Association of COPD exacerbations and acute cardiovascular events: a systematic review and meta-analysis

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Abstract
Background: The majority of patients with chronic obstructive pulmonary disease (COPD) suffer from comorbid cardiovascular (CV) disease. Accumulating evidence suggests a temporal association between COPD exacerbations and acute CV events, possibly due to lung hyperinflation, increased hypoxemia and systemic inflammation. The aims of the study were to estimate the risk of [1] acute CV events [acute myocardial infarction (AMI), CV-related death] or stroke in the months following a COPD exacerbation and [2] COPD exacerbation in the months following an acute CV event.

Methods: A systematic literature review of observational studies published since 2000 was conducted by searching literature databases (Medline and Embase). Studies were eligible if conducted in adults with COPD, exposed to either COPD exacerbation or acute CV events, with outcomes of acute CV events or COPD exacerbation reported. Studies were appraised for relevance, bias and quality. Meta-analyses, using random-effect models, were performed for each outcome of interest, thus providing a pooled relative risk (RR) and its 95% confidence interval.

Results: Eight studies were identified, of which seven were used for the meta-analyses examining the risk of CV events 1–3 months after an exacerbation compared with none. For stroke (six studies), RR was 1.68 (95% CI = 1.19–2.38). For AMI (six studies), RR was 2.43 (95% CI = 1.40–4.20). No studies exploring risk of exacerbation following an acute CV event were identified.

Conclusion: This meta-analysis identified a markedly increased risk of stroke or AMI within a relatively short period of time following a COPD exacerbation. Although the underlying mechanisms are not fully elucidated, patients with COPD should be monitored for risk of CV outcomes after exacerbations. In addition, preventing exacerbations may decrease the risk of subsequent acute CV events.

Registration: The study protocol was published via PROSPERO: International Prospective Register of Systematic Reviews (#CRD42020211055).

Keywords: acute myocardial infarction, chronic obstructive pulmonary disease, exacerbations, meta-analysis, stroke, systematic review

Introduction
Chronic obstructive pulmonary disease (COPD) and cardiovascular (CV) or cerebrovascular diseases frequently occur together.1,2 Meta-analyses of observational studies suggest a two-fold increase in the odds of having chronic CV disease in people with COPD, in a lifetime.3 For instance, COPD is significantly associated with an increased risk of hypertension, heart failure, dysrhythmia, acute myocardial infarction (AMI), stroke and...
diabetes compared with an age-matched general population. The patients with comorbid COPD and CV disease experience high rates of morbidity, worse quality of life, higher risk of hospitalisation and increased mortality risk.

The underlying pathophysiological mechanisms that are responsible for the association between CV disease and COPD are only partially understood. Potential mechanisms include arterial stiffness, inflammation and endothelial dysfunction, at least partially explained or confounded by a common etiological pathway through exposure to smoking or air pollution.

In addition to the association between COPD and CV or cerebrovascular disease, recent evidence implicates there is an association between COPD exacerbations and acute CV events. The presence of CV disease increases the risk of frequent exacerbations, and COPD exacerbations were found to be associated with increased risk of acute CV events and mortality. This association between acute presentations of COPD and CV events opens a new avenue to better understand clinical burden of chronic comorbidity and their underlying pathophysiological relationships.

Therefore, we aimed to systematically review and pool evidence to address two linked research questions: (1) what is the risk of acute CV outcomes following a COPD exacerbation, and (2) has there been an association described for the risk of COPD exacerbations following an acute CV event? Acute cardiovascular disease (CVD) events considered by this review were AMI, stroke, or cardiac/cardiovascular death.

Methods

Search strategy
This study was conducted in accordance with the Meta-analysis of Observational Studies in Epidemiology and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for conducting and reporting systematic reviews. The study protocol was published via PROSPERO: International Prospective Register of Systematic Reviews (#CRD42020211055) and is available at the following link: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020211055. A PRISMA checklist is provided in Supplementary Table S1. We searched for full-text reports containing original data in Ovid MEDLINE, MEDLINE In-Process Citations & Daily Update and EMBASE, and in reference lists of included articles, until 14 May 2021. The detailed search strategy is available in Supplementary Table S2. In addition, reference lists of relevant articles were searched, and systematic reviews were identified by searching the Cochrane Database of Systematic Reviews, Cochrane Library and PROSPERO, to cross-check reference lists.

Eligibility criteria, screening and abstraction
We included full publications meeting the following criteria: (1) cohort, case–control, case–crossover or case series studies, or secondary observational analyses of cohorts from randomised controlled trials (RCTs); (2) conducted in adult patients with COPD; (3) including at least 50 subjects; (4) reporting the assessment of risk of CV-related death, AMI or stroke using hazard ratio, rate ratio, risk ratio (RR), odds ratio, incidence rate ratio, proportionate morbidities ratio, standardised mortality rate, standardised incidence rate or any other risk measure with 95% confidence intervals (CIs) (or with data to calculate them) from studies containing a comparative arm; (5) published from 2000 to the date of the search; and (6) full text in English. The original searches were run from 2000 to 13 August 2020, and updated searches were run to 14 May 2021.

Results from RCTs were excluded, as were studies indexed as editorials, letters, case reports or conference abstracts/proceedings. We included studies where patients with the exposure were compared either with their own non-exposure period or with patients with COPD without the exposure. There was no limit on countries included in any given publication.

Other eligibility criteria differed according to the two research questions. For the first question, we searched for studies of the risk of acute CV outcome after an exposure to mild, moderate or severe COPD exacerbation. For the second question, we searched for studies of the risk of mild, moderate or severe COPD exacerbation after an acute CV event.

Two reviewers (N.P. and Z.M.) independently performed two-stage screening (title/abstract and...
full-text screening), with disagreement resolved by discussion. Studies that met eligibility criteria and reported original data were included in the review. Data extraction and risk of bias assessment were performed by one reviewer, and a second independent reviewer conducted data checking. Data on study characteristics and the outcomes of interest were extracted.

**Quality assessment**

Risk of bias was assessed by the Newcastle–Ottawa scale, which assessed study quality in three domains: (1) selection of the study groups; (2) comparability of cohorts on the basis of the design or analysis and (3) ascertainment of outcomes of interest (Supplementary Table S3). Studies were classified as low risk of bias if they scored ≥3/5 for selection, ≥1/2 for comparability and 3/3 for outcome domains in the Newcastle–Ottawa Scale. If a study did not meet these criteria, it was classified as high risk of bias.

**Statistical analysis**

Pairwise meta-analyses were performed for the outcomes within the period of 1–3 months following COPD exacerbation. This period was selected based on its highest frequency of reporting for this time period by individual studies. In the case of studies with partially overlapping populations, a decision on whether to include them in the main analysis was made on a case-by-case basis, supported by study quality criteria.

A feasibility assessment was performed to determine whether it was recommended to combine identified studies in a pairwise meta-analysis, based on study population source, identification and inclusion/exclusion criteria for study population, baseline characteristics, ascertainment and definition of CV events and COPD exacerbations, controls, time period and reference period, outcome reporting and potential subgroup analyses. Timepoints reported in the studies were assessed, and the risks from the most comparable timepoints across studies included in the analysis.

Odds ratios, hazard ratios, rate ratios, standardised incidence ratios and standardised mortality ratios were considered equal estimates. All are referred to in this article as ‘risk ratios’, and the most adjusted RRs were log-transformed and used in analysis. Weights were calculated using the inverse variance method (weight = 1/variance). Random-effects DerSimonian and Laird models were fitted to calculate pooled RR and 95% CI for all outcomes.

Heterogeneity was measured using the Cochran’s Q statistic with statistical significance set at $p < 0.10$ and quantified by the $I^2$ test. Publication bias was assessed with funnel plots and Egger’s test.

The robustness of the results was evaluated using the leave-one-out method to assess the effect on pooled estimates of removing individual studies. A range of sensitivity analyses were conducted, including least-adjusted analysis, only low risk of bias studies, excluded RCTs, only moderate exacerbations, only severe exacerbations, removal of the 91-day timepoint, only ischemic stroke and removed potential population overlap.

All statistical analyses were conducted using R version 3.5.1, using the packages metafor and forestplot.

**Results**

**Literature search**

After removing duplicates, the searches identified 1587 records for screening, of which 206 full-text articles were retrieved and assessed for eligibility. A separate assessment was conducted for each of the two research questions. The PRISMA flow diagram for studies investigating the risk of acute CV outcomes after COPD exacerbation is shown in Supplementary Figure S1. A total of seven studies were identified for inclusion in the meta-analysis. The PRISMA flow diagram for studies investigating the risk of COPD exacerbation after an acute CV event is shown in Supplementary Figure S2. No studies met our criteria for inclusion in a meta-analysis, and therefore, this research question did not yield any summary results.

**Study characteristics**

The characteristics of the seven included studies reporting risk of acute CV outcomes after COPD exacerbation are summarised in Supplementary Table S4, which details the country, study period, patient data source, reference population, outcomes reported and relative risk (RR) reported by the included studies. Supplementary Table S5
Therapeutic Advances in Respiratory Disease

includes further details of definitions of exacerbation and its severity used, the identification of CVD outcomes, the number of participants and the timepoints at which risk was reported. Details on the study controls, timepoints and risk of bias are reported in Appendix 1.

Five studies reported AMI and stroke as outcomes,\(^{18,25,26,29,30}\) one reported only AMI\(^{27}\) and one reported only stroke.\(^{28}\) Therefore, a total of six studies reporting stroke as an outcome and six studies reporting AMI as an outcome were available, and meta-analyses were conducted for these outcomes only. Only one study reported the risk of cardiovascular death.\(^{29}\) Stroke was reported only as ischemic stroke by two studies;\(^{18,30}\) a combination of haemorrhagic and ischemic stroke was reported by the other studies, although only one stratified risk by type of stroke.\(^{25}\)

**AMI risk after COPD exacerbation**

The meta-analysis found a statistically significantly increased risk of AMI in the 1–3 months after a COPD exacerbation, RR 2.43 (95% CI = 1.40–4.20) (Figure 1).

Heterogeneity between the studies was high with an \(I^2\) value of 99.2%. This reflects the highly variable study designs included in the analysis, due to the disparate nature of the available data.

Post-exacerbation follow-up periods other than 1–3 months were reported heterogeneously by individual studies; an increase of the AMI risk was strongest immediately after exacerbation\(^{18,27,30}\) and persisting for a period of up to 1 year.\(^{27}\) The association was increased with severe (hospitalised) versus moderate (outpatient) exacerbations (Incidence Rate Ratio [IRR] within

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**Table 1.** Summary of studies included in the meta-analysis on AMI following COPD exacerbation.

| Author and Year | N in study | Weight | Risk Ratio [95% CI] |
|-----------------|------------|--------|---------------------|
| Donaldson 2010  | [N = 25,857]| 17.81  | 1.11 [0.70, 1.70]   |
| Goto 2018       | [N=562,867]| 20.04  | 1.28 [1.17, 1.39]   |
| Halpin 2011     | [N = 3,900]| 5.37   | 13.04 [7.17, 19.70] |
| Kunisaki 2018   | [N = 16,485]| 16.64  | 7.00 [4.00, 12.30]  |
| Reilev 2019     | [N = 118,807]| 20.12 | 3.57 [3.43, 3.71]   |
| Rothnie 2018    | [N = 5,696]| 20.02  | 1.65 [1.50, 1.81]   |

**Figure 1.** Meta-analysis results on effect of prior COPD exacerbation on risk of AMI (random effects), 1–3 months after exacerbation.

AMI, acute myocardial infarction; CI, confidence interval; df, degrees of freedom; RE, random effects.

Weight is calculated from the inverse of the variance.
Stroke risk after COPD exacerbation

The meta-analysis found a statistically significantly increased risk of stroke after a COPD exacerbation, RR 1.68 (95% CI = 1.19–2.38) for 1–3 months after exacerbation event (Figure 2).

Heterogeneity between the studies was high with an I² value of 96.7%. This reflects the highly variable study designs included in the analysis due to the disparate nature of the available data.

Leave-one-out analysis (Supplementary Figure S4) found the main analysis did not lose statistical significance when each study was individually removed, indicating that the results were generally robust. The results of the sensitivity analyses are presented in Table 2. All showed a similar result to the main analysis with no loss of statistical significance, again indicating that the results were generally robust. Several analyses indicated that I² decreased when studies were excluded.

Table 1. Results of sensitivity analyses conducted on the meta-analysis on effect of prior COPD exacerbation on risk of AMI (random effects).

| Sensitivity analysis                      | Risk ratio (95% CI) | Q   | df | Q p-value | I² (%) |
|------------------------------------------|---------------------|-----|----|-----------|--------|
| Low risk of bias/non-RCT                 | 1.72 (0.93–3.21)    | 602.27 | 3  | <0.0001 | 99.5   |
| Moderate exacerbation                    | 1.58 (0.47–1.70)    | 0.00 | 1  | 0.095    | 0.00   |
| Severe exacerbation                      | 1.74 (0.81–3.75)    | 86.35 | 1  | <0.0001 | 98.84  |
| Population overlap                       | 2.87 (1.57–5.26)    | 598.55 | 4  | <0.0001 | 99.33  |
| 28- to 49-day timepoints only            | 2.74 (1.36–5.52)    | 481.00 | 4  | 0.0047   | 99.17  |

AMI, acute myocardial infarction; CI, confidence interval; COPD, chronic obstructive pulmonary disease; df, degrees of freedom; RCT, randomised controlled trial.

Figure 2. Meta-analysis results on effect of prior COPD exacerbation on risk of stroke (random effects), 1–3 months after exacerbation.

CI, confidence interval; df, degrees of freedom; RE, random effects.

Weight is calculated from the inverse of the variance.
Based on type of stroke or severity of COPD exacerbation, which may indicate that these factors could be a source of heterogeneity between the included studies.

Study-level data indicate a complex relationship between exacerbation and subsequent stroke, dependent on the exacerbation definition, with higher risk observed after severe exacerbation. The peak risk increase might be reached within 1 or 2 weeks after exacerbation. 

Publication bias
For both stroke and AMI risk after COPD exacerbation, no evidence of publication bias was found when using Egger’s test (AMI p-value = 0.11; stroke p-value = 0.94), although the funnel plots showed some signs of asymmetry which could indicate publication bias (Supplementary Figures S5 and S6). However, the small number of studies makes it difficult to draw conclusions.

Discussion
To our knowledge, this is the first systematic literature review and meta-analysis of observational studies to investigate the risk of acute CV, cerebrovascular events and death following an exacerbation of COPD, and the risk of exacerbation of COPD following an acute CV or cerebrovascular event.

Table 2. Results of sensitivity analyses conducted on the meta-analysis on effect of prior COPD exacerbation on risk of stroke (random effects).

| Sensitivity analysis                  | Risk ratio (95% CI) | Q   | df | Q p-value | I² (%) |
|--------------------------------------|---------------------|-----|----|-----------|--------|
| Least adjusted                       | 1.69 [1.19–2.39]    | 149.06 | 5  | <0.0001   | 96.65  |
| Low risk of bias/non-RCT             | 1.61 [1.13–2.30]    | 148.42 | 4  | <0.0001   | 97.3   |
| Moderate exacerbation                | 1.50 [1.22–1.85]    | 4.34 | 2  | 0.110     | 53.94  |
| Severe exacerbation                  | 2.01 [1.53–2.63]    | 7.35 | 2  | 0.025     | 72.79  |
| Only ischemic stroke                 | 1.51 [1.24–1.84]    | 9.07 | 2  | 0.011     | 77.96  |
| Population overlap                   | 1.88 [1.30–2.72]    | 136.91 | 4  | <0.0001   | 97.08  |
| 28- to 49-day timepoints only        | 1.73 [1.18–2.55]    | 63.40 | 4  | <0.0001   | 93.7   |

CI, confidence interval; COPD, chronic obstructive pulmonary disease; df, degrees of freedom; RCT, randomised controlled trial

Timepoints at which risk of AMI and stroke were reported ranged widely within the included studies (3, 5, 28, 30, 49, 91 and 180 days, and 1 year). The most comparable timepoints were between 28 and 91 days and, therefore, used in this meta-analysis. However, evidence from the included studies suggests that risk of acute CV events or stroke starts increasing within days of COPD exacerbation and remains high up to a year after COPD exacerbation. RR of MI and stroke may also be highest immediately after COPD exacerbation; one study reported a significant twofold increase in risk of MI 1–5 days after exacerbation, which decreased progressively over time, while another study reported that, in patients with severe COPD exacerbation, RR was highest in the first week and declined over the following 91 days.

Risks stratified by exacerbation severity (moderate and severe) were only reported by two studies for AMI and three studies for stroke; due to the
low number of studies and the heterogeneity between studies, sub-analyses for the different exacerbation severities were not performed. However, some results from the individual studies imply a greater risk of stroke and AMI after a severe exacerbation than after a moderate exacerbation. While Goto et al.\textsuperscript{25} reported similar risks of AMI, ischemic and haemorrhagic stroke for moderate and severe exacerbations at 1-year post-exacerbation, Rothnie et al.\textsuperscript{30} reported higher risks at 91 days compared with controls after severe exacerbation than after moderate exacerbation for both AMI (incidence rate ratio = 2.58, 95% CI = 2.26–2.95 versus 1.58, 95% CI = 1.46–1.71) and stroke (incidence rate ratio = 1.97, 95% CI = 1.66–2.33 versus 1.45, 95% CI = 1.33–1.57). Portegies et al.\textsuperscript{28} reported an even higher risk of stroke in severe patients than moderate patients; at 7 weeks post-exacerbation, the hazard ratio for severe exacerbation patients was 6.66 (95% CI = 2.42–18.20) compared with 1.09 (95% CI = 0.66–1.79) for moderate exacerbation patients. While further studies are required for a clearer understanding of the impact of exacerbation severity on the risks of AMI and stroke, the evidence from these studies implies that patients with severe exacerbations may be most in need of monitoring and early interventions.

There is currently limited evidence available for the risk of cardiovascular death after a COPD exacerbation. The single study identified in our analysis that reported this outcome indicated a fourfold higher risk of cardiovascular death after an exacerbation than in non-exacerbation periods.\textsuperscript{29} Further studies to investigate these outcomes would be valuable.

The analysis has a number of limitations. First, only seven studies were identified for inclusion, indicating that the evidence base is relatively sparse. Second, high heterogeneity between the included studies was identified. Third, whereas some of the included studies reported outcomes for various subgroups, including age, sex and exacerbation severity, it was not possible to perform informative subgroup analyses due to lack of comparability and the low number of included studies. In addition, heterogeneity in the type of stroke included by the studies is a potential source of bias. Ischemic and haemorrhagic stroke could not be analysed separately as only one study reported stratified ischaemic and haemorrhagic stroke risk,\textsuperscript{25} two studies reported only ischemic stroke,\textsuperscript{18,30} and the remaining three studies combined both ischemic and haemorrhagic stroke patients in their stroke risk analysis.\textsuperscript{26,28,29}

Timepoints and periods at which risks were reported by the included studies ranged from 1 to 3 days to greater than 1 year. Our meta-analyses selected a time period of 28–91 days, which allowed all studies reporting risk of AMI or stroke to be included in the analyses. Sensitivity analyses of only studies reporting risk in the 28- to 49-day time period after exacerbation were also performed, excluding the single study that only reported risk at 91 days.\textsuperscript{7} In both the AMI and stroke sensitivity analyses, removal of this 91-day timepoint did not result in loss of significance from the main analysis. However, an additional limitation of this study is that meta-analyses to determine the risk of CV events over time could not be performed due to a scarcity of comparable data. Three studies reported risk at multiple timepoints. Rothnie et al.\textsuperscript{30} found a high risk of both stroke and MI at 1–3 and 4–7 days after severe exacerbation that declined over time up to 91 days, while this decline was less pronounced after moderate exacerbation. Kunisaki et al.\textsuperscript{27} also reported a decline in AMI risk from 30 days to 1 year, while Goto et al.\textsuperscript{25} found similar risks at 30 days and 1 year for both stroke and AMI; however, this analysis only included patients alive at 1 year after the index exacerbation.

Regarding our second research question, our searches did not identify any studies of the risk of COPD exacerbation after acute CV events that met our inclusion criteria, and therefore, this research question could not be summarised in this study. However, five studies that did not meet inclusion criteria reported significantly higher COPD exacerbation rates in the period up to 3 years after an acute CV event of stroke or AMI.\textsuperscript{31–35} Two other studies found no significant association.\textsuperscript{36,37} These studies were excluded at full-text screening as they were not assessing risk of CVD events or exacerbations in a controlled study design but were evaluating possible associations of exacerbations or CVD events with a range of patient characteristics and comorbidities. Inclusion of this study design into the review may have resulted in selection bias, as other similar studies where the outcomes of interest were not reported as a significant finding may not have been identified by our search term. Further studies could, however, explore this potential association using a controlled study design.
Future research should also allow for better understanding of subgroup analyses defined in our study by exacerbation type (moderate or severe) and their relationship with prior history of exacerbations. Identification of patients at risk of exacerbation could be clinically valuable, as it may allow earlier intervention to limit the progression of COPD and reduce its impact on CV outcomes. Other possible areas include the potential influence of COPD maintenance therapy on acute CV risk after exacerbation.

Interpretation and clinical implication

The mechanisms connecting COPD exacerbations to increased risk of acute CV outcomes are complex and uncertain. Cardiovascular and cerebrovascular diseases and COPD frequently coincide, which in part is related to shared risk factors like active smoking history, more advanced age, obesity or low socioeconomic status. However, patients with COPD are at a higher risk of chronic CV comorbidity independently of shared risk factors.7,14 Plausible mechanisms related to the risk of acute CV events include systemic inflammation (i.e. interleukin-6, C-reactive protein and fibrinogen)38–40 and hypoxemia arising from COPD exacerbations that increases pulmonary arterial pressure, leading to right heart strain.41 Others include oxidative stress, increased platelet activity and risk of thrombus formation, and tachycardia.42–44 Precipitating events like an exacerbation of COPD may lead to atherosclerotic plaque rupture and thrombosis, further modulating the risk of acute CV events.15,46 Chronic systemic inflammation can alter structure and function of arteries, contributing to endothelial dysfunction, atherosclerotic plaque formation, platelet activation and hyperactive coagulation state. Furthermore, systemic inflammation is not a constant but varies in response to infections or to other proinflammatory stimuli and acute viral or bacterial infections can trigger myocardial infarction or stroke even in populations of people without COPD.47

Although causality cannot be ascertained, it may also be possible that interventions to prevent or reduce the risk of COPD exacerbations could have wider clinical benefits in reducing the risk of acute CV events, and thus, more research is needed on this subject.

The increased risk of acute CV outcomes following COPD exacerbation, found in our meta-analysis, provides a strong rationale for patients with COPD to be monitored carefully in the months following an exacerbation to detect any warning signs of CV events or worsening of existing CV disease. This could allow treatment for CV disease to be initiated as soon as possible, which may have the potential to help reduce CV-related mortality and morbidity in patients with COPD. Although causality cannot be ascertained, interventions to prevent or reduce the risk of COPD exacerbations could have wider clinical benefits in reducing the risk of acute CV events, highlighting the need to identify patients who are at increased risk of exacerbations to optimise their treatment. A recent study, ETHOS, which compared triple inhaled therapy with dual therapy in symptomatic patients with one or more exacerbations in the previous year, provides support for this approach. In this study, triple therapy compared with long-acting muscarinic antagonist/long-acting beta agonist (LAMA/LABA) therapy reduced exacerbations, all-cause mortality (which was largely driven by a reduction in CV-related deaths) and a reduction in major adverse cardiac.48,49 One can hypothesise that ensuring COPD is optimally managed and controlled may lead to reduction of CV events. However, more research is needed to confirm these findings and the relationship between exacerbations with CV events and CV-related mortality.

Conclusion

This systematic review and meta-analysis identified a markedly increased risk of stroke and AMI following a COPD exacerbation. This suggests that patients with COPD should be closely monitored for risk of acute CV events after exacerbations, and prevention of exacerbations should be a key focus of patient management. The large heterogeneity of the studies included in this analysis, particularly the timings at which risk was reported and the variable definitions of types of CV events, as well as the limited data available on risk of CV death, highlights the need for further
research to precisely understand, prevent and manage acute CV events in the days, weeks and month after exacerbation.

**Declarations**

**Ethics approval and consent to participate**
Not applicable.

**Consent for publication**
Not applicable.

**Author contributions**

**Hana Müllerová:** Conceptualization; Funding acquisition; Investigation; Methodology; Project administration; Supervision; Writing – original draft; Writing – review & editing.

**Jonathan Marshall:** Conceptualization; Investigation; Writing – review & editing.

**Enrico de Nigris:** Conceptualization; Investigation; Writing – review & editing.

**Precil Varghese:** Conceptualization; Investigation; Writing – review & editing.

**Nick Pooley:** Data curation; Formal analysis; Methodology; Validation; Writing – review & editing.

**Nina Embleton:** Formal analysis; Methodology.

**Clementine Nordon:** Investigation; Project administration; Writing – review & editing.

**Zoe Marjenberg:** Data curation; Formal analysis; Writing – original draft; Writing – review & editing.

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**Availability of data and materials**
Not applicable.

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**Supplemental material**
Supplemental material for this article is available online.

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