

Estimating the Effect of Reduced Attendance at Emergency Departments for Suspected Cardiac Conditions on Cardiac Mortality During the COVID-19 Pandemic

Running title: *Katsoulis et al; Indirect Effect of COVID-19 on Cardiac Mortality*

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The wider health impacts of the Coronavirus Disease (COVID-19) pandemic are of increasing concern, with an observed increase in rates of non-COVID-19 excess mortality. In England and the US, the early pandemic was accompanied by a decline in patient visits to Emergency Departments (ED), including those for cardiac diseases^{1,2}. The decline may have been influenced by patient's reluctance to visit hospital due to the public health messages to protect National Health Service capacity, concerns about the risk of coronavirus infection, or difficulties in accessing medical care. The impact of delayed or non-presentation to EDs with suspected cardiac disease on cardiac mortality is unknown. In this study, we used instrumental variable analysis to estimate the effects of reduced ED visits on cardiovascular mortality in England.

To quantify the change in daily ED visits for suspected cardiac disease, we extracted data from the Public Health England Emergency Department Syndromic Surveillance System (EDSSS) weekly bulletins, a sentinel network of EDs across England using Web Plot Digitizer (<https://automeris.io/WebPlotDigitizer>). For cardiovascular disease outcomes, we obtained weekly mortality counts for cardiovascular disease from the Office of National Statistics (ONS) for England. We estimated daily mortality counts from the weekly data by assuming a linear trend. Cardiac mortality was defined as death due to coronary heart disease, heart failure, or sudden cardiac death (ICD-10 codes used to classify these outcomes are available online on the HDR UK Phenotype ID portal: <https://portal.caliberresearch.org/phenotypes/katsoulis-noncovid19cvd-death-a69hszdh3dcgzpn4hjcng>). We excluded deaths where COVID-19 was included in the registration. To enable comparison with mortality data for England, we scaled the daily EDSSS visit data up by a factor of 3; since, EDSSS¹ covers 60 of a total of 180 EDs in England³. Data on mortality outcomes are available from the Office of National statistics upon request and ED attendance data are available online

(<https://www.gov.uk/government/publications/syndromic-surveillance-weekly-summaries-for-2020>). The analysis script is available upon request to Michail Katsoulis (m.katsoulis@ucl.ac.uk). This study used population-level data for emergency department visits and mortality and was performed in accordance with guidelines for study procedures provided by the UCL Research Ethics Committee.

To explore how the reduction of suspected cardiac disease affected cardiac mortality, we performed an instrumented difference-in-difference analysis, using the COVID-19 pandemic as the instrument^{4,5}. To define the level of the instrumental variable, we selected March 12, the date when the UK Chief Medical Officers raised the UK risk from COVID-19 to high, following the WHO declaration of a global pandemic (March 11). We estimated the relationship between daily ED visits and cardiac deaths by using the two-stage least squares method⁵. First, we regressed the exposure (ED visits for cardiac diseases) on the instrument (COVID-19 pandemic), assigning the value of 0 if the ED visit occurred before 3/12/2020, or 1 if on or after this date. Second, we regressed the outcome (number of cardiac deaths) on the predicted exposure. In both steps, the following four terms were included to adjust for seasonality⁵: (i) period (0 for previous years, 1 for this year (12/18/2019-4/15/2020)), (ii) t (time in days from 12/18), (iii) squared t and (iv) cubic t . The mortality associated with untreated acute cardiac disease may occur immediately or after a delay, or lag period, the length of which is determined by the type and severity of the presenting disease. For example, untreated myocardial infarction may result in early arrhythmic death or later death due to heart failure. We, therefore, estimated the effects of reduced ED visits on cardiac deaths for a range of time lag periods (delays), between non-presentation and the associated mortality, from 0 to 20 days.

During the COVID-19 pandemic period (3/12/20-4/15/20), we observed a decline of 2750 (95%CI: 2504, 2996) ED visits per week for suspected cardiac disease (~35% decrease compared to the average weekly admission before the pandemic this year). We estimated that every 100 non-attendances at EDs for suspected cardiac disease were associated with between 3.1 (95%CI: 1.5-4.6) and 8.4 (95%CI: 7.0-9.8) excess cardiac deaths, corresponding to the lower and upper bound of the estimated mortality lag times of 0 and 18 days respectively.. The weekly excess cardiac mortality during the pandemic period, due to non-attendance at EDs, was estimated to be between 84 (95%CI: 42, 127) and 232 (95%CI, 193, 270) deaths (see Figure). This corresponds to an increase in weekly non-COVID19 cardiac mortality of up to 18%, compared to the previous 5 years, and implies that one cardiac death could have been prevented or delayed for every 12 ED visits with suspected cardiac disease. These estimates were robust to sensitivity analysis whereby we altered the date used to define the COVID19 pandemic period by three days, before and after March 12.

In our study, we use modern causal inference methodology^{4,5} to estimate to what extent cardiac mortality was affected by reduced attendances in EDs for cardiac conditions. It is likely that premature non-COVID-19 mortality, due to undertreatment of acute cardiac disease, will continue to accumulate beyond the 20-day follow-up period attainable at the time of this study. The validity of our estimates rests upon the assumption that the COVID-19 pandemic only affects excess deaths from cardiac disease through the reduction in ED admissions (exclusion restriction assumption), and not through other factors, such as, increased anxiety leading to an increased incidence rate of myocardial infarction. Another potential limitation of this study is the possible misclassification of CVD deaths as not related to COVID-19, since SARS-CoV-2 viral infection was excluded on clinical grounds rather than through systematic viral ribonucleic acid

testing. Finally, this study was based on attendance data for a sample of 60, from a total of 180 EDs, in England; we were unable to assess the representativeness of this sample and cannot exclude the possibility that our estimates differ from the true effects due to biased sampling.

We found evidence of reduced ED attendances of patients with suspected cardiac disease during the COVID19 pandemic peak in England and an associated time-lagged increase in cardiac mortality. We estimate the unintended harm that may have resulted from the effect of the COVID19 pandemic response on healthcare-seeking behaviour and/ or the provision of healthcare for non-COVID19 cardiovascular disease. Our study was limited to evaluating the short-term mortality associated with reduced ED presentations; however, there is a risk that longer term impacts of undertreatment on cardiovascular morbidity and mortality will continue to emerge over time. These findings should alert policymakers to the importance of ensuring that any measures introduced to control and manage SARS-CoV-2 infection do not adversely impact the management of acute cardiovascular disease.

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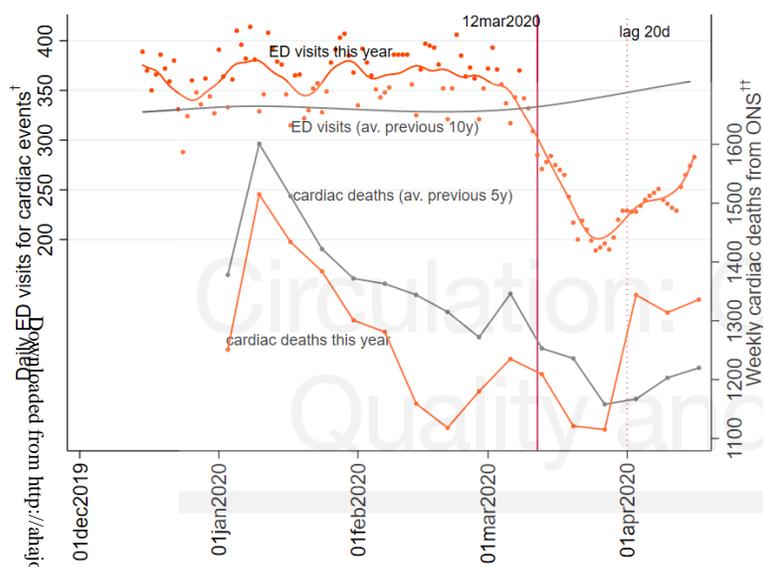


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Figure Legend:**Figure 1.**

Left panel: Observed number of attendances in emergency department (EDs) for suspected cardiac events (left y-axis) in England from EDSSS, compared to the average of the previous 10 years and N of cardiac deaths in England, compared to the average of the previous 5 years from the Office of National Statistics. **Right panel:** Estimated effect of reduced ED[†] attendance for suspected cardiac events on cardiac deaths, in England, during the COVID-19 pandemic, using instrumented difference-in-difference. To define the level of the instrumental variable, we selected 3/12/2020 as the 1st day of the pandemic. Estimates are given for a range of mortality[‡] lag times, the time between the reduced ED attendance for suspected cardiac conditions and cardiac deaths, from 0 to 20 days. [†]Data provided from Public Health England from 60 EDs that are part of EDSSS (out of the 180 in England). ^{††}Data provided from Office of National Statistics for England. [‡]Cardiac deaths caused per 100 reduced ED attendances for suspected cardiac events. ^{‡‡}Excess weekly cardiac deaths due to reduced ED attendance for suspected cardiac events.



Excess cardiac deaths due to reduced attendances at EDs

