

MEDICAL RISK CLASSIFICATION FOR SEVERE COVID-19 BASED ON CHRONIC MEDICAL CONDITIONS: A COMPARATIVE ANALYSIS

3363 words

Ilse Westerhof¹, Annemarijn de Boer¹, Angela Lupattelli², Isabel Slurink¹, Otilia Boldea³, Hedvig Marie Egeland Nordeng^{2,4}, Jizzo R. Bosdriesz^{5,6,7}, Frank Pijpers^{8,9}, Maarten Schim van der Loeff^{5,6,7}, Mirjam Knol⁵, Janneke van de Wijgert^{1,5}, Patricia Bruijning¹, and Ganna Rozhnova^{1,10,11,12}

¹Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht, Utrecht University, Utrecht, The Netherlands

²Pharmacoepidemiology and Drug Safety Research group, Department of Pharmacy, University of Oslo, Oslo, Norway

³Department of Econometrics and OR, Tilburg School of Economics and Management, Tilburg University, Tilburg, The Netherlands

⁴Department of Child Health and Development, National Institute of Public Health, Oslo, Norway

⁵Department of Infectious Disease Control, National Institute for Diseases, Public Health and the Environment, Bilthoven

⁶Amsterdam UMC location University of Amsterdam, Infectious Diseases, Meibergdreef 9, Amsterdam, the Netherlands

⁷Amsterdam institute for Immunology & Infectious Diseases, Amsterdam, the Netherlands

⁸Statistics Netherlands, The Hague, Netherlands

⁹Korteweg-de Vries Institute for Mathematics, University of Amsterdam, Amsterdam, The Netherlands

¹⁰Center for Complex Systems Studies (CCSS), Utrecht University, Utrecht, The Netherlands

¹¹BioISI—Biosystems & Integrative Sciences Institute, Faculdade de Ciências, University of Lisbon, Lisbon, Portugal

¹²Faculdade de Ciências, University of Lisbon, Lisbon, Portugal

Abstract (299 words)

Background: The European Centre for Disease Prevention and Control (ECDC) provides listings of medical conditions conferring high- or moderate-risk for severe COVID-19. In addition, individual European countries developed their own risk classifications for severe COVID-19 to select individuals recommended for annual COVID-19 vaccination. We assessed the discordance between the European and respective national medical risk classifications in assigning children and adults to risk groups for developing severe COVID-19 in populations of the Netherlands and Norway.

Methods: This multi-country, healthcare data-linkage study covered 17.4 million inhabitants of the Netherlands and 5.6 million inhabitants of Norway by 1 January 2020. Medical conditions were defined based on ICD-10 hospital discharge codes in the European and Dutch classifications, and on ICD-10 and ICPC-2 primary care codes in the Norwegian classification. Subjects were classified as high-, moderate-, or low-risk. Discordance was calculated as the proportion of the population with a different risk status in the respective national compared to the European classification.

Findings: The overall discordance between European and national risk classification was 12.0% in the Dutch and 13.8% in the Norwegian population. The European classification assigns more individuals to high-risk (9.0% and 9.2% of the Dutch and Norwegian populations, respectively) than the national classifications (1.5% and 3.0%, respectively). National classifications define more individuals as moderate-risk (11.3% and 12.7%, respectively) than the European classification (1.0% and 1.3%, respectively). Classification discordances most frequently involved subjects with cardiovascular disease, lung disease, and diabetes mellitus.

Interpretation: The European classification defines a substantially larger percentage of the population as high-risk for severe COVID-19 than the national classifications. This may have implications for post-pandemic vaccination programs. Further research should assess to what extent the medical conditions responsible for the classification discordances determine the risk of developing severe COVID-19.

Funding: ZonMw, EU, FCT, Norwegian Research Council's COVID-19 Emergency Call, iAPOGEE.

Research in context

Evidence before this study

We searched PubMed for English-language articles published from 1 January 2020 to 1 July 2024, using the search terms (((("COVID-19"[Title] OR "SARS-CoV-2"[Title]) AND ("sever*" [Title] OR "hospital*" [Title] OR "death"[Title] OR "decease*" [Title]) AND ("chronic condition*" [Title/Abstract] OR "comorbidit*" [Title/Abstract]) AND ("guideline"[Title] OR "classification"[Title] OR "system"[Title]) AND 2020/01/01:2024/07/01[Date - Create]) NOT "clinical trial"[Publication Type]) NOT "case reports"[Publication Type])). This search identified 64 studies, but none of them assessed the impact of different medical risk classifications for severe COVID-19 or compared them across countries or to the European classification.

Added value of this study

To the best of our knowledge, this is the first study that compared the impact of European and national medical risk classifications for severe COVID-19 by assigning the populations of the Netherlands and Norway to medical risk groups using national healthcare registries. We demonstrated important discrepancies between the European and respective national schemes in classifying high- and moderate-risk individuals in both countries. The chronic conditions responsible for the classification discordances were lung disease, cardiovascular disease, neurological disorders, diabetes mellitus, cancer, and hypertension.

Implications of all the available evidence

Our comparative analysis suggests that the choice between the European and national classifications may have important consequences for public health interventions such as vaccination campaigns. The variability in risk assignment based on chronic medical conditions underscores the absence of an international uniform approach. More research is needed to determine the extent to which each chronic medical condition impacts COVID-19 severity in the post-pandemic period, facilitating the refinement of risk classifications and supporting targeted public health interventions.

Introduction

The impact of public health measures, including COVID-19 vaccination, depends on the accurate identification of populations at elevated risk for severe outcomes, including hospitalization and death¹. The World Health Organization recommends targeting vaccination programs to population groups at the highest risk of severe COVID-19¹, but disparities exist in the risk classifications developed by different health authorities. While COVID-19 currently presents as common cold- or flu-like illness, older individuals and those with certain chronic medical conditions still face higher hospitalization and death rates compared to the general population^{2,3}. Most risk classifications group individuals into high-, moderate-, and low-risk for severe COVID-19, based on factors like medical conditions and age. High-risk individuals have chronic conditions that lead to a much higher likelihood of severe outcomes, while those in the moderate-risk group face an elevated but lower risk.

Informed by influenza risk classifications and studies on risk factors for severe COVID-19, national (e.g., the Health Council of the Netherlands⁴ and the Public Health Institute in Norway⁵) and international (e.g., the European Centre for Disease Prevention and Control⁶) public health authorities assigned high- or moderate-risk of developing severe COVID-19 to specific pre-existing medical conditions. These medical risk classifications have remained unchanged^{6,7} or undergone minor alterations^{4,5,8,9} since their development at the beginning of the pandemic. They have continued to guide epidemiological research and policy decisions on eligibility criteria and prioritization for vaccination programs aimed at reducing the incidence of severe COVID-19. While these European and national classifications can be applied within the same country, it is unclear to what extent they differ in assigning medical risk status to individuals.

To inform evidence-based decision-making for severe COVID-19, we conducted a comparative analysis of risk status in the respective national versus the European classification. This observational national registry-based cohort study used Dutch and Norwegian health and administrative data from 1 January 2020, linked at the individual level, including 17.4 million inhabitants of the Netherlands and 5.6 million inhabitants of Norway. We aimed to examine discordance between the respective national and European medical risk classifications for severe COVID-19 and investigate related factors.

Methods

Data Collection

Data collection – The Netherlands

The Dutch dataset included hospital discharge registry (DHD) data for all inhabitants of the Netherlands as per the Dutch Population Registry on 1 January 2020. The two registries were linked using unique personal identification numbers. The Population Registry was used to extract age, immigration, and emigration dates. The DHD provided information on chronic medical conditions diagnosed in hospitals since 1 January 1995, including the date of diagnosis. All diagnoses were registered according to the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10)¹⁰.

Data collection – Norway

The Norwegian dataset included data from multiple Norwegian registries for all inhabitants of Norway as per the National Population Registry on 1 January 2020. The registries included the Statistics Norway (SSB) registry, the Norwegian Patient Registry (NPR), and the Norway Control and Payment of Health Reimbursements (KUHR) registry. These registries were linked using unique personal identification numbers. The NPR and SSB registries were used to extract age, immigration, and emigration dates for all inhabitants of Norway. The KUHR registry provided information on medical diagnoses in primary and secondary outpatient care using the International Classification of Primary Care (ICPC-2/ICPC-2B) and ICD-10 codes, respectively^{10,11}. The NPR provided information on medical diagnoses in specialist outpatient and inpatient care, using ICD-10 coding. Both KUHR and NPR provided medical diagnosis data since 1 January 2010.

Risk classifications for severe COVID-19

The Dutch risk classification was obtained from the ‘Adviesnota Vaststelling volwassen medische risicogroepen COVID-19-vaccinatiecampagne’ [‘Recommendation on establishing adult medical risk groups for the COVID-19 vaccination campaign’] in February 2023⁴. This classification contains a list of chronic medical condition categories defined as either high- or moderate-risk for severe COVID-19. Each

medical condition was independently coded using ICD-10 by two authors (AvB and IW), with no discrepancies found.

The Norwegian risk classification was obtained from the Norwegian Health Institute in July 2023⁵. This scheme includes chronic medical condition categories with corresponding ICPC-2 and ICD-10 codes classified as either high-risk or increased-risk, which we renamed as high- and moderate-risk for consistency with other classifications.

The European risk classification was obtained from the ‘Core protocol for ECDC studies of COVID-19 vaccine effectiveness against hospitalization with Severe Acute Respiratory Infection (SARI), laboratory-confirmed with SARS-CoV-2 or with seasonal influenza – Version 3.0’ dated February 2024⁶. This protocol provides ICD-10 codes for medical condition categories that are mandatory or optional for reporting in the ECDC studies. We classified the former medical condition categories as high-risk and the latter as moderate-risk.

Individuals in the Dutch or Norwegian datasets were assigned to have moderate- or high-risk chronic medical conditions if at least one relevant ICD-10 (both datasets) or ICPC-2 code (Norwegian cohort only) was recorded for that individual within the six months prior to 1 January 2020. For cancer diagnoses, records within five years prior to 1 January 2020 were used. Different medical risk classifications may use different codes for the same chronic medical condition, as each classification was developed with its own coding system. The ICD-10 and ICPC-2 codes used for this analysis are detailed in **Supplementary Tables 1-3**.

Individuals with one or more high-risk chronic medical condition categories, regardless of whether they also had one or more moderate-risk conditions, were defined as being at high-risk for severe COVID-19. Individuals with one or more moderate-risk chronic medical condition categories and no high-risk chronic medical condition were defined as being at moderate-risk for severe COVID-19. Individuals without any listed chronic medical condition categories were defined as low-risk. Pregnancy was not a criterion for categorizing individuals into the high- or moderate-risk groups in all classifications.

Statistical Analysis

Data for the Netherlands and Norway were analyzed separately. Descriptive analyses were performed to compare the respective national with the ECDC classification. The prevalence of high- and moderate-risk medical condition categories, and the most frequent combinations of medical condition categories, were shown in upset plots which visualize co-occurrence of chronic medical condition categories in the population.

We reported both absolute numbers and proportions of individuals by 10-year age groups, classified into high-, moderate-, and low-risk groups for severe COVID-19. The discordance between the European and each national classification was calculated as the proportion of the population with a different European versus national risk status and visualized with matrix plots. Different medical risk classifications may use different codes for the same chronic medical condition because they were formulated as such by the classifications. The 95% confidence intervals (CI) of discordance and concordance proportions were calculated using the Clopper-Pearson method¹².

To understand the factors related to discordance, we visualized the co-occurrence of chronic medical condition categories in the discordant populations with upset plots. Since the Netherlands and Norway consider individuals above a certain age as high-risk for severe COVID-19, we assessed the discordance in three scenarios: 1) the entire population regardless of age, 2) individuals younger than 60 years of age, aligning with the Dutch schemes¹³, and 3) individuals younger than 65 years of age, aligning with the Norwegian schemes⁵.

A sensitivity analysis was conducted to assess the importance of the reference date by evaluating the discordance for 1 January 2018, 1 January 2019, and 1 January 2021, instead of 1 January 2020.

Code Availability

The codes reproducing the results of this study are publicly available at

<https://github.com/IWesterhof/COVID-19-risk-classifications>.

Data Availability

The aggregated tables of counts generated and analyzed in this study are publicly available at

<https://github.com/IWesterhof/COVID-19-risk-classifications>.

Results are based on calculations by the authors using non-public microdata from Statistics Netherlands.

Under certain conditions, these microdata are accessible for statistical and scientific research. For further information: microdata@cbs.nl.

Ethics

The analyses conducted with data from the Netherlands did not fall under the scope of the Dutch Medical Research Involving Human Subjects Act (WMO) and, therefore, did not require approval from an accredited ethics committee in the Netherlands. For the analyses conducted with data from Norway, the Regional Committee for Medical and Health Ethics of South/East Norway (no. 285687) approved the study. The Norwegian Data Protection Services for research and the University of Oslo approved the Data Protection Impact Assessment – DPIA (no. 341884).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

The Dutch cohort contained records of 17.4 million individuals (median age 42, interquartile range (IQR) 22-60), while the Norwegian cohort contained records of 5.6 million individuals (median age 39, IQR 21-57).

Comparison of risk classifications for severe COVID-19

Chronic medical condition categories included in the European, Dutch, and Norwegian risk classifications and their respective risk groups for severe COVID-19 are shown in **Table 1**. Several chronic medical condition categories were consistently considered high-risk (e.g., cancer, immunodeficiency, and organ transplants) and moderate-risk (e.g., dementia) in the European and national classifications. There was some variability in the risk classifications of other conditions. Obesity was considered high-risk in the European classification but moderate-risk in both national classifications; lung disease, heart disease, and diabetes mellitus were considered high-risk in the European classification but moderate-risk in both national classifications. Hypertension was only listed in the European classification. Down syndrome and neurological disorders with impaired breathing were not included in the European classification but were considered high-risk in both national classifications.

Classification of the general population by risk for severe COVID-19

Based on the national classifications, the most prevalent chronic medical condition categories in the Netherlands were lung disease, followed by cardiovascular disease, reduced immunity, and neurological/muscular disorder; all classified as moderate-risk (**Figure 1 A**). In Norway, the most prevalent conditions were cardiovascular disease, lung disease, and diabetes mellitus; these were also classified as moderate-risk (**Figure 1 B**). Based on the European classification, the most prevalent chronic medical condition categories in the Netherlands were cardiovascular disease, hypertension, and cancer, and in Norway cardiovascular disease, diabetes mellitus, and cancer; all classified as high-risk (**Figure 1 C-D**).

Differences in the prevalence between classifications arise from variations in the diagnosis codes to define a specific medical risk condition. For example, in the Netherlands, 0.54% of the population was classified as having cancer using the national classification, compared to 2.0% using the European classification because this classification included seven additional ICD-10 codes (**Supplementary Tables 1-2**). In Norway, 2.3% of the population was classified as having cancer using the national classification compared to 2.1% using the European classification due to differences in included codes.

In both countries and across all classifications, most individuals under 80 years of age were assigned low-risk for developing severe COVID-19 (**Figure 2**). Among children and adolescents (under 20 years old), 92.8% were classified as low-risk, 6.9% as moderate-risk, and 0.3% as high-risk, according to national schemes, while this was 98.5%, 0.4%, and 1.2%, respectively, according to the European classification. In Norway, the national classification identified 98.5% as low-risk, 0.4% as moderate-risk, and 1.2% as high-risk, while this was 96.4%, 0.5%, and 3.1%, respectively, according to the European classification. In both countries and across all classifications, the percentage of individuals in moderate- and high-risk groups increased with age, reaching 41.1% and 53.6% for those over 80 years in the national classifications, and 41.8% and 37.7% in the European classifications in the Netherlands and Norway, respectively.

Discordance between risk classifications and the related factors

In the Netherlands and Norway, risk classification differed for 12.0% and 13.8% of the general population, respectively, between the national and the European classification schemes (**Figure 3 A-B**). The European classification assigned more people as high-risk (9% in the Netherlands, 9.2% in Norway) compared to national classifications (1.5% and 3.0%, respectively). Conversely, the national classifications identified more people as moderate-risk (11.3% and 12.7%, respectively) than the European classification (1.0% and 1.3%, respectively). According to the national classifications, 87.2% of the population in the Netherlands and 84.4% in Norway were classified as low-risk. These percentages were slightly higher using the European classification (90.1% and 89.5%, respectively). Discordance was higher in elderly because the number of individuals with one or more medical risk conditions was higher than in younger age groups (**Figure 2; Figure 3 C-F**).

Figure 4 shows the chronic medical condition categories in individuals who were classified differently by the European and respective national classification schemes (the discordant population). In the discordant population in the Netherlands, 23.5% had neurological/muscular disorders, 23.8% reduced immunity, and 13.6% kidney disease according to the national classification (**Figure 4A**). In the discordant population in Norway, 6.7% had reduced immunity, and 2.3% neurological/muscular disorders, classified as moderate- and high-risk, respectively (**Figure 4B**). None of the discordant individuals in the Netherlands had cancer, while 0.6% did in Norway, explained by differences in ICD-10 and ICPC-2 coding practices between the European and Norwegian classifications. On the contrary, the European classification included chronic medical condition categories that were not included in the national classifications. In the Netherlands, examples were hypertension and kidney disease with prevalences of 25.5% and 6.3% in the discordant population. According to the European classification, 11.7% of the discordant Dutch population had cancer in contrast to none according to the national classification, as the European classification encompassed additional ICD-10 codes for cancer. In Norway, 8.2% of the discordant population had hypertension and 3.6% had kidney disease according to European schemes, but not included in national schemes. Unlike Norway, none of the discordant individuals in the Netherlands were classified as overweight/obese or diabetic based on the European classification.

In the Netherlands, the most common chronic medical condition categories varied by age group (**Supplementary Figures 1-2**). In those younger than 60 or 65, lung disease was the most prevalent condition, followed by neurological/-muscular disorder and cardiovascular disease. In Norway, the national classification showed no differences between all ages and individuals younger than 65 and 60 years of age in most pronounced chronic conditions. In the Netherlands, based on the European classification there was no change in the order of most prominent conditions contributing to discordance in the population aged below 60 years compared to all ages. In contrast, for those aged below 65 years, the most prevalent conditions were cardiovascular disease, diabetes mellitus, and lung disease, but not hypertension and cancer.

Sensitivity analyses

No meaningful differences in discordance percentages were observed when using different reference dates to define the study populations (data not shown).

Discussion

In this multi-country, nationwide registry-linkage study, we compared the respective national with the European medical risk classification for severe COVID-19, and classified the populations of the Netherlands and Norway according to this risk, across different age groups. Our findings revealed substantial differences between these risk classifications, with the European classification scheme assigning a broader range of chronic medical condition categories to the high-risk category than the two national classifications. Consequently, a larger proportion of the population is classified as high-risk when using the European classification compared to the national classifications. Conversely, a larger proportion of the population is classified as moderate-risk when using the respective national classifications compared to the European classification.

These discrepancies may have implications for COVID-19 vaccination programs, which prioritize specific risk populations. Although primarily designed for research focusing on COVID-19 vaccine effectiveness and enhancing SARI surveillance in Europe, the European protocols have influenced public health policy in the past, as demonstrated, for example, with influenza vaccination strategies¹⁴. Therefore, the European classification for severe COVID-19 could remain relevant for broader public health decisions and policy. Our comparative analysis suggests that using the European classification, 9.0% of the population in the Netherlands and 9.2% of the population in Norway are high-risk due to chronic medical condition categories and should be vaccinated, while these percentages are only 1.5% and 3.0%, respectively, when using the national classifications. Vaccination programs that prioritize both moderate- and high-risk groups, the European classification would result in 10.0% of the Dutch population and 10.5% of the Norwegian population having to be vaccinated, compared to 12.8% and 13.7%, respectively, if using the respective national classifications. Moreover, chronic medical condition categories are defined based on

different ICD-10 and ICPC-2 codes in the three classifications, resulting in differences in prevalence of individual medical risk categories across classifications. Therefore, the choice between the European or national classifications may have important consequences for vaccination prioritization and coverage, potentially influencing the impact of vaccination campaigns in preventing severe COVID-19.

The dominant medical condition categories generating the discordance in risk status were lung and cardiovascular disease in both Norway and the Netherlands, neurological disorders in the Netherlands, and diabetes in Norway. Hypertension was one of the most pronounced discordant chronic condition categories between classifications. According to the European classification, but not to the national ones, hypertension was considered a high-risk disorder for severe COVID-19, and its prevalence estimate was 3.5% in the Netherlands and 1.4% in Norway. Several studies have indicated that hypertension was not an independent predictor of severe COVID-19^{15,16}. Therefore, the high-risk population might be overestimated in the European classification. Lung disease, cardiovascular disease, and diabetes mellitus were also among the most pronounced medical condition categories leading to discordance, which were diagnosed in 1.7-4.6% of the population according to the national and European classifications. These conditions were classified as moderate-risk in the national classifications but as high-risk in the European classification. Although multiple studies have shown an increased risk of severe COVID-19 in individuals with these medical condition categories¹⁷⁻¹⁹, it is unknown whether they should be part of the high- or moderate-risk group. Interestingly, the European classification does not include Down syndrome and neurological/-muscular disorder as risk factors for severe COVID-19, while the national classifications consider them as moderate- or high-risk chronic conditions. Several studies have demonstrated an increased risk of COVID-19 hospitalization and death among individuals with Down syndrome^{20,21} and multiple sclerosis^{22,23}. This supports the need to assess the discordant conditions in relation to severe COVID-19 to ensure vaccination prioritization and coverage of individuals at high-risk.

Our study has several limitations. There is a potential underestimation of the population with high- and moderate-risk for severe COVID-19 in the Netherlands. The detection of chronic medical condition categories in the Netherlands relied solely on ICD-10 codes from hospital discharge data. Individuals without recent hospital admission may be missed, as hospital data might not capture those whose

conditions are managed in primary care. Consequently, there is a potential underestimation of the number of individuals at moderate- and high-risk. Conversely, the analyses conducted for the population in Norway, based on diagnostic records from both outpatient and inpatient specialist care, as well as from primary care, were less susceptible to this bias. Another limitation is the absence of ICD-10 codes for asplenia in the Norwegian registries. However, since asplenia is a very rare condition, with 0.44 surgical asplenia per 100,000 person-years in Norway, it is unlikely to affect our overall conclusions²⁴.

Future research should aim to establish a consensus on which chronic medical condition categories are universally recognized as conferring moderate- and high-risk for severe COVID-19. We propose a matched multi-country cohort study to estimate the risk of hospitalization and death due to COVID-19 in individuals with and without specific chronic conditions, accounting for confounders like age, vaccination status, and variants. This research will help decide which classification best captures the population most at risk. Moreover, mathematical modeling studies can help to understand the impact of different risk classifications and optimal vaccination strategies^{25–28}. Incorporating risk stratification into modeling studies has the potential to design more effective strategies, a consideration often overlooked in current research efforts. Furthermore, exploring emerging data sources and digital health technologies could improve the identification and monitoring of moderate- and high-risk populations.

Conclusion

There are substantial differences between the European and the respective national medical risk classifications for severe COVID-19 based on pre-existing chronic medical condition categories, which may have important implications for vaccination strategies. The European classification suggests that a larger proportion of the population is at high-risk for severe COVID-19 and may require vaccination. The difference in classification is most pronounced for chronic medical condition categories belonging to the categories of cardiovascular disease, lung disease, and diabetes mellitus. Further research should identify to what extent the discordant chronic conditions are associated with severe COVID-19 risk.

Author Contributions

Conceptualization: I Westerhof, G Rozhnova. Data management: I Westerhof, A de Boer. Methodology: I Westerhof, A de Boer, G Rozhnova. Investigation: I Westerhof, A de Boer. Formal analysis: I Westerhof, A de Boer. Visualization: I Westerhof. Writing—original draft: I Westerhof, A de Boer, G Rozhnova. Writing—review and editing: I Westerhof, A de Boer, A Lupattelli, I Slurink, O Boldea, HME Nordeng, JR Bosdriesz, F Pijpers, M Schim van der Loeff, M Knol, JHHM van de Wijgert, P Bruijning, and G Rozhnova.

Declaration of interests

We declare no competing interests.

Acknowledgments

GR, IW, AdB, and OB were supported by the ZonMw project (10430362220002). GR was supported by Fundação para a Ciência e a Tecnologia project 2022.01448.PTDC, DOI 10.54499/2022.01448.PTDC. GR, IW, AL, and PB were supported by the VERDI project (101045989), funded by the European Union. Views and opinions expressed are however those of the author(s) only and do not necessarily reflect those of the European Union or the Health and Digital Executive Agency. Neither the European Union nor the granting authority can be held responsible for them. IW was supported by the scholarship program iAPOGEE “International Alliance for PharmacoGenetic Epidemiology Excellence” at the University of Oslo, Norway. We are grateful to all the participating families in the Netherlands and Norway who are part of the health registries and made this research possible. Data acquisition of the Norwegian data in this study was funded by HN’s EU-COVID-19 project, funded by the Norwegian Research Council’s COVID-19 Emergency Call (project no. 31270). The work on the Norwegian data was performed on the TSD (Tjeneste for Sensitive Data) facilities, owned by the University of Oslo, operated and developed by the TSD service group at the University of Oslo, IT-Department (USIT) (tsd-drift@usit.uio.no).

References → max 30 references

- 1 World Health Organization. Global Covid-19 Vaccination Strategy in a Changing World July 2022 update. 2022 <https://www.who.int/publications/m/item/global-covid-19-vaccination-strategy-in-a-changing-world--july-2022-update> (accessed April 30, 2024).
- 2 Antos A, Kwong ML, Balmorez T, Villanueva A, Murakami S. Unusually High Risks of COVID-19 Mortality with Age-Related Comorbidities: An Adjusted Meta-Analysis Method to Improve the Risk Assessment of Mortality Using the Comorbid Mortality Data. *Infect Dis Rep* 2021; **13**: 700–11.
- 3 Zhang J, Dong X, Liu G, Gao Y. Risk and Protective Factors for COVID-19 Morbidity, Severity, and Mortality. *Clin Rev Allergy Immunol* 2022; **64**: 90–107.
- 4 Gezondheidsraad. Adviesnota Vaststelling volwassen medische risicogroepen COVID-19-vaccinatiecampagne. 2023 <https://lci.rivm.nl/sites/default/files/bestanden/COVID-19/COVID-19-vaccinatie/Adviesnota-vaststelling-volwassen-medische-risicogroepen-covid-19-vaccinatiecampagne.pdf> (accessed April 1, 2024).
- 5 Norwegian Institute of Public Health. Coronavirus vaccine. ups-and-childrenadolescents-with-underlying-conditions. 2023. <https://www.fhi.no/en/id/corona/coronavirus-immunisation-programme/coronavirus-vaccine> (accessed April 17, 2024).
- 6 European Centre for Disease Prevention and Control. Core protocol for ECDC studies of COVID-19 vaccine effectiveness against hospitalisation with Severe Acute Respiratory Infection, laboratory-confirmed with SARS-CoV-2 or with seasonal influenza - Version 3.0. 2024 <https://www.ecdc.europa.eu/en/publications-data/core-protocol-ecdc-studies-covid-19-vaccine-effectiveness-3> (accessed March 10, 2024).
- 7 European Centre for Disease Prevention and Control. Core protocol for ECDC studies of COVID-19 vaccine effectiveness against hospitalisation with Severe Acute Respiratory Infection laboratory-confirmed with SARS-CoV-2, version 1.0. Stockholm, 2021.
- 8 Norwegian Institute of Public Health. Coronavirus vaccine. 2020. <https://www.fhi.no/en/id/corona/coronavirus-immunisation-programme/coronavirus-vaccine> (accessed Sept 1, 2022).
- 9 Gezondheidsraad. Advies Strategieën voor COVID-19-vaccinatie. 2020 <https://www.gezondheidsraad.nl/documenten/adviezen/2020/11/19/strategieen-voor-covid-19-vaccinatie> (accessed April 1, 2024).
- 10 World Health Organization. International Statistical Classification of Diseases Related Health Problems 10th Revision Geneva. <https://icd.who.int/browse10/2019/en>. 2019.
- 11 World Health Organization. International Classification of primary care, 2nd edition (ICPC-2). <https://www.who.int/standards/classifications/other-classifications/international-classification-of-primary-care>. 2024.
- 12 Clopper CJ, Pearson ES. The Use of Confidence or Fiducial Limits Illustrated in the Case of the Binomial. *Biometrika* 1934; **26**: 404.
- 13 Rijksinstituut voor Volksgezondheid en Milieu. COVID-19 vaccination. 2024; published online March. <https://www.rivm.nl/en/coronavirus-covid-19/vaccination> (accessed April 22, 2024).
- 14 Mereckiene J, Cotter S, Nicoll A, *et al.* Seasonal influenza immunisation in Europe. Overview of recommendations and vaccination coverage for three seasons: pre-pandemic (2008/09), pandemic (2009/10) and post-pandemic (2010/11). *Eurosurveillance* 2014; **19**. DOI:10.2807/1560-7917.ES2014.19.16.20780.

- 15 D'Elia L, Giaquinto A, Zarrella AF, *et al.* Hypertension and mortality in SARS-COV-2 infection: A meta-analysis of observational studies after 2 years of pandemic. *Eur J Intern Med* 2023; **108**: 28–36.
- 16 Fresán U, Guevara M, Trobajo-Sanmartín C, Burgui C, Ezpeleta C, Castilla J. Hypertension and Related Comorbidities as Potential Risk Factors for COVID-19 Hospitalization and Severity: A Prospective Population-Based Cohort Study. *J Clin Med* 2021; **10**: 1194.
- 17 Ge E, Li Y, Wu S, Candido E, Wei X. Association of pre-existing comorbidities with mortality and disease severity among 167,500 individuals with COVID-19 in Canada: A population-based cohort study. *PLoS One* 2021; **16**: e0258154.
- 18 Wee LE, Tan JYJ, Chiew CJ, *et al.* A Nationwide Cohort Study of Delta and Omicron SARS-CoV-2 Outcomes in Vaccinated Individuals With Chronic Lung Disease. *Chest* 2024; published online June. DOI:10.1016/j.chest.2024.05.017.
- 19 Rainer L, Bachner F, Eglau K, Ostermann H, Siebert U, Zuba M. Comorbidities and COVID-19 hospitalization, ICU admission and hospital mortality in Austria. *Wien Klin Wochenschr* 2022; **134**: 856–67.
- 20 Bedston S, Almaghrabi F, Patterson L, *et al.* Risk of severe COVID-19 outcomes after autumn 2022 COVID-19 booster vaccinations: a pooled analysis of national prospective cohort studies involving 7.4 million adults in England, Northern Ireland, Scotland and Wales. *The Lancet Regional Health - Europe* 2024; **37**: 100816.
- 21 Semenzato L, Botton J, Drouin J, *et al.* Chronic diseases, health conditions and risk of COVID-19-related hospitalization and in-hospital mortality during the first wave of the epidemic in France: a cohort study of 66 million people. *The Lancet Regional Health - Europe* 2021; **8**: 100158.
- 22 Prosperini L, Tortorella C, Haggiag S, Ruggieri S, Galgani S, Gasperini C. Increased risk of death from COVID-19 in multiple sclerosis: a pooled analysis of observational studies. *J Neurol* 2022; **269**: 1114–20.
- 23 Moreno-Torres I, Meca Lallana V, Costa-Frossard L, *et al.* Risk and outcomes of COVID-19 in patients with multiple sclerosis. *Eur J Neurol* 2021; **28**: 3712–21.
- 24 Orangzeb S, Watle SV, Caugant DA. Adherence to vaccination guidelines of patients with complete splenectomy in Norway, 2008–2020. *Vaccine* 2023; **41**: 4579–85.
- 25 Béraud G. Mathematical models and vaccination strategies. *Vaccine* 2018; **36**: 5366–72.
- 26 Bubar KM, Reinholt K, Kissler SM, *et al.* Model-informed COVID-19 vaccine prioritization strategies by age and serostatus. *Science (1979)* 2021; **371**: 916–21.
- 27 Viana J, van Dorp CH, Nunes A, *et al.* Controlling the pandemic during the SARS-CoV-2 vaccination rollout. *Nat Commun* 2021; **12**: 3674.
- 28 Matrajt L, Eaton J, Leung T, Brown ER. Vaccine optimization for COVID-19: Who to vaccinate first? *Sci Adv* 2021; **7**. DOI:10.1126/sciadv.abf1374.

Table 1. Comparison of European and national risk classifications for severe COVID-19. Chronic medical condition categories based on ICD-10 and ICPC-2 codes (see **Supplementary Tables 1-3**) and their respective risk groups for severe COVID-19 are shown. Different medical risk classifications may use different codes for the same chronic medical condition.

Chronic medical condition categories	Classification		
	European	Dutch	Norwegian
Cancer (solid organ and haematological)			
Immunodeficiency			
Organ transplant			
Overweight and obesity			
Lung disease			
Cardiovascular disease			
Diabetes mellitus			
Hypertension			
Kidney disease dialysis required			
Anaemia			
Kidney disease			
Liver disease/cirrhosis			
Neurological disorder (without impaired breathing)			
Dementia			
Tuberculosis			
Stroke			
Asplenia			
Rheumatologic disease			
Sickle cell disease			
Down syndrome			
Neurological disorder with impaired breathing			
Reduced immunity			
HIV infection			
Cochlear implants			
Risk due to chronic medical conditions = High = Moderate = low			

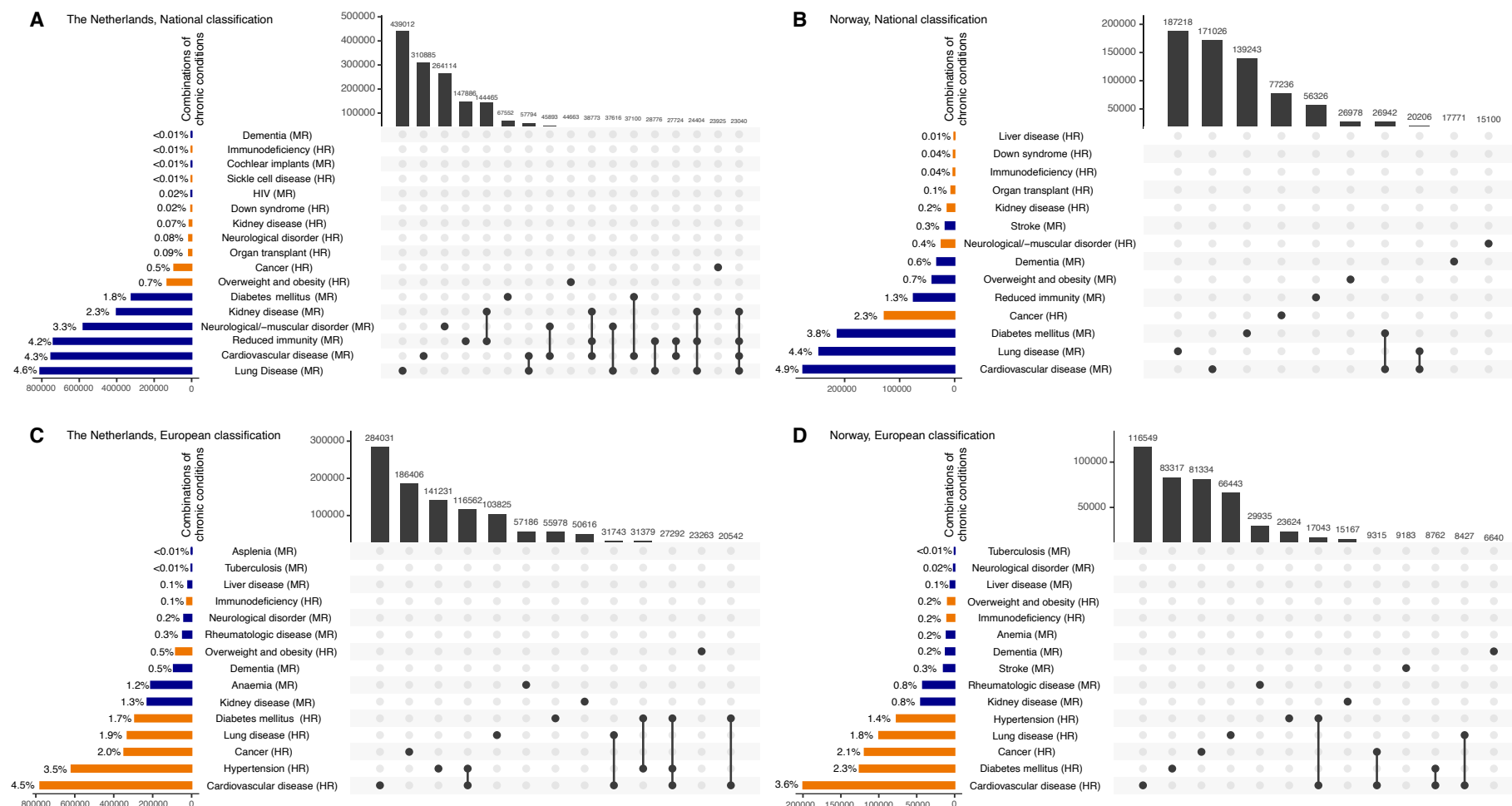


Figure 1. Chronic conditions in the general population. A-B) National and C-D) European medical risk classification for severe COVID-19. In all classifications, chronic medical condition categories were assigned if registered in the past six months prior to 1 January 2020, except for cancer which was assigned if registered in the prior five years. The left bars show the number and proportion of each chronic medical condition categories in the population. Orange bars indicate the high-risk chronic conditions according to the classification, while blue bars indicate moderate-risk chronic conditions. The dots represent the presence of one or more chronic medical condition categories in an individual, with the upper bars showing the combinations that occur in at least 1% of the population with chronic conditions.

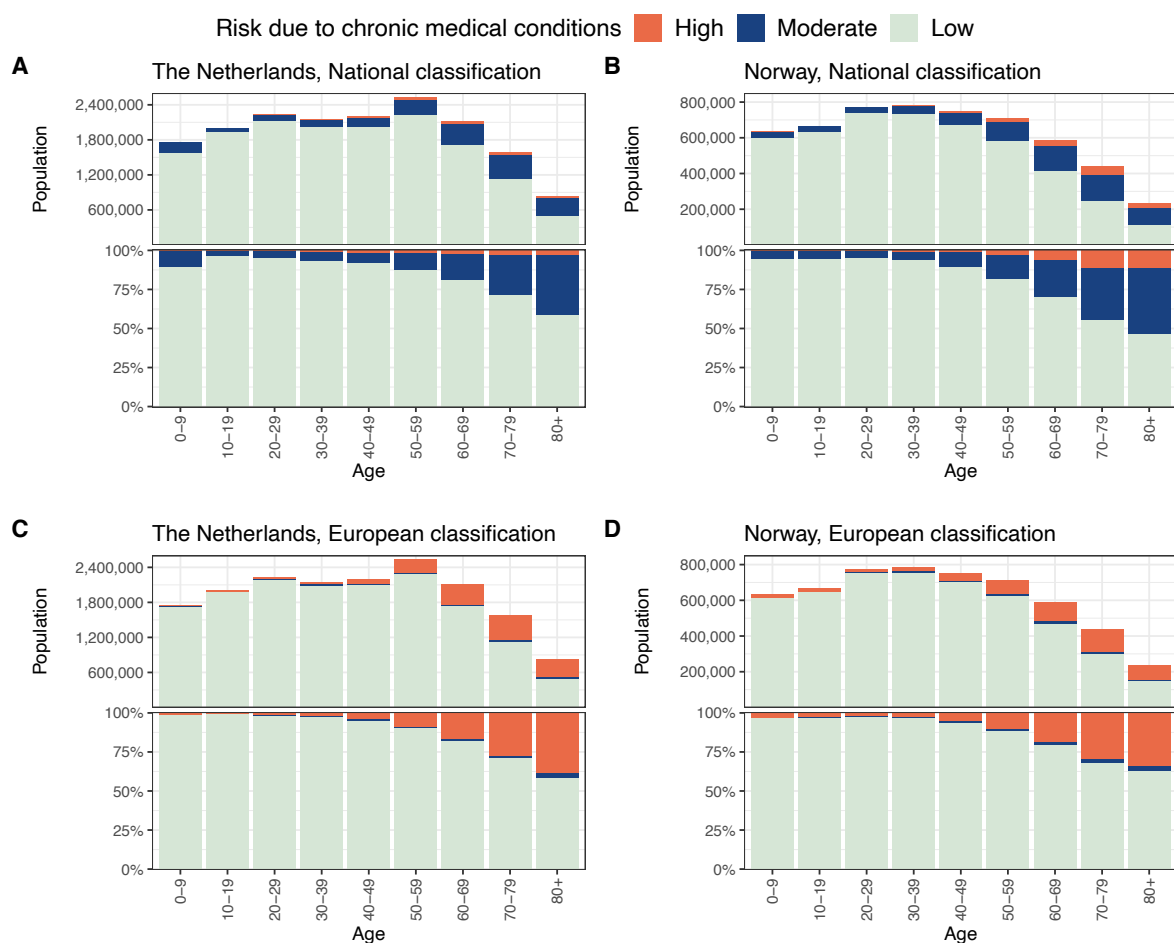


Figure 2. Classification of the general population by risk for severe COVID-19. Population shown as absolute numbers (top) and proportions (bottom) classified by age and risk for severe COVID-19 due to chronic medical condition categories in the **A-B)** national and **C-D)** European classifications.

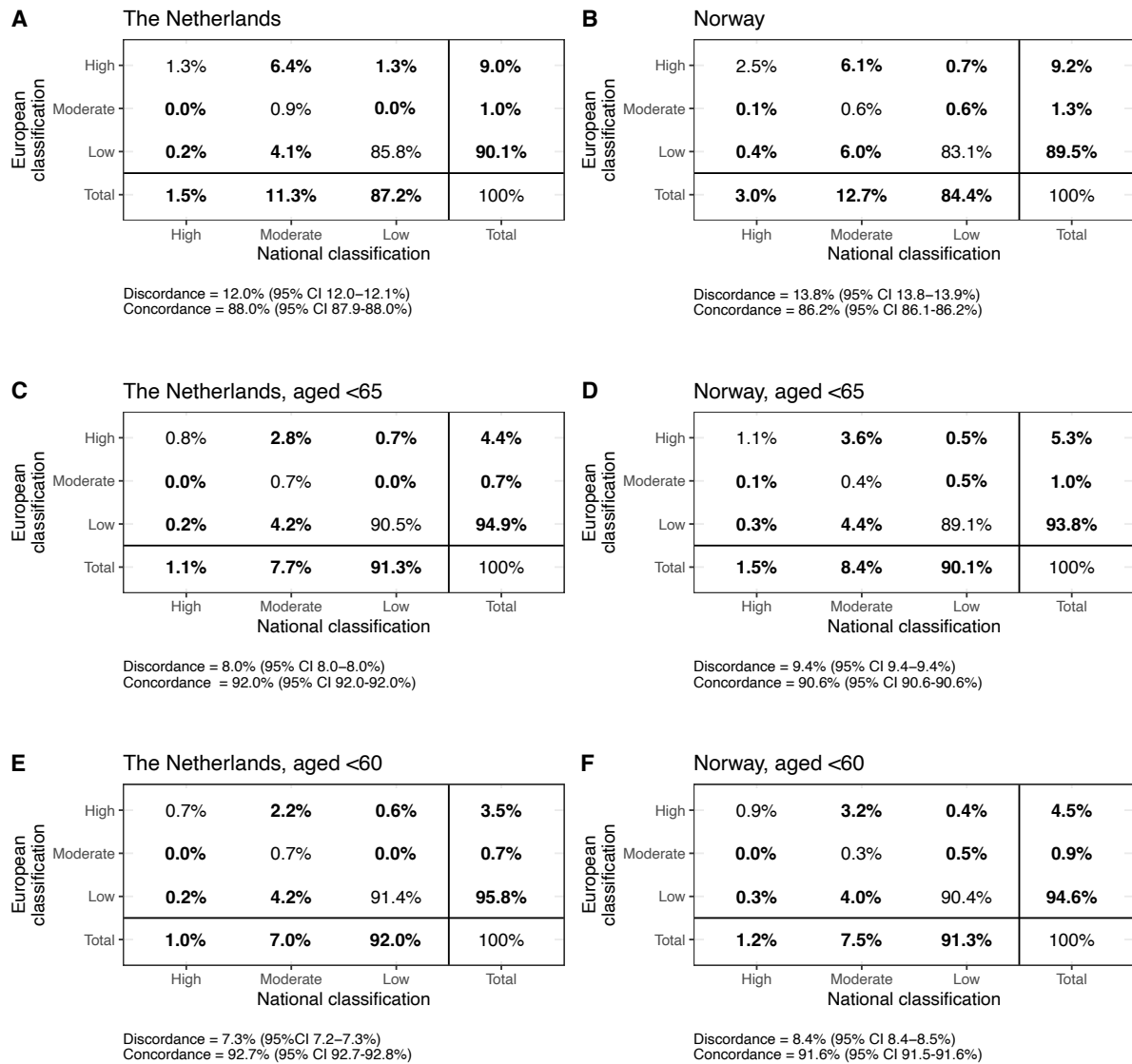


Figure 3. Discordance and concordance in assigning risk status to individuals between the European and national classifications. General population of A-B) all ages, C-D) ages below 65 years, and E-F) ages below 60 years. The discordance between the European and each national classification was calculated as the proportion of the general populations with a different risk status (off-diagonal elements). Concordance is the proportion of the population classified into the same risk group (diagonal elements). Since every individual belongs to one of the risk groups, the elements of the matrix plots add up to 100%.

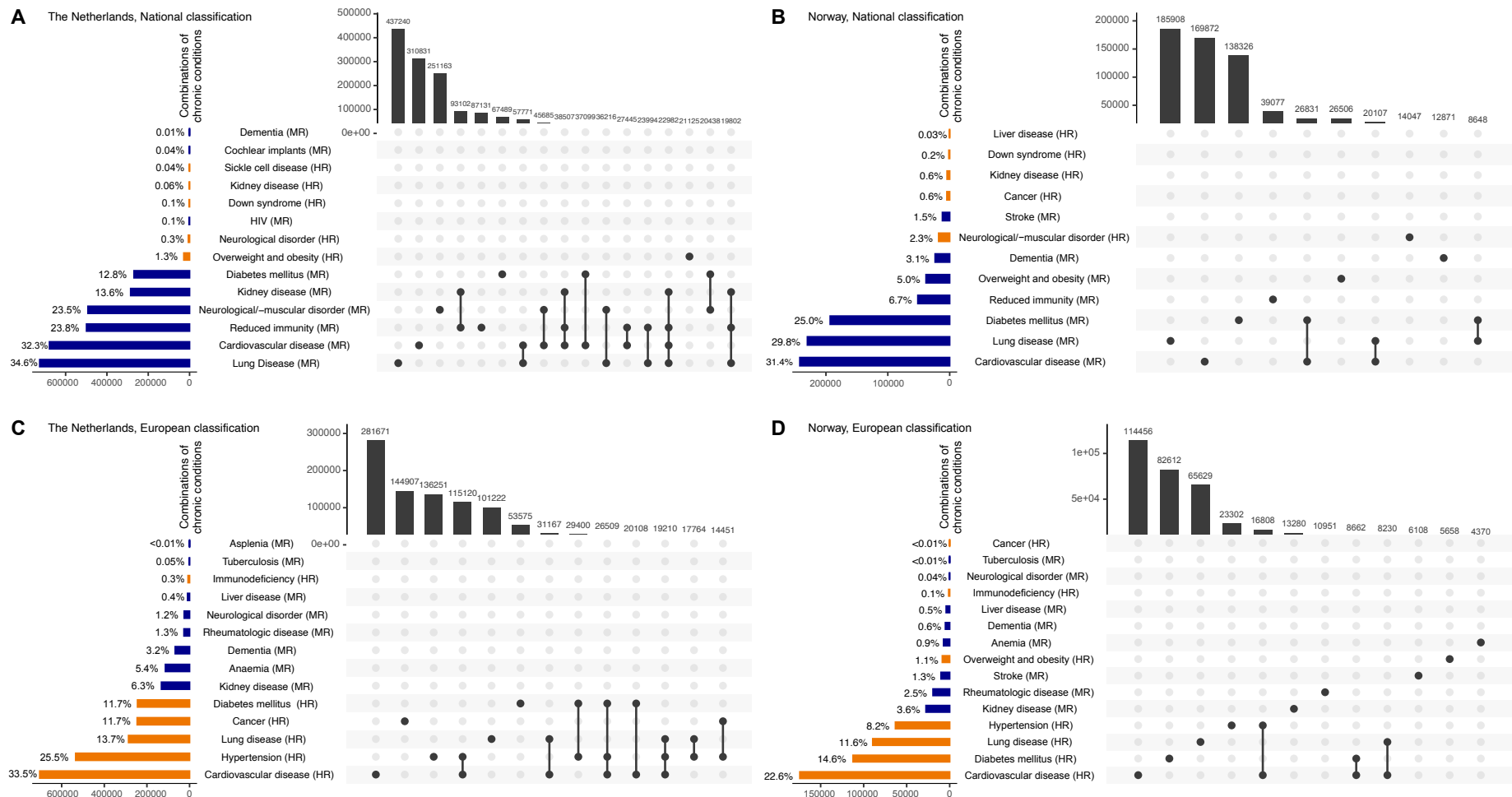


Figure 4. Chronic conditions in the discordant population. A-B) National and C-D) European medical risk classification for severe COVID-19. In all classifications, chronic medical condition categories were those that had been registered in the past six months prior to 1 January 2020, except for cancer which was included as a chronic medical condition if registered in the past five years preceding 1 January, 2020. The dots represent the presence of one or more chronic medical condition categories. The left bars show the number and proportion of each chronic medical condition categories in the population. Orange bars indicate the high-risk chronic conditions according to the classification, while blue bars indicate moderate-risk chronic conditions. The upper bars show the combinations of chronic conditions that occur in at least 1% of the population with chronic conditions.

Supplementary Table 1 European risk classification, ICD-10 codes⁶.

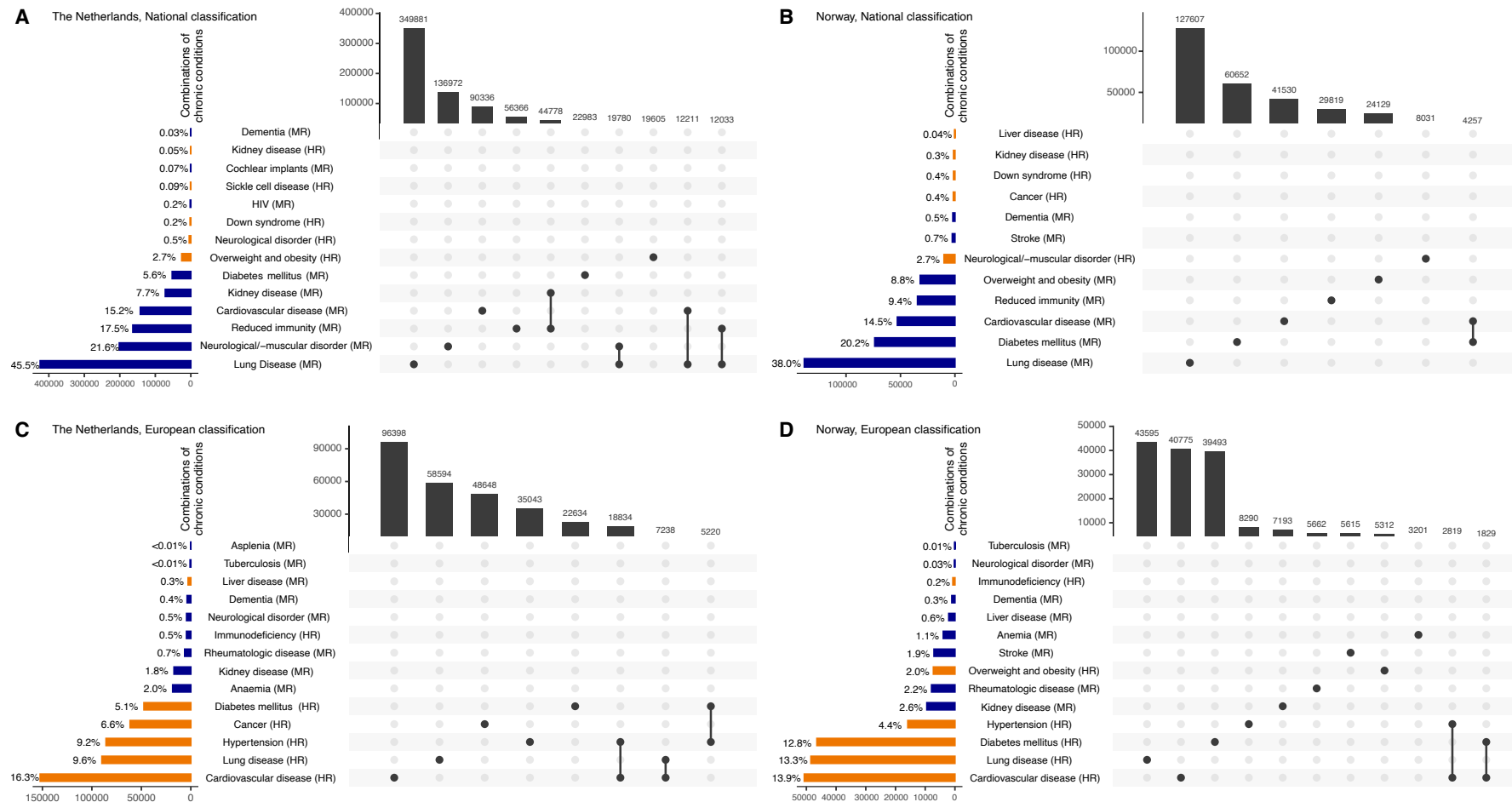
Risk group	Disease category	ICD-10 codes
High	Cardiovascular disease	A52.01, B37.6, B58.81, I05-09, I11, I13, I20-25, I26.9, I27, I30-51, I97.0-97.1, R00.1, T81.718A, T81.72XA, T82.817A, T82.818A, Q20-24, Q25.1-25.2, Q26.0-26.1, Q26.8, Q87.4, R01.1, R02
High	Cancer	C00-96
High	Diabetes mellitus	E10-11
High	Hypertension	I10, I15, I15.1, I15.2, I15.8, I27.0, I97.3
High	Immunodeficiency or organ transplant	B20, D80-84, D89.8-89.9, Z21, Z94
High	Lung disease	A15, J18.2, J40-47, J60-94, J96, J99, M34.81, M05.10
High	Obesity	E66.01, E66.2, E66.9
Moderate	Anemia	D50-64
Moderate	Asplenia (<i>not available in Norwegian registries</i>)	Q89.01, Q20.6, Z90.81
Moderate	Dementia	F01, F03, F05, G30-31, G91, G94
Moderate	Kidney disease	M10.30, N00-19, N20.0, N28.9
Moderate	Liver disease	K70, K72-74, K75.4, K76.9
Moderate	Neurological disorder	G70, G73.7
Moderate	Rheumatologic diseases	M30-34, M35.5, M35.8-35.9, M05-06, M08, M12.00
Moderate	Stroke	G93, I67.83, I69
Moderate	Tuberculosis	A15-19

Supplementary Table 2 Dutch risk classification, ICD-10 codes⁴.

Risk group	Disease category	ICD-10 codes
High	Cancer	C00-C75, C81-86, C88, C90-96.
High	Down syndrome	Q90
High	Immunodeficiency disease	D800.0, D81, D830.0-830.2, D83.8-83.9
High	Kidney failure (dialysis required)	N18.5
High	Neurological disorders compromising respiration	G00-G99 in combination with R06
High	Organ transplantation	Z94.0-94.4, Z94.8
High	Overweight and obesity	E66
High	Sickle cell disease	D57.0-57.2
Moderate	Cardiovascular disease	C38, C49.3, D511, D213, I00-2, I05-9, I20-3, I30-52, Q20-8, P29.3, Z950
Moderate	Chronic kidney disease	N00-N39
Moderate	Cochlear implants	Z96.2
Moderate	Dementia	F00-01, F03, F10.6
Moderate	Diabetes mellitus	E10-14
Moderate	HIV	B20-24
Moderate	Lung disease	A15-19, C30-34, C39, D86, E84, J00-99, Q30-34
Moderate	Neurological disorders	G00-99, I60-69
Moderate	Reduced immunity	B17.0, B18.0-18.1, C81-96, D50-89, E24-27, K50-51, K70-77, M0-14, M353, N0-39.

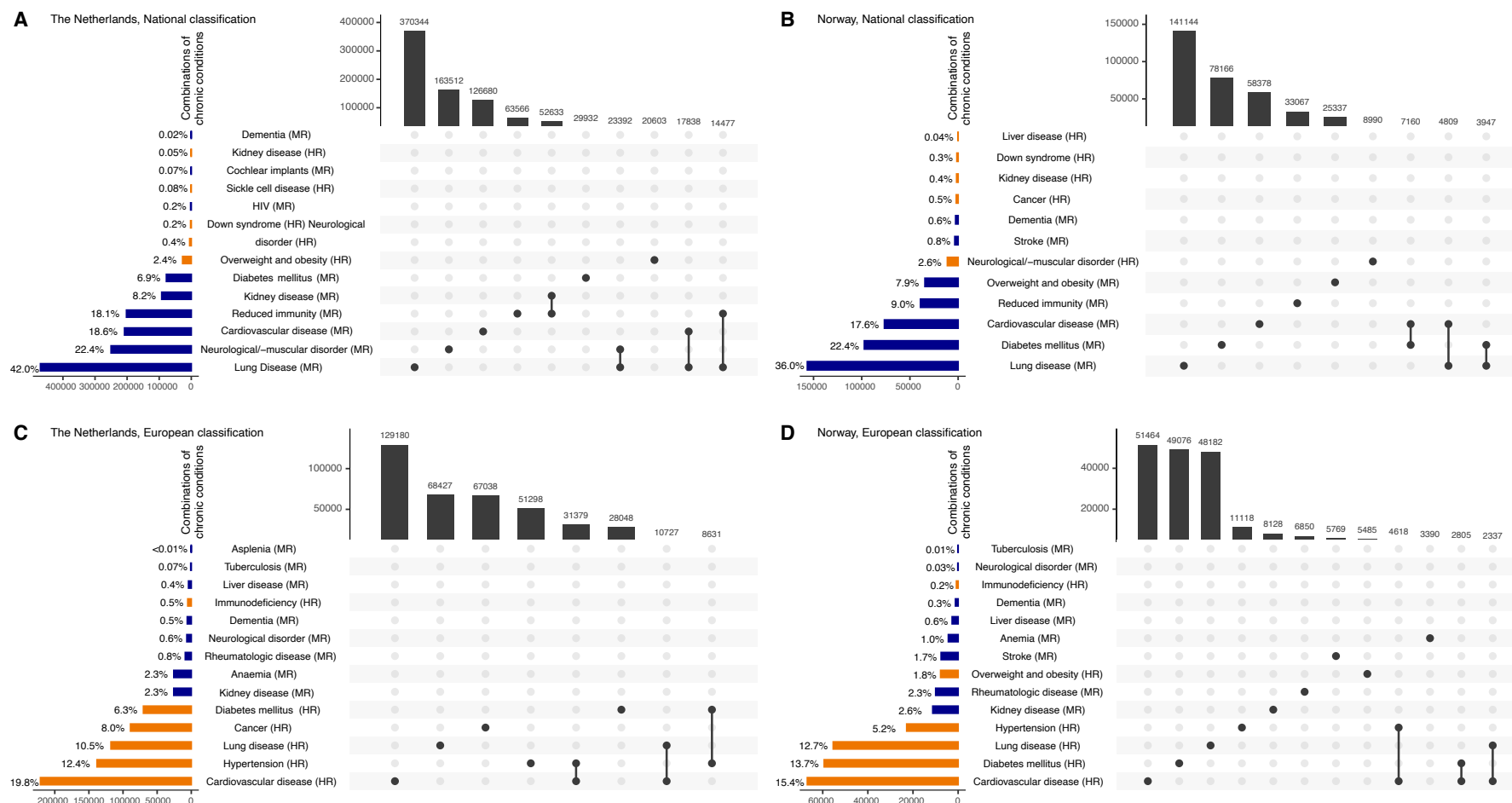
Supplementary Table 3 Norwegian risk classification, ICD-10 and ICPC-2 codes⁵.

<u>Risk group</u>	<u>Disease category</u>	<u>ICD-10 codes</u>	<u>ICPC-2 codes</u>
High	Cancer	C0-7, C80-96, D45, D47	-
High	Down Syndrome	Q90	-
High	Immunodeficiency disease	D80-84	-
High	Organ transplantation	Z94.0-94.4, Z94.8	-
High	Neurological disorders	G1, G20-21, G23-24, G40.5, G61.0, G70-73, F84.0-84.1, Q05.0-05.6, G80.0, G80.2-80.3	-
High	Kidney failure	N18.3-18.5	-
High	Liver disease	K70.4, K72	-
Moderate	Diabetes mellitus	E10-14	T89-90
Moderate	Lung disease	E84, J41-J47, J84, J98	R95-96
Moderate	Overweight and obesity	E66	T82
Moderate	Cardiovascular disease	I05-09, I2, I31-32, I34-37, I39-43, I46, I48-50	K74-78, K82-83, K87
Moderate	Stroke	I60-64, I69.1-69.4, I69.8, I69.0	K90-91
Moderate	Dementia	F0, G30-31	P70
Moderate	Reduced immunity	G35, M05-09, M13-14, K50-51	-



Supplementary Figure 1. Chronic conditions in the discordant population aged <60 years. A-B) National and C-D) European medical risk classification for severe COVID-19.

In all classifications, chronic medical condition categories were those that had been registered in the past six months prior to 1 January 2020, except for cancer which was included as a chronic medical condition if registered in the past five years preceding 1 January, 2020. The dots represent the presence of one or more chronic medical condition categories. The left bars show the number and proportion of each chronic medical condition categories in the population. Orange bars indicate the high-risk chronic conditions according to the classification, while blue bars indicate moderate-risk chronic conditions. The upper bars show the combinations of chronic conditions that occur in at least 1% of the population with chronic conditions.



Supplementary Figure 2. Chronic conditions in the discordant population aged <65 years. A-B) National and C-D) European medical risk classification for severe COVID-19.

In all classifications, chronic medical condition categories were those that had been registered in the past six months prior to 1 January 2020, except for cancer which was included as a chronic medical condition if registered in the past five years preceding 1 January 2020. The dots represent the presence of one or more chronic medical condition categories. The left bars show the number and proportion of each chronic medical condition categories in the population. Orange bars indicate the high-risk chronic conditions according to the classification, while blue bars indicate moderate-risk chronic conditions. The upper bars show the combinations of chronic conditions that occur in at least 1% of the population with chronic conditions.