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Oral health of elite athletes and association with performance: a systematic review

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ABSTRACT

Background We aimed to systematically review the epidemiology of oral disease and trauma in the elite athlete population and to investigate the impact of oral health on sporting performance.

Methods Authors searched Ovid MEDLINE (1950 to October 2013), Ovid EMBASE (1980 to October 2013), EBSCO SPORTDiscus (up to October 2013) and OpenGrey (<http://www.opengrey.eu>). No date or language restrictions were applied. Papers were included if they evaluated the oral health of professional athletes. The methodological quality of papers was evaluated using a modification of the Newcastle-Ottawa scale.

Results The literature search led to 9858 potentially relevant citations. Following a set of predefined exclusion criteria, 34 studies remained. Twenty-six studies reported on dental trauma, which ranged in prevalence from 14% to 47% varying by sport and country. Sixteen studies considered the oral health of athletes and reported high prevalence of oral diseases: dental caries 15–75%, dental erosion 36–85%, periodontal disease 15%. In four studies, a range between 5% and 18% of athletes reported negative impact of oral health or trauma on performance. The methodological quality of included studies was generally low.

Conclusions Within the limits of the review, oral health of athletes is poor. We hypothesise that poor oral health associates with self-reported performance; however, this needs to be tested. Further studies on representative samples of athletes are needed to assess the size of the problem of poor oral health as well as to investigate the possible impact on performance using objective measures of performance.

INTRODUCTION

Oral health is an important element of overall health, well-being and quality of life. The nexus between sport and oral health has largely been investigated through studies focused on the risk of trauma to oral health. However, athletes may have poor oral health including high levels of dental caries, dental erosion and dental trauma.¹ Poor oral health can reduce quality of life and induce a systemic inflammatory response.^{2–3} Thus, poor oral health could affect athletic performance.⁴ However, the relationship between oral health and performance is not well understood. Therefore, we aimed to systematically review the evidence to determine the epidemiology of oral disease and trauma in the elite athlete population. We also investigated the impact of oral health on sporting performance.

METHODS

We conducted a systematic review of the available literature to answer the focused question—What is

the oral health of athletes and what is the effect of oral health on athletic training and performance?

The following eligibility criteria were used when considering studies for this review:

- All types of study design;
- Elite/professional athletes;
- Any outcome measure of oral health (eg, Decayed Missing Filled Teeth (DMFT)) or any impact of oral health on athletic performance.

Studies assessing the impact of *interventions* on oral health were not included as the aim of this study was to review the epidemiology of oral conditions.

Search methods for identification of studies

Electronic searches

We searched Ovid MEDLINE (1950 to October 2013), Ovid EMBASE (1980 to October 2013), EBSCO SPORTDiscus (up to October 2013) and OpenGrey (<http://www.opengrey.eu>). No date or language restrictions were applied. We anticipated a wide range of terms for possibly relevant studies and therefore designed a sensitive electronic search strategy.

In MEDLINE we developed a subject-specific search strategy using the following MeSH terms: Dentistry, Oral Health, Stomatognathic Diseases, Dental Auxiliaries, Dental Staff, Dentists, Halitosis, Stomatognathic System, Facial Pain, Dental Health Education, Maxillofacial Injuries, Jaw Fractures, Mandibular Injuries, Sports, Physical Fitness, Exercise, Physical Exertion, Athletic Injuries, Sports Medicine, Athletes. This search strategy was adapted for EMBASE and SPORTDiscus. The following search filters were used to identify randomised controlled trials and observational studies: Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity-maximising version (2008 revision); SIGN Observational Studies search filter (MEDLINE); SIGN Randomised Controlled Trials search filter (EMBASE); SIGN Observational Studies search filter (EMBASE).⁵

Searching other resources

We checked the reference lists of included studies.

Data extraction

Papers potentially suitable for inclusion were selected from the title and abstracts by one of the authors (PA). Data extraction was then carried out by two of the authors in duplicate and independently (EC and AT). Disagreements were resolved by discussion. Data extraction was carried out with a specially developed form (piloted before use). Data extracted related to the type of study, methodological quality, type of sport and oral health and its impact or association with performance.

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Since the research question was answerable by observational studies, we assessed their methodological quality using a modification of the Newcastle-Ottawa scale for cross-sectional or cohort studies.⁶ Papers were assessed according to the type of study design, whether they had a clearly stated study objective, if a control population was used and whether oral health was assessed using examination by a dental health professional or athlete self-report. In view of the anticipated heterogeneity of studies we did not plan to conduct meta-analysis of the data.

RESULTS

We carried out the searches in October 2013. The adopted search strategies led to 9858 potentially relevant citations. After examination of the title and/or abstract, 9723 of these studies were excluded because they did not meet the inclusion criteria. Of the 135 studies retrieved for full text screening, we excluded a further 101 as they were not relevant to the research question. Thirty-four studies were finally eligible for the review.^{1 7–39}

Characteristics of included studies

The greatest proportion of studies was from Europe (38%) with the remainder distributed across the globe. Publication dates ranged from 1969¹⁹ to 2013¹ (table 1). A wide range of sports were evaluated, with Olympic events well represented. The average number of participants per study was 324 with a minimum of 18¹⁵ and a maximum of 2739.⁹ These studies are summarised in online supplementary table S1.

Methodological quality

In general, methodological quality was low with all the studies being at risk of bias (online supplementary table S2). Three of the studies attempted to relate the athlete data to a comparison population.^{17 25 29} Examiner training or calibration was limited or not reported. Convenience sampling (as opposed to complete or random) was commonly used, particularly when studies were carried out as part of larger sporting events.

For the purposes of this review, studies were divided into two different categories:

1. Epidemiological survey—These were studies where athletes were examined to determine the prevalence of a specific condition (34% of all studies). They were characterised by either having an independent dental examiner screening a population for a particular disease or by relying on self-reported data with no validation by oral examination. Sampling was either by random selection or a convenience sampling approach.
2. Injury or treatment audit—These were studies where prevalence or incidence of a specific condition was determined by presentation at a clinic for treatment of that condition or by using retrospective cohort data from treatment records or databases (32% of all studies).

Epidemiology of oral diseases and trauma

Oral diseases or conditions in the context of this review were divided into dental trauma, caries, periodontal disease, erosion/wear and pericoronitis/impacted third molars. These are summarised below. We judged that data from epidemiological studies were likely to be less susceptible to bias than data from injury/treatment audits and that self-reported oral health data were subject to the highest bias. Therefore data for the different oral conditions are presented separately in each of these three categories.

Dental trauma

Study characteristics

Trauma was reported in the majority of studies (n=28 papers, 82% of all included studies) and as primary outcome in 19 studies (56%). Basketball, ice hockey and rugby were the most frequently investigated sports (table 1). The types of trauma evaluated also varied greatly with studies evaluating some or all of the following: maxillary/mandibular fractures, tooth fractures/avulsions, oral lacerations, facial lacerations and contusions. These were often grouped together so it was not always possible to separate out data for tooth injuries from other injuries of the face or head.

Data were reported either as a proportion of all injuries, of all participants or of all athlete exposures. Sampling frames were either the incidence of trauma recorded over a set period of time or over the entire career of an athlete (usually retrospective) or prevalence of trauma as assessed at the examination. Data on incidence was difficult to summarise, as the total time period was often not reported. We have assumed that data were reported per patient rather than per tooth, although this was not always clear.

Injury audits were the most common design (n=13, 38%). With the exception of Dorney,¹⁷ Ma,²⁵ and Persson and Kiliaridis,²⁹ control groups were not used for comparison of trauma incidence.

Outcome data

We could not summarise the range of incidence as sampling frames were poorly reported (table 1). The prevalence of sport-related dental trauma varied greatly between studies (range 14–57%) and between the types of sport investigated. Studies where comparison groups were reported showed a higher prevalence of trauma in the professional/elite group compared with the controls: professional basketball players 80.6% versus semi-professional players 47.7%,²⁵ wrestlers 57.7% versus controls (non-athletes) 26.9%.²⁹ Data on mouthguard use (or other facial protection) were reported in 43% of studies. When reported, it was unclear whether mouthguards were used before or after a dental injury was experienced. Uptake of mouthguards was variable (0–84.6%) with the highest uptake rates seen in rugby.

Despite these limitations, it appears that approximately half of athletes in certain sports when asked about their career to date reported an experience of mouth or face injury. However, in one study, although 48% had experienced dental trauma, only 26% of the entire sample had experienced dental trauma related to their sport.⁷

Caries

Caries was evaluated in 15 studies (44%) and recorded as DMFT or Decayed Missing Filled Surfaces (DMFS), treatment provided or proportions of athletes with caries. Most of the studies were epidemiological surveys (n=11, 73%) with the remainder treatment audits (table 2). There was a significant burden of disease in the athlete population. Where caries was recorded as a proportion, it ranged from 15% to 75% of all athletes (excluding fillings, extractions, etc). Only one of the studies attempted to compare the athletes with a control population²⁹ (age-matched non-athlete control). Caries levels in wrestlers and the control population were similarly high. However, the control group was selected from ‘regular patients’ and may not represent a normal population. None of the other studies compared data with either controls or population norms. Owing to this lack of comparative data, it is difficult to make

Table 1 Maxillofacial trauma in sport for different study types

Sport	Study type	Author/number of participants	Sport-related maxillofacial/dental injury	Sampling frame	Mouthguard use
Basketball	Injury or treatment audit	Deitch <i>et al</i> ¹⁶ n=1145	1.2% National Basketball Association, 1% Womens National Basketball Association	1996–2002	Not reported
	Epidemiological survey (self-reporting)	Azodo <i>et al</i> ⁸ n=156 Frontera <i>et al</i> ²⁰ n=388 Ma ²⁵ n=77	69.2% 50% 42%	Previous year (unclear) Any sport-related trauma to date Any sport-related trauma to date	Not reported 1% Not reported
Field hockey	Epidemiological survey (self-reporting)	Bolhuis <i>et al</i> ¹⁰ n=279	62%	Self-report, ever been injured	33%
Football	Epidemiological survey (oral examination)	Gay-Escoda ²¹ n=30	23%	2003–2006	0%
Karate	Injury or treatment audit	Randell ³¹ n=34	26.5%	1983	Not reported
		McLatchie ²⁶ n=295	2%	1975	Not reported
Ice hockey	Epidemiological survey(oral examination)	Stuart <i>et al</i> ³⁶ n=282	14.2% all head and neck injuries	One season	Unclear
	Injury or treatment audit	Kuzuhara <i>et al</i> ²³ n=94 Petterson and Lorentzon ³⁰ n=376 Sane <i>et al</i> ³² number unclear	13% of all injuries reported 2.2% all traumatic injuries 11.5% all traumatic injuries	2002–2005 1986–1990 Unclear	Not reported Not reported Not reported
Multisports games	Epidemiological survey (oral examination)	Andrade <i>et al</i> ⁷ n=120	26.3%	Any sport-related trauma to date	Not reported
Rugby	Injury or treatment audit	Needleman <i>et al</i> ¹ n=278	17.6% athletes attending the clinic	2012 Olympic games	32.7% all athletes presenting with trauma
		Sharma <i>et al</i> ³³ n=342	0.6% athletes attending the clinic	2010 Commonwealth games	Not reported
		Soler Badia <i>et al</i> ³⁴ n=266	1% athletes attending the clinic	1992 Olympic Games	Not reported
		Vougiouklakis <i>et al</i> ³⁸ n=658	3% athletes attending the clinic	2004 Olympic and Paralympic games	Not reported
	Epidemiological survey (self-reporting)	Yang <i>et al</i> ³⁹ n=795	0.4% athletes attending the clinic	2008 Olympic games	Not reported
		Needleman <i>et al</i> ¹ n=278	30%	Self-report, ever been injured	98% all athletes
	Injury or treatment audit	Dorney ¹⁷ n=25	52%	Unclear	62% of all players who experienced trauma
		Chapman and Nasser ¹² n=102	26.9–42.3%	Any sport-related trauma to date	79.2–84.6%
		Davies <i>et al</i> ¹³ n=281	45%	Any sport-related trauma to date	24%
		Kay <i>et al</i> ²² n=63	54%	Any sport-related trauma to date	63%
Epidemiological survey (self-reporting)	Muller-Bolla <i>et al</i> ²⁸ n=1140	29.6%	Any sport-related trauma to date	64%	
	Stokes and Chapman ³⁵ n=21	47.6%	Any sport-related trauma to date	85.7	
	Beis <i>et al</i> ⁹ n=2739	3 per 1000 athlete exposures (oral and facial)	1994/1995	Not reported	
Wrestling	Epidemiological survey (oral examination)	Persson and Kiliaridis ²⁹ n=51	57.7% wrestlers 26.9% age-matched controls (non-athlete)	Unclear	Not reported
Wrestling	Injury or treatment audit	Faye <i>et al</i> ¹⁸ n=125	63%	Any sport-related trauma to date	0%

Data is reported as proportion of athletes experiencing trauma unless described otherwise in the text. Data from audits and self-reported surveys describes incidence; data from epidemiological surveys with oral examination describes prevalence.

Table 2 Caries, periodontal disease, dental erosion/tooth wear, pericoronitis and TMJ disease

Sport	Study type	Author/number of participants	Caries	Periodontal disease	Dental erosion/tooth wear	Pericoronitis/impacted third molar	TMJ disease
Biathlon	Epidemiological survey (oral examination)	Lundell ²⁴ n=31	22% with caries	Periodontal disease requiring care=6%	Not reported	39% required wisdom tooth removal	6% TMJ disorder
Cycling	Epidemiological survey (oral examination)	Milosevic <i>et al</i> ²⁷ n=20	Mean DMFS=11.6 (SD 8.4)	Not reported	85% athletes with wear into dentine	Not reported	Not reported
Football	Epidemiological survey (oral examination)	de Sant'Anna <i>et al</i> ¹⁵ n=18	Mean DMFT=8	Not reported	Not reported	Not reported	Not reported
		Gay-Escoda <i>et al</i> ²¹ n=30	Mean DMFT=5.7 (SD 4.1)	Plaque score=2.3 (SD 1.1) Gingival score=1.1 (SD 0.8) Pocket depth=1.9 mm (SD 0.3)	Not reported	Not reported	6.7% with deviation on opening, clicking in 16.7%
		Randell ³¹ n=34	21% with untreated caries/pulp exposures	3% advanced periodontal disease	Not reported	32% with impacted third molars	Not reported
Olympic sports/ Mixed sports	Epidemiological survey (oral examination)	de Cardenas ¹⁴ n=209	75.12% with caries	Not reported	Not reported	Not reported	Not reported
	Injury or treatment audit	Forrest ¹⁹ n=350	Mean DMFT ranged from 2.8 to 16.8	Mean periodontal score ranged from 0.6 to 2.2	Not reported	4% all emergency visits were for pericoronitis	Not reported
		Needleman <i>et al</i> ¹ n=278	41% with caries into dentine	76% BPE 1 or 2 15% BPE 3 or 4	Present in 44.6% of athletes	9.9% with pericoronitis	Not reported
		Szekely ³⁷ n=197	Caries was 23% of all diseases	Not reported	Not reported	Not reported	Not reported
		Sharma <i>et al</i> ³³ n=342	Fillings/temporary fillings 20%, endodontics 3%, extractions 1%	Not reported	Not reported	Not reported	Not reported
		Soler Badia <i>et al</i> ³⁴ n=266	Broken/lost filling 20%, pulpitis 18%, caries 15.8% (athletes only)	Not reported	Not reported	4.6% with pericoronitis or impacted wisdom teeth	Not reported
Vougiouklakis <i>et al</i> ³⁸ n=658	Fillings/temporary fillings 50%, endodontics 13%, extractions 16%	Not reported	Not reported	Not reported	Not reported		
Swimming	Epidemiological survey (oral examination)	Yang <i>et al</i> ³⁹ n=795	Fillings/temporary fillings 29%, endodontics 16%, extractions 3%	Periodontal treatment 4%, Data from athletes and non-athletes	Not reported	Not reported	0.15% of all visits to the Olympic dental clinic
		Milosevic <i>et al</i> ²⁷ n=205	DMFS=6.2 (SD 8.6)	Not reported	36% wear into dentine	Not reported	Not reported
Triathlon	Epidemiological survey (oral examination)	Bryant <i>et al</i> ¹¹ n=31	DMFT 0–4 in 6 cases, 9 in 2 cases Patients self-reported as moderate to high caries risk	'Good'	Not reported	Not reported	Not reported
Wrestling	Epidemiological survey (oral examination)	Persson and Kiliaridis ²⁹ n=51	DFT 9.4 (SD 3.9) wrestlers DFT 8.2 (SD 5.5) control population	Not reported	Not reported	Not reported	No difference between test wrestling and control (<0.05) (1 individual per group with TMJ tenderness)

BPE, basic periodontal examination; DFT, decayed and filled teeth; DMF, Decayed Missing Filled; DMFS, DMF surfaces; DMFT, DMF Teeth; TMJ, temporomandibular joint.

any statements regarding the oral health of elite athletes relative to a non-athlete population.

Periodontal disease

Periodontal disease was evaluated in seven (21%) of the studies by a diverse group of measures including the Basic Periodontal Examination, plaque, gingivitis and an overall qualitative assessment (table 2). The prevalence of irreversible moderate to severe periodontal disease was reported to be up to 15% with gingivitis up to 76%.¹ Data from control groups, or population norms, were not presented.

Dental erosion/tooth wear

Dental erosion/tooth wear was reported in four studies (12%) with no data from control populations. Proportions of athletes with wear into dentine were high, ranging from 36% to 85% (table 2), with only one study recording no wear.¹¹

Pericoronitis/impacted third molar

Five studies reported on pericoronitis or impacted third molars. In all of the studies at least some athletes were either exhibiting symptoms related to pericoronitis or were judged to require removal of one or more wisdom teeth (range, 4.6–39%; table 2).

Other oral health problems

Temporomandibular joint dysfunction (TMD) was reported by four studies,^{21 24 29 39} with a low reported prevalence overall (table 2).

Impact of oral health on well-being, training and performance

Four studies reported the impact of oral health on performance using athlete-reported outcome measures with two studies focusing on Olympic athletes,^{1 34} one on basketball players²⁰ and one on footballers.²¹ Impact was not the primary outcome for any of these studies and the validity of most tools to assess impact is unknown. However, all studies reported an impact of oral health on performance. In one of these,³⁴ data from athletes and non-athletes were combined (only 54% of respondents were athletes). Eight per cent of those surveyed thought that oral problems had disturbed their training and 5% thought it had affected their sporting performance. A second study was a cross-sectional, prospective evaluation of the oral health of athletes competing in the 2012 London Olympics.¹ Athletes underwent a full oral examination, and the impact of oral health on performance was assessed using a modification of the shortened global evaluation of impact of oral health on quality of life.⁴⁰ Responses were scored on a five-point scale. More than 40% of athletes were bothered by their oral health with 28% reporting an impact on quality of life and 18% on training and performance. Exploratory analysis suggested that impact was significantly associated with levels of caries whether analysed by median number of carious lesions per athlete or number of athletes with caries ($p < 0.001$).

A relationship between oral health (dental plaque index) and performance (number of intrinsic injuries, ie, muscle, ligament/tendon or bone) was also found in a study at Barcelona football club.²¹ However, the potential significance of this, or mechanism for the relationship, was not explored.

Finally, Brazilian basketball players reported in a questionnaire-based study²⁰ increased insecurity about playing after match-related orofacial trauma (33% of those sampled).

Sixty-six per cent reported that oral problems could ‘diminish their strength’.

DISCUSSION

Key findings

Our primary outcome is that in contrast to the common perception that athletes are healthy ‘all over’, the oral health of sampled athletes is poor. Caries occurred in up to 75% of athletes surveyed; athletes experienced other oral problems such as periodontal disease, dental erosion and dental trauma. Data from studies examining oral health and performance suggested that poor oral health had a negative effect on athlete’s self-reported training and performance.

Strength and limitations of included evidence

There were many challenges to drawing robust conclusions from the available literature. For instance, while we retrieved 34 eligible studies, most were focused on dental trauma with less than half of the studies reporting more broadly on oral health. A low level of methodological quality of many of the studies further restricted our ability to draw conclusions. In addition, data on the impact of oral health on well-being and performance was extracted mostly from one study and should be interpreted with caution.

Risk of bias

In general all studies assessed in this review were subject to one or more forms of methodological bias (online supplementary table S2). These included lack of reported training or calibration of outcome assessors and use of convenience samples. Therefore, it is not clear whether the data are truly representative of athletes. A lack of data for comparison groups within studies—that is, matched other than elite sport participation—is another common issue. Without an understanding of the control group, it is more difficult to determine the portion of risk of disease attributable in some way to elite sport and also to compare differences between sports and locations.

Outcome assessment

The outcome measures varied between studies. For example, caries-related outcomes included DMFT, untreated decay, decayed surfaces and filled teeth. This lack of consistency between trials made comparison of results difficult. Agreement on a common data set would facilitate comparison between studies and changes over time. Most studies did not report on examiner calibration or repeatability training resulting in greater uncertainty around the accuracy and validity of the data. The large number of studies (34%) relying on non-validated self-reporting of health data was also problematic.

Athlete-reported impacts on performance, like other patient-reported outcome measures, could be an important approach for capturing outcomes from athletes.⁴¹ Further research of such outcomes is potentially a promising approach to understanding the athlete perspective on injury and illness. In addition, outcome measures that quantify effects on performance could also be assessed including time lost to training and severity of impact.⁴²

Significance of findings and possible mechanisms

Data from this review suggest that athletes have poor oral health. This is a striking finding considering that the most prevalent oral health conditions in this review are preventable, that is, dental caries, erosion and periodontal diseases and also that these individuals have otherwise excellent general health.

According to the Olympic Charter, the International Olympic Committee and the International Sport Federations have an obligation 'to encourage and support measures protecting the health of athletes'.⁴³ Oral health is an area that has perhaps been overlooked previously when considering athletes' health.

The possible negative impact from poor oral health on elite performance warrants further investigation, although this is not a new finding.¹⁹ It is highly plausible that oral health could affect performance in view of the well-recognised effects of oral health on health-related quality of life.⁴⁰ Mechanisms could include pain, effects on eating, psychological impacts and raised systemic inflammatory burden, and will need detailed investigation. Reduced performance due to poor oral health is unacceptable as well as preventable. The effect of poor oral health on these athletes in later life is also unknown but is likely to cause considerable impacts, including a high treatment need, tooth loss, reduced oral function and psychological effects.⁴⁰

Possible sport-related causes of poor oral health include frequent dietary intake of carbohydrates,¹¹ physiological changes such as decreased salivary flow and drying of the mouth during exercise⁴⁴ and exercise-induced immune suppression.⁴⁵ Demanding training regimes might make it difficult to access preventive care. Other challenges to oral health might include low levels of oral health literacy, beliefs of the athlete and their support network, and a lack of prioritisation of oral health within sport. There is a clear need to investigate these barriers and facilitators.

Interestingly, poor oral health did not seem to be related to availability (or lack thereof) of highly organised dental care. Many of the athletes in this survey were from countries with well-developed healthcare systems; this suggests that current strategies for oral care of elite athletes are not effective in maintaining oral health. Further information on the general oral health of the non-athlete population is needed for comparison.

Potential biases in this review

We made the decision to only include elite athletes as we felt this group warranted specific investigation. This focus resulted in several studies being excluded because they investigated non-elite sport including recreational athletes, schoolchildren and university-level athletes. Therefore, the findings cannot be extrapolated to other types of sport participants. Otherwise, we attempted to minimise bias in the review by developing the protocol a priori and employing duplicate data extraction. Eligibility assessment was carried out by only one researcher, which might have introduced bias in study selection.

Future research

In order to determine the true extent and severity of oral diseases in athletes across a wide range of sports and their impact on performance, epidemiological studies on representative samples are needed,⁴² employing trained examiners and validated outcome measures. Impact on performance should be investigated with the development of validated self-reporting tools¹ and by using other outcomes such as missed training or competition as a result of oral health-related illness. It is likely that poor oral health will have a negative impact on performance, this assumption should also be tested. Finally, prospective cohort studies are needed to evaluate incidence and risk.

Conclusions

Within the limits of the review, oral health of athletes is poor. We hypothesise that poor oral health associates with self-reported performance but that needs to be tested. Further

studies on representative samples of athletes are needed to assess the size of the problem of poor oral health as well as to investigate the possible impact on performance using objective measures of performance.

What are the new findings

- ▶ The oral health of athletes appears to be poor across a wide range of sports.
- ▶ Dental caries and dental erosion affect the majority of sampled athletes with irreversible periodontitis affecting up to 15% of participants.
- ▶ Poor oral health may affect athletic performance.

Contributors EC, AT, PA and IN designed the data collection tools. EC and AT extracted data from the initial data set. Search strategy and literature retrieval was by ADI. Initial analysis and draft was by EC. Final analysis and re-draft were by PA and IN. PA is the guarantor.

Competing interests None.

Provenance and peer review Not commissioned; externally peer reviewed.

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