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Title:

The collateral damage of COVID-19 on cardiovascular services: a meta-analysis

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Abbreviations

ACHD: adult congenital heart disease

ACS: acute coronary syndrome

AF: atrial fibrillation

CABG: coronary artery bypass graft

CIED: cardiac implantable electrical device

COVID-19: coronavirus 2019

CT: computer tomography

CV: cardiovascular

D2B: door-to-balloon time

ECG: electrocardiogram

ESC: European Society of Cardiology

HF: heart failure

HIC: high income country

ICD: implantable cardioverter defibrillator

IE: infective endocarditis

IRR: incidence rate ratio

LMIC: low-middle income country

NSTEMI: non-ST-segment elevation myocardial infarction

OHCA: out-of-hospital cardiac arrest

PCI: percutaneous coronary intervention

PPCI: Primary PCI

RR: risk ratio

S-FMC: symptom to first medical contact

STEMI: ST-segment elevation myocardial infarction

TAVI: transcatheter aortic valve implantation

UA: unstable angina

UK: United Kingdom

USA: United States of America

VA: ventricular arrhythmia

WHO: World Health Organization

WMD: weighted mean difference

Introduction

During the coronavirus 2019 (henceforth referred to as 'COVID-19') pandemic reports described fewer hospitalisations, procedures, and consultations for non-COVID-19 cardiovascular (CV) diseases.[1-3] After a short period of 'recovery' the emergence and rapid spread of the Omicron variant triggered the re-introduction of 'lockdown' restrictions;[4, 5] portending a future of preparing for and coping with waves of the contagion.

Previous systematic reviews of the impact of the COVID-19 pandemic on CV services have provided an incomplete overview. Some studies focussed on hospitalisations,[6, 7] others were restricted to specific conditions,[8-16] and one investigated only a specific outcome.[17] Only one report has considered the impact of the pandemic across different geographic territories, and was limited to one CV care pathway.[9] None have considered whether the effect of the pandemic on CV services has varied over time. A quantitative understanding of the global impact of the COVID-19 pandemic on the breadth of CV services and health of individuals with CV disease could facilitate better preparation for future waves.

We therefore provide a systematic review of the literature with meta-analysis to quantify the effects of the pandemic on cardiovascular services in terms of access, treatment and outcomes. We investigate for variation across CV conditions, geographic region, country income classification, and the time-course of the pandemic. Finally, we consider how to better manage CV services to minimise collateral cardiovascular damage.

Methods

We searched the Medline and Embase databases through the Ovid platform from 1 January 2019 through 15 December 2021 (because the earliest case was diagnosed in Wuhan, China in November 2019) for studies that reported a comparison of hospitalisations, diagnostic and interventional procedures, outpatient and community consultations, and mortality. The full search strategy is available in Supplementary material (S1). We defined CV services as healthcare services provided by any CV practitioner (cardiologist, cardiac surgeon, cardiac physiologist, cardiac nurse or trainee) relating to CV diseases specified in the ESC Textbook of Cardiovascular Medicine.[18] We excluded CV diseases where care would primarily be overseen by other medical and surgical specialities - venous thromboembolism and peripheral vascular diseases (including aortic, peripheral arterial and cerebrovascular disease) – which have been summarised elsewhere.[6, 19] This review was registered on PROSPERO (CRD42021265930) and informed by the PRISMA statement (Table S63).[20] The risk of bias for each report for each outcome were assessed using the ROBINS-I tool.[21] Reports with critical risk of bias were excluded.

We undertook quantitative syntheses of cohort studies that compared the COVID-19 pandemic period and a pre-pandemic period (all definitions in Supplementary material S1). Meta-analysis was performed to synthesize observational data for binary and continuous outcomes. Incidence rate ratios (IRR - a comparison of incidence rates during each period) and risk ratios (RR - a ratio of the probability of an event occurring in the intervention compared to the probability of the event occurring in the control, where each event is independent) were used for binary outcomes and counts data; weighted mean differences (WMD) were used for continuous outcomes measured with the same scale. The DerSimonian and Laird random effects models were fitted in all analyses because of the variation amongst

studies in population, intervention, comparator, timing and setting.[22] Funnel plots and Egger's test were used to assess publication bias.[23] Heterogeneity scores were measured by I^2 statistic and Cochran's Q test, with 40% or $p < 0.10$ respectively indicative of substantial heterogeneity.[24] Where quantitative synthesis could not be undertaken we have provided a narrative synthesis.

To explore for differences in effect of the pandemic across geographic boundaries, country wealth, and time-course we performed meta-regression by geographic region, country-level income and wave of pandemic covered by each report. Geographic regions were defined as Europe, North America and other countries, and country-level income as high income (HIC) versus low-middle income (LMIC) using the World Bank classification of income.[25] We also investigated for sources of heterogeneity by meta-regression of a range of study characteristics: sample size, data source, duration of study period during the pandemic, presence or absence of matched comparator periods, study definition of pandemic period, and whether or not patients with co-existent COVID-19 diagnosis were included. Detailed methods are available in Supplementary material (S2).

Results

We identified 4613 unique records, reviewed 497 full-text reports and included 189 studies; 158 of which were used in quantitative synthesis (Supplementary material S4, Table S38-S61). Figure 1 shows the PRISMA flow diagram. In total 49 countries were covered across six continents. There was geographic and economic disparity in the number of available studies; the majority were from Europe (n = 111, 59%; of which United Kingdom (UK) n = 25, 13% and Italy n = 21, 11%) and North America (n = 34, 18%) (Figure 2). Most

studies provided information exclusively relating to high-income countries (n = 151, 80%). Over half of studies described acute coronary syndromes (n = 96, 51%), followed by heart failure (n = 16, 8%) and arrhythmias (n = 15, 8%). The vast majority of studies reported data from the first wave of the pandemic (n = 152, 80%). A minority of studies (n = 19, 10%) excluded patients diagnosed with concurrent SARS-CoV-2 infection. We classified 26% of studies across all outcomes as being at severe risk of bias, with 57% at moderate risk of bias (Figure 3, Supplementary material S3 Table S1-S37). Confounding was the most common source of elevated risk of bias (26% severe, 56% moderate). Studies reporting mortality outcomes were the most likely to be classified as being at severe risk of bias (51%), partly due to incomplete reporting of concurrent SARS-CoV-2 infection. Egger's test did not identify any significant publication bias (Supplementary material S6 Figure S19-S22, all p-values were non-significant).

Acute cardiovascular disease hospitalisations

Hospitalisations declined across the breadth of CV disease during the pandemic. Hospitalisation rates for each subtype of acute coronary syndrome (ACS) declined; ST-segment elevation myocardial infarction (STEMI) (IRR = 0.78, 95% CI 0.72 – 0.85, I^2 = 97.4%), non-STEMI (NSTEMI) (IRR = 0.66, 95% CI 0.60 – 0.72, I^2 = 98.3%), and unstable angina (UA) (IRR = 0.80, 95% CI 0.66 – 0.98, I^2 = 85.8%) (Figure 4, S1-3). Hospitalisations with HF declined during the pandemic (IRR = 0.66, 95% CI 0.59 – 0.73, I^2 = 99.9%) (Figure S4); reflective of a decline in admissions both with decompensated chronic HF and de novo presentations.[26]

The total number of hospitalisations for arrhythmias also declined (IRR 0.70, 95% CI 0.57 – 0.85, I^2 = 95.2%) (Figure S5), an effect consistently reported for each of

bradyarrhythmias,[27-29] atrial fibrillation/flutter,[30-32] and ventricular arrhythmias (VAs).[28] However, studies reporting arrhythmias detected by remote monitoring of cardiac implantable electronic devices (CIEDs) painted a different picture of arrhythmia incidence in the community in individuals with CV disease. Three studies reported increases in episodes of AF during the pandemic, which correlated with areas of high COVID-19 prevalence.[33-35] During the peak COVID-19 incidence in New York City, New Orleans and Boston an increase in implantable cardioverter defibrillator (ICD) shock burden was observed,[36] whilst two large studies found a reduction in VA incidence amongst individuals with ICDs after major public health restrictions.[37, 38]

On meta-regression we found that the decline in hospitalisations for CV disease was consistent across different geographical regions (Table S62). However, there was a greater decline in STEMI hospitalisations during the pandemic in LMICs (RR = 0.79, 95% CI 0.66 – 0.94). Notably, between the first and second wave we found no difference in decline of hospitalisations for STEMI, NSTEMI and HF. However, studies that reported data pertaining to a longer time span within the pandemic demonstrated a less extreme effect size for decline in hospitalisations for STEMI and NSTEMI compared to studies that reported a shorter time span (STEMI hospitalisations RR = 1.17, 95% CI 1.00 – 1.38; NSTEMI hospitalisations RR = 1.30, 95% CI 1.09 – 1.57).

For other acute CV presentations, there is limited evidence for the impact of the pandemic. A single-centre study reported that the number of hospitalisations with pericarditis and hypertensive crisis did not increase during the pandemic.[39] A Danish nationwide study of infective endocarditis (IE) hospitalisations found no difference during the pandemic whereas a Mexican single centre study showed a 93% reduction.[40, 41] One single-centre study reported

a decline in hospitalisations with adult congenital heart disease (ACHD) during the pandemic,[42] and two studies demonstrated a significant increase in the incidence of stress cardiomyopathy.[43, 44]

Invasive management of acute myocardial infarction

The number of percutaneous coronary intervention (PCI) procedures for STEMI and NSTEMI declined during the pandemic to a similar extent to the decline in hospitalisations (PCI for STEMI: IRR = 0.72, 95% CI 0.67 – 0.77, I^2 = 92.5%; PCI for NSTEMI: IRR 0.70, 95% CI 0.61 – 0.80, I^2 = 88.1%) (Figure 4, S6-7). However, amongst patients hospitalised for STEMI and NSTEMI the proportion who received revascularisation did not change during the pandemic (PCI for STEMI hospitalisations: RR 0.98, 95% CI 0.96 – 1.01, I^2 = 82.3%; PCI for NSTEMI hospitalisations: RR 1.05, 95% CI 0.93 – 1.17, I^2 = 88.3%) (Figure S8-9).

The detrimental effect of the pandemic is evident in system delays related to the STEMI care pathway. Whilst door-to-balloon times (D2B) did not increase significantly during the pandemic (WMD: 3.33 minutes, 95% CI -0.32 – 6.98 minutes, I^2 = 94.2%) we estimated that there was over an hour greater delay between symptoms to first medical contact (S-FMC) during the pandemic (WMD 69.45 minutes, 95% CI 11.00 minutes – 127.89 minutes, I^2 = 99.4%) (Figure S10).

There was divergence by geographic region and country-level income in the management of acute myocardial infarction during the pandemic. Meta-regression demonstrated that the decline in revascularisation was greater in LMICs compared to HICs (PCI for STEMI RR: 0.73, 95% CI 0.62 – 0.87; PCI for NSTEMI RR: RR 0.69, 95% CI 0.48 – 0.99) (Table S62). Increases in D2B and S-FMC time were only found to be significant in

countries outside of Europe and North America (Table 1). Finally, the proportion of patients treated for STEMI with thrombolysis increased during the pandemic (RR: 1.41, 95% CI 1.08 – 1.84, I^2 = 55.3%) (Figure S8), driven by increased use of thrombolysis in LMICs and countries outside of Europe and North America (Table 1).

Interventional procedures

Nationwide data from England and from the United States of America (USA), found that elective PCI decreased by over 50% during the pandemic,[45, 46] and disproportionately affected older ages and Black, Asian and minority ethnic (BAME) groups.[45] During the pandemic, we observed a reduction in implantations of permanent pacemakers (IRR = 0.55, 95% CI: 0.44 – 0.69, I^2 = 98.3%), implantations of all CIEDs (IRR = 0.51, 95% CI: 0.44 – 0.59, I^2 = 86.0%), and the overall number of percutaneous catheter ablations performed (IRR = 0.42, 95% CI: 0.24 – 0.75, I^2 = 99.4%) (Figure 4, Figure S11). By contrast, we found conflicting reports for rates of transcatheter aortic valve implantations (TAVIs) during the pandemic compared with pre-pandemic (IRR 0.76, 95% CI 0.43 – 1.33, I^2 = 99.2%) (Figure S12). Whilst reports from most of Europe showed a decline in TAVI rates,[1, 47-50] there was an increase in the number of TAVI procedures performed during the pandemic in Poland and Ontario, Canada.[51, 52]

The total number of cardiac surgical operations fell during the pandemic (IRR = 0.66; 95% CI: 0.55 – 0.79, I^2 = 99.6%) (Figure S12). There were clear declines in coronary artery bypass graft operations (IRR = 0.58, 95% CI: 0.44 – 0.76, I^2 = 99.0%) and surgical interventions for the aortic valve (IRR 0.59, 95% CI: 0.48 – 0.73, I^2 = 85.6%).

Diagnostic Procedures

Observational studies reporting a comparison of the number of diagnostic CV procedures during and pre-pandemic were infrequent. Available studies reported declines in exercise tolerance tests (IRR 0.32 95% CI 0.17 – 0.61, I^2 = 92.9%), ambulatory ECG monitoring (IRR: 0.25, 95% CI 0.12 – 0.51, I^2 = 96.6%), ambulatory blood pressure monitoring (IRR: 0.12, 95% CI 0.03 – 0.50, I^2 = 97.1%), 12 lead ECGs (IRR: 0.21, 95% CI 0.08 – 0.57, I^2 = 99.3%), and transthoracic echocardiograms (IRR: 0.29, 95% CI 0.19 – 0.46, I^2 = 98.1%) during the pandemic (Figure 4, S13). The use of diagnostic invasive coronary angiography has been reported to fall by as much as 74%.[53] Single-centre studies demonstrated that transoesophageal echocardiograms, CT coronary angiograms and myocardial perfusion scans either ceased or sharply declined.[27, 54, 55]

Outpatient and community consultations

During the pandemic we found a marked decline in in-person outpatient consultations (IRR = 0.27, 95% CI: 0.09 – 0.75, I^2 = 100%) (Figure S14). Five studies reported an increase in telemedicine cardiology outpatient appointments in both HICs and LMICs during the pandemic.[54, 56-59] However, multi-centre reports from the USA and Germany suggested overall deficits of 61%, 33% and 5% in outpatient CV consultations even after including telemedicine appointments.[56, 58, 60] Surveys showed that almost half of all exercise-based cardiac rehabilitation programs closed during the pandemic,[61-63] and of programmes that continued many used technology to provide virtual consultations.[62-64]

Mortality

In-hospital all-cause mortality

For patients hospitalised with acute CV disease, in-hospital all-cause mortality was reported frequently and 30-day all-cause mortality rarely. For both STEMI and heart failure, in-hospital mortality increased during the pandemic (STEMI, RR: 1.17, 95% CI: 1.07 – 1.28, I^2 = 23.3%; HF, RR 1.11, 95% CI 1.03 – 1.20, I^2 = 63.9%) and did not differ for NSTEMI (RR: 0.94, 95% CI: 0.83 – 1.07, I^2 = 0.0%) (Figure 4, S15-16). For both STEMI and HF in-hospital mortality increased during the pandemic in LMICs but not in HICs (Table 1).

30-day all-cause mortality

Only six studies reported 30-day all-cause mortality for NSTEMI, STEMI or HF.[65-70] Three studies showed that 30-day mortality increased during the pandemic for NSTEMI but not STEMI.[65-67] In one report, higher 30-day mortality for NSTEMI was correlated with concurrent SARS-CoV-2 infection.[67] For the other two studies infection status was not reported but primary PCI (PPCI) was 'protected' during the pandemic whilst patients admitted for NSTEMI received lower rates of and greater delay to angiography.[65, 66] An analysis of nationwide health records described increased odds of 30-day mortality following admission with HF.[70] Notably, studies of mortality in the mid-to-long term suggest these trends may continue. One-year cardiac-related mortality for patients admitted for STEMI during the pandemic was reported to be no different to a historical control group, in-spite of worse in-hospital outcomes.[71] Patients admitted for NSTEMI during the pandemic, who on average waited longer for revascularisation, have been reported to have over twice as high a risk of all-cause mortality and a twenty-fold increased risk of hospitalisation with heart failure at six months compared to historical controls.[72] Patients surviving hospitalisation for heart failure during the pandemic also have higher all-cause mortality at one year compared

to patients hospitalised in 2019, correlated with fewer receiving their inpatient care on specialist cardiology wards.[73]

Out-of-hospital cardiac arrest

We found no evidence for an increase during the pandemic period of out-of-hospital cardiac arrest (OHCA) of presumed medical or cardiac cause - as defined by attending emergency medical service personnel (OHCA medical cause IRR: 0.78, 95% CI 0.58 – 1.04, I^2 = 95.1%; OHCA cardiac cause IRR: 1.04, 95% CI 0.76 – 1.40, I^2 = 98.6%) (Figure 4, S17-18).

Population level cardiovascular mortality

Four studies using UK nationwide data reported increased non-COVID-19 acute CV mortality compared with the historical average in the early months of the pandemic,[74-77] with a 'displacement of death' occurring in homes (30.9% vs. 23.5%) and care homes (15.7% vs 13.5%).[77] In the USA two studies demonstrated increased deaths from heart disease during the pandemic compared with previous years,[78, 79] with a greater excess in areas of higher density of COVID-19 infection.[78] This pattern was also noted in LMICs, with the greatest excess cardiovascular mortality reported in the most deprived cities.[80, 81]

Discussion

This systematic review and meta-analysis of the effect of the COVID-19 pandemic on CV services has identified a number of important points. First, the COVID-19 pandemic witnessed a substantial global decline in hospitalisations with acute cardiovascular disease,

fewer diagnostic and interventional procedures and less outpatient and community consultations. Second, we found no difference in the decline in hospitalisations for STEMI, NSTEMI and HF during the second wave compared to the first wave. Third, there is disparity in the severity of collateral cardiovascular damage across geographic and economic boundaries. Across LMICs and countries outside of Europe and North America we observed a more severe decline in hospitalisations and revascularisation for STEMI, greater delays in STEMI care pathways with more frequent use of thrombolysis, and elevated in-hospital mortality for both STEMI and HF.

Previous reviews have observed a decline in hospitalisations for ACS during the pandemic,[8-10] but here we extend the quantitative analysis of hospitalisation rates to HF and arrhythmias and demonstrate similar patterns. Other authors have shown that in-hospital mortality rose during the pandemic when studies reporting different CV diseases are combined,[17] and specifically in patients who underwent PPCI for STEMI.[9] In this analysis we are able to demonstrate elevated in-hospital mortality during the pandemic for both STEMI and HF, and demonstrate variation across geographic regions and by country economic development. Finally, we provide the first estimates of the detrimental effect of the pandemic on interventional procedures, diagnostic procedures and outpatient consultations.

We found that the decline in hospitalisation for acute CV disease occurred across the breadth of CV diseases, and reports suggest reductions occurred irrespective of formal restrictions on movement,[65, 82, 83] or the extent of COVID-19 diagnoses within the local population.[84] We observed delays to seeking help and receiving medical attention, independent reports of increased CV deaths in homes and care homes, and reports of

increased case severity amongst those who did reach hospital.[3, 42, 85-87] One may infer that fear of the contagion, 'stay at home campaigns' and overwhelmed emergency medical services prevented and delayed hospitalisation of unwell patients. The scale of disruption to public interaction with CV services was not fully anticipated before the pandemic. In response information campaigns, such as "You can't pause a heart" by the European Society of Cardiology (ESC),[88] aimed to equilibrate public health messaging by accentuating the importance of expediently seeking medical attention for symptoms of acute CV disease. Whilst some studies reported that information campaigns quickened recovery in rates of hospitalisation for acute myocardial infarction,[82, 83, 89, 90] we did not find a significant difference in the decline of hospitalisation rates between the first and second wave across STEMI, NSTEMI and heart failure. However, we did observe that studies reporting a longer time span of the pandemic period, and thus better reflecting both 'decline' and 'recovery' phases of hospitalisation rates related to public health restrictions,[65] evidenced a less extreme decline in hospitalisations for acute CV disease. Initial evidence on the Omicron variant suggests that it is more easily spread, but generally causes less severe disease, than previous SARS-CoV-2 variants.[91] As the public and healthcare services become more familiar with 'living with' COVID-19 and widespread vaccination in HICs limits morbidity and mortality directly related to SARS-CoV-2 infection,[92] it remains to be seen if hospitalisation rates for acute CV disease will be robust to future waves.

There was comparatively little available data for the effect of the pandemic on CV services in LMICs. Only in hospitalisations, STEMI care pathways and in-hospital mortality were we able to investigate for disparities compared to HICs and we consistently found more severe collateral cardiovascular damage. The 143 LMICs constitute 80% of the world's population - approximately six billion people - and the World Health Organisation (WHO)

estimates that 80% of all cardiovascular deaths now occur in LMICs.[93] Whilst guideline-based therapy for STEMI has dramatically improved outcomes in HICs, regional systems of care for STEMI in LMICs are sparse. There are few emergency medical services, catheterisation labs tend to be clustered in urban centres, and poor insurance coverage for the majority of the population limits the applicability of expensive procedures, leaving fibrinolysis as the most common treatment of STEMI.[94] Historically, in-patients with acute heart failure in North America and Europe have had lower mortality rates than patients in South America and Asia,[95] and 6-month mortality rates of almost 20% after heart failure hospitalisation have been reported in sub-Saharan Africa.[96] Access to diagnostic and interventional cardiac procedures is limited in LMICs,[97] as is the ability to be able to provide guideline-directed management for other CV diseases.[98] The pandemic exacerbated established challenges to the delivery of STEMI and HF care in LMICs. We are concerned the gap in CV care and outcomes between HICs and LMICs may have widened during the pandemic across the breadth of CV diseases and services, yet data are not available to evidence this notion.

Collateral cardiovascular damage from missed diagnoses and delayed treatments will continue to accrue unless mitigation strategies are speedily implemented (Figure 5). The deferral of interventional procedures, especially for structural heart disease, leaves many patients at high risk of adverse outcomes.[99] Risk stratification and prioritisation will be needed to avert substantial excess mortality,[100, 101] and the pragmatic use of percutaneous over surgical options should be considered.[102-104] A digital transformation in the healthcare model could cut the deficit in outpatient care and improve risk factor control. During the pandemic there have been fewer contacts for CV diagnoses and risk factor monitoring,[105, 106] and lockdowns led to a significant decline in physical activity, weight gain, and worsening

psychological health.[107, 108] Virtual consultations and tele-rehabilitation can provide better patient engagement with similar outcomes to in-person interactions, and patients can be empowered to manage their CV health by integrating home health equipment into routine clinical practice.[59, 109, 110] Nonetheless, inequitable access to telemedicine and digital technology has been described for female, non-English speaking, older and poorer patients and we must guard against reinforcing such inequities to healthcare.[111]

As this review evidences, there is limited information about CV health and care from LMICs (data gaps exist in the African, South American and Western Pacific regions). There are a few nationwide initiatives to systematically collect and report data on CV health in LMICs,[112] and the WHO is engaging with member states and technology partners to strengthen their local health information systems.[113] The ESC Atlas of Cardiology provides an enviable resource for data of population health in Europe.[114] A global living collaborative network focusing on CV care during the pandemic at an institutional level could be established,[115] and internationally harmonised CV data available in a responsive fashion could enable a 'global barometer' of the consequences of the pandemic as well as the opportunity to prepare for future major health crises.[116]

There are limitations to our analysis. The evidence base is skewed to HICs in Europe and North America, the earlier part of the pandemic, certain CV diseases, and short-term outcome measures, which limits quantitative insights. We classified most studies as being at severe or moderate risk of bias across all outcomes, which accords with previous reports of the methodological quality of publications during the COVID-19 pandemic.[17, 117] Many studies did not report the number or proportion of included patients that had co-existent COVID-19 infection, which introduces bias and prohibits detailed analysis of what

contribution the direct effect of COVID-19 on the cardiovascular system may have had on our estimates for in-hospital mortality and hospitalisations. Nonetheless, a meta-analysis including more than 27,000 patients demonstrated that in-hospital mortality in CV disease was increased during the pandemic independent of co-infection with COVID-19 and the direction of effect was consistent between studies at moderate and severe risk of bias.[17] Furthermore, the direct CV consequences of COVID-19 include myocarditis, heart failure, arrhythmias and acute myocardial injury,[118] so the number of hospitalisations for acute CV disease would likely increase if direct COVID-19 pathology was the predominant factor, in contrast to our findings.

Heterogeneity was high in most analyses, which we investigated through meta-regression for a range of factors in outcomes of hospitalisations, invasive management of acute myocardial infarction and in-hospital mortality. We found that geographic region, income classification and whether the first or second wave were reported introduced variability in effect size, as did study characteristics such as the data source, presence of a matched comparator period, the length of the pandemic study period and the time-point at which data collection started during the pandemic period (Table S62). Significance was often not reached for individual factors due to the small number of studies. The smaller number of studies reporting procedures and outpatient consultations precluded meta-regression to investigate heterogeneity. Nevertheless, the direction of association is consistent across outcomes (Figures S1-18) suggesting that the conclusions we draw for trends during the pandemic are reliable.

Conclusions

This systematic review with meta-analysis provides, to date, the most comprehensive summary of the effect of the COVID-19 pandemic on CV services and individuals with CV disease. From 189 articles we show evidence of fewer hospitalisations, procedures and consultations with increased mortality amongst in-hospital and community populations. We identified disparity by geographical region and country income classification in the availability of data and the severity of the detrimental effect of the pandemic on CV services and presently there are insufficient data to fully characterise the effects to CV services in LMICs. Notwithstanding this, we provide synthesised evidence that the COVID-19 pandemic resulted in substantial global collateral cardiovascular damage.

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Authors' Contributions

CPG conceived the idea of the study. RN and BH screened the studies and reviewed the selected articles. RN and BH undertook data extraction. JW carried out the statistical analysis. RN, JW and CPG interpreted the findings and RN drafted the manuscript. JW, BH, SA, DLB, GBZ, LSM, CVSR, APLR, HGCVS, JED, TFL, MM and CPG critically reviewed the manuscript and RN revised the manuscript for final submission. All authors have approved the final draft of the manuscript. RN is the guarantor. RN accepts full responsibility for the work and the conduct of the review, had access to the data and controlled the decision to publish. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Ethical approval

Ethical approval was not required.

Data sharing

Data are available on reasonable request. Technical appendix, statistical code and dataset are available from the corresponding author at r.nadarajah@leeds.ac.uk.

Disclosure

All authors have completed the ICMJE uniform disclosure form at www.icjme.org/col_disclosure.pdf and declare: CPG reports personal fees from AstraZeneca, Amgen, Bayer, Boehrinher-Ingelheim, Daiichi Sankyo, Vifor, Pharma, Menarini, Wondr Medical, Raisio Group and Oxford University Press. He has received educational and research grants from BMS, Abbott inc., the British Heart Foundation, National Institute of Health Research, Horizon 2020, and from the European Society of Cardiology, outside the submitted work. JED has received consulting fees from GENinCode UK Ltd., CME honoraria and/or consulting fees from Amgen, Boehringer Ingelheim, Merck, Pfizer, Aegerion, Novartis, Sanofi, Takeda, Novo Nordisk and Bayer. He is the Chief Medical Advisor for Our Future Health and at Public Health England is a Senior Advisor for cardiovascular disease prevention, Chair of the Review of the National Health Check Programme and a member of the NHS Healthcheck Expert Scientific and Clinical Advisory Panel. GBZ has received consulting fees from Cardinovum, Crannmedical, Innovheart, Meditrial, Opsens Medical and Replycare. TFL has received educational or research grants within the past 36 months from Abbot Inc., Amgen Inc., Astrazeneca, Boehringer Ingelheim, Novartis, Servier, Sanofi and Vifor, and has received consulting and/or speaker fees from Pfizer, Daichi Sankyo, Amgen and Menarini International. He is also Treasurer/Secretary of the European Society of Cardiology, Chairman of the Research Committee of the Swiss Heart

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Legends

Structured Graphical Abstract: Major findings of the collateral damage of the COVID-19 pandemic on cardiovascular services. Abbreviations in text.

Figure 1: Flowchart of selected studies. Flowchart based on the Preferred Reported Items for Systematic Review and Meta-Analysis (PRISMA) statement.

Figure 2: The origin of included studies demonstrated on a global choropleth (A), and a chart including the number of studies per country for the 20 most commonly represented countries (B).

Figure 3: Summary of overall risk of bias scores assessed using the ROBINS-I tool for all studies across all outcomes (A) and subdivided by categories of outcomes (B-E). AMI, acute myocardial infarction.

Figure 4: Summary estimates for analyses across hospitalisations, in-hospital management, diagnostic and interventional procedures and mortality. The full forest plots for each analysis are available in supplementary material (Figure S1–S18). EP, electrophysiology.

Figure 5: Potential collateral damage of the COVID-19 pandemic to cardiovascular services. The height and time scale of the three peaks depicted are not certain or to scale. We do expect

the disruption to cardiovascular services to accumulate over time unless mitigation strategies are utilised.