ASTHMA-RELATED SUDDEN DEATH IN ATHLETES:

A RETROSPECTIVE ANALYSIS OF THE U.S. NCCSIR DATABASE (1982-2018)

Oliver J. Price[1,2] PhD, Kristen L. Kucera[3] MSPH, PhD, Hannah M. Price[3] BS, Jonathan A. Drezner[4] MD, Andrew Menzies-Gow[5] PhD, FRCP, James H. Hull[5,6] PhD, FRCP

[1]Clinical Exercise and Respiratory Physiology Research Group, Carnegie School of Sport, Leeds Beckett University, Leeds, United Kingdom (UK); [2]Leeds Institute of Medical Research at St. James's, University of Leeds, Leeds, UK; [3]National Center for Catastrophic Sport Injury Research in the Department of Exercise and Sport Science at the University of North Carolina at Chapel Hill, United States (US); [4]Department of Family Medicine, Sports Medicine Section, University of Washington, US; [5]Department of Respiratory Medicine, Royal Brompton Hospital, London, UK; [6]Institute of Sport, Exercise and Health (ISEH), University College London (UCL), London, UK

Corresponding author:

Dr Oliver J. Price BSc (Hons.) MRes PhD FHEA

Clinical Exercise and Respiratory Physiology Research Group

Leeds Beckett University, Leeds, Headingley Campus, LS6 3QT, UK

tel: +44 (0)113 8123 532

e-mail: o.price@leedsbeckett.ac.uk

Word count: 1090.

Running title: Asthma-related sudden death in competitive athletes.

To the Editor,

Asthma is the most common medical condition in athletes with a reported prevalence of approximately 20% [1]. Over the past two decades, the impact of asthma on athletic performance has been extensively studied [2], however, research focussing specifically on asthma-related death in athletes is limited to one study; with Becker and colleagues reporting a series of sixty-one deaths over a seven year period (1993-2000), either during or in close proximity with a sporting event [3]. We therefore undertook this study to provide comprehensive insight into the incidence of asthma-related mortality in competitive athletes.

This study was conducted as a longitudinal retrospective analysis of the United States (U.S.) National Center for Catastrophic Sport Injury Research (NCCSIR) database between 1982-2018. The NCCSIR evaluates catastrophic events including sudden death in U.S. youth, high school, collegiate, and professional athletes and has previously been employed to identify and characterise sudden cardiac death in athletes. Information concerning sudden death was obtained via autopsy reports and/or news and media reports. Fatal asthma-related cases were identified using two methods; firstly, asthma as primary diagnosis and/or cause of death, and secondly, “asthma” appearing in database text fields and subsequent review. To identify susceptible cohorts and highlight potential risk factors, athlete age, sex, sporting discipline/event, athletic standard, date of death and cause of death were examined. A systematic evaluation of prior studies reporting asthma-related deaths was conducted to consolidate findings. Data are reported descriptively and presented as absolute and percentage of total deaths. A data use and distribution agreement were granted by the NCCSIR and the study was approved by the local research ethics committee (ethics ID: 50286).

In total, one thousand two hundred and ninety-seven cases of sudden death were identified over the thirty-six-year study period. Of these, asthma was the sixth most identified cause of sudden death, with twenty-seven cases (2.1%). Twenty cases (74.1%) occurred during sporting activity (practice: n = 14; 51.9% or competition: n = 6; 22.2%), four cases (14.8%) during non-athletic activity (i.e., fatal event occurred outside sporting activity or vigorous physical exertion) and three cases (11.1%) remained unclassified. Asthma-related deaths occurred most frequently in male athletes (n = 25; 96%) (age range: 12-22 years) regularly participating in high-intensity intermittent-based sports: American football (74.1%); basketball (7.4%); soccer (3.7%), swimming (3.7%), wrestling (3.7%), volleyball (3.7%) and cheerleading (3.7%). Other causes of sudden death included seven-hundred and sixty-five (59%) attributed to a cardiac aetiology; one hundred and ninety-nine (15.3%) to catastrophic traumatic brain injury; ninety-one (7%) to heat stroke; forty-four (3.4%) to other traumatic injury; thirty-two (2.5%) to commotio cordis; twenty-two (1.7%) to cervical spine injury, and 9% to all other causes. Of note, an additional ten cases (male: n = 6) (age range: 15-18 years) of sudden death attributed to a cardiac aetiology (primary cause listed) also had a confirmed asthma diagnosis: American football (n = 2); basketball (n = 3); soccer (n = 3); swimming and other (n = 1), respectively. Overall, thirty-seven asthma-related cases (2.9%) were identified via autopsy reports: n = 13; media reports: n = 34; autopsy + media report: n = 12.

This longitudinal analysis of a national database revealed that asthma is the sixth most common cause of death in young competitive athletes. Although comparatively rare when compared with cardiac aetiologies, asthma still accounted for approximately one death per year over almost four decades of study. This finding highlights the need for on-going work to understand the factors underpinning asthma mortality in young athletes, but at the same time, should act to provide data to allow clinicians to have a balanced and informed discussion with asthma patients regarding the low risk of undertaking exercise.

It is now widely recognised that regular exercise plays an important role in asthma management [4]. Despite this, some individuals with asthma may be actively discouraged from participating in sport because of a perceived risk of serious adverse events. Indeed, most scientific publications reviewing asthma in athletes cite a recognised morbidity and mortality in any introductory text. Our data aligns with prior data in the sport-related literature [3, 5-10] (Table 1), indicating that sudden death associated with asthma is uncommon (range of total deaths: 0.8-4.9%). It is also consistent with prior retrospective case analyses, such as the UK National Review of Asthma Deaths (NRAD). Specifically, one hundred and ninety-five asthma-related deaths were identified over a one-year period [11], yet none were associated with sporting activity or vigorous physical exertion (personal communication with Dr Mark Levy - Clinical Lead for NRAD 2011-2014).

On this basis, it would be scientifically unjustified to amplify the risk of asthma-related complications to discourage sporting engagement. Irrespective, any death in a young otherwise healthy individual is tragic and thus moving forward there is a need to prospectively record and interrogate events in a more robust way, to help determine pathophysiological mechanism(s) and identify factors that might mitigate risk (e.g., measurement of inflammatory patterns to determine whether treatment strategies are in line with modern Global Initiative for Asthma Management (GINA) recommendations etc.) [12]. Our ability to draw robust conclusions in this respect and evaluate temporal change is confounded by the small number of events, however we found that cases of asthma-related death occurred most frequently within the past ten years in association with sporting events characterised by vigorous intensity with repeated sprint activity, notably in male adolescent or young adults. That being said, the incidence of asthma-related death according to sporting discipline may be impacted by the popularity and frequency of participation in certain countries. For example, the number of young athletes participating in American football and basketball is significantly greater in the US in comparison to

mainland Europe, whereas epidemiological studies conducted over the past decade consistently report a higher prevalence of asthma in winter and pool-based athletes [13]. A further potential limitation of our analysis is the paucity of accessible details regarding treatment, prior severity of disease and other clinical characteristics (e.g., markers of airway inflammation). We were also unable to interrogate or re-analyse pathological findings and for the most part reliant on the attending pathologist statement.

In summary, asthma remains a rare but important cause of sudden death in young athletes. Over the study period, approximately one athlete with asthma died per year (amongst an estimated 8-million high school and college athletes), thus highlighting that with appropriate medical management, sports participation for people with asthma is generally safe and associated with a low risk of serious adverse outcome. Further prospective evaluation remains a priority to improve our understanding of associated risk factors and to prevent future fatalities.

Acknowledgements

Nil.

Funding statement

The National Center for Catastrophic Sports Injury Research (University of North Carolina at Chapel Hill), is funded by the National Collegiate Athletic Association, the National Federation of State High School Associations, the American Football Coaches Association, the National Athletic Trainers' Association, the National Operating Committee on Standards for Athletic Equipment, and the American Medical Society for Sports Medicine.

Competing interests

AMG reports grants and personal fees from Astra Zeneca, personal fees and other from Teva, personal fees from Glaxo SmithKline, personal fees from Novartis, personal fees from Vectura, personal fees from Sanofi, outside the submitted work. OP, KK, HP, JD, JH have no real or perceived conflict of interest in respect of this manuscript.

Contribution statement

Conception and design: OP, KK, JD, JH; analysis and interpretation: OP, JH; drafting the manuscript for important intellectual content: OP, KK, HP, JD, AMG, JH.

Guarantor statement

OP and JH confirm full responsibility for the content of the manuscript.

References

1. Parsons JP, Hallstrand TS, Mastronarde JG, Kaminsky DA, Rundell KW, Hull JH, Storms WW, Weiler JM, Cheek FM, Wilson KC, Anderson SD, Bronchoconstriction ATSSoE-i. An official American Thoracic Society clinical practice guideline: exercise-induced bronchoconstriction. *Am J Respir Crit Care Med* 2013: 187(9): 1016-1027.

2. Price OJ, Hull JH, Backer V, Hostrup M, Ansley L. The impact of exercise-induced bronchoconstriction on athletic performance: a systematic review. *Sports Med* 2014: 44(12): 1749-1761.

3. Becker JM, Rogers J, Rossini G, Mirchandani H, D'Alonzo GE. Asthma deaths during sports: report of a 7-year experience. *J Allergy Clin Immunol* 2004: 113(2): 264-267.

4. Hansen ESH, Pitzner-Fabricius A, Toennesen LL, Rasmusen HK, Hostrup M, Hellsten Y, Backer V, Henriksen M. Effect of aerobic exercise training on asthma in adults: a systematic review and meta-analysis. *Eur Respir J* 2020: 56(1).

5. Van Camp SP, Bloor CM, Mueller FO, Cantu RC, Olson HG. Nontraumatic sports death in high school and college athletes. *Med Sci Sports Exerc* 1995: 27(5): 641-647.

6. Maron BJ, Shirani J, Poliac LC, Mathenge R, Roberts WC, Mueller FO. Sudden death in young competitive athletes. Clinical, demographic, and pathological profiles. *JAMA* 1996: 276(3): 199-204.

7. Maron BJ, Doerer JJ, Haas TS, Tierney DM, Mueller FO. Sudden deaths in young competitive athletes: analysis of 1866 deaths in the United States, 1980-2006. *Circulation* 2009: 119(8): 1085-1092.

8. Boden BP, Breit I, Beachler JA, Williams A, Mueller FO. Fatalities in high school and college football players. *Am J Sports Med* 2013: 41(5): 1108-1116.

9. Maron BJ, Haas TS, Ahluwalia A, Murphy CJ, Garberich RF. Demographics and Epidemiology of Sudden Deaths in Young Competitive Athletes: From the United States National Registry. *Am J Med* 2016: 129(11): 1170-1177.

10. Boden BP, Fine KM, Breit I, Lentz W, Anderson SA. Nontraumatic Exertional Fatalities in Football Players, Part 1: Epidemiology and Effectiveness of National Collegiate Athletic Association Bylaws. *Orthop J Sports Med* 2020: 8(8): 2325967120942490.

11. Royal College of Physicians. Why Asthma Still Kills: The National Review of Asthma Deaths (NRAD) Confidential Enquiry Report. London, RCP, 2014. www.rcplondon.ac.uk/sites/default/files/why-asthma-still-kills-full-report.pdf

12. Reddel HK, FitzGerald JM, Bateman ED, Bacharier LB, Becker A, Brusselle G, Buhl R, Cruz AA, Fleming L, Inoue H, Ko FW, Krishnan JA, Levy ML, Lin J, Pedersen SE, Sheikh A, Yorgancioglu A, Boulet LP. GINA 2019: a fundamental change in asthma management: Treatment of asthma with short-acting bronchodilators alone is no longer recommended for adults and adolescents. *Eur Respir J* 2019: 53(6).

13. Price OJ, Ansley L, Menzies-Gow A, Cullinan P, Hull JH. Airway dysfunction in elite athletes--an occupational lung disease? *Allergy* 2013: 68(11): 1343-1352.

Table 1. Studies reporting asthma-related deaths in athletes.

First author (ref)	Year	Method and study population	Key findings
Van Camp et al. [5]	1995	Analysis of non-traumatic deaths in high school and college athletes obtained by NCCSIR between 1983-1993	• Total cases of sudden death (n = 160) (n = 136 with adequate information available to review death); cardiovascular aetiology (n = 99; 73%); non-cardiovascular (n = 29; 21.3%); cardiovascular + non-cardiovascular (n = 1; 0.7%); undetermined cause (n = 7; 5%); a**sthma: n = 4; 2.9%**
Maron et al. [6]	1996	Analysis of clinical information and circumstances associated with sudden death in US athletes between 1985-1995	• Total cases of sudden death (n = 158); cardiovascular aetiology (n = 134; 85%); non-cardiovascular (n = 24; 15%); **asthma: n = 3; 1.9%**
Becker et al. [3]	2004	Analysis of a US news release service and autopsy reports to identify subjects who had died during or immediately after a sporting or athletic event between 1993-2000	• **Total cases of asthma-related death (n = 61)** • Age: n = 49/61 (81%) of the cohort were younger than 21 years • Sex: n = 42/61 (69%) of the cohort were male • Race: white deaths n = 39 (64%); black deaths n = 20 (33%); others n = 2 (3%) • Standard: n = 35/61 (57%) competitive athletes; n = 26/61 (43%) recreational athletes • Event: n = 18/35 (51%) competitive athletes had a fatal event during sport • Sport: basketball (21%) and track events (12%) most common activities associated with asthma-related death
Maron et al. [7]	2009	Analysis of the US National Registry of Sudden Death in Athletes between 1980-2006	• Total cases of sudden death (n = 1866); cardiovascular aetiology (n = 1049; 56%); non-cardiovascular (n = 817; 44%); **asthma: n = 15; 0.8%**
Boden et al. [8]	2013	Analysis of football fatalities reported to the NCCSIR between 1990-2010	• Total cases of sudden death (n = 243); cardiovascular aetiology (n = 100; 41%); non-cardiovascular (n = 143; 59%); **asthma: n = 7; 2.9%**
Maron et al. [9]	2016	Analysis of the US National Registry of Sudden Death in Athletes between 1980-2011	• Total cases of sudden death (n = 2406); unknown cause (n = 214; 9%); cardiovascular aetiology (n = 842; 35%); collapse without diagnosis (n = 464; 19%); non-cardiovascular (n = 886; 37%); **asthma: n = 20; 0.8%**
Boden et al. [10]	2020	Analysis of non-traumatic fatalities in football players using the National Registry of Catastrophic Sports Injuries (NRCSI) between 1998-2018	• Total cases of sudden death (n = 191) (n = 182 included for comprehensive review); cardiovascular aetiology (n = 105; 57.7%); non-cardiovascular (n = 77; 42.3%); **asthma: n = 9; 4.9%**
*Price et al.	2020	Analysis of NCCSIR database between 1982-2018	• Total cases of sudden death (n = 1297); cardiovascular aetiology (n = 765; 59%); non-cardiovascular (n = 532; 41%); **asthma: n = 27; 2.1%**