%CI**	**p**	**OR**	**95%CI**	**p**	**OR**	**95%CI**	**p**	**OR**	**95%CI**	**p**
Country							**0.008**			**0.008**			**0.010**			**0.010**
Belgium	122	27.7	30	6.8	Ref			Ref			Ref			Ref		
Netherlands	568	36.7	176	11.4	1.19	0.91–1.57	0.20	1.56	1.02–2.37	**0.039**	1.14	0.87–1.50	0.36	1.74	1.12–2.71	**0.014**
Germany	277	34.6	55	6.9	1.38	1.03–1.84	**0.033**	1.07	0.67–1.73	0.78	1.26	0.94–1.69	0.12	1.17	0.71–1.92	0.53
Number of pre-pandemic border crossings per month (continuous) Mean (SD)	7.86 (6.97)		5.75 (6.96)				**<0.001**			**<0.001**			**<0.001**			**<0.001**
					1.36	1.32–1.41	**<0.001**	1.30	1.25–1.35	**<0.001**	1.43	1.38–1.48	**<0.001**	1.30	1.25–1.36	**<0.001**
Sex							**<0.001**			**<0.001**			**<0.001**			**<0.001**
Female	559	34.6	119	7.4	Ref			Ref			Ref			Ref		
Male	408	34.8	142	12.1	0.91	0.76–1.10	0.32	1.57	1.20–2.06	**0.001**	0.91	0.75–1.09	0.30	1.57	1.20–2.07	**0.001**

Age group							0.77			0.77						
18–29	72	31.6	26	11.4	1.02	0.69–1.53	0.91	1.69	0.95–2.98	0.072						
30–39	91	31.8	20	7.0	0.99	0.68–1.42	0.94	0.96	0.53–1.75	0.90						
40–49	139	33.9	33	8.0	0.97	0.70–1.36	0.87	1.06	0.63–1.80	0.82						
50–59	239	34.4	70	10.1	0.99	0.74–1.33	0.96	1.35	0.86–2.11	0.20						
60–69	274	36.3	77	10.2	1.09	0.82–1.45	0.57	1.34	0.86–2.09	0.20						
≥70	152	36.6	35	8.4	Ref			Ref								
Level of education							0.98			0.98						
Theoretical	453	34.1	126	9.5	Ref			Ref								
Practical	514	35.2	135	9.3	1.00	0.84–1.20	0.98	0.97	0.74–1.28	0.84						
Work situation							**<0.001**			**<0.001**			**<0.001**			**<0.001**
Working in own country	526	33.8	147	9.5	Ref			Ref			Ref			Ref		
Working in other country	29	45.3	14	21.9	0.20	0.09–0.47	**<0.001**	1.00	0.41–2.41	1.00	0.21	0.086–0.49	**<0.001**	1.01	0.41–2.44	0.99
Not working	412	35.2	100	8.5	0.93	0.78–1.12	0.46	0.82	0.62–1.09	0.18	0.94	0.78–1.13	0.49	0.83	0.63–1.10	0.20

Presence of comorbidities							0.89			0.89						
No comorbidities	382	34.1	109	9.7	Ref			Ref								
Comorbidities	585	35.1	152	9.1	1.00	0.83–1.20	1.00	0.94	0.71–1.23	0.65						
Having family/friends across the border							**<0.001**			**<0.001**			**<0.001**			**<0.001**
No	504	31.4	122	7.6	Ref			Ref			Ref			Ref		
Yes	463	39.1	139	11.7	0.57	0.46–0.69	**<0.001**	0.94	0.70–1.26	0.66	0.57	0.46–0.70	**<0.001**	0.94	0.70–1.26	0.68
Perceived difficulty (R1)																
Limit group size							0.14			0.14						
(very) easy/neutral	785	34.7	198	8.7	Ref			Ref								
(very) difficult	182	34.7	63	12.0	1.06	0.84–1.34	0.61	1.39	1.01–1.92	**0.044**						
Minimalize travel							0.20			0.20						
(very) easy/neutral	814	34.1	211	8.8	Ref			Ref								
(very) difficult	153	38.0	50	12.4	0.98	0.75–1.27	0.85	1.35	0.95–1.93	0.099						

Work from home [A]							0.073			0.073						
(very) easy/neutral/not applicable	700	34.8	174	8.6	Ref			Ref								
(very) difficult	267	34.5	87	11.2	1.03	0.84–1.26	0.76	1.40	1.05–1.87	**0.023**						
Perceived usefulness (R1)																
Limit group size							**0.009**			**0.009**			**0.032**			**0.032**
(very) useful/neutral	880	35.0	219	8.7	Ref			Ref			Ref			Ref		
(very) useless	87	31.3	42	15.1	0.92	0.68–1.26	0.60	1.73	1.18–2.55	**0.005**	0.93	0.68–1.27	0.65	1.61	1.09–2.37	**0.017**
Minimalize travel							**0.027**			**0.027**						
(very) useful/neutral	904	34.9	233	9.0	Ref			Ref								
(very) useless	63	31.7	28	14.1	0.73	0.50–1.07	0.11	1.41	0.89–2.24	0.14						
Work from home [A]							0.10			0.10						
(very) useful/neutral/not applicable	911	34.9	237	9.1	Ref			Ref								
(very) useless	56	32.0	24	13.7	0.76	0.51–1.13	0.18	1.32	0.81–2.15	0.27						

Reference = no change in short cross-border visits for everyday activities. OR, odds ratio; 95%CI = 95% confidence interval. Nagelkerke pseudo-R^2 value of the multivariable model = 0.29. Decrease > 1 indicates a decrease of 1 or more short cross-border visits for everyday activities (e.g., grocery shopping, visiting restaurants) per month in autumn 2021, compared to before the COVID-19 pandemic. Increase > 1 indicates an increase of 1 or more short cross-border visits for everyday activities (e.g., grocery shopping, visiting restaurants) per month in autumn 2021, compared to before the COVID-19 pandemic.

R1, round 1 questionnaire. [A]For 'work from home', all participants who were not working (e.g., retired, students) were grouped 'not applicable'. This group was then included in the categories of '(very) useful or neutral' for perceived usefulness, and '(very) easy or neutral' for perceived efficacy of working from home.

Participants with cross-border social contacts more often had an increase or decrease in CBM for everyday activities. This factor was associated with lower likeliness for a decrease (aOR = 0.6; 95%CI 0.5–0.7). Furthermore, working across the border was associated with lower odds for a decrease (aOR = 0.2; 95%CI 0.09–0.5). A higher number of pre-pandemic border crossings was associated with higher odds for both a decrease (aOR = 1.4; 95%CI 1.4–1.5) and increase (aOR = 1.3; 95%CI 1.3–1.4) in CBM for everyday activities. Other factors independently associated with an increase were Dutch residency, compared to Belgian (aOR = 1.7; 95%CI 1.1–2.7), male sex (aOR = 1.6; 95%CI 1.2–2.1), and low perceived usefulness of 'limit group size' (aOR = 1.6; 95%CI 1.1–2.4; Table 4).

Outcome 3: experienced negative impact of border restrictions

Out of the 2,900 participants with pre-pandemic CBM, 1299 (45%) reported having experienced the border restrictions during the pandemic as negatively for themselves (Table 5).

Table 5. Proportions and logistic regression analysis for negative experience with border restrictions in participants with baseline CBM (*N* = 2,900).

	Negative experience of border restrictions		Univariate-corrected for country, change in cross-border visits, and number of pre-pandemic cross-border visits per month			Multivariable		
	N=1,299	**%**	**OR**	**95%CI**	**p**	**OR**	**95%CI**	**p**
Country					**0.002**			**<0.001**
Belgium	169	37.0	Ref			Ref		
Netherlands	808	50.2	1.34	1.07–1.68	**0.012**	1.44	1.14–1.82	**0.003**
Germany	322	38.7	1.01	0.79–1.29	0.94	1.09	0.84–1.41	0.51
Change in cross-border visits per month between autumn 2021 and before the pandemic					**<0.001**			**<0.001**
No change	548	38.3	Ref			Ref		
Decrease of >1	548	47.8	1.96	1.51–2.55	**<0.001**	1.84	1.41–2.41	**<0.001**
Increase of >1	203	62.7	0.68	0.55–0.83	**<0.001**	0.69	0.56–0.84	**<0.001**
Number of pre-pandemic border crossings per month					**<0.001**			**<0.001**
1–2	430	32.6	Ref			Ref		
3–5	418	47.4	2.07	1.70–2.52	**<0.001**	1.91	1.56–2.34	**<0.001**
>5	451	64.4	4.68	3.67–5.97	**<0.001**	3.91	3.02–5.08	**<0.001**

Sex					0.14			
Female	717	42.2						
Male	582	48.4	1.13	0.96–1.32	0.14			
Age group					**0.002**			
18–29	114	46.7	1.37	0.99–1.91	0.062			
30–39	136	45.9	1.38	1.01–1.89	**0.043**			
40–49	196	46.7	1.34	1.01–1.78	**0.044**			
50–59	336	47.3	1.25	0.98–1.61	0.078			
60–69	324	41.1	0.90	0.71–1.16	0.42			
≥70	193	43.7	Ref					
Level of education					**0.047**			
Theoretical	643	46.7	Ref					
Practical	656	43.1	0.86	0.73–1.00	**0.047**			
Work situation					**<0.001**			**0.005**
Working in own country	730	45.8	Ref			Ref		
Working in other country	51	75.0	2.09	1.16–3.77	**0.014**	2.21	1.21–4.01	**0.010**
Not working	518	41.9	0.79	0.67–0.93	**0.003**	0.88	0.74–1.03	0.11
Presence of comorbidities					0.92			
No comorbidities	524	45.2	Ref					
Comorbidities	775	44.5	0.99	0.85–1.16	0.92			

Having family/friends across the border					**0.001**			**0.002**
No	613	37.8	Ref			Ref		
Yes	686	53.7	1.31	1.11–1.55	**0.001**	1.31	1.10–1.55	**0.002**
Perceived difficulty (R1)								
Limit group size					**<0.001**			**<0.001**
(very) easy/neutral	978	41.5	Ref			Ref		
(very) difficult	321	58.9	1.97	1.62–2.41	**<0.001**	1.54	1.24–1.91	**<0.001**
Minimalize travel					**<0.001**			**<0.001**
(very) easy/neutral	1,027	41.4	Ref			Ref		
(very) difficult	272	65.2	2.60	2.07–3.27	**<0.001**	1.99	1.55–2.56	**<0.001**
Work from home [A]					**0.009**			
(very) easy/neutral/ not applicable	914	43.4	Ref					
(very) difficult	385	48.5	1.26	1.06–1.49	**0.009**			
Perceived usefulness (R1)								
Limit group size					**<0.001**			
(very) useful/neutral	1,134	43.4	Ref					
(very) useless	165	57.5	1.64	1.26–2.12	**<0.001**			
Minimalize travel					**<0.001**			**0.007**
(very) useful/neutral	1,168	43.3	Ref			Ref		
(very) useless	131	64.2	2.23	1.63–3.05	**<0.001**	1.58	1.13–2.21	**0.007**

Work from home [A]					**0.011**
(very) useful/neutral/not applicable	1,196	44.0	Ref		
(very) useless	103	56.9	1.52	1.10–2.10	**0.011**

Reference = no negative experience of border restrictions. OR, odds ratio; 95%CI = 95% confidence interval. Nagelkerke pseudo-R^2 value of the multivariable model = 0.17. Decrease > 1 indicates a decrease of 1 or more cross-border visits per month in autumn 2021, compared to before the COVID-19 pandemic. Increase > 1 indicates an increase of 1 or more cross-border visits per month in autumn 2021, compared to before the COVID-19 pandemic. R1, round 1 questionnaire. [A]For 'work from home', all participants who were not working (e.g., retired, students) were grouped 'not applicable'. This group was then included in the categories of '(very) useful or neutral' for perceived usefulness, and '(very) easy or neutral' for perceived efficacy of working from home.

The adjusted odds ratios for a negative experienced impact of border restrictions was 1.4 (95%CI 1.1–1.8) for Dutch participants, compared to Belgian. Those with a decrease had a 1.8 odds (95%CI 1.4–2.4) and those with an increase a 0.7 odds (95%CI 0.6–0.8) for a negative experienced impact. Odds for negative experience increased as pre-pandemic cross-border visits were higher (3–5 visits: aOR = 1.9; 95%CI 1.6–2.3 and ≥ 6 visits: aOR = 3.9; 95%CI = 3.0–5.1). Working across the border increased the likelihood of a negative experience (aOR = 2.2; 95%CI = 1.2–4.0). Odds for negative impact were 1.3 times higher (95%CI 1.1–1.6) when having family, friends or acquaintances across the border. Difficulty adhering to 'minimalize travel' resulted in twice the odds for a negative experience with border restrictions (aOR = 2.0; 95%CI 1.6–2.6), while a low perceived usefulness had an odds of 1.6 (95%CI 1.1–2.2). Difficulty adhering to 'limit group size' presented a 1.5 odds (95%CI 1.2–1.9) for a negative experience (Table 5).

CBM and happiness

Pre-pandemic, 28% of participants with no CBM were classified as unhappy, compared to 17% of participants with >5 cross-border visits per month. In autumn 2021, proportions of unhappiness ranged between 33 and 36% for participants with CBM, and was 41% for participants with no CBM (Figure 4).

Adjusted logistic regression analyses indicated statistically significant differences between the '0 visits' group and the other groups pre-pandemic [1–2 visits: aOR = 0.68 (95%CI 0.54–0.85); $p < 0.001$; 3–5 visits: aOR = 0.55 (95%CI 0.43–0.72); $p < 0.001$; >5 visits: aOR = 0.45 (95%CI 0.34–0.61); $p < 0.001$].
In autumn 2021, a statistically significant difference was observed between the '0 visits' group and the '1–2 visits' and '>5 visits' groups [1–2 visits: aOR = 0.74 (95%CI 0.61–0.90); $p = 0.002$; 3–5 visits: aOR = 0.90 (95%CI 0.74–1.11); $p = 0.32$; >5 visits: aOR = 0.83 (95%CI 0.69–1.00); $p = 0.049$; Figure 4].

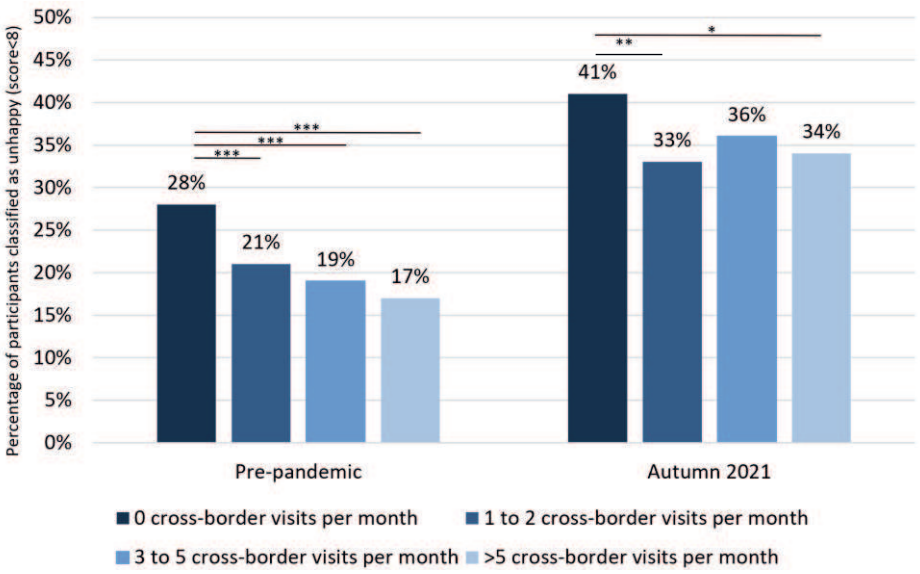

Figure 4. Proportion of participants classified as unhappy (happiness score < 8) pre-pandemic and in autumn 2021, compared for the number of cross-border visits per month (0 visits, 1–2 visits, 3–5 visits, and > 5 visits; $N = 3{,}540$). ***$p < 0.001$; **$p < 0.01$; *$p < 0.05$ for logistic regression analysis corrected for country, age, sex, and having social contacts across the border. Nagelkerke pseudo-R^2 value = 0.031.

DISCUSSION

Summary

This study examined changes in CBM and the impact of border restrictions in the EMR during the COVID-19 pandemic. Pre-pandemic, CBM was frequent, reported by 82%, with the highest proportion reported among Dutch participants. In autumn 2021, 40% of participants with pre-pandemic CBM, had decreased their number of cross-border visits (35% reduced CBM for everyday activities and 26% for visiting social contacts), while 49% had no change or a minor change, and 11% had an increase. A negative experienced impact of border restrictions was reported by 45% of participants who had pre-pandemic CBM. Negative experience was associated with Dutch residency, working across the border, having social contacts across the border, and finding measures useless or difficult to adhere to. CBM was associated with being happy, both pre-pandemic and during the pandemic, in autumn 2021.

Pre-pandemic CBM and changes in CBM

This study provides unique insights as it is the first to investigate changes in CBM for visiting social network members and everyday activities in the EMR. Pre-pandemic, CBM was high (82%) among participants, with some variation in the three countries, with the highest rate in Germany and especially in Dutch participants. The latter observation might be explained by the fact that Dutch participants lived closest to a border; and as a result also might have been more impacted by border restrictions. Overall, 31% had at least one visit per month to cross-border social network members and 79% had at least one visit for everyday activities per month. The assessment of pre-pandemic CBM in the current study allowed for improved understanding of changes in CBM during the pandemic.

A substantial proportion of participants decreased their number of cross-border visits during the pandemic. Prior research in 25 country pairs using phone and Facebook similarly demonstrated a sharp decline in CBM of up to 82% compared to pre-pandemic levels (28). Compared to Belgium and German participants, Dutch participants more frequently showed an increase in both overall visits and short visits, adjusted for other characteristics. A previous study showed that Dutch citizens were less likely to restrict CBM for everyday activities or social contacts, compared to Belgian citizens (29). This can pose challenges for

implementing policies, as cultural differences impact people's responses to measures in different places. It was suggested that culture can influence pandemic-related behaviors, even apart from individual beliefs (29). To demonstrate, we previously showed that in the EMR, compliance and evaluation of COVID-19 measures, as well as intention to take the COVID-19 booster vaccine, were highest among German citizens and lower among Dutch citizens (30, 31).

Expectedly, finding travel-related measures difficult to adhere to or useless was associated with the CBM outcomes in the present study. Previous research has also linked beliefs on policies' effectiveness to a greater likelihood of engaging in the associated behaviors (29). Other factors such as (health) literacy and communication of measures are also associated with compliance (32).

Despite the absence of CBM restrictions in autumn 2021, CBM remained lower compared to the pre-pandemic period, suggesting the presence of longer-lasting effects and structural changes in citizens' mobility behavior. These changes likely resulted from the necessary adaptations in routines during the pandemic when work, school, family situations, and social interactions were disrupted (33).

Impact of border restrictions

Overall, a significant portion of participants (45%) reported a negative experienced impact of border restrictions, with the highest proportion among Dutch participants. Approaches to border restrictions varied per country, with Belgium physically closing its borders, Germany implementing border checks, and the Netherlands only discouraging CBM. CBM has been linked to wellbeing and happiness, in line with findings of the current study. Previous research has shown links between free movement and experienced health, as daily mobility and spatial behavior can influence individuals' wellbeing and happiness (10, 33). Negative experiences with border restrictions have been associated with worse mental health outcomes in Australia (34). Additionally, a report on 20 case studies conducted in several European border regions indicated that border restrictions had a negative impact on residents' personal lives as families living on both sides of the border were divided (15). EMR-residents also faced challenges in accessing up-to-date country-specific information and keeping track of constantly changing rules, highlighting a need for improved communication and access to information (16, 17).

Having social contacts (friends or family) across the border was a crucial independent factor associated with a negative experience with border restrictions. It has been argued that the social isolation resulting from the pandemic and its measures worsened existing public health challenges (35). People's social network size and composition were impacted by the pandemic. For example, a study in the Dutch subregion showed that network size and the number of emotional and practical supporters decreased, with a shift toward a smaller more family-oriented network (23). National policies tend to overlook the interconnected social lives of residents in border regions, which extend beyond geographical borders (5). Therefore, policies that prevent loss of social contact, as well as sustainable cross-border communication and collaboration, are essential to ensure effective pandemic management in border regions.

Strengths and limitations

A main strength of the current study is the standardized data collection across the three countries, ensuring consistency in methodology and timing, along with the accessibility of questionnaires in all three languages. A limitation is the absence of information on the actual distance of residence and a border. It is plausible that participants residing closer to the border experienced a greater impact from border restrictions, as is likely for the Dutch participants. Among the EMR regions included in this study, the Dutch subregion has the smallest surface area, with most municipalities bordering Belgium or Germany, possibly resulting in higher rates of CBM and experienced negative impact among Dutch participants.

Another limitation is that pre-pandemic CBM was assessed in spring 2021, which may have been a potential for recall bias.

A further limitation is that we did not obtain information on which countries were predominantly visited (for example Dutch participants reporting CBM may have visited either Germany or Belgium). Regions with existing cultural or language separation might have been less affected, for example the experienced impact may have been different for Liège (French-speaking) compared to Dutch-or German-speaking regions in Belgium. A final limitation is that, while we have shown associations, no causal effects can be determined.

Implications

Fostering social contact, such as by maintaining mobility, is not usually included in public health policy or pandemic preparedness, giving room for improvement.

Furthermore, policies are generally shaped at the national level rather than the regional level. Regions may place a higher emphasis on cross-border collaboration, experiencing the repercussions of lacking such policies, while it might be perceived as less urgent at the national level. Currently, cross-border collaboration mainly occurs at the operational level. Prevention officers, united in a cross-border collaboration know each other and establish direct contact during crises like COVID-19. However, this interaction is largely driven by personal connections rather than being supported by a structured government policy. Further investigation is needed to explore the added value of these collaborative networks. The present initiative for cross-border cooperation is largely driven by practical needs. Whether this level should also lead the initiation of national policies, should be further examined.

To make informed decisions about implementing, adjusting, easing, or suspending border restrictions, it is crucial to assess not only their effectiveness but also any unintended consequences, such as adverse impact on social, mental, and physical health, that may arise (36).

As the virus enters an endemic phase, it is important to update legal frameworks and establish enforceable measures to prepare for possible public health threats in the future. It has been established that in a highly globalized world and a Europe with open borders, imposing border restrictions is detrimental and should only be implemented in crisis situations (37). Border restrictions should be temporary, proportionate, and coordinated between countries, rather than a unilateral action. Targeted measures are considered more effective and less disruptive (37).

It has been suggested that border-related movements are not inherently more risky for SARS-CoV-2 transmission compared to in-country movements, and public health professionals have questioned the emphasis on restricting borders while leaving in-country movements largely unrestricted (5). If border restrictions or other measures are implemented, they should be aligned with neighboring countries to prevent adverse effects and impact on citizens (13, 37, 38). Therefore, cross-border collaboration on interventions that limit transmission but also minimize impact on citizens, especially in border regions, should be encouraged.

Conclusion

The COVID-19 pandemic has had significant implications for CBM in the EMR. We highlight the importance of considering the unique circumstances of border regions and the substantial impact of border restrictions on citizens' lives. Cross-border social networks, cross-border commuting, and the perception of measures played an important role in the changes observed in CBM and the negative experienced impact of border restrictions. Overall, our study shows the implications of the pandemic on CBM and emphasizes the importance of collaborative policies. In this way, public health goals can be prioritized while mitigating disruptions to citizens' lives and preserving the well-being of border regions.

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SUPPLEMENTARY MATERIALS

Supplementary table 1. Univariate and multivariable logistic regression analysis investigating factors associated with baseline CBM (before the pandemic; N=3543).

	Univariate-corrected for country			Multivariable		
	OR	**95% CI**	**p**	**OR**	**95% CI**	**p**
Country			**<0.001**			**<0.001**
Belgium	Ref			Ref		
Netherlands	5.16	4.16-6.40	**<0.001**	4.35	3.47-5.45	**<0.001**
Germany	2.45	1.97-3.05	**<0.001**	2.42	1.94-3.04	**<0.001**
Sex			0.65			
Female	Ref					
Male	0.96	0.80-1.15	0.65			
Age group			**<0.001**			
18-29 vs ≥70	1.11	0.79-1.56	0.56			
30-39 vs ≥70	1.56	1.10-2.20	**0.012**			
40-49 vs ≥70	1.92	1.39-2.66	**<0.001**			
59-59 vs ≥70	1.58	1.20-2.09	**0.001**			
60-69 vs ≥70	1.52	1.16-2.00	**0.003**			
≥70	Ref					
Level of education			**0.021**			
Theoretical	Ref					
Practical	0.81	0.68-0.97	**0.021**			
Work situation			**<0.001**			**<0.001**
Working in own country	Ref			Ref		
Working in other country	6.62	2.04-21.43	**0.002**	2.74	0.84-9.01	0.096
Not working	0.65	0.55-0.78	**<0.001**	0.63	0.53-0.76	**<0.001**
Presence of comorbidities			0.53			
No comorbidities	Ref					
Comorbidities	0.94	0.79-1.13	0.53			
Having family/friends/acquaintances across the border			**<0.001**			**<0.001**
No	Ref			Ref		
Yes	4.57	3.57-5.86	**<0.001**	4.41	3.43-5.66	**<0.001**

OR for CBM at baseline vs. no CBM at baseline.
OR=odds ratio; 95%CI=95% confidence interval. Nagelkerke pseudo-R^2 value of the multivariable model=0.19.

Supplementary table 2. Proportions on CBM for participants with pre-pandemic CBM per EMR-country (N=2900).

	Netherlands (N=1610)	%	Belgium (N=457)	%	Germany (N=833)	%
CBM pre-pandemic						
Yes, social visits and visits for everyday activities	644	40.0	118	25.8	239	28.7
Yes, only visits for everyday activities	909	56.5	329	72.0	568	68.2
Yes, only social visits	57	3.5	10	2.2	26	3.1
Number of pre-pandemic border crossings per month						
1-2	593	36.8	286	62.6	439	52.7
3-5	543	33.7	94	20.6	245	29.4
≥6	474	29.4	77	16.8	149	17.9
CBM in round 1 (spring 2021)						
Yes, social visits and visits for everyday activities	126	7.8	43	9.4	49	5.9
Yes, only visits for everyday activities	422	26.2	97	21.2	198	23.8
Yes, only social visits	85	5.3	13	2.8	32	3.8
No	977	60.7	304	66.5	554	66.5
CBM in round 2 (autumn 2021)						
Yes, social visits and visits for everyday activities	338	21.0	65	14.2	122	14.6
Yes, only visits for everyday activities	910	56.5	199	43.5	413	49.6
Yes, only social visits	71	4.4	16	3.5	21	2.5
No	291	18.1	177	38.7	277	33.3
Having family/friends across border						
In the Netherlands	-	-	127	27.8	216	25.9
In Belgium	566	35.2	-	-	152	18.2
In Germany	455	28.3	52	11.4	-	-
No	788	48.9	298	65.2	537	64.5
Work in other country						
Total	26	1.6	31	6.8	12	1.4
In the Netherlands	-	-	23	5.0	11	1.3
In Belgium	5	0.31	-	-	1	0.12
In Germany	15	0.93	7	1.5	-	-
Other	6	0.37	1	0.22	0	0



Chapter 5

Differences in non-positive intention to accept the COVID-19 booster vaccine between three countries in the cross-border region Meuse-Rhine Euroregion: The Netherlands, Belgium, and Germany.

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ABSTRACT

Introduction

COVID-19 booster vaccination has shown to add to the protection against infection with SARS-CoV2 and subsequent severe disease. This longitudinal cross-border study aimed to identify factors associated with COVID-19 booster vaccine intentions in an initially vaccinated adult population living in the Meuse-Rhine Euroregion (EMR; including the Netherlands, Belgium, and Germany) and differences between countries.

Methods

Data collection took place in autumn of 2021 and consisted of online questionnaires sent to a random sample of the population based on governmental registries. Data from 3,319 fully and partially vaccinated adults were used to examine determinants of non-positive intention for a booster vaccination (i.e., uncertain or do not want), using multivariable logistic regression analyses weighted by age group, sex, and country.

Results

Compared to German residents, Dutch residents (OR = 2.4) and Belgian residents (OR = 1.4) were more likely to be uncertain or not want to receive a booster vaccine in September-October 2021. Factors independently associated with non-positive intention were female sex (OR = 1.6), absence of comorbidities (OR = 1.3), time since last vaccination less than 3 months ago for those fully vaccinated (OR = 1.6), being partially vaccinated (OR = 3.6), a negative experience with communication of COVID-19 measures (OR = 2.2), and regarding measures as ineffective (OR = 1.1).

Conclusion

Results indicate that booster vaccine intentions differ between countries in the cross border Meuse-Rhine Euroregion. Non-positive intention for the booster vaccine is prevalent in all three countries of the EMR, but to a different extent, as shown in this study. Cross-border collaboration and sharing information and knowledge about vaccination strategies could play a role in limiting the impact of COVID-19.

INTRODUCTION

In 2021, vaccination campaigns worldwide were a breakthrough in the battle against coronavirus disease 2019 (COVID-19) (1). However, with the emergence of new variants it became apparent that later in the same year, COVID-19 booster vaccination would become necessary. Since antibody response declines over time and new variants can be more transmissible and evade immune responses, boosters provide additional protection (2, 3). COVID-19 vaccination coverage was already challenging, but to keep the situation manageable and with new variants emerging, booster hesitance is the next challenge.

Bivalent vaccines by BioNTech/Pfizer and Moderna are to be used in the autumn of 2022 and will be offered to adults to reduce the hospitalizations and deaths. These vaccines contain the mRNA components of both the Wuhan and the omicron variant. Apart from mRNA vaccines, Janssen and Novavax offer booster vaccines. All 4 types of booster vaccines are approved by the European Medicines Agency (EMA) (4, 5). While moving to a context where booster vaccination is expected to remain important, it is crucial to understand attitudes towards booster vaccination.

Different countries have approached vaccination differently, potentially resulting in different uptakes (6). For example, a cross-sectional study conducted in Croatia in December 2021 showed a percentage of 79% for positive intention among vaccinated participants (7). Higher percentages for intention were determined by Rzymski et al. (Poland, 82.3%) and Yadete et al. (United States of America, 87.1%), who collected data from vaccinated participants in July 2021 and September 2021, respectively (8, 9). An observational study of 22,139 fully vaccinated adults in the UK also examined predictors of uncertainty and unwillingness to receive a COVID-19 booster vaccine in November-December 2021 and showed a 4% rate of unwillingness and a 4% rate for uncertainty (10). Distinct factors have been associated with booster vaccine intentions, such as age, sex, and risk perception. In several studies, young adults and women were more likely to have a non-positive intention for booster vaccination (8, 11). Young adults may be more hesitant about accepting a booster vaccine because they generally have lower risk perception of being severely affected by the disease (12). Likewise, people without comorbidities generally are less favorable towards booster vaccination

(10, 13), which might suggest that they have a lower risk perception and are therefore less likely to take the booster vaccine.

It is not known what factors are associated with booster vaccine intention in a border region such as the Euroregion Meuse-Rhine (EMR), which is the border region of the Netherlands, Belgium, and Germany. The population of the different regions, in total 4 million, is relatively homogeneous in terms of age distribution, social-economic situation, lifestyle, and health profile. Because of the open-border nature of the region, normally most inhabitants do not feel borders exist in daily life. However, during the COVID-19 pandemic the disparity in approaches to tackle the situation between countries became apparent (14). In September 2022, the percentage of the adult population that had received at least one COVID-19 vaccine was 91% in Nord Rhine-Westphalia, to which the German part of the EMR belongs, between 86% (Ostbelgien and Wallonia, to which Liège belongs) and 95% (Flanders, to which Belgian Limburg belongs) in the Belgian part of the EMR, and 81% in South Limburg, the Dutch part of the EMR (15-17).

While booster vaccination is expected to remain important, pandemic fatigue and vaccine hesitancy form a threat for global health (18, 19). Therefore, it is relevant to understand the handling and effects of booster campaigns in different countries to share knowledge and inform policy optimization. Here, we aimed to identify factors associated with COVID-19 booster vaccine intentions in the fully and partially vaccinated adult population living in the EMR and to identify differences between countries. Given that the uptake of the initial COVID-19 vaccine differed between countries, we hypothesized that intentions for booster vaccination would also differ between the three EMR-countries. Additionally, we expected previously established factors such as age, sex, and presence of comorbidities to be associated with booster vaccine intention.

METHODS

Context of the study

Data on booster intention were collected in September-October 2021, when the Delta variant was dominant and at its peak (20).

The Netherlands

In the Netherlands, several measures were in place in this period: the advice to work from home, closing of night clubs, and the obligation to make reservations and register for visiting restaurants, hotels, and cafes (21). Booster vaccination in the Netherlands started in the end of November 2021 for vulnerable groups, elderly, and healthcare workers. In January 2022, booster vaccination also became available for other adults (22, 23).

Germany

The German regions of the EMR all belong to the state of Nordrhein-Westfalen. In September-November 2021, masks were obligated and a 3G (negatively tested, vaccinated, or recovered from a recent infection) policy was implemented for visiting events, restaurants, and facilities when the national 7-day incidence would exceed 35 (24). In Germany, booster vaccination for elderly people and healthcare workers was available from October 2021, and was recommended for all adults from the end of November 2021 (25, 26).

Belgium

In Belgium, most measures that were enforced during summer, were relaxed in September 2021 (27). Masks were still obligated in public transport and certain places of activity. However, at the end of October 2021, changes regarding masks were reversed again, working from home was strongly encouraged, and the "Covid safe ticket" (QR code) for events was introduced (28). In September 2021, most elderly and vulnerable groups could receive the booster vaccine. From December 2021 onwards, the capacity further increased so that the majority of adults could receive the booster (29), (30).

Study design and participants

This study is part of a larger longitudinal study in inhabitants of the EMR: 'Impact of COVID-19 on the EMR'. An interregional partnership was established to study the impact of the pandemic in a cross-border setting by using comparative data collection. Data were collected in April-June 2021 (round 1) and September-November (round 2) 2021, and consisted of two self-finger prick antibody tests and two online questionnaires, available in Dutch, German, and French. The

questionnaire included information on general health, COVID-19 infection and symptoms, booster vaccine intention, cross-border mobility changes, infection prevention attitudes and behavior, and loneliness. An online tool was used to manage fieldwork procedures and monitor participation and antibody test results, with a multilingual helpdesk set up to support participants. A complete overview of the sampling, design and participation is described elsewhere (31).

The Meuse-Rhine Euroregion covers the border area between Belgium, the Netherlands and Germany. The subregions included in this study are the Belgian provinces Limburg and Liège (including the German-speaking community Ostbelgien), South Limburg (the Netherlands), and the German City Region Aachen and Districts of Düren and Heinsberg (Fig. 1). Citizens of 18 years and older and residing in private households in the EMR were selected from the national registers in each country. A random sample was selected from the latest version of the National Register (NR) in Belgium, the Basic Registration of Persons (BRP) in The Netherlands, and the Registration Offices (Einwohnermeldeämter) in Germany. The sample size was set at 3,500 in each country, which was distributed among the sub-regions based on the size of the adult population. The included adult population was classified according to age group and sex. After ordering, a stepwise selection was applied, where the step size in each sub region was based on the total eligible population of that sub region divided by its sample size, starting from a random number. In Germany, the citizens from District Heinsberg and City Region Aachen were only classified by sex and a randomized sample was taken. Invitations were sent in the official language of the sub-region, along with an information brochure, personal ID-code, link to the online questionnaire, and informed consent form. Detailed information about the sampling methods applied in the three different countries, stepwise selection, and opt-out procedures can be accessed elsewhere (31).

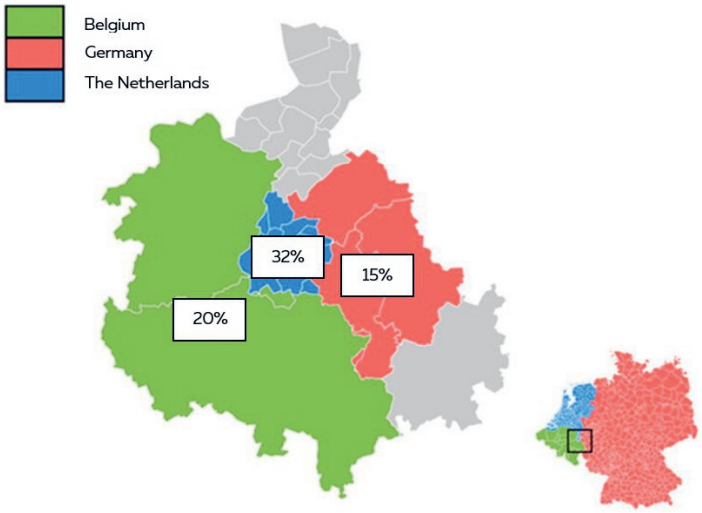

Figure 1. Non-positive intentions for booster vaccination in the Meuse-Rhine Euroregion in autumn 2021 (weighted percentages).

Round 1 participation rates differed from 15.3% in the Belgian subregions (8,911 invitees and 1,366participants) to 23.7% (6,748 invitees and 1,598participants) and 27% (11,266 invitees and 3,042 participants) in the German and Dutch subregions, respectively. In round 2, participants of round 1 were invited (N = 6,006). Full participation in both rounds was 3,344.

Current analyses

In the current study, complete case analysis was used. Participants who filled out both questionnaires, were fully or partially vaccinated at the time of round 2 data collection, and had no missing data were included. Fully vaccinated was defined as having received 2 vaccines, 1 vaccine in the case of Janssen vaccine, or a previous SARS-CoV2 infection plus 1 vaccine. Data on COVID-19 booster vaccination intention were collected between September 21 and November 22, 2021. Results from this group of participants are described in this paper.

Variables

Outcome

Intention to receive a COVID-19 booster vaccination was measured via the question: 'Do you intend to take the booster vaccine, once it is available?'.

Response options were 'Yes', 'No', or 'Not sure yet'. The primary outcome is booster vaccine intention, regrouped into: 'positive intention (reference group)' versus 'negative/neutral intention (no and not sure yet)'.

Personal factors

Various socio-demographic factors were included: country of residence, (including Germany, Belgium, and the Netherlands), sex (male or female), age group (18–59 or ≥ 60 years), and level of education (theoretical or practical). Employment status was categorized into 5 categories: retired, working in healthcare, working in education/childcare/youth assistance, working in another sector, not working or student. To measure interpersonal trust, one item of the de Jong-Gierveld scale for loneliness was used: "There are many people that I can count on completely". Response options were (totally) agree, neutral or (totally) disagree. In the first round of the study, presence of comorbidities (yes or no) was assessed.

COVID-19 related factors

Participants reported whether they had a previous COVID-19 infection (yes or no). Time to last COVID-19 vaccination at the time of questionnaire completion was included as a factor and was divided in 3 groups: fully vaccinated with the last vaccination received ≤ 3 months ago, fully vaccinated with the last vaccination received >3 months ago, and partially vaccinated. Apart from that, the questionnaire included an item about the experience of the communication of measures: "Please indicate the extent to which you agree with the following statement: I have found the communication of infection prevention measures to be good. Think about communication from the government through the news, television, newspaper and radio". Response options were (totally) agree, neutral, (totally) disagree. Finally, participants were asked in round 2 whether they find COVID-19 infection prevention measures useful or effective, including social distancing, washing hands with water and soap, sneezing and coughing in the elbow, wearing a mask, restricting group size at home, minimalizing travel, working from home, requiring a QR code for attendance of activities, and testing and staying home in case of symptoms. Response options ranged from 1 (very effective) to 7 (not effective at all). A score was calculated by adding all responses together, where a high score indicates regarding measures as lowly effective.

Weighted results

To increase representativeness of the study for the general population, data were weighted to the proportions of country (the Netherlands, Belgium, and Germany), age group (18–29, 30–39, 40–49, 50–59, 60–69, 70–79 or ≥80 years), and sex (male or female) obtained from national registers. Weigh factors were calculated taking into account non-response and selection probability for each of the age- and sex strata per country.

Weigh factors were calculated for each of the 3 EMR-regions separately (the Netherlands, Belgium, and Germany) per age and sex stratum (male/female and 18–29, 30–39, 40–49, 50–59, 60–69, 70–79, 80–89, and 90+ years). Sex and age distributions of the total populations were obtained from governmental registries. Composite weigh factors were used in the statistical analyses to obtain weighted results. These weigh factors were calculated by multiplying the non-response weights and the post-stratification weights. All weigh factors had a mean value of 1.

Non-response weights were obtained by dividing the response numbers by the number of citizens invited. The reciprocal of this was multiplied by the total response in the age and sex stratum. This number was then divided by the total number of invitees of the age and sex stratum. Post-stratification weights were calculated by taking the reciprocal of the selection probability (invitees divided by number of citizens in population) multiplied by the total number of invitees in the age and sex stratum. This value was then divided by the total number of citizens in the population of the age and sex stratum.

Statistical methods

After calculating weighted proportions with 95% confidence intervals (95% CI), weighted univariate and multivariate logistic regression analyses were performed to assess factors associated with intention to receive a COVID-19 booster vaccination. The multivariable model was adjusted for the confounders sex, age group, and level of education. Other variables with a two-sided p-value of <0.10 in univariate analyses were included in the multivariable model. With these variables, a backwards selection procedure was applied to create the final multivariable model (while always keeping the confounders in the model). A two-

sided p-value of <0.05 was considered statistically significant. Data were analyzed with IBM Statistical Package for the Social Sciences (SPSS) version 27.

Missing data

Questions in the questionnaire were not compulsory, leading to the possibility of missing data. Participants with missing data for at least one of the predictor variables were excluded from the analysis.

Multicollinearity and interaction

There was no multicollinearity since all Variance Inflation Factor (VIF) values were < 3. We tested for statistical interactions (effect modification) of sex and age group with country. Sex showed a statistically significant interaction ($p < 0.10$) with country. However, stratified analysis by country showed that odds for non-positive booster intention by sex slightly differed per country and that in each country the intention to take the booster vaccine was higher among men. Therefore, results presented in this article were not stratified. There was no statistically significant interaction between age group and country.

Ethics approval and consent to participate

The study protocol, questionnaires, participant information form and written informed consent form were reviewed and approved by the Medical Ethical Committee of the MUMC+ (2020-2463-A-1). In Belgium, the study was approved by the Medical Ethical Committee of the University Hospital Ghent and the University of Ghent (BC-09754). In Germany, no ethical assessment of the project was required. The project was approved by the heads of Gesundheitsamt Heinsberg, Düren, and Aachen, and the in-house lawyers of Kreisverwaltung Heinsberg, Düren, and Städteregion Aachen. All participants provided fully informed consent.

RESULTS

Participants

Missing data resulted in exclusion of 62 participants, totaling in a final N of 3,319 (Fig. 2). Neutral intention of taking the booster vaccine was expressed by 601 participants, whereas negative intention was expressed by 211 participants.

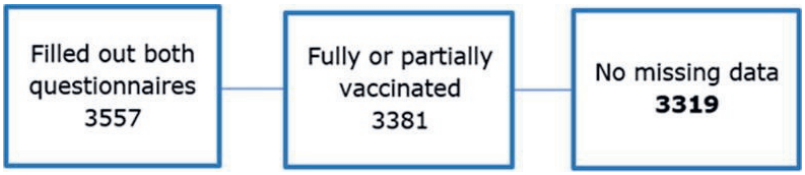

Figure 2. Participation and formation of the study population.

Booster intention proportions

Weighted proportions for booster intention are presented in Table 1. Non-positive intention differed per country and ranged from 14.6% in the German subregion to 19.8% in the Belgian subregion and 32.1% in the Dutch subregion (Fig. 1). In Belgium, notable differences between the different provinces were observed, where non-positive intention ranged from 14% in Limburg to approximately 30% in Liège and Ostbelgien.

Table 1. Proportions of non-positive intention by personal factors and COVID-related variables.

		Non-positive intention		
		N (total)	Weighted %	95%CI
Country	Germany	150 (985)	14.6	12.5–16.9
	Netherlands	526 (1655)	32.1	29.9–34.4
	Belgium	136 (679)	19.8	16.9–22.9
Age group	18–59	567 (1872)	25.9	23.5–28.5
	≥60	245 (1447)	13.1	11.0–15.6
Sex	Male	239 (1376)	16.2	13.7–18.9
	Female	573 (1943)	23.3	21.0–25.7
Level of education[a]	Theoretical	360 (1565)	21.4	18.8–24.2

	Practical	452 (1754)	19.3	17.1–21.7
Comorbidities	Yes	434 (2017)	17.3	15.3–19.4
	No	378 (1302)	25.2	22.3–28.4
Work situation	Retired	130 (907)	11.4	9.0–14.3
	Working in healthcare	129 (370)	30.9	25.0–37.5
	Working in education, childcare or youth assistance	65 (229)	24.4	18.1–32.0
	Working in other sector	339 (1230)	23.8	21.0–27.0
	Not working	112 (450)	20.5	16.0–25.8
	Student	37 (133)	22.2	14.6–32.3
Time to last vaccination	Fully vaccinated- more than 3 months ago	501 (2565)	17.0	15.2–19.0
	Fully vaccinated- less than 3 months ago	251 (643)	32.7	28.1–37.6
	Partially vaccinated	60 (111)	47.8	36.5–59.3
Previous positive COVID test	No	713 (3002)	19.8	18.0–21.6
	Yes	99 (317)	25.8	19.9–32.8
Communication of measures was good	(totally) agree	422 (2216)	15.2	13.4–17.2
	neutral	214 (646)	27.9	23.7–32.6
	(totally) disagree	176 (457)	34.0	28.8–39.7
Score effectiveness measures[b]		18.7 (mean score)		18.2–19.4
There are many people that I can count on completely	(totally) agree	638 (2638)	20.4	18.5–22.5
	Neutral	114 (442)	19.4	15.2–24.3
	(totally) disagree	60 (239)	21.2	15.2–28.6

[a]Practical training is also referred to as vocational training, and theoretical training as college-bound.
[b]A high score indicates regarding COVID-19 infection prevention measures in September-December 2021 as ineffective.

Non-positive intention was higher in the age group 18–59 years (25.9%), compared to 60 and above (13.1%). Non-positive intention was voiced more often by females, compared to males (23.3% vs 16.2%). Booster vaccine intention

differed between work situations. Non-positive intention was least often expressed by the retired group (11.4%), while those working in healthcare most frequently voiced non-positive intention (30.9%). Those with a negative experience with the communication of measures showed higher non-positive intention (34.0%) than those who had a neutral (27.9%) or a positive attitude (15.2%). Similarly, a negative attitude towards the effectiveness of infection prevention measures was more frequently observed in those with non-positive intention (mean score 18.7), compared to the group with positive intention (mean score 14.9).

Logistic regression analysis

Assessing intention to take a booster vaccine by univariate logistic regression revealed significant differences between countries (Table 2). These differences were still present when correcting for other factors in the multivariable model. Statistically significant factors in the multivariable model included country, sex, absence of comorbidities, time to last vaccination, experience with communication of measures, and opinion on effectiveness of measures. Compared to German residents, Dutch (OR = 2.41; 95% CI = 1.90–3.04) and Belgian residents (OR = 1.40; 95%CI = 1.05–1.86) were more likely to be uncertain or unwilling to receive a booster vaccine. Female sex (OR = 1.55; 95%CI = 1.18–2.03), absence of comorbidities (OR = 1.33; 95% CI = 1.03–1.71), a neutral (OR = 1.64; 95% CI = 1.22–2.21) or negative (OR = 2.17; 95%CI = 1.56–3.02) experience with communication of COVID-19 measures, and regarding measures as ineffective (OR = 1.09; 95%CI = 1.06–1.11) were independently associated with non-positive intention. Those partially vaccinated (OR = 3.62; 95%CI = 1.98–6.63) and those fully vaccinated who received their last vaccine<3 months ago (OR = 1.61; 95%CI = 1.18–2.19) were more likely to have a non-positive intention.

Table 2. Weighted univariate and multivariable logistic regression models examining factors associated with non-positive intention.[a]

		Crude OR	95% CI	p	Adjusted OR	95% CI	p
Country	Germany	**1**		**<0.001**	**1**		**<0.001**
	Netherlands	**2.78**	**2.27–3.41**		**2.41**	**1.90–3.04**	
	Belgium	**1.45**	**1.12–1.87**		**1.40**	**1.05–1.86**	
Age group	≥60	**1**		**<0.001**	1		0.17
	18–59	**2.32**	**1.82–2.94**		1.30	0.89–1.90	
Sex	Male	**1**		**<0.001**	**1**		**0.002**
	Female	**1.57**	**1.25–1.99**		**1.55**	**1.18–2.03**	
Level of education[b]	Practical	1		0.24	1		0.56
	Theoretical	1.14	0.92–1.41		1.08	0.84–1.39	
Work situation	Retired	**1**		**<0.001**	**1**		**0.050**
	Working in healthcare	**3.48**	**2.34–5.17**		**1.86**	**1.07–3.24**	
	Working in education, childcare or youth assistance	**2.51**	**1.58–3.98**		1.10	0.61–1.99	
	Working in other sector	**2.44**	**1.78–3.33**		1.24	0.79–1.94	
	Not working	**2.00**	**1.34–2.99**		1.50	0.95–2.37	
	Student	**2.22**	**1.25–3.96**		0.73	0.34–1.54	
Comorbidities	Yes	**1**		**<0.001**	**1**		**0.030**
	No	**1.62**	**1.30–2.01**		**1.33**	**1.03–1.71**	
Time to last vaccination	Fully vaccinated- more than 3 months ago	**1**		**<0.001**	**1**		**<0.001**
	Fully vaccinated- less than 3 months ago	**2.37**	**1.84–3.06**		**1.61**	**1.18–2.19**	

		Crude OR	95% CI	p	Adjusted OR	95% CI	p
	Partially vaccinated	**4.46**	**2.75–7.23**		**3.62**	**1.98–6.63**	
Previous positive COVID test	No	1		0.055			
	Yes	1.42	0.99–2.02				
Communication of measures was good	(totally) agree	**1**		**<0.001**	**1**		**<0.001**
	neutral	**2.17**	**1.66–2.84**		**1.64**	**1.22–2.21**	
	(totally) disagree	**2.89**	**2.17–3.84**		**2.17**	**1.56–3.02**	
Score effectiveness (high score = don't find measures effective)[c]	per 1 unit change	**1.12**	**1.10–1.14**	**<0.001**	**1.09**	**1.06–1.11**	**<0.001**
There are many people that I can count on completely	(totally) agree	1		0.89			
	neutral	0.94	0.68–1.28				
	(totally) disagree	1.05	0.69–1.59				

[a] OR of "uncertainty or unwillingness" vs "willingness" responses of intention to take a booster vaccine.
[b] Practical training is also referred to as vocational training, and theoretical training as college-bound.
[c] 1 unit change indicates an increase of 1 in score. A high score indicates regarding COVID-19 infection prevention measures in September–December 2021 as ineffective.

DISCUSSION

This is the first study to assess COVID-19 booster intention in the EMR border region comparing the Netherlands, Belgium, and Germany. Intention for booster vaccination differs between the subregions of the EMR with the Netherlands showing the lowest intention, followed by Belgium, and Germany showing the highest intention for booster vaccination. Female sex, absence of comorbidities, time since the last COVID-19 vaccination less than 3 months ago or being partially vaccinated, a negative experience with communication of COVID-19 measures, and regarding measures as ineffective were independently associated with non-positive intention.

We assessed booster intention in a group of fully or partially vaccinated adults. Eventually, booster vaccination uptake rates in September 2022 reached 77% in Nordrhein-Westfalen, to which the German part of the EMR belongs, between 68% (Ostbelgien and Wallonia, to which Liège belongs) and 85% (Flanders, to which Belgian Limburg belongs) in the Belgian part of the EMR, and 63% in South Limburg, the Dutch part of the EMR (15–17). Notably, similar differences between countries were observed for booster intention measured in our study and booster uptake, underscoring the validity of our study.

What can we learn from each other?

Even though the EMR is a small region and people live at only a few kilometers distance from each other, differences exist between countries. This could be explained by differences in policies regarding COVID-19 and vaccination, as well as compliance with policies. In our study, citizens from the German side of the EMR were most positive about and adherent to the COVID-19 measures, whereas compliance was lowest in the Netherlands. Similarly, in other studies Germany showed a higher rating than other countries regarding the usefulness of measures and COVID-19 communication by the government was perceived as clear and understandable (32). In Belgium, we observed larger differences in intention between different provinces. Nonetheless, this supports findings from another study on COVID-19 vaccine willingness among Belgians, where French-speaking participants were favorable to vaccination in general but less willing to be vaccinated against COVID-19 (33). The COVID-19 pandemic proves the necessity of cross-border cooperation. It is recommended to keep up regular

exchange and learn from each other, also outside of a pandemic situation. Cross-border care should be given more attention in national policy making. A large potential lies in exchanging protocols, organizing collaborative exercises, and supporting each other with resources (14).

Determinants of non-positive booster intention

The finding that female sex and absence of comorbidities are associated with non-positive intention is consistent with other studies (8, 34, 10-13). The proportion of healthcare workers was relatively large in our study, and this group was more likely to have a non-positive intention of taking the booster vaccine. We had no data on employment status of the population in the EMR and thus could not include this factor in our weighting. However, COVID-19 vaccination and booster hesitancy in this group has been reported several times (35, 36).

We as well as other studies showed perceived effectiveness of measures and the experience of communication of measures by the government to be associated with booster vaccine intentions (9, 10, 37). These factors are related to trust, which includes interpersonal trust, governmental trust, and trust in information , 38). To measure interpersonal trust, we asked participants whether they have many people they can count on completely. In our study, no statistically significant effect was found, though interpersonal trust was associated with vaccine coverage in a study of 177 countries (38) In this study, high levels of government and interpersonal trust, as well as less government corruption, were associated with higher COVID-19 vaccine coverage. Public trust in the government can be strengthened by effective, consistent, and transparent communication (39). Finally, lack of trust in vaccine information, related to an 'infodemic' forms another threat for vaccine acceptance. Susceptibility to misinformation has also been linked to lower COVID-19 risk perception (40, 41), indicating that policies focusing on modifiable risks such as battling misinformation and increasing governmental trust in general may be helpful in increasing COVID-19 vaccination intentions.

Strengths and limitations

Differences in policies in the different countries at time of data collection likely affected the results of our study. However, a strength is that data were collected at the same time point in the three countries and booster intentions were asked exactly at the time when booster vaccination became or was about to become available. People might have participated in the study because of the incentive of getting to know their antibody status. However, bias may be present given that people who participate in research might also have a more positive attitude towards COVID-19 vaccination, which was illustrated by the high vaccination rate of the participants, compared to the general population at that time. A strength is that analyses were weighted and thus more representative of the general population of the EMR. Differences in booster vaccine intention between the three countries remained apparent after correcting for other factors. Nevertheless, the variables we included only partially explain the differences in booster vaccine intention between the countries. Other factors that we did not measure or were not able to measure could be responsible for the differences observed. Predictive factors identified in other studies on booster vaccine intention involved cultural differences, marital status, socioeconomic status, political orientation, religion, ethnicity, smoking status, and optimism (7, 9-11). Also, people's social network can influence decisions about health and vaccination (42).

A limitation of this study is that we did not ask participants' reasons behind their booster vaccine intention, since this could provide a basis for interventions. Given that all participants in our study were vaccinated against COVID-19 at least once, reasons for non-positive intention might not have been related to skepticism towards COVID-19 vaccines in general. A report from April 2022 from the National Institute for Public Health and the Environment in the Netherlands reported on the most frequently cited reasons to not take a booster vaccine among 46,441 participants (43). A commonly cited reason was that vaccination cannot continue forever and that the first series should give enough protection. It was also argued that vaccines are not the solution for the pandemic and booster vaccines are only effective for a short time. Some respondents indicated that they have enough trust in their own immune system or that booster vaccination is not necessary after experiencing a SARS-CoV-2 infection.

Implications

It has been suggested that data and evidence should play a larger role in decision making, and that countries should comply with international health regulations during the pandemic. Comparable cross-border data collection allows for evaluation of different infection prevention policies on public health. An important step to prepare for future infectious disease outbreaks is committing to a treaty that keeps the issue elevated. This way, collaboration between countries could be facilitated and better coordinated (44). Countries should be committed to working together to improve pandemic response in the future. Greater efforts are needed to ensure that the pandemic, including new variants, cases, and impact on the healthcare and other sectors remains manageable, partly through booster vaccination. Therefore, an important practical implication includes taking into consideration the situation in border areas. Besides, this study indicates which groups of the population should be focused on to reduce booster vaccine hesitancy.

Conclusions

Booster vaccine intentions differ between countries in the EMR. Similar differences were observed in the eventual booster vaccine uptake, underscoring the validity of our study. Other factors associated with non-positive booster vaccine intention in this study were female sex, absence of comorbidities, time since last vaccination, and opinion on efficacy and communication of measures. The existence of differences between countries in this region highlights the need for cross-border collaboration to merge information and knowledge about vaccination strategies and ultimately limit the impact of COVID-19.

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Chapter 6

Social networks and COVID-19 vaccination intention in Dutch middle- aged and older adults in 2020: Insights into individual, interpersonal, community, and societal determinants – The SaNAE study.

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ABSTRACT

Background

Social networks, our social relationships, influence the spread of infectious diseases and preventive behaviors such as vaccination. Here, we aimed to assess which individual, interpersonal (social network characteristics), community and societal factors are associated with coronavirus disease 2019 (COVID-19) vaccination intention during the second wave of the COVID-19 pandemic in 2020, prior to vaccine availability.

Methods

This cross-sectional study collected primary data from 5,001 community-dwelling adults aged 40 years and older in the Netherlands, using an online questionnaire from August and November 2020. COVID-19 vaccination intention was measured by assessing whether respondents were willing to receive a COVID-19 vaccination if the vaccines became available. Associations between individual (sociodemographic variables, health, health concerns), interpersonal (social network characteristics including structure, function, and quality), community (social and labor participation) and societal factors (degree of urbanization), and the outcome variables COVID-19 vaccination intention (yes vs no, yes vs unsure, unsure vs no) were assessed in stepwise multivariable logistic regression analyses. p-values < 0.05 indicated statistical significance.

Results

Among participants (N = 3,396), 59 % reported a positive intention to vaccinate, 35 % were unsure, and 6 % had no intention. Men, individuals of older age, those with a college or university degree, those concerned about their personal and family health, and knowledge about protecting oneself from the virus were more likely to have the intention to vaccinate (versus no intention). Interpersonal factors associated included having a larger network size (social network structure) and a larger proportion of informational supporters (social network function). Living outside of urban areas, a societal factor, was associated with vaccination intention (versus no intention).

Conclusion

This study identified key factors influencing COVID-19 vaccination intention. Health promotion efforts should address not only individual factors but also incorporate the social environment. Our findings highlight the importance of organizing social networks to mobilize social support for pandemic preparedness.

INTRODUCTION

Infection prevention measures, such as washing hands frequently, wearing facemasks, or social distancing, as applied during the coronavirus disease (COVID-19) pandemic, are crucial to containing the spread of the virus [1]. Immunization is another effective public health strategy. Vaccines prevent and control infectious disease outbreaks (2-4). After sequencing the SARS-CoV-2 genome, rapid vaccine development started in early 2020, leading to approved vaccines by the end of the year (5). However, vaccine effectiveness depends on both the uptake and individuals' willingness to be vaccinated. The decision to be vaccinated in general lies on a continuum of hesitancy, ranging from refusal to acceptance (6, 7). Various individual factors influence this decision, including gender, age, concerns about long-term effects, and risk perception defined by perceived susceptibility and perceived severity of disease (8, 9). Additionally, the decision is influenced by multiple levels – individual, interpersonal, community, and societal factors- as outlined in the socio-ecological framework (10-13). This comprehensive framework helps to understand that vaccination intention is shaped not only by individual factors but also by interactions with one's social environment, including interpersonal relationships and other community and societal factors (10-13).

The social environment includes communities and social networks, our social relationships. Social network members may influence each other's vaccination intentions and behaviors. A study in the United States demonstrated that individuals with family members and friends who did not support COVID-19 vaccinations were also less likely to be vaccinated against COVID-19 (14). Moreover, people who had no intention to vaccinate against COVID-19 were also less likely to be surrounded by network members who were performing or supporting preventive measures (15). Social support from network members is important in stimulating vaccination intention and uptake. Perceived social support from others is associated with a higher intention to vaccinate against COVID-19 (16). Previous studies have shown that social support was also positively associated with the uptake of other vaccinations such as influenza or pneumococcal vaccines (17, 18).

Most studies examining factors associated with COVID-19 vaccination intention have focused on either individual factors or (social) environmental factors such as social support or trust in governmental institutions (13, 17-21). However, social environmental factors, including social networks, encompass more than merely social support. Social networks can be described based on their structure, function, and quality (19-21). Structural social network characteristics include network size, i.e., the number of social relationships, and network diversity, which pertains to the variety of relationships (e.g., family, friends, neighbors, and colleagues). Network density indicates the interconnectedness between different types of relationships. Other structural aspects involve homogeneity of the network members in terms of age and gender, geographical proximity, and mode or frequency of contact. Functional social network characteristics encompass various forms of social support, including informational (advice), emotional (discussing important topics), or practical (help with jobs in or around the house) support (19, 21). Additionally, social strain, i.e., relationships perceived as burdensome, demanding, or involving criticism, along with the varying strengths of relationships (from strong to strained) can serve as proxies for assessing the quality of social networks (21, 22).

To the best of our knowledge, there is limited insight into the associations between COVID-19 vaccination intention and social environment factors including social network structure, function, and quality. In this study, we aimed to assess which individual and social environmental factors (interpersonal, community, and societal) are associated with COVID-19 vaccination intention in independently living adults aged 40 years and older. Gaining insight into the factors associated with vaccination intention helps better prepare for and respond to pandemics. It also highlights the importance of including the social environment in infection prevention strategies for pandemic preparedness.

METHODS

Study design and population

The research proposal of the current study was pre-registered (23) and relevant supportive materials are open access available. This cross-sectional study used data from the Dutch SaNAE (Social Network Assessment among Adults and Elderly) cohort (https://www.sanae-study.nl) and was reported according to the

STROBE guidelines (24). The SaNAE cohort includes community-dwelling adults aged 40 years and older living in Limburg, the Netherlands. Between August and November 2020, 5,001 people were invited to complete an online questionnaire.

Measurements

Dependent variables: COVID-19 vaccination intention

During data collection between August and November 2020, COVID-19 vaccines were not yet available, as they were still being developed, and approval from the European Medicines Agency (EMA) was pending (25). Hence, intention was measured by asking participants if they were planning on getting the COVID-19 vaccine if it became available. Answer categories were yes, I don't know (yet), and no.

Independent variables: individual factors

Individual factors included were sociodemographic characteristics, health, and health concerns (Fig. 1).

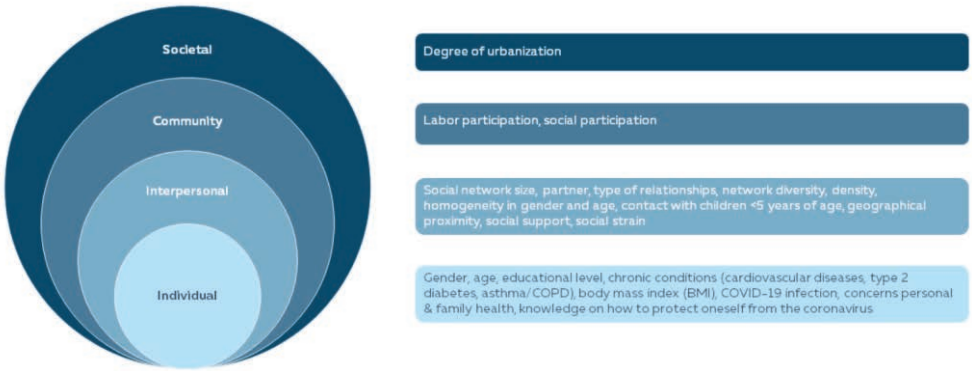

Figure 1. Overview of determinants of COVID-19 vaccination intention in the socio-ecological framework.

Sociodemographic characteristics

Sociodemographic variables included gender (men/women/other) and age. Educational attainment was categorized into three levels: less than vocational education (no education, primary education (not completed), and lower vocational education), vocational education (intermediate vocational and higher secondary education), and college or university degree (higher professional and university education) [26].

Health

Health was determined by participants reporting any chronic conditions such as cardiovascular diseases, type 2 diabetes mellitus, or asthma/chronic obstructive pulmonary disease (COPD). Body Mass Index (BMI) was calculated by dividing weight by height squared. Suspected SARS-CoV-2 infection was assessed by asking if they (think they) had been infected with SARS-CoV-2. Answer categories were yes, maybe, and no.

Health concerns

Several health concerns during the COVID-19 pandemic were assessed. Concerns about one's personal or family's health were assessed on a five-point Likert scale with answer categories being very unconcerned, unconcerned, neither concerned nor unconcerned, concerned, or very concerned. Knowledge of how to protect oneself from SARS-CoV-2 was assessed using the statement "I know how to protect myself from the coronavirus" and a five-point Likert scale with answer categories totally agree, agree, neutral, disagree, and totally disagree.

Independent variables: interpersonal factors

Social networks were measured using a name-generator questionnaire (27-29). A more detailed description of the name generator questionnaire with name interpreter items is available elsewhere (30-32). Participants were asked to provide the names of up to fifteen family members, ten friends, ten acquaintances, five other persons, and five healthcare professionals (HCP) who are important to them or provide social support, up to a maximum of 45 network members. Social network size was then calculated by tallying all listed network members. Social network size was further categorized based on quartiles and used as an indicator for social isolation (category 0–4 network members). Additional information about the network members was collected using name interpreter items which were then used to describe social network structure, function, and quality, as described below (see also Supplementary Table 1).

Social network structure

Partner status was determined by a yes/no question. Relationship types were evaluated by calculating the proportion of each type (family, friends, acquaintances, others, HCP) in the total network. Network diversity was categorized based on the presence of combinations of different relationship types. Network density was measured by how well friends and family know each

other, rated on a five-point scale. The homogeneity of social networks was assessed by the proportion of members of the same gender and age. Contact with children younger than five years of age was categorized by frequency (yes, daily or weekly; yes, monthly or less often; no), and living situation was determined by a single question, identifying those living alone. Geographical proximity was calculated by the proportion of network members living in the same house, within walking distance, less than thirty minutes away by car, more than thirty minutes away by car, or further away (Supplementary Table 1) (27-29).

Social network function

The proportion of network members who provided informational support was calculated by dividing the total number of network members providing informational support by the total network size. The proportion of network members who provide emotional support was calculated by dividing the total number of network members providing emotional support by the total network size. Lastly, the proportion of network members who provide practical support was calculated similarly (27-29).

Social network quality

The proportion of network members with whom there is social strain was calculated by dividing the sum of the number of network members who are demanding, straining, or criticizing by the total network size. The proportion of network members with whom the relationship is good was calculated by dividing the number of network members with whom the relationship is good by the total network size (27-29).

Labor participation

Labor participation was assessed by asking participants if they were employed, (e.g., contract workers, freelancers), unemployed (due to incapacity, students or homemakers), or retired.

Social participation

Participation in social activities was evaluated by asking participants to report club memberships. This included sports clubs (e.g., sports or walking clubs), cultural organizations (music, dance, theater, carnival organizations), volunteer work, and other memberships.

Degree of urbanization

The 4-digit postal codes were converted into the degree of urbanization based on address density: rural areas (<500 addresses per km^2), hardly urbanized areas (500 to 1000 addresses per km^2), moderately urbanized areas (1000–1500 addresses per km^2), strongly or extremely urbanized areas (>1500 addresses per km^2) (33, 34).

Statistical analyses

Descriptive analyses were performed to describe the study population. Univariable logistic regression analyses were conducted with dummy variables of COVID-19 vaccination intention as the outcome variables (yes versus no, yes versus unsure, and unsure versus no), and all individual, interpersonal, community, and societal separately as independent categorical variables (except for age, BMI, network size, and proportions concerning network members, which were included as continuous variables). Correlations between variables were assessed and no multicollinearity was observed (all correlations < 0.7, VIF < 10, and tolerance > 0.1). All factors were then added stepwise per level in a multivariable logistic regression model using forward selection. Individual determinants were added in the first block, as these individual factors are most proximal to intention. Then, interpersonal, community, and societal factors were included to assess associations on all different levels. A p-value < 0.05 indicated statistical significance and all analyses were performed using IBM SPSS Statistics (version 27.0).

Ethics statement

The Medical Ethical Committee of Maastricht University approved this study (METC 2018-0698, 2019-1035, and 2020-2266). Participants gave electronic informed consent.

RESULTS

Study population

Of the 5,001 invited participants, 3,505 (67 %) completed the questionnaire. Respondents were slightly older (mean difference 2.2 years, $p < 0.001$), and more likely to have obtained a college or university degree ($\chi^2 = 25{,}117$; df = 2; $p < 0.001$), but did not differ from non-responders in gender ($\chi^2 = 0{,}726$;

df = 1; $p = 0.394$) or network size (mean difference −0.4, $p = 0.112$). In total, complete data were available for 3,396 participants. Among these participants, 55 % were men and the mean age was 67 years. 59 % of the participants reported intention to vaccinate against COVID-19, 35 % were unsure, and 6 % had no intention to vaccinate against COVID-19 (Table 1).

Table 1. Characteristics of the SaNAE study population in 2020 (n = 3,396).

	COVID-19 vaccination intention			
	Yes	Unsure	No	
	59% (201/3396	35% (1175/3396)	6% (220/3396	
Individual factors				
Background characteristics				
Gender				$p < 0.001$
Men	63 (1259/2001)	46 (536/1175)	36 (79/220)	
Women	37 (742/2001)	54 (639/1175)	64 (141/220)	
Age	67.3 (9.4)	62.6 (9.6)	59.6 (9.1)	$p < 0.001$
Educational attainment				$p < 0.001$
Less than vocational training	26 (529/2001)	28 (323/1175)	29 (63/220)	
Vocational training	25 (504/2001)	35 (412/1175)	42 (93/220)	
College or university degree	48 (968/2001)	37 (440/1175)	29 (64/220)	
Health				
Chronic conditions [a]	32 (643/2001)	25 (290/1175)	25 (54/220)	$p < 0.001$
Body Mass Index (BMI)	26.6 (4.4)	27.0 (4.9)	26.9 (4.5)	$p = 0.101$
(suspected) SARS-CoV-2 infection[b]				$p = 0.002$
Yes/maybe	18 (359/2001)	22 (263/1175)	25 (54/220)	
No	82 (1642/2001)	78 (166/1175)	75 (166/220)	
Health concerns				

Concerns about personal health				$p < 0.001$
(very) Concerned	26 (515/2001)	18 (210/1175)	11 (25/220)	
Neutral	36 (713/2001)	40 (465/1175)	30 (66/220)	
(very) Unconcerned	39 (773/2001)	43 (500/1175)	59 (129/220)	
Concerns about family health				$p < 0.001$
(very) Concerned	41 (804/2001)	35 (402/1175)	27 (60/220)	
Neutral	36 (712/2001)	39 (457/1175)	32 (70/220)	
(very) Unconcerned	24 (485/2001)	27 (316/1175)	41 (90/220)	
Knowledge of how to protect oneself from SARS-CoV-2				$p < 0.001$
(totally) agree	87 (1731/2001)	77 (909/1175)	76 (167/220)	
Neutral	11 (223/2001)	20 (238/1175)	21 (47/220)	
(totally) disagree	2 (47/2001)	3 (28/1175)	3 (6/220)	
Interpersonal factors				
Social network structure				
Network size (including health care professionals)	10.3 (7.3)	10.5 (7.3)	9.7 (7.0)	$p = 0.339$
0–4 network members	25 (507/2001)	25 (290/1175)	26 (58/220)	$p = 0.387$
5–8 network members	26 (514/2001)	24 (276/1175)	29 (64/220)	
9–12 network members	20 (402/2001)	22 (253/1175)	16 (36/220)	
≥13 network members	29 (578/2001)	30 (356/1175)	28 (62/220)	
Partner				$p = 0.079$

Yes	80 (1604/2001)	78 (921/1175)	74 (163/220)	
No	20 (397/2001)	22 (254/1175)	26 (57/220)	
Type of relationships (proportion of network members:)				
Family members	51.1 (24.9)	51.2 (25.1)	51.9 (27.0)	$p = 0.907$
Friends	24.0 (18.2)	24.9 (18.3)	26.2 (21.3)	$p = 0.167$
Acquaintances	16.0 (15.5)	16.1 (15.3)	14.4 (14.6)	$p = 0.294$
Extra members	4.8 (11.5)	4.6 (10.4)	4.7 (10.5)	$p = 0.853$
Healthcare professionals (HCP)	4.2 (9.4)	3.3 (8.5)	2.9 (7.9)	$p = 0.011$
Network diversity				$p = 0.248$
No family, but friends, acquaintances, others, or HCP	2 (38/2001)	2 (19/1175)	3 (6/220)	
Only family, no friends/acquaintances/others/HCP	12 (241/2001)	13 (147/1175)	15 (33/220)	
Family and friends, no acquaintances/others/HCP	14 (270/2001)	15 (178/1175)	16 (35/220)	
Family and friends and acquaintances/others/HCP	62 (1230/2001)	62 (730/1175)	58 (127/220)	
Family and acquaintances/others/HCP, no friends	11 (222/2001)	9 (101/1175)	9 (19/220)	
Network density (my friends know my family)				$p = 0.851$
Yes	75 (1507/2001)	75 (880/1175)	74 (162/220)	
No	25 (494/2001)	25 (295/1175)	26 (58/220)	
Proportion of network members of the same gender	52.1 (22.6)	55.8 (23.9)	55.2 (22.7)	$p < 0.001$
Proportion of network members of the same age	39.4 (23.9)	39.9 (23.8)	38.4 (24.1)	p = 0.674
Contact with children < 5 years of age				$p = 0.002$

Yes, daily or weekly	20 (405/2001)	22 (261/1175)	27 (59/220)	
Yes, monthly or less often	20 (392/2001)	24 (279/1175)	18 (40/220)	
No	60 (1204/2001)	54 (635/1175)	55 (121/220)	
Living alone	21 (413/2001)	21 (241/1175)	25 (56/220)	$p = 0.229$
Geographical proximity (proportion of network members who live:)				
In the same house	15.8 (20.7)	16.3 (21.2)	18.6 (24.1)	$p = 0.173$
Within walking distance	29.0 (25.5)	27.5 (24.4)	28.1 (26.1)	$p = 0.267$
Less than 30 min away	35.7 (27.0)	38.4 (26.4)	38.7 (28.5)	$p = 0.014$
More than 30 min away	10.2 (16.3)	9.8 (15.9)	8.3 (14.1)	$p = 0.234$
Further away	9.1 (16.1)	7.8 (14.8)	6.0 (14.6)	$p = 0.005$
Social network function				
Proportion of network members who provide informational support	49.3 (33.4)	50.6 (33.5)	46.9 (34.2)	$p = 0.279$
Proportion of network members who provide emotional support	63.4 (31.2)	61.4 (31.4)	62.8 (31.6)	$p = 0.195$
Proportion of network members who provide practical support	22.3 (24.9)	21.5 (23.9)	21.5 (23.0)	$p = 0.669$
Social network quality				
Proportion of network members with whom the relationship is demanding, straining, or criticizing (social strain)	9.9 (18.5)	11.3 (19.5)	9.8 (15.7)	$p = 0.102$
Proportion of network members with whom there is a good relationship:	94.9 (23.0)	93.2 (17.6)	92.7 (14.0)	$p = 0.038$
Community factors				
Labor participation				
Employed	26 (515/2001)	42 (498/1175)	53 (117/220)	$p < 0.001$

Retired	52 (1034/2001)	34 (398/1175)	21 (47/220)	
Unemployed	23 (452/2001)	24 (279/1175)	26 (56/220)	
Social participation (club membership)				
Sports club membership	33 (625/2001)	31 (369/1175)	28 (61/220)	$p = 0.313$
Music organization membership	15 (306/2001)	12 (139/1175)	12 (27/220)	$p = 0.019$
Volunteer work	16 (323/2001)	13 (154/1175)	10 (22/220)	$p = 0.008$
Other (religious groups, talking groups, etc.)	25 (509/2001)	22 (259/1175)	21 (45/220)	$p = 0.044$
Societal factors				
Degree of urbanization				$p < 0.001$
Rural areas	28 (554/2001)	28 (334/1175)	19 (42/220)	
Hardly urbanized areas	25 (493/2001)	23 (270/1175)	21 (47/220)	
Moderately urbanized areas	19 (372/2001)	17 (204/1175)	26 (57/220)	
(Extremely) strongly urbanized areas	29 (582/2001)	31 (367/1175)	34 (74/220)	

Numbers are presented in % (n/N) or mean (standard deviation).
$^{\#}p < 0.100$, $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.
[a] Chronic conditions include self-reported cardiovascular diseases, type 2 diabetes mellitus, asthma, and chronic obstructive pulmonary disease (COPD).
[b] SARS-CoV-2 infection: Severe Acute Respiratory Syndrome Coronavirus 2.

Among participants with the intention to vaccinate against COVID-19, 26 % were concerned about personal health, 41 % were concerned about family health, and 87 % indicated knowing what to do to protect themselves. Among participants who were unsure or had no intention to get vaccinated, 77 % and 76 % respectively, indicated knowing what to do to protect themselves.

Overall social network characteristics

On average, participants, regardless of intention to vaccinate, had ten network members. Of these, slightly more than half were family members, a quarter were friends, and the remainder were acquaintances, neighbors, colleagues, informal healthcare professionals, or others (Table 1). Participants reported receiving informational support (information or advice) from half of their network members and emotional support (discussing important topics or health status) from just over 60 % of their network members.

Determinants of COVID-19 vaccination intention

COVID-19 vaccination intention: yes versus no

Individual factors associated with COVID-19 vaccination intention versus no intention were gender (men), older age, having obtained a college or university degree, having chronic conditions, having no previous (suspected) COVID-19 infection, having concerns about one's personal and family health, and knowledge of how to protect oneself from the virus (Table 2). Interpersonal factors associated with COVID-19 vaccination intention were having a partner and having a larger proportion of network members who live far away. Community factors associated with COVID-19 intention were being unemployed or retired (versus employed) and doing volunteer work. Living in rural areas was a societal factor associated with COVID-19 intention (Table 2).

Table 2. Univariable logistic regression analyses of individual, interpersonal, community, and societal factors and COVID-19 vaccination intention.

	COVID-19 vaccination intention		
	Yes versus no	Yes versus unsure	Unsure versus no
	OR (95%CI)	OR (95%CI)	OR (95%CI)
Individual factors			
Background characteristics			
Gender			
Men	**3.03 (2.27–4.05)*** **	**2.02 (1.75–2.34)*** **	**1.50 (1.11–2.02)** **
Women	Ref	Ref	Ref
Age	**1.08 (1.07–1.10)*** **	**1.05 (1.04–1.06)*** **	**1.03 (1.02–1.05)*** **
Educational attainment			
Less than vocational training	Ref	Ref	Ref
Vocational training	**0.65 (0.46–0.91)***	**0.75 (0.62–0.90)** **	0.86 (0.61–1.23)
College or university degree	**1.80 (1.25–2.59)** **	**1.34 (1.12–1.61)** **	1.34 (0.92–1.95)
Health			
Chronic conditions [a]	**1.46 (1.06–2.01)***	**1.45 (1.23–1.70)*** **	1.01 (0.72–1.41)
Body Mass Index (BMI)	0.99 (0.96–1.02)	**0.98 (0.97–1.00)***	1.00 (0.97–1.04)
(suspected) SARS-CoV-2 infection [b]			
Yes/maybe	Ref	Ref	Ref
No	**1.49 (1.07–2.07)***	**1.32 (1.10–1.58)** **	1.13 (0.81–1.58)
Health concerns			

Concerns about personal health			
(very) Concerned	**3.44 (2.21–5.35)*** **	**1.59 (1.30–1.93)*** **	**2.17 (1.37–3.43)*** **
Neutral	**1.80 (1.32–2.47)*** **	0.99 (0.84–1.17)	**1.82 (1.32–2.51)*** **
(very) Unconcerned	Ref	Ref	Ref
Concerns about family health			
(very) Concerned	**2.49 (1.76–3.51)*** **	**1.30 (1.08–1.57)** **	**1.91 (1.33–2.73)*** **
Neutral	**1.89 (1.35–2.63)*** **	1.02 (0.84–1.22)	**1.86 (1.32–2.62)*** **
(very) Unconcerned	Ref	Ref	Ref
Knowledge of how to protect oneself from SARS-CoV-2			
(totally) Agree	**2.19 (1.54–3.11)*** **	**2.03 (1.67–2.48)*** **	1.08 (0.76–1.53)
Neutral	Ref	Ref	Ref
(totally) Disagree	1.65 (0.67–4.09)	**1.79 (1.08–2.96)***	0.92 (0.36–2.35)
Interpersonal factors [c]			
Social network structure			
Network size (including health care professionals)	1.01 (0.99–1.03)	1.00 (0.99–1.01)	1.02 (1.00–1.04)
Partner			
Yes	**1.41 (1.03–1.95)***	1.11 (0.93–1.33)	1.27 (0.91–1.77)
No	Ref	Ref	Ref
Type of relationships (proportion of network members:)			
Family members	1.00 (0.56–1.79)	0.95 (0.69–1.29)	1.07 (0.58–1.96)

Friends	0.50 (0.24–1.02)#	0.79 (0.53–1.19)	0.63 (0.30–1.33)
Acquaintances	1.75 (0.66–4.67)	0.97 (0.59–1.58)	1.80 (0.64–5.10)
Extra members	1.02 (0.30–3.42)	1.24 (0.64–2.40)	0.77 (0.20–2.97)
Healthcare professionals (HCP)	5.84 (0.96–35.47)#	**2.98 (1.29–6.87)***	1.86 (0.31–11.19)
Network diversity			
No family, but friends, acquaintances, others, or HCP	0.87 (0.34–2.21)	1.22 (0.68–2.20)	0.71 (0.26–1.92)
Only family, no friends/acquaintances/others/HCP	Ref	Ref	Ref
Family and friends, no acquaintances/others/HCP	1.06 (0.64–1.75)	0.93 (0.70–1.22)	1.14 (0.68–1.93)
Family and friends and acquaintances/others/HCP	1.33 (0.88–1.99)	1.03 (0.82–1.29)	1.29 (0.85–1.97)
Family and acquaintances/others/HCP, no friends	1.60 (0.88–2.90)	1.34 (0.98–1.83) #	1.19 (0.64–2.22)
Network density (my friends know my family)			
Yes	1.09 (0.80–1.50)	1.02 (0.87–1.21)	1.07 (0.77–1.48)
No	Ref	Ref	Ref
Proportion of network members with different gender	1.88 (0.99–3.57)#	**2.02 (1.47–2.77)*****	0.90 (0.49–1.66)
Proportion of network members of the same age	1.19 (0.67–2.12)	0.92 (0.68–1.25)	1.27 (0.70–2.30)
Contact with children < 5 years of age			
Yes, daily or weekly	Ref	Ref	Ref
Yes, monthly or less often	1.43 (0.93–2.18)	0.91 (0.73–1.13)	1.19 (0.84–1.67)
No	**1.45 (1.04–2.02)***	**1.22 (1.02–1.47)***	**1.58 (1.02–2.44)***
Living alone	0.76 (0.55–1.05)#	1.01 (0.84–1.21)	0.76 (0.54–1.06)

Geographical proximity (proportion of network members who live:)			
In the same house	0.61 (0.31–1.19)	0.83 (0.57–1.20)	0.74 (0.37–1.46)
Within walking distance	1.11 (0.64–1.92)	1.28 (0.96–1.72)#	0.88 (0.49–1.56)
Less than 30 min away	0.65 (0.39–1.07)	**0.69 (0.53–0.91)****	0.89 (0.52–1.53)
More than 30 min away	2.10 (0.81–5.48)	1.18 (0.75–1.86)	1.81 (0.67–4.87)
Further away	**3.86 (1.33–11.21)***	**1.74 (1.09–2.79)***	2.18 (0.75–6.40)
Social network function			
Proportion of network members who provide informational support	1.28 (0.84–1.94)	0.89 (0.72–1.10)	1.42 (0.93–2.18)
Proportion of network members who provide emotional support	1.09 (0.70–1.70)	1.23 (0.98–1.55) #	0.89 (0.56–1.40)
Proportion of network members who provide practical support	1.24 (0.69–2.22)	1.12 (0.82–1.51)	1.12 (0.61–2.09)
Social network quality			
Proportion of network members with whom the relationship is demanding, straining, or criticizing (social strain)	0.98 (0.45–2.10)	**1.47 (1.01–2.14)***	0.64 (0.28–1.45)
Proportion of network members with whom there is a good relationship:	2.25 (0.95–5.33)#	**1.76 (1.11–2.78)***	1.14 (0.50–2.62)
Community factors			
Labor participation			
Employed	Ref	Ref	Ref
Retired	**5.00 (3.51–7.13)*****	**2.51 (2.12–2.98)*****	**1.99 (1.38–2.86)*****
Unemployed	**1.83 (1.30–2.58)*****	**1.57 (1.29–1.90)*****	1.17 (0.82–1.66)
Social participation (club membership)			

Sports club membership	1.26 (0.92–1.72)	1.06 (0.90–1.23)	1.19 (0.87–1.64)
Music organization membership	1.29 (0.85–1.97)	**1.35 (1.09–1.67)****	0.96 (0.62–1.49)
Volunteer work	**1.73 (1.10–2.73)***	**1.28 (1.04–1.57)***	1.36 (0.85–2.18)
Other (religious groups, talking groups, etc.)	1.33 (0.94–1.87)	**1.21 (1.02–1.43)***	1.10 (0.77–1.57)
Societal factors			
Degree of urbanization			
Rural areas	**1.68 (1.13–2.49)***	1.05 (0.87–1.26)	**1.60 (1.07–2.41)***
Hardly urbanized areas	1.33 (0.91–1.96)	1.15 (0.95–1.40)	1.16 (0.78–1.72)
Moderately urbanized areas	0.83 (0.57–1.20)	1.15 (0.93–1.43)	0.72 (0.49–1.06)#
(Extremely) strongly urbanized areas	Ref	Ref	Ref

#$p < 0.100$, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.
OR (95 % CI) = Odds Ratio (95 % Confidence Interval).
[a] Chronic conditions include self-reported cardiovascular diseases, type 2 diabetes mellitus, asthma, and chronic obstructive pulmonary disease (COPD).
[b] SARS-CoV-2 infection: Severe Acute Respiratory Syndrome Coronavirus 2.
[c] All proportion variables are adjusted for network size.

COVID-19 vaccination intention: yes versus unsure

Individual factors associated with COVID-19 vaccination intention versus being unsure were gender (men), older age, having obtained a college or university degree, having chronic conditions, having no previous (suspected) COVID-19 infection, being concerned about personal and family health and knowledge of how to protect oneself from the virus (Table 2). A higher BMI was inversely associated with COVID-19 vaccination intention. Interpersonal factors associated were having a larger proportion of network members who were healthcare professionals, a larger proportion of network members of a different gender, no contact with children younger than five years of age, a larger proportion of network members living further away, a larger proportion of network members with whom there is no social strain, and a larger proportion with whom the relationship is good. Community factors associated with COVID-19 intention were being retired or unemployed (versus employment), having a music organization membership, doing volunteer work, or having other club memberships.

COVID-19 vaccination intention: unsure vs no

Individual factors associated with being unsure about getting a COVID-19 vaccination versus no intention were gender (men), older age, and having concerns about one's personal and family health (Table 2). Not having contact with children younger than five years of age was an interpersonal factor associated with being unsure about getting a vaccination. A community factor associated with being unsure was being retired (versus employed). Living in rural areas was a societal factor associated with being unsure about getting a COVID-19 vaccination.

Multivariable logistic regression models COVID-19 vaccination intention

After including all variables in the multivariable models, the individual factors gender, age, and concerns about family health remained significantly associated with COVID-19 vaccination intention compared to no intention (Table 3), intention compared to being unsure (Table 4), and being unsure compared to no intention (Table 5). Additionally, educational attainment, concerns about personal health, and knowledge of how to protect oneself from the virus remained associated with both intention versus no intention and intention versus being

unsure. Interpersonal factors such as network size and proportion of informational supporters were associated with intention versus no intention, whereas the proportion of emotional supporters was associated with intention versus being unsure. Furthermore, club membership in a music organization, a community factor, was associated with intention versus being unsure. Lastly, at the societal level, living in rural areas was associated with intention or being unsure versus no intention.

Table 3. Multivariable logistic regression analyses of individual, interpersonal, community, and societal factors and COVID-19 intention (yes versus no).

	Model A: COVID-19 vaccination intention – yes versus no (n = 2,221)			
	Block I: OR (95%CI)	**Block II: OR (95%CI)**	**Block III: OR (95%CI)**	**Block IV: OR (95%CI)**
Individual factors				
Background characteristics				
Gender				
Men	**2.36 (1.72–3.22)*****	**2.53 (1.83–3.50)*****	**2.53 (1.83–3.50)*****	**2.52 (1.82–3.49)*****
Women	Ref	Ref	Ref	Ref
Age in years	**1.08 (1.06–1.10)*****	**1.09 (1.07–1.11)*****	**1.09 (1.07–1.11)*****	**1.09 (1.07–1.11)*****
Educational attainment				
Less than vocational training	Ref	Ref	Ref	Ref
Vocational training	0.96 (0.65–1.40)	0.92 (0.63–1.36)	0.92 (0.63–1.36)	0.95 (0.64–1.39)
College or university degree	**2.38 (1.60–3.55)*****	**2.20 (1.46–3.31)*****	**2.20 (1.46–3.31)*****	**2.25 (1.49–3.39)*****
Health concerns				
Concerns about own health				
(very) concerned	**2.64 (1.52–4.57)*****	**2.81 (1.61–4.88)*****	**2.81 (1.61–4.88)*****	**2.78 (1.60–4.84)*****
neutral	1.52 (0.99–2.34)$^{\#}$	**1.59 (1.03–2.45)***	**1.59 (1.03–2.45)***	1.54 (1.00–2.39)$^{\#}$
(very) unconcerned	Ref	Ref	Ref	Ref
Concerns about family's health				
(very) concerned	**2.02 (1.27–3.23)****	**1.96 (1.22–3.13)****	**1.96 (1.22–3.13)****	**1.95 (1.22–3.12)****
neutral	**1.60 (1.02–2.50)***	1.55 (0.98–2.43) $^{\#}$	1.55 (0.98–2.43)$^{\#}$	1.55 (0.98–2.44) $^{\#}$

(very) unconcerned	Ref	Ref	Ref	Ref
Knowledge of how to protect oneself from SARS-CoV-2[a]				
(totally) agree	**2.88 (1.94–4.28)*** **	**2.86 (1.92–4.27)*** **	**2.86 (1.92–4.27)*** **	**2.92 (1.95–4.38)*** **
neutral	Ref	Ref	Ref	Ref
(totally) disagree	2.01 (0.72–5.63)	1.93 (0.69–5.41)	1.93 (0.69–5.41)	1.95 (0.69–5.53)
Interpersonal factors				
Social network structure				
Number of network members		**1.03 (1.01–1.06)***	**1.03 (1.01–1.06)***	**1.03 (1.00–1.05)***
Partner		**1.50 (1.05–2.14)***	**1.50 (1.05–2.14)***	1.36 (0.95–1.96)#
Social network function				
Proportion of informational supporters		**1.78 (1.12–2.83)***	**1.78 (1.12–2.83)***	**1.81 (1.13–2.89)***
Community factors				
No factors included				
Societal factors				
Degree of urbanization				
Rural areas				**1.93 (1.25–2.99)** **
Hardly urbanized areas				1.52 (1.00–2.33)#
Moderately urbanized areas				0.97 (0.64–1.46)
(extremely) Strongly urbanized areas				Ref

Block I: Individual factors, Block II: Individual + Interpersonal factors, Block III: Individual + Interpersonal + community factors, Block IV: Individual + Interpersonal + community + societal factors. OR (95 % CI) = Odds Ratio (95 % Confidence Interval). #$p < 0.100$, * $p < 0.05$, **$p < 0.01$, ***$p < 0.001$. [a] SARS-CoV-2 Infection: Severe Acute Respiratory Syndrome Coronavirus 2.

Table 4. Multivariable logistic regression analyses of individual, interpersonal, community, and societal factors and COVID-19 intention (yes versus unsure).

	Model B: COVID-19 vaccination intention – yes versus unsure (n = 3,176)			
	Block I: OR (95%CI)	**Block II: OR (95%CI)**	**Block III: OR (95%CI)**	**Block IV: OR (95%CI)**
Individual factors				
Background characteristics				
Gender				
Men	**1.75 (1.50–2.05)*****	**1.80 (1.53–2.11)*****	**1.79 (1.52–2.10)*****	**1.79 (1.52–2.10)*****
Female	Ref	Ref	Ref	Ref
Age in years	**1.05 (1.04–1.06)*****	**1.05 (1.04–1.06)*****	**1.05 (1.04–1.06)*****	**1.05 (1.04–1.06)*****
Educational attainment				
Less than vocational training	Ref	Ref	Ref	Ref
Vocational training	0.94 (0.77–1.16)	0.93 (0.75–1.14)	0.92 (0.75–1.14)	0.92 (0.75–1.14)
College or university degree	**1.55 (1.28–1.88)*****	**1.51 (1.24–1.84)*****	**1.50 (1.23–1.83)*****	**1.50 (1.23–1.83)*****
Health concerns				
Concerns about own health				
(very) concerned	**1.42 (1.10–1.83)****	**1.41 (1.09–1.82)****	**1.41 (1.09–1.82)****	**1.41 (1.09–1.82)****
neutral	0.99 (0.79–1.23)	0.99 (0.79–1.23)	0.98 (0.79–1.22)	0.98 (0.79–1.22)
(very) unconcerned	Ref	Ref	Ref	Ref
Concerns about family's health				
(very) concerned	**1.43 (1.11–1.84)****	**1.42 (1.11–1.83)***	**1.42 (1.11–1.83)****	**1.42 (1.11–1.83)****
neutral	1.13 (0.89–1.45)	1.13 (0.89–1.44)	1.13 (0.89–1.45)	1.13 (0.89–1.45)

(very) unconcerned	Ref	Ref	Ref)	Ref)
Knowledge of how to protect oneself from SARS-CoV-2[a]				
(totally) agree	**2.40 (1.93–2.97)*** **	**2.36 (1.90–2.92)*** **	**2.37 (1.91–2.94)*** **	**2.37 (1.91–2.94)*** **
neutral	Ref	Ref	Ref	Ref
(totally) disagree	**1.73 (1.02–2.94)***	1.66 (0.99–2.87)#	**1.72 (1.01–2.93)***	**1.72 (1.01–2.93)***
Interpersonal factors				
Social network structure				
Number of network members		1.01 (1.00–1.02)	1.01 (1.00–1.02)	1.01 (1.00–1.02)
Contact children < 5 years of age				
No		1.10 (0.91–1.34)	1.11 (0.91–1.35)	1.11 (0.91–1.35)
Yes, daily or weekly		Ref	Ref	Ref
Yes, monthly or less often		0.85 (0.67–1.07)	0.86 (0.68–1.08)	0.86 (0.68–1.08)
Social network function				
Proportion of emotional supporters		**1.31 (1.02–1.67)***	**1.31 (1.03–1.68)***	**1.31 (1.03–1.68)***
Community factors				
Social participation				
Club membership music organization			**1.27 (1.01–1.60)***	**1.27 (1.01–1.60)***
Societal factors				
No factors included				

Block I: Individual factors, Block II: Individual + Interpersonal factors, Block III: Individual + Interpersonal + community factors, Block IV: Individual + Interpersonal + community + societal factors. OR (95 % CI) = Odds Ratio (95 % Confidence Interval). #$p < 0.100$, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. [a] SARS-CoV-2 Infection: Severe Acute Respiratory Syndrome Coronavirus 2.

Table 5. Multivariable logistic regression analyses of individual, interpersonal, community, and societal factors and COVID-19 intention (unsure vs no).

	Model C: COVID-19 vaccination intention – unsure versus no (n = 1,395)			
	Block I: OR (95%CI	**Block II: OR (95%CI)**	**Block III: OR (95%CI)**	**Block IV: OR (95%CI)**
Individual factors				
Background characteristics				
Gender				
Men	**1.42 (1.04–1.93)***	**1.52 (1.10–2.08)***	**1.52 (1.10–2.08)***	**1.58 (1.15–2.18)****
Women	Ref	Ref	Ref	Ref
Age in years	**1.04 (1.02–1.05)*****	**1.04 (1.02–1.05)*****	**1.04 (1.02–1.05)*****	**1.04 (1.02–1.05)*****
Educational attainment				
Less than vocational training	Ref	Ref	Ref	Ref
Vocational training	1.02 (0.71–1.48)	0.98 (0.68–1.42)	0.98 (0.68–1.42)	0.97 (0.67–1.41)
College or university degree	**1.65 (1.12–2.45)***	**1.53 (1.02–2.28)***	**1.53 (1.02–2.28)***	1.47 (0.98–2.20)#
Health concerns				
Concerns about family's health				
(very) concerned	**2.26 (1.56–3.27)*****	**2.25 (1.55–3.25)*****	**2.25 (1.55–3.25)*****	**2.36 (1.62–3.43)*****
neutral	**1.97 (1.39–2.80)*****	**1.99 (1.40–2.82)*****	**1.99 (1.40–2.82)*****	**1.96 (1.38–2.80)*****
(very) unconcerned	Ref	Ref	Ref	Ref
Interpersonal factors				
Social network structure				
Number of network members		1.02 (1.00–1.04)#	1.02 (1.00–1.04)#	1.02 (1.00–1.04)

Community factors	
No factors included	
Societal factors	
Degree of urbanization	
Rural areas	**1.69 (1.11–2.57)***
Hardly urbanized areas	1.17 (0.78–1.76)
Moderately urbanized areas	0.73 (0.49–1.08)
(extremely) strongly urbanized areas	Ref

Block I: individual factors, Block II: individual + interpersonal factors, Block III: individual + interpersonal + community factors, Block IV: individual + interpersonal + community + societal factors.
OR (95 % CI) = Odds Ratio (95 % Confidence Interval).
$^{\#}p < 0.100$, $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

DISCUSSION

In this study, we assessed associations between individual, interpersonal, community, and societal factors and COVID-19 vaccination intention among adults aged 40 years and older living independently in the Netherlands. Of all participants, 59 % had the intention to get a COVID-19 vaccination if it would become available, 35 % were unsure, and 6 % had no intention.

Individual factors associated with COVID-19 vaccination intention (yes versus no) included sociodemographic characteristics such as gender, age, and educational attainment. Men, older individuals, and those who had obtained a college or university degree were more likely to have the intention to get a COVID-19 vaccination. Gender and age were also associated with having intention versus being unsure and being unsure versus no intention. Additionally, educational attainment was associated with having the intention versus being unsure. These findings align with previous studies that identified sociodemographic characteristics as significant predictors of COVID-19 vaccination intention (35-39). The higher levels of intention observed among men and older individuals may be explained by their increased risk of contracting SARS-CoV-2, experiencing more severe infections, and facing higher mortality rates (40-42).

Moreover, concerns about personal and family health and knowledge of how to protect oneself from SARS-CoV-2 were associated with COVID-19 vaccination intention as opposed to being unsure. Previous studies have established that individuals worried about their health, those more vulnerable, and those at higher risk for SARS-CoV-2 infection were more willing to get vaccinated (37). Additionally, concerns about family health, in terms of potential COVID-19, were also associated with being more willing to vaccinate against COVID-19 (43). These findings suggest that concerns about personal and family health contribute to higher vaccination intentions, highlighting the importance of achieving herd immunity to safeguard social network members (44).

In addition to individual factors, interpersonal, community, and societal factors such as social support, club memberships, and degree of urbanization, were also associated with COVID-19 vaccination intention. Individuals who had a larger network size and a larger proportion of network members who provide

informational support were more likely to have the intention to vaccinate against COVID-19 (versus no intention), and those who had a larger proportion of emotional supporters within the network were also more likely to have the intention to vaccinate against COVID-19 (versus being unsure). Previous studies have already established that higher perceived social support is associated with willingness to vaccinate and higher uptake of the COVID-19 vaccination (45, 46). This might be explained by the theory of strong and weak ties by Granovetter (47), which postulated that weaker social ties (e.g., acquaintances or new network members) play an important role in the provision of information. However, in the current study, it remained unknown what kind of information was exchanged and whether this was related to vaccination intention. Higher levels of social support and increased social contact may also expose individuals to diverse views on COVID-19, helping them assess their own risk and need for the vaccine (45). The social support roles of the network members emphasize the need to strengthen or expand social networks to have larger and more diverse networks in which different types of social support are provided, especially in times of a pandemic.

Lastly, participants living in rural areas versus those living in urban areas were more likely to have the intention or be unsure of getting a COVID-19 vaccination (versus no intention). These results are inconsistent with previous studies assessing COVID-19 vaccination intention and urban–rural differences. Several studies have reported that people living in rural areas are less willing to vaccinate or have lower actual vaccination rates (48, 49). An explanation for these contradicting results might be related to the network composition for middle-aged and older adults in the Southern part of the Netherlands. Individuals living in rural areas tended to have larger and more diverse social networks with more social supporters compared to those living in urban areas (31). We suggest future research take a neighborhood-specific approach.

Implications

The various factors identified in this study present opportunities for health promotion and improved pandemic preparedness. These key characteristics associated with vaccination intention can be incorporated into a practical toolkit to inform researchers, healthcare professionals, and policymakers to identify sociodemographic groups with potentially low vaccination intentions, allowing for a focused approach. One example might be a neighborhood-specific approach

to promote health behaviors such as vaccination. For instance, mobile vaccination buses were introduced during the COVID-19 pandemic to increase vaccine uptake in neighborhoods with low vaccination rates (50). Additionally, offering vaccinations at more accessible locations within communities, such as pharmacies, could contribute to increasing vaccination intention and uptake (51, 52).

In addition to individual factors, interpersonal factors such as social network size, and informational, and emotional social support were evident, emphasizing the need to strengthen and expand social networks and mobilize social support roles within the network. Strengthening and expanding social networks is particularly relevant for pandemic preparedness, as large, diverse, and supportive social networks can act as buffers during stressful times, such as pandemics (31, 53). Moreover, networks are valuable at all times, contributing to overall health, well-being, and resilience (21). While directly modifying social networks might be challenging, we argue that they might be influenced indirectly through policy interventions. For example, policies can address other environmental factors such as important local influencers in communities (50) or implementing changes to the physical environment, thereby enhancing the social environment and creating opportunities for social interaction.

Strengths and limitations

The strengths of this study are the inclusion of multiple levels of the socio-ecological model. In doing so, social networks were measured using a name generator questionnaire which is a reliable method for a detailed assessment of social networks, especially in larger surveys (27-29). With this method, a distinction in social network characteristics can be made, allowing for the inclusion of a broad range of social network aspects and differentiating between structure, function, and quality of social networks rather than just focusing on network size and social support. However, limitations should be mentioned as well. During the period of data collection, vaccines were still in development. Therefore, it was not possible to include actual vaccination uptake in this study. Future studies should investigate whether the individual, interpersonal, community, and societal factors identified in this study are also associated with actual COVID-19 vaccination uptake. Furthermore, middle-aged and older adults were included in the current study. External validity is therefore restricted to this age group and statements about younger individuals should not be made.

Conclusion

In the present study, we aimed to assess which individual, interpersonal, community, and societal factors are associated with COVID-19 vaccination intention. Key individual determinants include various sociodemographic characteristics, concerns about one's personal and family health, and knowledge of how to protect oneself from the virus. Beyond individual factors, informational and emotional social support at the interpersonal levels also plays a significant role. These findings suggest that health promotion and vaccination communication strategies should focus on these factors and highlight the importance of organizing social networks to mobilize social support, particularly during a pandemic.

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SUPPLEMENTARY MATERIALS

Supplementary Table 1. Overview of social network characteristics described by structure, function, and quality

Social network structure	
Network size and social isolation	Respondents could report up to fifteen family members, ten friends, ten acquaintances, five other network members, and five healthcare professionals (HCP). The sum of all network members per relationship type provided the total network size, resulting in a maximum of 45 persons. Network size was then further categorized based on quartiles: 0-4, 5-8, 9-13, and more than 13 network members. Network size was categorized to provide a quantitative measure for social isolation (0-4 network members)
Partner	Partner was assessed by a single question: do you have a partner? Answer categories included yes or no.
Type of relationships	The proportions of types of relationships were calculated by dividing the number of family members by the total network size. The same was performed for friends, acquaintances, other network members, and healthcare professionals.
Network diversity	Social network diversity was constructed based on the relationship types reported and included the following categories: • Having no family, but friends, acquaintances, others, or HCP; • Having only family members; • Having only family members and friends; • Having family members, others, HCP, but no friends • Having family members, friends, acquaintances, other network members, and HCP.
Network density	Respondents could answer a 5-scaled statement about whether their friends and family know each other.
Homogeneity in gender and age	The proportion of network members of the same gender was calculated by dividing the number of network members of the same gender by the total network size. The proportion of network members of the same age (~5-year age range) was calculated by dividing the number of network members of the same age by the total network size.
Contact with children aged five years and younger	Contact with young children aged five years and younger was assessed by a single question with answer categories: yes daily, yes weekly, yes monthly, yes less often, no. Answer categories yes daily and yes weekly were combined into yes, daily, or weekly, and categories yes monthly and yes less often were combined into yes, monthly, or less often.
Living alone	The living situation was assessed by a single question with several answer categories: living alone, living with a partner, living with children, living with parents, living with

	other adults. Living alone was constructed based on the answer category: living alone.
Geographical proximity	Proportions of network members who live in the same house, within walking distance, less than 30 minutes away by car, more than 30 minutes away by car, or further away were calculated by dividing the number of network members living in the same house by the total network size, and so on.
Social network function	
Informational support	The proportion of informational supporters was calculated by dividing the number of network members who advised on problems or gave information by the total network size.
Emotional support	The proportion of emotional supporters was calculated by dividing the number of network members who provided the opportunity to discuss important matters or health-related topics by the total network size.
Practical support	The proportion of practical supporters was calculated by dividing the number of network members who helped with small or larger tasks in or around the house by the total network size.
Social network quality	
Social strain	The proportion of network members with whom social strain was experienced was calculated by dividing the sum of network members who are demanding, straining, or criticizing by the total network size.
Good relationships	The proportion of network members with whom there is a good relationship was calculated by dividing the number of social network members with whom there is a good relationship by the total network size.



Chapter 7

Social networks, environmental, and individual factors associated with COVID-19 vaccination and booster uptake: the prospective PRIME cohort study.

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ABSTRACT

Background

Social networks (a person's social relationships) are important for health and in health behavior, including infection prevention behavior. This study aims to identify factors associated with coronavirus disease 2019 (COVID-19) vaccine and booster uptake, focusing on social networks and community participation factors, the physical environment, and individual level factors.

Methods

In the PRIME longitudinal cohort study, we used online questionnaires to collect baseline data at the end of 2021, including participants' COVID-19 vaccination status and various factors, i.e., structural and functional social network characteristics (interpersonal factors), societal (social and physical living environment) community (work and social participation), and individual (sociodemographics, health) factors. At follow-up (summer of 2022), we measured COVID-19 booster uptake. Associations between the factors and vaccine and booster uptake were analyzed using multivariable logistic regression analyses.

Results

At baseline ($N = 9501$), COVID-19 vaccine uptake was 94 %. In vaccinated participants at follow-up ($N = 3620$), booster uptake was 91 %. Community and societal factors associated with (booster) vaccine uptake included social participation, higher neighborhood livability and walkability scores, and a moderate level of urbanization. Interpersonal factors included a larger social network size, network diversity, network density, and not living alone. Associated individual factors included age ≥ 60 years, male sex, college/university education, being born in the Netherlands, having chronic conditions, being a never/former smoker, higher health literacy, and no loneliness.

Conclusion

The social and physical environment are key in COVID-19 vaccine and booster uptake. Health promotion and vaccination strategies should address the environmental context (community, societal and interpersonal factors) alongside individual-level factors to contribute to pandemic preparedness.

INTRODUCTION

The pandemic of coronavirus disease 2019 (COVID-19), caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), has profoundly impacted the world, with more than 775 million cases and over 7 million lives lost globally (1). The development of vaccines marked a significant breakthrough, offering protection against severe illness and reducing virus transmission (2). It is estimated that COVID-19 vaccines have averted nearly 20 million deaths worldwide since their availability in early 2021 (3). As the virus mutated and new variants emerged, the need for booster vaccinations to sustain immunity became apparent. In the Netherlands, booster vaccine campaigns were launched in early 2022 (4). However, suboptimal (booster) vaccine uptake formed a significant challenge. In the Netherlands, 90 % of adults received the primary vaccine series, but booster uptake was lower, reaching 60 % by the end of 2022 (5,6). This underscores the importance of gaining insights into the factors associated with vaccination, including potentially modifiable factors (to promote vaccination behavior) and non-modifiable factors (to identify subgroups with lower uptake), to tailor public health campaigns effectively.

According to the socio-ecological framework, health and health behavior are shaped by individual factors and interactions with the environment, including interpersonal relationships and broader social and physical influences at the community and societal levels (7, 8, 9). Studies examining factors associated with COVID-19 (booster) vaccination have primarily identified individual factors. These findings are based on both factual data from registers and perceptional data from cross-sectional studies, and include sociodemographics, health, risk perception, institutional trust, and health literacy (8, 10-15). The built environment or external exposome includes neighborhood characteristics such as the socio-economic status of the neighborhood, population density, access to facilities and transport, and green space (16). Environmental characteristics such as built environment density, open space, and air quality also played a role in SARS-CoV-2 transmission (17). To lower transmission rates, infection prevention measures such as social distancing, mobility restrictions, and restricted access to facilities and public spaces were implemented to alter the (social) environment (18). Neighborhood socio-economic status has been linked to COVID-19 vaccination coverage (19, 20), yet other factors of the (social) environment remain less explored.

At the interpersonal level, social networks -all social relationships in which an individual is involved- play a key role in health outcomes and behaviors, including vaccination and adherence to COVID-19 social distancing guidelines (21,22). Social networks can be defined by their structure and function. Structural social network aspects include network size, diversity of relationships, geographical proximity, mode and frequency of contact, and homogeneity in age and gender. A larger social network, more network members, could lead to a higher exposure to information on vaccine effectiveness (23), depending on network members that advocate for vaccines or those who are skeptical (22-25). Individuals also tend to adopt behaviors and attitudes from their social network (26). People's vaccination beliefs may mirror those of their social network, and frequent discussing vaccination with family or friends can shape these beliefs (23). COVID-19 vaccination even emerged as a distinct social identity, as lower risk perception of COVID-19 was associated with having an unvaccinated network, while people with a higher risk perception were more selective in their social network (22). Furthermore, a higher proportion of vaccinated friends and family has been associated with increased booster uptake (23).

Functional social network aspects often refer to social support. Different types of relationships are linked to varying forms of social support (27), where weak ties (such as acquaintances or new connections) are often associated with informational support and exposure to new information (28). Higher levels of perceived social and emotional support have also been linked to COVID-19 vaccine uptake (10). Other principles that have been associated with COVID-19 vaccination are social norm theory, indicating a relationship between descriptive and subjective social norms and vaccination intentions through influence and selection (29), and social influence (peer pressure) (30).

Many studies emphasize vaccination intentions, which do not always translate into actual vaccine behavior or booster uptake and may therefore overestimate adherence (23). Social networks have been evaluated in relation to COVID-19 vaccine intention in older adults in the Netherlands with findings indicating that a larger network size (social network structure) and a greater proportion of informational and emotional supporters (social network function) are associated with higher vaccine intention (31). Despite these insights, the specific aspects of social networks that are connected to COVID-19 vaccine and booster uptake remain unclear. Given that individuals are embedded in a social environment and

that the physical environment can shape this social context and influence health, we best consider both individual and (social) environmental factors comprehensively (32,33). A better understanding of factors on all levels can inform optimized pandemic preparedness and highlight the importance of the social environment in infection prevention strategies. Our study aims to address the gap in knowledge regarding the specific aspects of social networks and other social environment characteristics that influence either or both vaccine and booster uptake, in addition to individual factors and the physical environment.

METHODS

Study design and participants

The PRIME (Prevalence, Risk factors, and IMpact Evaluation) post-COVID study is a longitudinal cohort study of adults in South Limburg, the Netherlands. Between November–December 2021, 61,655 adults who had a valid SARS-CoV-2 polymerase chain reaction (PCR) test result and email address recorded in the public health registry in South Limburg, the Netherlands were invited to complete an online baseline questionnaire. A total of 12,453 participants completed the questionnaire. Detailed information on the recruitment process has been described previously (34,35). Between July 2022 and August 2022, baseline participants were invited to complete a follow-up questionnaire (Fig. 1). Participants who showed inconsistencies between baseline and follow-up in sex, age, or test results, or who had missing data for factors included in the current analyses, were excluded.



Figure 1. Timeline of data collection and vaccination campaigns.

Measurements

The outcome measures (COVID-19 vaccine and booster uptake) and all factors on the individual, interpersonal, and community level were self-reported via the online questionnaire, while the factors on the societal level were obtained via linking on the 4-or 6-digit postal code (census tract data). Vaccine uptake (outcome 1) was assessed at baseline and booster uptake (outcome 2) was assessed at follow-up. All associated factors were measured at baseline, except for health literacy, which was measured at follow-up (Fig. 1). Therefore, associations with vaccine uptake (outcome 1) are cross-sectional, while associations with booster uptake (outcome 2) are predictive.

Outcome 1: COVID-19 vaccine uptake

At baseline, participants were asked about the number of COVID-19 vaccines they had received. Those who reported having received at least one dose of the COVID-19 vaccine were classified as vaccinated. Since vaccination campaigns in the Netherlands started at the beginning of 2021 and were aimed at all adults, participants would have had the opportunity to decide about vaccination by the end of that year.

Outcome 2: booster uptake

The booster vaccination campaign was conducted mainly in early 2022 and booster vaccine uptake was assessed at follow-up (summer 2022). All adults received an invitation letter for the booster, with the rollout proceeding from older and high risk groups to younger age groups (4). Participants were asked whether they had received the booster (yes/no). Only participants eligible for the booster vaccine were included. Eligibility was defined as having received the primary series of COVID-19 vaccination, meaning having received two vaccinations (or one in the case of the Janssen vaccine) or a SARS-CoV-2 infection confirmed by a registered PCR test followed by at least one vaccination.

Societal factors of living environment (census tract data)

Degree of urbanization

The degree of urbanization was based on address density and categorized into rural areas (<500 addresses per km^2), little urbanized areas (500 to 1000 addresses per km^2), moderately urbanized areas (1000–1500 addresses per km^2), and highly or strongly urbanized areas (>1500 addresses per km^2) (36).

Physical and social living environment

Environmental factors of living area were obtained from Geoscience and Health Cohort Consortium (GECCO) (16,37) and awarded to the participants based on 4- or 6-digit postal codes as present in the South Limburg Public Health Service registry.

We included scores on green space density, components of walkability including street connectivity and density and public transport density, mean household size, financial wellbeing (mean percentile of postal code area), and components of livability including physical environment, facilities, housing stock, neighborhood cohesion, and nuisance and safety. A higher score indicated a higher score or presence of the factors in the 4-digit or 6-digit postal code area of the participant. Details regarding the GECCO variables used are outlined in Supplementary Table 1.

A small portion of participants (up to 5 % of the study population) could not be linked to environmental data due to missing postal codes or postal code areas with fewer than five inhabitants (due to privacy concerns) (Supplementary table 1).

Community factors

Work participation

Work participation was assessed by asking participants whether they were employed, (e.g., contract workers, freelancers) or unemployed (retirement, incapacitated, students, or homemakers).

Social participation

Social participation (yes/no) was evaluated by asking participants about club memberships, including sports clubs (e.g., sports or walking clubs), music organizations (music, dance, theatre, carnival organizations), or other memberships (religious groups, volunteering, talking groups, etc.).

Interpersonal factors

Social networks were measured using a name-generator questionnaire. A more detailed description of the name generator questionnaire with name interpreter items is available elsewhere ((38), (39), (40)). Participants were asked to provide the names of up to fifteen family members, ten friends, ten acquaintances, five

other persons, and five healthcare professionals who are important to them or provide social support, up to a maximum of 45 network members.

Social network structure

Social network size was calculated by summing all listed network members. Additional information about the network members was collected and used to describe social network structure, function, and quality, as described in Supplementary table 2. Relationship types were evaluated by calculating the proportion of each type (family, friends, acquaintances, others, healthcare professionals) within the total network. Network diversity was categorized based on the presence of combinations of different relationship types.

Network density was measured by how well friends and family know each other, rated on a five-point scale and dichotomized into 'agree' or 'disagree'. The homogeneity of social networks was assessed by the proportion of members of similar gender and age (less than five years of age difference), as well as older or younger age (more than five years of age difference). There were missing values for several variables used to calculate the age of the network members, resulting in incomplete data for the homogeneity in age factors. Since it concerned less than 2 % of the total study population, the analysis of age homogeneity was conducted only for the participants who had complete data (i.e., no missing values; Supplementary table 2).

Living situation was determined by a single question, identifying participants who live alone (yes/no). Geographical proximity was calculated by the proportion of network members living in the same house, within walking distance, or further away (Supplementary Table 2).

Social network function

Participants reported the number of network members who provided informational support (advice), emotional support (support for important decisions and support in the form of talking about health, or both), practical support, support by doing fun things together, and support in the form of giving or receiving care.

Social network quality

Social network quality was measured by asking participants the number of network members who were demanding, straining, or criticizing, indicating social

strain. The proportion of network members with whom there is social strain was calculated by dividing the sum of the number of network members who are either demanding, straining, or criticizing by the total network size.

Individual factors

Individual factors included were sociodemographic characteristics, physical and mental health factors, health behavior and health literacy, and loneliness.

Sociodemographic characteristics

Sociodemographic variables measured included age (categorized as <60 or ≥ 60 years old, according to the booster policy), sex (male or female). Educational attainment was categorized into three categories: less than vocational education (no education or primary education), vocational education (intermediate vocational and higher secondary education), and college or university degree (higher professional and university education). Country of birth was included as either the Netherlands or elsewhere.

Health

Participants selected chronic conditions from a predefined list, if applicable. These conditions were then categorized into chronic conditions associated with more severe COVID-19 (including COPD, asthma, lung disease, diabetes, obesity, cardiovascular diseases, Parkinson's disease, cancer, kidney disease, liver disease, dementia, and multiple sclerosis) (41), chronic conditions not associated with more severe COVID-19 (including migraine, ME/CVS, neck or back pain, (rheumatoid) arthritis, fibromyalgia, osteoporosis, hypertension, eczema, concentration problems, and 'other'), and mental health conditions (including anxiety, depression, and burnout). This classification follows the guidelines of the Dutch National Institute for Public Health and the Environment (RIVM), meaning that participants with chronic conditions associated with more severe COVID-19 were more encouraged to take the (booster) vaccine (42).

Body mass index (BMI) was calculated by dividing weight by height squared and reported as a continuous factor (kg/m^2).

The confirmed SARS-CoV-2 PCR test result was registered as positive or negative.

Long-term symptoms (long COVID or post-COVID-19 condition (PCC)) were assessed via a confirmed positive PCR test and by asking about recovery from COVID-19. Participants were classified as having PCC (feeling unrecovered) if their first positive PCR test was taken more than three months prior to completing the baseline questionnaire.

Health behavior and health literacy

Smoking status was reported as current smoker, former smoker, or never smoker.

Health literacy scores were assessed at follow-up, using four domains from the Health Literacy Questionnaire (HLQ) to measure whether participants have sufficient information to manage health (HLQ2), receive social support for health (HLQ4), are able to actively engage with healthcare providers (HLQ6) and are able to navigate the healthcare system (HLQ7). Each domain consisted of 4, 5 or 6 items. HLQ2 and HLQ4 included a Likert scale ranging from 1 ("strongly disagree") to 4 ("strongly agree"), while the Likert scale of HLQ6 and HLQ7 ranged from 1 ("always difficult") to 5 ("always easy"). The score for each domain was determined by averaging its items. Higher scores correspond to higher health literacy (43).

Loneliness

Loneliness was assessed via de Jong-Gierveld 6-item scale and categorized into 'not lonely', 'moderately lonely', and 'severely lonely' (44).

Statistical analyses

Descriptive analyses were performed to describe the study population for both outcomes, reporting N and proportion for categorical variables and mean and standard deviation (SD) for continuous variables. Non-response analyses (Chi-square and *t*-tests) were conducted to compare vaccinated participants at baseline who did not participate in follow-up with participants included in the follow-up assessment of booster uptake.

Logistic regression analyses were performed with COVID-19 vaccination uptake and booster uptake as the outcome variables and the societal, community, interpersonal, and individual factors as independent variables. Analyses were adjusted for age, sex, educational attainment, chronic conditions, and level of urbanization. Correlations between variables were assessed multicollinearity was observed (all correlations <0.7 and VIF < 10). However, due to a correlation

greater than 0.7 between the walkability variables (street connectivity density and public transport density) and the degree of urbanization, the walkability variables were not adjusted for urbanization levels. Social network proportion variables were additionally adjusted for network size. For both vaccine uptake and booster uptake, interactions between age group and sex were tested and showed no statistically significant interaction.

Statistically significant factors were analyzed in a multivariable logistic regression model using forward selection to study independent associations. A p-value ≤0.05 indicated statistical significance, and all analyses were performed using IBM SPSS Statistics version 27.0.

Ethics statement

The Medical Ethical Committee of Maastricht University Medical Center+, Maastricht Netherlands waived this study (METC2021–2884), as the Medical Research Involving Human Subjects Act (WMO) did not apply to this study. The study is registered at ClinicalTrials.gov Protocol Registration and Results System (NCT05128695). Participants gave electronic informed consent.

RESULTS

Study population

Outcome 1: COVID-19 vaccine uptake

Of 12,453 baseline participants, 9501 were included in the current analyses (Fig. 1). Of those, 94 % reported COVID-19 vaccine uptake. Among the included participants, 43 % were male and 39 % were ≥ 60 years old (mean age was 53 years) (Fig. 2, Table 1). In vaccinated participants, time between baseline completion and vaccination was six months on average, while 60 % of them were vaccinated ≥3 months after their PCR test.

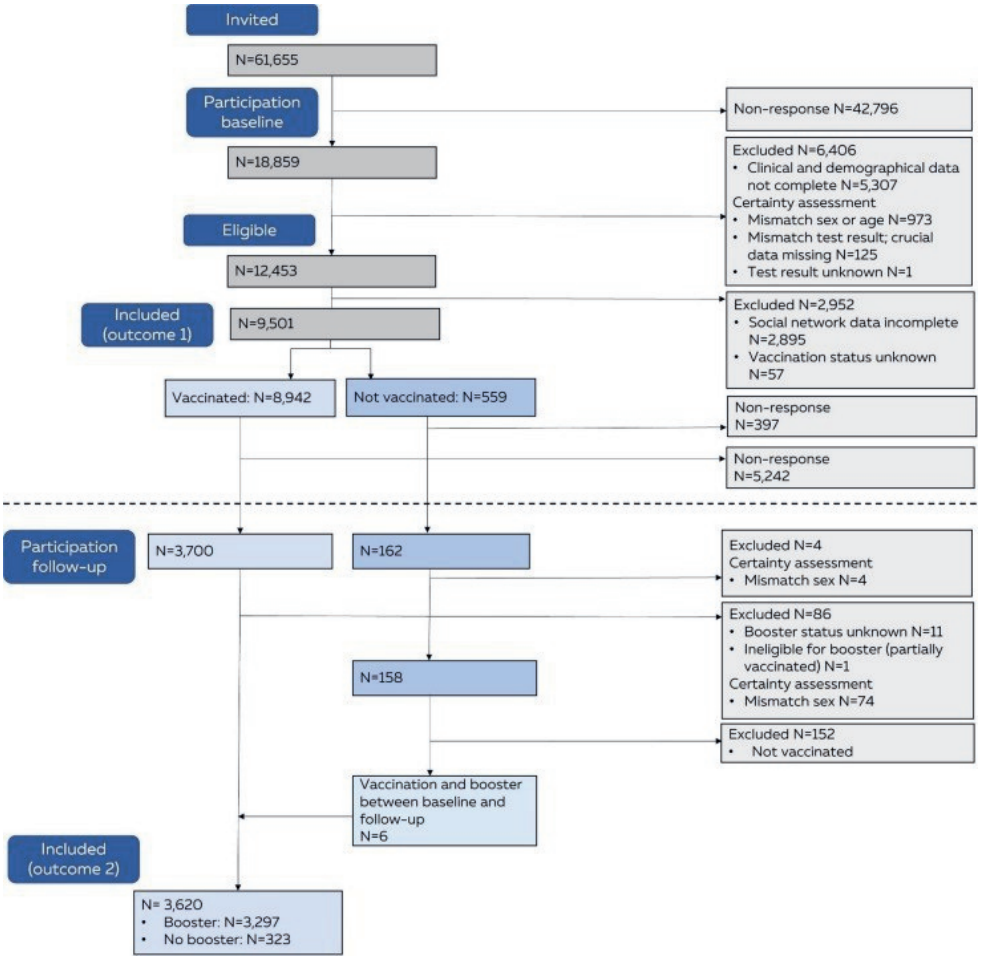

Figure 2. Flowchart of invitees, respondents, exclusion criteria, participants eligible for inclusion, and study population included in the analyses.

Table 1. Study population characteristics

	COVID-19 vaccine uptake *Baseline: November/December 2021*				COVID-19 booster uptake *Follow-up: July/August 2022*			
	Vaccinated (N=8,942/ 9,501)		Not vaccinated (N=559/9,501)		Booster (N=3,297/3,620)		No booster (N=323/3,620)	
Societal factors								
Urbanization of living area								
Not urbanized	1525	17%	91	16%	575	17%	52	16%
Little urbanized	2187	25%	108	19%	807	25%	82	25%
Moderately urbanized	1902	21%	155	28%	708	22%	70	22%
Highly urbanized	3328	37%	205	37%	1207	37%	119	37%
Green space density score of living area	67.0	10.3	66.6	9.8	67.0	10.2	66.4	9.9
Walkability - street connectivity density score	0.59	0.27	0.62	0.27	0.59	0.27	0.59	0.26
Walkability - public transport density score	0.10	0.072	0.11	0.069	0.10	0.072	0.10	0.069
Mean household size in living area	2.2	0.46	2.2	0.44	2.2	0.45	2.2	0.42
Financial wellbeing in living area (mean percentile)	47.9	9.2	46.6	9.0	48.2	9.3	47.8	9.2
Livability - physical environment score	-0.022	2.1	-0.18	2.3	0.0094	2.0	-0.26	2.3
Livability – facilities score	-2.2	7.2	-2.3	6.6	-2.2	7.0	-2.2	7.0
Livability - housing stock score	1.99	3.56	1.27	3.72	2.1	3.6	1.8	3.4
Livability - neighborhood cohesion score	1.2	4.1	0.55	4.1	1.9	4.1	0.90	3.8
Livability - nuisance and safety score	-0.50	7.8	-2.4	8.4	-0.085	7.7	-0.93	7.8
Community factors								
Being employed	5775	65%	451	81%	1918	58%	235	73%
Social participation								
Sports memberships	2788	31%	129	23%	1093	33%	94	29%
Music/cultural organizations	1158	13%	45	8%	477	15%	31	10%
Other club membership (religious groups, talking groups, etc)	2517	28%	119	21%	1058	32%	89	28%
Interpersonal factors								
Social network structure								
Social network size	10.3	6.8	9.4	6.7	11.1	7.0	10.2	6.4
Type of relationship (proportion of network members)								
Family	48.0	24.9	50.7	26.4	47.0	24.4	49.4	25.2

Friends	26.7	19.0	28.6	21.1	25.8	18.2	28.3	19.2
Acquaintances	14.7	15.0	12.6	15.1	16.0	15.2	14.0	13.9
Extra members	5.6	11.4	4.5	10.6	5.7	11.0	4.2	8.6
Caregivers	5.0	10.4	3.6	8.7	5.4	10.5	4.1	8
Proportion of network members of the same gender	55.9	22.2	54.4	23.5	56.7	20.7	57.4	23.5
Proportion of network members of the same age	42.5	23.6	43.9	24.0	41.7	22.2	42.3	22.7
Proportion of network members of younger age	36.8	27.5	28.1	27.3	40	25.7	35.3	25.4
Proportion of network members of older age	20.7	20.8	28.1	22.9	18.5	19.2	22.8	19.4
Network diversity								
Only family, no friends/acquaintances/caregivers/other	959	11%	80	14%	389	12%	45	14%
Family, friends. acquaintances, and/or caregivers or other	5658	63%	312	56%	2074	63%	191	59%
Only family and friends	1446	16%	117	21%	581	18%	72	22%
No family, but friends/acquaintances/caregivers/other	162	2%	15	3%	37	1%	2	1%
Family and acquaintances, no friends	717	8%	35	6%	209	6%	13	4%
Network density: family and friends know each other	7412	83%	442	79%	2735	83%	264	82%
Living alone	1489	17%	94	17%	595	18%	65	20%
Geographical proximity (proportion of network members who live)								
In the same house	19.4	22.4	23.3	25.3	16.8	20.4	20.4	22.4
Walking distance	22.9	22.9	18.3	22.7	24.0	22.7	22.3	21.7
Further away	57.7	27.2	58.4	28.7	59.3	26.1	57.3	27.6
Proportion of network members with in-person contact in the last two weeks	68.6	25.5	73.5	27.1	66.7	24.8	70.5	23.9
Social network function								
I have many people around me that I can trust completely								
No	566	6%	42	8%	187	6%	17	5%
More or less	1925	22%	134	24%	730	22%	72	22%
Yes	6451	72%	383	69%	2380	72%	234	72%
Proportion of network members who provide support								
Informational support	52.6	32.6	58.6	33.7	49.9	31.7	54.0	32.3
Practical support	23.4	24.7	25.8	28.1	21.5	22.6	26.6	24.9
Emotional support (total)	67.7	30.3	71.2	30.8	68.1	29.3	72.2	27.4
Emotional support - important decisions	60.3	31.5	65.7	32.9	60.2	30.7	65.7	28.5
Emotional support – talking about health	46.2	33.9	47.9	35.1	46.1	33.2	50.1	33.7
Doing fun things together	59.4	31.6	62.2	32.7	58.2	30.5	63.2	30.2

Giving care to network	4.3	10.7	4.9	13.4	4.9	11.0	4.6	10.5
Receiving care from network	5.7	13.2	4.5	12.4	6.1	12.9	4.4	10.2
No support	3.7	11.9	4.3	14.2	3.6	10.8	3.3	10.6
Social network quality								
Proportion of network members with whom the relationship is demanding, straining, or criticizing (social strain)	9.6	17.4	11.1	19.6	3.5	9.2	3.0	7.7
Individual factors								
Sociodemographic								
Age								
<60 years	5294	52%	490	88%	1614	49%	238	74%
≥60 years	3648	41%	69	12%	1683	51%	85	26%
Sex								
Male	3923	44%	199	36%	1533	47%	118	37%
Female	5019	56%	360	64%	1764	54%	205	64%
Educational attainment								
Less than vocational training	900	10%	52	9%	277	8%	23	7%
Vocational training	4267	48%	272	49%	1514	46%	150	46%
College or university degree	3775	42%	235	42%	1506	46%	150	46%
Country of birth								
The Netherlands	8467	95%	508	91%	3141	95%	299	93%
Other country	475	5%	51	9%	156	5%	24	7%
Health								
Chronic conditions								
Chronic conditions associated with more severe COVID-19	2164	24%	86	15%	857	26%	59	18%
Chronic conditions not associated with more severe COVID-19	3640	41%	162	29%	1480	45%	127	39%
Mental health conditions	566	6%	45	8%	174	5%	27	8%
BMI (kg/m^2)	26.8	4.9	25.8	5.0	27.0	4.62	26.8	4.96
SARS-CoV-2 PCR test result (up until baseline questionnaire)								
Positive PCR test	6343	71%	486	87%	2256	68%	245	76%
Negative PCR test	2599	29%	73	13%	1041	32%	78	24%
Post-COVID-19 condition (PCC) at time of baseline questionnaire (feeling unrecovered from COVID-19)	2516	28%	149	27%	924	28%	116	36%
Health behavior and health literacy								
Smoking								

Current	964	11%	95	17%	269	8%	41	13%
Former	3355	38%	139	25%	1361	41%	138	43%
Never	4623	52%	325	58%	1667	51%	144	45%
Health literacy score[A]								
Ability to actively engage with healthcare providers (HLQ-6)					4.4	0.74	4.2	0.83
Navigating the healthcare system (HLQ-7)					4.1	0.81	3.9	0.86
Having sufficient information to manage my health (HLQ-2)					3.1	0.58	3.0	0.57
Social support for health (HLQ-4)					3.2	0.56	3.3	0.55
Loneliness								
Not lonely	5938	66%	329	59%	2242	68%	221	68%
Moderately lonely	2259	25%	165	30%	819	25%	80	25%
Severely lonely	745	8%	65	12%	236	7%	22	7%

Numbers are presented as N (%) or mean (SD).

BMI=Body Mass Index. PCR=Polymerase Chain reaction. HLQ= Health Literacy Questionnaire.

[A]Only measured at follow-up, no baseline data available.

Vaccinated participants had a larger social network (10 vs. 9 members), a larger proportion of acquaintances (15 % vs. 13 %), a more diverse network, a larger proportion of network members living within walking distance (23 % vs. 18 %), and had less personal contact as opposed to online contact (69 % vs. 74 %), compared to unvaccinated participants. Those vaccinated tended to live in neighborhoods with lower street connectivity density (walkability variable), but higher scores for livability (housing stock, neighborhood cohesion, and nuisance and safety) (Table 1).

Outcome 2: COVID-19 booster uptake

Of vaccinated baseline participants, 3700 (41 %) participated in the follow-up measurement. Six participants, who were unvaccinated at baseline, reported having received a (booster) vaccine in between baseline and follow-up. In total, 3620 participants were included in the analysis for outcome 2, of which 46 % were male and 49 % was ≥60 years old (mean age was 57 years). 91 % of participants reported uptake of the booster vaccine (Fig. 2, Table 1). Participants who took the booster vaccine had a larger social network (11 vs. 10 members) and a lower proportion practical support (22 % vs. 27 %), compared to those who did not take the booster.

Non-response analysis

Of the 8942 participants who were vaccinated at baseline, 5242 (59 %) did not participate in the follow-up questionnaire and 86 participants were not included in the analysis for outcome 2 due to a mismatch in sex (compared to baseline), unknown booster status, or being partially vaccinated (not having completed the full primary series of the vaccine) (Fig. 2). Those who were included in the follow-up (N = 3620) were older, more often had a college or university degree, more often reported chronic conditions, had a larger and more diverse network with more social supporters, and reported higher social participation (Supplementary table 3).

Factors associated with COVID-19 vaccine uptake (outcome 1)

Living in moderately urbanized areas (compared to non-urbanized areas) or areas with higher street connectivity density (walkability) was associated with lower vaccine uptake. A higher livability score in terms of housing

stock, neighborhood cohesion, and safety and nuisance were associated with being vaccinated against COVID-19. On the community level, a sports or music/cultural club membership was associated with vaccine uptake (Table 2, Fig. 3).
Interpersonal factors associated with COVID-19 vaccine uptake included a larger network size, a larger proportion of acquaintances, and a more diverse network with different types of relationships, as opposed to only having family members in the network. Apart from that, a higher network density and a larger proportion of network members living within walking distance were associated with vaccine uptake. Having more in-person contact (as opposed to online-only contact) was associated with lower odds of being vaccinated, as well as living alone.

Participants with higher odds of being vaccinated were ≥ 60 years old, men, who obtained a college or university degree (versus less than vocational education), and born in the Netherlands. Besides, being a former or never smoker (versus current smokers), having no registration of a previous SARS-CoV-2 infection, having chronic physical health conditions, having a higher BMI, and not being lonely were associated with being vaccinated. There was no statistically significant association between having PCC and vaccine uptake (Table 2, Fig. 3).

The multivariable forward logistic regression analysis showed that living in a highly urbanized area (as opposed to a non-urbanized area), the livability component on nuisance and safety, sports memberships, a larger proportion of acquaintances, a lower proportion of network members with in-person contact in the last two weeks, age above 60, male sex, being born in the Netherlands, having chronic conditions associated with more severe COVID-19, a higher BMI, a negative PCR test result, and loneliness were independently associated with COVID-19 vaccine uptake (Supplementary table 4).

Factors associated with booster uptake (outcome 2)

On the societal level, a higher score for physical environment (livability component) was associated with booster uptake (Table 2, Fig. 3). On the

community level, social participation in music/cultural organizations was associated with booster uptake. Interpersonal factors associated with booster uptake were having a larger network, not living alone, and having a smaller proportion of network members from whom practical support was received. Individual factors associated with booster uptake were age ≥ 60, male sex, being a never smoker, being born in the Netherlands, having chronic health conditions associated with more severe COVID-19, and not having PCC. Higher health literacy scores were associated with booster uptake: the ability to actively engage with healthcare providers (HLQ-6), navigating the healthcare system (HLQ-7), and having sufficient information to manage my health (HLQ-2).

The multivariable forward logistic regression analysis revealed that the livability component on physical environment, not living alone, a lower proportion of practical support, age above 60, male sex, being born in the Netherlands, being a former smoker (versus current smoker), having chronic conditions associated with more severe COVID-19, and having sufficient information to manage health (HLQ-2) were independent factors associated with booster uptake (Supplementary table 4).

Table 2. Logistic regression analyses of individual, interpersonal, community, and societal factors and COVID-19 vaccine and booster uptake, adjusted for age, sex, educational attainment, chronic conditions, and level of urbanization

	COVID-19 vaccine uptake (N=9,501)		COVID-19 booster uptake (N=3,620)	
	OR[A]	95%CI	OR[A]	95%CI
Societal factors				
Urbanization of living area				
Not urbanized	1		1	
Little urbanized	1.24	0.93–1.65	0.92	0.66–1.31
Moderately urbanized	**0.75***	**0.58–0.99**	0.89	0.61–1.31
Highly/strongly urbanized	1.02	0.79–1.33	0.90	0.62–1.29
Green space density of living area	1.01	1.00–1.01	1.01	0.99–1.03
Walkability - street connectivity density[B]	**0.71***	**0.51–0.99**	0.98	0.63–1.52
Walkability - public transport density[B]	0.98	0.29–3.25	2.04	0.39–10.58
Mean household size in living area	1.08	0.89–1.32	1.14	0.87–1.49
Financial wellbeing in living area (mean percentile)	1.01	1.00–1.03	1.00	0.98–1.02
Livability - physical environment	1.04	0.99–1.08	**1.07***	**1.01–1.13**
Livability - facilities	1.01	0.99–1.03	1.00	0.98–1.03
Livability - housing stock	**1.05*****	**1.02–1.08**	1.02	0.98–1.06
Livability - neighborhood cohesion	**1.04****	**1.01–1.07**	1.03	1.00–1.07
Livability - nuisance and safety	**1.03*****	**1.02–1.04**	1.01	1.00–1.03
Community factors				
Work situation				
Employed	1		1	
Not employed	1.03	0.80–1.32	1.24	0.90–1.72
Social participation				
Sport memberships	**1.47*****	**1.20–1.81**	1.19	0.92–1.55
Music/cultural organizations	**1.50***	**1.09–2.06**	**1.51***	**1.02–2.22**
Other club membership (religious groups, talking groups, etc)	1.15	0.93–1.43	1.05	0.80–1.36
Interpersonal factors[C]				
Social network structure				
Social network size	**1.02****	**1.01–1.04**	**1.02***	**1.00–1.04**
Type of relationship (proportions)				
Family	0.80	0.55–1.16	0.87	0.52–1.46
Friends	0.76	0.48–1.18	0.56	0.30–1.03
Acquaintances	**2.12***	**1.09–4.11**	1.96	0.82–4.69
Extra members	1.45	0.62–3.38	1.47	0.70–8.75
Caregivers	1.90	0.67–5.39	2.16	0.54–8.67
Proportion of network members of the same gender	**1.55***	**1.03–2.33**	0.88	0.49–1.57
Proportion of network members of the same age	1.11	0.76–1.60	1.20	0.70–2.06
Proportion of network members of younger age	1.21	0.84–1.75	0.70	0.42–1.17
Proportion of network members of older age	0.70	0.47–1.06	1.20	0.63–2.27
Network diversity				
Only family, no friends/acquaintances/healthcare professionals/others	1		1	

Family, friends, acquaintances, and/or healthcare professionals or others	**1.56*** **	**1.21–2.02**	1.34	0.99–2.01
Only family and friends	1.21	0.91–1.61	1.34	0.94–1.92
No family, but friends/acquaintances/healthcare professionals/others	0.73	0.41–1.31	1.87	0.43–8.17
Family and acquaintances, healthcare professionals or others, no friends	**1.60***	**1.01–2.53**	1.79	0.94–3.42
Network density: family and friends know each other	**1.36** **	**1.09–1.68**	1.15	0.85–1.56
Living alone	**0.79***	**0.62–1.00**	**0.75***	**0.55–1.00**
Geographical proximity (proportion of network members who live)				
In the same house	0.89	0.59–1.34	0.75	0.42–1.36
Walking distance	**1.55***	**1.02–2.36**	0.86	0.50–1.47
Further away	0.81	0.58–1.13	1.31	0.83–2.06
Proportion of network members with in-person contact in the last two weeks	**0.69***	**0.48–1.00**	0.74	0.45–1.22
Social network function				
I have many people around me that I can trust completely				
No	1		1	
More or less	0.97	0.67–1.40	0.87	0.49–1.53
Yes	1.27	0.90–1.78	0.94	0.55–1.60
Proportion of network members who provide support				
Informational support	0.91	0.69–1.19	1.05	0.72–1.54
Practical support	0.99	0.95–1.03	**0.48** **	**0.30–0.78**
Emotional support (total)	0.82	0.58–1.14	0.77	0.51–1.16
Emotional support – important decisions	0.98	0.95–1.01	0.75	0.50–1.11
Emotional support – talking about health	0.86	0.64–1.16	0.84	0.59–1.19
Doing fun things together	0.98	0.95–1.01	0.78	0.52–1.16
Giving care to network	0.99	0.97–1.02	1.87	0.61–5.70
Receiving care from network	1.03	0.79–1.32	2.79	0.88–8.84
No support	0.79	0.59–1.05	1.10	0.37–3.27
Social network quality				
Proportion of network members with whom the relationship is demanding, straining, or criticizing (social strain)	0.90	0.57–1.42	1.97	0.49–7.91
Individual factors				
Sociodemographic				
Age				
<60	1		1	
≥60	**4.44*** **	**3.41–5.77**	**2.66*** **	**2.04–3.47**
Sex				
Female	1		1	
Male	**1.22***	**1.02–1.47**	**1.29***	**1.01–1.65**
Educational attainment				
Less than vocational education	1		1	
Vocational education	1.24	0.90–1.69	1.07	0.67–1.71
College or university degree	**1.40***	**1.02–1.93**	1.12	0.70–1.79
Country of birth				
Other country	1		1	
The Netherlands	**1.61** **	**1.18–2.20**	**1.57***	**0.99–2.47**

Health				
Chronic conditions				
Chronic conditions associated with more severe COVID-19	**1.33***	**1.04-1.70**	**1.36***	**1.00-1.84**
Chronic conditions not associated with more severe COVID-19	**1.40*****	**1.15-1.70**	1.11	0.87-1.41
Mental health conditions	0.80	0.58-1.11	0.65	0.42-1.01
BMI (per 1 unit increase kg/m^2)	**1.04*****	**1.02-1.06**	1.00	0.97-1.03
Negative SARS-CoV-2 PCR test	**2.57*****	**1.98-3.34**	1.23	0.94-1.61
Post-COVID-19 condition (PCC) at time of baseline questionnaire (feeling unrecovered from COVID-19)	1.16	0.95-1.41	**0.75***	**0.58-0.96**
Health behavior and health literacy				
Smoking				
Currently	1		1	
Former	**1.67*****	**1.26-2.20**	1.15	0.78-1.69
Never	**1.41****	**1.10-1.81**	**1.91*****	**1.30-2.81**
Health literacy	Only measured at follow-up			
Ability to actively engage with healthcare providers (HLQ-6)			**1.20***	**1.04-1.39**
Navigating the healthcare system (HLQ-7)			**1.21****	**1.05-1.39**
Having sufficient information to manage my health (HLQ-2)			**1.34****	**1.10-1.63**
Social support for health (HLQ-4)			0.91	0.74-1.12
Loneliness				
Not lonely	1		1	
Moderately lonely	**0.71*****	**0.58-0.86**	0.98	0.74-1.29
Severely lonely	**0.64****	**0.48-0.86**	1.09	0.68-1.74

OR= odds ratio; 95%CI= 95% confidence interval. BMI=Body Mass Index. PCR=Polymerase Chain reaction. HLQ= Health Literacy Questionnaire.

[A] *p≤0.05, **p≤0.01, ***p≤0.001

[B] Walkability variables were not adjusted for degree of urbanization.

[C] Social network proportion variables were additionally adjusted for the variable 'Social network size'.

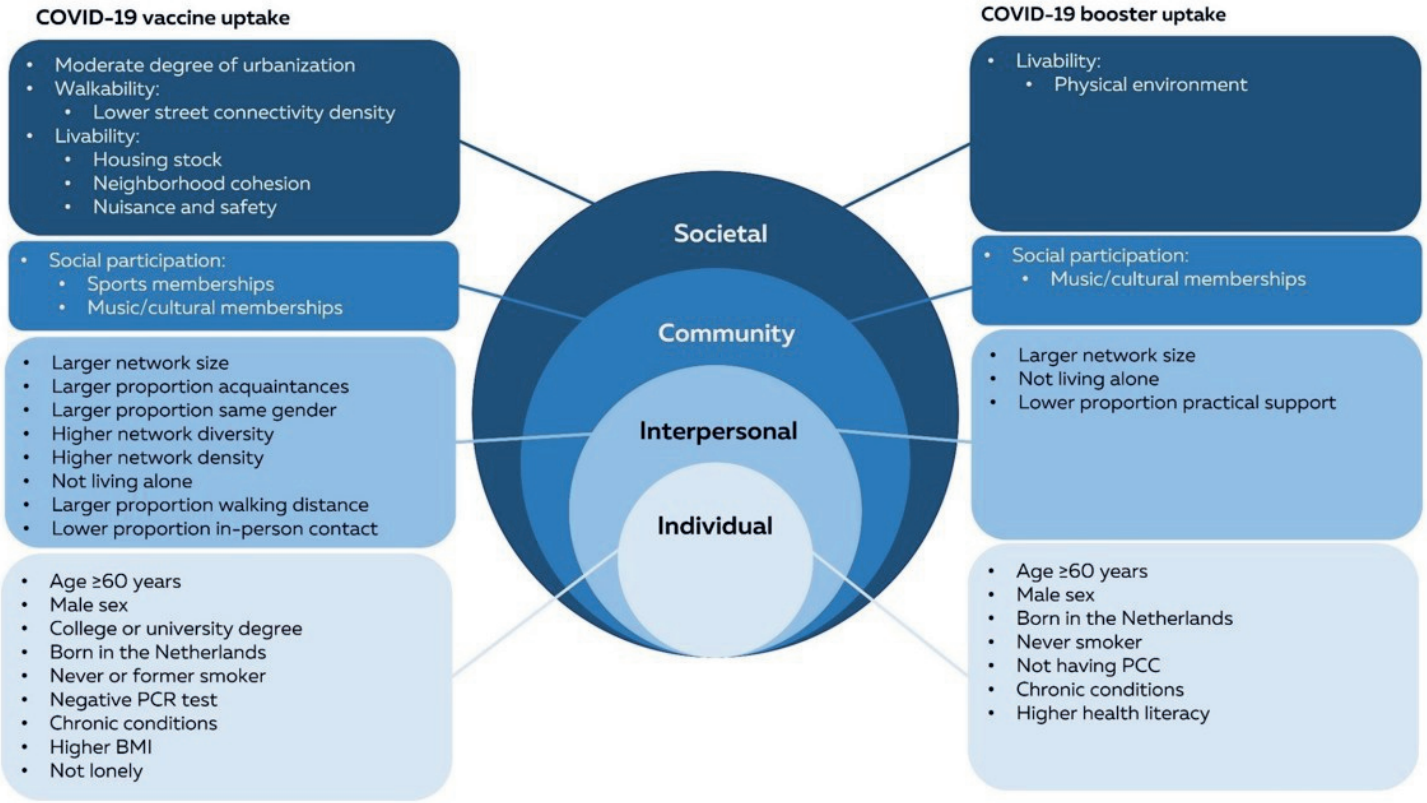

Figure 3. Overview of factors associated with COVID-19 vaccination or booster uptake in the socio-ecological framework*
*Adjusted for age, sex, educational attainment, chronic conditions, and degree of urbanization.

DISCUSSION

This study assessed associations between societal, community, interpersonal, and individual factors and COVID-19 vaccination and booster uptake among adults in South Limburg, the Netherlands. Vaccine uptake was 94 % at baseline and booster uptake was 91 % at follow-up (7–9 months later) in our study population. Both COVID-19 vaccine and booster uptake were associated with a variety of social, community, interpersonal, and individual factors. For COVID-19 vaccine uptake, these included higher scores for neighborhood cohesion, safety and nuisance, and housing stock (societal); social participation (community); larger and more diverse and dense social networks, a larger proportion of acquaintances (weak ties), and not living alone (interpersonal); and older age, male sex, college or university education, being born in the Netherlands, non-smoking, having chronic conditions, and a higher BMI (individual). Booster uptake was linked to similar, but fewer factors, mainly involving livability, social participation, larger networks and lower proportions practical support, and individual factors such as age, male sex, chronic conditions, and higher health literacy. This study utilized a comprehensive approach based on the socio-ecological framework to examine factors influencing COVID-19 (booster) vaccine uptake.

Societal level

Previous studies have shown that both individual and social environmental characteristics are relevant factors in COVID-19 (booster) vaccination uptake (8,14,20), indicating that both factors should be considered to understand and address vaccination patterns more effectively. Inadequate infrastructure or access to facilities is a known barrier for vaccine uptake (45), in line with our higher scores for the physical environment (encompassing air quality, green space, noise, and infrastructure) associated with booster uptake. We identified several aspects of livability, including housing quality, neighborhood cohesion, and nuisance and safety linked to COVID-19 vaccine uptake. Housing stock may be a reflection of the neighborhood's socioeconomic status (SES), which often corresponds to the individual SES (20). However, neighborhood financial well-being was

not a statistically significant factor in our study. Low neighborhood safety has been linked to reduced 'outside-the-door' activities (46), potentially impacting vaccine uptake. These findings can help identify characteristics of neighborhoods where vaccine uptake tends to be lower, to use neighborhood-specific approaches. For example, vaccination buses were used during the COVID-19 pandemic to increase vaccine uptake in neighborhoods with low vaccination rates (47), and trusted community leaders can play an important role in managing mistrust and motivating health behaviors (48,49).

Community level

Social participation impacts COVID-19 vaccine intention (31), and was also associated with both vaccine and booster uptake in our study. Participants with social participation, particularly within sports and music/cultural organizations were more likely to be (booster) vaccinated, possibly to protect others or to feel safer to attend these events while vaccinated. Additionally, at the end of 2021, COVID-19 vaccine certificates were required to attend sports club training sessions and sports games and other venues, which may have further incentivized vaccination (50).

Interpersonal level

In the current study, larger and more diverse social networks and a larger share of acquaintances was associated with vaccine uptake. Relationships can be described as having strong or weak ties, where strong ties are important for emotional connections and weak ties (i.e., more distant relationships such as acquaintances) are important for the provision of (new) information, and link individuals to diverse perspectives and social norms and values (28), which may include information on COVID-19 vaccination. A higher network diversity was also reflected in network density and geographical proximity, both of which were associated with vaccine uptake. A large or more dense network may indicate a stronger desire to protect both oneself and others, potentially contributing to higher vaccine uptake. Living alone was associated with lower uptake for both the vaccine and the booster. Living alone is an important factor for health and mortality, especially in older adults (51), and has been associated

with lower COVID-19 vaccine uptake previously (52), indicating that this group may need extra attention to mitigate low vaccine uptake. A lower proportion of network members providing practical support (e.g., help with chores or household tasks) was associated with higher booster uptake. These participants might have been less dependent on practical support, suggesting they were less vulnerable. Instead, they reported higher proportions of emotional and informational support from their networks.

Individual level

Individual factors associated with both vaccine and booster uptake were sociodemographics (age, sex, educational attainment, country of birth), health and smoking behavior. These findings align with previous studies (13,53,54). Evidence on the effect of vaccination on PCC is conflicting, with some studies showing no impact, others indicating reduced risk or symptom improvement, and some suggesting worsening of symptoms (55). Virus variant, reinfections, and time since vaccination complicate this link (55). We found no difference in initial vaccine uptake between PCC and non-PCC participants, but those with PCC were less likely to receive the booster, possibly due to concerns about worsening of symptoms (56,57).

Loneliness was associated with lower COVID-19 vaccine uptake and has previously been linked to several structural and functional social network aspects, including network size, diversity, and social support (40). Strengthening social networks could contribute to decreased loneliness and may thereby also possibly impact vaccine uptake.

Higher health literacy (assessed at follow-up) was significantly associated with booster vaccination, in line with previous studies (58,59), and refers to the degree to which individuals have the ability to find, understand, and use information and services to inform health-related decisions (60). However, health literacy is also influenced by the social environment (32), as social support and social participation may buffer the negative effects of low health literacy (59) and a strong social network (large, diverse, and supportive) may help individuals with lower health literacy to make better informed decisions on vaccination.

Implications

Our findings provide insights into the factors associated with COVID-19 (booster) vaccine uptake, including both non-modifiable factors that help identify subgroups with lower uptake and potentially modifiable factors that can promote vaccination behavior. Non-modifiable factors include sociodemographics, chronic health conditions, country of birth, and PCR test status. Besides, social network characteristics, including living alone, social isolation (a small social network), and a family-focused network (low network diversity) can be used as indicators for lower vaccine uptake to inform researchers, healthcare professionals, and policymakers. We identified potentially modifiable factors including the living environment, loneliness, and health literacy, suggesting that policies addressing these factors might increase vaccine uptake. These may include improved access to vaccination venues, mobile vaccination clinics, community outreach programs, trainings, and social media campaigns to disseminate accurate vaccine information. Our analyses indicated more factors associated with vaccine uptake, compared to booster uptake, possibly because the included follow-up population was already vaccinated.

Vaccination behavior is shaped not only by individual characteristics, but also by social factors and the living environment. Neighborhood social cohesion has even been associated with better antibody response to the COVID-19 vaccine and with lower levels of loneliness, illustrating the interplay between the individual and societal level (61). Environments that foster social connections -through improved infrastructure, accessible facilities, and community engagement- could promote health behaviors (33,62), including vaccination. Neighborhood-specific strategies, such as vaccination buses or involving trusted community figures may further enhance vaccination uptake by strengthening social networks. Social cohesion and community engagement were also key factors for the social and economic recovery from the pandemic (63). Finally, social network interventions can serve as a public health tool by leveraging platforms like social media and friend groups by creating support groups or peer influence campaigns to maintain or modify health behaviors.

Strengths and limitations

A strength of this study is the inclusion of a large group of participants and factors on all levels of the socio-ecological framework. The use of the name generator questionnaire to measure social networks allowed for a detailed assessment of various social network aspects, differentiating between structure, function, and quality. However, we did not assess the vaccination status of network members, nor did we include participants' attitudes and beliefs regarding COVID-19 and vaccination. Furthermore, we did not have data on political orientation and institutional trust. Lastly, while we collected environmental data at the postal code level and radii, data availability was limited in the border areas of South Limburg, as data based on radii were not available across the border. The generalizability of our findings is supported by a diverse adult population, although not fully representative of the general Dutch adult population, with 94 % of participants vaccinated -higher than the national average. Non-response bias may have occurred, as individuals with lower (digital) literacy may have been less able to participate. Non-response at follow-up led to some differences in the occurrence of factors between the baseline and follow-up population, potentially affecting the associations identified. The smaller follow-up population also reduced statistical power, which may have limited the ability to detect associations. However, we believe this impact is minimal, as the study included a large population, and the patterns identified remain significant, highlighting key factors related to (booster) vaccine uptake.

Conclusion

We aimed to assess factors at societal, community, interpersonal, and individual levels associated with COVID-19 (booster) vaccine uptake. Key determinants included neighborhood livability, social participation, social network size and diversity, living alone, health literacy, loneliness, and sociodemographics. These results suggest that public health vaccination strategies should incorporate both individual and social and physical environmental factors to promote vaccination and contribute to pandemic preparedness.

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SUPPLEMENTARY MATERIALS

Supplementary table 1. Overview and description of societal factors from census tract data (GECCO)

Factor	Description	Missing data (number of missings/study population)
Green space density	Green space density of 2017 expressed in percentages with a buffer radius of 1500m on a 10x10 meter resolution, which was aggregated to 6-digit postal codes. Green space included grass, trees, shrubs, and agriculture. Scores ranged from 9,6 to 93,4.	Outcome 1: N=147/9501 Outcome 2: N=54/3620
Walkability – street connectivity density	Street connection in 3000-meter radius in 2019, expressed as number of road connections (including footpaths) per area unit, based on TOP10 road intersection data. This component was processed on a 25x25 meter grid cell resolution and calculated for the Euclidean distances in circular buffer radius of (3000 meter). Subsequently the resulting cell values were extracted to PC6 centroid locations. Scores ranged from 0,086 to 1,15.	Outcome 1: N=117/9501 Outcome 2: N=44/3620
Walkability - public transport density	Public transport density in 2018 (weighted with the number of connections per OV stop). Based on a point dataset with all public transport stops in the Netherlands (bus, ferry, metro, taxi, tram), but train stations excluded. The density in number of public transport stops is for each buffer distance weighted with the number connecting lines per public transport stop. This component was processed on a 25x25 meter grid cell resolution and calculated for the Euclidean distances in circular buffer radius of (3000 meter). Subsequently the resulting cell values were extracted to PC6 centroid locations. Scores ranged from 0,0042 to 0,29.	Outcome 1: N=117/9501 Outcome 2: N=44/3620
Livability	Livability scores were defined as the extent to which the living environment is in line with the conditions and needs of residents, and consists of 9 classes from 1 (very insufficient) to 9 (excellent). These scores from the 'Leefbaarometer 3.0' of 2020 are based on 45 environment characteristics (regarding population, neighborhood cohesion, public space, safety, level of resources, and housing) with 94 variables in the underlying models. A detailed description of the development of the instrument can be found at	Outcome 1: N=488/9501 Outcome 2: N=178/3620

	https://open.overheid.nl/documenten/ronl-c3a3e37d03f0afa9f80d224a0278647389d8a686/pdf (in Dutch). The 6-digit postcode point locations were linked to the scores on the 100x100 m scale level. For the current analysis, all livability scores were multiplied by 100 to facilitate interpretation of the values.
Livability-neighborhood cohesion	Score for the neighborhood social cohesion dimension of livability. This score represents the deviation from the Dutch average social cohesion score and was based on the following characteristics: (diversity by) stage of life, social cohesion, mutation rate, density of inhabitants, and population development. Scores ranged from -10,7 to 22,2.
Livability – physical environment	Score for the physical environment dimension of livability. This score represents the deviation from the Dutch average score and was based on the following characteristics: -Natural environment: air quality, noise pollution, on-ionizing radiation, perceived temperature (wind chill)/ heat stress, groundwater flooding/ soil subsidence, earthquakes flood depth, proximity to forest/green space, proximity of landscape attractive for recreation, and variety of landscapes. -Infrastructure: proximity to (main) roads, proximity to rail infrastructure, traffic safety, car density, proximity to wind turbines, proximity to high voltage pylons, quality of hiking and biking trails, functional mix, vacancy of non-residential real estate, and walkability. Scores ranged from -17,5 to 8,86.
Livability - facilities	Score for the facilities dimension of livability. This score represents the deviation from the Dutch average score and was based on the following characteristics: (public) transportation, shops/retail, education, care and support, hospitality, meeting points, leisure and culture, sports accommodations, and job accessibility. Scores ranged from -21,2 to 27,2.
Livability – housing stock	Score for the housing stock dimension of livability. This score represents the deviation from the Dutch average score and was based on the following characteristics: residential vacancy, density of buildings, foundation problems (pile rot), mix of ownerships, energy quality, home ownership, specific poorly maintained segments (ownership, value), home ownership in relation to

	insufficient income, use of solar panels, share of monumental housing, housing renovations (based on proxy energy quality), overcrowding, and housing types (size, year of construction, type, height). Scores ranged from -27,8 to 24,1.	
Livability – nuisance and safety	Score for the nuisance and safety dimension of livability. This score represents the deviation from the Dutch average score and was based on the following characteristics: registered crimes, experienced safety, and experienced nuisance. Scores ranged from -43,4 to 14,6.	
Mean household size	Based on the dataset 'Statistische gegevens per vierkant en postcode'[1] from Statistics Netherlands (CBS) contains basic statistics on (a.o.) number of inhabitants, dwellings, residential density, housing, urbanity and from 2015 onwards accessibility to several social, cultural and commercial destinations. This dataset contained postcode 6 areas as of 2022. Mean household size per 6-digit postal code area ranged from 1 to 4.	Outcome 1: N=451/9501 Outcome 2: N=156/3620
Financial wellbeing	Financial wellbeing (based on assets and income) mean percentile of 4-digit postal code area as of 2014. Background information on the methodology used are outlined in the document Berekenwijze sociaal economische statusscores_SES-WOA.pdf. Data source: https://www.cbs.nl/nl-nl/maatwerk/2022/34/sociaal-economische-status-per-postcode-2014-2019 Mean percentile values ranged from 26,8 to 68,8.	Outcome 1: N=131/9501 Outcome 2: N=51/3620

Supplementary table 2. Overview of social network characteristics described by structure, function, and quality, as used in the Name Generator Questionnaire

Social network structure	
Social network size	Respondents could report up to fifteen family members, ten friends, ten acquaintances, five other network members and five healthcare professionals. The sum of all network members per relationship type provided the total network size, resulting in a maximum of 45 persons.
Type of relationships	Proportion of types of relationship were calculated by dividing the number of family members by the total network size. The same was performed for friends, acquaintances, others, and healthcare professionals.
Network diversity	Social network diversity was constructed based on the relationship types reported and included the following categories: • Having no family, but friends, acquaintances, others or healthcare professionals • Having only family members • Having only family members and friends • Having family members and others, but no friends • Having family members, friends, and acquaintances, other network members or healthcare professionals.
Network density	Respondents could answer a 5-scaled statement in whether their friends and family know each other.
Homogeneity in gender and age	Proportions of network members of the same gender and same age (~5 year age range) were calculated by dividing the number of network members of same gender/age by the total network size. For the factor 'Proportion of network members of the same age', results were presented for N=9,305 due to missing data for N=196 participants for outcome 1 (vaccination), and N=3,549 due to missing data for N=71 participants for outcome 2 (booster). For the factors 'proportion of network member of younger age' and 'proportion of network member of older age', results were presented for N=9,302 due to missing data for N=199 participants for outcome 1, and N=3,548 due to missing data for N=72 participants for outcome 2.
In-person contact	The proportion in-person contact was calculated by dividing the number of network members with whom participants had in-person contact (solely in person or both in-person and online) by the total network size.
Living alone	Living situation was assessed by a single question with several answer categories: living alone, living with a partner, living with children, living with parents, living

	with other adults. Living alone was constructed based on the answer category: living alone.
Geographical proximity	Proportions of network members who live in the same house, within walking distance, or further away (less than 15 minutes driving away, between 15 and 30 minutes driving away, 30 minutes to two hours driving away, or further away) were calculated by dividing the number of network members living in the same house by the total network size, and so on.
Social network function	
Informational support	The proportion informational support was calculated by dividing the number of network members who advised on problems or give information by the total network size.
Emotional support	The proportion emotional support was calculated by dividing the number of network members who provided the opportunity to discuss important matter or health-related topics by the total network size.
Practical support	The proportion practical support was calculated by dividing the number of network members who helped with small or larger tasks in or around the house by the total network size.
Doing fun things together	The proportion support via doing fun things together was calculated by dividing the number of network members with whom participants do fun things by the total network size.
Giving care to the network	The proportion support via giving care was calculated by dividing the number of network members to whom participants provide care by the total network size.
Receiving care from the network	The proportion support via receiving care was calculated by dividing the number of network members from whom participants receive care by the total network size.
Social network quality	
Social strain	The proportion of network members with whom social strain was experienced was calculated by dividing the sum of network members who are demanding, straining or are criticizing by the total network size.

Supplementary table 3. Non-response analysis comparing follow-up participants included for outcome 2 on booster uptake and vaccinated participants at baseline.

	Included in follow-up (N=3,620)		Not included in follow-up (N=5,328)		P[A]
Societal factors[B]					
Urbanization of living area					0.81
Not urbanized	627	17%	900	17%	
Little urbanized	889	25%	1299	24%	
Moderately urbanized	778	22%	1125	21%	
Highly urbanized	1326	37%	2004	38%	
Green space density score of living area	67.0	10.1	67.0	10.3	0.91
Walkability - street connectivity density score	0.59	0.27	0.59	0.27	0.36
Walkability - public transport density score	0.10	0.072	0.10	0.073	0.49
Mean household size in living area	2.2	0.45	2.1	0.47	0.93
Financial wellbeing in living area (mean percentile)	48.1	9.3	47.7	9.12	**0.009**
Livability - physical environment score	-0.014	2.03	-0.026	2.09	0.80
Livability – facilities score	-2.22	6.98	-2.15	7.32	0.65
Livability - housing stock score	2.07	3.56	1.94	3.56	0.094
Livability - neighborhood cohesion score	1.33	4.06	1.13	4.06	**0.022**
	-0.16	7.68	-0.73	7.85	**<0.00**
Livability - nuisance and safety score					**1**
Community factors					
	2196	61%	3585	67%	**<0.00**
Being employed					**1**
Social participation					
Sports memberships	1187	33%	1601	30%	**0.006**
Music/cultural organizations	508	14%	651	12%	**0.012**
					<0.00
Other club membership (religious groups, talking groups, etc)	1147	32%	1370	26%	**1**
Interpersonal factors					
Social network structure					
					<0.00
Social network size	11.0	7.0	9.8	6.6	**1**
Type of relationship (proportion of network members)					
Family	47.2	24.5	48.5	25.2	**0.018**
Friends	26	18.3	27.1	19.4	**0.011**
					<0.00
Acquaintances	15.9	15.1	13.9	14.8	**1**
Extra members	5.6	11.8	5.6	11.8	0.86
Caregivers	5.3	10.3	4.9	10.4	0.066
Proportion of network members of the same gender	56.8	20.9	55.2	23	**0.001**
Proportion of network members of the same age[C]	41.7	22.2	43.0	24.4	**0.010**
					<0.00
Proportion of network members of younger age[D]	39.5	25.7	35.0	28.5	**1**

Proportion of network members of older age[D]	18.9	19.3	22.0	21.7	**<0.001**
Network diversity					**<0.001**
Only family, no friends/acquaintances/caregivers/other	434	12%	714	13%	
Family, friends, acquaintances, and/or caregivers or other	2265	63%	3014	57%	
Only family and friends	653	18%	1177	22%	
No family, but friends/acquaintances/caregivers/other	39	1%	104	2%	
Family and acquaintances, no friends	222	6%	307	6%	
Network density: family and friends know each other	2999	83%	4408	83%	0.89
Living alone	660	18%	830	16%	**<0.001**
Geographical proximity (proportion of network members who live)					
In the same house	17.1	21%	21.0	23%	**<0.001**
Walking distance	23.8	23%	22.3	23%	**0.003**
Further away	59.1	26%	56.7	28%	**<0.001**
Proportion of network members with in-person contact in the last two weeks	67.0	24.7	69.7	26	**<0.001**
Social network function					
I have many people around me that I can trust completely					0.058
No	204	6%	362	7%	
More or less	802	22%	1124	21%	
Yes	2614	72%	3842	72%	
Proportion of network members who provide support					
Informational support	50.3	31.8	54.2	33.1	**<0.001**
Practical support	22.0	22.8	24.4	25.9	**<0.001**
Emotional support (total)	68.4	29.2	67.1	31	**0.047**
Emotional support – important decisions	60.6	30.5	60.1	32.2	0.38
Emotional support – talking about health	46.5	33.3	46	34.4	0.46
Doing fun things together	58.7	30.5	59.9	32.3	**0.077**
Giving care to network	4.9	10.9	4.0	10.6	**<0.001**
Receiving care from network	6.0	12.7	5.6	13.6	0.15
No support	3.5	10.8	3.9	12.5	0.20
Social network quality					
Proportion of network members with whom the relationship is demanding, straining, or criticizing (social strain)	3.5	9.1	3.5	10.1	0.78
Individual factors					
Sociodemographic					

Age					**<0.001**
<60 years	1852	51%	3447	65%	
≥60 years	1768	49%	1881	35%	
Sex					**0.006**
Male	1651	46%	2273	43%	
Female	1969	54%	3055	57%	
Educational attainment					**<0.001**
Less than vocational training	300	8%	600	11%	
Vocational training	1664	46%	2604	49%	
College or university degree	1656	46%	2124	40%	
Country of birth					0.24
The Netherlands	3440	95%	5033	95%	
Other country	180	5%	295	6%	
Health					
Chronic conditions					
Chronic conditions associated with more severe COVID-19	916	25%	1249	23%	**0.044**
Chronic conditions not associated with more severe COVID-19	1607	44%	2034	38%	**<0.001**
Mental health conditions	201	6%	365	7%	**0.013**
BMI (kg/m^2)	27.0	4.7	26.7	5.1	**0.013**
PCR test result (up until baseline questionnaire)					**0.001**
Positive PCR test	2501	69%	3848	72%	
Negative PCR test	1119	31%	1480	28%	
Post-COVID-19 condition (PCC) at time of baseline questionnaire (feeling unrecovered from COVID-19)	1040	29%	1478	28%	0.31
Health behavior and health literacy					
Smoking					**<0.001**
Current	310	9%	654	12%	
Former	1499	41%	1856	35%	
Never	1811	50%	2818	53%	
Health literacy score[E]					N.A.
Ability to actively engage with healthcare providers (HLQ-6)	4.4	0.75			
Navigating the healthcare system (HLQ-7)	4.1	0.80			
Having sufficient information to manage my health (HLQ-2)	3.1	0.58			
Social support for health (HLQ-4)	3.2	0.56			
Loneliness					**0.001**
Not lonely	2463	68%	3480	65%	
Moderately lonely	899	25%	1361	26%	
Severely lonely	258	7%	487	9%	

Numbers are presented as N (%) or mean (SD).

BMI=Body Mass Index. PCR=Polymerase Chain reaction. HLQ= Health Literacy Questionnaire.
[A] p-value for Chi-square or T-test
[B] Different N because of missing data: For 'included in follow-up': N=3,566 (green space density), N=3,460 (household size), N=3,569 (financial wellbeing), N=3,576 (walkability), N=3,442 (livability). For 'not included in follow-up': N=5,244 (green space density), N=5,063 (household size), N=5,256 (financial wellbeing), N=5,261 (walkability), N=5,044 (livability).
[C] Different N because of missing data: For 'included in follow-up': N=3,549. For 'not included in follow-up': N=5,218.
[D] Different N because of missing data: For 'included in follow-up': N=3,548. For 'not included in follow-up': N=5,216.
[E] Only measured at follow-up.

Supplementary table 4. Multivariable forward selection logistic regression analyses of individual, interpersonal, community, and societal factors and COVID-19 vaccine and booster uptake, adjusted for age, sex, educational attainment, chronic conditions, and level of urbanization.

	COVID-19 vaccine uptake (N=9,013)[A]		COVID-19 booster uptake (N=3,442)[A]	
	OR[B]	95%CI	OR[B]	95%CI
Societal factors				
Urbanization of living area				
Not urbanized	1		1	
Little urbanized	1.33	0.98–1.81	0.96	0.65–1.42
Moderately urbanized	0.94	0.69–1.28	0.92	0.62–1.37
Highly/strongly urbanized	**1.44***	**1.05–1.98**	0.97	0.68–1.41
Green space density of living area				
Walkability - street connectivity density				
Walkability - public transport density				
Mean household size in living area				
Financial wellbeing in living area (mean percentile)				
Livability - physical environment			**1.07***	**1.01–1.13**
Livability - facilities				
Livability - housing stock				
Livability - neighborhood cohesion				
Livability - nuisance and safety	**1.03*****	**1.01–1.04**		
Community factors				
Work situation				
Employed				
Not employed				
Social participation				
Sport memberships	**1.35****	**1.09–1.67**		
Music/cultural organizations				
Other club membership (religious groups, talking groups, etc)				
Interpersonal factors				
Social network structure				
Network size including healthcare professionals				
Type of relationship (proportions)				
Family				
Friends				
Acquaintances	**2.15***	**1.13–4.08**		
Extra members				
Caregivers				
Proportion of network members of the same gender				
Proportion of network members of the same age				

Proportion of network members of older age				
Network diversity				
Only family, no friends/acquaintances/healthcare professionals/others				
Family, friends, acquaintances, and/or healthcare professionals or others				
Only family and friends				
No family, but friends/acquaintances/healthcare professionals/others				
Family and acquaintances, healthcare professionals or others, no friends				
Network density: family and friends know each other				
Living alone			**0.72***	**0.53–0.98**
Geographical proximity (proportion of network members who live)				
In the same house				
Walking distance				
Further away				
Proportion of network members with in-person contact in the last two weeks	**0.58****	**0.40–0.85**		
Social network function				
I have many people around me that I can trust completely				
No				
More or less				
Yes				
Proportion of network members who provide support				
Informational support				
Practical support			**0.42*****	**0.26–0.68**
Emotional support (total)				
Emotional support – important decisions				
Emotional support – talking about health				
Doing fun things together				
Giving care to network				
Receiving care from network				
No support				
Social network quality				
Proportion of network members with whom the relationship is demanding, straining, or criticizing (social strain)				
Individual factors				
Sociodemographic				
Age				
<60	1		1	
≥60	**3.80*****	**2.86–5.05**	**2.92*****	**2.19–3.88**
Sex				
Female	1		1	
Male	**1.23***	**1.02–1.50**	**1.38***	**1.07–1.78**
Educational attainment				
Less than vocational education	1		1	
Vocational education	1.22	0.88–1.69	1.01	0.63–1.64

College or university degree	1.20	0.86–1.68	0.91	0.56–1.49
Country of birth				
Other country	1		1	
The Netherlands	**1.55****	**1.12–2.16**	**1.64***	**1.03–2.62**
Health				
Chronic conditions				
Chronic conditions associated with more severe COVID-19	1.29	1.00–1.66	**1.38***	**1.01–1.88**
Chronic conditions not associated with more severe COVID-19	**1.34****	**1.09–1.64**	1.17	0.91–1.51
Mental health conditions	0.93	0.66–1.31	0.67	0.43–1.05
BMI (per 1 unit increase kg/m^2)	**1.04*****	**1.02–1.06**		
Negative PCR test	**2.30*****	**1.77–2.99**		
Post-COVID-19 condition (PCC) at time of baseline questionnaire (feeling unrecovered from COVID-19)				
Health behavior and health literacy				
Smoking				
Currently			1	
Former			**1.84****	**1.23–2.76**
Never			1.11	0.74–1.66
Health literacy[C]				
Ability to actively engage with healthcare providers (HLQ-6)				
Navigating the healthcare system (HLQ-7)				
Having sufficient information to manage my health (HLQ-2)			**1.27***	**1.04–1.56**
Social support for health (HLQ-4)				
Loneliness				
Not lonely	1			
Moderately lonely	**0.76***	**0.62–0.94**		
Severely lonely	**0.68***	**0.50–0.92**		

OR= odds ratio; 95%CI= 95% confidence interval. This table shows results for variables retained in the multivariable model.

[A] N was 9,013 for outcome 1 (instead of N=9,501) and N=3,442 for outcome 2 (instead of 3,620) because of missing data for the variables at the societal level (GECCO data).

[B] *p≤0.05, **p≤0.01, ***p≤0.001

[C] Only measured at follow-up.



Section 3

Post-COVID-19 condition



Chapter 8

Workforce exit and work productivity loss in adults with and without post-COVID-19 condition: the PRIME post-COVID cohort study.

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Under review.

ABSTRACT

Background

Post-COVID-19 condition (PCC) is highly prevalent, yet evidence on its long-term impact on work participation remains limited. This study aimed to assess workforce exit and work productivity loss among adults with PCC compared to those recovered or without PCC.

Methods

In this prospective cohort study (PRIME post-COVID) conducted in South Limburg, the Netherlands, we used online questionnaire data from adults with a positive COVID-19 test between June 1, 2020, and September 11, 2022. Participants were categorized into the groups (1) PCC (not feeling recovered at least three months post-infection), (2) Recovered, and (3) Never PCC. All were employed in 2022 and followed until 2024. Workforce exit and associated factors, work productivity loss, work incapacity, and financial strain were evaluated at follow-up.

Findings

The two-year workforce exit rate was 17% in PCC (N=790), 10% in Recovered (N=437), and 9% in Never PCC (N=2,115). Rates were higher among those with PCC, older age, and with a range of physical and mental health conditions. Absenteeism and presenteeism were up to three times higher in PCC and two times higher in Recovered, compared to Never PCC. Full or partial work incapacity among non-employed participants was 46% in PCC, 17% in Recovered, and 12% in Never PCC. Financial strain was highest among non-employed PCC participants (54%) and lowest among employed Never PCC participants (19%).

Conclusion

PCC substantially impacts workforce participation and productivity. Support, interventions, and awareness are urgently needed.

INTRODUCTION

Post-COVID-19 condition (PCC) or long COVID are persistent symptoms that last for at least 3 months after a SARS-CoV-2 infection. Around six percent of individuals infected with COVID-19 develop PCC, highlighting its substantial impact as a global public health problem (1). Key symptoms include fatigue, cognitive problems, dyspnea, orthostatic intolerance, and post-exertional malaise (2-6). PCC is a heterogeneous, multisystem condition, causing functional which impair everyday life and everyday activities, including work participation (3, 5-7).

The COVID-19 pandemic has shaped employment outcomes in multiple ways. Economic disruptions, business closures, and widespread uncertainty led to job losses and reduced work opportunities (8, 9). High infection rates further affected workforce participation due to illness, quarantine, and broader public health measures (10). While the immediate effects of the pandemic have largely diminished, PCC remains a significant factor influencing employment, as persistent symptoms can continue to limit work ability (3).

Early studies indicated that employees infected with SARS-CoV-2 experienced a delayed return to work (11), and PCC has been linked to long-term reductions in employment, increased workforce exit, lower likelihood of full-time work, and financial strain (3, 11-14). Six months post-infection, 22% of individuals with PCC were unable to work and 45% reduced their work schedule (11). In participants with 7 months of long-term symptoms, 19% could not work, 10% reduced hours, and 37% had lower income (15). After 12 months, 5.8% experienced occupational effects, with 1.6% leaving the workforce (16). A meta-analysis found ~60% returned to work after ≥12 weeks, often requiring modified duties or hours to manage residual impairments (3).

Among those who remain employed, ongoing PCC symptoms may impair concentration and reduce overall work productivity (16, 17). Presenteeism (impairment while working) often compromises performance and can

worsen health issues (3). Dutch data showed persistent absenteeism (52%) and presenteeism (60%) six months post-infection (18). Up to three years post-infection, PCC patients had increased odds of work impairment and poorer financial outcomes compared to those without PCC (12). Patients with PCC were over three times more likely to report productivity loss and more than four times more likely to report impaired work performance compared with those without persistent symptoms (19).

Employment supports financial stability, social participation, and well-being (9), highlighting the importance of understanding long-term workforce outcomes in individuals with PCC. However, evidence remains limited regarding long-term workforce exit and productivity loss in those with persistent PCC compared with recovered or never-infected individuals. This study aims to compare workforce exit and productivity among these groups in the Netherlands to inform strategies for social participation and reintegration.

METHODS

Setting: Dutch occupational health system

In the Netherlands, employees who fall ill initially enter sick leave, followed by long-term absence if symptoms persist. Occupational physicians are involved early. Under the Gatekeeper Improvement Act (Wet Verbetering Poortwachter), employers must report sickness within one week, and within six weeks the physician prepares a problem analysis to guide reintegration. By week eight, an action plan is jointly established. If disability continues beyond two years, medical documentation is submitted to the UWV for assessment under the WIA (Work and Income according to Labor Capacity Act), requiring ≥35% work incapacity. Benefits depend on the degree and permanence of disability. Partially disabled workers receive 70% of prior earnings, while those fully and permanently incapacitated receive 75% and are exempt from reassessment, and the received benefits are more readily recognized as stable income (20, 21). However, functional capacity is often

judged too optimistically, and exertion testing can worsen symptoms. Individuals with PCC frequently face difficulties gaining recognition of their condition (22). PCC patients often face overestimation of work capacity, resulting in reduced benefits (23). Among thousands of PCC-related WIA applications, ~10% receive full benefits, 25% partial, and 15% are rejected (24).

Study design

The Prevalence, Risk factors, and Impact Evaluation (PRIME) post-COVID study is an observational cohort study with retrospective and prospective elements (25). Adults tested for SARS-CoV-2 at the local public health service in South Limburg, The Netherlands, between June 2020 and November 2021 (N=61,655) were invited for a baseline questionnaire in November-December 2021 (baseline 1); of which 12,453 participants were invited for follow-up 1 in July-August 2022. Another group (N=58,318) tested in March 2022 was invited for baseline 2. In April-June 2024, 18,132 participants from these cohorts were invited for a follow-up measurement (follow-up 2) (Figure 1, Supplementary figure 1).

Participants

Eligible participants were employed at the 2022 measurement, had a confirmed or self-reported positive SARS-CoV-2 test between June 2020 and October 2022, and completed the 2022 (baseline 2 or follow-up 1) and 2024 (follow-up 2) questionnaires without missing data for variables used in analyses. Self-reported positive tests included self-tests, tests for admission, or tests at other healthcare providers. Participants who likely represented another person than the intended invitee (reported inconsistent information regarding sex and test result compared to the baseline questionnaire) were excluded (Supplementary figure 1). Participants with inconsistent responses suggesting they were not the intended invitee were excluded (Supplementary Figure 1). Data were collected via the online MWM2 application (Crowdtech, ISO 27001 certified). Digital informed consent was obtained before data collection

and for linkage from the questionnaire to the public health registry data for verification of age, sex, and test results (25).

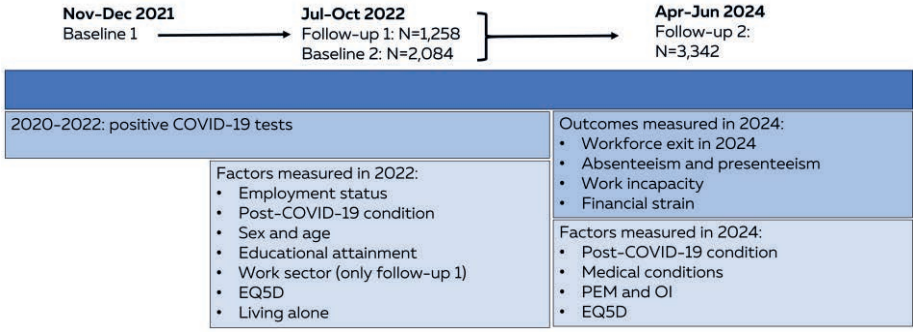


Figure 1: Timeline of questionnaires, data collection, and included study population

Post-COVID-19 condition

PCC-status was determined using the question, 'Do you feel recovered from COVID-19?' Participants who answered 'no' in 2024 were classified as having PCC. Those who reported not feeling recovered >3 months after infection in 2021 or 2022 but did feel recovered in 2022 or 2024 were classified as recovered from PCC in 2024 ('Recovered') and those who had never reported not feeling recovered in 2024 were classified as 'Never PCC'.

Outcomes: Workforce exit, absenteeism and presenteeism

The primary outcome was workforce exit in 2024, determined from follow-up 2 work status. Participants employed by an employer or self-employed were classified as "employed," while those fully or partially incapacitated, unemployed, homemakers, or retired were classified as having exited the workforce.

Among participants employed in 2024, we calculated absenteeism and presenteeism using the Work Productivity and Activity Impairment (WPAI) questionnaire (26). Absenteeism was defined as the percentage of work time missed due to health problems in the past 7 days, with reported hours truncated at 60 per week to limit extreme values. Presenteeism represented the percentage of impairment while working due to health problems in the past 7 days, with higher percentages indicating lower

productivity. Both outcomes were reported for all employed participants and for the subset with any absenteeism or presenteeism. Changes in work hours between 2022 and 2024 were calculated for participants employed at both time points by summing hours worked and hours missed due to health problems.

PCC-related

PCC duration was estimated from the first report of not feeling recovered and categorized as less than two years, two to three years, or at least three years. The two-year cutoff reflects the maximum period Dutch employers must continue paying wages for sick employees, after which WIA benefits may be applied for. In participants who had recovered from PCC, recovery duration was similarly estimated as less than two or at least two years.

Sociodemographics

Sociodemographic variables included sex (male/female), age in 2022 (18–49, 50–66, or ≥67 years), and living alone. Education level (practical/mixed or theoretical) and work sector were also recorded in 2022. Work sector was analyzed only in participants who completed follow-up 1 and categorized as office/knowledge/government/other; healthcare and social services; education and childcare; service, hospitality, and retail; or technology, industry, transport, and agriculture.

Health

Participants reported medical conditions as of 2024, including cardiovascular disease; lung disease, chronic obstructive pulmonary disease (COPD) or asthma; diabetes; cancer; mental health conditions; joint or bone conditions; concentration disorder or migraine; chronic fatigue syndrome, fibromyalgia or sclerosis; and obesity. Post-exertional malaise (PEM) was assessed using the five-item DePaul Symptom Questionnaire (DSQ-PEM), and orthostatic intolerance (OI) using four DSQ-2 items based on ME/CFS classifications. Health status was measured in 2022 and 2024 using EuroQol five-dimensions (EQ5D), covering mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Individual items were

evaluated and an EQ5D index score was calculated by attaching weights to each level in each dimension (27). A higher score represents better health, with the highest score being 1. Scores were categorized into <0.80, 0.80–0.90, and >0.90, based on the distribution of the data.

Financial strain

Financial strain (defined as the ability to make ends meet) was evaluated in 2024 among employed and non-employed participants, stratified by PCC status. Response options included: "I can make ends meet and have money left," "I can make ends meet but have no money left," and "I cannot make ends meet." Participants who chose "Do not want to say" were excluded from the analysis.

Statistical analysis

Differences in participant characteristics between PCC, Recovered, and Never PCC groups were analyzed using descriptive statistics. Associations between workforce exit and included factors were determined using descriptives and logistic regression analyses, stratified for the three PCC groups and adjusted for age. Multivariable logistic regression was then used to assess the odds of workforce exit according to PCC-status and other factors in the total study population, including PCC-status and age, sex, educational attainment, living alone, health conditions, and EQ5D score as other factors. As a sensitivity analysis, this analysis was performed in a group excluding participants aged ≥67 years to account for workforce exit due to retirement at the official retirement age.

Correlations between variables were all below 0.7, indicating no multicollinearity.

In the group who had exited the workforce, we described various types of incapacity by PCC-status, including full incapacity and partial incapacity out of employment. As a sensitivity analysis, participants aged ≥67 years were excluded to assess the proportion of incapacity among those below the official retirement age. In the group who was employed in 2024, we described mean percentages of absenteeism and presenteeism,

proportions for partial incapacity, weekly working hours in 2024, and the change in weekly working hours between 2022 and 2024 by PCC-status. All analyses were performed using IBM SPSS Statistics version 27.0 and a p-value of <0.05 was considered statistically significant.

Ethical Considerations & Disclosure(s)

The PRIME-post COVID study was waived by the Medical Ethical Committee of Maastricht University Medical Centre+ (METC2021-2884). This study was registered at ClinicalTrials.gov Protocol Registration and Results System (NCT05128695). The participants provided their written informed consent to participate in this study.

RESULTS

Study population

Within 3,342 participants included, mean age was 53 years, with 7% aged 67 or older; about half were theoretically trained; and 60% were women. A confirmed PCR test was recorded for 87%, while 13% self-reported a positive test result. In 2024, 24% reported PCC (feeling unrecovered), over 80% of whom had symptoms lasting more than two years; 13% had recovered, and 63% never reported PCC (Table 1).

Characteristics of the PCC and Never PCC group

PCC participants had the highest prevalence of post-exertional malaise, orthostatic intolerance, and various physical and mental health conditions, followed by Recovered and Never PCC. EQ5D scores were lowest in PCC across all domains in both 2022 and 2024. Vaccination prior to infection was reported by 67% of PCC, 74% of Recovered, and 81% of Never PCC participants; overall, 5% of participants were unvaccinated (Table 1).

Table 1: Study population characteristics, stratified by PCC-status (N=3,342)

	PCC N=790	Recovered N=437	Never PCC N=2,115	P
	% (N)	% (N)	% (N)	
PCC duration				*N.A.*
At least 3 years	38% (297/790)	41% (178/437)		
Between 2 and 3 years	40% (314/790)	59% (259/437)		
Less than 2 years	23% (179/790)	N.A.		
Recovery duration				*N.A.*
At least 2 years		23% (101/437)		
Less than 2 years		77% (336/437)		
Age in 2022				**<0.001**
18-49 years	32% (249/790)	32% (140/437)	40% (845/2,115)	
50-66 years	66% (523/790)	66% (287/437)	57% (1,213/2,115)	
≥67 years	2% (18/790)	2% (10/437)	3% (57/2,115)	
Sex				0.86
Women	60% (474/790)	61% (258/437)	60% (1,268/2,115)	
Men	40% (316/790)	39% (169/437)	40% (847/2,115)	
Educational attainment in 2022				**<0.001**
Theoretical	42% (331/790)	51% (222/437)	60% (853/2,115)	
Practical/ mixed	58% (459/790)	49% (215/437)	40% (853/2,115)	
Work sector[A] in 2022				*0.22*
Office work, knowledge sector, government, other	*40% (157/397)*	*41% (92/222)*	*44% (279/639)*	
Health care and social services	*29% (115/397)*	*23% (50/222)*	*26% (166/639)*	
Education and childcare	*9% (37/397)*	*14% (30/222)*	*12% (77/639)*	
Service, hospitality, retail	*9% (36/397)*	*11% (24/222)*	*7% (42/639)*	
Technology, industry, transport, agriculture	*13% (52/397)*	*12% (26/222)*	*12% (75/639)*	
Living alone in 2022	17% (131/79)	16% (68/437)	14% (303/3,342)	0.30
Vaccination status				**<0.001**
Vaccinated before infection	67% (530/790)	74% (321/437)	81% (1,703/2,115)	
Not vaccinated before infection or never vaccinated	32% (251/790)	26% (115/437)	19% (396/2,115)	
Vaccination status or vaccination date unknown	1% (9/790)	0.2% (1/437)	1% (16/2,115)	
Medical conditions				
Cardiovascular disease	11% (84/790)	9% (39/437)	5% (106/2,115)	**<0.001**

Lung disease, COPD or asthma	19% (151/790)	14% (61/437)	7% (146/2,115)	**<0.001**
Diabetes	7% (57/790)	4% (17/437)	4% (85/2,115)	**0.001**
Cancer	2% (16/790)	2% (8/437)	3% (56/2,115)	0.44
Mental health condition	15% (116/790)	9% (40/437)	6% (132/2,115)	**<0.001**
Joint or bone condition	38% (297/790)	29% (126/437)	21% (436/2,115)	**<0.001**
Concentration disorder or migraine	24% (191/790)	12% (52/437)	6% (123/2,115)	**<0.001**
Chronic fatigue syndrome, fibromyalgia or sclerosis	11% (86/790)	5% (20/437)	2% (47/2,115)	**<0.001**
Obesity	15% (116/790)	11% (48/437)	7% (137/2,115)	**<0.001**
Post-exertional malaise (PEM) in 2024	29% (227/790)	10% (42/437)	4% (91/2,115)	**<0.001**
Orthostatic intolerance (OI) in 2024	13% (101/790)	6% (25/437)	2% (31/2,115)	**<0.001**
EQ5D in 2022				
EQ5D score in 2022				**<0.001**
<0.80	45% (352/790)	24% (106/437)	9% (184/2,115)	
0.80 – 0.90	37% (294/790)	48% (209/437)	31% (660/2,115)	
>0.90	18% (144/790)	28% (122/437)	60% (1,271/2,115)	
EQ5D- problems with mobility in 2022	17% (33/790)	7% (32/437)	3% (65/2,115)	**<0.001**
EQ5D- problems with self-care in 2022	2% (18/790)	1% (3/437)	0.3% (7/2,115)	**<0.001**
EQ5D- problems with performing daily activities in 2022	27% (215/790)	12% (51/437)	3% (66/2,115)	**<0.001**
EQ5D- pain or discomfort in 2022	33% (263/790)	19% (83/437)	7% (145/2,115)	**<0.001**
EQ5D- anxiety or depression in 2022	14% (114/790)	7% (29/437)	5% (98/2,115)	**<0.001**
EQ5D in 2024				
EQ5D score in 2024				**<0.001**
<0.80	51% (401/790)	21% (91/437)	13% (271/2,115)	
0.80 – 0.90	36% (285/790)	50% (218/437)	37% (784/2,115)	
>0.90	13% (104/790)	29% (128/437)	50% (1,060/2,115)	
EQ5D- problems with mobility in 2024	19% (640/790)	6% (24/437)	4% (90/2,115)	**<0.001**
EQ5D- problems with self-care in 2024	3% (23/790)	1% (3/437)	1% (12/2,115)	**<0.001**
EQ5D- problems with performing daily activities in 2024	29% (228/790)	8% (36/437)	4% (94/2,115)	**<0.001**
EQ5D- pain or discomfort in 2024	40% (317/790)	17% (73/437)	11% (234/2,115)	**<0.001**
EQ5D- anxiety or depression in 2024	14% (111/790)	7% (29/437)	3% (64/2,115)	**<0.001**

[A] Work sector was only evaluated for the follow-up 1 population and was therefore only available for a subgroup of N=1,258 (PCC: N=397; Recovered: N=222; Never PCC: N=639)

Workforce exit by PCC-status

By 2024, 11% of workers in 2022 had exited the workforce. Workforce exit was highest in the PCC group (17%), compared to Recovered (10%) and Never PCC (9%; p < 0.001). PCC was associated with over twice the odds of workforce exit versus Never PCC (aOR = 2.07; 95% CI: 1.60–2.67). This association remained after adjusting for other factors and excluding participants aged ≥67 years. Workforce exit did not differ between the Recovered group and the Never PCC group (Table 2).

Table 2. Logistic regression analysis for associations between PCC-status and workforce exit in 2024.

	Workforce exit	**Univariable model, adjusted for age aOR (95% CI); p**	**Multivariable model aOR (95% CI); p**	**Multivariable model, excluding participants ≥67 years[A] aOR (95% CI); p**
PCC	17% (132/790)	2.07 (1.60-2.67); **p<0.001**	1.38 (1.02-1.86); **p=0.038**	1.41 (1.04-1.92); **p=0.028**
Recovered	10% (42/437)	1.03 (0.71-1.49); p=0.88	0.87 (0.59-1.28); p=0.48	0.89 (0.59-1.32); p=0.55
Never PCC	9% (232/2,552)	1	1	1

[A] OR calculated within N=3,257 (PCC: N=772, Recovered: N=427, Never PCC: N=2,058).

Factors associated with workforce exit

In the PCC group, workforce exit was associated with older age, post-exertional malaise, orthostatic intolerance, respiratory, musculoskeletal, neurological, and mental health conditions, lower EQ5D scores across all domains. In Recovered participants, associations included older age, cardiovascular disease, diabetes, cancer, and limitations in mobility and daily activity. In Never PCC, associated factors included older age, practical/mixed education, post-exertional malaise, orthostatic intolerance, cardiovascular disease, diabetes, cancer, and lower EQ5D scores for activities of daily living and pain or discomfort (Table 3).

Table 3: Proportions and logistic regression analysis for factors associated with workforce exit in 2024, adjusted for age, stratified by PCC-status.

	PCC				Recovered				Never PCC			
	% workforce exit	OR	95% CI	P	% workforce exit	OR	95% CI	P	% workforce exit	OR	95% CI	P
Overall (N workforce exit/total study population)	17% (132/790)				10% (42/437)				9% (232/2,552)			
PCC duration				**0.044**								
At least 3 years	19% (55/297)	2.09	1.13–3.87	**0.020**	10% (17/178)							
Between 2 and 3 years	18% (56/314)	2.07	1.12–3.83	**0.020**	10% (25/259)							
Less than 2 years	12% (21/179)	1			N.A.							
Recovery duration												
Between 2 and 3 years					10% (17/178)	1.47	0.62–3.51	0.39				
Less than 2 years					10% (25/259)	1						
Age				**<0.001**				**<0.001**				**<0.001**
18–49 years	9% (23/249)	1			3% (4/140)	1			2% (16/845)	1		
50–66 years	18% (96/523)	2.21	1.36–3.58	**0.001**	11% (32/287)	2.95	0.86–10.16	0.086	11% (136/1,213)	4.18	2.36–7.39	**<0.001**
≥67 years	72% (13/18)	25.55	8.36–78.07	**<0.001**	60% (6/10)	73.94	18.95–288.47	**<0.001**	67% (38/57)	92.19	49.04–173.32	**<0.001**
Sex												
Women	16% (76/474)	1			7% (18/268)	1			8% (96/1,268)	1		
Men	18% (56/316)	0.85	0.55–1.30	0.45	14% (24/169)	1.59	0.75–3.38	0.23	11% (94/847)	1.05	0.74–1.49	0.80
Educational attainment												
Theoretical	16% (54/331)	1			8% (18/222)	1			7% (83/1,262)	1		
Practical/ mixed	17% (78/459)	1.11	0.72–1.70	0.64	11% (24/215)	1.29	0.61–2.74	0.51	13% (107/853)	1.96	1.37–2.80	**<0.001**
Work sector[A]				*0.81*				*0.70*				*0.49*
Office work, knowledge sector, government, other	*18% (28/157)*	*1*			*10% (9/92)*	*1*			*11% (31/279)*	*1*		

Health care and social services	*15% (17/115)*	*0.79*	*0.38–1.65*	*0.53*	*10% (5/50)*	*1.79*	*0.48–6.71*	*0.39*	*9% (15/166)*	*0.97*	*0.47–2.01*	*0.94*
Education and childcare	*16% (6/37)*	*1.04*	*0.36–3.02*	*0.95*	*7% (2/30)*	*0.67*	*0.095–4.70*	*0.69*	*9% (7/77)*	*0.83*	*0.31–2.22*	*0.72*
Service, hospitality, retail	*22% (8/36)*	*1.22*	*0.46–3.26*	*0.69*	*8% (2/24)*	*0.48*	*0.064–3.58*	*0.47*	*5% (2/42)*	*0.22*	*0.043–1.16*	*0.075*
Technology, industry, transport, agriculture	*23% (12/52)*	*1.38*	*0.60–3.21*	*0.45*	*12% (3/26)*	*1.84*	*0.37–9.02*	*0.46*	*13% (10/75)*	*1.08*	*0.45–2.62*	*0.86*
Living alone	16% (21/131)	0.92	0.53–1.62	0.78	7% (5/68)	0.30	0.084–1.05	0.059	9% (28/314)	0.64	0.38–1.09	0.10
Vaccination status				0.66				*1.00*				0.43
Vaccinated before infection	16% (84/530)	1			10% (31/321)	*1*			9% (151/1,703)	1		
Not vaccinated before infection or never vaccinated	19% (47/251)	1.22	0.79–1.89	0.36	10% (11/115)	*1.01*	*0.44–2.36*	0.98	9% (36/396)	1.15	0.74–1.79	0.54
Vaccination status or vaccination date unknown	11% (1/9)	0.97	0.12–7.97	0.98	0%	*0*			19% (3/16)	2.66	0.53–13.48	0.24
Medical conditions												
Cardiovascular disease	18% (15/84)	1.41	0.60–2.16	0.69	26% (10/39)	2.87	1.07–7.72	**0.037**	20% (21/106)	2.32	1.29–4.19	**0.005**
Lung disease, COPD or asthma	21% (32/151)	1.81	1.12–2.91	**0.016**	10% (6/61)	0.96	0.33–2.83	0.94	9% (13/146)	1.18	0.61–2.28	0.63
Diabetes	25% (14/57)	1.82	0.92–3.60	0.084	35% (6/17)	6.15	1.73–21.93	**0.005**	25% (21/85)	2.46	1.31–4.62	**0.005**
Cancer	19% (3/16)	0.79	0.18–3.52	0.76	38% (3/8)	9.64	2.11–43.97	**0.003**	25% (14/56)	2.44	1.15–5.18	**0.020**
Mental health condition	29% (34/116)	3.50	2.12–5.78	**<0.001**	5% (2/40)	0.49	0.094–2.54	0.39	8% (11/132)	1.54	0.77–3.09	0.23
Joint or bone condition	21% (63/297)	1.63	1.07–2.47	**0.022**	10% (12/126)	0.66	0.28–1.54	0.34	12% (51/436)	1.18	0.79–1.76	0.42
Concentration disorder or migraine	24% (46/191)	2.17	1.39–3.38	**<0.001**	6% (3/52)	0.64	0.17–2.47	0.52	7% (9/123)	1.23	0.59–2.59	0.59
Chronic fatigue syndrome, fibromyalgia or sclerosis	23% (20/86)	1.89	1.06–3.37	**0.031**	5% (1/20)	0.87	0.11–6.85	0.89	4% (2/47)	0.72	0.17–3.03	0.66
Obesity	21% (24/116)	1.34	0.78–2.30	0.30	6% (3/48)	0.91	0.25–3.39	0.89	7% (9/137)	0.74	0.34–1.60	0.44
Post-exertional malaise (PEM) 2024	23% (53/227)	3.03	1.96–4.69	**<0.001**	5% (2/42)	0.46	0.090–2.38	0.36	10% (9/91)	2.09	1.01–4.33	**0.047**
Orthostatic intolerance (OI) 2024	26% (26/101)	2.20	1.30–3.73	**0.004**	12% (3/25)	1.46	0.33–6.55	0.62	19% (6/31)	3.70	1.40–9.80	**0.009**
EQ5D 2022												
EQ5D score				**<0.001**				0.44				**0.029**

<0.80	24% (86/352)	5.39	2.40–12.07	**<0.001**	12% (13/106)	1.04	0.40–2.71	0.93	13% (24/184)	2.06	1.19–3.54	**0.010**
0.80–0.90	13% (38/294)	2.26	0.97–5.28	0.060	7% (15/209)	0.62	0.25–1.51	0.29	10% (68/660)	1.29	0.88–1.89	0.19
>0.90	6% (8/144)	1			12% (14/122)	1			8% (98/1,271)	1		
EQ5D- problems with mobility	32% (42/133)	2.92	1.82–4.69	**<0.001**	19% (6/32)	3.06	1.03–9.07	**0.044**	19% (12/65)	1.96	0.92–4.20	0.082
EQ5D- problems with self-care	56% (10/18)	6.27	2.26–17.42	**<0.001**	33% (1/3)	7.22	0.63–83.49	0.11	14% (1/7)	1.08	0.077–15.14	0.96
EQ5D- problems with performing daily activities	31% (67/215)	4.15	2.69–6.40	**<0.001**	16% (8/51)	3.57	1.39–9.15	**0.008**	21% (14/66)	4.76	2.45–9.25	**<0.001**
EQ5D- pain or discomfort	25% (66/263)	2.77	1.81–4.23	**<0.001**	13% (11/83)	1.95	0.82–4.61	0.13	17% (24/145)	2.11	1.22–3.62	**0.007**
EQ5D- anxiety or depression	32% (35/111)	3.79	2.31–6.22	**<0.001**	10% (3/29)	1.36	0.31–6.01	0.69	5% (3/64)	0.53	0.14–1.96	0.34
EQ5D 2024												
EQ5D score				**<0.001**				0.74				0.058
<0.80	22% (88/401)	4.11	1.75–9.66	**0.001**	9% (8/91)	1.27	0.42–3.86	0.67	12% (32/271)	1.82	1.12–3.00	**0.018**
0.80–0.90	13% (36/285)	1.15	0.46–2.89	0.77	11% (23/218)	1.42	0.58–3.47	0.44	10% (80/784)	1.12	0.77–1.65	0.55
>0.90	8% (8/104)	1			9% (11/128)	1			7% (78/1,060)	1		
EQ5D- problems with mobility	31% (46/150)	3.47	2.19–5.51	**<0.001**	29% (7/24)	4.98	1.63–15.19	**0.005**	19% (17/90)	2.49	1.33–4.67	**0.005**
EQ5D- problems with self-care	61% (14/23)	10.97	4.54–26.48	**<0.001**	33% (1/3)	9.84	0.81–120.33	0.073	8% (1/12)	0.66	0.062–6.99	0.73
EQ5D- problems with performing daily activities	27% (62/228)	3.25	2.11–4.99	**<0.001**	8% (3/36)	1.24	0.32–4.75	0.76	18% (17/94)	3.28	1.77–6.09	**<0.001**
EQ5D- pain or discomfort	21% (67/317)	2.09	1.37–3.19	**<0.001**	10% (7/73)	1.12	0.42–2.99	0.82	10% (23/234)	1.18	0.70–1.99	0.54
EQ5D- anxiety or depression	25% (29/114)	2.83	1.71–4.68	**<0.001**	7% (2/29)	1.02	0.20–5.33	0.98	7% (7/98)	1.12	0.47–2.66	0.80

[A] Work sector was only evaluated for the follow-up 1 population and was therefore only available for a subgroup of N=1,258 (PCC: N=397; Recovered: N=222; Never PCC: N=639)

Population not employed in 2024 and work incapacity

Among those who exited the workforce, full incapacity was reported by 36% in PCC, 12% in Recovered, and 9% in Never PCC. Partial incapacity was 10%, 5%, and 3%, respectively. Sensitivity analysis excluding participants aged ≥67 showed full incapacity was 48% in PCC, 23% in Recovered, and 17% in Never PCC (Table 4). Mean age among retired participants was 67 years across all groups.

Table 4: Proportions for incapacity and reasons for workforce exit in the study population not employed in 2024

	PCC		**Recovered**		**Never PCC**	
Participants who had left the workforce in 2024 (N=364)	N=132	%	N=42	%	N=190	%
Fully incapacitated	47	36%	5	12%	17	9%
Partially incapacitated, not employed	13	10%	2	5%	6	3%
Homemaker	1	1%	2	5%	8	4%
Searching for work	26	20%	4	10%	24	13%
Retired	45	34%	29	69%	135	71%
Participants who had left the workforce in 2024 Sensitivity analysis only including participants <67 years (N=219)	N=95	%	N=22	%	N=102	%
Fully incapacitated	46	48%	5	23%	17	17%
Partially incapacitated, not employed	13	14%	2	9%	6	6%
Homemaker	1	1%	2	9%	8	8%
Searching for work	25	26%	4	18%	24	24%
Retired	10	11%	9	41%	47	46%

Chi square: P<0.001

Population employed in 2024

Of 2,978 employed participants, absenteeism due to health reasons was calculated for 2,902 participants (76 participants did not work for non-health related reasons, e.g., vacation) and presenteeism for 2,784 participants (118 participants reported zero hours worked due to health problems).

In 2024, mean work time missed due to health (absenteeism) was highest in the PCC group (14%), followed by Recovered (8%) and Never PCC (5%). Any absenteeism was reported by 22% of PCC, 13% of Recovered, and 8% of Never PCC participants; among these, mean absenteeism was 62–64%. Mean

impairment while working due to health (presenteeism) was 43% in PCC, 23% in Recovered, and 13% in Never PCC. Any presenteeism was reported by 87% of PCC, 57% of Recovered, and 39% of Never PCC. Among those, mean presenteeism was 50% in PCC, 40% in Recovered, and 33% in Never PCC.

Partial work incapacity was reported by 4% of employed PCC, 2% Recovered, and 1% Never PCC participants. Mean weekly working hours were 33 across groups (Table 5). Between 2022 and 2024, 20% reduced and 23% increased their hours.

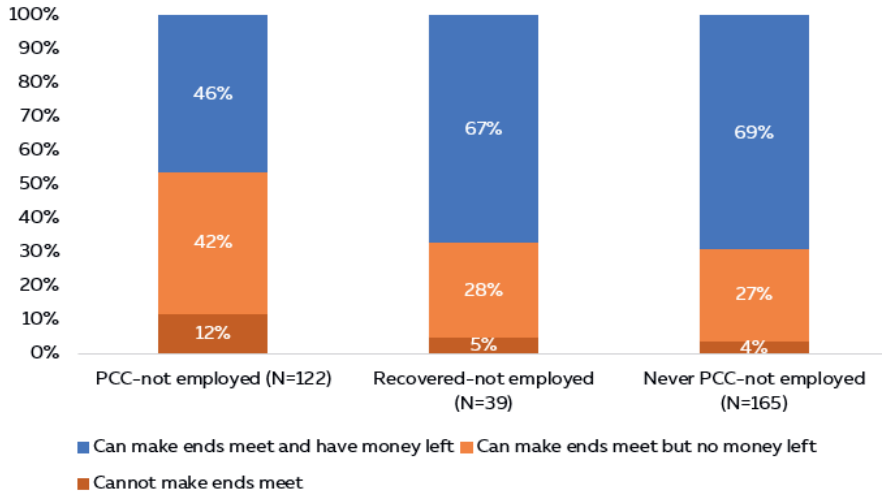
Table 5: Absenteeism, presenteeism, partial incapacity, and working hours in the study population employed in 2024.

	PCC N=658		Recovered N=395		Never PCC N=1,925		P[D]
Work time missed due to health (absenteeism) in 2024 (N=2,902[A])							
Overall, mean % and 95% CI	13.5% (N=648)	11.2%-15.8%	8.4% (N=380)	5.9%-10.8%	4.9% (N=1,874)	4.0%-5.8%	**<0.001**
Number of hours absent in the past week, mean and 95% CI	4.8	3.9-5.7	3.0	2.0-3.9	1.7	1.3-2.0	**<0.001**
Any absenteeism (≥1%) (%, N)	22% (142/648)		13% (5/38)		8% (144/1,874)		**<0.001**
Mean % absenteeism in participants with ≥1% (95% CI)	61.6%	56.0%-67.2%	63.6%	54.3%-72.9%	63.7%	57.7%-69.6%	0.91
Impairment while working due to health (presenteeism) in 2024 (N=2,784[B])							
Overall, mean % and 95% CI	43.3% (N=599)	41.0%-45.5%	22.7% (N=366)	19.8%-25.5%	12.8% (N=1,819)	11.8%-13.9%	**<0.001**
Any presenteeism (≥1%) (%, N)	87% (522/599)		57% (209/366)		39% (708/1,819)		**<0.001**
Mean % presenteeism in participants with ≥1% (95%CI)	49.7%	47.6%-51.7%	39.7%	36.1%-43.2%	33.0%	31.2%-34.8%	**<0.001**
Employed and partially incapacitated in 2024	5% (N=30/658)		2% (N=9/395)		1% (N=22/1,925)		**<0.001**
Weekly working hours (N=2,978[C])							
Mean working hours in 2024	32.9 ± 11.7		32.7 ± 12.6		33.1 ± 12.0		0.42
Mean delta working hours (2024-2022)	1.15 ± 11.2		1.63 ± 11.7		0.54 ± 11.3		0.40

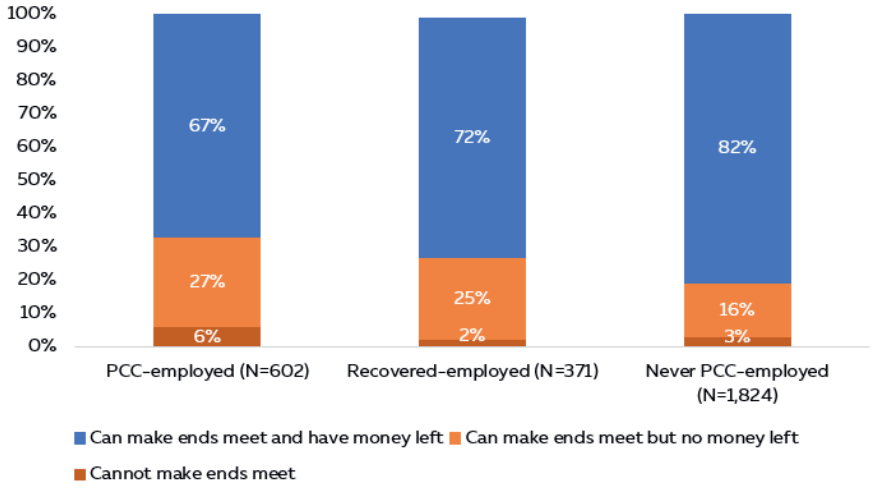
[A] Participants employed in both 2022 and 2024 (N=2,978), minus participants who did not work in the past 7 days but for other reasons than health (N=76). [B] Participants employed in both 2022 and 2024 (N=2,978), minus participants who did not work in the past 7 days but for other reasons than health (N=76) and participants worked zero hours because of health problems (N=118). [C] Participants employed in both 2022 and 2024 (N=2,978). [D] P-value from Chi-square or Kruskal-Wallis test.

Financial strain

In 2024, over half of participants (54%) with PCC who were not employed reported difficulty making ends meet. This proportion was 33% among Recovered and 31% among Never PCC who were not employed (p<0.001). Among employed participants, financial strain was reported by 33% (PCC), 27% (Recovered), and 19% (Never PCC) (p<0.001) (Figure 1).



A. **Financial strain in the study population not employed in 2024**



B. **Financial strain in the study population employed in 2024**

Figure 1. Financial strain, stratified by PCC-status and employment status in 2024.

DISCUSSION

In this large population-based cohort in a Western European setting, individuals with long-term post-COVID-19 condition (PCC) showed markedly higher rates of workforce exit and productivity loss compared with those recovered or never affected. Between 2022 and 2024, 17% of workers with PCC left the workforce, versus 9 to 10% in those recovered or who never had PCC. Productivity loss due to absenteeism and presenteeism was up to three times higher in those with current PCC and notably also twice as high in recovered participants, compared to those who never had PCC. Individuals with PCC also more frequently reported work incapacity and financial strain. These findings highlight the sustained occupational and socioeconomic impact of PCC and the need for targeted support strategies.

Medical conditions and PCC-related factors

Previous research also found a significant difference in workforce exit between individuals with PCC and those without, reporting a 59% work-loss rate in the PCC group attributed directly to SARS-CoV-2 infection (12). Our results strengthen this evidence by showing that the difference remains significant after controlling for confounders, indicating that PCC independently contributes to work impairment. Among participants with PCC, factors reflecting the severity of the disease, including lower EQ5D scores across all domains, respiratory, joint, neurological, chronic fatigue syndrome, fibromyalgia, or sclerosis, and mental health conditions, were strongly linked to workforce exit and were more prevalent than in those without PCC (7, 28). Key PCC features are post-exertional malaise and orthostatic intolerance, which likely further reduce work ability (4, 7, 29), consistent with evidence from related post-viral chronic illnesses and ME/CFS (29-31). The isolation and financial strain caused by extended absence may contribute to psychological problems, including depression, lower financial wellbeing, and existential fears (32, 33).

Longer PCC duration was associated with greater workforce exit, likely reflecting higher severity and prolonged recovery. Infections with earlier variants generally correspond to longer disease duration. An estimated 40% of participants were infected with earlier variants, and 60% with Omicron, with similar workforce exit rates. Other studies suggest return-to-work times were longest with Alpha and

shorter with Delta and Omicron (34) and that prolonged PCC duration hinders work reintegration (3). Vaccination status was not associated with workforce exit, though participants with PCC were less often vaccinated prior to infection, potentially missing the vaccine's protective effect against developing PCC (35).

Sociodemographic factors

PCC prevalence is highest among individuals of working age (16, 36), while workforce exit increases near retirement age. Earlier studies suggest that those already considering retirement may leave work sooner when affected by PCC (37). In our study, retirement age did not differ between groups, but older adults showed higher exit rates, likely reflecting age-related factors. Work sector was not associated with workforce exit, although prior research indicates higher infection and long-term symptom risks among healthcare, social, and education workers (38, 39).

Workforce exit rates were similar between women and men. However, since PCC more often affects women in most studies (40), its overall impact may translate into greater workforce loss among this group. Women worldwide, including in the Netherlands, perform over an hour more unpaid work daily than men (41), reducing time and energy for paid employment and adversely affecting health and workforce participation. Combined with a persistent gender pay gap of 3 to 6%, these disparities mean that women, on average, earn less per hour while also managing greater unpaid workloads (42, 43).

Work productivity, incapacity, and financial strain

The high rates of partial and total incapacity in our PCC group show that sustained employment was often not feasible. Within those who were employed, work productivity loss was highest among participants with PCC, followed by those recovered, and lowest in Never PCC, consistent with previous findings (12). Absenteeism and presenteeism were higher in participants with PCC and those who had recovered, compared with Never PCC, despite similar working hours across all three groups and comparable workforce exit rates between Recovered and Never PCC. This likely reflects residual symptoms and reduced work capacity in those recovered, possibly influenced by limited workplace support or changes in job demands. Compared to a similar study in the U.S (12), we observed higher percentages of presenteeism across all groups, but especially in PCC, where

nearly 90% reported any absenteeism. These differences may reflect variation in work environments, occupational cultures, or self-reporting of productivity, as well as cross-country differences in disability support systems. Further, participants with PCC were nearly twice as likely to report financial strain compared with Never PCC in both the employed and the unemployed group, indicating that PCC adversely affects financial wellbeing irrespective of employment status. These findings underscore a dual burden: individual financial hardship and broader societal costs arising from reduced work productivity and increased reliance on social support systems.

Implications

PCC substantially affects work participation and functioning, with personal, societal, and economic consequences that clinicians, health systems, and employers must recognize and address. As we previously demonstrated, recovery from PCC is often slow; after nine months only about one in three patients with mild PCC and one in ten with severe PCC have recovered (44). This highlights the need for sustained rather than short-term support. Employment may be better maintained through flexible hours, remote work, phased return-to-work programs, and low-stimulation environments (7, 19). Job adaptations and modified duties, such as reduced hours and lighter physical or cognitive tasks, might also improve work ability and facilitate reintegration (3). Supportive workplace policies and occupational rehabilitation have been linked to more successful return-to-work outcomes (11, 45). Financial strain following work loss may further restrict access to care and worsen health, highlighting the importance of integrated medical, occupational, and social support. Repeated work capacity assessments can create stress and uncertainty, potentially hindering recovery and prompting calls to limit such reassessments (24). Because PCC symptoms fluctuate, single-point evaluations may not adequately capture the variability of an individual's condition. On top of that, unclear criteria for diagnosing PCC means that many cases may be missed, preventing affected individuals from receiving appropriate workplace accommodations. At a broader level and given the large prevalence of PCC worldwide, the economic impact of PCC extends beyond individuals and organizations. Investments in pandemic preparedness are therefore essential (8). Productivity loss measured by the WPAI enables estimation of these direct costs, informing policymakers and employers

about the scale of the problem and guiding targeted interventions and resource allocation.

Strengths and limitations

Strengths of this study include a large, population-based design and the inclusion of a comparison group without PCC, allowing differentiation between general and PCC-specific factors associated with workforce exit. Another strength is the use of the validated WPAI instrument to assess productivity loss. Several limitations should be noted. The WPAI reflects only the previous seven days, which may not capture the fluctuating course of PCC, particularly regarding presenteeism. Severe PCC cases may be underrepresented, as completing the PRIME questionnaires could have been too demanding, potentially underestimating workforce exit. Misclassification is also possible if some participants classified as Never PCC had prior PCC before the baseline measurement. Recovered and Never PCC groups were analyzed separately, though the smaller Recovered sample may have limited statistical power. Finally, adults with lower digital literacy are likely underrepresented.

Conclusion

Between 2022 and 2024, 17% of adults with post-COVID-19 condition (PCC) left the workforce, compared with 10% of those recovered and 9% who never had PCC. Workforce exit was linked to PCC, older age, longer symptom duration, and comorbid physical or mental health conditions. Productivity loss was up to three times higher in PCC and twice as high in recovered participants, versus Never PCC. Work incapacity was highest in PCC (46%). These results highlight the substantial personal, societal, and economic burden of PCC and the urgent need for long-term support, workplace accommodations, and targeted interventions.

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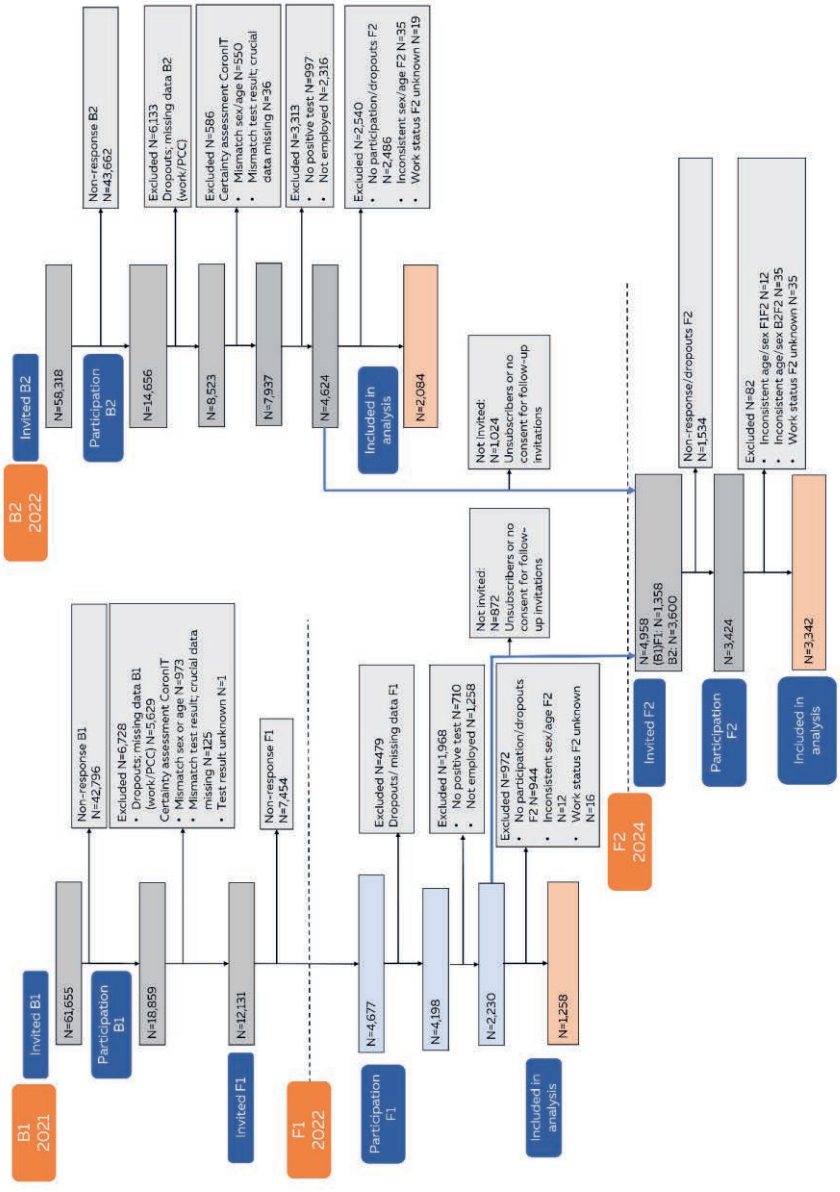
SUPPLEMENTARY MATERIALS



Supplementary figure 1: Flowchart.



Chapter 9

Recovery from post-COVID-19 condition and associated factors: the PRIME post-COVID study.

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Submitted

ABSTRACT

Background

Despite the high number of post-COVID-19 condition (PCC) cases worldwide, little is known about recovery and its associated factors yet. This study aimed to estimate the proportion of PCC patients that recover, and identity environment and individual factors.

Methods

Longitudinal data of the PRIME cohort were analysed. Patients with past infection who felt unrecovered at baseline (November 2021) were grouped by daily functioning capacity (moderate-severe problems (PCC-impairedDA) or no-slight problems (PCC-affectedDA)). Recovery or deterioration proportions after nine-month follow-up were calculated. Individual, interpersonal, network, and environment factors were assessed for lower likelihood of recovery, using multivariable logistic regression.

Results

Of patients with PCC-affectedDA (n=602), 36.9% recovered and 9.8% deteriorated to PCC-impairedDA. Of patients with PCC-impairedDA (n=277), 10.8% recovered and 31.8% improved in daily functioning. Recovery was 2.1% when acute illness was >12 months before baseline, and 12.5% and 13.6% when acute illness was 6-12 and 3-6 months before baseline, respectively. In both PCC groups, lower recovery likelihood was linked to worse physical health (mild/severe fatigue, severe dyspnea, severe symptoms of amnesia, concentration difficulties, muscle pain or -weakness, loss/change of smell/taste), worse mobility (hours spent lying down, problems with walking), worse mental health (depression), worse acute illness (more symptoms, hospitalization/oxygen use), former smoking, living in a rural area, having a relationship, and having more practical social network supporters (in those with chronic co-morbidities).

Conclusions

Only 11%-37% of PCC patients recovered after nine months, leaving significant room for improvement. Future research should identify modifiable factors and treatments to help assist the recovery of PCC patients.

INTRODUCTION

At least one out of six people experience persisting symptoms after a SARS-CoV-2 infection (1). These long-term symptoms, referred to as post-COVID-19 condition (PCC), manifests in a wide variety and combinations, of which fatigue, post-exertional malaise and cognitive dysfunction are the most pronounced symptoms (2, 3). The global number of people having PCC is unknown but estimated at 1.9 million people in the UK (4) and 7.5% (~25 million) of all US adults (5). For the Netherlands, an estimated 90,000 adults are living with severely limiting PCC (6).

Patients with PCC deal with its multifaceted impact, which may include limitations in their capacity to perform activities of daily living (7). There is no scientific or practice consensus on how to classify the severity of PCC, but efforts included to account for severity of symptoms (8), a combination between symptoms and quality of life (9), and type of experienced symptoms (10).

In recent years, a growing body of research identified risk factors for developing PCC, highlighting subgroups more likely to develop PCC, including women, people with more severe acute illness, and people with chronic diseases (11-16). In contrast, there is limited evidence on the proportion of patients that recover and on factors assisting recovery. A recent cross-sectional study estimated that 48.5% of US adults with PCC had recovered (not having these symptoms now) (17), but the duration of PCC was not assessed. Another study showed that 48% of German adults that reported symptoms at 4-12 weeks after acute illness, recovered after 12 weeks (no symptoms) (18). Factors associated with being recovered were younger age (being 40 years or younger), male, employed, mild/moderate symptoms at acute illness (17), being infected with Omicron variant, and not requiring medical care at acute illness (18).
More insight into the progression in terms of recovery or deterioration over time is needed to inform treatment strategies. At current, knowledge is lacking, but it is evident that PCC is a multisystemic and complex illness and recovery from PCC is not universal.

This study aimed to estimate the proportion of patients with PCC – moderate to severe problems with performing daily activities (PCC-impairedDA) or with no or slight problems with performing daily activities (PCC-affectedDA) – who recover or deteriorate over time, and to identify associated factors from the environment to the individual level.

METHODS

Study design and participants

Longitudinal data of the Prevalence Risk factors and Impact evaluation (PRIME) post-COVID study was used (19). In short, PRIME is an observational prospective cohort study, started in 2021, that consists of multiple continued questionnaire rounds. The study assesses various health conditions in relation to COVID-19 illness and PCC. All adults tested for SARS-CoV-2 with a valid test result and email address (recorded in the public health registry) were invited for participation in an online questionnaire. Research platform Crowdtech (ISO 27001 certified) was used for online data collection. Baseline and follow-up data were used for the current analyses. At baseline (November 2021), 12,453 adults participated, who were invited to participate in the first follow-up questionnaire (August 2022).

Adults with a history of acute COVID-19 illness, meaning a positive SARS-CoV-2 PCR test that was ≥3 months before baseline, who did not feel recovered, and participated at follow-up were selected for this study.

Individual, interpersonal, social network, and social and physical environment factors

The baseline questionnaire covered individual (demographics, general physical health, symptoms at baseline, mobility, (severity of) acute COVID-19 illness, vaccination status, mental and social health, lifestyle), interpersonal (steady partner, home situation, social network), and societal (physical environment) factors (table 1), which were all explored for their association with recovery from PCC.

The questionnaire did not cover duration of PCC. We considered time since first acute COVID-19 illness as a suitable proxy for PCC duration, as the risk of new-onset PCC has been suggested to be lower following second infection compared to first (20).

Table 1. Overview of all factors tested to be associated with changing post-COVID-19 condition (recovered, PCC-affectedDA, PCC-impairedDA) status from baseline to follow-up

	Measured at baseline	
Individual level	Currently	Retrospectively
Demographic factors		
Sex (men/women)	x	
Age (years)	x	
Born in the Netherlands (yes/no)	x	
Level of education (practically/theoretically trained)	x	
Paid job (yes/no)	x	
General (physical) health		
Obese (body mass index (BMI)≥30 kg/m^2; yes/no)	x	
Diabetes (yes/no)		x
Chronic obstructive pulmonary disease (COPD; yes/no)		x
Asthma (yes/no)		x
Lung disease (yes/no)		x
Heart disease (yes/no)		x
General health score (EuroQol-visual analogue scales (EQvas; range 0-100)		
Year before test		x
At baseline	x	
Fatigue (checklist individual strength-subscale subjective fatigue (CIS-fatigue) (21); normal/mild/severe)	x	
Dyspnea (modified medical research council (mMRC) (22); normal to mild/severe)	x	
Symptoms at baseline		
Amnesia (no/severity 1-5/severity ≥5-10)	x	
Brain fog (no/severity 1-5/severity ≥5-10)	x	
Concentration difficulties (no/severity 1-5/severity ≥5-10)	x	
Confusion (no/severity 1-5/severity ≥5-10)	x	
Dizziness (no/severity 1-5/severity ≥5-10)	x	
Headache (no/severity 1-5/severity ≥5-10)	x	

Palpitations (no/severity 1-5/severity ≥5-10)	x	
Increased resting heart rate (no/severity 1-5/severity ≥5-10)	x	
Joint pain (no/severity 1-5/severity ≥5-10)	x	
Muscle pain or -weakness (no/severity 1-5/severity ≥5-10)	x	
Sleeping problems (no/severity 1-5/severity ≥5-10)	x	
Loss/change of smell/taste (no/severity 1-5/severity ≥5-10)	x	
Mobility		
Time spent lying down (hours/day)	x	
Problems with walking (item EuroQol 5-Dimensions (EQ5D) (23); no to slight/moderate to (very) severe)	x	
(severity of) acute COVID-19 illness		
Symptoms when tested (total number from 0-44)		x
Hospitalization/oxygen use at home or hospital (yes/no)		x
Months since SARS-CoV-2 test (based on date of positive test; 3-6 months/6-12 months/≥12 months)	x	
Vaccination status		
COVID-19 vaccinated (yes/no)	x	
Mental and social health		
Depression (patient health questionnaire-9 (PHQ-9) (24); yes/no)	x	
Loneliness (De Jong-Gierveld (25); not lonely/moderately lonely/severely lonely)	x	
Emotional loneliness (yes/no)	x	
Social loneliness (yes/no)	x	
Anxiety (yes/no)	x	
Lifestyle		
Smoking behaviour (never/former/current)	x	
Interpersonal level		
Steady partner		
Having a relationship (yes/no)	x	
Home situation		
Living alone (yes/no)	x	
Children (yes/no)	x	
Social network factors (name generator method) (26)		
Size of social network (number of relations from 0-45)	x	
Number of members giving emotional support	x	
Number of members giving practical support	x	
Number of members giving informational support	x	
Network diversity (no family, but friends or acquaintances or caregivers/only family, no friends or acquaintances or caregivers/family and friends, no	x	

acquaintances or caregivers/family and friends and acquaintances or caregivers/family and acquaintances or caregivers, no friends)	
Network density (best friends know family (yes/no))	x
Societal level	
Physical environment	
Urbanity of living area (based on postal code; (very) strongly urban/moderately urban/little urban/rural)	x

PCC-affectedDA=post-COVID-19 condition with no or slight problems with performing daily activities; PCC-impairedDA=post-COVID-19 condition with moderate to severe problems or unable to perform daily activities.

Outcome measure

The outcome measure was PCC status at follow-up, based on a) whether participants currently felt fully recovered from their COVID-19 infection b) their current capacity of daily functioning. The latter indicated severity of PCC based on the EuroQol-5 Dimensions (EQ5D) item (the domain usual activities) regarding health today. The answers to this item were dichotomized into no or slight problems (in short: PCC-affectedDA) and moderate to severe problems or not able to perform daily activities (in short: PCC-impairedDA). At baseline and follow-up, patients were grouped as PCC-affectedDA or PCC-impairedDA, and recovered at follow-up only.

Statistical analysis

Proportions and 95% confidence intervals (CI) of participants with no PCC, PCC-affectedDA and PCC-impairedDA at follow-up were calculated, additionally stratified for time since first acute COVID-19 illness (3-6 months, 6-12 months and ≥12 months).

Chi-square or Fisher's Exact tests (for categorical) and analysis of variance (ANOVA; for continuous) variables were used to assess differences in the prevalence of factors by PCC status.

Multivariable logistic regression analyses were performed to assess the factors (measured at baseline) for their association with PCC status at follow-up (nine months later), adjusted for confounders and stratified by baseline PCC status. PCC status could thus either improve to recovered or better daily functioning, or could remain unaltered over time. Unaltered status was selected as the reference group. Included confounders were age (years), time since testing (3-6 months, 6-12 months, and ≥12 months) and having had another COVID-19 infection between baseline and follow-up (yes/no). Interactions between statistically significant factors and sex (men/women) and having chronic conditions (yes/no) were tested to evaluate possible heterogeneity of effects of the identified factors.

Analyses were performed using Statistical Package for Social Sciences (SPSS version 27, IBM, Armonk, USA); a p-value <0.05 was considered statistically significant.

Ethical statement

This study was waived by the Medical Ethical Committee of Maastricht University Medical Centre+ (METC2021-2884), as the Medical Research Involving Human Subjects Act (WMO) did not apply. This study was registered at Clinical Trials.gov Protocol Registration and Results System (NCT05128695).

RESULTS

Overall, 3,922 test positive participants in the cohort had complete data at baseline and follow-up. Participants were excluded from further analysis when they felt recovered at baseline (n=1,607), tested SARS-CoV-2 negative until the follow-up questionnaire (n=621), or tested SARS-CoV-2 positive <3 months prior to completing the baseline or follow-up questionnaire (n=122). Also, participants that were likely not the intended invitee (i.e., mismatch on sex or test result between baseline and follow-up; n=156) were excluded. The final study population in analyses consisted of 879 participants, of whom 602 (68.5%) had PCC-affectedDA and 277 (31.5%) had PCC-impairedDA at baseline.

Baseline characteristics

People with PCC-affectedDA differed from people with PCC-impairedDA: generally PCC-impairedDA scored worse on having a paid job, chronic conditions (obesity, COPD, asthma, heart disease), general health before their COVID-19 test and at baseline, current fatigue, dyspnea, mobility (hours spent lying down; problems with walking), depression, emotional loneliness, severity of acute illness (more symptoms, hospitalization or oxygen use), current symptoms (amnesia, brain fog, concentration difficulties, confusion, dizziness, headache, palpitations, increased resting heart rate, joint pain, muscle pain or -weakness, sleeping problems, and loss/change of smell/taste), having more social (emotional, practical, informational) network supporters (table 2).

Table 2. Baseline characteristics of people with PCC-affectedDA and PCC-impairedDA

	People living with PCC at baseline (n=879)				
	PCC-affectedDA (n=602)		PPC-impairedDA (n=277)		Chi-square/ ANOVA
Individual level	n	%	n	%	p
Demographic factors					
Women	350	58.1	180	65	0.054
Age, mean (SD)	55 (12)		56 (12)		0.798
Born in NL, (yes)	565	93.9	266	96	0.187
Level of education					
Practically trained	362	60.1	183	66.1	0.092
Theoretically trained	240	39.9	94	33.9	
Paid job (yes)	450	74.8	158	57	**<0.001**
General (physical) health					
BMI, mean (SD)	27.5 (4.8)		28.8 (5.6)		0.89
Obese (yes)	179	29.7	101	36.5	**0.047**
Diabetes (yes)	43	7.1	27	9.7	0.185
COPD (yes)	23	3.8	22	7.9	**0.01**
Asthma (yes)	42	7	40	14.4	**<0.001**
Lung disease (yes)	7	1.2	5	1.8	0.446
Heart disease (yes)	25	4.2	21	7.6	**0.034**
General health score, mean (SD)					
Year before test	82.9 (14.5)		74.6 (21.3)		**<0.001**
At baseline	74.1 (15.6)		52.1 (19.8)		**<0.001**
Fatigue					
Normal	201	33.4	10	3.6	**<0.001**
Mild	181	30.1	36	13	
Severe	220	36.5	231	83.4	
Dyspnea					
Normal to mild	557	92.5	172	62.1	**<0.001**
Severe	45	7.5	105	37.9	
Symptoms at baseline					
Amnesia					
No	534	88.7	181	65.3	**<0.001**
Severity 1-4	29	4.8	27	9.7	
Severity ≥5-10	39	6.5	69	24.9	
Brain fog					

No	566	94	208	75.1	**<0.001**
Severity 1–4	13	2.2	10	3.6	
Severity ≥5–10	23	3.8	59	21.3	
Concentration difficulties					
No	451	74.9	118	42.6	**<0.001**
Severity 1–4	52	8.6	28	10.1	
Severity ≥5–10	99	16.4	131	47.3	
Confusion					
No	590	98	249	89.9	**<0.001**
Severity 1–4	7	1.2	9	3.2	
Severity ≥5–10	5	0.8	19	6.9	
Dizziness					
No	554	92	215	77.6	**<0.001**
Severity 1–4	26	4.3	27	9.7	
Severity ≥5–10	22	3.7	35	12.6	
Headache					
No	524	87	201	72.6	**<0.001**
Severity 1–4	26	4.3	20	7.2	
Severity ≥5–10	52	8.6	56	20.2	
Palpitations					
No	560	93	238	85.9	**0.003**
Severity 1–4	24	4	20	7.2	
Severity ≥5–10	18	3	19	6.9	
Increased resting heart rate					
No	578	96	227	81.9	**<0.001**
Severity 1–4	13	2.2	14	5.1	
Severity ≥5–10	11	1.8	36	13	
Joint pain					
No	590	98	249	89.9	**<0.001**
Severity 1–4	3	0.5	4	1.4	
Severity ≥5–10	9	1.5	24	8.7	
Muscle pain or –weakness					
No	538	89.4	185	66.8	**<0.001**
Severity 1–4	18	3	13	4.7	
Severity ≥5–10	46	7.6	79	28.5	
Sleeping problems					
No	498	82.7	181	65.3	**<0.001**

Severity 1–4	27	4.5	15	5.4	
Severity ≥5–10	77	12.8	81	29.2	
Loss/change of smell/taste					
No	418	69.4	171	61.7	**0.025**
Severity 1–4	120	19.9	60	21.7	
Severity ≥5–10	61	10.6	46	16.6	
Mobility					
Time spent lying down (hours/day)	1.6 (2.6)		2.4 (3.0)		**<0.001**
Problems with walking					
No to slight	536	89	142	51.3	**<0.001**
Moderate to (very) severe or unable to	66	11	135	48.7	
(severity of) acute COVID-19 illness					
Symptoms when tested, mean (SD)	8.0 (6.1)		11.6 (8.5)		**<0.001**
Hospitalization/oxygen use at home or hospital (yes)	48	8	55	19.9	**<0.001**
Months since test, mean (SD)					
3–6	49	8.1	22	7.9	0.244
6–12	422	70.1	208	75.1	
>12	131	21.8	47	17	
Vaccination status					
COVID-19 vaccine (yes)	583	96.8	264	95.3	0.258
Mental and social health status					
Depression (yes)	231	38.4	223	80.5	**<0.001**
Loneliness					
Not lonely	370	61.5	143	51.6	**<0.001**
Moderately lonely	180	29.9	84	30.3	
Severely lonely	52	8.6	50	18.1	
Emotional loneliness (yes)	135	22.4	97	35	**<0.001**
Social loneliness (yes)	150	24.9	75	27.1	0.496
Anxiety (yes)	9	1.5	9	3.2	0.088
Lifestyle					
Smoking behaviour					
Never	306	50.8	144	52	0.942
Former	250	41.5	113	40.8	
Current	46	7.6	20	7.2	
Interpersonal level					
Steady partner					
Having a relationship (yes)	499	82.9	227	81.9	0.733

Home situation					
Living alone (yes)	102	16.9	49	17.7	0.785
Children (yes)	196	32.6	93	33.6	0.766
Social network factors					
Size of social network, n(SD)	10.5 (7.0)		12.0 (7.6)		0.328
Support from social network, n(SD)					
Number of members giving emotional support	7.6 (6.0)		8.6 (6.4)		**<0.001**
Number of members giving practical support	2.1 (2.1)		2.9 (3.2)		**0.005**
Number of members giving informational support	5.1 (4.6)		5.6 (5.2)		**<0.001**
Network diversity					
Family and friends and acquaintances/caregivers	364	60.5	166	59.9	0.545
Only family, no friends/acquaintances/caregivers	69	11.5	26	9.4	
Other	169	28.1	85	30.7	
Network density					
Best friends know family (yes)	504	84.8	222	81.6	0.231
Societal level					
Physical environment					
Urbanity of living area					
(very) strongly urban	226	37.5	93	33.6	0.619
Moderately urban	137	22.8	70	25.3	
Little urban	140	23.3	63	22.7	
Rural	99	16.4	51	18.4	

PCC-affectedDA=post-COVID-19 condition with no or slight problems with performing daily activities; PCC-ImpairedDA=post-COVID-19 condition with moderate to severe problems with performing daily activities
SD: standard deviation, NL: Netherlands.

Proportion of patients who changed to different PCC groups at follow-up

Of patients with PCC-affectedDA at baseline (n=602), 222 (36.9% [95% CI:30.0%-40.7%]) recovered, 321 (53.3% [95% CI:49.3%-57.3%]) persisted having PCC-affectedDA, and 59 (9.8% [95% CI:7.4%-12.2%]) deteriorated to PCC-impairedDA at follow-up (figure 1). Recovery proportions did not differ by duration of PCC (Chi-square p=0.166); for those with first acute COVID-19 illness 3-6 months before baseline it was 44.9% [95% CI:40.9%-48.9%], 6-12 months 36.0% [95% CI:32.2%-39.9%], and ≥12 months 36.6% [95% CI:32.8%-40.5%].

Of patients with PCC-impairedDA at baseline (n=277), 30 (10.8% [95% CI:7.2%-14.5%]) recovered, 88 (31.8% [95% CI:26.3%-37.3%]) improved somewhat to PCC-affectedDA, and 159 (57.4% [95% CI:51.6%-63.2%]) persisted having PCC-impairedDA at follow-up (figure 1). Recovery was 2.1% [95% CI:0.4%-3.8%] when first acute COVID-19 illness was long ago (≥12 months before baseline), and was 12.5% [95% CI:8.6%-16.4%] (p=0.036) and 13.6% [95% CI:9.6%-17.7%] (p=0.092) when acute illness was 6-12 and 3-6 months before baseline, respectively.

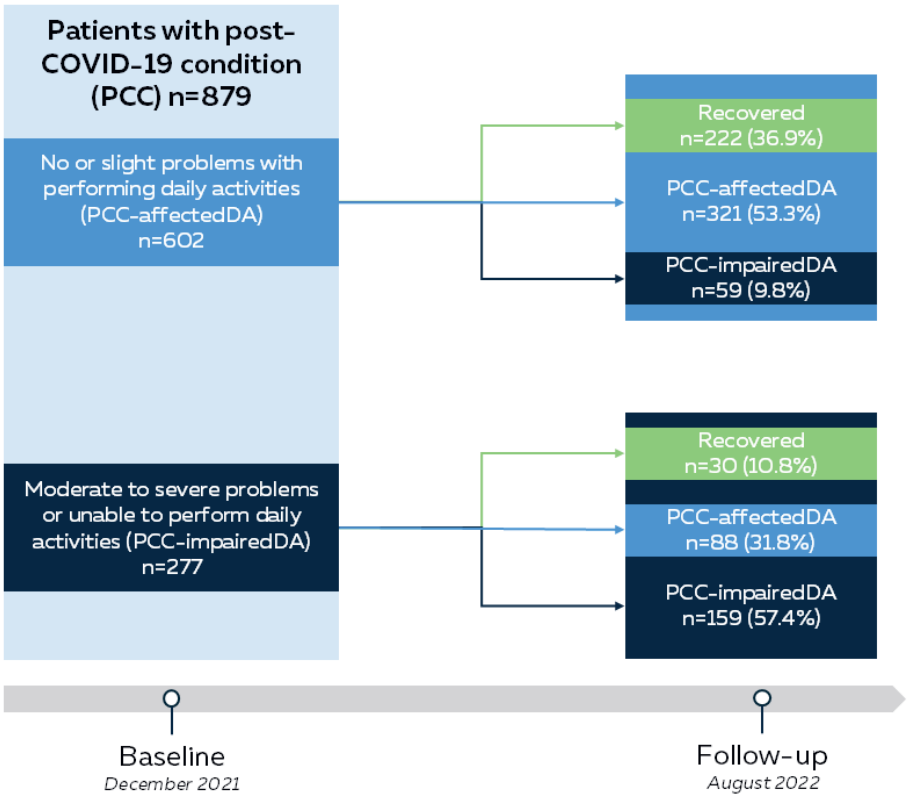

Figure 1. Overview of the shift in post-COVID-19 condition (PCC) status from baseline to follow-up.

Factors associated with recovery

A detailed description of the proportions of all factors within each PCC group (i.e., recovered, PCC-affectedDA and PCC-impairedDA) at baseline and follow-up is presented in supplementary tables 1 and 2.

In patients with PCC-affectedDA

On individual level, the following health factors were associated with a lower likelihood for recovery: worse general health, worse physical health (mild/severe fatigue, severe symptoms of amnesia, concentration difficulties, muscle pain or -weakness, loss/change of smell/taste) worse mobility (hours spent lying down), worse acute illness (more symptoms when tested, hospitalization/oxygen use), worse mental health (depression), and former smoking. Having a relationship and having more practical social network supporters (in patients with chronic co-

morbidities) on interpersonal level, and living in a rural area on societal level were associated with a lower likelihood for recovery (figure 2).

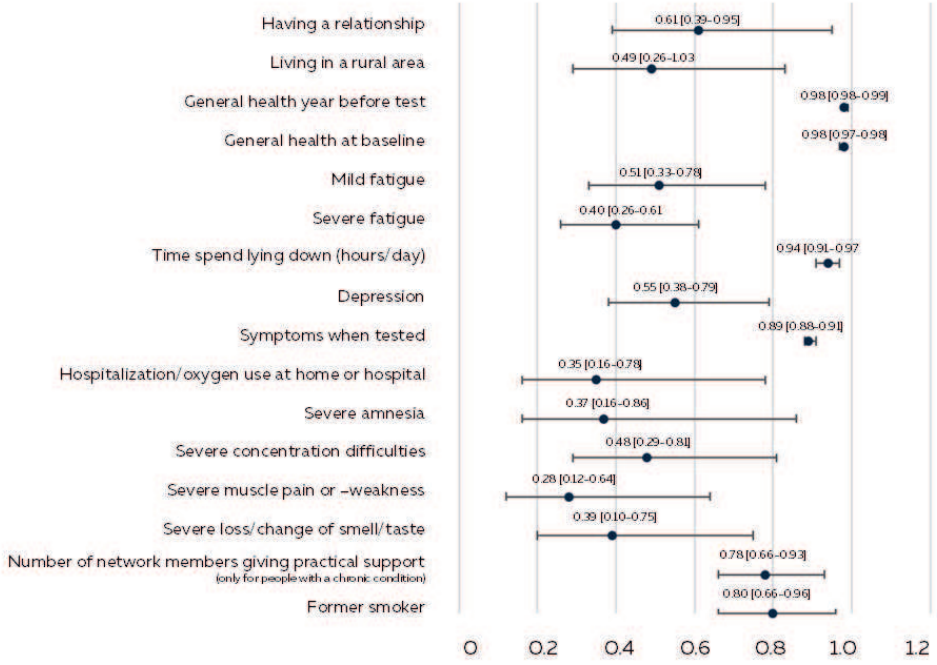

Figure 2. Forest plot of factors associated with lower likelihood for recovery from post-COVID-19 condition with no or slight problems with performing daily activities (PCC-affectedDA).

In patients with PCC-impairedDA

On individual level, factors associated with a lower likelihood for recovery were: worse general health, worse physical health (mild/severe fatigue, severe dyspnea, severe symptoms of amnesia or concentration difficulties), worse mobility (moderate to (very) severe problems with walking), worse acute illness factors (more symptoms when tested), and worse mental health (depression) (figure 3).

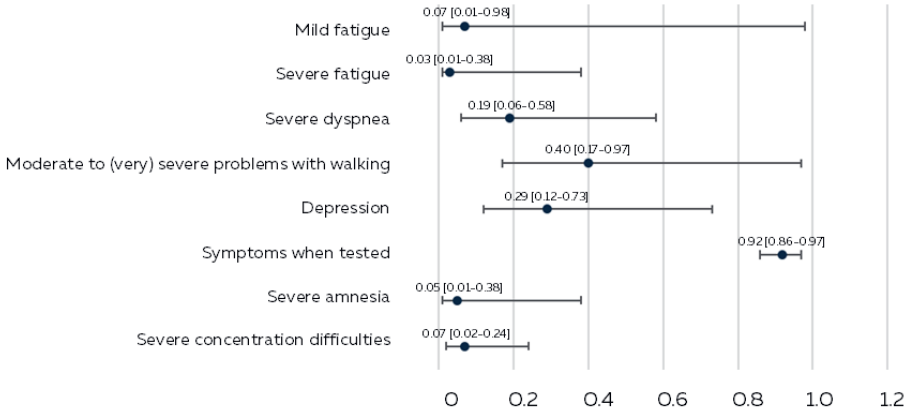

Figure 3. Forest plot of factors associated with lower likelihood for recovery from post-COVID-19 condition with moderate to severe problems with performing daily activities (PCC-impairedDA).

On individual level, improvement to PCC-affectedDA was negatively associated with worse general health, worse physical health (mild/severe fatigue, symptoms of severe brain fog or concentration difficulties), worse acute illness factors (hospitalization/oxygen use), worse mental health (depression, moderate loneliness or emotional loneliness (in women and patients without chronic co-morbidities)) (figure 4).

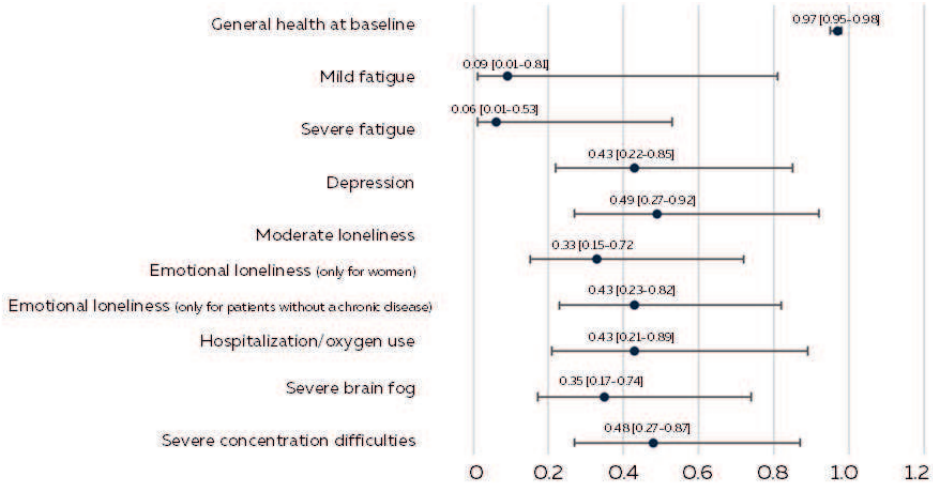

Figure 4. Forest plot of factors associated with a lower likelihood for improvement from post-COVID-19 condition with moderate to severe problems with performing daily activities (PCC-ImpairedDA) to post-COVID-19 condition with no or slight problems with performing daily activities (PCC-affectedDA).

Factors associated with deterioration in patients with PCC

Factors associated with deterioration to PCC-impairedDA were severe fatigue (adOR=2.68 [95%CI:1.23-5.81]), severe dyspnea (adOR=2.92 [95% CI:1.33-6.42]), and moderate to (very) severe problems with walking (adOR=2.71 [95% CI:1.32-5.54]) (supplementary table 1). A worse general health score was positively associated with deterioration (adOR=1.02 [95%CI: 1.01-1.04]) (supplementary table 1).

Description of PCC groups at follow-up

Demographic and health characteristics were described for people who recovered, had PCC-affectedDA or had PCC-impairedDA at follow-up (figure 5).

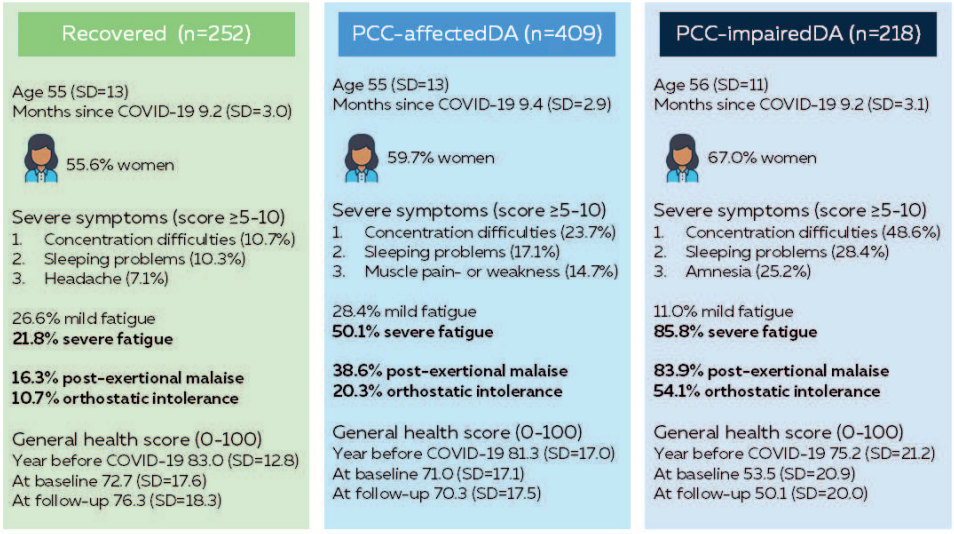

Figure 5. Description of PCC groups (i.e., recovered, post-COVID-19 condition with no or slight problems with performing daily activities (PCC-affectedDA), and post-COVID-19 condition with moderate to severe problems with performing daily activities (PCC-impairedDA)) at follow-up

Patients with PCC-impairedDA were more often women (67.0%), compared to PCC-affectedDA patients (59.7%) and to recovered people (55.6%; p=0.039). In patients with PCC-impairedDA, 48.6% had post-exertional malaise (PEM), 54.1% had orthostatic intolerance (OI), and 85.8% had severe fatigue, which was higher than in patients with PCC-affectedDA (38.6% PEM; p<0.001, 20.3% OI; p<0.001, and 50.1% severe fatigue; p<0.001) or in people who recovered (16.3% PEM; p<0.001, 10.7% OI; p<0.001, and 21.8% severe fatigue; p<0.001). In all PCC groups, concentration difficulties and sleeping problems were the most reported

severe symptoms which were most often reported in patients with PCC-impairedDA compared to patients with PCC-affectedDA or people who recovered. The general health score was the highest a year before acute COVID-19 illness, for all PCC groups. For patients who recovered, the general health score improved, while general health on average had deteriorated in those who had PCC-affectedDA or PCC-ImpairedDA at follow-up.

Discussion

One in three PCC-affectedDA patients and one in ten PCC-impairedDA patients, participating in the PRIME cohort, had recovered in a nine-month period. Identified factors associated with a lower likelihood for recovery included a range of individual and environment factors; worse general, physical and mental health, and worse acute COVID-19 illness.

Recently, the National Academies of Sciences, Engineering, and Medicine (NASEM) definition of PCC was formed, emphasizing that severity variability is an important feature in defining PCC (27). Nevertheless, currently, no proposed definition of PCC includes a minimum level of symptom severity or functional impairment (28). The definition of PCC used in our study, based on the capacity of daily functioning, allowed for differentiation by PCC severity. Notable differences between patients with impaired daily functioning and patients not or slightly affected in daily functioning were observed, including higher occurrence of problems with walking (48.7% in vs. 11.0%), depression (80.5% vs. 38.4%) and presence of severe symptoms (e.g., concentration difficulties 47.3% vs. 16.4%). Thereby, our study suggests a way to define PCC severity by its accompanying impairment of daily living, instead of classifying PCC severity groups based on symptom clusters alone (8-10).

Comparing our results on recovery proportions with previous studies is nearly impossible, as PCC and recovery lack a clear definition. Different use of study designs and inclusion of diverse study populations further complicate comparison of research output. We demonstrated that only 37% of patients with PCC-affectedDA recovered, and only 11% of patients with PCC-impairedDA recovered in nine months, which is less than suggested by previous studies which estimated recovery to be around 50% (17, 18). One explanation could be the inclusion of more patients with longer PCC duration, since longer time since first COVID-19

illness was negatively associated with recovery in our study. In previous studies, participants were classified as having PCC when they reported having symptoms 4-12 weeks after infection, or the presence of any symptoms lasting ≥3 months that were absent prior to infection (17, 18). Thus, these PCC definitions were focused on presence of symptoms alone, instead of (our study) combining experienced recovery with current degree of impairment of daily living. Unlike other studies defining recovery as absence of symptoms, our findings demonstrate that people who felt recovered had better health but still experiences severe or key symptoms such as PEM and OI. Possibly, the patients experienced their condition as better than before and the still present symptoms are manageable. On the other hand, patients in our study who were unrecovered, had either (or both) symptoms or impairment in daily functioning. This questions whether only asking for just presence of symptoms in clinical practice is a good indicator to identify patients' recovery, without some assessment of impact on functioning.

Recovered people had improved general health during the course of PCC, although, it is notable that their score was still under the Dutch average reference value (86.9, measured in 2016) (29) and lower than the average in people who never reported to have had COVID-19 before (79.2, measured in 2021) (7).

Overall, it must be acknowledged that defining PCC and recovery are complex. Yet, alignment of definitions used in practice is urgently needed to enhance comparability between studies to estimate the proportion of people with PCC that can recover over time.

Factors that lowered the likelihood for recovery - or even were associated with deterioration - included individual (worse general health, physical health (mild/severe fatigue, severe dyspnea, severe symptoms of amnesia, brain fog, concentration difficulties, muscle pain or -weakness, loss/change of smell/taste) worse mobility (hours spent lying down, moderate to (very) severe problems with walking), worse acute illness (number of symptoms when tested, hospitalization/oxygen use), worse mental and social health (depression, moderate or emotional loneliness) and former smoking), interpersonal (having a relationship, having more practical social supporters in patients with chronic co-morbidities) and societal (living in a rural area) factors. PCC-impairedDA patients who were more often women or had severe symptoms (i.e., concentration

difficulties, sleeping problems, amnesia, fatigue, PEM and OI) were less likely to recover.

We demonstrated that a worse health before and during PCC are associated with a lower likelihood for recovery, which is unfortunately largely unchangeable and requires biological targets to be treated. This study was not designed to reveal therapeutic targets for recovery, and we recommend future biomedical and therapeutic research to give insight into possible biological targets to ultimately treat PCC.

Strengths and limitations

We were able to offer insights into recovery trajectories in a large sample of PCC patients, using longitudinal, population-based data to estimate the proportion of PCC patients (having PCC for 3 up to 21 months) who subsequently recover. Additionally, a wide range of individual and environment health factors were evaluated for their association with recovery. The extensive measures used provided detailed information on various mental, physical, and social health conditions, and social and physical living environment factors; most measured with validated scales. To the best of our knowledge, this is the first study that demonstrates distinct PCC groups based on capacity of daily functioning, by combining the outcome of two relatively simple questions, which could be used in future studies and clinical practice.

A limitation is the lack of biomedical data, clinical assessments and biomarkers. Due to the nature of the cohort, data was self-reported. Even so, various measures (i.e., fatigue, impairments of daily living) are difficult to determine clinically or with biomedical assessments. Loss-to-follow-up in the PRIME study possibly leads to selection or attrition bias, which might be differential by PCC severity. PCC patients with profound impairment of daily living are possibly less capable to complete the relatively long questionnaire, and therefore we consider it likely that the most severely impacted PCC patients are underrepresented in this study. This might have resulted in an overestimation of recovery. Nevertheless, we included a substantial sample of PCC patients with severe impact in daily functioning. The exact duration of PCC is unknown. We considered time since first acute COVID-19 illness as a proxy, demonstrating that PCC patients with severe impact on daily functioning who had acute COVID-19 illness ≥12 months before baseline were least likely to recover. Furthermore, the measure

on impairment of daily living reflected the situation "today", having its limitations to indicate participants general state, specifically in PCC which is known for its intermittent symptoms; hence recovery might have been underestimated when patients were currently in remission or overestimation when patients were currently having a relapse. It was unknown if, and if so, what kind of treatment patients had received. Currently, there is no universal accepted treatment for PCC. The mainstay treatments of PCC are symptom management, rehabilitation, reassurance and support, and therapies to reduce sympathetic hyperactivity (30). Received treatment might differentially affect recovery from PCC, as receiving an effective treatment enhances recovery likelihood and subsequently leads to an underestimation of recovery rates without treatment.

Conclusion

Only one in ten of severely impaired and only one in three patients with milder PCC recovered in a nine-month period, urgently calling for therapeutic options for PCC patients. Recovery was less likely when patients already had worse general, physical, mental or social health, adding to the complexity of problems that patients with PCC face during their illness. Future research should focus on identifying changeable factors, including biomedical factors not assessed in this study, that assist recovery and improve quality of life of PCC patients. Furthermore, we recommend a clinical PCC definition that differentiates by severity, such as based on capacity of daily functioning.

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SUPPLEMENTARY MATERIALS

Supplementary table 1. Factors associated with changing PCC status from post-COVID-19 condition with no or slight problems with performing daily activities (PCC-affectedDA)

	Patients with PCC-affectedDA at baseline (n=602)							
	Recovered (n=222)			PCC-affectedDA (n=321) ref.		PCC Impaired DA (n=59)		
Individual level	n	%	adOR [95% CI]	n	%	n	%	adOR [95% CI]
Demographic factors								
Women	122	55.0	0.86 [0.61-1.22]	188	58.6	40	67.8	1.54 [0.84-2.82]
Age, mean(SD)	54 (13)			55 (13)		55 (10)		
Born in NL, (yes)	204	91.9	0.64 [0.32-1.28]	304	94.7	57	96.6	1.63 [0.36-7.26]
Level of education								
Practically trained	122	55.0	ref.	199	62.0	41	69.5	ref.
Theoretically trained	100	45.0	1.34 [0.95-1.91]	122	38.0	18	30.5	0.72 [0.39-1.33]
Paid job (yes)	163	73.4	1.16 [0.75-1.81]	243	75.7	44	74.6	1.03 [0.51-2.08]
General (physical) health status								
Obesity (yes)	63	28.4	0.95 [0.65-1.38]	95	29.6	21	35.6	1.30 [0.72-2.34]
Diabetes (yes)	15	6.8	0.89 [0.45-1.75]	24	7.5	4	6.8	0.86 [0.28-2.62]
COPD (yes)	6	2.7	0.61 [0.23-1.61]	14	4.4	3	5.1	1.19 [0.33-4.30]
Asthma (yes)	13	5.9	0.75 [0.37-1.50]	24	7.5	5	8.5	1.11 [0.40-3.06]
Lung disease (yes)	4	1.8	1.97 [0.43-9.01]	3	0.9	0	0.0	-
Heart disease (yes)	7	3.2	0.63 [0.25-1.60]	15	4.7	3	5.1	1.05 [0.29-3.79]
General health score, mean(SD)								
Year before test	83.7 (11.9)		**0.98 [0.98-0.99]****	82.9 (15.6)		79.8 (16.6)		1.01 [1.00-1.03]
At baseline	75.3 (15.8)		**0.98 [0.97-0.98]****	74.4 (15.4)		67.9 (15.2)		**1.02 [1.01-1.04]***
Fatigue								
Normal	101	45.5	ref.	90	28.0	10	16.9	ref.
Mild	62	27.9	**0.51 [0.33-0.78]***	105	32.7	14	23.7	1.19 [0.50-2.83]
Severe	59	26.6	**0.40 [0.26-0.61]****	126	39.3	35	53.9	**2.68 [1.23-5.81]***
Dyspnea								
Normal to mild	211	95.0	ref.	298	92.8	48	81.4	ref.
Severe	11	5.0	0.67 [0.32-1.42]	23	7.2	11	18.6	**2.92 [1.33-6.42]***
Symptoms at baseline								
Amnesia								
No	207	93.2	ref.	280	87.2	47	79.7	ref.
Severity 1-4	8	3.6	0.73 [0.30-1.75]	15	4.7	6	10.2	2.32 [0.85-6.31]

Severity ≥5–10	7	3.2	**0.37 [0.16–0.86]***	26	8.1	6	10.2	1.41 [0.55–3.62]
Brain fog								
No	213	95.9	ref.	298	92.8	55	93.2	ref.
Severity 1–4	3	1.4	0.46 [0.12–1.73]	9	2.8	1	1.7	0.60 [0.07–4.85]
Severity ≥5–10	6	2.7	0.62 [0.23–1.65]	14	4.4	3	5.1	1.24 [0.34–4.55]
Concentration difficulties								
No	182	82.0	ref.	230	71.7	39	66.1	ref.
Severity 1–4	17	7.7	0.70 [0.37–1.30]	31	9.7	4	6.8	0.78 [0.26–2.32]
Severity ≥5–10	23	10.4	**0.48 [0.29–0.81]***	60	18.7	16	27.1	1.60 [0.83–3.07]
Confusion								
No	219	98.6	ref.	314	97.8	57	96.6	-
Severity 1–4	2	0.9	0.98 [0.16–5.91]	3	0.9	2	3.4	
Severity ≥5–10	1	0.5	0.36 [0.04–3.22]	4	1.2	0	0.0	
Dizziness								
No	205	92.3	ref.	296	92.2	53	89.8	ref.
Severity 1–4	10	4.5	1.34 [0.56–3.22]	11	3.4	5	8.5	2.57 [0.86–7.71]
Severity ≥5–10	7	3.2	0.73 [0.29–1.86]	14	4.4	1	1.7	0.39 [0.05–3.03]
Headache								
No	201	90.5	ref.	276	86.0	47	79.7	ref.
Severity 1–4	7	3.2	0.58 [0.23–1.45]	16	5.0	3	5.1	1.11 [0.31–3.99]
Severity ≥5–10	14	6.3	0.68 [0.35–1.32]	29	9.0	9	15.3	1.91 [0.84–4.35]
Palpitations								
No	210	94.6	ref.	297	92.5	53	89.8	ref.
Severity 1–4	8	3.6	0.94 [0.38–2.35]	12	3.7	4	6.8	1.83 [0.56–5.96]
Severity ≥5–10	4	1.8	0.49 [0.15–1.53]	12	3.7	2	3.4	0.96 [0.21–4.44]
Increased resting heart rate								
No	216	97.3	ref.	308	96.0	54	91.5	ref.
Severity 1–4	2	0.9	0.35 [0.07–1.65]	8	2.5	3	5.1	2.04 [0.52–8.00]
Severity ≥5–10	4	1.8	1.18 [0.31–4.46]	5	1.6	2	3.4	2.28 [0.43–12.11]
Joint pain								
No	220	99.1	-	314	97.8	56	94.9	-
Severity 1–4	1	0.5		0	0.0	2	3.4	
Severity ≥5–10	1	0.5		7	2.2	1	1.7	
Muscle pain or -weakness								
No	209	94.1	ref.	278	86.6	51	86.4	ref.
Severity 1–4	6	2.7	0.79 [0.28–2.21]	10	3.1	2	3.4	1.05 [0.22–4.96]
Severity ≥5–10	7	3.2	**0.28 [0.12–0.64]***	33	10.3	6	10.2	0.97 [0.38–2.44]

Sleeping problems								
No	191	86.5	ref.	262	81.6	44	74.6	ref.
Severity 1–4	9	4.1	0.97 [0.40–2.32]	13	4.0	5	8.5	2.38 [0.80–7.09]
Severity ≥5–10	21	9.5	0.62 [0.36–1.08]	46	14.3	10	16.9	1.31 [0.62–2.80]
Loss/change of smell/taste								
No	169	76.1	ref.	214	66.7	35	59.3	ref.
Severity 1–4	40	18.0	0.75 [0.48–1.16]	66	20.6	14	23.7	1.27 [0.64–2.51]
Severity ≥5–10	13	5.9	**0.39 [0.20–0.75]***	41	12.8	10	16.9	1.46 [0.66–3.21]
Mobility								
Time spent lying down (hours/day)	1.5 (2.7)		**0.94 [0.91–0.97]****	1.5 (2.6)		1.9 (2.4)		1.04 [0.94–1.15]
Problems with walking								
No to slight	203	91.4	ref.	288	89.7	45	76.3	ref.
Moderate to(very)severe	19	8.6	0.81 [0.44–1.48]	33	10.3	14	23.7	**2.71 [1.32–5.54]***
(severity of) acute COVID-19 illness								
Symptoms when tested, mean (SD)	7.2 (5.1)		**0.89 [0.88–0.91]****	8.3 (6.6)		9.6 (6.0)		1.03 [0.99–1.07]
Hospitalization/oxygen use at home or hospital (yes)	8	3.6	**0.35 [0.16–0.78]***	31	9.7	9	15.3	1.71 [0.78–3.87]
Months since test, mean (SD)								
3–6	22	9.9	-	19	5.9	8	13.6	-
6–12	152	68.5		234	72.9	36	61.0	
>12	48	21.6		68	21.2	15	25.4	
New COVID-19 illness between baseline and follow-up (yes)	62	27.9	-	96	29.9	15	25.4	-
Vaccination status								
COVID-19 vaccine (yes)	217	97.7	1.93 [0.67–5.58]	308	96.0	58	98.3	2.56 [0.32–20.18]
New COVID-19 vaccine between baseline and follow-up (yes)	1	0.5	0.73 [0.06–8.29]	2	0.6	1	1.7	2.98 [0.26–34.04]
Mental health status								
Depression (yes)	64	28.8	**0.55 [0.38–0.79]****	135	42.1	32	54.2	1.67 [0.95–2.96]
Loneliness								
Not lonely	141	63.5	ref.	198	61.7	31	52.5	ref.
Moderately lonely	65	29.3	0.98 [0.67–1.44]	94	29.3	21	35.6	1.46 [0.79–2.68]
Severely lonely	16	7.2	0.77 [0.41–1.48]	29	9.0	7	11.9	1.51 [0.60–3.77]
Emotional loneliness (yes)	48	21.6	0.97 [0.64–1.47]	72	22.4	15	25.4	1.19 [0.63–2.27]
Social loneliness (yes)	49	22.1	0.81 [0.54–1.22]	83	25.9	18	30.5	1.26 [0.68–2.31]
Anxiety (yes)	0	0.0	-	9	2.8	0	0.0	-
Lifestyle								
Smoking behaviour								
Never	114	51.4	ref.	161	50.2	31	52.5	ref.
Former	87	39.2	**0.80 [0.66–0.96]***	140	43.6	23	39.0	0.82 [0.44–1.53]

Current	21	9.5	0.79 [0.57–1.10]	20	6.2	5	8.5	1.26 [0.44–3.65]
Interpersonal level								
Steady partner								
Having a relationship (yes)	173	77.9	**0.61 [0.39–0.95]***	274	85.4	52	88.1	1.28 [0.55–2.99]
Home situation								
Living alone (yes)	44	19.8	1.30 [0.83–2.02]	52	16.2	6	10.2	0.59 [0.24–1.44]
Children (yes)	77	34.7	1.17 [0.80–1.71]	101	31.5	18	30.5	0.97 [0.52–1.83]
Social network factors								
Size of social network, n(SD)	10.8 (7.3)		1.0 [0.99–1.01]	10.2 (7.1)		9.9 (5.4)		1.00 [0.95–1.04]
Support from social network, n(SD)								
Number of members giving emotional support	7.5 (6.3)		0.99 [0.98–1.00]	7.6 (6.00		6.9 (4.8)		0.98 [0.93–1.03]
Number of members giving practical support	1.9 (2.1)		**0.94 [0.91–0.98]****	2.1 (2.2)		1.9 (1.6)		0.95 [0.83–1.10]
Number of members giving informational support	5.1 (4.6)		1.00 [0.98–1.02]	5.1 (4.7)		4.3 (3.6)		0.96 [0.89–1.03]
Network diversity								
Family and friends and acquaintances/caregivers	143	64.4	ref.	181	56.4	40	67.8	ref.
Only family, no friends/acquaintances/caregivers	24	10.8	0.77 [0.44–1.34]	39	12.1	6	10.2	0.69 [0.27–1.75]
Other	55	24.8	0.69 [0.46–1.02]	101	31.5	13	22.0	0.58 [0.30–1.13]
Network density								
Best friends know family (yes)	189	85.1	1.19 [0.74–1.92]	267	83.2	52	88.1	1.56 [0.67–3.66]
Societal level								
Physical environment								
Urbanity of living area								
(very) strongly urban	100	45.0	ref.	109	34.0	17	28.8	ref.
Moderately urban	47	21.2	0.68 [0.43–1.06]	76	23.7	14	23.7	1.15 [0.53–2.48]
Little urban	48	21.6	0.67 [0.43–1.06]	77	24.0	15	25.4	1.20 [0.56–2.57]
Rural	27	12.2	**0.49 [0.29–0.83]***	59	18.4	13	22.0	1.39 [0.63–3.07]

*p<0.05 **p<0.001 PCC-affectedDA=post-COVID-19 condition with no or slight problems with performing daily activities; PCC-impairedDA=post-COVID-19 condition with moderate to severe problems with performing daily activities. Adjusted for age (years), time since test (3–6, 6–12, >12 months), and having had a new COVID-19 infection between baseline and follow-up (yes/no).

Supplementary table 2. Factors associated with changing PCC status from post-COVID-19 condition with moderate to severe problems with performing daily activities (PCC-ImpairedDA)

	Patients with PCC-ImpairedDA at baseline (n=277)							
	Recovered (n=30)			PCC-affectedDA (n=88)			PCC-ImpairedDA (n=159) ref.	
Individual level	n	%	adOR [95% CI]	n	%	adOR [95% CI]	n	%
Demographic factors								
Women	18	60.0	0.72 [0.31-1.67]	56	63.6	0.85 [0.48-1.49]	106	66.7
Age, mean(SD)	56 (11)			56 (13)			57 (11)	
Born in NL, (yes)	27	90.0	0.39 [0.09-1.77]	86	97.7	1.66 [0.33-8.47]	153	96.2
Level of education								
Practically trained	18	60.0	ref.	55	62.5	ref.	110	69.2
Theoretically trained	12	40.0	1.39 [0.60-3.20]	33	37.5	1.31 [0.75-2.31]	49	30.8
Paid job (yes)	19	63.3	0.84 [0.32-2.18]	47	53.4	1.45 [0.79-2.64]	92	57.9
General (physical) health status								
Obesity (yes)	9	30.0	0.72 [0.31-1.70]	31	35.2	0.89 [0.52-1.54]	61	38.4
Diabetes (yes)	2	6.7	0.60 [0.13-2.77]	6	6.8	0.54 [0.21-1.43]	19	11.9
COPD (yes)	3	10.0	1.44 [0.37-5.59]	5	5.7	0.67 [0.23-1.94]	14	8.8
Asthma (yes)	3	10.0	0.55 [0.15-1.97]	11	12.5	0.73 [0.34-1.56]	26	16.4
Lung disease (yes)	2	6.7	3.30 [0.49-22.41]	0	0.0	-	3	1.9
Heart disease (yes)	0	0.0	-	10	11.4	1.90 [0.75-4.78]	11	6.9
General health score, mean(SD)								
Year before test	77.8 (17.5)		0.99 [0.97-1.01]	75.5 (20.4)		1.00 [0.98-1.01]	73.5 (22.4)	
At baseline	53.5 (18.5)		0.98 [0.96-1.00]	58.6 (17.5)		**0.97 [0.95-0.98]****	48.2 (20.3)	
Fatigue								
Normal	3	10.0	ref.	6	6.8	ref.	1	0.6
Mild	5	16.7	**0.07 [0.01-0.98]***	12	13.6	**0.09 [0.01-0.81]***	19	11.9
Severe	22	73.3	**0.03 [0.01-0.38]***	70	79.5	**0.06 [0.01-0.53]***	139	87.4
Dyspnea								
Normal to mild	26	86.7	ref.	56	63.6	ref.	90	56.6
Severe	4	13.3	**0.19 [0.06-0.58]***	32	36.4	0.75 [0.43-1.28]	69	43.4
Symptoms at baseline								
Amnesia								
No	28	93.3	ref.	60	68.2	ref.	93	58.5
Severity 1-4	1	3.3	0.16 [0.02-1.30]	9	10.2	0.78 [0.32-1.87]	17	10.7

Severity ≥5–10	1	3.3	**0.05 [0.01–0.38]***	19	21.6	0.55 [0.29–1.05]	49	30.8
Brain fog								
No	26	86.7	-	73	83.0	ref.	109	68.6
Severity 1–4	0	0.0		3	3.4	0.60 [0.15–2.42]	7	4.4
Severity ≥5–10	4	13.3		12	13.6	**0.35 [0.17–0.74]***	43	27.0
Concentration difficulties								
No	22	73.3	ref.	41	46.6	ref.	55	34.6
Severity 1–4	4	13.3	0.59 [0.17–2.09]	10	11.4	0.86 [0.34–2.17]	14	8.8
Severity ≥5–10	4	13.3	**0.07 [0.02–0.24]****	37	42.0	**0.48 [0.27–0.87]***	90	56.6
Confusion								
No	29	96.7	-	79	89.8	ref.	141	88.7
Severity 1–4	1	3.3		2	2.3	0.57 [0.11–2.92]	6	3.8
Severity ≥5–10	0	0.0		7	8.0	1.01 [0.38–2.69]	12	7.5
Dizziness								
No	27	90.0	ref.	69	78.4	ref.	119	74.8
Severity 1–4	2	6.7	0.63 [0.13–2.97]	10	11.4	1.20 [0.51–2.83]	15	9.4
Severity ≥5–10	1	3.3	0.18 [0.02–1.37]	9	10.2	0.59 [0.26–1.35]	25	15.7
Headache								
No	25	83.3	ref.	67	76.1	ref.	109	68.6
Severity 1–4	1	3.3	0.42 [0.05–3.40]	7	8.0	0.89 [0.33–2.41]	12	7.5
Severity ≥5–10	4	13.3	0.49 [0.16–1.53]	14	15.9	0.55 [0.27–1.12]	38	23.9
Palpitations								
No	30	100.0	-	75	85.2	ref.	133	83.6
Severity 1–4	0	0.0		6	6.8	0.75 [0.28–2.04]	14	8.8
Severity ≥5–10	0	0.0		7	8.0	0.98 [0.37–2.62]	12	7.5
Increased resting heart rate								
No	26	86.7	ref.	76	86.4	ref.	125	78.6
Severity 1–4	2	6.7	1.60 [0.31–8.34]	4	4.5	0.81 [0.23–2.81]	8	5.0
Severity ≥5–10	2	6.7	0.37 [0.08–1.67]	8	9.1	0.49 [0.21–1.15]	26	16.4
Joint pain								
No	28	93.3	-	78	88.6	ref.	143	89.9
Severity 1–4	0	0.0		2	2.3	1.80 [0.24–13.43]	2	1.3
Severity ≥5–10	2	6.7		8	9.1	1.01 [0.40–2.53]	14	8.8
Muscle pain or -weakness								
No	25	83.3	-	58	65.9	ref.	102	64.2
Severity 1–4	0	0.0		3	3.4	0.50 [0.13–1.92]	10	6.3
Severity ≥5–10	5	16.7		27	30.7	1.01 [0.57–1.81]	47	29.6

Sleeping problems								
No	24	80.0	ref.	61	69.3	ref.	96	60.4
Severity 1–4	1	3.3	0.39 [0.05–3.19]	3	3.4	0.43 [0.11–1.60]	11	6.9
Severity ≥5–10	5	16.7	0.37 [0.13–1.03]	24	27.3	0.75 [0.42–1.34]	52	32.7
Loss/change of smell/taste								
No	22	73.3	ref.	51	58.0	ref.	98	61.6
Severity 1–4	4	13.3	0.46 [0.14–1.48]	22	25.0	1.23 [0.65–2.33]	34	21.4
Severity ≥5–10	4	13.3	0.49 [0.15–1.64]	15	17.0	1.03 [0.50–2.26]	27	17.0
Mobility								
Time spent lying down (hours/day)	2.5 (2.4)		1.00 [0.88–1.14]	2.5 (2.8)		1.00 [0.92–1.09]	2.4 (3.2)	
Problems with walking								
No to slight	20	66.7	ref.	49	55.7	ref.	73	45.9
Moderate to(very)severe	10	33.3	**0.40 [0.17–0.97]***	39	44.3	0.70 [0.40–1.21]	86	54.1
(severity of) acute COVID-19 illness								
Symptoms when tested, mean (SD)	7.6 (6.2)		**0.92 [0.86–0.97]***	11.0 (8.3)		0.98 [0.95–1.01]	12.7 (8.7)	
Hospitalization/oxygen use at home or hospital (yes)	4	13.3	0.51 [0.16–1.58]	11	12.5	**0.43 [0.21–0.89]***	40	25.2
Months since test, mean (SD)								
3–6	3	10.0	-	8	9.1		11	6.9
6–12	26	86.7		65	73.9		117	73.6
>12	1	3.3		15	17.0		31	19.5
New COVID-19 illness between baseline and follow-up (yes)	4	13.3	0.99 [0.95–1.03]	21	23.9	0.99 [0.97–1.02]	35	22.0
Vaccination status								
COVID-19 vaccine (yes)	26	86.7	0.37 [0.09–1.46]	86	97.7	2.31 [0.46–11.70]	152	95.6
New COVID-19 vaccine between baseline and follow-up (yes)	0	0.0	-	1	1.1	0.92 [0.08–10.44]	2	1.3
Mental health status								
Depression (yes)	20	66.7	**0.29 [0.12–0.73]***	66	75.0	**0.43 [0.22–0.85]***	137	86.2
Loneliness								
Not lonely	15	50.0	ref.	54	61.4	ref.	74	46.5
Moderately lonely	9	30.0	0.70 [0.28–1.77]	20	22.7	**0.49 [0.27–0.92]***	55	34.6
Severely lonely	6	20.0	0.94 [0.33–1.70]	15	15.9	0.62 [0.30–1.28]	30	18.9
Emotional loneliness (yes)	10	33.3	0.76 [0.33–1.75]	24	27.3	**0.55 [0.31–0.98]***	63	39.6
Social loneliness (yes)	9	30.0	1.01 [0.42–2.40]	20	22.7	0.71 [0.38–1.30]	46	28.9
Anxiety (yes)	1	3.3	0.96 [0.11–8.49]	2	2.3	0.61 [0.12–3.10]	6	3.8
Lifestyle								
Smoking behaviour								
Never	16	53.3	ref.	47	53.4	ref.	81	50.9
Former	13	43.3	1.09 [0.46–2.56]	35	39.8	0.99 [0.56–1.77]	65	40.9

Current	1	3.3	0.41 [0.05–3.41]	6	6.8	0.84 [0.30–2.39]	13	8.2
Interpersonal level								
Steady partner								
Having a relationship (yes)	27	90.0	2.39 [0.65–8.72]	71	80.7	0.99 [0.51–1.93]	129	81.1
Home situation								
Living alone (yes)	3	10.0	0.45 [0.12–1.65]	17	19.3	1.09 [0.56–2.15]	29	18.2
Children (yes)	10	33.3	0.86 [0.35–2.14]	29	33.0	0.86 [0.47–1.56]	54	34.0
Social network factors								
Size of social network, n(SD)	11.4 (7.2)		0.98 [0.93–1.04]	11.6 (7.4)		0.99 [0.96–1.02]	12.4 (7.9)	
Support from social network, n(SD)								
Number of members giving emotional support	7.6 (5.4)		0.96 [0.90–1.03]	8.5 (6.1)		0.99 [0.95–1.03]	8.9 (6.7)	
Number of members giving practical support	2.5 (1.3)		0.97 [0.84–1.12]	3.1 (2.9)		1.03 [0.95–1.12]	2.9 (3.5)	
Number of members giving informational support	4.6 (3.7)		0.95 [0.87–1.04]	5.7 (5.5)		1.00 [0.95–1.05]	5.6 (5.3)	
Network diversity								
Family and friends and acquaintances/caregivers	20	66.7	ref.	53	60.2	ref.	93	58.5
Only family, no friends/acquaintances/caregivers	2	6.7	0.46 [0.10–2.19]	6	6.8	0.57 [0.21–1.54]	18	11.3
Other	8	26.7	0.85 [0.34–2.12]	29	33.0	1.06 [0.60–1.88]	48	30.2
Network density				6				
Best friends know family (yes)	23	79.3	1.11 [0.41–2.98]	73	83.9	1.31 [0.66–2.59]	126	80.8
Societal level								
Physical environment								
Urbanity of living area								
(very) strongly urban	8	26.7	ref.	25	28.4	ref.	60	37.7
Moderately urban	8	26.7	1.29 [0.44–3.82]	24	27.3	1.49 [0.74–2.98]	38	23.9
Little urban	5	16.7	1.17 [0.35–3.93]	25	28.4	1.88 [0.93–3.80]	33	20.8
Rural	9	30.0	2.28 [0.77–6.71]	14	15.9	1.11 [0.50–2.49]	28	17.6

*p<0.05 **p<0.001 PCC-affectedDA=post-COVID-19 condition with no or slight problems with performing daily activities; PCC-impairedDA=post-COVID-19 condition with moderate to severe problems with performing daily activities. Adjusted for age (years), time since test (3–6, 6–12, >12 months), and having had a new COVID-19 infection between baseline and follow-up (yes/no).



Chapter 10

General discussion

The studies performed in this thesis aimed to map the impact of COVID-19. Impact was considered broadly, ranging from the influence of infection prevention measures on cross-border mobility, the role of social networks in vaccination behavior, and the emergence of post-COVID-19 condition and its impact on work. Large, population-based epidemiological studies were conducted using a unique multi-country, multi-domain approach, addressing both short- and long-term impact of the pandemic. By drawing lessons from COVID-19, this thesis ultimately seeks to inform scientists and policymakers to strengthen and protect public health and be prepared for times of crisis. In this chapter, we summarize the key findings across these themes and provide recommendations for future research and policy.

DATA COLLECTION AND STUDY SETUP DURING THE COVID-19 PANDEMIC

A main strength of this thesis lies in demonstrating that rigorous scientific practice informing research can be conducted during an ongoing pandemic, enabled by close collaboration between the public health service (GGD), the Regional Academic Medical Microbiological Laboratory, universities, and local public health authorities. Policy decisions are only as strong as the data that support them, underscoring the need for timely and coordinated data collection during health crises.

Box 1. Impact of COVID-19 on the Meuse-Rhine Euroregion (EMR) - study
This study was launched to examine pandemic response and impact of infectious disease control in the border region of Netherlands, Belgium, and Germany. This longitudinal project involved extensive collaboration among public health institutes, universities, and regional health authorities in the three countries. A random sample of 26,925 adult citizens selected from governmental registries were invited to complete online questionnaires and at-home finger-prick tests to measure SARS-CoV-2 antibodies. An online tool was set up to coordinate fieldwork procedures and real-time monitoring of participation, and where participants could consult their antibody test results. In Spring 2021 (round 1), 6,006 citizens participated and in Autumn 2021 (round 2) 4,286 citizens participated. In total, 3,344 citizens in the Meuse-Rhine Euroregion completed all components of participation in both rounds. The questionnaire included items on sociodemographics and general health; attitudes and behaviors related to infection prevention measures; cross-border mobility; social networks and social support; COVID-19 infection; and vaccination.

In chapter 2, we showed that comparative data collection in the EMR during a pandemic is possible via a centralized online environment. Challenges related to national regulations were identified during the preparation phase and regional coordination structures were in place to ensure familiarity and trust among the involved organizations. The self-finger-prick method, combined with the incentive of receiving antibody results afterwards, proved a cost-effective way to collect serological data on a large scale. Knowing one's antibody status was an incentive to participate, demonstrating that incentives can play a role in participation rates. However, participation rates were relatively low, possibly due to difficulties performing the self-finger-prick test and completing the online questionnaire. Providing clear, concise, and multilingual instructions in the letters and questionnaires was essential to minimizing practical barriers.

Box 2. The Prevalence, Risk Factors, and Impact Evaluation post-COVID (PRIME) – study

The PRIME study is an observational prospective cohort study. It assesses the prevalence and risk factors of post-COVID-19 condition, as well as its social, physical, mental, and socioeconomic impact. All adults tested for SARS-CoV-2 at the GGD South Limburg between 1 June 2020 and 1 November 2021 with a valid test result and a recorded email address in the public health registry were invited to participate. At baseline (November–December 2021), 12,453 adults participated and were subsequently invited to complete the first follow-up questionnaire (July–August 2022). In addition, adults tested in March 2022 (N=58,318) were invited to participate in a separate baseline measurement. In April–June 2024, a total of 18,132 participants who had participated at earlier measurement time points were invited to complete a follow-up questionnaire.

In chapter 3, we described the PRIME study in which we invited over 120,000 individuals, who were all adults who tested positive for COVID-19 at the South Limburg public health service during a certain period early pandemic, and a comparison group of negatively tested adults matched on sex, age, and testing period, to gather in-depth data on the prevalence, risk factors, and impact of post-COVID-19 condition. Measuring the effects of the pandemic versus the disease itself is challenging, particularly when multiple policy measures are implemented simultaneously. The retrospective aspect of the study design allowed us to obtain crucial data on health status, symptoms, and healthcare use during the acute infection. The major strength of the prospective assessments is the opportunity to study changes in outcomes and determinants before, during, and after (re)infection and recovery. The open cohort design, with participants tested in both 2020-2021 and during the omicron period in 2022, enabled studying post-COVID-19 prevalence as new variants emerge.

Both studies show that large-scale, population-based data collection during the COVID-19 pandemic is feasible and can produce meaningful insights for clinical and public health, as described later in this chapter. Using digital recruitment and data-collection systems and strong coordination, they combined representative sampling with multiple data sources, including questionnaires, serology, and registry data. Their longitudinal design enables tracking changes over time. Shared limitations included participation and non-response bias, and reliance on self-reported data. Bias can never be fully eliminated. Selection bias may occur

because participants are often more educated, health-conscious, or digitally skilled, attrition may distort longitudinal findings and recall bias may affect retrospective symptom reporting. Confounding by factors such as age, sex, socioeconomic status, or comorbidities also remains a concern. To address these issues, we used population-based sampling, reference groups, matching on key variables, and careful statistical adjustment to strengthen validity and generalizability. The studies provide complementary public health insights for regional and national pandemic response and for understanding the prevalence, risk factors, and long-term effects of COVID-19.

Limited time during a pandemic can hinder high-quality study setup. While a substantial data infrastructure already exists, including dashboards, registries, and digital reporting systems, there is potential to further improve and maintain coordination to facilitate timely and comprehensive data collection. For future pandemics, an effective data infrastructure is essential for monitoring and understanding the spread and impact of disease. Key measures include establishing centralized, real-time dashboards accessible to researchers; harmonizing ethical and data governance frameworks, particularly in cross-border regions, to enable secure and rapid data sharing; creating regional coordination platforms before crises occur; and investing in interoperable digital systems and patient registries that integrate with existing infrastructure. Well-prepared data systems or patient registries that integrate with existing infrastructure are essential for managing large-scale data during both acute disease phases and potential long-term consequences. Together, these measures can strengthen preparedness, enable rapid response, and improve the effectiveness of public health policy.

> Recommendation 1: Invest in interoperable and sustainable data infrastructures and long-term academic–public health collaboration to enable timely and coordinated data collection in future pandemics.

Living labs in public health (academische werkplaatsen publieke gezondheid) demonstrate clear added value for data collection during infectious disease outbreaks by structurally linking academic expertise with the operational capacity of Public Health Services. During a pandemic such as COVID-19, this collaboration enables the rapid, large-scale collection and analysis of high-quality population

data that are both scientifically robust and directly relevant for policy and practice. The presence of a regional (and particularly cross-border) knowledge infrastructure further strengthens this capacity, allowing timely insights into transmission dynamics, behavioral responses, and intervention effects across interconnected populations. Importantly, such infrastructures do not emerge spontaneously in times of crisis; they require sustained commitment, trust-based collaboration, and continuous investment in academic and public health staff to maintain readiness, data governance, and methodological expertise. When these conditions are met, living labs function as durable platforms that bridge research and practice and substantially enhance preparedness and responsiveness for future public health emergencies.

CROSS-BORDER MOBILITY IS ESSENTIAL FOR WELLBEING AND FOR SOCIAL CONNECTION

In this section, both the resilience and vulnerabilities of border regions when faced with border restrictions are highlighted. Although border restrictions are aimed at protecting public health, they also created social, economic, and psychological burdens and disrupted everyday cross-border activities. It has been shown that cross-border movement itself did not pose greater infection risk than domestic mobility, and COVID-19 transmission across borders had minimal impact on national case numbers. Most infection clusters aligned with domestic waves rather than cross-border spread, suggesting that border closures were not a key factor in controlling the pandemic in the EMR (1). National policy decisions can disrupt border region daily life, emphasizing the need for coordinated approaches in border regions.

Chapter 4 confirmed that cross-border mobility (CBM) is a central part of daily life in the EMR. Pre-pandemic, 82% of participants reported regular cross-border mobility for social contacts (31%) or everyday activities (79%), which decreased substantially during the pandemic. Border restrictions were perceived negatively by 45% of participants, especially by those with cross-border social networks or work-related mobility. CBM was associated with happiness, both pre-pandemic and during the pandemic in autumn 2021. Both freedom of movement and social contact are strongly linked to health and wellbeing; freedom of movement is also a fundamental right (2, 3). Border restrictions may therefore contribute to social isolation, which was already a problem during the pandemic (4), and thereby impair public health.

In large-scale population studies in cross-border settings conducted during a pandemic, several methodological challenges inevitably emerge. First, the reliance on self-reported data (particularly for reconstructing pre-pandemic CBM) may introduce information and recall bias. Such biases can affect the precision of behavioural estimates and are difficult to avoid when retrospective reporting is required. Second, our study could not capture all relevant spatial and social nuances: exact residential proximity to national borders and the structure of individuals' social networks were only partially measured, which reduced the level of detail in our contextual analyses. To better measure mobility, studies could for example integrate objective measures including mobility tracking or geographical information system (GIS) data, while adhering to General Data Protection Regulations, and include qualitative components to explore motivations and barriers. Third, as is common in cross-national research in crisis settings, heterogeneity in national policies, cultural norms, and communication strategies across the EMR likely contributed to observed differences between countries in reported CBM outcomes (chapter 4) or booster intentions (chapter 5). Together, these limitations reflect broader challenges inherent to conducting timely, large-scale research in rapidly evolving pandemic contexts.

Recommendation 2: Prioritize cross-border health research to protect mobility and social connections in border communities. Insights gained from regional collaboration can inform public health strategies across Europe.

Public health and pandemic preparedness policies rarely address the importance of maintaining social contact and mobility, and are often shaped nationally rather than regionally, overlooking the needs of border communities. The EU emphasizes that uncoordinated public health measures by individual member states can negatively affect neighboring countries and advocates for proportionate, coordinated responses to cross-border threats without undermining free movement (5). Governments should build dormant but prepared systems ahead of future public-health crises. This includes maintaining effective digital tools and infrastructure for long-term planning. Travel measures must be clear, transparent, and based on consistent, data-driven criteria. Policies should be equitable, avoiding disproportionate impacts on groups such as cross-border workers or those with cross-border social ties, ensuring fair access to services and proportionality to societal costs. When restrictions would be

implemented, these should be regularly evaluated and lifted as soon as they are no longer needed (6, 7). Legal frameworks should ensure that any border restrictions are temporary, proportionate, and coordinated between countries. While cross-border collaboration through informal personal networks is valuable, structured policies and institutional support can make this process more robust and resistant to changes. Building trust, maintaining collaboration, and regularly sharing knowledge across borders are key to ensuring compliance, effective communication, and the overall wellbeing of the large proportion of citizens living in border regions.

Health threats do not observe political demarcations. Infectious diseases, environmental exposures, and social determinants of health travel with people and goods, often more rapidly than regulatory or policy frameworks can adapt. This makes border regions an area for collaboration, but also vulnerable to fragmented policies. Differences in legislation, surveillance systems, data infrastructures, healthcare organization, and preventive policies can produce misalignments that make coordinated action more challenging (1). The COVID-19 pandemic showed that neighboring regions followed divergent rules for testing, quarantine, vaccination, and travel. Therefore, research in the EMR is not only locally relevant but has broader significance. The EMR mirrors systemic challenges faced by the approximately 360 border regions across Europe, home to around one-third of the EU population (8-10). The high level of daily mobility in the EMR for work, education, healthcare, leisure, and family life creates closely connected social and economic systems. This makes the region an ideal "real-world laboratory" for studying how health challenges arise and are addressed across national boundaries. Insights generated in this region therefore provide an evidence base that may inform European discussions on cross-border governance, pandemic preparedness, mental health promotion, and environmental health protection.

Cross-border collaboration within the EMR has resulted in initiatives in surveillance, outbreak response, youth health, and environmental monitoring, supported by academic institutions and the WHO Regions for Health Network (RHN) (11). The establishment of the WHO Collaborating Centre Regions for Health and Cross-Border Public Health in 2025 further enhances this capacity by focusing on three mutually reinforcing missions: generating evidence on cross-border health challenges, building capacity among regional professionals and

institutions, and facilitating structured knowledge exchange across Europe (12). In this context, the findings of the present dissertation contribute to a broader agenda aimed at advancing "Health for All by All" (13). By focusing on cross-border mobility, health behaviours, and policy alignment within the EMR, this work highlights that health should be seen not just at the national level, but as a connected cross-border regional issue.

STRONG SOCIAL NETWORKS AND SUPPORTIVE ENVIRONMENTS SHAPE COVID-19 VACCINATION BEHAVIORS

Vaccination intention and uptake is influenced not only by individual choices but also by social and physical environmental factors. Our findings highlight the importance of the environment in COVID-19 vaccine behavior.

In chapter 5, we observed differences in booster vaccine intentions across the EMR and in attitudes towards non-pharmaceutical measures, which may reflect country-variations in COVID-19 policies, communication, and vaccination strategies. German residents generally had the highest positive intention and the most positive attitudes toward the measures, Dutch residents showed lower intention, and Belgium exhibited regional variation. Despite these differences, in all countries, sociodemographics, individual health, and peoples' attitudes towards measures and government communication of measures were associated with booster intention. These findings highlight the central role of trust in institutions and clear and transparent communication of information in vaccination intention.

Disinformation is a major challenge for successful public health approaches. People may tend to seek out and trust information that confirms their existing views, such as in those with higher health literacy (14, 15). Individuals who are least trusting of the government, and those with higher levels of conspiratorial thinking (a general deeply skeptical mindset) are more likely to believe misinformation and refuse vaccination (16). Attention to vaccine information tends to be higher among individuals who are satisfied with health authority communication and confident in their ability to identify accurate information. Public health practitioners could identify vaccine literacy gaps and address misinformation through community engagement, trusted messengers, and clear, accurate

communication. These strategies can build trust and encourage positive health behaviors (17).

Beyond national policies, the living environment may influence vaccination uptake through accessible (vaccination) resources and locations, informational availability, and supportive community connections. In chapters 6 and 7, we highlighted social networks and the living area as important associated factors for COVID-19 vaccine intention and uptake. Associated factors included higher neighborhood livability and walkability scores and a moderate level of urbanization. Neighborhood characteristics may create barriers or opportunities for vaccine uptake, for example by affecting accessibility of health services via infrastructure. Facilitating vaccine access through community-based locations or mobile vaccination services may help increase uptake. Neighborhood green space can strengthen social cohesion and community engagement, which are known to increase trust, support, and information sharing (18). Although we could not measure exact mechanisms in our study, residents may be more likely to engage in health services in communities with more inviting public spaces.

Social connection can impact health and health behaviors through social support, access to resources, behavioral influence, and direct impact on emotional wellbeing (19). In chapter 6, factors associated with COVID-19 vaccine intention included having a larger network size and a larger proportion of informational supporters. Concerns about personal and family health were associated with higher vaccination intentions, underscoring the value of herd immunity for protecting social network members. In chapter 7, factors associated with vaccine or booster uptake included a larger social network size, network diversity, network density, not living alone, not being lonely, and social participation. These associations may reflect processes of social selection and social influence, whereby individuals tend to associate with similar others and adopt behaviors that are common within their networks. Findings highlight that the structure, function, and quality of social networks are linked to COVID-19 vaccination behavior or intention, suggesting that strengthening networks could improve uptake and inform public health interventions.

By providing support, social networks may also influence how individuals cope with the broader psychosocial challenges of the COVID-19 pandemic. The ever-changing measures, lockdowns, conflicting information, and disruptions to daily life caused by COVID-19 contributed to pandemic fatigue. Pandemic fatigue is a state of exhaustion which leads to distress and negatively affects emotions, cognition, and behavior (20). Apart from that, vaccine information fatigue

impacted vaccine uptake, and the resulting increase in vaccine hesitancy also disrupted routine immunization, raising the risk of reemergence of childhood and adult vaccine-preventable diseases (14). It has been shown that perceived social support moderated the effect of the disruptions on pandemic fatigue and perceived stress. Perceived social support may help buffer the stress caused by the pandemic's disruptions to daily life. Support from family, friends, and communities reduces stress and pandemic fatigue by preserving emotional resources and promoting more adaptive coping (21).

Network characteristics such as size, diversity, and informational support were also associated with adherence to infection prevention behaviors (22). This suggests that fostering and maintaining strong social networks can serve as an important preventive strategy, both during a pandemic and in preparation for future public health crises. During pandemics, the protective benefits of social connection need to be balanced with infection risks, emphasizing the importance of limiting specific high-risk contacts while maintaining supportive connections where possible. Integrating social network analysis into pandemic preparedness and behavioral surveillance could therefore be valuable. Network features could be monitored via surveys. It should be noted that evaluations of network size can be influenced by both participant characteristics and the timing of the pandemic. For instance, participants with a higher education level (who are often overrepresented in studies) tend to have more contacts than average when measures are relaxed and fewer contacts than average when measures are stringent. As a result, contact numbers may be overestimated during periods of relaxed measures and underestimated during periods of strict measures (23).

Recommendation 3: Integrate the strengthening of social networks and supportive living environments into public health vaccination strategies. Foster strong social networks, characterized by a certain number of contacts (network size), various different types of contacts (network diversity), social support, and community participation (e.g., in clubs), as part of pandemic preparedness and health promotion. Clear, accurate, and trusted communication should accompany these efforts to strengthen trust, counter misinformation, and encourage vaccine uptake. Inviting (green) public spaces where people can meet others are essential in this respect as well.

Taken together, our findings suggest that strengthening social networks can have benefits beyond individual behavior, supporting broader social health and guiding policies to enhance community well-being. According to the WHO, social connection is as social health the third pillar of health, alongside physical and mental health, serving both as a determinant of health and as health itself. Social disconnection has serious consequences for physical and mental health, education, the economy, and society at large (24). While directly modifying social networks may be challenging, they may be shaped indirectly through policy interventions, for example by engaging local influencers, improving public spaces, or by supporting programs that promote participation and social interaction (25, 26). Investing in social networks and local infrastructures not only saves lives but also strengthens communities, both during emergencies and in everyday life.

POST-COVID-19 CONDITION SUBSTANTIALLY AFFECTS WORK PARTICIPATION AND RECOVERY IS LOW

Post-COVID-19 condition is a complex, multisystem disease that can affect nearly every organ, and it is debilitating for individuals, communities, and society due to its high prevalence, significant impact on health and daily functioning, slow recovery, chronic nature, and limited treatment options (27). In Chapter 8, we showed that the two-year workforce exit rate was twice as high in individuals with PCC, compared to those without PCC. Work incapacity missed workdays due to health problems, and impaired performance while working, were up to three times higher in both individuals with PCC and those who had recovered, indicating potential residual impairments. Financial strain was reported most frequently among the PCC group. Beyond work and economic impacts, patients may experience social isolation and changes to their sense of identity. For example, it has been reported that one in four individuals with PCC limit activities outside of work in order to continue working (28). To support individuals in the workplace, policies such as flexible hours, scheduled breaks to allow pacing, remote work options, and comprehensive sick leave should be implemented.

In Chapter 9, we showed that only 11% of individuals with severe PCC and 37% with mild PCC felt recovered after nine months. Factors associated with lower recovery likelihood also reflected PCC severity, including poorer overall health. Better general health prior to PCC may be protective, highlighting the role of

prevention. Recovery appears largely determined by biological rather than social or environmental factors but identifying subgroups more likely to recover can provide perspective on disease progression. Longitudinal studies are needed to track patients over time and identify modifiable factors, while clinical trials evaluating pharmacological interventions remain scarce due to diagnostic uncertainty, societal pressures, and misconceptions about PCC. While studying factors that support recovery is valuable, patients would ultimately benefit most from a deeper understanding of PCC's pathophysiology. Improved insight could inform clear definitions and effective interventions, provided these are accessible and the disease is recognized by healthcare professionals, policymakers, and employers. Because PCC likely presents a disease with many subtypes, patients may respond differently to treatments. It should also be taken into account that future prognosis is still uncertain and that some manifestations of PCC such as ME/CFS and dysautonomia are generally lifelong (27, 29).

To date, there is no clear definition of PCC or of recovery from the condition, and patients often encounter substantial misunderstandings in both their personal and professional lives. Defining a condition is essential for case registration, estimating disease burden, and enabling access to social security benefits. For patients with PCC, the absence of a formal diagnosis creates uncertainty for insurers, limiting reimbursable treatment options. This may also place an even greater burden and exacerbate inequality for individuals who are already disadvantaged health-wise or financially. PCC substantially impairs quality of life (30), and it has been suggested that this impact is more severe for people with lower socioeconomic positions. Factors such as low education, low income, and unemployment may amplify the effects of PCC on fatigue, depression, pain, sleep, and social participation. This indicates that sociodemographic inequalities shape not only PCC risk but also its consequences, underscoring the need for equitable management and further longitudinal research (31). We did not assess formal diagnoses, and many people with post-COVID-19 condition (PCC) are likely undiagnosed, which can make coping with the illness more difficult. Addressing underdiagnosis is an important area for future research.

Recommendation 4: Address the impact of post-COVID-19 condition through clear criteria for diagnosis and recovery, accessible care, and flexible workplace policies. Specialized post-COVID care centers and collaboration are essential for coordinated support and global knowledge sharing. Assess underdiagnosis and inequity in diagnosis and care.

For the future and for emerging new viruses, the possibility of long-term consequences should be anticipated. This also still applies to SARS-CoV-2, as each infection or reinfection remains a risk for developing PCC or exacerbating existing PCC (27). Therefore, measures such as non-pharmaceutical interventions (masks, improved air quality) and increased vaccine uptake may reduce PCC risk. Continued research into pathophysiology and treatment options is essential, including longitudinal studies, randomized controlled treatment trials, and biomarker research to improve diagnostics, develop consensus on definitions, and identify effective interventions. The PRIME research group is part of the post-COVID network Netherlands (PCNN), a national partnership of (university) hospitals, patient organizations, paramedical partners, and organizations, which together form an open network expertise in the field of post-COVID. The PCNN network helps develop effective treatments and improve care and support for adults and children with post-COVID. This involves knowledge about the cause, diagnosis, prognosis, and treatments. Within this network, post-COVID research projects are coordinated and knowledge and data are shared. Standardized care pathways, including post-COVID expertise centers, need to be established, maintained and made accessible. Furthermore, international organizations should promote collaboration and knowledge-sharing across countries to increase equity and address PCC as a global health challenge.

CONCLUSION

Mapping the impact of COVID-19 has revealed profound effects on individuals, communities, and society, exposing existing inequities while highlighting both the resilience and vulnerabilities of public health systems. This thesis demonstrates that large-scale, population-based research is feasible during a pandemic and that (cross-border) collaboration and timely data collection are essential for informed decision-making. The EMR provides a valuable setting to understand how health behaviors and risks develop across linked social, cultural, and policy

contexts, highlighting both the vulnerabilities of fragmented systems and the potential of coordinated cross-border public health action. Findings emphasize the importance of considering individual, interpersonal, community, and environmental factors in health promotion and in vaccination strategies. This includes strong social networks and inviting public spaces, including green spaces. Post-COVID-19 condition represents a substantial long-term burden, affecting work participation and recovery, underscoring the need for recognition, equitable diagnosis and care, and continued research into pathophysiology and interventions. Lessons from COVID-19 stress the necessity of proactive pandemic preparedness, robust physical and technological infrastructure, and adaptive strategies that balance public health protection with the importance of social health (i.e., social connection). Preparedness must also recognize the potential for long-term consequences, implementing structured care pathways and equitable support for affected populations. Furthermore, cross-border and regional collaboration should be strengthened to ensure that policies are coordinated, proportionate, and responsive to the needs of border communities. By integrating these insights, we can create actionable strategies that strengthen public health resilience and better protect individuals and communities in future pandemics.

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Summary

The studies described in this thesis mapped processes of data collection, cross-border mobility and booster intention in the Meuse-Rhine Euroregion (EMR) during the COVID-19 pandemic. Besides, we described the impact of post-COVID-19 condition (PCC) on employment and factors associated with recovery from PCC. Finally, we assessed, and social, individual, and environmental factors associated with COVID-19 vaccination intention and uptake. **Chapter 1** provides an outline of the COVID-19 pandemic in the Netherlands and the EMR and introduces concepts central to this thesis, including vaccination, social networks, and PCC. The aim of this thesis was to map the impact of COVID-19 using quantitative cohort data, thereby providing insight into its multifaceted effects.

Chapter 2 described the process of comparative data collection in the three countries of the EMR during the COVID-19 pandemic. In the spring and autumn of 2021, adult citizens were selected from governmental registries and invited to collect a blood sample at home for SARS-CoV-2 antibody testing and to fill in an online questionnaire on infection prevention measure attitudes and behaviors, cross-border mobility, social networks, COVID-19 infections and vaccination, overall health, and sociodemographics. Collecting comparative data may help to better evaluate pandemic responses and infectious disease control in cross-border regions. Inclusion of a central online platform, early consideration of national regulatory differences, and regional coordination centers to strengthen collaboration and trust may facilitate this process.
Persistent symptoms after COVID-19 (longCOVID or PCC) pose a potential public health challenge. **Chapter 3** described the design and recruitment of the PRIME post-COVID study, a population-based observational cohort aiming to improve understanding of the prevalence, risk factors, and social, physical, mental, emotional, and socioeconomic impact of PCC. The study included retrospective and prospective assessments of health conditions and demographic, social, and behavioral factors. Participants were identified via the Dutch public health COVID-19 registry CoronIT and had taken a COVID-19 test at the Public Health Service South Limburg. In November 2021, 61,655 individuals were contacted, including all PCR-positive adults tested between 1 June 2020 and 1 November 2021, and a matched sample of PCR-negative adults (2:1 ratio) by age, sex, municipality, and test quarter. Participants were followed over time findings may guide societal, clinical, and public health strategies to manage the long-term impacts of COVID-19.

In the EMR, cross-border mobility (CBM) is an important and substantial part of daily life for citizens. In **Chapter 4** we assessed changes in CBM during the pandemic in 3,543 participants. 82% reported CBM (at least one visit per month): 31% for social contacts and 79% for everyday activities. Among these, 26% decreased social CBM and 35% decreased CBM for everyday activities by autumn 2021. CBM was highest in the Netherlands (90% of participants), followed by Germany (81%) and Belgium (63%). Decreased CBM was seen in 40% of Dutch and German participants and 32% in Belgian participants. Border restrictions were valued as negative by 45% of participants and this was associated with Dutch residency, working across the border, having social contacts across the border, and perception of measures. Policymakers should consider the negative effects of CBM restrictions when planning future pandemic strategies.

After the initial COVID-19 vaccination campaign in early 2021, booster vaccines became available in the EMR in winter 2021-2022. In **Chapter 5**, we identified factors associated with non-positive COVID-19 booster vaccine intention in 3,319 initially vaccinated adults in the EMR. Compared to German residents, Dutch residents (aOR = 2.41 [95%CI:1.90-3.04]) and Belgian residents (aOR = 1.40 [95%CI:1.05-1.86]) were more likely to be uncertain or not want to receive a booster vaccine in autumn 2021. Factors independently associated with non-positive intention were female sex (aOR = 1.55 [95%CI:1.18-2.03]), absence of comorbidities (aOR = 1.33 [95%CI:1.03-1.71]), time since last vaccination <3 months ago (aOR = 1.61 [95%CI:1.18-2.19]), being partially vaccinated (aOR = 3.62 [95%CI:1.98-6.63]), a negative experience with communication of COVID-19 measures (aOR = 2.17 [95%CI:1.56-3.02]), and regarding measures as ineffective (aOR = 1.09 [95%CI:1.06-1.11]), suggesting communication, risk perception, and cross-border collaboration as targets to strengthen booster intention.

Social networks, our social relationships, influence the spread of infectious diseases and preventive behaviors such as vaccination. In **Chapter 6** we aimed to assess which individual, interpersonal (social network characteristics), community and societal factors are associated with coronavirus disease 2019 (COVID-19) vaccination intention during the second wave of the COVID-19 pandemic in 2020. As part of the SaNAE study, 3,396 community-dwelling adults aged 40 years and older in the Netherlands completed an online questionnaire on COVID-19 vaccine intention and individual, interpersonal, community, and societal factors. 59 % reported a positive intention to vaccinate, 35 % were unsure, and 6 % had no intention. Men, individuals of older age, those with a college or university degree, those concerned about their personal and family health, and knowledge

about protecting oneself from the virus were more likely to have the intention to vaccinate (versus no intention). Interpersonal factors associated included having a larger network size (social network structure) and a larger proportion of informational supporters (social network function). Living outside of urban areas, a societal factor, was associated with vaccination intention (versus no intention). Health promotion efforts should therefore address both individual and social environmental factors.

Measuring vaccine uptake alongside intention provides a complete picture of vaccination behavior. In the PRIME study, we measured both COVID-19 vaccine uptake (end of 2021, N=9,501) and booster uptake (summer 2022, N=3,620) via online questionnaires in adults, as described in **Chapter 7**. COVID-19 vaccine uptake was 94%, while in vaccinated participants at follow-up booster uptake was 91%. Community and societal factors associated with (booster) vaccine uptake included social participation, higher neighborhood livability and walkability scores, and a moderate level of urbanization. Interpersonal factors included a larger social network size, network diversity, network density, and not living alone. Associated individual factors included age ≥60 years, male sex, college/university education, being born in the Netherlands, having chronic conditions, being a never/former smoker, higher health literacy, and no loneliness. Vaccination strategies should address the environmental context (community, societal and interpersonal factors) alongside individual-level factors to contribute to pandemic preparedness

PCC has considerable effects on employment, impacting both individuals and society. In **Chapter 8**, we assessed workforce exit and work productivity loss among adults with PCC compared to those recovered or without PCC. We used PRIME online questionnaire data from adults with a positive COVID-19 test between June 1, 2020, and September 11, 2022. Participants were categorized into the groups (1) PCC (not feeling recovered at least three months post-infection), (2) Recovered, and (3) Never PCC. All were employed in 2022 and followed until 2024. Workforce exit and associated factors, work productivity loss, work incapacity, and financial strain were evaluated at follow-up. The two-year workforce exit rate was 17% in PCC (N=790), 10% in Recovered (N=437), and 9% in Never PCC (N=2,115). Rates were higher among those with PCC, older age, and with a range of physical and mental health conditions. Absenteeism and presenteeism were up to three times higher in PCC and two times higher in

Recovered, compared to Never PCC. Full or partial work incapacity among non-employed participants was 46% in PCC, 17% in Recovered, and 12% in Never PCC. Financial strain was highest among non-employed PCC participants (54%) and lowest among employed Never PCC participants (19%). PCC substantially impacts workforce participation and productivity. Support, interventions, and awareness are urgently needed.

Due to the high number of PCC cases worldwide it is crucial to study factors associated with recovery and remaining illness. In **Chapter 9**, we used longitudinal data from the PRIME study to estimate the proportion of patients living with PCC that recover over time and associated individual and environmental factors. PCC groups were classified based on feeling recovered combined with the capacity of daily functioning (PCC-affectedDA=no or slight problems with performing daily activities; PCC-impairedDA=moderate to severe problems with performing daily activities). Of the participants with PCC-affectedDA (n=602), 222 (36.9%) recovered and 59 (9.8%) deteriorated to PCC-impairedDA. Of patients with PCC-impairedDA (n=277), 30 (10.8%) recovered and 88 (31.8%) improved in daily functioning to PCC-affectedDA. In both PCC-affectedDA and PCC-impairedDA, baseline individual and environment factors that lowered recovery likelihood included worse physical health (mild/severe fatigue, severe dyspnea, severe symptoms of amnesia, concentration difficulties, muscle pain or -weakness, loss/change of smell/taste), worse mobility (hours spent lying down, problems with walking), worse mental health (depression), worse acute illness (more symptoms, hospitalization/oxygen use); former smoking; living in a rural area, having a relationship, and having more social network members giving practical support (in patients with chronic co-morbidities). Only 11%-37% of patients with PCC in the PRIME cohort recovered after 9 months, leaving significant room for improvement and for future research to identify modifiable factors and treatment to help assist recovery of patients with PCC.

Chapter 10 discusses the main findings of this thesis and their implications for public health. The chapter reflects on the methods and necessity of population-based research during a pandemic and emphasizes the importance of timely data collection and (cross-border) collaboration. It underscores the role of social networks, environmental, and systemic factors in vaccination strategies and pandemic preparedness. This includes fostering strong social networks, promoting community participation, providing supportive and inviting public spaces, and ensuring clear and trusted communication. Lastly, it highlights the

substantial burden of post-COVID-19 condition on individuals and communities, calling for clear criteria for diagnosis and recovery, flexible workplace policies, accessible care, and support.



Nederlandse samenvatting

De studies beschreven in dit proefschrift hebben de processen van dataverzameling, grensoverschrijdende mobiliteit en intentie tot booster-vaccinatie in de Maas-Rijn Euroregio (EMR) tijdens de COVID-19-pandemie in kaart gebracht. Daarnaast is de impact van de post-COVID-19-conditie (PCC) op werkparticipatie en factoren die geassocieerd met herstel van PCC beschreven. Tot slot zijn sociale, individuele en omgevingsfactoren onderzocht die verband houden met de COVID-19-vaccinatie intentie en uptake. **Hoofdstuk 1** geeft een overzicht van de COVID-19-pandemie in Nederland en de EMR en introduceert concepten die centraal staan in dit proefschrift, waaronder vaccinatie, sociale netwerken en PCC. Het doel van dit proefschrift was om de impact van COVID-19 in kaart te brengen met kwantitatieve cohortdata, om zo beter inzicht te krijgen in de veelzijdige effecten ervan.

Hoofdstuk 2 beschreef het proces van vergelijkende dataverzameling in de drie landen van de EMR tijdens de COVID-19-pandemie. In het voorjaar en najaar van 2021 werden volwassen burgers geselecteerd uit overheidsregisters en uitgenodigd om een bloedmonster thuis af te nemen voor SARS-CoV-2-antistoftesten en een online vragenlijst in te vullen over hun houding en gedrag ten aanzien van infectiepreventiemaatregelen, grensoverschrijdende mobiliteit, sociale netwerken, COVID-19-infecties en vaccinatie, algemene gezondheid en sociodemografische gegevens. Het verzamelen van vergelijkende gegevens kan helpen om pandemieresponsen en infectieziektebestrijding in grensregio's beter te evalueren. Het gebruiken van een centraal online platform, het van tevoren rekening houden met nationale regelgevingsverschillen en regionale coördinatiecentra om samenwerking en vertrouwen te versterken kan dit proces vergemakkelijken. Aanhoudende klachten na COVID-19 (longCOVID of PCC) vormen een potentieel volksgezondheidsprobleem. **Hoofdstuk 3** beschreef het ontwerp en de werving van de PRIME post-COVID-studie, een populatie gebaseerd observationeel cohortonderzoek dat tot doel heeft inzicht te geven in prevalentie, risicofactoren en de sociale, fysieke, mentale, emotionele en sociaaleconomische impact van PCC. De studie omvatte retrospectieve en prospectieve beoordelingen van gezondheidstoestand en demografische, sociale en gedragsfactoren. Deelnemers werden geïdentificeerd via het Nederlandse volksgezondheidsregister CoronIT en hadden een COVID-19-test ondergaan bij de GGD Zuid-Limburg. In november 2021 werden 61.655 personen benaderd, waaronder alle PCR-positieve volwassenen getest tussen 1 juni 2020 en 1 november 2021, en een gematchte van PCR-negatieve volwassenen (verhouding

2:1) op basis van leeftijd, geslacht, gemeente en testkwartaal. Deelnemers werden over tijd gevolgd en bevindingen kunnen maatschappelijke, klinische en volksgezondheidsstrategieën sturen om de langetermijneffecten van COVID-19 te beheersen.

In de EMR is grensoverschrijdende mobiliteit (cross-border mobility; CBM) een belangrijk en substantieel onderdeel van het dagelijks leven van burgers. In **Hoofdstuk 4** hebben we veranderingen in CBM tijdens de pandemie onderzocht bij 3.543 deelnemers. 82% rapporteerde CBM (minstens één bezoek per maand): 31% voor sociale contacten en 79% voor dagelijkse activiteiten. Hiervan verminderde 26% hun sociale CBM en 35% hun CBM voor dagelijkse activiteiten in het najaar van 2021. CBM was het hoogst in Nederland (90% van de deelnemers), gevolgd door Duitsland (81%) en België (63%). Vermindering in CBM werd gerapporteerd door 40% van de Nederlandse en Duitse deelnemers en 32% van de Belgische deelnemers. Grensbeperkingen werden door 45% van de deelnemers als negatief ervaren, vooral onder Nederlanders, deelnemers die over de grens werkten, deelnemers met sociale contacten over de grens, en bij lagere perceptie van effectiviteit en gemak van de maatregelen. Beleidsmakers moeten rekening houden met de negatieve effecten van CBM-beperkingen bij toekomstige pandemiestrategieën.

Na de eerste COVID-19-vaccinatiecampagne begin 2021 kwamen in de winter van 2021-2022 boostervaccins beschikbaar in de EMR. In **Hoofdstuk 5** werden factoren geïdentificeerd die verband houden met een niet-positieve intentie om een COVID-19-boostervaccin te nemen bij 3.319 initieel gevaccineerde volwassenen in de EMR. Vergeleken met Duitse inwoners waren Nederlandse (aOR = 2,41 [95%CI:1,90-3,04]) en Belgische inwoners (aOR = 1,40 [95%CI:1,05-1,86]) meer geneigd om onzeker te zijn of geen boostervaccin te willen krijgen in het najaar van 2021. Factoren die onafhankelijk geassocieerd waren met een niet-positieve intentie waren vrouwelijk geslacht, afwezigheid van comorbiditeiten, tijd sinds laatste vaccinatie <3 maanden, gedeeltelijke gevaccineerd zijn, negatieve ervaring met communicatie over COVID-19-maatregelen en het beschouwen van maatregelen als ineffectief. Dit suggereert dat communicatie, risicoperceptie en grensoverschrijdende samenwerking belangrijke doelwitten zijn om booster-intentie te versterken.

Sociale netwerken beïnvloeden de verspreiding van infectieziekten en preventief gedrag, zoals vaccinatie. In **Hoofdstuk 6** werd onderzocht welke individuele, interpersoonlijke (sociale netwerkkenmerken), gemeenschaps- en

maatschappelijke factoren geassocieerd zijn met COVID-19-vaccinatie-intentie tijdens de tweede pandemiegolf in 2020. Van 3.396 volwassenen in Nederland rapporteerde 59% een positieve vaccinatie-intentie, 35% was onzeker en 6% had geen intentie. Factoren geassocieerd met intentie waren onder meer mannelijk geslacht, hogere leeftijd, hoger opleidingsniveau, bezorgdheid over eigen en familiegezondheid en kennis over virusbescherming. Interpersoonlijke factoren waren een groter netwerk en een hoger aandeel informatieondersteuners. Het wonen buiten stedelijke gebieden, een maatschappelijke factor, werd ook geassocieerd met vaccinatie-intentie. Gezondheidsbevordering moet zowel individuele als sociale omgevingsfactoren adresseren.
Het meten van vaccinatie uptake naast intentie geeft een volledig beeld van vaccinatiegedrag. In de PRIME-studie werd zowel COVID-19-vaccinatie (eind 2021, N=9.501) als booster-uitvoering (zomer 2022, N=3.620) gemeten, zoals beschreven in **Hoofdstuk 7**. De COVID-19-vaccinatiegraad in onze studiepopulatie was 94%, terwijl bij gevaccineerde deelnemers bij de follow-up de uptake van de booster 91% bedroeg. Gemeenschaps- en maatschappelijke factoren geassocieerd met (booster)vaccinatie waren sociale participatie, hogere leefbaarheid en loopbaarheid in de buurt, en gematigde urbanisatie. Interpersoonlijke factoren waren een groter sociaal netwerk, grotere diversiteit en dichtheid van het netwerk, en niet alleen wonen. Individuele factoren waren leeftijd ≥60 jaar, mannelijk geslacht, hoger opleidingsniveau, in Nederland geboren zijn, chronische aandoeningen, nooit/voormalig roker, hogere gezondheidsvaardigheden en lage eenzaamheid. Vaccinatiestrategieën moeten zowel omgevingscontext als individuele factoren adresseren om pandemieparaatheid te versterken.

PCC heeft een groot effect op werkparticipatie en beïnvloedt zowel individuen als de samenleving. In **Hoofdstuk 8** hebben we werkuitstroom en het verlies van werkproductiviteit onder volwassenen met PCC vergeleken met volwassenen die hersteld zijn of geen PCC hebben. We hebben gebruikgemaakt de PRIME data en includeerden volwassenen die tussen 1 juni 2020 en 11 september 2022 positief testten op COVID-19. De deelnemers werden ingedeeld in de volgende groepen: (1) PCC (zich ten minste drie maanden na infectie nog niet hersteld voelen), (2) hersteld en (3) nooit PCC. Alle deelnemers waren in 2022 werkzaam en werden gevolgd tot 2024. Bij de follow-up werd de werkuitstroom en daarmee samenhangende factoren, het verlies van werkproductiviteit, arbeidsongeschiktheid en moeite met rondkomen geëvalueerd. Het

werkuitstroom percentage over twee jaar was 17% in PCC (N=790), 10% in Hersteld (N=437) en 9% in Nooit PCC (N=2.115). De percentages waren hoger bij PCC, hogere leeftijd, en deelnemers een reeks lichamelijke en geestelijke gezondheidsproblemen. Het ziekteverzuim en presenteïsme (niet productief kunnen werken door gezondheidsproblemen) waren tot drie keer hoger bij PCC en twee keer hoger bij herstelde deelnemers, vergeleken met Nooit PCC. Volledige of gedeeltelijke arbeidsongeschiktheid onder niet-werkende deelnemers was 46% bij PCC, 17% bij herstelde deelnemers en 12% bij nooit PCC. Moeite met rondkomen was het hoogst onder niet-werkende PCC-deelnemers (54%) en het laagst onder werkende Nooit PCC-deelnemers (19%). PCC heeft een aanzienlijke invloed op werkparticipatie en werkproductiviteit. Ondersteuning, interventies en bewustwording zijn dringend nodig.

Vanwege het hoge aantal PCC-gevallen wereldwijd is het van cruciaal belang om factoren te onderzoeken die verband houden met herstel en blijvende ziekte. In **Hoofdstuk 9** hebben we longitudinale gegevens uit het PRIME-onderzoek gebruikt om het percentage PCC-patiënten dat na verloop van tijd herstelt te schatten, evenals de daarmee samenhangende individuele en omgevingsfactoren. PCC-groepen werden ingedeeld op basis van het gevoel van herstel in combinatie met het vermogen om dagelijkse activiteiten uit te voeren (PCC-affectedDA = geen of lichte problemen bij het uitvoeren van dagelijkse activiteiten; PCC-impairedDA = matige tot ernstige problemen bij het uitvoeren van dagelijkse activiteiten). Van de deelnemers met PCC-impairedDA (n = 602) herstelden 222 (36,9%) en verslechterden 59 (9,8%) naar PCC-beperkte DA. Van de patiënten met PCC-impairedDA (n=277) herstelden 30 (10,8%) en verbeterden 88 (31,8%) in hun dagelijks functioneren naar PCC-affectedDA. Bij zowel PCC-affectedDA als PCC-impairedDA verminderden de volgende individuele en omgevingsfactoren de kans op herstel: een slechtere fysieke gezondheid (milde/ernstige vermoeidheid, ernstige dyspneu, ernstige symptomen van geheugenverlies, concentratieproblemen, spierpijn of -zwakte, verlies/verandering van reuk/smaak), slechtere mobiliteit (uren liggend doorbrengen, problemen met lopen), slechtere geestelijke gezondheid (depressie), ernstigere acute ziekte (meer symptomen, ziekenhuisopname/zuurstofgebruik); voormalig roken; wonen in een landelijk gebied, een relatie hebben en meer leden in het sociale netwerk hebben die praktische ondersteuning bieden (bij patiënten met chronische comorbiditeiten). Slechts 11%-37% van de patiënten met PCC in het PRIME-cohort herstelde na 9 maanden, waardoor er aanzienlijke ruimte is voor verbetering en voor toekomstig

onderzoek om beïnvloedbare factoren en behandelingen te identificeren die het herstel van patiënten met PCC kunnen ondersteunen.

Hoofdstuk 10 bespreekt de belangrijkste bevindingen van dit proefschrift en de implicaties voor de volksgezondheid. Het hoofdstuk reflecteert op de methoden en het belang van onderzoek op populatieniveau tijdens een pandemie, en benadrukt de noodzaak van tijdige dataverzameling en (grensoverschrijdende) samenwerking. Daarbij wordt de rol van sociale netwerken, omgevings- en systemische factoren in vaccinatiestrategieën en pandemieparaatheid belicht. Dit omvat het bevorderen van sterke sociale netwerken, het stimuleren van sociale participatie, het creëren van ondersteunende en uitnodigende openbare ruimtes, en het waarborgen van duidelijke en betrouwbare communicatie. Ten slotte wordt gewezen op de aanzienlijke impact van post-COVID-19 conditie op individuen en gemeenschappen, en wordt het belang van duidelijke criteria voor diagnose en herstel, flexibel werkplekbeleid, en toegankelijke zorg en ondersteuning benadrukt.



Impact

This thesis mapped the impact of COVID-19, with a focus on cross-border mobility, social networks, vaccination, and post-COVID-19 condition. These themes are particularly important because they are understudied, and this thesis highlights their societal relevance. Large, population-based epidemiological studies were conducted to capture the multifaceted impact of the pandemic. The obtained insights have important implications for public health policy, highlighting the need for integrated strategies that consider social, environmental, and cross-border factors. The work done here also stresses that strengthening collaborative networks and infrastructures is crucial to minimizing the impact of future pandemics.

Knowledge development

During both the cross-border study and the PRIME study, knowledge was developed through close collaboration with experts from multiple disciplines. These included researchers, epidemiologists, and physicians from Ciro (a specialized center for severe chronic lung diseases), Maastricht University and the Maastricht University Medical Center, and public health services in the Netherlands, Belgium, and Germany. These experts contributed to study design, participant recruitment strategies, logistics and communication, survey items, informational materials, and the interpretation of findings in every stage of the research. The PRIME study questionnaire was community-informed and developed with input from patients and patient organizations. This interdisciplinary collaboration ensured that the studies were methodologically robust and contextually relevant. It also facilitated real-time problem solving and adaptation of study procedures in response to emerging challenges during the pandemic.

Societal and policy impact

The studies in this dissertation demonstrate that cross-border mobility is not merely a logistical feature of life in the Meuse-Rhine Euroregion, but a fundamental contributor to citizens' wellbeing, social networks, and sense of connectedness. Mobility was linked to happiness, and nearly half of residents perceived border restrictions negatively. This demonstrates how national policies can unintentionally disrupt border communities. Importantly, it has been shown that cross-border movement itself did not pose greater epidemiological infection risk than domestic mobility, underscoring that border closures—while intended to protect public health—also generated social, psychological, and economic

burdens without substantially reducing transmission. Through detailed analyses of mobility, communication, and vaccination behaviors, this dissertation offers benefits to citizens by informing more proportionate, coordinated, and citizen-centered public health policies for future crises. These insights support the development of interventions that better reflect the lived realities of residents whose daily routines, family ties, and access to care transcend national boundaries. Ultimately, these findings emphasize that safeguarding the wellbeing of citizens requires protecting not only their health, but also their freedom of movement, social interaction, and cross-border access to essential services. By demonstrating both the vulnerabilities and strengths of border communities, this dissertation contributes to building more resilient, coordinated, and equitable public health systems that serve citizens on all sides of the border.

By providing insight into the factors that influence vaccination behaviors, this dissertation provides evidence to enhance quality of life across the population. Social networks and the living environment are not merely background factors, but fundamental contributors to health and health behaviors. This research shows that larger, diverse, and supportive networks, as well as a livable environment are associated with vaccine intentions and uptake, supporting interventions which strengthen social connections, and societal resilience.

The studies on post-COVID-19 condition (PCC) underscore how a chronic, multisystem illness affects mental and physical health, but also work capacity, social participation, and financial stability By identifying the groups most affected, the probability of recovery, and factors associated with lower recovery, this research validates the severity and long-term impacts of PCC, often overlooked by workplaces and society. It also highlights the economic and social consequences, emphasizing the need for flexible workplace policies, clear diagnostic criteria, preventive measures, and specialized care pathways. These insights can guide interventions that support individuals in maintaining work and social engagement, while supporting equitable access to care and the recognition of PCC as a serious health condition and a major public health problem. The PRIME research group is part of the Post-COVID Network Netherlands (PCNN), a national partnership that coordinates post-COVID research and shares knowledge and data to improve care.

Knowledge sharing and knowledge exchange

Effective valorization of research requires actively studying relevant stakeholders who can use these insights to influence policy and practice. Key stakeholders include policymakers at national and regional levels, healthcare professionals, public health institutions, community organizations, patients, and citizens. This work is part of the Living Lab Public Health Mosa (a collaboration between Public Health Service South Limburg and Maastricht University), which aims to connect research, practice, and policy.

Findings were shared with experts, professionals and the public (including patients) through multiple channels. They were published in international peer-reviewed journals, disseminated via email to general practitioners and healthcare professionals, websites of GGD Zuid-Limburg and post-COVID NL, and social media platforms such as LinkedIn, and presented at conferences including CAPHRI Research Day, at meetings of the National Institute for Public Health and the Environment (RIVM), the Consortium van Academische Werkplaatsen Publieke Gezondheid Infectieziekten (CAPI), and the European Scientific Conference on Applied Infectious Disease Epidemiology (ESCAIDE). Engagement with an international audience of policymakers and healthcare experts was further facilitated through an online conference in December 2021, featuring over twelve speakers from universities, public health institutions in the EMR, and the WHO, discussing the impact of COVID-19 in the region. Reports and factsheets tailored to regional and cross-border contexts complemented these efforts. Engagement with the scientific and professional community was strengthened through lectures and panel discussions. At a symposium for Physician-Clinical Researcher master students, an in-depth lecture on post-COVID-19 condition stimulated dialogue and knowledge exchange. Experiences from the COVID-19 study in the EMR were also shared on a panel discussion for the Master European Public Health program, focusing on cross-border collaboration and environmental health. To reach citizens and study participants, results were translated into accessible formats such as factsheets, infographics, and public summaries, which were widely disseminated via email, websites, and social media. Citizen summits were organized in the EMR to explore the societal impact of COVID-19 in depth, with outcomes compiled into a report.

Ultimately, these dissemination and engagement efforts strengthen the societal relevance of the research, inform policy, and support communities in building resilience against public health crises.



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Portfolio

PRESENTATIONS

International

Poster presentation 'Differences in non-positive intention to accept the COVID-19 booster vaccine between three countries in the cross-border region Meuse-Rhine Euroregion: the Netherlands, Belgium, and Germany' at the European Scientific Conference on Applied Infectious Disease Epidemiology (ESCAIDE)
Stockholm | October 2022

National

Oral presentation and poster 'Prevalentie, Risicofactoren en Impact Evaluatie van post-COVID-19 conditie (PRIME) - Definities en prevalentie PCC' at the Rijksinstituut voor Volksgezondheid en Milieu (RIVM) Transmissiedag
Amersfoort | March 2023

Poster presentation 'Cross-border mobility in the Meuse-Rhine Euroregion: Impact of border restrictions during the COVID-19 pandemic' at the Care and Public Health Research Institute (CAPHRI) Research Day
St. Gerlach | June 2023

Oral presentation 'Cross-border mobility in the Meuse-Rhine Euroregion: Impact of border restrictions during the COVID-19 pandemic' at the Consortium van Academische Werkplaatsen Publieke Gezondheid Infectieziekten (CAPI) symposium
Utrecht | January 2024

Oral presentation 'Social networks, environmental, and individual factors associated with COVID-19 vaccination and booster uptake– the prospective PRIME cohort study' at the Consortium van Academische Werkplaatsen Publieke Gezondheid Infectieziekten (CAPI) symposium
Utrecht | January 2025

COURSES AND TRAINING

Research Ethics and Integrity | 2022
Science Communication | 2022
Open Science | 2022
Time- and project management for PhD candidates and postdocs | 2023
Presenteren met Impact | 2024
Advanced Scientific Writing (PhD-2) | 2025
Basiscursus Regelgeving en Organisatie voor Klinische Onderzoekers (eBROK) | 2025

TEACHING

Supervision of Longyue Zhang | 2023
MSc student Sociology, Utrecht University
'The impact of social network on the experienced health in people with post-COVID-19 condition'

Supervision of Dylan Souer | 2023
BSc student Gezondheidswetenschappen, Digitale Techonologie en Zorg, Maastricht University
'De prevalentie van depressie onder PCC-patiënten in Zuid-Limburg en de toepassing van digitale interventies ter behandeling voor depressie onder deze patiënten'

Supervision of Kjell Lemmen | 2023
BSc student Gezondheidswetenschappen, Digitale Technologie en Zorg, Maastricht University
'Understanding the long-term impact of post-COVID-19 condition on healthcare: exploring patterns of healthcare utilization, the role of telemedicine and (digital) support platforms'

Supervision of Artur Czaban | 2023
BSc student Data Science and Artificial Intelligence, Maastricht University
'Understanding long covid using cluster analysis'



List of publications

2025

van Bilsen CJA, Wijnen SMCE, Pagen DME, Hoebe CJPA, Dukers-Muijrers NHTM. Workforce exit and work productivity loss in adults with and without post-COVID-19 condition: the PRIME post-COVID cohort study. *Under review.*

Pagen-Arets DME, **van Bilsen CJA**, Wijnen SMCE, den Heijer CDJ, Hoebe CJPA, Dukers-Muijrers NHTM. Recovery from post-COVID-19 condition and associated factors: the PRIME post-COVID study. *Submitted.*

Wijnen SMCE, **van Bilsen CJA**, Pagen DME, Koster A, Hoebe CJPA. Perceived stress and associated societal, community, interpersonal, and individual factors in adults with post-COVID-19 condition: the PRIME study. *Submitted.*

Huth K, Wijnen SMCE, Skjerdingstad N, Bartoš F, Finnemann A, Ebrahimi OV, Siepe B, Steijvers LCJ, **van Bilsen CJA**, Bosma H, Schumacher L, Dukers-Muijrers NHTM. Social connection features predicting loneliness: A longitudinal, interpretable machine-learning analysis. *Submitted.*

Hanssen DAT, **van Bilsen CJA**, den Heijer CDJ, Stabourlos C, Moonen, CPB, de Vries R, Brinkhues S, Philipssen D, van der Zanden BAM, Dukers-Muijrers NHTM, Hoebe CJPA., Savelkoul PHM, van Loo IHM. Nucleocapsid directed antibody testing is unsuitable to estimate hybrid immunity against SARS-CoV-2, a longitudinal cross-border study in the Meuse-Rhine Euroregion. *Journal of Clinical Virology. 2025 Apr:177:105780. doi: 10.1016/j.jcv.2025.105780.*

van Bilsen CJA, Steijvers LCJ, Wagner S, Pagen DME, Wijnen SMCE, Konings K, Hoebe CJPA, Koster A, Dukers-Muijrers NHTM. Social networks, environmental, and individual factors associated with COVID-19 vaccination and booster uptake– The prospective PRIME cohort study.*Vaccine X. 2025 Feb:23:100626. doi:10.1016/j.jvacx.2025.100626.*

2024

Steijvers LCJ, **van Bilsen CJA**, Wagner S, Stutterheim SE, Crutzen R, Ruijter RAC, Hoebe CJPA, Dukers-Muijrers NHTM. Social networks and COVID-19 vaccination intention in Dutch middle-aged and older adults in 2020: Insights into individual, interpersonal, community, and societal determinants - The SaNAE study. *Vaccine X. 2024 Sep 24:20:100562. doi: 10.1016/j.jvacx.2024.100562. PMID: 39399819 PMCID: PMC11466667.*

van Bilsen CJA, Brinkhues S, Hoebe CJPA, Stabourlos C, Moonen CPB, Demarest S, Hanssen DAT,van Loo, IHM, Savelkoul PHM, Philippsen D, van der Zanden BAM, Dukers-Muijrers NHTM. Cross border mobility in the Meuse-Rhine Euroregion: impact of COVID-19 border restrictions on everyday activities and visiting social network members. *Front Public Health. 2024 Apr 18:12:1281072. doi: 10.3389/fpubh.2024.1281072. PMID: 38726234 PMCID: PMC11079879.*

Van Herck M, Pagen DME, **van Bilsen CJA**, Brinkhues S, Konings K, den Heijer CDJ, Mujakovic S, Ter Waarbeek HLG, Burtin C, Janssen DJA, Hoebe CJPA, Spruit MA, Dukers-Muijrers NHTM. Impact of post-COVID-19 condition on health status and activities of daily living: the PRIME post-COVID study. *Thorax. 2024 Apr 15;79(5):457-464. doi: 10.1136/thorax-2023-220504. PMID: 38499346.*

2023

Pagen DME, Van Herck M, **van Bilsen CJA**, Brinkhues S, Konings K, den Heijer CDJ, Spruit MA, Hoebe CJPA, Dukers-Muijrers NHTM. High proportions of post-exertional malaise and orthostatic intolerance in people living with post-COVID-19 condition: the PRIME post-COVID study. *Front Med (Lausanne). 2023 Dec 15:10:1292446. doi: 10.3389/fmed.2023.1292446. PMID: 38162880 PMCID: PMC10757844.*

Pagen DME, **van Bilsen CJA**, Brinkhues S, Van Herck M, Konings K, den Heijer CDJ, Ter Waarbeek HLG, Spruit MA, Hoebe CJPA, Dukers-Muijrers NHTM. Prevalence of Long-term Symptoms Varies When Using Different Post-COVID-19 Definitions in Positively and Negatively Tested Adults: The PRIME Post-COVID Study. *Open Forum Infect Dis. 2023 Sep 18;10(10):ofad471. doi: 10.1093/ofid/ofad471. PMID: 37885796 PMCID: PMC10599319.*

van Bilsen CJA, Stabourlos C, Moonen CPB, Brinkhues S, Demarest S, Hanssen DAT, van Loo, IHM, Savelkoul PHM, Philippsen D, van der Zanden BAM, Dukers-Muijrers NHTM, Hoebe CJPA. Differences in non-positive intention to accept the COVID-19 booster vaccine between three countries in the cross-border region Meuse-Rhine Euroregion: The Netherlands, Belgium, and Germany. *Vaccine X. 2023 Aug:14:100306. doi: 10.1016/j.jvacx.2023.100306. PMID: 37113740 PMCID: PMC10116119.*

Stabourlos C, **van Bilsen CJA**, Brinkhues S, Moonen CPB, Demarest S, Hanssen DAT, van Loo IHM, Savelkoul PHM, Philippsen D, van der Zanden BAM, Dukers-Muijrers NHTM, Hoebe CJPA. COVID-19 pandemic response in the Meuse-Rhine Euroregion: methods, participation and recommendations of a longitudinal cross-border study. *Arch Public Health. 2023 May 13;81(1):91. doi: 10.1186/s13690-023-01102-6. PMID: 37179369 PMCID: PMC10182536.*

2022

Pagen DME, **van Bilsen CJA**, Brinkhues S, Moonen CPB, Van Herck M, Konings K, den Heijer CDJ, Mujakovic S, Ter Waarbeek HLG, Bouwmeester-Vincken N, Vaes AW, Spruit MA, Hoebe CJPA, Dukers-Muijrers NHTM. Design and recruitment of a large-scale cohort study on prevalence, risk factors and impact evaluation of post-COVID-19 condition and its wider long-term social, mental, and physical health impact: The PRIME post-COVID study. *Front Public Health. 2022 Dec 15:10:1032955. doi: 10.3389/fpubh.2022.1032955. PMID: 36589958 PMCID: PMC9799054.*

Partners:

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This thesis presents epidemiological studies that map the impact of the COVID-19 pandemic, including cross-border mobility and booster uptake in the Meuse-Rhine Euregional border region, social network aspects in relation to vaccination behavior, the impact of post-COVID-19 condition on employment, and factors associated with recovery from post-COVID-19 condition. The findings highlight the multifaceted impact of COVID-19 on individuals and society and offer evidence to inform future research and policy responses.

