Association of childhood tracheomalacia with bronchiectasis: a case–control study

Rahul Thomas, Anne Chang, Ian Brent Masters, Keith Grimwood, Julie Marchant, Stephanie Yerkovich, Mark Chatfield, Christopher O’Brien, Vikas Goyal

ABSTRACT
Objective Children with tracheomalacia can develop chronic lower airway infection and neutrophilic inflammation. It is plausible children with tracheomalacia are at increased risk of developing bronchiectasis. We hypothesised that compared with controls, tracheomalacia in children is associated with bronchiectasis.

Design Single-centre, case–control study.

Setting and patients 45 children with chest high-resolution CT (c-HRCT) confirmed bronchiectasis (cases) and enrolled in the Australian Bronchiectasis Registry were selected randomly from Queensland, and 90 unmatched children without chronic respiratory symptoms or radiographic evidence of bronchiectasis (disease controls). Cases and controls had flexible bronchoscopy performed for clinical reasons within 4 weeks of their c-HRCT.

Interventions The bronchoscopy videos were reviewed in a blinded manner for: (a) any tracheomalacia (any shape deformity of the trachea at end-expiration) and (b) tracheomalacia defined by the European Respiratory Society (ERS) statement (>50% expiratory reduction in the cross-sectional luminal area).

Main outcome measures and results Cases were younger (median age=2.6 years, IQR 1.5–4.1) than controls (7.8 years, IQR 3.4–12.8), but well-balanced for sex (56% and 52% male, respectively). Using multivariable analysis (adjusted for age), the presence of any tracheomalacia was significantly associated with bronchiectasis (adjusted OR (ORadj)=13.2, 95% CI 3.2 to 55), while that for ERS-defined tracheomalacia further increased this risk (ORadj=24.4, 95% CI 3.4 to infinity).

Conclusion Bronchoscopic-defined tracheomalacia is associated with childhood bronchiectasis. While causality cannot be inferred, children with tracheomalacia should be monitored for chronic (>4 weeks) wet cough, the most common symptom of bronchiectasis, which if present should be treated and then investigated if the cough persists or is recurrent.

INTRODUCTION
The structural airway disorders of tracheomalacia and bronchiectasis have been recognised increasingly in children in recent years, but whether there is a relationship between these two disorders remains unclear.1–4 Bronchiectasis can have many underlying causes (eg, cystic fibrosis (CF), aspiration, immunodeficiency, retained foreign body and congenital syndromes),5 6 and it has been suggested that tracheomalacia might also lead to bronchiectasis;2 5–7 The postulated mechanism for tracheomalacia causing bronchiectasis is of impaired mucociliary clearance secondary to an ineffective cough from partial airway closure,3 leading to retained secretions and subsequently to chronic lower airway infection and inflammation,4 8 9 and airway wall injury.5 10 However, an association between these two has not been evaluated by case-control or prospective studies.

Flexible bronchoscopy (FB) is the current gold standard for diagnosing tracheomalacia,4 which is defined as either a deformity in the shape of the trachea at end-expiration during spontaneous respiration11–13 or a reduction in the tracheal cross-sectional lumen during expiration.4 Although there is no consistent evidence that the anatomical severity of tracheomalacia reflects clinical severity,4 the European Respiratory Society (ERS) statement on tracheomalacia and bronchiectasis in children1 defined tracheomalacia according to the degree of tracheal collapse observed during expiration (estimated >50% reduction in the cross-sectional luminal area).

There is acknowledged limited published evidence examining whether tracheomalacia is a cause or an outcome of airway suppuration found in bronchiectasis.2 6 7 Animal model studies have demonstrated an association between tracheal collapse and bronchiectasis.14 While some retrospective cohort studies describe bronchoscopy-demonstrated
airway malacia being more common in children with recurrent lower airway infections than in controls (52% vs 13%, p=0.001). Others have failed to observe this association. A higher level of evidence is required to define if a relationship between tracheomalacia and bronchiectasis exists, since if confirmed clinicians will have to monitor their patients closely for symptoms and signs of underlying bronchiectasis. Indeed, prompt diagnosis, early treatment to avoid irreversibility and prevention of bronchiectasis are all emphasised in the ERS clinical practice guidelines for managing children and adolescents with bronchiectasis.

We therefore undertook a case–control study to determine if tracheomalacia is associated with bronchiectasis in children. Our hypothesis was that compared with controls, children with tracheomalacia (defined at bronchoscopy) have an increased risk of bronchiectasis.

METHODS

Study subjects and study design

‘Cases’ were children aged ≤18 years with radiographically confirmed bronchiectasis unrelated to CF. All who were from a single tertiary paediatric centre in Queensland (only centre in the state performing paediatric FB), Australia and enrolled in the Australian Bronchiectasis Registry were selected randomly. Cases and controls had undergone chest high-resolution CT (c-HRCT) between January 2012 and December 2018 and had an FB within 4 weeks of the c-HRCT scan. We defined bronchiectasis using paediatric radiographic criteria (bronchoarterial ratio >0.8) (see figure 1 for example) and with consistent clinical features (details in the online supplemental file 1).

‘Controls’ were children aged ≤18 years without chronic respiratory symptoms and whose c-HRCT scan did not show evidence of bronchiectasis. All had an FB within 4 weeks of their c-HRCT scan. Controls were children with a recent bone marrow transplant or had cancer and had undergone c-HRCT scans and FB because of febrile neutropaenia. Exclusion criteria for cases and controls were (1) incomplete FB recordings or (2) mediastinal lymphadenopathy resulting in extrinsic tracheal compression (thereby excluding a reversible cause of secondary tracheomalacia).

Details of FB recordings and evaluation of tracheomalacia

In our centre, all FBs are undertaken either intranasally (cases, n=45) or through a laryngeal mask (controls, n=90). The FBs for the controls (oncology patients) used a laryngeal mask to reduce the likelihood of contamination of the bronchoalveolar lavage by upper airway respiratory secretions. At our centre, FB is performed during spontaneous breathing under general anaesthesia. Muscle relaxant is not used. When assessing for tracheomalacia during FB, we do not use positive pressure ventilation. FB videos are also recorded digitally and stored. The FB videos were reviewed in a random order by an experienced respiratory paediatrician (IBM), blinded to the child’s case/control status.

The FBs were examined for the presence of tracheomalacia, recording location (upper, middle, or lower third or at the junction of these points), shape (as described previously, figure 2) and scored for severity. As definitions of tracheomalacia vary according to shape and anatomical severity (cross-sectional lumen) criteria, we used two definitions in our study to improve generalisability. Our definitions were: (a) any tracheomalacia (Any-TM) and (b) tracheomalacia as per the ERS Task Force statement (ERS-TM). For Any-TM, tracheomalacia was based on expiratory shape abnormality at end-expiration during quiet respiration, and the severity was defined as: mild (<50%), moderate (50%–75%), severe (>75%–90%) or very severe (>90%) reduction in cross-sectional area. For ERS-TM, tracheomalacia was considered present if there was >50% expiratory reduction in the cross-sectional luminal area during quiet breathing, with the severity described as mild (50%–75%), moderate (>75%–90%) and severe (>90%) reduction. When there was any doubt, another experienced respiratory paediatrician (AC) who was also blinded to the case–control status of the subject reviewed and scored the FB using the same criteria, and consensus was obtained.

Adopting a standardised data sheet, one author (RT) extracted data from the children’s medical records, bronchoscopy database, radiology results and laboratory investigations.

Statistical analysis

The sample size calculated a-priori was based on the 1:2100 reported general population incidence of airway malacia. The hypothetical proportion of cases with exposure (tracheomalacia) was assumed to be 15%. We planned two controls for each case. For a study power of 85% (two-tailed significance level of 0.05), the required sample size was 45 cases and 90 controls (using Fleiss calculation with continuity correction method).

Summary statistics are presented as medians with their corresponding IQRs for continuous variables, and as percentages for categorical variables. Logistic regression for univariable and multivariable analyses was undertaken, and ORs and adjusted

Figure 1 Axial slice from the chest tomography scan of a patient in the bronchiectasis cases group. The marked arrow shows the most obvious signet ring abnormality, characteristic of bronchiectasis (increased bronchoarterial ratio >0.8). In this slice, there are also other abnormally dilated bronchi.

Figure 2 Different shapes of tracheomalacia.
OR (ORadj) were calculated, and 95% CIs presented. We planned a-priori to assess differences between groups for age, sex and ethnicity (Indigenous Australian or non-Indigenous Australian) as these are known risk factors for either tracheomalacia or bronchiectasis. Tracheomalacia is found more common in younger children\textsuperscript{23} and males,\textsuperscript{21} while bronchiectasis is more common in Indigenous children.\textsuperscript{23} We also planned a-priori to adjust for variables in the multivariable model based on variables in the univariable analysis with p values of <0.2.

If either ‘cases’ or ‘controls’ had no patients with tracheomalacia, we planned to use exact logistic regression\textsuperscript{24} to calculate the OR and OR\textsubscript{adj} and analysed using STATA V.16 (StataCorp, Texas, USA). The rest of the data was analysed using SPSS V.26 (IBM Corporation).

**RESULTS**

The median age of the 45 (56% male) bronchiectasis cases was 2.6 years (IQR 1.5–4.1), considerably younger than that of the 90 (52% male) controls of 7.8 years (IQR 3.4–12.8). There were three (7%) and nine (10%) Indigenous children in the case and control groups, respectively. The most common aetiology of bronchiectasis was post-infectious, while haematological malignancy was the predominant disorder in controls (table 1). Four children had congenital heart disease (two each in case and control groups, see the online supplemental file 1 for further details).

The frequency of tracheomalacia in the bronchiectasis and control groups is presented in table 2. Using the Any-TM definition, tracheomalacia was diagnosed in 14 of 45 (31%) bronchiectasis cases and 3 of 90 (3%) controls. In contrast, the ERS-TM definition identified nine subjects with tracheomalacia, seven of whom (9 of 45; 20%) were bronchiectasis cases. By either definition, seven of nine (78%) cases of tracheomalacia in those with bronchiectasis were mild (50%–75%) severity. Demonstrated both age and tracheomalacia were associated with bronchiectasis, while there was no association with either sex or ethnicity. After adjusting for age, tracheomalacia remained significantly associated with bronchiectasis (OR\textsubscript{adj}=13.2 (95% CI 3.4 to infinity) using the ERS-TM definition, exact logistic regression was performed.\textsuperscript{24} The corresponding OR\textsubscript{adj}=24.4 (95% CI 3.4 to infinity) was higher than when the Any-TM definition was employed.

**Sensitivity analysis**

A post hoc sensitivity analysis was undertaken given the significant between-group disparity in ages. Removing the 16 oldest controls and the 8 youngest bronchiectasis cases (online supplemental table 1), the OR\textsubscript{adj} for the association of tracheomalacia (Any-TM) with bronchiectasis remained significant (OR\textsubscript{adj}=13.3, 95% CI 3.2 to 55) as did the association of ERS-TM with bronchiectasis (OR\textsubscript{adj}=26.4, 95% CI 3.9 to infinity) (online supplemental table 2).

**DISCUSSION**

Our case–control study involving 45 children with bronchiectasis (cases) and 90 ‘disease controls’ found that tracheomalacia was significantly associated with bronchiectasis with an OR\textsubscript{adj} up to 24.2 (95% CI 3.4 to infinity) using the ERS-TM definition. Our finding is important for several reasons. First, to our knowledge, there are no prior case–control or retrospective studies that have evaluated the association between tracheomalacia and bronchiectasis in children without CF. Second, the

---

**Table 1** Aetiology of bronchiectasis cases and the non-bronchiectasis disease controls

<table>
<thead>
<tr>
<th>Aetiology of bronchiectasis cases: n (%)</th>
<th>Control subjects: n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-infective</td>
<td>Haematological malignancy</td>
</tr>
<tr>
<td>17 (38)</td>
<td>69 (77)</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>Post-bone marrow transplant</td>
</tr>
<tr>
<td>15 (33)</td>
<td>9 (10)</td>
</tr>
<tr>
<td>Aspiration</td>
<td>Solid tumours</td>
</tr>
<tr>
<td>7 (16)</td>
<td>8 (9)</td>
</tr>
<tr>
<td>Primary ciliary dyskinasia</td>
<td>Others†</td>
</tr>
<tr>
<td>3 (7)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Others†</td>
<td></td>
</tr>
<tr>
<td>3 (7)</td>
<td></td>
</tr>
</tbody>
</table>

*Percentages do not add up to 100 because of rounding.
†One patient with haemophagocytic lymphohistiocytosis secondary to Epstein-Barr virus, one with ALK-positive histiocytosis, one with autoimmune hepatitis on immunosuppression and one with Li-Fraumeni syndrome.

**Table 2** Distribution of the shape, location and severity of tracheomalacia according to Any-TM and ERS-TM diagnostic scoring criteria

<table>
<thead>
<tr>
<th>Shape</th>
<th>Location</th>
<th>Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tracheomalacia present</td>
<td>Any-TM N=45</td>
<td>Control subjects N=90</td>
</tr>
<tr>
<td>Shape</td>
<td>Bronchiectasis</td>
<td></td>
</tr>
<tr>
<td>Triangle (left to right)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Triangle (right to left)</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Oval/flattening</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Bulging pars membranosa</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Location</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Junction upper-middle third</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Middle third</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Junction middle-lower third</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Lower third</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Throughout</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Severity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild (&lt;50%)</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Moderate (50%–75%)</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Severe (&gt;75%–90%)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Very severe (&gt;90%)</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Any-TM, presence of any tracheomalacia; ERS-TM, European Respiratory Society definition of tracheomalacia requiring >50% reduction in cross-sectional luminal area during quiet breathing.\textsuperscript{4} *Tracheomalacia was not observed in controls using ERS-TM criteria.
 association between tracheomalacia and bronchiectasis was strong and increased further when the more stringent ERS-TM diagnostic criteria were used. Third, this finding is clinically relevant as clinicians managing children with tracheomalacia will need to consider the possibility of underlying bronchiectasis if the child develops a chronic (>4 weeks) or recurrent wet/ productive cough that responds incompletely to antibiotics. Tracheomalacia, being a significant risk factor for bronchiectasis in children, is not unexpected. A retrospective study of dogs with tracheal collapse reported a six-times higher than expected prevalence of bronchiectasis. Tracheomalacia is also found commonly in children with recurrent or chronic respiratory symptoms, which can be either a precursor or a marker of underlying bronchiectasis. A retrospective Spanish study reported airway malacia (defined by >50% dynamic collapse of the airway lumen during expiration while breathing spontaneously) was more common in children with recurrent lower airway infections than in disease controls lacking this history, but undergoing FB for other clinical indications (52% vs 13%, p=0.001). Another retrospective study using the same diagnostic criteria described tracheomalacia at the time of FB in 15 of 108 (14%) children with a chronic wet cough, while in a review of 70 children with protracted bacterial bronchitis (PBB), 22 (31%) had tracheomalacia (defined as dynamic collapse of the trachea during spontaneous respiration) identified at FB. Furthermore, a prospective cohort study reported children with malacia had increased likelihood of respiratory illness frequency, severity, ‘clinically significant’ cough and often a delayed recovery, although the site and severity of malacia did not impact on the illness profile. Nevertheless, in the 5-year prospective follow-up of 166 patients with PBB, where 45% had tracheomalacia (defined as Any-TM), the prevalence of bronchiectasis was not associated with recent PBB episodes. Finally, a retrospective study involving 109 children with CF reported the prevalence of bronchiectasis was similar in those with or without tracheomalacia. However, this study did not report a sample size calculation, bronchiectasis was not a primary outcome and CF itself is an independent risk factor for developing bronchiectasis, thus compromising the study findings.

It has been hypothesised that tracheomalacia impairs mucociliary clearance leading to retained secretions from secondary to airway closure during coughing, which can lead to recurrent and/or prolonged respiratory infections. Cole’s ‘vicious cycle hypothesis’ for the pathogenesis of bronchiectasis suggests a trigger event compromises mucociliary clearance, which perpetuates endobronchial infection and inflammation, further impairing mucociliary clearance and creating a vicious cycle of infection and inflammation resulting in airway wall destruction. Another suggested mechanism is developing squamous metaplasia, which may interrupt mucociliary clearance. It is possible that tracheomalacia could predispose children to a similar vicious cycle of infection and inflammation and ultimately, bronchiectasis. Our study strengthens this biological plausibility, although a strong association does not automatically infer causality.

Given the strong association between bronchiectasis and tracheomalacia found in this study, it is reasonable to suggest that children with tracheomalacia are monitored closely for wet or productive cough. Indeed, the ERS statement on tracheomalacia and bronchiectasis recommends a low threshold for commencing antibiotics in those with wet/productive cough. Another potential intervention is introducing airway clearance techniques to aid mucociliary clearance, such as positive expiratory pressure (PEP), as recommended for children with bronchiectasis. Indeed, a PEF of 5–10 cm H₂O has been shown to increase the peak cough expiratory flow of children with tracheoesophageal repair accompanied by tracheomalacia. Although more evidence is required, a proactive approach in children with tracheomalacia might prevent bronchiectasis developing in at least some children.

The strengths of our study include a-priori case–control design with sample size calculations and tracheomalacia characterised by experienced paediatric bronchoscopists (IBM, AC) blinded to the clinical history. Additionally, we used two different commonly used definitions of tracheomalacia and undertook a sensitivity analysis to further strengthen our findings. Nonetheless, there are important limitations. First, this was a retrospective case–control study and the controls and ‘bronchiectasis cases’ were not matched evenly for age. This is important as while the natural history of tracheomalacia has not been adequately studied, its symptoms do improve with age. We accounted for this potential confounding factor by multivariable regression (correcting for age) and a sensitivity analysis demonstrated a higher OR and ORadj when tracheomalacia was defined using the ERS-TM criteria. Second, controls were children with a recent bone marrow transplant or cancer who had a c-HRCT and FB for febrile neutropaenia and thus were unlikely to be truly representative of the general population. However, this was the only feasible option as these were the only sizeable cohort of children in our centre who had the combined investigations (FB and c-HRCT) done without an underlying chronic respiratory condition. The controls had their FBs done via a laryngeal mask. In our experience, a laryngeal mask can distort the trachea which may create the appearance of tracheomalacia. However, this was not borne out in the results as there were less patients with tracheomalacia in the control group than in our cases group. Third, overall small case numbers and no tracheomalacia (using the ERS-TM definition) in controls posed a statistical challenge when performing univariable and multivariable analyses. Despite our sample size calculations with the reported incidence of airway malacia of 1 in 2100, it is possible that with a larger

### Table 3: Univariable and multivariable analyses

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>95% CI</th>
<th>P value</th>
<th>ORadj*</th>
<th>95% CI</th>
<th>P value</th>
<th>ORadj+</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchiectasis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any-TM</td>
<td>13.1</td>
<td>3.5 to 48</td>
<td>&lt;0.001</td>
<td>13.2</td>
<td>3.2 to 55</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ERS-TM</td>
<td>30.1</td>
<td>4.6 to infinity</td>
<td>&lt;0.001</td>
<td>24.4</td>
<td>3.4 to infinity</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.8</td>
<td>0.7 to 0.9</td>
<td>&lt;0.001</td>
<td>0.8</td>
<td>0.7 to 0.9</td>
<td>&lt;0.001</td>
<td>0.8</td>
<td>0.7 to 0.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>0.6</td>
<td>0.2 to 2.5</td>
<td>0.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>0.9</td>
<td>0.4 to 1.8</td>
<td>0.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Adjusted OR from multivariable analysis of Any-TM and age. 
+Adjusted OR from multivariable analysis of ERS-TM and age.
cohort, this issue may not have risen. However, we were able to overcome the issue of no tracheomalacia cases (using ERS-TM definition) by performing exact logistic regression.

In conclusion, our case–control study found tracheomalacia is significantly associated with bronchiectasis. We suggest careful monitoring and follow-up (using a multidisciplinary model) of children with tracheomalacia. Airway clearance techniques and antibiotics for wet or productive cough should be considered, especially if these symptoms become chronic or recurant, leading to investigations for underlying bronchiectasis. However, our findings require confirmation from prospective long-term observational and intervention studies.

**Author affiliations**
1 Australian Centre for Health Services Innovation, Queensland University of Technology, Brisbane, Queensland, Australia
2 Respiratory and Sleep Department, Queensland Children’s Hospital, South Brisbane, Queensland, Australia
3 Child Health Division, Menzies School of Health Research, Darwin, Australia’s Northern Territory, Australia
4 School of Medicine and Menzies Health Institute Queensland, Griffith University Faculty of Health, Gold Coast, Queensland, Australia
5 Departments of Infectious Diseases, Gold Coast University Hospital, Southport, Queensland, Australia
6 Department of Paediatrics, Gold Coast Health, Southport, Queensland, Australia
7 Faculty of Medicine, The University of Queensland Faculty of Health Sciences, Herston, Queensland, Australia
8 Department of Radiology, Queensland Children’s Hospital, South Brisbane, Queensland, Australia
9 Department of Paediatrics, Queensland Children’s Hospital, South Brisbane, Queensland, Australia

**Contributors** AC, IBM, KG, JM and VG contributed to the study design and concept. RT contributed to data extraction and collection while IBM and AC contributed to flexible bronchoscopy review part of the data collection process. RT, VG, SY and MC contributed to data analysis and had access to all data. RT contributed to drafting of the manuscript with supervision and revisions contributed to by AC, KG, IBM and JM. CO’R contributed to the manuscript draft in regard to the methods for HRCT of the chest. RT is the guarantor of the paper (taking responsibility for the integrity of the work as a whole, from inception to published article).

**Funding** The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

**Competing interests** RT has a postgraduate scholarship (for PhD) from National Health and Medical Research Council, Australia (APP1190908) and PhD top-up scholarship from Children’s Health Foundation, Queensland (RCP000077) during the conduct of the study. AC has received grants from National Health and Medical Research Council, Australia (NHMRC) and other fees to the institution from work relating to being an IDMC member of an unlicensed vaccine (GSK) and an advisory member of study design for unlicensed molecule for chronic cough (Merck) outside the submitted work.

**Patient consent for publication** Not required.

**Ethics approval** The Children’s Health Queensland Hospital and Health Service Human Research Ethics Committee granted exemption for ethics review.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** Data are available upon reasonable request. Data available from corresponding author of this manuscript.

**Supplemental material** This content has been supplied by the author(s).

**ORCID iD** Rahul Thomas http://orcid.org/0000-0001-8171-3261

**REFERENCES**
24 Exact Logistic Regression - STATA Data analysis examples. Available: https://stats.idre.ucla.edu/stata/dae/exact-logistic-regression/#:~:text=Exact%20logistic%20regression%20is%20used,combination%20of%20the%20predictor%20variables.&text=The%20estimates%20given%20by%20exact,not%20depend%20on%20the%20sample%20size.