Factors potentially influencing case fatality rate in different stages of the COVID-19 outbreak in Europe

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Abstract

Introduction: The aim of this study was to analyze the changes in COVID-19 case fatality rates (CFR) in time and to examine the link between CFR and country-specific indicators referring to quality of healthcare, population and epidemiology in different stages of the COVID-19 outbreak in 30 European countries (EU27 + Switzerland, Norway and United Kingdom).

Material and methods: We distinguished three 70-day time phases of the outbreak: 17 March–25 May; 1 June–9 August; 15 August–23 October 2020. The applied COVID-19 dataset was based on data maintained by OurWorldInData.org retrieved in November 2020. Spearman's rank correlation coefficient analysis was used to examine the link between CFR and country-specific indicators referring to population, epidemiology and quality of healthcare.

Results: COVID-19 CFR in analyzed European countries declined from mid-March to end-October. CFR phase 1 was positively correlated with COVID-19 mortality, daily cumulative index (DCI), urbanization and proportion of the population aged > 80; CFR phase 2 was positively correlated with COVID-19 mortality and DCI; CFR phase 3 was positively correlated with COVID-19 mortality, median age, poverty, prevalence of obesity, smoking and cardiovascular disease and negatively correlated with Healthcare Access and Quality Index, Health Care Index and gross domestic product per capita.

Conclusions: Results of our correlation analyses support the concept that the decline in CFR is real and, depending of the phase of the outbreak, different factors play a role. From the public health perspective, measures implemented to reduce the viral transmission, isolating the most vulnerable and improving the overall quality of the healthcare system are advisable.

Key words: case fatality rate, COVID-19, public health, quality of health care.

Introduction

The first confirmed case of SARS-CoV-2 infection in Europe was reported on the 24th of January, 2020 in Bordeaux, France [1]. As of 17th of March all countries within Europe had reported confirmed cases of SARS-CoV-2 infections and at least one death due to COVID-19. In an attempt to dampen viral spread many non-pharmaceutical interventions, such as physical distancing, border and school closures, isolating symptomatic individuals and large-scale lockdowns were introduced later on in March.

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There is consistent evidence that these interventions achieved measurable beneficial health outcomes [2, 3]. At the turn of May and June lockdowns were lifted in an attempt to slowly resume national economies. It was speculated that constraint easing would result in an increase of infection rates and a second wave of the pandemic was expected in fall 2020 [4]. Based on these facts, the transmission of SARS-CoV-2 in Europe can be divided into three phases: phase 1, when policy packages were employed to reduce the rate of transmission, phase 2, when lockdowns were lifted, and phase 3, when the second wave of the pandemic was observed.

European countries showed wide disparities in indicators that might have potentially influenced COVID-19 fatality. The proportion of elderly people tended to be higher in the southern countries, with the highest percentages registered in 2019 in Italy (7.17%) and Greece (7.09%). In contrast, Slovakia (3.29%), Ireland (3.34%) and Cyprus (3.7%) registered the lowest proportions of elderly people in their population [5]. In the group of 27 European Union (EU) countries plus the United Kingdom, Norway and Switzerland, prevalence of smoking varied from 12.4% in Sweden to 36.2% in Greece [6], prevalence of obesity is lowest in Switzerland (19.5%) and highest in Malta (28.9%) and the United Kingdom (28%) [7]. The highest prevalence of cardiovascular diseases (CVD) was observed in Bulgaria (14,234 per 100,000), Croatia (13,691 per 100,000) and Lithuania (13,238 per 100,000), and the lowest value in Ireland (5,445 per 100,000) [8]. Health care quality and terms of the Healthcare Access and Quality (HAQ) Index was highest in the Netherlands (97), Luxembourg, Switzerland and Latvia (96) and lowest in Bulgaria (77) and Portugal (78) [9]. In terms of the Health Care Index (HCI) the quality of healthcare varies between 48 in Hungary and 79 in Austria, Belgium and Denmark [10].

The aim of this study was to analyze the changes in COVID-19 case fatality rates (CFR) in time and to examine the link between CFR and country-specific indicators referring to quality of healthcare, population and epidemiology in three different stages of the COVID-19 outbreak in 30 European countries (EU27 + Switzerland, Norway and United Kingdom).

Material and methods

Thirty European countries (EU27 + Switzerland, Norway and United Kingdom) were included in the analysis. The COVID-19 dataset is a collection of the COVID-19 data maintained by OurWorldInData.org [11]. It is updated daily and includes data on confirmed cases and deaths retrieved from the European Centre for Disease Prevention and Control (ECDC) and national government reports.

Country-specific variables of potential interest referring to population, epidemiology and quality of healthcare are listed in Table I. To assess healthcare access and quality two indicators were chosen: the HAQ Index and the HCI. The HAQ Index enables cross-national comparison of amenable mortality rates. It encompasses 32 causes of death considered to be avoidable, provided that quality healthcare is available. The HAQ Index is scaled from 0 to 100 – lower scores indicate high mortality rates for causes amenable to health care. HCI is an estimation of the overall quality of the health care system, including health care professionals, infrastructure, equipment, cost and government readiness.

Data from three 70-day time periods were analyzed: phase 1 (March 17th to May 25th, 2020), phase 2 (June 1st to August 9th, 2020) and phase 3 (August 15th to October 23rd, 2020).

For each country COVID-19 CFR phase 1, CFR phase 2 and CFR phase 3 were calculated assuming a 13-day time lag between case and death occurrence [12, 13]. Due to data not meeting the assumption of a Gaussian distribution or given in an ordinal scale, Spearman's rank correlation coefficient (SRCC) analysis was used to examine the link between CFR and country-specific indicators referring to population, epidemiology and quality of healthcare. A significance level of $p < 0.05$ was applied (2-tailed tests).

CFR, defined as the proportion of cases of a specified condition that are fatal within a specified time, received widespread attention as one of the key epidemiologic indicators used during outbreaks to measure severity of the disease, epidemic impact, effectiveness of treatment and various policy packages. As the CFR value is partly driven by a choice of time lag from reporting to death, we considered the sensitivity of our estimates to other assumed time lags: 20 days [14] and 0 days (crude CFR). Excel 2016 was used to record, calculate and analyze the data and draw figures.

Results

COVID-19 CFR phase 1, CFR phase 2 and CFR phase 3 in individual countries are presented in Table II. In all analyzed countries CFR phase 2 was considerably lower than CFR phase 1, with a median reduction of 0.75. In absolute values this reduction was most evident in countries with the highest CFR phase 1: Belgium, France, the Netherlands, Sweden, Spain and the United Kingdom. CFR continued downwards between phases 2 and 3 in 24 countries, with a median reduction of 0.5. Bulgaria, the Czech Republic, Estonia, Luxembourg, Malta and Slovakia, after an apparent reduction in CFR between phases 1 and 2, presented a slight CFR increase between phases 2 and 3.

Table I. Country-specific parameters referring to population, epidemiology and quality of healthcare and sources of data

Parameter	Source of data
Daily confirmations of COVID-19 cases and deaths in 2020	COVID-19 data, accessed 5 November 2020: https://www.ecdc.europa.eu/en/publications-data/download-todays-data-geographic-distribution-covid-19-cases-worldwide
Population in 2020, median age, proportion of urban population	Worldometer. European Countries by population, Accessed 5 November 2020: https://www.worldometers.info/population/countries-in-europe-by-population/
Proportion of the population aged 80 and older, most recent year available	Ageing Europe – statistics on population developments, accessed 18 November 2020: https://ec.europa.eu/eurostat/statistics-explained/index.php/Ageing_Europe_-_statistics_on_population_developments
Prevalence of cardiovascular diseases in 2017	European Cardiovascular Disease Statistics, accessed 18 November 2020: http://www.ehnheart.org/cvd-statistics/cvd-statistics-2017.html
Prevalence of smoking in adults aged 15 and above in 2020	Age-standardized prevalence of current tobacco smoking, age 15+, WHO estimates, accessed 18 November 2020: https://gateway.euro.who.int/en/indicators/hfa_622-3013-age-standardized-prevalence-of-current-tobacco-smoking-among-people-aged-15-years-and-over-who-estimates/
Prevalence of obesity (BMI > 30 kg/m²) among adults in 2020	Prevalence of obesity among adults World Health Organization (WHO), Global Health Observatory, accessed 18 November 2020: https://apps.who.int/gho/data/node.main.A900A?lang=en
Healthcare Access and Quality Index (HAQ Index) in 2016	GBD 2016 Healthcare Access and Quality Collaborators. Measuring performance on the Healthcare Access and Quality Index for 195 countries and territories and selected subnational locations: a systematic analysis from the Global Burden of Disease Study 2016. Lancet 2018; 391: 2236-71
Health Care Index (HCI) in 2020	Europe: Health Care Index by Country, accessed 5 November 2020: https://www.numbeo.com/health-care/rankings_by_country.jsp?title=2020&region=150
Gross domestic product (GDP) per capita at purchasing power parity (constant 2011 international dollars), most recent year available	World Bank – World Development Indicators, source from World Bank, International Comparison program database, accessed 18 November 2020: https://www.worldbank.org/en/programs/icp
Proportion of the population living in extreme poverty, most recent year available	Roser M, Ortiz-Ospina E. Global Extreme Poverty. Published online at OurWorldInData.org. Accessed 11 November 2020: https://ourworldindata.org/extreme-poverty

The reduction in CFR between phases 1 and 2 was accompanied by a reduction in incidence and mortality in almost all countries, while the reduction in CFR between phases 2 and 3 was accompanied by a considerable increase in incidence and increase in mortality (Figures 1 and 2). An alternative lag time from reporting to death resulted in a decline in CFR values in almost all countries (Table II).

Table III presents the results of correlation analyses. Statistically significant positive correlations were found between: CFR phase 1 and COVID-19 mortality, daily cumulative index (DCI), urbanization and proportion of the population aged > 80; CFR phase 2 and COVID-19 mortality and DCI; CFR phase 3 and COVID-19 mortality, prevalence of obesity, smoking and cardiovascular disease (CVD), median age and poverty. A statistically significant negative correlation was found only between CFR phase 3 and HAQ Index, HCI and gross domestic product (GDP) per capita. An alternative case-to-death time lag yields similar results (Table III, Figures 3–5).

Discussion

The results of our correlation analyses support the concept of a decline of COVID-19 CFR with time and are in line with previously published studies in different regions of the world [15, 16]. What sets our study apart is that it assesses the link between CFR in three different phases of the outbreak and various parameters related to epidemiology and healthcare resources' availability. This provides better understanding of the COVID-19 pandemic from a public health perspective. Due to the lack of reliable data, not all potential factors influencing CFR in time were included in the analysis, e.g. the change in the infected populations' age structure, the change in the populations' immunity or the evolution towards reduced virulence. However, our correlation analysis findings support the conclusion that the decline in CFR is real and, depending on the phase of the outbreak, different factors play a role. From the public health perspective, it is important to emphasize that implementing measures to reduce the transmission,

Table II. COVID-19 70-day CFR in individual countries in phases 1, 2 and 3. CFR was calculated by using a 13-, 20- and 0-day lag time from reporting to death

Country	CFR (adjusted for 13-day time lag)			CFR (adjusted for 20-day time lag)			Crude CFR (adjusted for 0-day time lag)		
	Phase 1	Phase 2	Phase 3	Phase 1	Phase 2	Phase 3	Phase 1	Phase 2	Phase 3
Austria	3.7	0.9	0.7	2.9	0.7	1.0	4.1	1.0	0.5
Belgium	15.0	1.6	0.7	12.2	1.5	1.0	16.5	2.3	0.4
Bulgaria	5.8	3.0	3.2	5.5	3.0	4.0	5.4	2.8	2.8
Croatia	4.4	1.7	1.5	4.0	1.9	1.9	4.5	1.6	1.0
Cyprus	1.3	0.7	0.2	0.9	0.3	0.4	1.9	0.7	0.3
Czech Republic	3.5	0.8	1.3	3.0	0.8	1.6	3.7	0.8	0.7
Denmark	4.8	0.8	0.4	3.8	0.7	0.4	5.4	1.6	0.3
Estonia	3.7	0.0	0.4	3.0	0.2	0.5	3.9	0.0	0.4
Finland	4.8	1.1	0.3	4.6	1.0	0.4	4.9	1.6	0.3
France	18.9	2.2	0.7	15.0	1.8	1.0	20.4	3.3	0.5
Germany	4.6	1.3	0.6	4.1	1.1	0.9	4.8	2.0	0.4
Greece	5.4	1.7	1.7	4.1	1.8	2.1	6.6	1.4	1.5
Hungary	13.5	6.1	2.3	13.1	4.9	2.9	13.2	9.8	1.5
Ireland	6.5	4.2	0.4	6.1	3.6	0.5	6.6	7.4	0.4
Italy	11.2	5.9	1.4	8.7	4.3	2.1	15.2	10.5	0.8
Latvia	2.3	2.0	1.2	2.4	1.4	1.6	2.2	3.6	0.6
Lithuania	3.7	1.3	1.1	3.5	1.3	1.5	3.9	2.0	0.7
Luxembourg	2.3	0.4	0.6	1.9	0.4	0.9	2.8	0.3	0.4
Malta	1.3	0.0	1.2	1.3	0.2	1.4	1.0	0.0	1.0
Netherlands	11.7	1.0	0.5	9.5	0.8	0.7	13.2	1.7	0.4
Norway	3.0	1.7	0.2	2.5	1.5	0.3	3.2	1.9	0.3
Poland	5.0	2.3	2.0	4.8	2.1	2.7	4.7	2.7	1.4
Portugal	4.2	1.3	1.2	3.7	1.3	1.5	4.3	1.7	0.8
Romania	6.8	3.7	2.6	6.4	3.8	2.7	6.6	3.4	2.5
Slovakia	2.0	0.4	0.5	2.0	0.4	0.7	2.0	0.3	0.3
Slovenia	7.9	1.9	0.8	6.5	1.9	1.1	8.7	1.6	0.3
Spain	9.2	2.1	1.1	6.6	0.6	1.2	12.0	1.8	0.9
Sweden	13.1	1.7	0.6	12.1	1.2	0.8	13.1	2.8	0.5
Switzerland	4.9	0.7	0.6	3.9	0.7	1.0	5.7	1.0	0.3
United Kingdom	14.7	3.7	0.9	13.2	2.8	1.2	14.9	7.1	0.6

isolating the most vulnerable and improving the overall healthcare system quality are advisable.

Assuming that CFR was always low (though reported higher in the initial phase of the pandemic, probably due to insufficient testing and contact tracing), we should expect that policy packages employed to reduce the rate of transmission would turn out to be futile. Elimination models implying contact tracing and isolation have shown that even if 100% of contacts were traced, the probability of controlling a simulated outbreak would only amount to approximately 30%, given that 10% of cases are asymptomatic and 30% of transmissions occur before the onset of symp-

toms [17]. In fact, the reduction in CFR between phases 1 and 2 (Table II) was accompanied by a decrease in both incidence and mortality, which may indicate that policy packages which were launched to reduce the rate of transmission were effective. Therefore, testing bias does not appear to make a major contribution to the falling trend in CFR between phases 1 and 2.

The positive correlation between CFR and the proportion of the population aged > 80 observed in phase 1 (Table III) suggests that the elderly are more vulnerable to our results show that COVID-19 and presumably died during the first wave of the outbreak, especially in countries with a high infec-
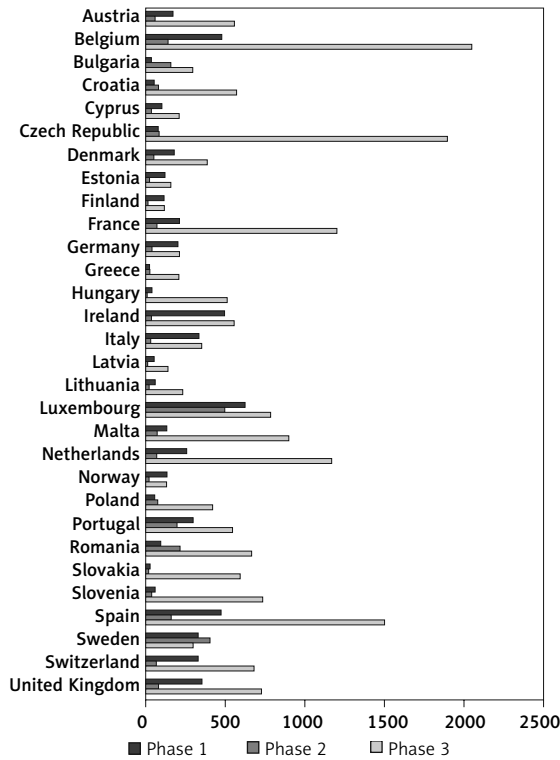
Figure 1. COVID-19 incidence (cases per 100,000) in 30 European countries in phases 1, 2 and 3
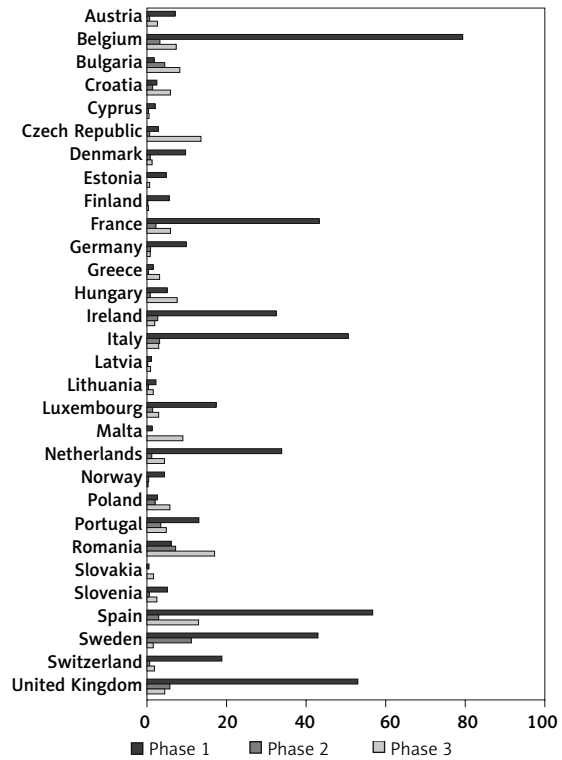

Figure 2. COVID-19 mortality (deaths per 100,000) in 30 European countries in phases 1, 2 and 3

tion rate. Hence, the most plausible explanation for the decrease of CFR between phases 1 and 2 might be a phenomenon known as the harvesting effect [18, 19]. Furthermore, in the early stage of the pandemic CFR was positively correlated with urbanization. This is in line with our knowledge about the spread of the virus and supports implementing measures to reduce further transmission (e.g. physical distancing) [20, 21]. A positive correlation between CFR and DCI in phases 1 and 2 is justifiable when considering DCI as an indirect indicator of healthcare burden leading to worse patient outcomes in the COVID-19 outbreak [22, 23].

A relaxation of lockdowns and people's precautionary behaviors resulted in an increase in reported cases and deaths across Europe. The decrease of CFR phase 3 might indicate a decline in the severity of the COVID-19 pandemic. A number of explanations are possible: reduced virulence of the SARS-CoV-2 virus, change in the age structure of the infected population, increased testing (i.e. detecting more mild or asymptomatic infections), medical staff experience in treating COVID patients. The latter is in line with our correlation analysis results. It is important to emphasize that CFR was negatively correlated with HAQ Index, HCI and GDP and positively correlated with poverty (Table III) only in phase 3. Given the surge of cases during the second wave of the outbreak, these correlations may indicate that the over-

all quality of the healthcare system (including professionals, infrastructure, equipment, budget and government readiness) plays an important role in the fight against the pandemic. Our analysis demonstrates that central Europe handled the first wave of the pandemic better than more developed economies of southern and western Europe. The second wave, however, seems less favorable, as the caseload may present a greater challenge to the poorly funded and often understaffed healthcare systems in central European countries. The fact that CFR phase 3 was positively correlated with median age, obesity, smoking and CVD prevalence (Table III) confirms that mortality due to COVID-19 is still strongly dependent on the presence of abovementioned risk factors [24–28].

The results should be interpreted in light of the knowledge about data-driven biases affecting CFRs. Numbers of confirmed cases and deaths might not be comparable across countries because of different definitions, different testing policies and reporting delays. These data-related issues might lead to over- or underestimation of CFRs throughout the epidemic. Adjusting CFRs for all of these potential biases is currently challenging. Nevertheless, we tried to minimize potential bias by analyzing countries from one geographical and economical region and by testing the impact of different symptoms-to-death time lag between the CFR values and correlation analysis results. Correlation analysis allows a concise

Table III. Correlations between CFR and country-specific indicators referring to population, epidemiology and quality of healthcare

Parameter	Case-to death time lag [days]	CFR phase 1 SRCC (p)	CFR phase 2 SRCC (p)	CFR phase 3 SRCC (p)
COVID-19 mortality	13	0.68 (0.0000)	0.61 (0.0003)	0.74 (0.000)
	0	0.72 (0.0000)	0.67 (0.0001)	0.71 (0.000)
	20	0.65 (0.0001)	0.53(0.0026)	0.72 (0.000)
DCI	13	0.66 (0.0001)	0.41 (0.0237)	0.26 (0.1578)
	0	0.69 (0.0000)	0.43 (0.0170)	0.20 (0.2993)
	20	0.65 (0.0001)	0.29 (0.1184)	0.25 (0.1830)
Proportion of urban population	13	0.40 (0.0288)	0.08 (0.6765)	-0.02 (0.9191)
	0	0.38 (0.0407)	0.20 (0.2925)	-0.06 (0.7445)
	20	0.39 (0.0321)	0.01 (0.9600)	-0.06 (0.7605)
Proportion of population aged > 80 years	13	0.39 (0.0000)	0.25 (0.1885)	0.23 (0.2143)
	0	0.45 (0.0130)	0.28 (0.1311)	0.24 (0.2055)
	20	0.38 (0.0360)	0.22 (0.2454)	0.22 (0.2376)
Median age	13	0.12 (0.5371)	0.19 (0.3197)	0.54 (0.0021)
	0	0.17 (0.3553)	0.11 (0.5710)	0.50 (0.0047)
	20	0.13 (0.4989)	0.19 (0.3145)	0.53 (0.0025)
Prevalence of obesity	13	-0.06 (0.7383)	0.29 (0.1234)	0.44 (0.0147)
	0	-0.15 (0.4290)	0.23 (0.2226)	0.53 (0.0029)
	20	-0.01 (0.9618)	0.27 (0.1517)	0.42 (0.0205)
Prevalence of smoking	13	-0.05 (0.7383)	0.13 (0.4802)	0.43 (0.0185)
	0	-0.07 (0.4290)	0.05 (0.7900)	0.42 (0.0197)
	20	-0.03 (0.8923)	0.14 (0.4584)	0.43 (0.0172)
Prevalence of CVD	13	0.03 (0.8711)	0.27 (0.1415)	0.60 (0.0004)
	0	-0.03 (0.8914)	0.20 (0.3001)	0.51 (0.0039)
	20	0.09 (0.6274)	0.39 (0.0346)	0.59 (0.0006)
HAQ Index	13	0.13 (0.4953)	-0.18 (0.3432)	-0.40 (0.0307)
	0	0.15 (0.4379)	-0.09 (0.6397)	-0.47 (0.0096)
	20	0.10 (0.6172)	-0.27 (0.1457)	-0.39 (0.0325)
HCI	13	0.14 (0.4600)	-0.34 (0.0636)	-0.37 (0.0444)
	0	0.19 (0.3082)	-0.21 (0.2699)	-0.33 (0.0764)
	20	0.11 (0.5775)	-0.41 (0.0228)	-0.39 (0.0313)
GDP per capita	13	0.05 (0.8018)	-0.28 (0.1351)	-0.71 (0.000)
	0	0.10 (0.5832)	-0.11 (0.5528)	-0.69 (0.000)
	20	0.01 (0.9693)	-0.34 (0.0682)	-0.71 (0.000)
Poverty	13	0.02 (0.9324)	0.3 (0.1068)	0.49 (0.0065)
	0	0.02 (0.8983)	0.24 (0.2059)	0.54 (0.0019)
	20	0.00 (1.0000)	0.26 (0.1670)	0.47 (0.0063)

DCI – daily cumulative index, SRCC – Spearman's rank correlation coefficient, CVD – cardiovascular disease, HAQ Index – Healthcare Access and Quality Index, HCI – Health Care Index, GDP – gross domestic product.

and clear summary of the relationship between two variables. However, it should be remembered that these relationships are to be interpreted as associations, not causal relationships.

In conclusion, our results show that COVID-19 CFR in 30 European countries declined from mid-March to end-October and support the hypothesis that this downward trend reflects a real change in case fatality rather than being an illusion caused by limitations attributable to the quality of data available at the time of analysis. It is important to emphasize that, depending on the phase of the outbreak, different factors play a role.

Acknowledgments

Conflict of interest

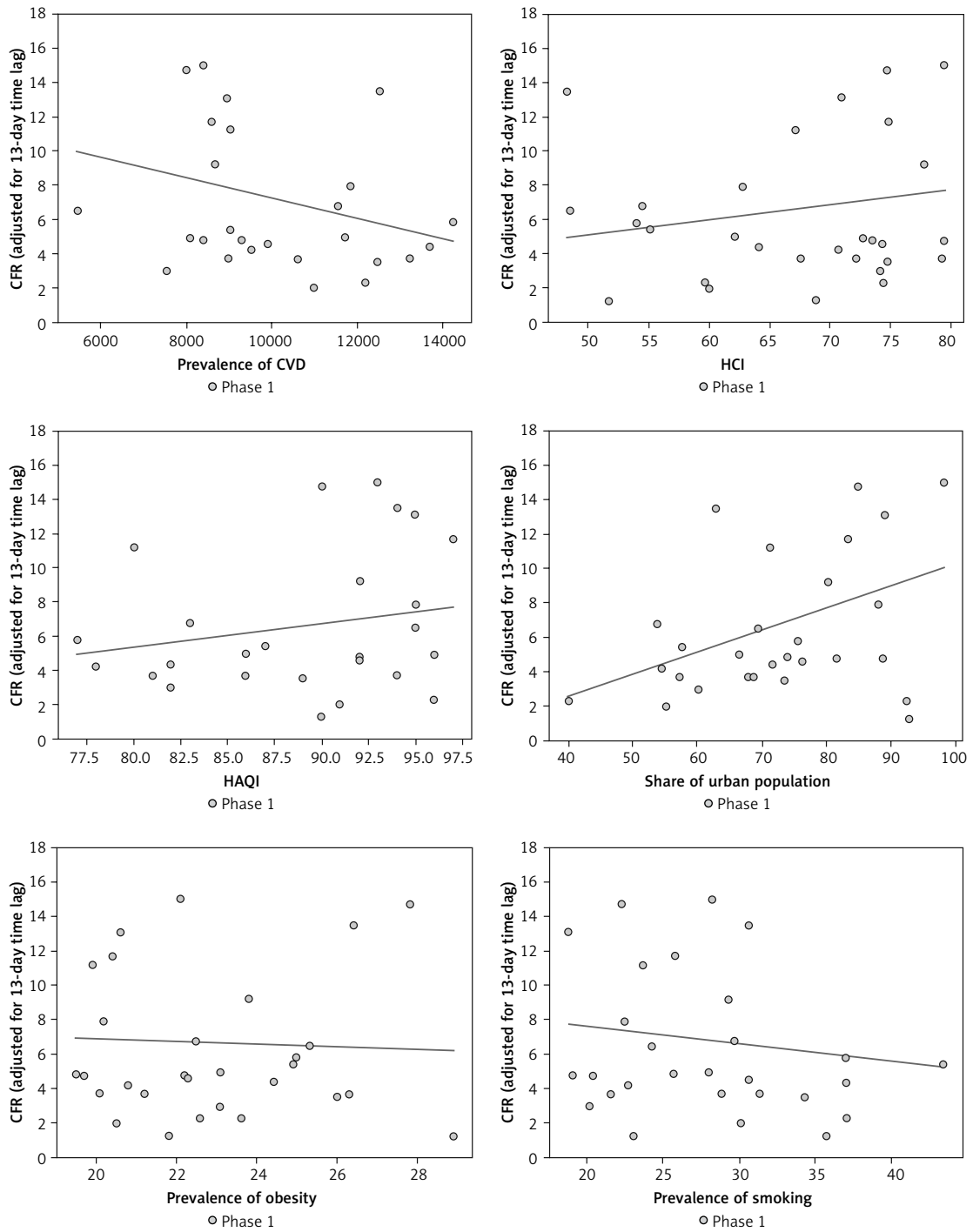The authors declare no conflict of interest.

Figure 3. Correlation between CFR and country-specific indicators referring to population, epidemiology and quality of healthcare in phase 1

CFR – COVID-19 case-fatality rate, CVD – cardiovascular diseases, DCI – daily cumulative index, HAQ Index – Healthcare Access and Quality Index, HCI – Health Care Index, GDP – gross domestic product.
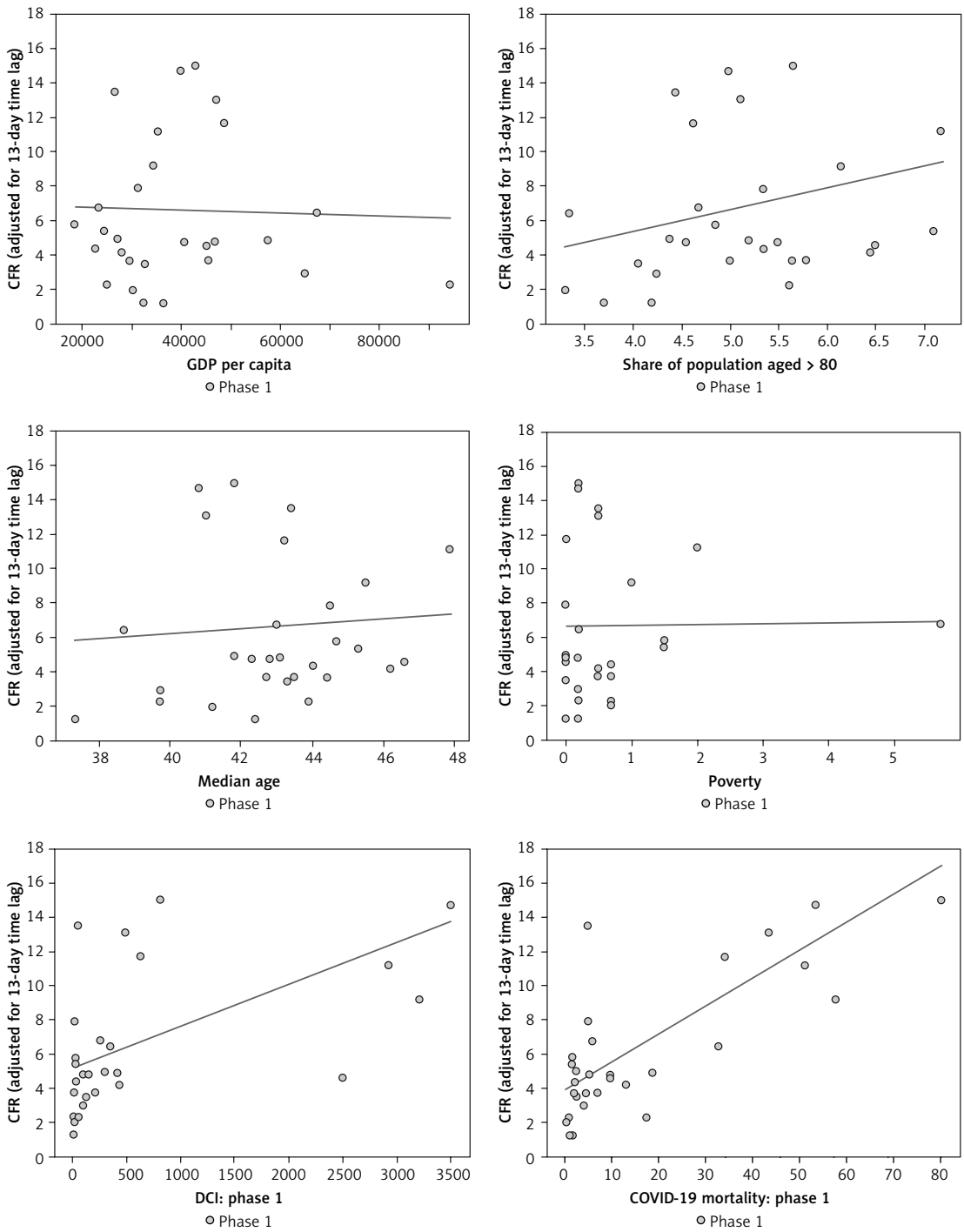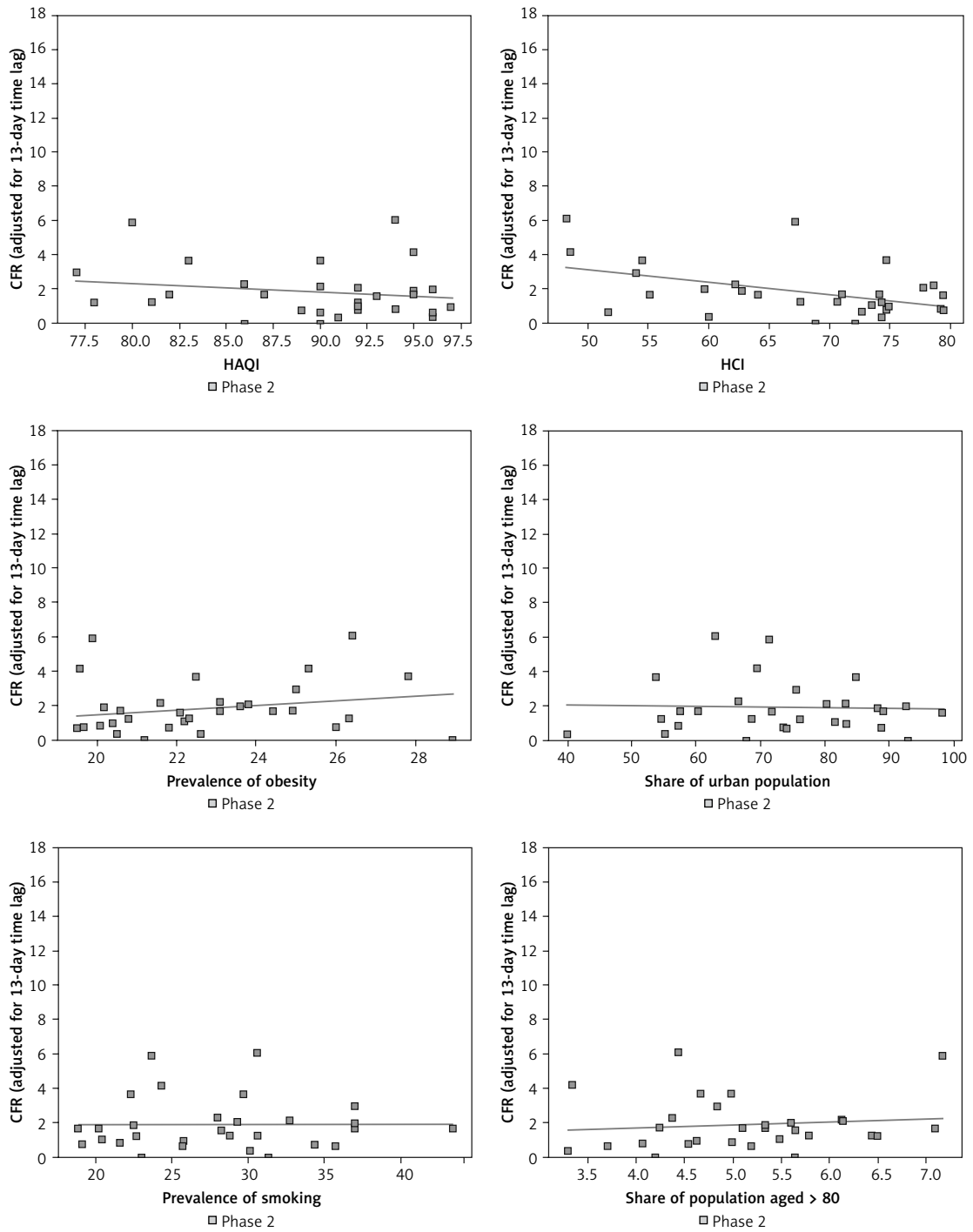
Figure 3. Cont.

CFR – COVID-19 case-fatality rate, CVD – cardiovascular diseases, DCI – daily cumulative index, HAQ Index – Healthcare Access and Quality Index, HCI – Health Care Index, GDP – gross domestic product.
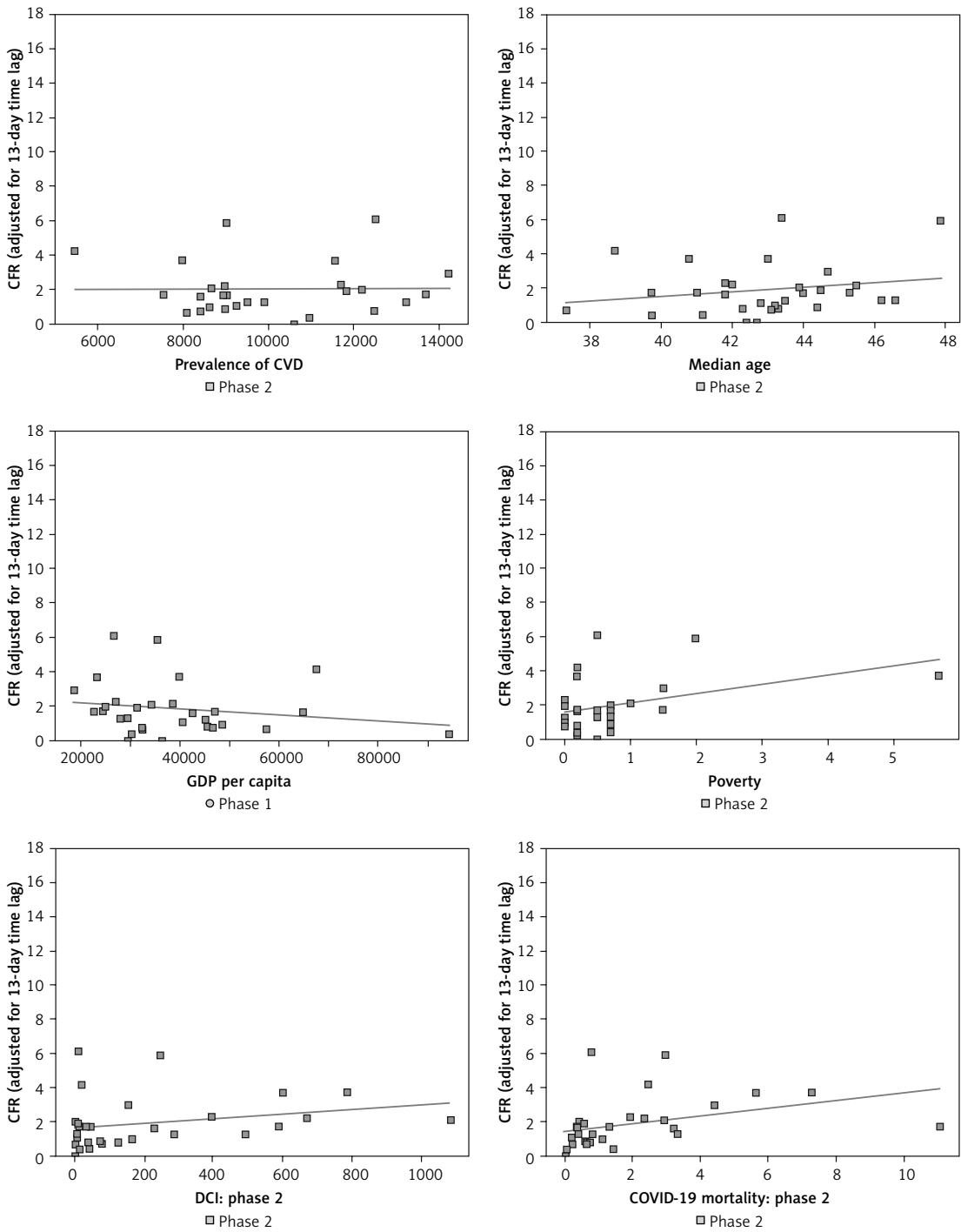
Figure 4. Correlation between CFR and country-specific indicators referring to population, epidemiology and quality of healthcare in phase 2

CFR – COVID-19 case-fatality rate, CVD – cardiovascular diseases, DCI – Daily Cumulative Index, HAQ Index – Healthcare Access and Quality Index, HCI – Health Care Index, GDP – gross domestic product.

Figure 4. Cont.

CFR – COVID-19 case-fatality rate, CVD – cardiovascular diseases, DCI – Daily Cumulative Index, HAQ Index – Healthcare Access and Quality Index, HCI – Health Care Index, GDP – gross domestic product.
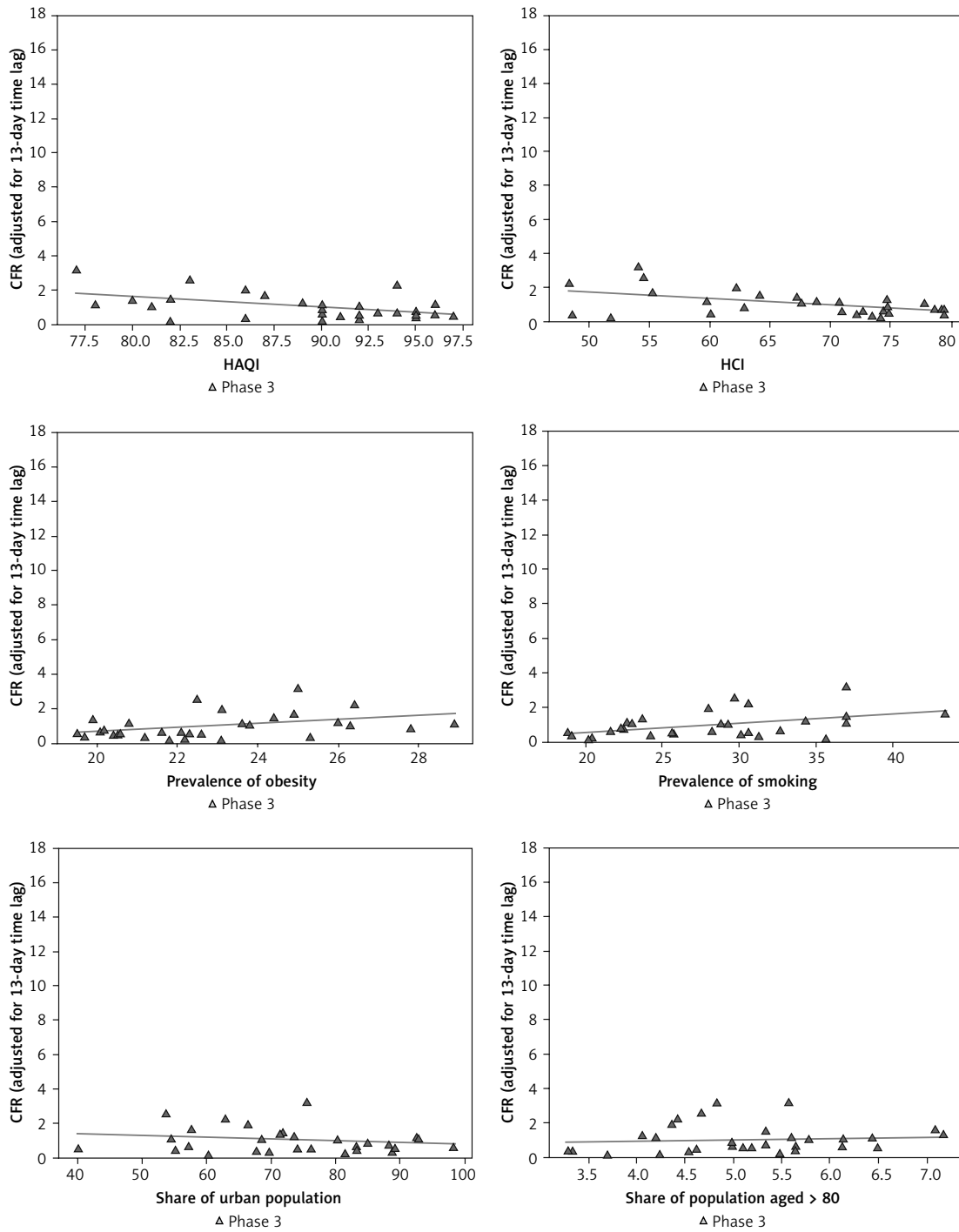
Figure 5. Correlation between CFR and country-specific indicators referring to population, epidemiology and quality of healthcare in phase 3

CFR – COVID-19 case-fatality rate, CVD – cardiovascular diseases, DCI – daily cumulative index, HAQ Index – Healthcare Access and Quality Index, HCI – Health Care Index, GDP – gross domestic product.
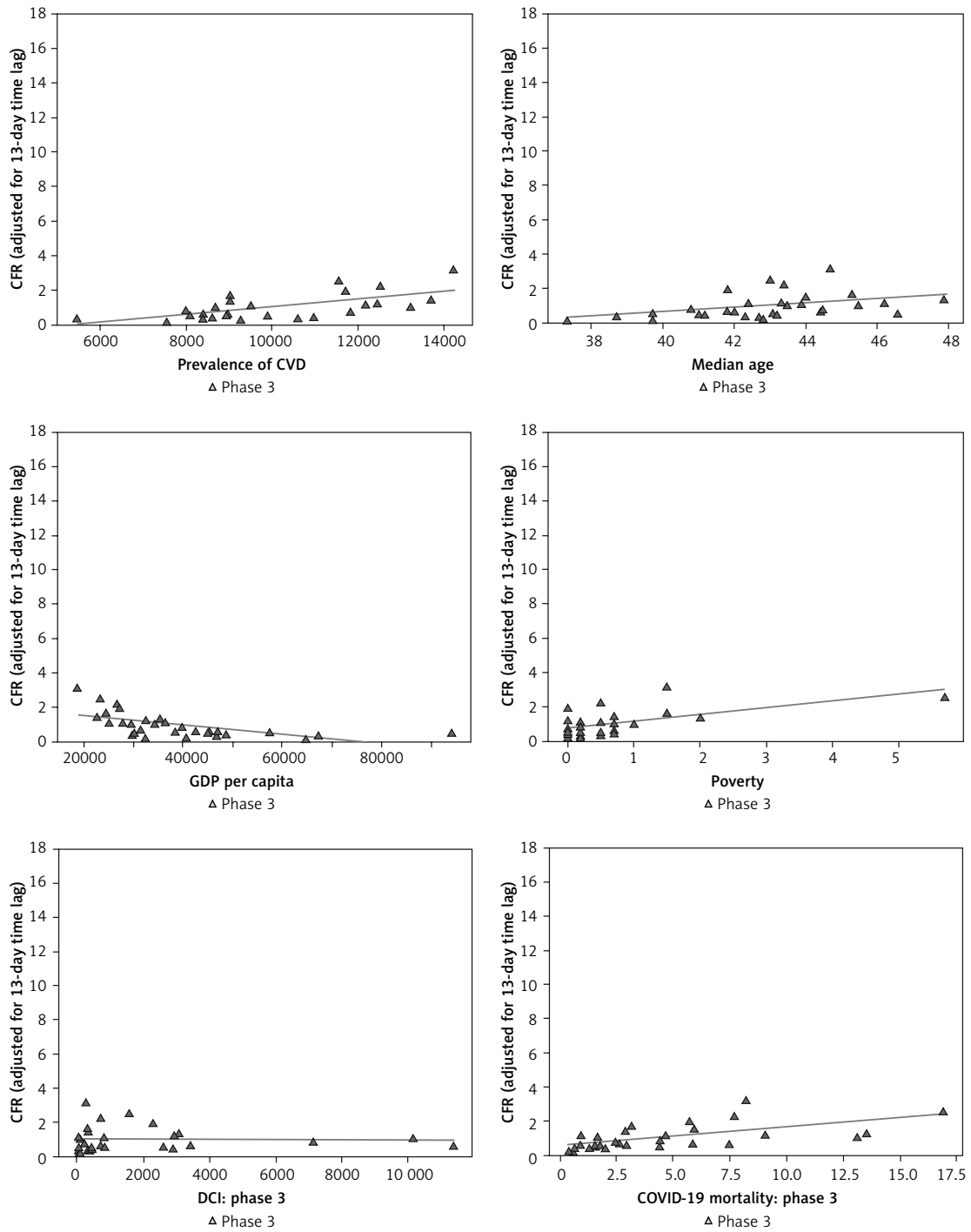
Figure 5. Cont.

CFR – COVID-19 case-fatality rate, CVD – cardiovascular diseases, DCI – daily cumulative index, HAQ Index – Healthcare Access and Quality Index, HCI – Health Care Index, GDP – gross domestic product.

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