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EPIDEMIOLOGICAL STUDY

The stringency of the containment measures in response to COVID-19 inversely correlates with the overall disease occurrence over the epidemic wave

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ABSTRACT
Non-pharmaceutical interventions (NPIs) were the only viable choice to mitigate or suppress transmission of COVID-19 in the absence of efficient and safe vaccines. In this study, we examined the association between the stringency of containment measures and cumulative incidence of the COVID-19 cases in the first wave of the pandemic across 28 European countries. Our results support the effectiveness of containment measures in the mitigation or suppression of COVID-19 epidemics. Early adoption of stringent containment measures prior to detection of the first confirmed case, together with ramping up containment stringency during the early days of epidemics, was associated with a lower disease occurrence. The delayed adoption of stringent containment measures did not fully compensate for the lack of early response. Containment measures continue to play a significant role in the control of COVID-19 in the post-vaccination period, when limited vaccination coverage, the emergence of vaccine resistance, and/or increased mobility enabled further disease transmission *(Tab. 4, Fig. 22, Ref. 50)*. Text in PDF *www.elis.sk*
KEY WORDS: non-pharmaceutical interventions, containment, COVID-19, mobility, social distancing, Containment and Health Index, epidemiology, public health measures, SARS-CoV-2.

Introduction

The continuing pandemic of the coronavirus disease 2019 (COVID-19) is a significant public health concern. Due to its considerable transmission and high level of morbidity and mortality especially among individuals with advanced age and underlying co-morbidities, this disease triggered an unprecedented global "lock-down" in an attempt to control its spread (1). First emerging in December 2019 as a cluster of pneumonia cases of unknown origin in Wuhan, the capital city of Hubei Province in China, the local outbreak rapidly expanded by travel, nosocomial infection, and close-contact transmission in families. By 23rd January 2020, when strict epidemic control measures were adopted, COVID-19 affected 29 provinces in mainland China and 6 other countries (2). By 11 March 2020, when the disease affected 114 countries, the World Health Organization (WHO) declared the rapidly spreading outbreak as pandemic. According to the data compiled by the John Hopkins University Center for Systems Science and Engineering, on 26 January 2021, the cumulative number of confirmed cases exceeded 100 million worldwide, of which more than 2.1 million were fatal (3).

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In the absence of vaccines or chemoprevention, only non-pharmaceutical interventions (NPIs) were available for public health response to the COVID-19 pandemic before December 2020, when vaccination programs started in several countries. These NPIs include: (i) case containment measures targeting individuals through early case detection, contact tracing, isolation of cases, and quarantine of contacts, (ii) community containment measures, including various degrees of travel restrictions and social distancing measures, (iii) infection control measures, such as hand hygiene, respiratory etiquette, environmental cleaning, and the use of respiratory protection or face coverings, and (iv) public education.

The imposition of unprecedented containment measures in China, which included a cordon sanitaire set up in Hubei Province, aroused controversies regarding their efficacy and societal costs. Along these lines, on 29 February 2020 the WHO advised against travel and trade restrictions to countries experiencing COVID-19 outbreaks (4). This position reflected the purpose of the WHO International Health Regulations, which is to "*prevent, protect against, control and provide a public health response to the international spread of disease in ways that are commensurate with and restricted to public health risks, and which avoid unnecessary interference with international traffic and trade*" (5).

Resistance to the implementation of some community containment measures stemmed from concerns, which were previously raised about the effectiveness of the NPIs in control of some epidemics. For instance, discussions about the response to an influenza H5N1 pandemic revealed doubts about the existence of adequate scientific support for some severe social distancing measures (6). Similarly, the effects of NPIs on the1918 – 1919 influenza H1N1 pandemic were found to be transient at best, and the cordon sanitaire set up in Liberia during the 2013 – 2016 Ebola epidemic was found counterproductive and potentially increasing the risk of disease transmission (7). These controversies may have contributed to the reluctance and delays in the adoption of travel restrictions, and possibly some other community containment measures in response to the COVID-19 pandemic. For this reason, an evaluation of the effectiveness and socioeconomic impact of the NPIs is needed to inform the epidemic risk management.

In this study, we examined the association between the stringency of containment and cumulative incidence of the COVID-19 cases in the first wave of the pandemic across 28 European countries. Europe became an epicenter of the pandemic early as the disease spread cross-borders both globally and regionally, which led to the restrictions on entry to the USA for travelers from 26 European countries from Schengen Area starting on 11 March 2020. Nevertheless, European countries displayed remarkable variations in the disease occurrence (8), which allows studying the role of differences in the stringency of containment measures across various European countries and possible identification of patterns responsible for better epidemic control.

Datasets and methods

This study considered 28 European countries: 25 EU countries (AT, BE, BG, HR, CY, CZ, DK, EE, FI, FR, DE, HU, IE, IT, LV, LT, LU, NL, PL, PT, RO, SK, SI, ES, SE), two EFTA countries (CH, NO) and the UK (country codes explained in Table 1). For each of these countries, population estimates for 2020 were retrieved from the world statistic project "Worldometer" (9).

Cumulative numbers of the confirmed COVID-19 cases were downloaded on 13 September 2020 as time series from the COVID-19 Data Repository (Center for Systems Science and Engineering (CSSE), Johns Hopkins University (3). The dataset covered the period from 22 January to 12 September 2020. Cumulative numbers per day were presented as scatterplots starting from the day of the first confirmed case of COVID-19 (day 1) per each country. For each curve of cumulative numbers of COVID-19 cases, first and second derivative curves were plotted based on the numerical differentiation and smoothing by the Lowess method (medium, 10 points in smoothing window) using GraphPad Prism version 8.0.1.244 for Windows (GraphPad Software, San Diego, California USA). Scatterplots were used for the determination of cumulative incidence (CI) and the end day of the first epidemic wave in each country.

For the purpose of this report, an epidemic wave is considered as a sigmoidal curve of cumulative cases with four distinguishable stages: (i) lagging phase with marginal daily increase in case numbers, (ii) acceleration stage with an increasing number of daily cases, (iii) deceleration stage with decreasing number of new cases, and (iv) stationary stage with marginal daily increases and stagnation of total number of cases. The first-order derivative curve (growth rate graph) is approximately bell shaped and the second-order derivative (growth acceleration) consists of two bell-shaped curves (10) (these patterns are shown on the Supplemental Fig. 1). The end day of the first wave and the cumulative incidence for the first wave of epidemic in each country were identified by examining patterns of these three curves, allowing for transient stationary intervals after identifiable peaks in first-order derivative curves.

Containment and Health Index (CHI) is one of the four aggregate indices reported by the Oxford COVID-19 Government Response Tracker (OxCGRT) project from the Blavatnik School of Government (11). These indices are calculated from indicators on (i) containment and closure policies (C1-C8), (ii) economic policies (E1-E4), and (iii) health system policies (H1-H7). Containment and Health Index (CHI) is composed of the following 11 individual containment and health response indicators recorded on ordinal scales: School closing (C1), Workplace closing (C2), Public events cancellation (C3), Restriction on gathering size (C4), Public transportation closing (C5), Stay at home orders (C6), Restrictions on internal movement (C7), Restriction on international travel (C8), Public information campaign (H1), Testing policy (H2), and Contact tracing (H3) (11). CHI values (a "display" version) for all EU countries and for each day of the first wave of the COVID-19 epidemic were downloaded as an "OxCGRT_latest.csv" file on 30 September 2020 (12). Cumulative CHI indices (cCHIs) from the day 1 of the epidemic were determined for each Day D as the sum of CHIs for all days starting with the day of the first confirmed diagnosis of COVID-19 (day 1) up to the Day D. Cumulative CHI indices for a pre-epidemic period in each country (cCHI (< 1)) were

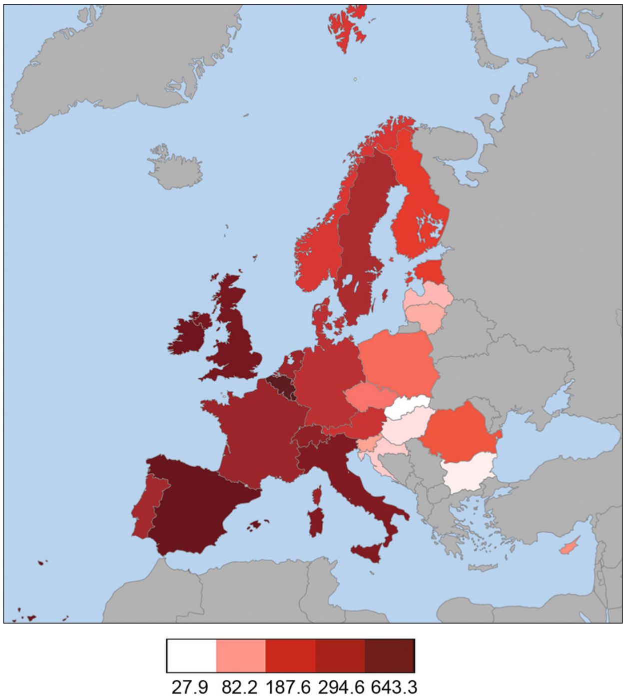


Fig. 1. Cumulative incidence of COVID-19 cases in 28 European countries at the end of the first epidemic wave. Colour coding reflects the number of confirmed cases per 100,000 people. Gray colour – data not shown.

determined by summing CHI values from 01 January 2020 to the day preceding day 1 of epidemic in each country.

The degree of association between cumulative incidences and cumulative CHI values was determined using Spearman's semi-partial correlations by eliminating the effect of population density on cumulative incidence, using the package "ppcor" (13) in R Environment version 3.5.1 (R Core Team, Vienna, Austria; https://www.R-project.org). Two-sided p-values for the significance of the Spearman's correlation were adjusted using the Benjamini-Hochberg procedure implemented in the p.adjust function in R Environment. Zero-order correlations between two variables without controlling for the influence of other variables were determined as Spearman's rank-order correlations using GraphPad Prism version 8.0.1.244 for Windows. All the reported p-values are two-tailed. Hierarchical clustering (Euclidian distance, average linkage) was performed on cCHI values using the CIMiner tool (http://discover.nci.nih.gov/cimminer).

Apple Mobility Trends Reports were accessed as the complete data in the .csv file format on 22 December 2020 (14). The data reflect the number of requests for directions in "Apple Maps" relative to the baseline on 13 January 2020, when each component of mobility was assigned the value of 100 %). The driving, walking, and transit transportation data were extracted for selected countries on a country level for each day after 13 January 2020 and their centered 7-day averages were calculated for each day and plotted over time.

Google Community Mobility Reports were accessed on 13th December 2020. These data include mobility trends in six different categories ("Grocery and Pharmacy", "Parks", "Transit Stations", "Workplaces", and "Residential Places") determined based on the location history for a sample of Google accounts and expressed relative to the baseline. The baseline is the median value for the corresponding day of the week across the 5-week period from 3 January to 6 February 2020 (15). For this study, only mobility trends for places of residence were used, which represent a duration of the time spent at places of residence relative to the baseline.

Results

Occurrence of COVID-19 over the first epidemic wave differed considerably across selected European countries

The last days of the first epidemic waves of COVID-19 in 28 European countries, and corresponding cumulative numbers of confirmed cases (Tab. 1) were determined from the scatterplots of cumulative numbers of cases vs. days, and their first and second-order derivative curves (Supplemental Figs 2–6).

The first waves of the COVID-19 epidemics in these countries started between 24 January and 9 March 2020, and lasted for 77–160 days (median 116.5 days). Cumulative incidence of confirmed cases displays high variability ranging 27.88–643.31 cases per 100,000 population (Tab. 1, Fig. 1), and appears to have a multimodal distribution (Supplemental Fig. 7).

Tab. 1. Demographic and epidemiological characteristics of 28 European countries.

Country (code)	Day 1	First Day of CHI measures[1]	Duration (days)[2]	Number of cases	Population (2020)	Area (km^2)	Population Density (per km^2)	Cumulative Incidence (per 100,000)	Cumulative Incidence Rank
Austria (AT)	25-02-20	01-02-20	103	16898	9006398	83858	107.40	187.62	14
Belgium (BE)	04-02-20	28-01-20	144	61106	11589623	30510	379.86	527.25	2
Bulgaria (BG)	08-03-20	03-02-20	78	2427	6948445	110994	62.60	34.93	27
Croatia (HR)	25-02-20	27-01-20	98	2247	4105367	56594	72.54	54.73	25
Cyprus (CY)	09-03-20	05-03-20	109	992	1207359	9251	130.51	82.16	21
Czechia (CZ)	01-03-20	24-01-20	94	9364	10708981	78866	135.79	87.44	20
Denmark (DK)	27-02-20	27-02-20	132	12888	5792202	44493	130.18	222.51	12
Estonia (EE)	27-02-20	12-03-20	122	1986	1326535	45339	29.26	149.71	16
Finland (FI)	29-01-20	27-01-20	158	7248	5540720	338145	16.39	130.81	17
France (FR)	24-01-20	23-01-20	148	191304	65273511	551695	118.31	293.08	9
Germany (DE)	27-01-20	22-01-20	132	185450	83783942	357386	234.44	221.34	13
Hungary (HU)	04-03-20	28-01-20	114	4123	9660351	93030	103.84	42.68	26
Ireland (IE)	29-02-20	04-02-20	119	25414	4937786	70273	70.27	514.68	4
Italy (IT)	31-01-20	23-01-20	160	242149	60461826	301338	200.64	400.50	6
Latvia (LV)	02-03-20	29-01-20	112	1111	1886198	64589	29.20	58.90	24
Lithuania (LT)	28-02-20	29-01-20	122	1815	2722289	65300	41.69	66.67	23
Luxembourg (LU)	29-02-20	01-03-20	97	4027	625978	2586	242.06	643.31	1
Netherlands (NL)	27-02-20	27-01-20	128	50487	17134872	41198	415.92	294.64	8
Norway (NO)	26-02-20	31-01-20	138	8981	5421241	385178	14.07	165.66	15
Poland (PL)	04-03-20	23-01-20	122	35405	37846611	312685	121.04	93.55	19
Portugal (PT)	02-03-20	26-01-20	77	29036	10196709	91568	111.36	284.76	10
Romania (RO)	26-02-20	27-01-20	93	18791	19237691	238397	80.70	97.68	18
Slovakia (SK)	06-03-20	01-01-20	88	1522	5459642	49036	111.34	27.88	28
Slovenia (SI)	05-03-20	04-03-20	82	1469	2078938	20273	102.55	70.66	22
Spain (ES)	01-02-20	24-01-20	138	244683	46754778	498511	93.79	523.33	3
Sweden (SE)	01-02-20	31-01-20	101	27301	10099265	450295	22.43	270.33	11
Switzerland (CH)	25-02-20	15-02-20	99	30874	8654622	41290	209.61	356.73	7
United Kingdom (UK)	31-01-20	20-01-20	159	286349	67886011	242495	279.95	421.81	5

[1]The date (after the 1st January 2020) when the Containment and Health Index first exceeded 0, [2]Duration of the first epidemic wave

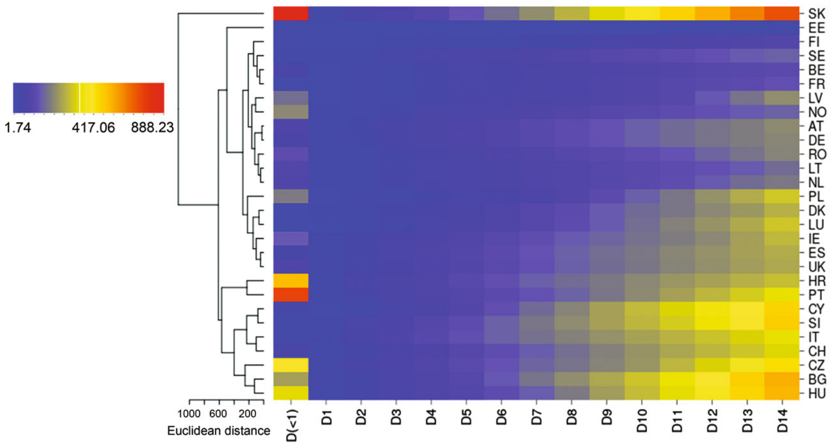


Fig. 2. Hierarchical clustering of cumulative Containment and Health Indices (cCHIs) for the pre-epidemic period (D < 1) and epidemic days 1–14 across 28 countries. Distance method: Euclidian; Cluster algorithm: Average linkage.

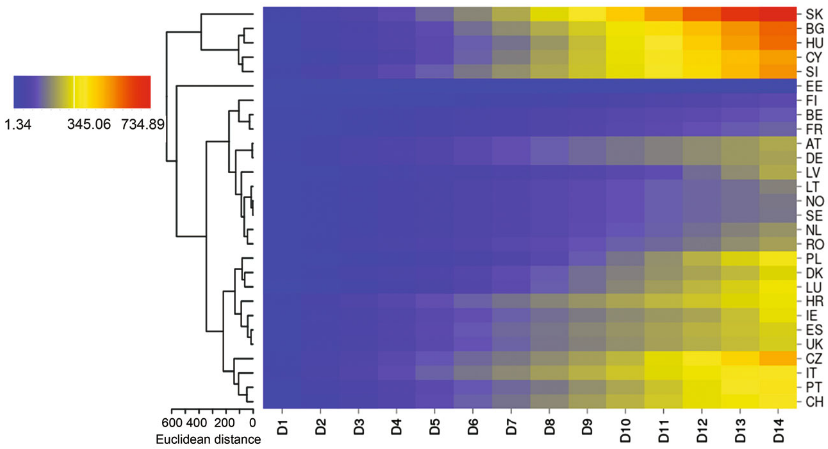


Fig. 3. Hierarchical clustering of cumulative Containment and Health Indices (cCHIs) for the epidemic days 1–14 across 28 countries. Distance method: Euclidian; Cluster algorithm: Average linkage.

Cumulative incidence is positively and statistically significantly correlated with population density (Spearman's ρ = 0.467; CI_{95}: 0.102–0.721; p = 0.0123; Supplemental Fig. 8A) and with the duration of the first epidemic wave (Spearman's ρ = 0.460; CI95: 0.093–0.717; p = 0.0138; Supplemental Fig. 8B). In addition, the cumulative incidence remains positively and significantly correlated with population density while controlling cumulative incidence for the effect of epidemic duration (semi-partial Spearman's ρ = 0.450, p = 0.0185, test statistic = 2.521). These results indicate that the overall risk of COVID-19 over the first epidemic waves in European countries increased with increasing population density.

Based on the cumulative incidence of confirmed COVID-19 cases, the three highest-ranking countries were identified as Luxembourg, Belgium and Spain. In contrast, Slovakia, Bulgaria, and Hungary reached the lowest cumulative incidences over the first epidemic waves (Fig. 1 and Tab. 1).

Stringency of the containment measures differed across European countries relative to the beginning of their COVID-19 epidemics

Containment and health measures that are reflected in the Containment and Health Indices (CHI) were first adopted in 28 European countries between 1st January and 12 March 2020 (Tab. 1). Intriguingly, Slovakia was the only country among 28 considered European countries, and one of 10 countries globally, which had some containment and health measures in place

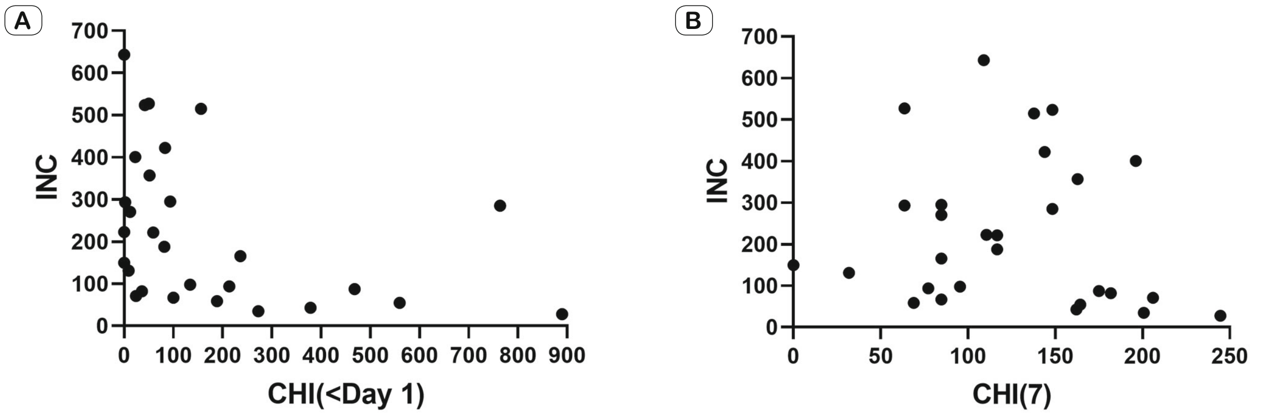


Fig. 4. Scatterplot of cumulative incidences of confirmed COVID-19 cases versus: (A) cumulative Containment Health Index prior to the first day of epidemic, and (B) cumulative Containment Health Index for the first 7 days of the epidemic. INC: cumulative incidence; cCHI (< Day 1): cumulative Containment Health Index prior to the first day; cCHI(7): cumulative Containment Health Index for the first 7 days

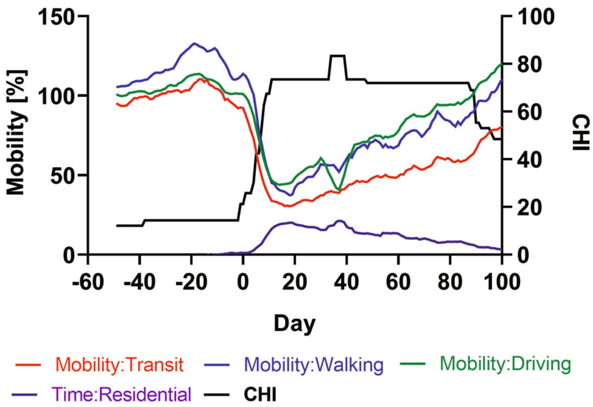


Fig. 5. Mobility and the Containment and Health Index (CHI) in the Slovak Republic. Vertical axis: change in mobility relative to the baseline (for details, see Datasets and Methods section). Horizontal axis: day relative to the start of the epidemic (day 1 = 6 March 2020).

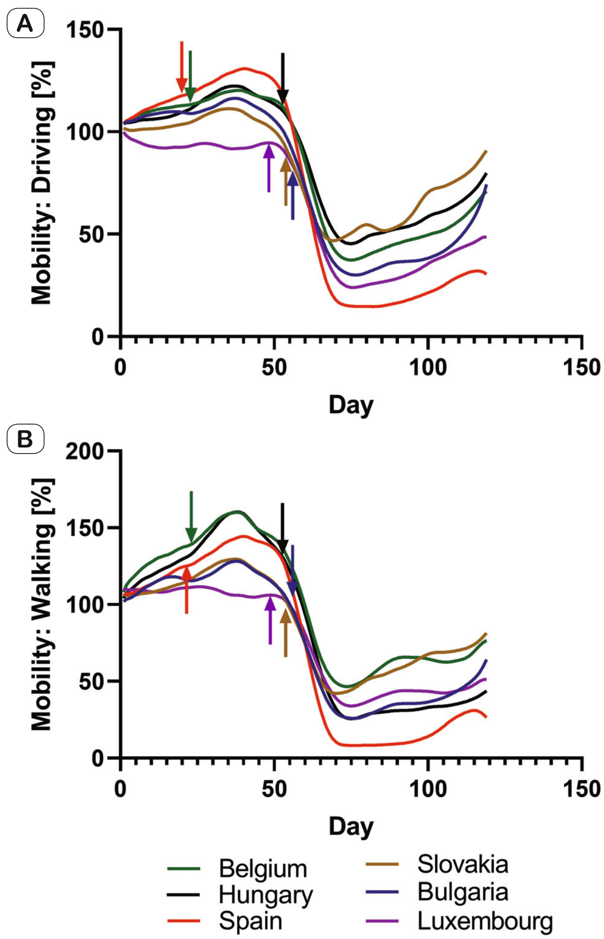


Fig. 6. Mobility trends for driving (A) and walking (B) across 3 countries with the highest and 3 countries with the lowest cumulative incidences over the first wave of COVID-19. Color-coded arrows indicate the days of the first confirmed COVID-19 cases in each country.

already on 01 January 2020. The CHI values accumulated over the pre-epidemic period (cCHI (< Day 1)) show considerable differences across individual European countries (Tab. 2). This measure, which reflects the stringency of the pre-epidemic containment measures, was highest in Slovakia (889.97), and lowest in Denmark, Estonia, and Luxembourg (0). Similarly, considerable differences across European countries were found for cumulative CHI values accumulated from day 1 up to the day 14 (Tab. 2), indicating different stringency of containment measures adopted in individual countries from the first days of their epidemics. Per these metrics, Slovakia ranks first among 28 European countries for days 5–14, and second for days 1–4 from the beginning of her epidemic (Tab. 2). Unsupervised hierarchical clustering for cumulative stringencies across days 1 to 14 with and without the inclusion of cumulative stringencies for pre-epidemic periods identified clusters of countries with similar stringencies of adopted containment measures (Figs 2 and 3). Interestingly, Slovakia forms a singleton in both cluster analyses, indicating its unique status (outlier) among European countries due to the high stringency and early timing of the containment measures adopted in that country. Considerable similarity is also visible for the low-cumulative incidence countries Bulgaria and Hungary, as well as Slovenia and Cyprus (Fig. 3). Bulgaria and Hungary show an appreciable stringency of CHIs in the pre-epidemic period, as well as early ramping-up of their stringencies after the diagnosis of the first COVID-19 cases, while Slovenia and Cyprus had

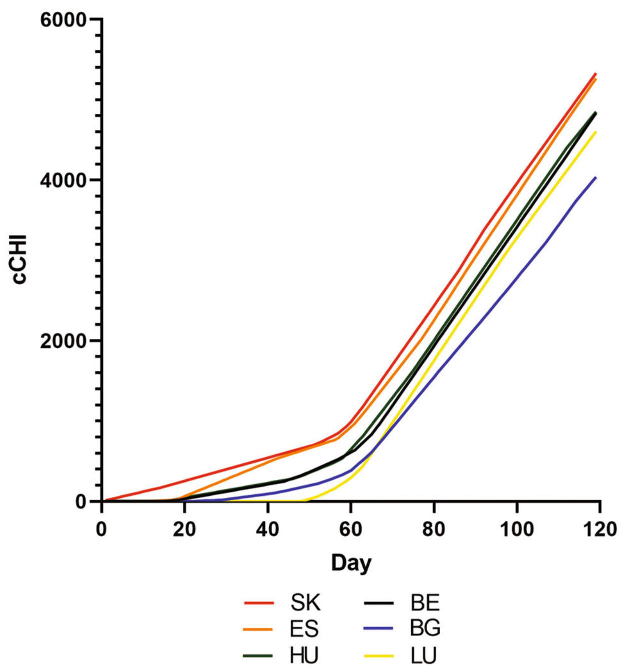
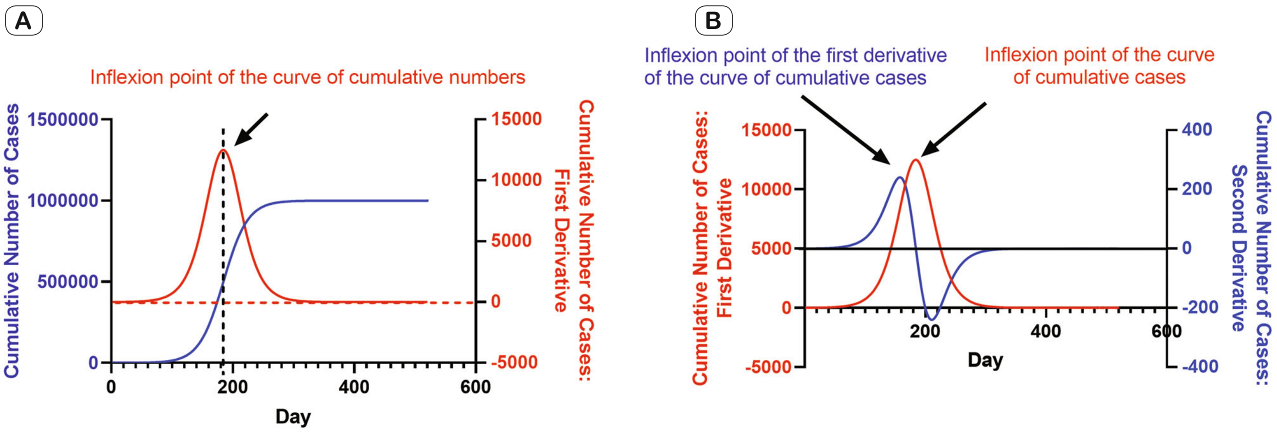


Fig. 7. Overall stringency trends by calendar days for 3 countries with the highest (LU, BE, ES) and 3 countries with the lowest (SK, BG, HU) cumulative incidences over the first wave of COVID-19 epidemics. cCHI: cumulative Containment and Health Index accumulated from 13 January 2020. Day: calendar day (1 = 13 January 2020).



Supplemental Fig. 1. Demonstration of the shapes of the curves for cumulative numbers of cases (A) and their first order (A, B) and second order (B) derivatives. Plotted for classical logistic growth (dN/dt = kN(1-N/K)), using 100 initial cases (N_0), growth rate of 0.05 day^{-1} (k) and carrying capacity of 1,000,000 (K).

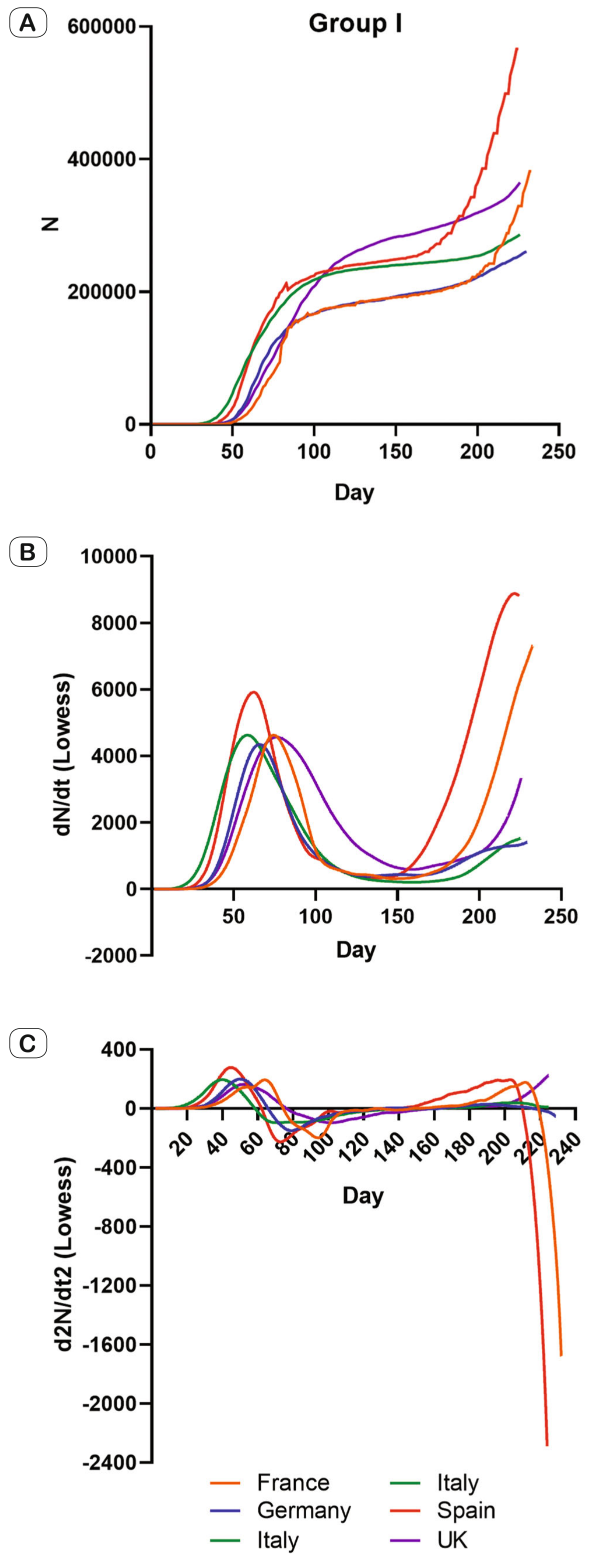
considerably lower pre-epidemic stringency of containment, but rapidly increasing cCHIs from the first days of their epidemics (Fig. 2 and Tab. 2). On the other hand, high-incidence countries display a more complex pattern of stringency over time, exemplified by differences between similar pairs BE and FR versus UK and ES (Figs 2 and 3).

Stringency of the containment measures inversely correlates with disease occurrence across European countries

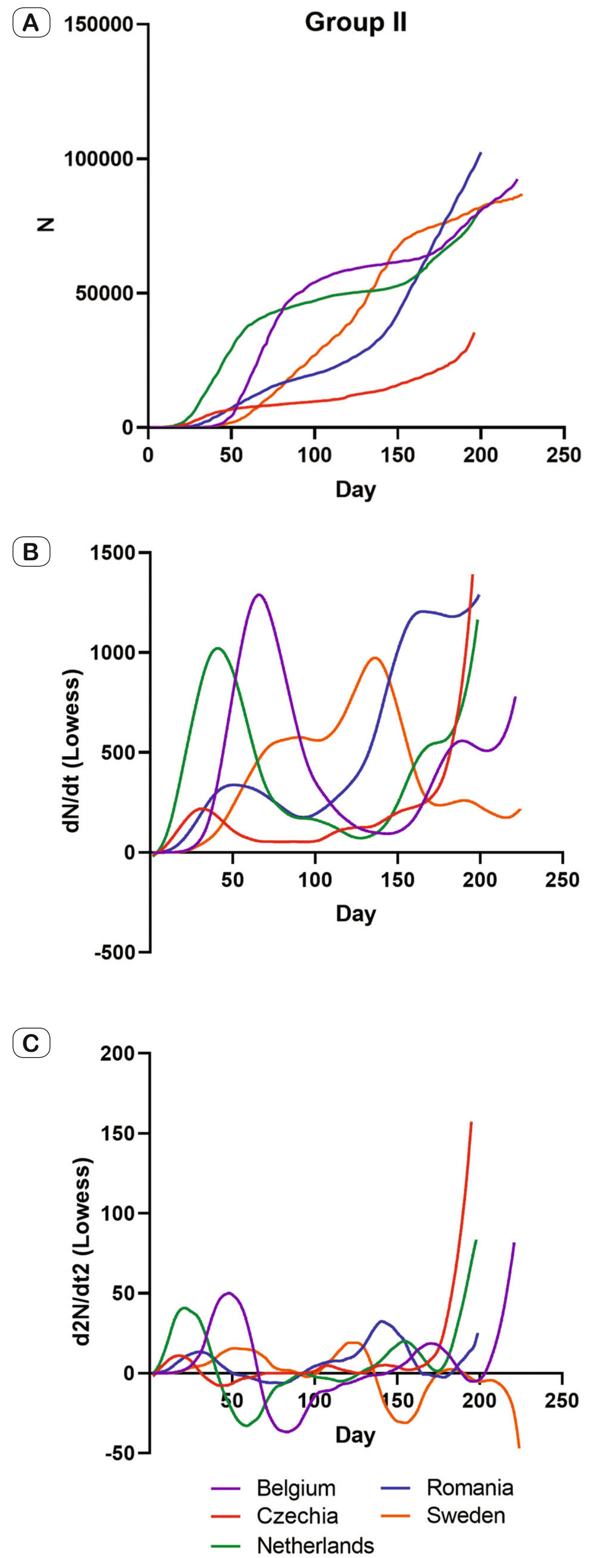
Slovakia, which displays the highest stringency of the pre-epidemic containment measures, as well as the first or the second highest stringency from day 1 of the epidemic, reached the lowest cumulative incidence of the confirmed COVID-19 cases across European countries at the end of the first epidemic wave (Fig. 1 and

Tab. 2. Cumulative values of the Containment and Health Index (cCHI) accumulated over pre-epidemic periods (< Day 1) or between day 1 of epidemic and day 2-14 (D2-D14). Colour coding reflects the value of cCHI (for pre-epidemic period: white = low, green = high; for epidemic period: blue = low, red = high).

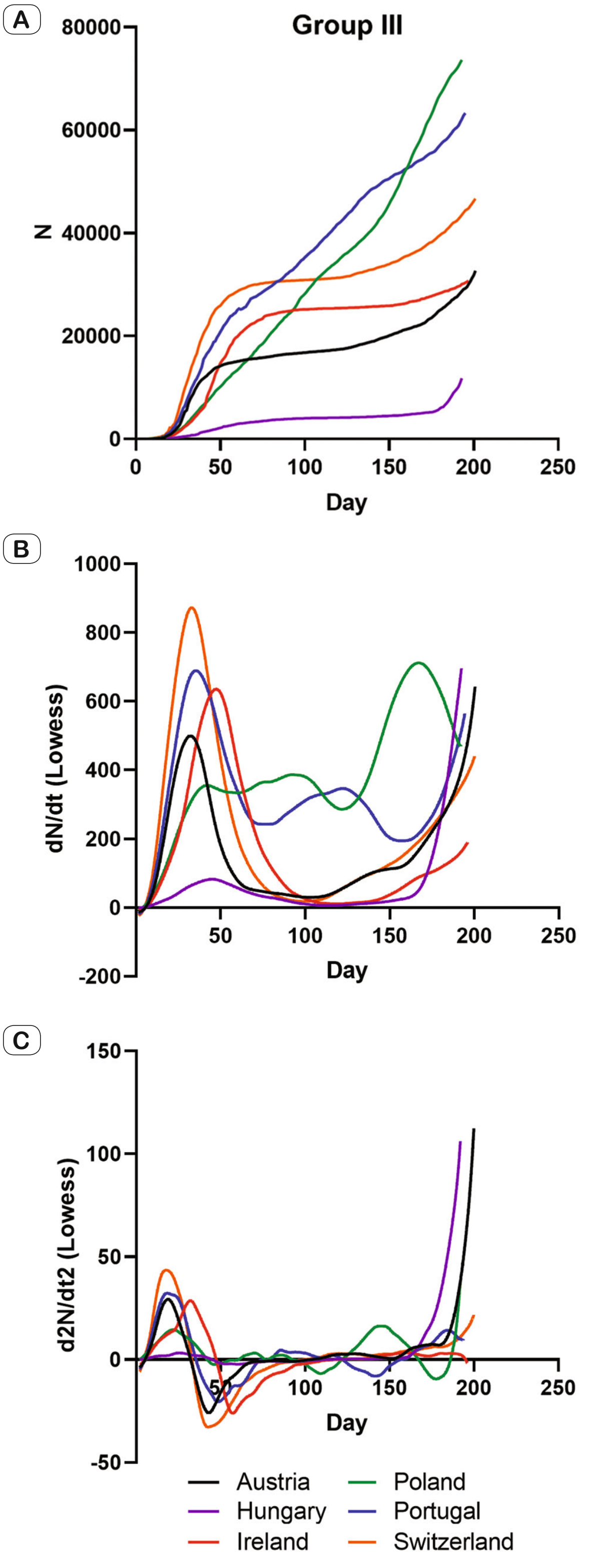
Day	<Day 1	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	D14
AT	81.81	16.67	33.34	50.01	66.68	83.35	100.02	116.69	133.36	150.03	166.7	183.37	200.04	216.71	240.19
BE	50.01	9.09	18.18	27.27	36.36	45.45	54.54	63.63	72.72	81.81	90.9	99.99	109.08	118.17	127.26
BG	272.68	20.45	40.9	61.35	86.35	111.35	156.05	200.75	245.45	290.15	339.39	400	460.61	521.22	584.1
HR	559.76	23.48	46.96	70.44	93.92	117.4	140.88	164.36	187.84	211.32	234.8	258.28	281.76	305.24	328.72
CY	36.36	9.09	27.27	45.45	68.18	104.54	140.9	181.81	228.78	275.75	322.72	369.69	416.66	463.63	510.6
CZ	468.3	25	50	75	100	125	150	175	200	228.03	260.61	311.37	364.4	423.49	485.61
DK	0	13.64	27.28	40.92	54.56	68.2	89.41	110.62	131.83	157.59	183.35	209.11	234.87	265.17	303.81
EE	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
FI	9.1	4.55	9.1	13.65	18.2	22.75	27.3	31.85	36.4	47.76	59.12	70.48	81.84	93.2	104.56
FR	2.27	9.09	18.18	27.27	36.36	45.45	54.54	63.63	74.99	86.35	97.71	109.07	120.43	131.79	143.15
DE	59.1	16.67	33.34	50.01	66.68	83.35	100.02	116.69	133.36	150.03	166.7	183.37	200.04	216.71	233.38
HU	378.76	21.21	42.42	63.63	84.84	106.05	134.08	162.11	215.14	271.2	327.26	383.32	439.38	506.8	574.22
IE	156.15	19.7	39.4	59.1	78.8	98.5	118.2	137.9	157.6	177.3	197	216.7	236.4	272.76	318.21
IT	22.71	28.03	56.06	84.09	112.12	140.15	168.18	196.21	224.24	252.27	280.3	308.33	336.36	364.39	392.42
LV	188.56	9.85	19.7	29.55	39.4	49.25	59.1	68.95	78.8	88.65	100.77	112.89	155.31	200.01	244.71
LT	100	12.12	24.24	36.36	48.48	60.6	72.72	84.84	96.96	109.08	121.2	133.32	145.44	157.56	185.59
LU	0	0	15.15	30.3	45.45	60.6	84.84	109.08	133.32	157.56	190.89	224.22	257.55	295.43	342.4
NL	93.93	12.12	24.24	36.36	48.48	60.6	72.72	84.84	96.96	110.6	124.24	137.88	158.33	185.6	212.87
NO	236.34	12.12	24.24	36.36	48.48	60.6	72.72	84.84	96.96	109.08	121.2	133.32	145.44	157.56	172.71
PL	213.79	9.09	18.18	27.27	36.36	45.45	56.81	77.26	97.71	131.8	165.89	206.04	253.01	299.98	346.95
PT	763.56	21.21	42.42	63.63	84.84	106.05	127.26	148.47	174.23	206.81	239.39	278.03	316.67	355.31	393.95
RO	134.19	13.64	27.28	40.92	54.56	68.2	81.84	95.48	109.12	122.76	136.4	150.04	175.04	202.31	229.58
SK	889.97	25.76	51.52	77.28	107.58	150	192.42	244.69	307.57	374.99	442.41	515.89	589.37	662.85	736.33
SI	24.24	24.24	48.48	77.27	106.06	134.85	170.46	206.07	241.68	277.29	315.93	354.57	411.39	468.21	525.03
ES	42.42	21.21	42.42	63.63	84.84	106.05	127.26	148.47	169.68	190.89	212.1	233.31	254.52	275.73	296.94
SE	12.12	12.12	24.24	36.36	48.48	60.6	72.72	84.84	96.96	109.08	121.2	133.32	145.44	157.56	169.68
CH	51.56	17.42	34.84	56.81	83.33	109.85	136.37	162.89	193.95	225.01	256.07	287.13	315.16	343.19	371.22
UK	83.38	18.94	37.88	59.09	80.3	101.51	122.72	143.93	165.14	186.35	207.56	228.77	249.98	271.19	292.4



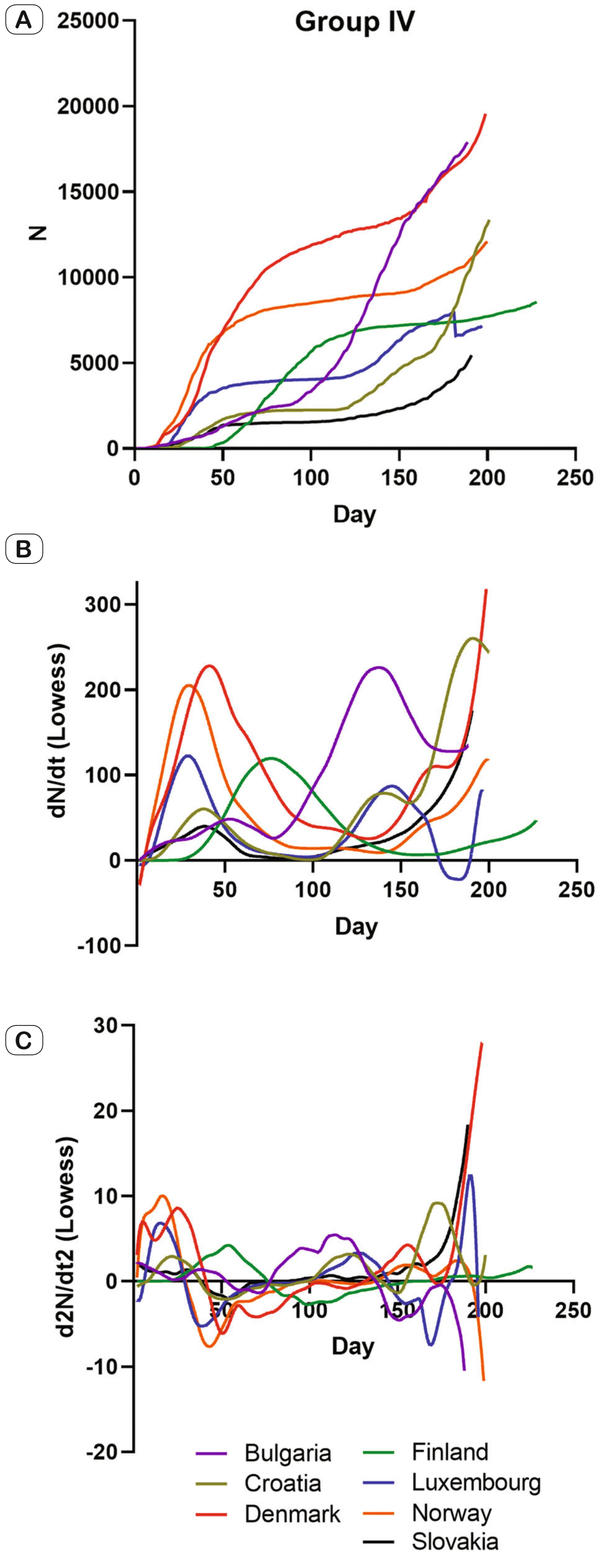
Supplemental Fig. 2. Cumulative number of confirmed COVID-19 cases vs. day since the first confirmed case (A), and its first-order derivative (B) and second-order derivative curves. Countries in Figs 2–6 were grouped based on the similarity of cumulative incidences over first waves of the epidemics.



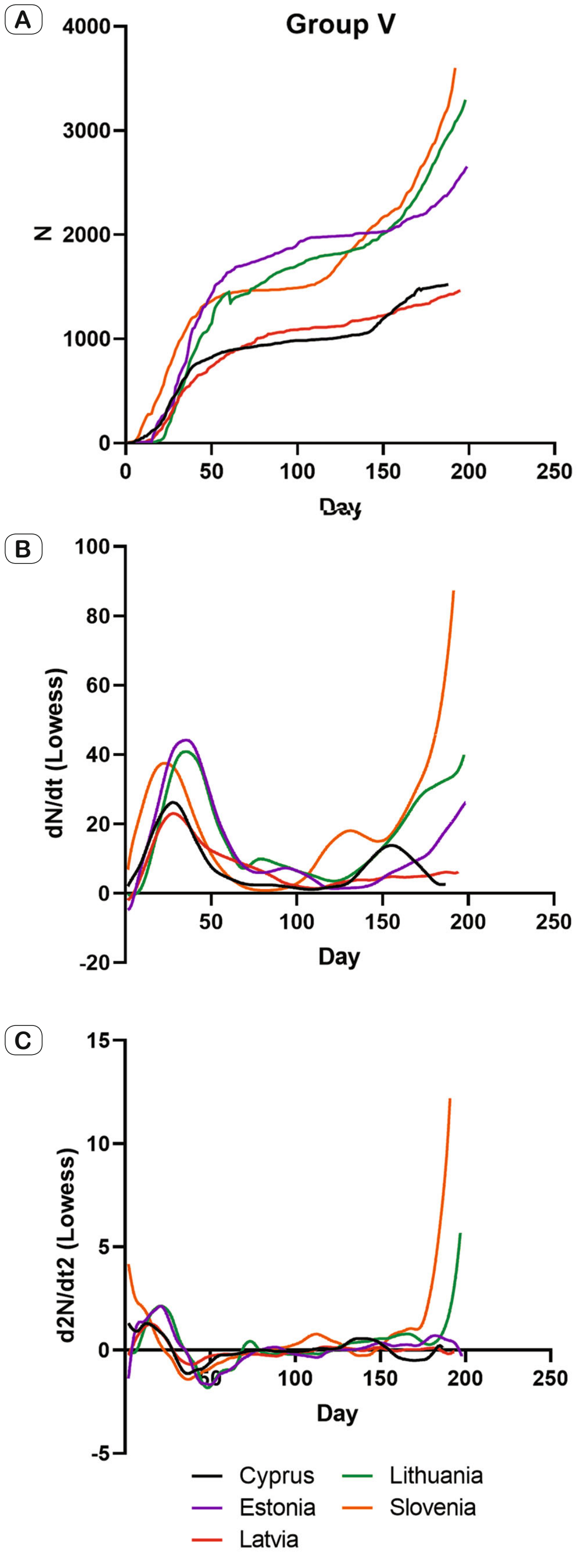
Supplemental Fig. 3. Cumulative number of confirmed COVID-19 cases vs. day since the first confirmed case (A), and its first-order derivative (B) and second-order derivative curves. Countries in Figs 2–6 were grouped based on the similarity of cumulative incidences over first waves of the epidemics.



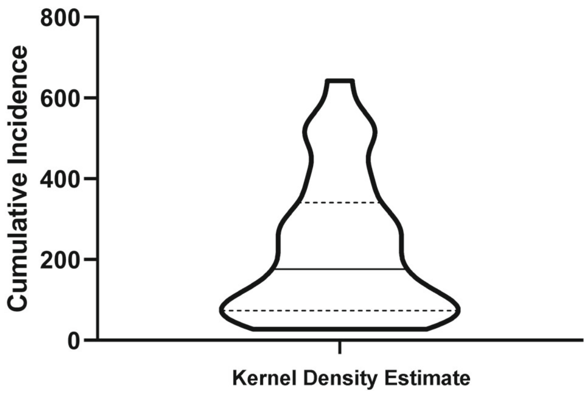
Supplemental Fig. 4. Cumulative number of confirmed COVID-19 cases vs. day since the first confirmed case (A), and its first-order derivative (B) and second-order derivative curves. Countries in Figs 2–6 were grouped based on the similarity of cumulative incidences over first waves of the epidemics.



Supplemental Fig. 5. Cumulative number of confirmed COVID-19 cases vs. day since the first confirmed case (A), and its first-order derivative (B) and second-order derivative curves. Countries in Figs 2–6 were grouped based on the similarity of cumulative incidences over first waves of the epidemics.



Supplemental Fig. 6. Cumulative number of confirmed COVID-19 cases vs. day since the first confirmed case (A), and its first-order derivative (B) and second-order derivative curves. Countries in Figs 2–6 were grouped based on the similarity of cumulative incidences over first waves of the epidemics.

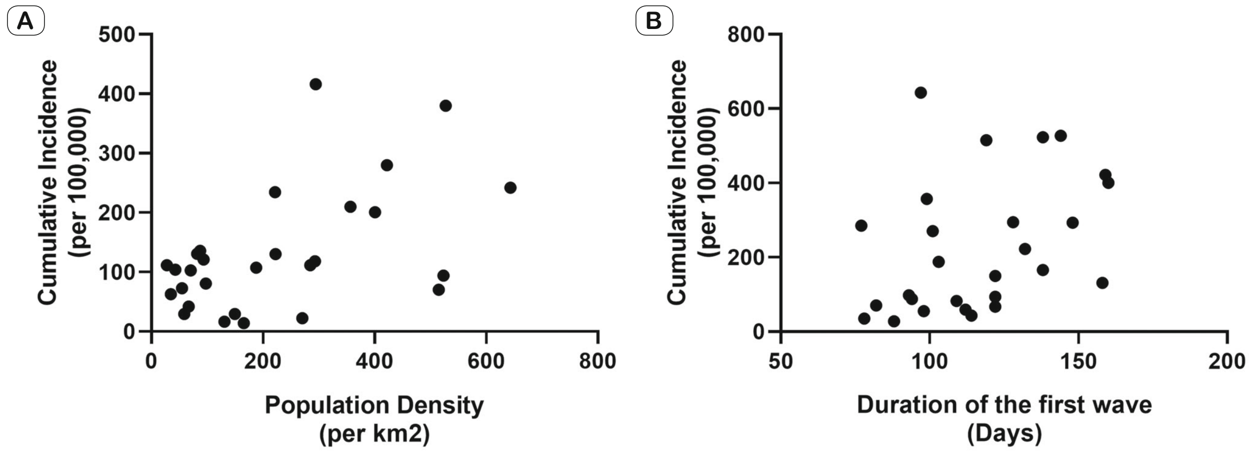


Supplemental Fig. 7. Violin plot for cumulative incidences reached 28 European countries during the first epidemic wave of COVID-19. Dashed lines: quartiles; full line: median.

Tab. 1). Conversely, Luxembourg, with the highest cumulative incidence of cases, displayed the lowest cumulative CHI for the period between 1st January and the first day of the epidemic. In addition, Luxembourg scored low in the cumulative CHIs from the day 1 of the epidemic, and its cCHI values were lower than median cumulative CHIs for the first 7 days of the epidemics across 28 countries. These findings suggested an existing association between cumulative incidence for the first epidemic wave and stringency of the containment measures across European countries (Fig. 4).

Next, semi-partial correlations were performed to determine the degree of associations between the cCHI values for specific time periods and cumulative incidences of COVID-19 whilst controlling the cumulative incidence for population density (Tab. 3). There was a moderate, inverse semi-partial correlation (ρ= -0.50) between the cumulative incidence of COVID-19 cases (average ± SD: 225.91 ± 173.95 per 100,000) and cCHI accumulated over the pre-epidemic period (176.11 ± 230.08), whilst controlling for population density (130.99 ± 100.98 km^{-2}), which was statistically significant (p adjusted = 0.0247). Likewise, a moderate inverse correlation was found between the cumulative incidence and cumulative CHI over the first 7 or more days of the epidemic (123.78 ± 56.24 for the first 7 days) whilst controlling for population density (Tab. 3). To conclude, a higher stringency of containment during the pre-epidemic period, and during the first 7 or more days of the epidemic, was associated with lower overall disease occurrence.

Zero-order correlations showed a moderate negative correlation (ρ = –0.50) between the cumulative incidence of COVID-19 and cumulative CHI index over the period from 1st January 2020 to the last day before the beginning of the epidemic, which was statistically significant (p = 0.0064, n = 28). As a result, population density had very little influence in controlling for the relationship between the cumulative incidence of the disease and the pre-epidemic stringency of containment and health measures. In contrast, a zero-order correlation between the cumulative incidence and cumulative CHI index over the first 7 days of the epidemic was weak



Supplemental Fig. 8. Scatter plots of cumulative incidences reached during the first epidemic waves of COVID-19 in 28 European countries vs population density (A) or duration of the first epidemic wave (B).

and not statistically significant (ρ = –0.26, p = 0.18, n = 28), and the same applied to the correlation between cumulative CHI index over the first 7 days and population density (ρ = 0.21, p = 0.28, n = 28). As a result, population density appears to be a suppressor variable that suppressed the effect cCHI on the cumulative incidence.

Tab. 3. Semi-partial correlations for association between cumulative Containment Health Indices (cCHIs) for various days of epidemic and cumulative incidences of COVID-19 in the first wave.

Day	Spearman's ρ correlation estimate	p	Benjamini–Hochberg Adjusted p	Test statistic
Up to 1	–0.500	7.87e-3	0.0247	–2.889
1	–0.265	0.182	0.182	–1.374
2	–0.301	0.127	0.147	–1.580
3	–0.289	0.143	0.153	–1.512
4	–0.332	0.0903	0.113	–1.762
5	–0.356	0.0680	0.0927	–1.908
6	–0.398	0.0399	0.0599	–2.167
7	–0.408	0.0348	0.0247	–2.232
8	–0.443	0.0206	0.0345	–2.471
9	–0.450	0.0186	0.0345	–2.517
10	–0.443	0.0207	0.0345	–2.469
11	–0.460	0.0157	0.0345	–2.593
12	–0.498	8.24e-3	0.0247	–2.869
13	–0.514	6.07e-3	0.0247	–2.998
14	–0.527	4.77e-3	0.0247	–3.098

Interestingly, Portugal featured the second-highest pre-epidemic cumulative CHI, but eventually ranked only 10th out of 28 countries with respect to the cumulative COVID-19 incidence. In spite of the relatively stringent pre-epidemic containment measures, that country reached a relatively high cumulative incidence, which was consistent with the observed lower stringency of the containment measures adopted from day 1 of the epidemic. The lower stringency of containment from day 1 of epidemic is demonstrated by Portugal ranking 7th to 10th in the cCHI values for days 1 up to 14. This finding, visualized by an outlier status for Portugal in the scatterplot of cumulative incidences vs. pre-epidemic cCHIs, indicates that pre-epidemic containment measures cannot fully compensate for the lack of adequate stringency of containment once the disease presence is confirmed in the population (Fig. 4A, second point from the left).

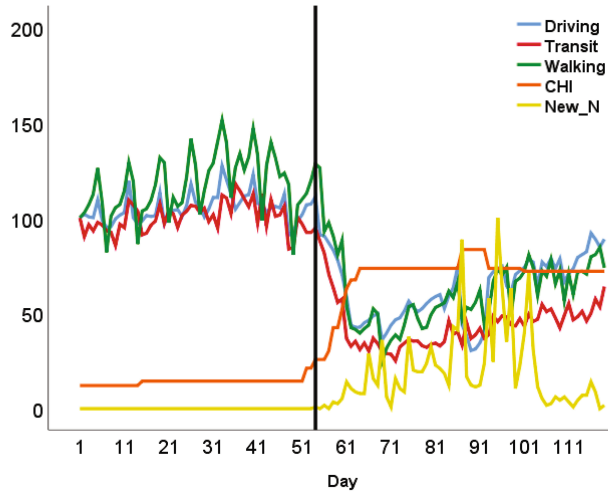
Countries, which were top-ranking based on their cumulative incidences (LU, BE, and ES), typically scored low on the pre-epidemic cCHIs (respective ranks 27, 18, 19), and low or intermediate on the cCHIs for day 14 (ranks 11, 26, 15). In contrast, countries scoring lowest on the cumulative incidence (SK, BG, and HU), scored high in the cumulative CHIs both in pre-epidemic period (ranks 1, 6, and 5) and epidemic days 1-14 (ranks 1, 2, and 3). Countries with poor scoring on pre-epidemic cumulative CHIs, such as CY and SI (ranks 20 and 21), could still display relatively low cumulative incidences (ranks 21 and 22), if their cumulative CHIs for day 14 scored high (ranks 5 and 4).

Tab. 4. Containment Health Indices (CHI) reached at day 1, 7 and 14 from the first diagnosed cases and maximum achieved CHI in three European countries with highest and lowest cumulative incidences of COVID-19 for the first epidemic wave.

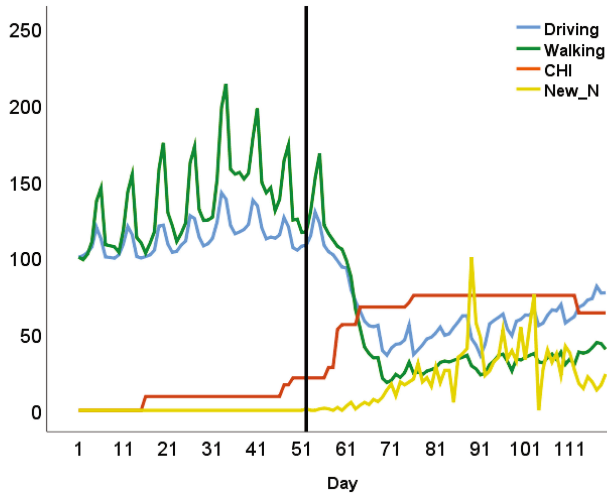
	Containment Health Index (CHI)				Time from the 1st diagnosed case to the reduction of mobility below 50% of the mobility on 13-01-2020 (in days)		
	Day 1	Day 7	Day 14	Maximum	Driving	Walking	Transit
Slovakia	25.76	52.27	73.48	83.33	8	8	7
Bulgaria	20.45	44.7	62.88	71.97	8	8	–
Hungary	21.21	28.03	67.42	75.00	16	14	–
Luxembourg	0	24.24	46.97	77.27	16	17	15
Belgium	9.09	9.09	9.09	77.27	43	43	41
Spain	21.21	21.21	21.21	80.30	43	42	42

Stringency of the containment measures impacted the mobility of the population

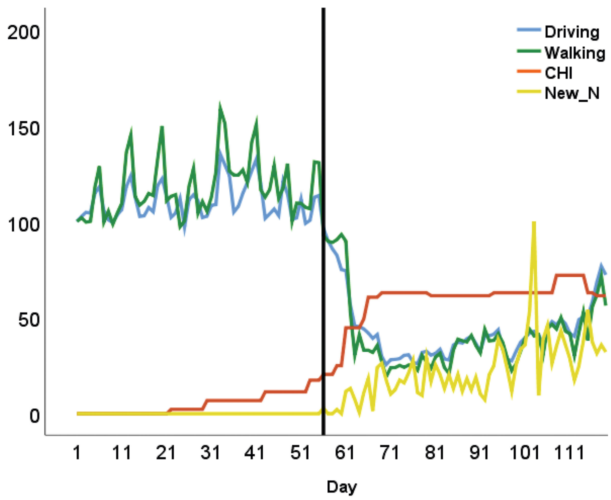
Cumulative CHI values influenced the occurrence of COVID-19 in the first epidemic wave through its impact on mobility, which can be recognized through exploration of the CHI and mobility trends over time. In Slovakia, visualization reveals an appreciable inverse relationship between



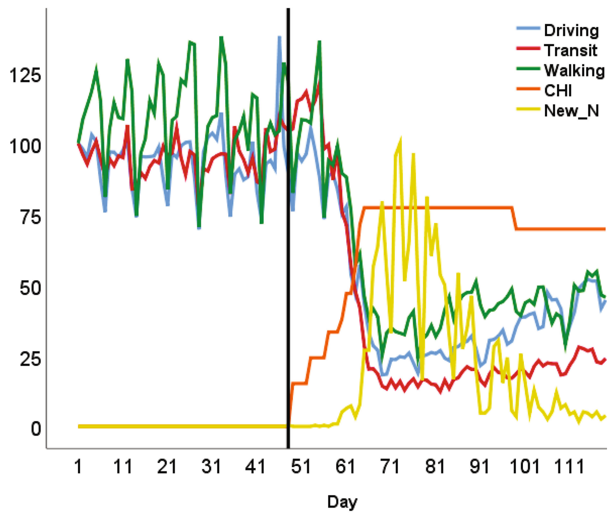
Supplemental Fig. 9. Slovakia - Mobility (driving, transit, and walking), containment health index (CHI), and numbers of daily COVID-19 cases normalized to a maximum during the period from 13 January (day 1) to 10 May 2020 (day 119). Day 1 = 13 January 2020; Vertical line = day of the first case diagnosis.



Supplemental Fig. 11. Hungary - Mobility (driving, transit, and walking), containment health index (CHI), and numbers of daily COVID-19 cases normalized to a maximum during the period from 13 January (day 1) to 10 May 2020 (day 119). Day 1 = 13 January 2020; Vertical line = day of the first case diagnosis.

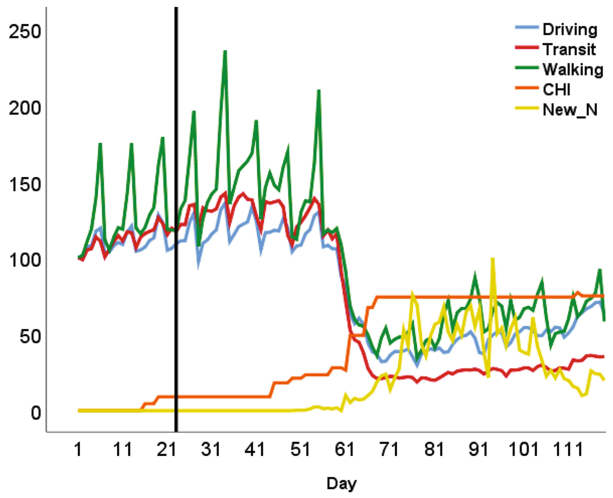


Supplemental Fig. 10. Bulgaria – Mobility (driving, transit, and walking), containment health index (CHI), and numbers of daily COVID-19 cases normalized to a maximum during the period from 13 January (day 1) to 10 May 2020 (day 119). Day 1 = 13 January 2020; Vertical line = day of the first case diagnosis.

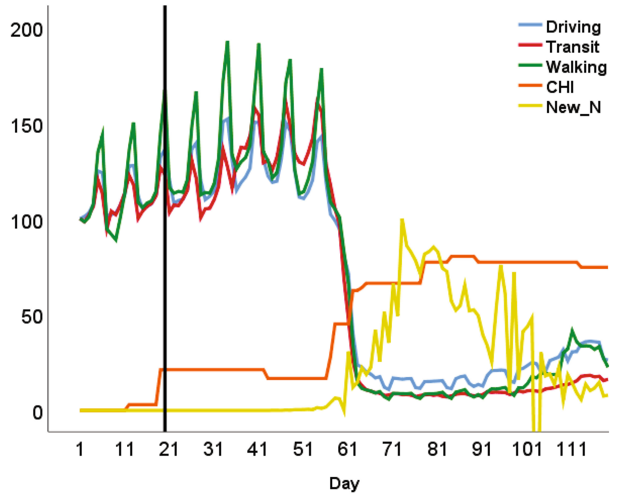


Supplemental Fig. 12. Luxembourg – Mobility (driving, transit, and walking), containment health index (CHI), and numbers of daily COVID-19 cases normalized to a maximum during the period from 13 January (day 1) to 10 May 2020 (day 119). Day 1 = 13 January 2020; Vertical line = day of the first case diagnosis.

CHI and mobility (Fig. 5). Mobility represented by transit, walking, and driving (Apple) tended to decrease, while the time spent in the areas of residence (Google) tended to increase with the increasing level of the containment stringency over the first epidemic wave (Fig. 3). This association is, however, influenced by compliance with public health measures, which mediates the relationship between adopted public health policies and mobility (16, 17). In addition, this compliance can change over time. The decrease in mobility in Slovakia can be observed for about 3 weeks preceding 6 March 2020, which is the date of the first diagnosis of a confirmed COVID-19 case (day 1). Thereafter, an additional steep decrease in mobility was visible starting from the day 1, which was consistent with increasing values of the CHIs. The mobility reached a minimum at about day 18, at which point it started increasing gradually without a parallel decrease in the CHI. Increasing mobility without decreasing CHI is suggestive of decreased public compliance up to the day ~37 when more stringent containment measures were introduced in the expectation of the risk of increased social interactions during the Easter holiday.



Supplemental Fig. 13. Belgium – Mobility (driving, transit, and walking), containment health index (CHI), and numbers of daily COVID-19 cases normalized to a maximum during the period from 13 January (day 1) to 10 May 2020 (day 119). Day 1 = 13 January 2020; Vertical line = day of the first case diagnosis.



Supplemental Fig. 14. Spain – Mobility (driving, transit, and walking), containment health index (CHI), and numbers of daily COVID-19 cases normalized to a maximum during the period from 13 January (day 1) to 10 May 2020 (day 119). Day 1 = 13 January 2020; Vertical line = day of the first case diagnosis.

European countries displayed similar patterns of mobility and stringency of the containment measures over calendar days, but these patterns differed relative to the beginning of their epidemics

Interestingly, European countries with the lowest (SK, BG, HU) and highest (LU, BE, ES) cumulative incidences in the first pandemic wave displayed similar calendar dates of mobility changes. Specifically, Slovakia, Bulgaria, and Hungary experienced increasing mobility from January 13th up to February 18–19th, but decreasing mobility thereafter, up to 22 March (Slovakia) or 27 March (Bulgaria and Hungary), and the same time courses were also found for Luxembourg and Belgium (Supplemental Figs 9–14). In contrast, however, the first COVID-19 cases were diagnosed later in the three lowest incidence countries than in the three highest incidence countries (Tab. 1). This finding indicates consistent patterns of mobility when considered relative to the calendar date, but different patterns of mobility with respect to the beginning of epidemics in these countries.

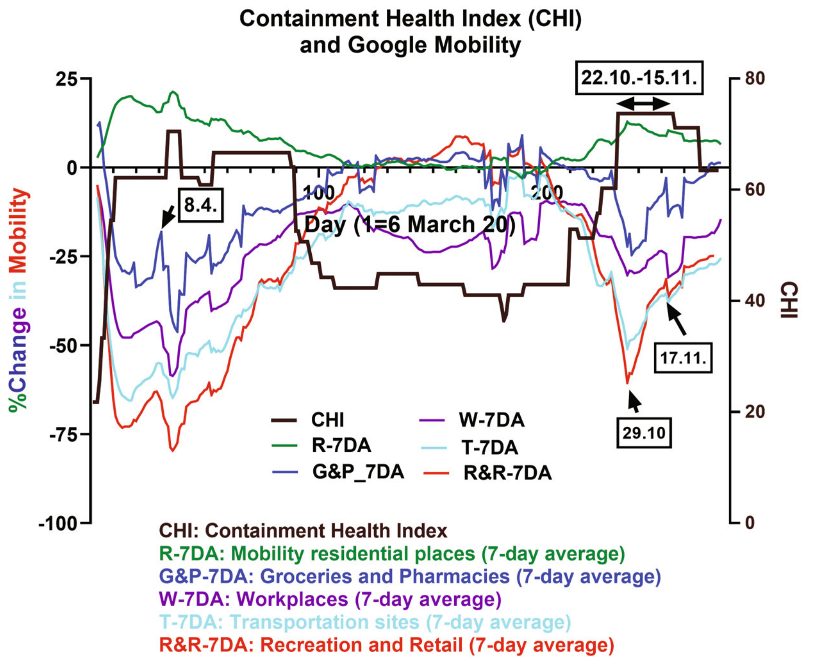
The similar patterns of mobility in calendar periods did not project into the similar disease occurrences across these countries, because the countries differed in their times of disease introduction. Decreased mobility coincided in time with disease introduction in the lowest incidence countries. In contrast, however, the highest incidence countries showed delayed reduction in mobility relative to the first days of their epidemics (Tab. 4). For instance, reduction of driving and walking mobility below 50 % of the baseline took 8 days for Slovakia, but 43 days for Belgium counting from the day of first case diagnosis. Likewise, on the day of the first case diagnosis, mobility has been already decreasing in Slovakia, Bulgaria, and Hungary, but it has been still increasing or not changing in Belgium, Spain, and Luxembourg relative to the baseline. Thus, the timing of mobility changes, although similar across the six countries, was more favorable in the lowest incidence countries, if assessed relative to the time of the first confirmed disease occurrence (Fig. 6).

Intriguingly, the overall stringency of containment measures, represented by the cCHI values, was remarkably similar in high-incidence Spain and low-incidence Hungary, when stringency was assessed based on calendar days (Fig. 7). Nevertheless, the overall stringency was still higher in Hungary than in Spain, when assessed based on the time from the beginning of the epidemic (Tab. 2).

Higher stringency of the containment measures adopted later in the course of epidemics could not fully compensate for delays in initial public health response to COVID-19

In Slovakia, Bulgaria, Hungary, and Spain, the CHI values exceeded 20 for the containment measures, which were in place on day 1 (Tab. 4). However, unlike SK, BG, and HU, whose CHI values raised above 60 on day 14, Spain displayed no further increase for the next 13 days and remained at the CHI~20. In contrast, Luxemburg and Belgium showed CHI<10 on day 1, and all the three highest prevalence European countries displayed CHI < 50 on day 14. Consequently, the lowest incidence countries differed not only with respect to the timing of their mobility changes relative to the days of the first disease occurrence, but also in the stringency of the containment and health measures reached at days 1 and 14 of their epidemics.

Eventually, the three highest prevalence countries adopted more stringent containment measures than two of the three lowest prevalence countries, in order to control their alarmingly growing epidemics. Nevertheless, this delayed ramping-up of the containment measures did not help to avoid high disease occurrences in Luxembourg, Belgium, and Spain during their first epidemic waves (Tab. 4).



Supplemental Fig. 15. Slovakia – Mobility (residential, groceries/pharmacies, workplaces, transportation, and recreation/retail from Apple and Google) and containment health index (CHI) over time. The time interval includes the first wave and a part of the second wave of the COVID-19 pandemic. Mobility substantially decreased during the first 3 weeks of the first wave, following the adoption of stringent containment. However, mobility increased thereafter, even though containment measures were not lifted. Mobility reached a maximum on April 8, 2020, which necessitated a further increase in containment stringency and enforcement, to address public non-compliance and reduce mobility again. In the second epidemic wave, high stringency was adopted between October 22 and November 15, 2020, but mobility was still increasing due to public non-compliance. This increase in mobility was associated with a dramatic increase in COVID-19 transmission.

Discussion

The pandemic of COVID-19 stressed the urgency of ongoing discussions in the field regarding the effect of non-pharmaceutical interventions (NPIs) on the spread of the epidemic disease. Various NPIs adopted in response to the past pandemics of respiratory viral diseases have reportedly demonstrated effectiveness, if used in their combinations, and if adopted with appropriate timing and duration, even though disease transmission tended to reoccur when the NPIs were later relaxed (18).

For instance, during the 1918–1919 influenza pandemic, the most commonly adopted NPIs in the USA involved a combination of school closures with public gathering bans, adopted for a median duration of 4 weeks. Early and sustained adoption of these NPIs was reportedly associated with decreased excess mortality rates from pneumonia and influenza, delayed time to peak mortality, and lower overall mortality (19). Although no single intervention showed association with improved outcome of the 1918–1919 pandemic influenza, early implementation of the multi-layered NPIs encompassing closure of schools, churches, and theatres, was associated with reduced peak mortality rates (18). More recently, the use of NPIs occurred in 2002–2003 during SARS (20, 21), and in 2009–2010 during the H1N1pmd09 influenza pandemics (22).

The effectiveness of the NPIs has been questioned within the scientific and professional community regarding the strength of existing evidence (23), but also by the general public, which is vulnerable to the COVID-19-related misinformation and conspiracy beliefs about the reasons behind the NPIs, and their alleged harm and inefficacy (24).

Our results indicate that a higher stringency of containment measures accumulated over days preceding the day of the first diagnosis of COVID-19 is associated with a lower cumulative incidence of confirmed cases over the epidemic wave. The same finding holds for cumulative stringency of containment measures adopted over the first 7 or more days of the epidemic. Our finding supports the effectiveness of early adopted and stringent containment measures in reducing the overall number of COVID-19 cases. This finding is consistent with expectations derived from the epidemiological theory, which posits that the reduction of person-to-person contact rates through containment measures leads to the reduction of reproduction number, which in turn results in a lower total number of infections, as well as a longer time to the peak daily incidence, and the lower peak of daily incidence (25).

Our study is subject to some potential limitations that need to be considered to allow an objective assessment of our results. Firstly, our estimation of the last days of the first pandemic waves in some countries was affected by the complexity of epidemic curves and their first and second-order derivatives. As a result, we may have underestimated the duration of the first epidemic waves and cumulative incidences in some countries, such as Sweden and Poland. Nevertheless, if we consider alternative durations of first epidemic waves of 137 days and 168 days for Sweden and Poland, respectively, our findings of associations between the cumulative stringency of containment and cumulative incidences would not change.

Secondly, cumulative pre-epidemic CHI values were not weighed with respect to their distance from day 1 of epidemics, which means that stringent measures adopted for a short time and lifted long before day 1 would count the same in the cCHI as stringent measures adopted closer to the day 1 and still in place at the beginning of epidemics. Indeed, the 28 European countries differed in (i) the length of pre-epidemic periods counted arbitrarily from the 1st January 2020 to the day preceding day1 of their epidemics, and (ii) times, when they adopted their first containment measures (Tab. 1). This in turn allowed individual countries to accumulate CHIs over different times. For example, France accumulated pre-epidemic CHIs over just 1 day, Finland over 2 days, and Belgium over 6 days, while Bulgaria and Slovakia accumulated pre-epidemic CHIs over 34 and 65 days, respectively. Nevertheless, we have not identified any country among considered 28 European countries that would adopt some containment measures in the pre-pandemic period after 1st January 2020 only transiently and lift them before day 1 of a epidemic. As a result, the potential bias in determining pre-epidemic cumulative CHIs is likely of limited influence.

Lastly, reduction of mobility was only considered relative to the baseline mobility in the same country at a specified time, which does not permit a comparison of absolute mobilities among different countries. For instance, the number of registered passenger cars in two countries with similar areas such as, Denmark and Estonia can be considerably different (2,329,580 vs 653,000 in 2014) (26) despite their similar geographic areas, which implies different absolute mobilities and different effect of the relative reduction of mobility expressed as percent of baseline values. This limitation does not affect comparison across countries with respect to times corresponding to changes in patterns of mobility.

Early adoption and stringent containment measures were previously found to be associated with a lower number of cases and deaths due to COVID-19. For instance, the implementation of restrictions on gatherings and public events in New Zealand when a number of daily cases was in single digits reduced the number of COVID-19 deaths by at least ten times relative to the number of deaths expected in the absence of stringent containment measures (27). Likewise, cities in China that pre-emptively suspended intra-city public transport and banned public gatherings and entertainment venues had in average 33.3 % fewer cases during the first weeks of their outbreaks, compared with cities that started control later (28). It should be also noted here that the Wuhan city shutdown and cordon sanitaire imposed on 23rd January 2020 was critical for the suppression of the epidemic in China, together with the NPIs adopted in other cities. This can be demonstrated by comparison of the number of cases in China outside Wuhan by day 50 of the epidemic (29,839 cases) and predicted estimates for the number of cases for the different scenarios: (i) without the cordon sanitaire around Wuhan but with the NPIs in other cities: 199,000 cases; (ii) with cordon sanitaire, but without the NPIs in other cities: 202,000 cases; and (iii) without any intervention: 744,000 cases (28).

The need for early adoption of containment measures was also demonstrated by Loewenthal et al who found a strong correlation between the time, at which containment measures were initiated and the number of deaths (29). Based on their results, a delay of 7.49 days in initiating containment measures would result in a twofold increase in the number of deaths. Interestingly, this study indicated that the response time was more important than its strictness.

Lastly, a multi-method study of the efficacy of individual NPIs implemented in March-April 2020 on 79 territories found that cancellation of small gatherings (closure of shops, restaurants, and gatherings of 50 persons or less), closure of educational institutions, and border restrictions were the most efficient in reducing effective reproduction number (Rt) when assessed by four different methods of analysis (30). Additionally, increased availability of personal protective equipment, individual movement restrictions, and national lockdowns were consistently identified as efficient. In contrast, the least effective interventions reportedly included tracing and tracking measures, enhanced capacity for testing and case detection, as well as border health checks and environmental cleaning (30).

Our finding of inverse correlation between cCHI values and cumulative incidences of COVID-19 is strengthened by controlling for population density. This is in line with previously reported finding that higher population density renders social distancing more difficult and that the effect of containment measures has been stronger in countries with lower population densities[27]. Further, our finding of a statistically significant and positive correlation between population density and cumulative incidence of COVID-19 across 28 European countries agrees with a previous report on greater rates of transmission of SARS-CoV-2 in the U.S. counties with greater population densities (31). On the other hand, our finding differs from the apparent lack of association between population density and the number of COVID-19 cases per 100,000 people across numerous global locations, which was reported by other investigators (32). This apparent lack of association, which was used as an argument to support numerous benefits of dense, mixed-use neighborhoods even in pandemic times, was likely caused by the third-variable effect of the containment stringency on the disease occurrence. As a result, hyper-dense metropolitan areas Singapore, Hong Kong, Tokyo, and Soul with stringent NPIs in place could still reach low cumulative incidences, despite their high population densities.

Following pre-publication of this study in the medRxiv preprint server (33), its conclusions have been supported by several published reports. For instance, Browne et al (34) developed a generalized SIR-type model for the case and mortality data from China between January 21 – March 19, 2020. Their results demonstrated that lockdowns significantly decreased final outbreak sizes, which were found to be inversely proportional to the population quarantine rates. In agreement with our findings, this study also demonstrated an importance of rapid implementation of lockdowns for outbreak containment, showing that a 2-week delay in a 95 % susceptible population would result in a 10-fold increase in final outbreak size. Furthermore, Browne et al. found that contact tracing was able to reduce the peak size of outbreaks, but this public health measure had a substantially lower impact on final outbreak size (34).

The protective effect of containment measures was also deonstrated by Pleninger et al (35) who used cantonal-level data for specific phases of the COVID-19 pandemic in Switzerland. These investigators showed that increases in the stringency of containment measures significantly reduced public mobility and the number of weekly infections in the population. In addition, Pleninger et al (35) identified business closures, recommendations to work from home, and restrictions on public gatherings as particularly effective containment measures in Switzerland (35). Similarly, Famiglietti et al (36) reported for the US states in the pre-vaccine period up to January 2021 that increasing stringency of containment by approximately one standard deviation of its variation across US states reduced COVID-19 deaths by approximately 75 % (36). Likewise, Xiu et al (37) determined that government policies directed at workplace closure, public transport closure, stay-at-home requirements, and restrictions on internal movement, international travel, and public gatherings were associated with a lower spread rate of COVID-19. These authors argued that school closures and cancellation of public events had no significant effects on reducing the COVID-19 spread (37). However, it should be noted that cancellation of public events and restrictions on gatherings do not represent truly independent variables. For this reason, finding a significant effect of the restriction on public gatherings argues against the reportedly non-significant effect of the cancellation of public events.

The importance of public events ban and school closure was supported by Li et al (38), who analysed the effect of NPIs on time-varying reproduction number (R_t) across 131 countries between 1 January and 20 July 2020. These investigators found a significantly decreased R_t on day 28, following the introduction of the public events ban, and a significantly increasing trend in R_t over time, following the relaxation of school closure, bans of public events, bans of gathering more than 10 people, requirements to stay at home, and internal movement restrictions (38).

On the other hand, several studies reported a limited efficacy or no benefit of containment measures. Hereby et al (39) performed a meta-analysis of 24 studies that analyzed the relative effect of lockdowns on COVID-19 mortality in geographically different areas. Seven of these studies examined the effect of the OxCGRT stringency index between March 16 and April 15, 2020, but only two of them were evaluated as higher-quality studies. These two studies found no evidence to support that mandated lockdowns in Europe and the United States reduced COVID-19 mortality (39). Moreover, 11 studies were found eligible for evaluation of the effect of shelter-in-place order, of which 4 studies were evaluated as higher quality studies. Unexpectedly, these 4 studies found on average a 3.7 % increase in COVID-19 mortality due to lockdown. This counterintuitive finding was interpreted as a possible unintended consequence of the isolation of infected persons at home, presumably causing the increased risk of infecting family members with higher viral load and causing more severe illness. We argue against this interpretation, which overemphasized the role of duration of within-household contacts and failed to appreciate the reduced number of extra-household contacts under shelter-in-place orders. In high-income nations, households represent limited opportunities for onward COVID-19 transmission, and during the first epidemic wave in Geneva (Switzerland), only less than a quarter of cases could be attributed to transmission among household members (40). It should be also noted that the results of this meta-analysis were significantly influenced by disputable criteria used for the evaluation of the quality of studies, for their inclusion in the metaanalysis.

Likewise, the study by Vickers et al (41), which analyzed data from Canadian provinces, found a minimal association between the stringency of containment and growth of COVID-19 cases in the first epidemic wave, and lack of association in the second epidemic wave. One possible explanation for discordance between the findings for the two waves can be lower compliance with public health measures, which was observed in subsequent epidemic waves across many countries. This non-compliance can project to an apparent lack of association between the stringency of containment and reduced disease transmission/occurrence, because containment stringency influences disease transmission through a decrease in mobility (16, 17). During the second wave of COVID-19 pandemic in Slovakia, we also observed an increasing mobility over time during a period of most stringent containment measures in place (Supplemental Fig. 15). This dissociation between the stringency of containment and mobility can be explained by a decreased compliance due to the loss of public trust in public health measures. Nevertheless, the authors argue that the reported lack of association between containment stringency and growth of COVID-19 in the second wave cannot be fully explained by changes in mobility.

Possible reasons for the discrepancy between the findings of Vickers et al (41) and our conclusions include methodological differences, such as different measures of disease transmission/disease burden and different modeling approaches. It should be also noted that their study was not likely to find a significance in the correlation between containment and disease frequency due to limited data size.

The resistance of governments to the early adoption of the NPIs stems mostly from their potential for negative economic and social consequences (42). Indeed, the COVID-19 pandemic has been considered by the World Trade Organization (WTO) and Organization for Economic Cooperation and Development (OECD) as the largest threat to the global economy since the global financial crisis of 2008–2009 (43). Nevertheless, the negative impact of NPIs on economic activity has been challenged. For instance, the recent study by Correia et al implied that economic disruptions during the 1918–1919 influenza pandemic in the USA were attributable to the impact of the pandemic rather than to the impact of the associated public health responses (12). Moreover, this study demonstrated that the US cities that responded earlier and more aggressively to the 1918–1919 pandemic did not experience worse economic disruptions than cities that adopted lenient NPIs later. In contrast, they reportedly tended to grow faster after the pandemic was over (12).

The resistance of government agencies towards the adoption of NPIs, or their re-adoption in the successive epidemic waves, can also reflect evolving public mistrust and unwillingness to comply with the NPIs, which can lead to overturning expert recommendations when pressed by public opinion (44). Therefore, the purpose of this study was to assess the effectiveness of containment measures to mitigate or suppress the spread of COVID-19 to inform the future responses to COVID-19. We can reasonably anticipate that some of these measures will be necessary in the future, at least locally, even if the effective and safe vaccines become available to general public (45–47). The appropriate NPIs will need to be adopted swiftly in locations where contact rates and vaccination coverages would allow disease transmission in the population.

Intriguingly, the top three countries with the lowest cumulative incidences of COVID-19 over the first epidemic waves received a relatively poor ranking among 195 countries by the Global Health Security Index (GHS) in the category "Rapid Response". The GHS Index evaluates the capabilities of 195 countries to prevent, detect, and rapidly respond to public health emergencies, and its "Rapid

Response" category specifically evaluates "rapid response to and mitigation of the spread of an epidemic" (48). The scores and ranks assigned to these countries were as follows: Hungary (score: 52.2 %, rank: 33), Slovakia (score: 34.1 %, rank: 105), and Bulgaria (score: 21.7 %, rank: 170). In contrast, two of the three countries with the highest cumulative incidences of COVID-19 were ranked more favourably by the GHS: Belgium (score: 47.35 %, rank: 53) and Spain (score: 61.9 %, rank: 15), while Luxembourg (score: 27.3 %, rank: 139) was not ranked as favourably as Belgium and Spain, but still better than Bulgaria. Our findings question the value of the GHS scoring at least in this context, which is consistent with the conclusion of other investigators, who found the poor predictive performance of the GHS scoring of the OECD countries in the context of COVID-19 pandemic (49, 50).

Conclusions

Our results support the effectiveness of non-pharmaceutical interventions, and specifically selected containment and health measures, in mitigation or suppression of COVID-19 epidemics. Early adoption of stringent containment measures, which lead to the high cumulative CHI values in pre-epidemic periods, together with ramping up of containment stringency during the early days of the epidemic, is associated with a lower cumulative incidence of COVID-19 cases. The late adoption of stringent containment measures does not fully compensate for the lack of early response.

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