Risk factors associated with acute respiratory illnesses in athletes: a systematic review by a subgroup of the IOC consensus on 'acute respiratory illness in the athlete'

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ABSTRACT

Objective To review risk factors associated with acute respiratory illness (ARill) in athletes, including non-infectious ARill and suspected or confirmed acute respiratory infections (ARinf).

Design Systematic review.

Data sources Electronic databases: PubMed-Medline, EbscoHost and Web of Science.

Eligibility criteria Original research articles published between January 1990 and July 2020 in English were searched for prospective and retrospective full text studies that reported quantitative data on risk factors associated with ARill/ARinf in athletes, at any level of performance (elite/non-elite), aged 15–65 years.

Results 48 studies (n=19 390 athletes) were included in the study. Risk factors associated with ARill/ARinf were: increased training monotony, endurance training programmes, lack of tapering, training during winter or at altitude, international travel and vitamin D deficits. Low tear-(SIgA) and salivary-(IgA) were immune biomarkers associated with ARill/ARinf.

Conclusions Modifiable training and environmental risk factors could be considered by sports coaches and athletes to reduce the risk of ARill/ARinf. Clinicians working with athletes can consider assessing and treating specific nutritional deficiencies such as vitamin D. More research regarding the role and clinical application of measuring immune biomarkers in athletes at high risk of ARill/ARinf is warranted.

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INTRODUCTION

Acute respiratory illnesses (ARill), especially respiratory tract infections (ARinf), are the most common illnesses affecting athletes.[1 2] At major events, such as Olympic and Paralympic Games, ARinf have been reported to be common among elite athletes, and can cause absence from both training and competition.[3–5] Exercise during ARinf may increase the risk of serious health complications, such as myocarditis.[6] In the general population, adults typically experience 2–4 ARill per year.[7 8]

Few studies have addressed the risk factors for ARill and ARinf in athletic cohorts. To date studies have not attempted to differentiate between ARill that can include both non-infective or infective causes, and suspected or confirmed ARinf. Non-infective causes of ARill can mimic symptoms of infections. These may be due to allergies or airway inflammation caused by factors such as pollution, chemical irritants and exposure to cold or dry air. As ARill and ARinf are common medical complaints in athletes, it is important for clinicians and training staff to understand the types and magnitude of risk factors predisposing athletes to ARill and/or ARinf.

Risk factors associated with ARill and ARinf can be categorised broadly into individual athlete factors (age, gender, medical history and co-morbidities), sport (type and level of participation), training and competition factors, nutritional factors, environmental factors (season, air temperature, pollution, altitude), exposure factors (international travel, household exposure, personal hygiene, physical distancing, crowded and indoor environments), and immune/haematological risk factors and biomarkers. Cross-sectional studies of athletes indicate that individuals with high training loads have a greater frequency of ARill.[9 10] Longitudinal studies of athletes report an increased incidence of ARill during periods of intense training or competition.[11–13] Elite athletes may be predisposed to ARinf during periods of increased physical and mental stressors which may suppress both innate and adaptive immunity.[14–18] Individual studies have reported that strenuous exercise-induced immunosuppression, mental stress, nutritional restrictions, air travel, human crowding, housing with other athletes, low temperature with low humidity, and competition all potentially increase the risk for ARinf, especially during the winter season when respiratory viruses are more prevalent.[4 12 18] No previous systematic review has been conducted that highlights important risk factors for ARill and ARinf in athletes.

The aim of this study was to conduct a systematic review of risk factors associated with general (undiagnosed) ARill and ARinf (suspected or confirmed by laboratory identification of the pathogen) in athletes.

METHODS

Protocol and registration

A protocol was developed according to guidelines outlined in the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)

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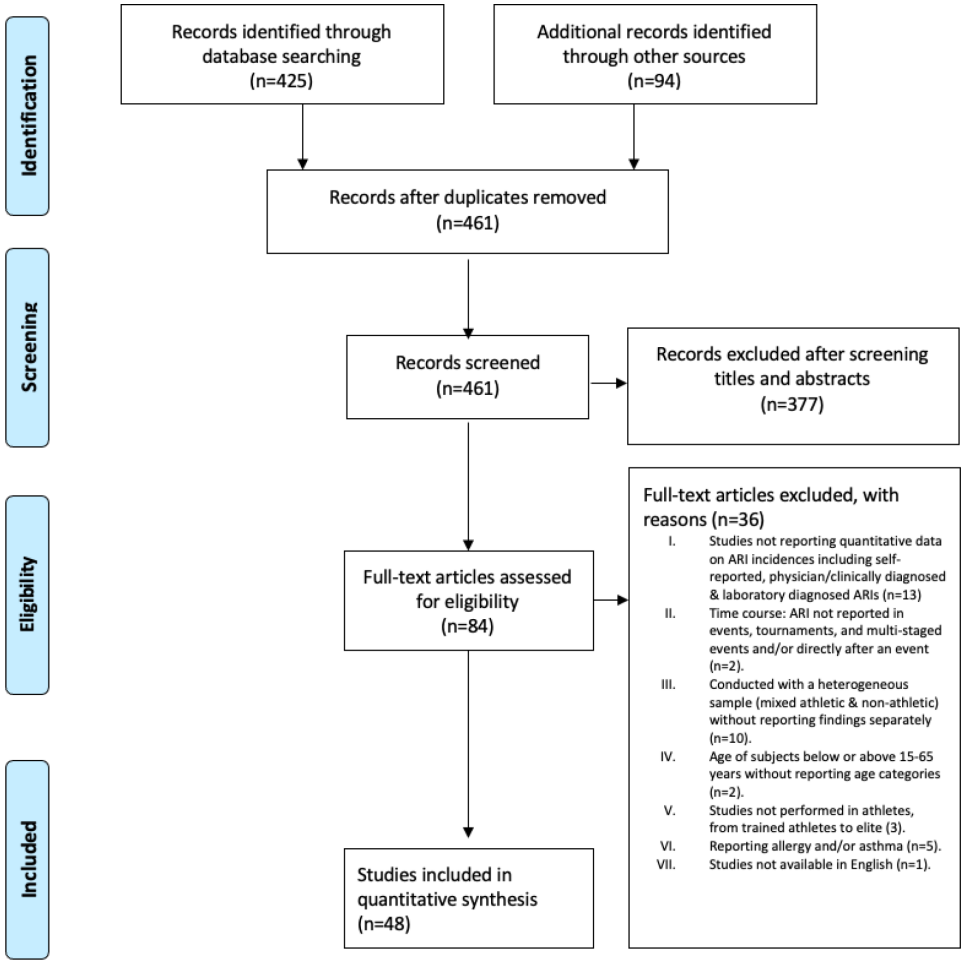

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram visualising the selection process of identified, screened and included articles following assessment of the eligibility critteria. ARI, acute respiratory illness.

statement.[19] The PRISMA checklist is presented in online supplemental file S1.

Study selection and eligibility criteria

Eligibility criteria were established and agreed on by all authors based on the concepts of population and outcome. Studies that met the following criteria were considered eligible for inclusion in this systematic review:

1. Participants, male and female, who are athletes at any level (recreational to elite) or military populations engaged in training, aged 15–65 years old.
2. Reporting on self-reported and/or physician diagnosed ARill, as well as clinically diagnosed and laboratory confirmed ARinf.
3. Reporting ARill during training, events/tournaments, multi-stage events and directly after an event.
4. Prior to the search strategy implementation it was agreed across all International Olympic Committee consensus groups that journal articles with full-text original prospective and/or retrospective studies published in English between 1 January 1990 and 31 July 2020 will be included.
5. Studies reporting factor/s predisposing athletes to ARill.

Exclusion criteria were set as studies:

1. Conducted with a heterogeneous sample (ie, mixed sample of athletic and non-athletic populations) without reporting individual group findings separately.
2. Available as an abstract only (ie, conference presentations), qualitative or case series, discussion paper, commentary or literature review.
3. Not available in English.

While asthma and allergy can be independent risk factors associated with ARill, it should be noted they were not included in this review, which has a focus on infections as a cause of ARill.

Search strategy

Researchers systematically searched three electronic databases: PubMed-Medline, EBSCOhost and Web of Science. Medical subject heading (MeSH) terms included: upper respiratory tract infection* OR upper respiratory illness* OR upper respiratory symptom* AND athlet* AND risk factors, and relevant exclusions (see online supplemental file S1). A secondary search of the reference lists of included articles and hand searching in Google Scholar were performed. Further articles the authors were aware of relating to the topic were added to the search results. Duplicate articles were removed from the combined searches. Article screening and selection utilised the online tool CADIMA.[20] The articles were then screened independently by three reviewers (LK, JG-E and KM). Full texts of articles were retrieved, and a second independent screening was undertaken by four independent reviewers (LK, JG-E, KM, MG). Any conflicts were resolved through discussion and consensus between reviewers.

Table 1 Number of studies (n; % of total studies) by pathological and anatomical classifications

	Upper	General	Total	References
All studies	40 (83.3%)	8 (16.7%)	**48**	
All general (undiagnosed) ARill	16 (33.3%)	1 (2.1%)	**17 (35.5%)**	
Self-reported symptoms only	6 (12.5.6%)	1 (2.1%)	7 (14.6%)	32 52 87–91
Self-reported symptoms with an algorithm	7 (14.6%)	–	7 (14.6%)	28 31 68 92–95
Symptoms reviewed by a physician, but without clinical or laboratory evaluation	1 (2.1%)	–	1 (2.1%)	82
Clinical diagnosis by a physician, based on history and examination	2 (4.2%)	–	2 (4.2%)	38 39
All infective (ARinf)	24 (50.0%)	7 (14.5%)	**31 (64.5%)**	
Suspected infective	19 (39.5%)	7 (14.5%)	26 (54%)	
Self-reported symptoms with an algorithm	12 (25%)	1 (2.1%)	13 (27.1%)	9 27 47 51 56 84 96–102
Symptoms reviewed by a physician, but without clinical or laboratory evaluation	1 (2.1%)	–	1 (2.1%)	103
Clinical diagnosis by a physician, based on history and examination	6 (12.5%)	6 (12.5%)	12 (25%)	13 33 57 66 67 69 83 104–108
Confirmed infective				
Diagnosis by a physician and confirmed by laboratory investigation to identify a specific pathogen	5 (10.4%)	–	5 (10.4%)	10 40 43 46 109

The numbers and percentages in bold represent the total number and percentages for all studies, undiagnosed ARill and infective ARill, respectively.
ARill, acute respiratory illness; ARinf, acute respiratory infections.

Data extraction

Data were extracted for each study independently and agreed by consensus (WD, MM, MG, JF, KM, MS, MB, JG-E, ME, LK). Extracted data included: Participant details (number, age, gender), study design, level of sport performance (elite/professional to non-elite/amateur), sport type, tournament or non-tournament and statistical measures of significance for risk ratios, prevalence ratios. Data related to risk factor/s and biomarkers associated with ARill and ARinf were grouped into the following main categories: (1) demographics (age, gender), (2) sport (type and level of participation), (3) training and competition factors, (4) nutritional factors, (5) environmental/exposure factors (season, altitude, international travel, household exposure) and (6) immune/haematological risk factors and biomarkers.

Criteria and definitions

The criteria and definitions of risk factor, odds ratio, risk, risk ratio/relative risk and level of athletic performance are outlined in online supplemental file S2.

Definitions and classification of subgroups of ARill

The methods used to diagnose ARill/ARinf in each study were classified as follows: (1) self-reported symptoms of ARill only, (2) self-reported symptoms but with an algorithm validated for ARinf, (3) self-reported symptoms of an ARinf reviewed by a physician, but without clinical or laboratory evaluation, (4) clinical diagnosis of an ARinf by a physician, based on history and clinical examination, (5) diagnosis of ARinf by a physician that was confirmed by laboratory investigation to identify a specific pathogen. Studies were classified by the five methods of diagnosis and included in one of the main and subgroups of ARill, based on a pathological classification (online supplemental file S2).

ARill, including ARinf, frequently present with both upper and lower respiratory tract symptoms/signs and it is not always possible to clearly distinguish between these anatomical regions when classifying ARill. A limitation of this anatomical classification is that several pathogens that cause predominantly upper ARinf can, in some cases, present with lower respiratory and/or systemic symptoms. A clear distinction was made in many studies, hence the anatomical classification was assessed in this review according to the following classifications:

- Upper (ARill or ARinf): Studies where the predominant symptoms, signs, or confirmed pathology was mainly related to the upper respiratory tract (ie, above the larynx), or if the study specifically referred to athletes with upper ARill or ARinf. A few studies referred to ARinf with non-specific terms such as 'influenza', 'influenza symptoms', 'common cold', 'symptoms suggestive of influenza', 'influenza symptoms' or 'influenza like'. Studies referring to these clinical syndromes were also included in this broad anatomical classification because they are caused by pathogens that all present with predominantly upper respiratory tract symptoms.[7 21–23] Notably, this includes the influenza viruses, which predominantly present with upper respiratory tract symptoms[24] and are listed as a cause of upper respiratory tract infections.[7 21 22]
- Lower (ARill or ARinf): Studies where the predominant symptoms were below the larynx (including chest symptoms ie, cough, chest pain), or if the diagnosis specifically referred to lower respiratory illness (tracheal, bronchial or lung pathology, eg, pneumonia).
- General (upper/lower) (ARill or ARinf): Studies where there were no data to distinguish between upper or lower respiratory tract ARill or ARinf, and could include upper, lower or both.

Measures of outcome and determination of strength of association

Risk factors and biomarkers reported in the studies for undiagnosed ARill and suspected and confirmed ARinf, were listed by category of risk and strength of each association evaluated. There was *significant* heterogeneity in outcome variables reported (eg, relative risk or % athletes affected, single or confounders analysis). As a result, a four level metric was developed to classify the type and strength of an association between a risk factor and ARill or ARinf as follows: no association (0, 00 or 000), some association (+), good association (++) or strong association (+++). A risk factor association was rated as weak evidence 'no association' when a simple analysis was performed, such as

Table 2 Main categories of risk factors and biomarkers associated with general (undiagnosed) ARill, by category of risk and strength of each association

Main categories of risk factors and biomarkers assessed	Association identified	Strength	Confounders	Variables adjusted for (confounders/ multivariable model)	Study
Demographics factors					
Age	No	0	–	No/No	Blume *et al*[28]
Gender	No	0	–	No/No	Blume *et al*[28]
Sport (type and level of participation)					
Being at a less competitive level	Yes	+++	Age, age of menarche, no of inhabitants living in the same house	Yes/Yes	Novas *et al*[95]
		+	–	No/No	Matthews *et al*[87]
Greater in runners	Yes	+	–	No/No	Ihalainen *et al*[92]
Training and competition factors					
Increased training load	Yes	+++	Subject (pre-exercise values), subject and session-intensity.	Yes/Yes	Novas *et al*[91]
	Yes	+	–	No/No	Novas *et al*[95]
	No	000	Training weeks and no of players	Yes/Yes	Tiernan *et al*[82]
		0	–	No/No	Matthews *et al*[87]
Intensified phase of training	Yes	+	–	No/No	Novas *et al*[91]
	No	000	Training macrocycle, internal-TL values, well-being, muscle soreness ratings and age.	Yes/Yes	Thornton *et al*[89]
Competition phase	No	000	Training macrocycle, internal-TL values, well-being, muscle soreness ratings and age.	Yes/Yes	Thornton *et al*[89]
Nutritional factors					
Lower (vitamin-D)	Yes	+++	Age, gender and years of training	Yes/Yes	Cox *et al*[39]
Serum (vitamin-D) in both winter and summer	No	0	–	No/No	Scullion *et al*[52]
Environmental/exposure factors					
Winter	Yes	+	–	No/No	Scullion *et al*[52]
Longer international travelling	Yes	+	–	No/No	Fowler *et al*[68]
Household size	No	00	Age, age of menarche, no of inhabitants living in the same house	Yes/No	Novas *et al*[91]
Immune/haematological risk factors and biomarkers					
Elevated WBC counts	Yes	+++	Age, gender and years of training	Yes/Yes	Cox *et al*[39]
Elevated neutrophil count	Yes	+++	Age, gender and years of training	Yes/Yes	Cox *et al*[39]
Detection of IgE antibodies to aero-allergens	Yes	+	–	No/No	Reid *et al*[38]
	No	000	Age, gender and years of training	Yes/Yes	Cox *et al*[39]
Higher atopic AQUA scores	Yes	+	–	No/No	Ansley *et al*[93]
Higher rates of expression of EBV-DNA in saliva (viral reactivation)	Yes	+	–	No/No	Reid *et al*[38]
Lower resting and post-exercise (IL-1ra) in illness-prone athletes	Yes	+	–	No/No	Cox *et al*[88]
High expression IL-2 genotype (GG)–lower incidence	Yes	+	–	No/No	Cox *et al*[32]
Low expression IL-4 genotype (CC)	Yes	+	–	No/No	Cox *et al*[32]
High expression IL-6 genotype (GG)	Yes	+	–	No/No	Cox *et al*[32]
Low expression IL6 genotype (CC)	Yes	+	–	No/No	Zehsaz *et al*[31]
Expression of IL-1ra, IL-8, IL-10, IFNɣ genotypes	No	0	–	No/No	Cox *et al*[32]
Higher post-exercise (IL-6)	Yes	+	–	No/No	Cox *et al*[88]
Lower resting (IL8) in illness-prone athletes	Yes	+	–	No/No	Cox *et al*[32]

Continued

Table 2 Continued

Main categories of risk factors and biomarkers assessed	Association identified	Strength	Confounders	Variables adjusted for (confounders/ multivariable model)	Study
High expression IL-10 genotype (GG)	Yes	+	–	No/No	Zehsaz *et al*[31]
Lower resting and post-exercise (IL-10) in illness-prone athletes	Yes	+	–	No/No	Cox *et al*[88]
Changes in post-exercise (IL-2), (IL-4), (IL-12)	No	0	–	No/No	Cox *et al*[32]
Reduction in salivary-AA, and IgM to total protein ratio	Yes	+	–	No/No	Ihalainen *et al*[92]
Lower serum (IgG3)	Yes	+	–	No/No	Reid *et al*[38]
Reduction in salivary-(Lysozyme)	No	0	–	No/No	Cunniffe *et al*[94]
Reduction in salivary flow rate	No	000	Training weeks and no of players	Yes/Yes	Tiernan *et al*[82]
		0	–	No/No	Nakamura *et al*[90]

Strength of association; no association, 0; no association with multiple models and/or correction for confounders, (00/000); some association, +; good association, ++; strong association, +++.
AA, alpha amylase; AQUA, automated quantitative analysis; ARill, acute respiratory illness; EBV, Epstein-Barr Virus; WBC, white blood cell.

any of the following statistical tests: descriptive analysis, Pearson's correlation analysis or grouping t-student's analysis (0). Good evidence for 'no association' was rated as (00) when the study performed a multivariable analysis without mentioning the confounding variables that were taken into account, while stronger evidence for 'no association' was reported as (000) that is, when the study documented a multivariable model analysis taking confounding factors into account (eg, sex, age, season and level of performance). A risk factor association was rated as 'some' association (+) if a study documented some form of single statistical analysis. 'Good' association (++) was attributed if the study used a statistical analysis which accounted for confounding factors. A risk-factor association was rated as 'strong' (+++) if the study documented a multivariable model analysis taking confounding factors into account.

Quality assessment and risk of bias

Studies were reviewed for the quality assessment and risk of bias using a modified Downs and Black tool.[25] This was conducted by seven reviewers (LK, JG-E, MB, WD, MB, KM and MG) independently scoring the articles and then discussing differences to reach a consensus score for each article. The same reviewers determined the level of evidence using the Oxford Centre for Evidence Based Medicine (OCEBM, 2009).[26] The articles fell into two main categories: Observational studies of the prevalence of symptoms of ARill; or Interventional studies where the incidence of ARill was determined in response to the intervention, with or without control groups. The OCEBM level of evidence was graded using the criteria for a Symptom Prevalence Study for the observational studies based on the degree of follow-up for prospective studies as level 1b for good follow-up, level 2b for retrospective studies and level 3b for non-consecutive cohort studies. The intervention studies were graded using the Therapy/Prevention studies criteria of level 1b for randomised control trials (RCTs) with narrow confidence intervals and level 2b for the non-RCT studies.

RESULTS

Study selection

Four hundred and sixty-one (461) studies were identified in the search. The study selection process and reasons for excluding studies is summarised in figure 1. Eighty-four full-text articles were assessed for eligibility, 36 were excluded and 48 were included. The characteristics of the 48 studies are presented in online supplemental file S3, and the quality assessment in online supplemental file S4. The 48 studies had a total of 19 390 (range: 9–12594) participants. Studies were conducted across 17 sports and 5 performance levels: only elite/professional athletes (n=26; 54.2%); only recreational/trained/competitive athletes (n=16; 33.3%); mixed levels (n=6; 12.5%).

Number of studies by pathological and anatomical classification of ARill

The pathological and anatomical classifications of ARill for each study are provided in table 1. Of the 48 studies, 40 (83.3%) reported upper ARill, 8 (16.7%) reported general ARill, with no studies reporting lower ARill only. Seventeen (35.5%) studies reported undiagnosed ARill. Of the 31 (64.5%) studies classified as ARinf, 26 (54%) were suspected infections and five (10.4%) were confirmed ARinf.

Risk factors and biomarkers associated with ARill and ARinf

Risk factors and biomarkers associated with general (undiagnosed) ARill

The main categories of risk factors and biomarkers associated with general (undiagnosed) ARill, by category of risk and strength of each association are presented in table 2. Risk factors that showed a strong association (+++) with general (undiagnosed) ARill were: being a less competitive athlete, elevated white blood cell and neutrophil counts, and a lower serum Vitamin D concentration. Risk factors for which there was strong evidence for no association (000) with general (undiagnosed) ARill were intensified phase of training, competition phase, detection of IgE antibodies to aero-allergens, and a reduction in salivary flow rate. Of interest is that there was both strong evidence for a positive association (+++) and no association (000) between ARill and increased training load.

Risk factors and biomarkers associated with suspected ARinf

The main categories of risk factors and biomarkers associated with suspected ARinf, by category of risk and strength of each association are presented in table 3. Risk factors that showed a strong association (+++) with suspected ARinf were: increments

Table 3 Main categories of risk factors and biomarkers associated with suspected acute respiratory infection by category of risk and strength of each association

Main categories of risk factors and biomarkers assessed	Association identified	Strength	Confounders	Variables adjusted for (confounders/ multivariable model)	Study
Demographic factors					
Younger athletes in the illness prone group	Yes	+	–	No/No	Gleeson *et al*[102]
Age	No	000	Performance level, sex, training phase and load, season	Yes/Yes	Svendsen *et al*[56]
Gender	No	000	Time, age, sex, training centre, and competition level	Yes/Yes	Hellard *et al*[57]
	No	0	–	No/No	He *et al*[101]
Sport (type and level of participation)					
Participating in endurance sports	Yes	++	Sex, type of sport	Yes/No	Edouard *et al*[105]
Participating in athletics compared with other Paralympic sports	Yes	+	–	No/No	Schwellnus *et al*[107]
Completing a marathon	No	0	–	No/No	Furusawa *et al*[98]
Being at a less competitive level	Yes	+++	Performance level, sex, training phase and load, season	Yes/Yes	Svendsen *et al*[56]
		+++	Age, sex, competition level, season	Yes/Yes	Hellard *et al*[13]
Training and competition factors					
Increased training load	Yes	+++	Age, sex, competition level, season	Yes/Yes	Hellard *et al*[13]
		+++	Time, age, sex, training centre, and competition level	Yes/Yes	Hellard *et al*[57]
		+	–	No/No	Moreira *et al*[96]
		+	–	No/No	Rama *et al*[47]
		+	–	No/No	Gleeson *et al*[102]
		+	–	No/No	Fricker *et al*[66]
		+	–	No/No	Leicht *et al*[97]
		+	–	No/No	Yamauchi *et al*[108]
		+	–	No/No	Hausswirth *et al*[100]
		+	–	*No/No*	Ikonen *et al*[103]
		+	–	No/No	Milanez *et al*[84]
		+	–	No/No	Gleeson *et al*[102]
	No	000	Performance level, sex, training phase and load, season	Yes/Yes	Svendsen *et al*[56]
		0	–	No/No	Dressendorfer *et al*[106]
		0	–	No/No	Neville *et al*[9]
Increased training intensity	Yes	+	–	No/No	Brisola *et al*[97]
	No	0	–	No/No	Dressendorfer *et al*[106]
Increased training intensity – lower incidence	Yes	+++	Performance level, sex, training phase and load, season	Yes/Yes	*Svendsen* et al[56]
Increased strength and speed training	Yes	+++	Age, sex, competition level, season	Yes/Yes	Hellard *et al*[13]
	No	000	Performance level, sex, training phase and load, season	Yes/Yes	Svendsen *et al*[56]
Increased training monotony	Yes	+++	Performance level, sex, training phase and load, season	Yes/Yes	Svendsen *et al*[56]
Endurance preparation phase	Yes	+++	Performance level, sex, training phase, and load, season	Yes/Yes	Svendsen *et al*[56]
Tapering phase – lower incidence	Yes	+++	Performance level, sex, training phase and load, season	Yes/Yes	Svendsen *et al*[56]
		+++	Age, sex, competition level, season	Yes/Yes	Hellard *et al*[13]
Competition period	Yes	+++	Gender, age, sport types	Yes/Yes	Schwellnus *et al*[69]
		+	–	No/No	Brisola *et al*[99]
	No	000	Age, sex, competition level, season	Yes/Yes	Hellard *et al*[13]
		000	Time, age, sex, training centre, and competition level	Yes/Yes	Hellard *et al*[57]
Nutritional factors					
Reduced serum (vitamin-D)	Yes	+++	Baseline values, time effect, exercise	Yes/Yes	Hanstock *et al*[27]
Vitamin D supplementation – lower incidence	Yes	+	–	No/No	He *et al*[101]

Continued

Table 3 Continued

Main categories of risk factors and biomarkers assessed	Association identified	Strength	Confounders	Variables adjusted for (confounders/ multivariable model)	Study
Lower intake of arginine and alanine amino acids during the overreaching phase	Yes	+	–	No/No	Ikonen *et al*[103]
Environmental/exposure factors					
Winter	Yes	+++	Performance level, sex, training phase and load, season	Yes/Yes	Svendsen *et al*[56]
		+++	Age, sex, competition level, season	Yes/Yes	Hellard *et al*[13]
		+	–	No/No	Fahlman and Engels[104]
Autumn – lower incidence	Yes	+++	Team home country, season, intercontinental travel and duration in a specific travel stage of the tournament.	Yes/Yes	Schwellnus *et al*[67]
Exposure to training at high altitude >1500 masl	Yes	+++	Performance level, sex, training phase and load, season	Yes/Yes	Svendsen *et al*[56]
Longer International travelling	Yes	+++	Performance level, sex, training phase and load, season	Yes/Yes	Svendsen *et al*[56]
		+++	Team home country, season, intercontinental travel and duration in a specific travel stage of the tournament.	Yes/Yes	Schwellnus *et al*[67]
Increased psychological stress	Yes	+	–	No/No	Moreira *et al*[96]
	No	0	–	No/No	Milanez *et al*[84]
Poor sleep quality	Yes	+	–	No/No	Hausswirth *et al*[100]
Household family exposure	No	000	Performance level, sex, training phase and load, season	Yes/Yes	Svendsen *et al*[56]
Immune/haematological risk factors and biomarkers					
Prior respiratory tract infections	Yes	+++	Age, sex, competition level, season	Yes/Yes	Hellard *et al*[13]
Higher rates of expression of EBV-DNA in saliva (viral reactivation)	Yes	+	–	No/No	Gleeson *et al*[33]
	No	0	–	No/No	Yamauchi *et al*[108]
Lower CD56 +cell counts (neutrophil cell marker)	Yes	+	–	No/No	Rama *et al*[47]
Higher CD56bright:CD56 dim ratio	Yes	+	–	No/No	Rama *et al*[47]
Lower salivary-IgA concentration	Yes	+	–	No/No	Gleeson *et al*[33]
		+	–	No/No	Fahlman and Engels[104]
	No	0	–	No/No	Gleeson *et al*[102]
		0	–	No/No	Leicht *et al*[97]
Larger decrease in salivary (IgA) across training weeks	Yes	+	–	No/No	Milanez *et al*[84]
Reduced pre-training salivary (IgA)	Yes	+	–	No/No	Neville *et al*[83]
		+	–	No/No	Milanez *et al*[84]
Reduced salivary-IgA secretion rate	Yes	+	–	No/No	Gleeson *et al*[102]
		+	–	No/No	Fahlman and Engels[104]
		+	–	No/No	Yamauchi *et al*[108]
		+	–	No/No	Neville *et al*[83]
		+	–	No/No	Milanez *et al*[84]
	No	0	–	No/No	Leicht *et al*[97]
Genetic risk score for predisposition to pro-inflammatory cytokine responses	Yes	+	–	No/No	Gleeson *et al*[33]
High expression IFN-γ genotype	Yes	+	–	No/No	Gleeson *et al*[33]
Higher IFN-γ production in illness prone athletes	Yes	+	–	No/No	Gleeson *et al*[102]
	No	0	–	No/No	Gleeson *et al*[9]
TNF-α production	No	0	–	No/No	Gleeson *et al*[102]
IL-1ra cytokine genotypes	No	0	–	No/No	Gleeson *et al*[33]
IL-1β production	No	0	–	No/No	Gleeson *et al*[102]
Higher IL-2 production	Yes	+	–	No/No	Gleeson *et al*[9]
		+	–	No/No	Gleeson *et al*[102]
Higher IL-4 cytokine production	Yes	+	–	No/No	Gleeson *et al*[9]
		+	–	No/No	Gleeson *et al*[102]
	No	0	–	No/No	Gleeson *et al*[33]

Continued

Table 3 Continued

Main categories of risk factors and biomarkers assessed	Association identified	Strength	Confounders	Variables adjusted for (confounders/ multivariable model)	Study
High expression IL-6 (CC) and IFNɣ (AA) genotypes	Yes	+	–	No/No	Gleeson *et al*[33]
Higher IL-6 production	No	0	–	No/No	Gleeson *et al*[102]
Higher IL-8 production	No	0	–	No/No	Gleeson *et al*[102]
Higher expression IL-8 cytokine genotypes	No	0	–	No/No	Gleeson *et al*[33]
Higher post exercise IL-10 production	Yes	+	–	No/No	Gleeson *et al*[102]
		+	–	No/No	Gleeson *et al*[9]
Higher expression IL-10 cytokine genotypes	No	0	–	No/No	Gleeson *et al*[33]
High expression IL-17 cytokine genotype	No	0	–	No/No	Gleeson *et al*[33]
Higher plasma (IgM)	Yes	+	–	No/No	Gleeson *et al*[102]
Plasma (IgA)	No	0	–	No/No	Gleeson *et al*[102]
Plasma (IgG)	No	0	–	No/No	Gleeson *et al*[102]

Strength of association, no association (0/00/000), + some association, ++ good association, +++ strong association.
AA, alpha amylase; EBV, Epstein-Barr virus; IL, interleukin; INF, interferon; masl, metre above sea level; TNF, tumour necrosis factor.

in training load, endurance training, training monotony, training at altitude, winter season, post international travel, less competitive athletes, having reduced serum Vitamin D concentration, and experiencing prior episodes of respiratory infection. A strong association (+++) was found between lower risk of suspected ARinf and autumn season, as well as the tapering phase of training and increased training intensity. Risk factors for which there was strong evidence for no association (000) with suspected ARinf were: age, gender and household family exposure. Of interest is that there was both strong evidence for a positive association (+++) and no association (000) between suspected ARinf and increased training load, increased speed and strength training, and the competition period.

Risk factors and biomarkers associated with confirmed ARinf

The main categories of risk factors and biomarkers associated with confirmed ARinf, by category of risk and strength of each association are presented in table 4. Risk factors and biomarkers that showed a strong association (+++) with confirmed ARinf were: increasing training intensity, lower salivary-(IgA) (preseason, pretraining and across a season) and reduced tear

Table 4 Main categories of risk factors and biomarkers associated with confirmed acute respiratory infection by category of risk and strength of each association

Main categories of risk factors and biomarkers assessed	Association identified	Strength	Confounders	Variables adjusted for (confounders/ Multivariable model)	Study
Sport and level of athlete					
Being a higher level athlete	Yes	+	–	No/No	Spence *et al*[10]
Training and competition factors					
Increased training intensity	Yes	+++	Baseline measures	Yes/Yes	Hanstock *et al*[40]
Immune/haematological risk factors and biomarkers					
Decline in Salivary (IgA) across a training season (slope)	Yes	+++	Gender, age, training intensity and volume, psychological stress	Yes/Yes	Gleeson *et al*[46]
Lower pre-season salivary-(IgA)	Yes	+++	Gender, age, training intensity and volume, psychological stress	Yes/Yes	Gleeson *et al*[46]
Pre or late season salivary-(IgA)	Yes	+	–	No/No	Gleeson *et al*[43]
Lower pre-training salivary-(IgA)	Yes	+++		Yes/Yes	Gleeson *et al*[46]
		+	–	No/No	Gleeson *et al*[43]
Post-season training salivary-(IgA)	No	000	Gender, age, training intensity and volume psychological stress	Yes/Yes	Gleeson *et al*[46]
Higher salivary-IgA secretion rate	Yes	+	–	No/No	Hanstock *et al*[40]
Lower pre-season salivary-(IgA1)	Yes	+	–	No/No	Gleeson *et al*[109]
Pre or late season salivary-(IgA2)or ratios of salivary(IgA1):(IgA2)	No	0	–	No/No	Gleeson *et al*[109]
Reduced tear-(SIgA)	Yes	+++	Baseline measures	Yes/Yes	Hanstock *et al*[40]
Reduced tear-SIgA secretion rate	Yes	+++	Baseline measures	Yes/Yes	Hanstock *et al*[40]

Strength of association: no association (0/00/000), + some association, ++ good association, +++ strong association.
SIgA, secretory IgA.

salivary-(IgA) and secretion rates. The only risk factor where there was strong evidence for no association (000) with suspected ARinf was postseason training salivary-(IgA).

DISCUSSION

The aim of this study was to conduct a systematic review of risk factors associated with general (undiagnosed) ARill and ARinf (suspected or confirmed) in athletes. The 48 studies meeting the eligibility criteria were graded as good or excellent, providing confidence in the quality of the studies. However, the small number of studies assessing each risk factor or biomarker made it difficult to draw firm conclusions for most risk factors. In addition, the differences in the methodologies for classifying respiratory illnesses/infections further impaired comparisons. Further discussion of the review findings now focuses on the evidence for associations between increased risk for ARill/ARinf in athletic populations and risk factors in six main categories.

Demographic factors

The findings of this review show that age and gender were not associated with increased risk of any ARill or ARinf (suspected or confirmed).

Sport type and level of participation

In general, sport type was not strongly associated with increased risk of ARill or ARinf (suspected or confirmed). There was some evidence of increased risk of ARill and ARinf in endurance athletes and runners specifically. There was a lower risk of prolonged ARill (symptom days) for elite athletes.[27–29] One study hypothesised that the individual training load threshold, above which the risk of illness increases,[30] is lower in national level athletes than in international athletes. Other studies concluded that the differences may relate to underlying genetic predispositions for better resistance to infections[31 32] or lower proinflammatory responses to infection that present as a reduced incidence of ARill.[32–35] Previous research has suggested that higher-level athletes (top professional or elite) are linked to a better athletic lifestyle (personal, academic or professional schedules; better recovery, sleep quality or nutrition) that reduces the risk of ARill.[14 36 37] One possibility, not examined, was that the differences are related to the type of sport rather than the level of performance.

Training and competition risk factors

While each risk factor had studies with conflicting results, the review findings for training factors indicated ARill/ARinf, irrespective of classifications, were mostly associated with increased training intensity, endurance phase training and competition periods, but there was a potential lower risk in the tapering phase of training. There was a higher risk for ARill/ARinf in less competitive level athletes, endurance sports and younger athletes. Training monotony, training in winter, at altitude and after international travel across time zones all increased the risk of ARill/ARinf.

Although the assessment of training intensity/load alone gave mixed results, the review indicates that high intensity training is a significant risk factor in athletes who experience recurrent episodes of ARinf/ARill and altered immune status.[10 38 39] Increments in high intensity training, including speed and strength training, were associated with a higher risk of ARinf/ARill in these athletes.[38 40] Intense exercise, particularly in endurance sports, can induce significant immune system disturbances.[41 42] This review confirms findings of individual studies reporting an increase in ARinf/ARill symptoms during training periods characterised by high loads imposed continuously over several weeks or months.[43–45] The accumulation of elevated training loads without adequate recovery may be associated with a chronic depletion of cellular and mucosal immune parameters, which may lower resistance to potential viral[43 46] and non-viral pathogens,[14] or allow viral reactivation,[43 46] thereby partially explaining the higher incidence of ARinf/ARill symptoms.[9 45 47 48]

Nutritional factors

Vitamin D is an important component for effective immunity.[49 50] The review confirmed previous research showing a vitamin D deficit predisposes athletes to longer and more severe ARill, compared with non-deficit athletes.[39 40 51] He *et al*[51] found that vitamin D supplementation reduced the incidence of ARill. Scullion *et al*[52] found that multivitamin supplementation in an athlete's diet did not result in fewer ARill in winter compared with summer, and also found that an overload of vitamin D did not reduce the prevalence of ARill in athletes.

Environmental and exposure factors

Seasonality

Seasonal factors are important parameters to consider, as external factors can influence and increase the risk of ARinf/ARill.[53–55] This review showed a consistent association of increased ARill with the winter months, supporting the previously established relationship of cold environments with a higher incidence of ARinf/ARill episodes and symptoms.[14 51] The exposure to respiratory pathogens is highest in winter, but also significant in autumn and spring.[52 56 57] Spring is associated with higher pollen counts that can cause symptoms of ARill in susceptible athletes, causing eosinophilic airway inflammation that is often confused with the symptoms of ARinf.[38 39 56 58–61] Cold air can also damage the respiratory epithelium due to airway drying causing airway inflammation.[59 62] These findings mirror the seasonal patterns for acute ARill and infections in the general population, as winter is characterised by a surge in viral acute respiratory infections.[63]

Furthermore, during the colder months selected hormones that regulate immune function and vitamin D concentrations are at their lowest. Recent research indicates that a vitamin D deficit is a predictor of infections,[51] but supraphysiological doses of vitamin D do not protect against respiratory infections.[64] In the Northern Hemispheres, winter-time is usually characterised by increments in load in certain sports such as skiing, skating and ice hockey, and the intense competition period coincides with the winter season[12 13 47 65] which potentially accentuates immune-suppression and increases the risk of infection. A similar pattern is evident in the Southern Hemisphere with swimmers preparing in winter months for major international competitions typically held in the Northern Hemisphere summer.[10 66] However, time of year (season) appears to influence infection risk to a lower degree than the impact of training phase/type of sport.

International travel

International travel was shown to be a significant risk factor for ARill/ARinf[56] when athletes travelled across >5[67] and >6[68] time zones. Svendsen *et al*[56] noted athletes were five times more likely to report symptoms the day following international air travel. Studies have reported that medical illness (most commonly affecting the respiratory system) affects elite athletes while travelling to international competitions.[12 67–69] The reasons for a higher incidence of illness/infection/symptoms during international travel include: drying of respiratory epithelium, close

Table 5 A summary of risk factors and biomarkers associated with ARill and ARinf (suspected and confirmed) for which there is strong evidence of a positive association, no association or both

Pathological classification	Strong evidence supporting a positive association	Strong evidence supporting no association	Strong evidence supporting both a positive association and no association
General (undiagnosed) ARill (Table 5a)	► Less competitive athletes ► Elevated neutrophil and WBC counts ► Low serum (vitamin D)	► Intensified training phase ► Competition ► Reduction in salivary flow rate ► Detection of IgE antibodies to aero-allergens	► Increased training load
Suspected ARinf (Table 5b)	► Less competitive athletes ► Decreased training intensity ► Increased training monotony ► Endurance preparation phase ► No tapering phase ► Winter ► Exposure to high altitude ► International travel ► Previous respiratory infections ► Low serum (vitamin-D)	► Age ► Gender ► Household family exposure	► Increased training load ► Increased strength and speed training ► Competition period
Confirmed ARinf (Table 5c)	► Increased training intensity ► Lower salivary-(IgA) preseason and pretraining and decline across a training programme ► Reduced tear-(SIgA) and secretion rate	► Post-season salivary-(IgA)	

ARill, acute respiratory illness; ARinf, acute respiratory infections; WBC, white blood cell.

contact with air travellers and exposure to re-circulated air (infections), time-zone changes associated with sleep/circadian rhythm disruption, variation of diet. Other travel factors that can augment the risk of ARill include: exposure to different environmental conditions (temperature, humidity, atmospheric pollution, aeroallergens) or exposure to different strains of pathogenic organisms, and high population density at competition venues.

Altitude

It is well established that ascent to high altitude alters physiological and metabolic function and can influence immune function.[70] In this review, training at altitude was shown to increase the risk of ARill but not when findings were adjusted for sex, performance level, training phases and season.[56] Tiollier *et al*[71] found no significant differences in mucosal immunity between elite cross-country skiers sleeping at 2500–3500 m above sea level and training at 1200 m for 18 days, compared with a control group living and training at 1200 m. However, the typical cold and dry conditions of training at altitude may present with upper respiratory symptoms due to airway drying and inflammation and be considered a risk factor for non-infective ARill through this effect on respiratory mucosal membranes.[72 73]

Immune/haematological biomarkers and risk factors

Changes in systemic and mucosal immune parameters have been extensively studied in response to exercise training and competitions at all levels of sports and in many different types of sports. This systematic review of associations between immune parameters with ARinf/ARill revealed only a limited number of studies combining both ARill and exercise/training measures. The major factor affecting the immune response that appears to be associated with a higher risk of upper ARinf/ARill in athletes is a reduction in tear or salivary-(IgA). Salivary-(IgA) is the most studied immune parameter and represents a biomarker for altered mucosal immunity in the respiratory tract. It is well established that low concentrations of salivary-(IgA) at mucosal surfaces is a risk for mucosal infections in the general population.[74] Salivary-(IgA) plays a major role in immune defence not only at mucosal surfaces but also in responding to and eliminating pathogens that cross mucosal surfaces.[75 76] The studies in this review revealed an association between the appearance of EBV-DNA (viral reactivation) in saliva and the incidence of ARinf/ARill and the time frame for association with low concentrations of salivary-IgA. These biomarkers reflect immune parameters that are known risk factors associated with respiratory illness in the general population and have therefore been evaluated as tools to monitor ARill/ARinf risks in athletic populations known to have exercise-induced alterations in immune function and parameters.[4 14 41 42 48 77–80]

Regardless of the methodology used for characterising ARinf/ARill, this review found a consistent association between lower concentrations of salivary-(IgA) and tear salivary-(IgA) with an increased incidence of ARinf/ARill, with 83% of studies reporting this association. The majority, but not all studies that assessed secretions rates, also found an increased incidence of ARinf/ARill with reduced secretion rates of salivary-IgA or tear-IgA. It is possible that the one study with the reverse finding of higher salivary-IgA concentrations with increased ARill was sampled during the infective period[40] when salivary-IgA would be expected to increase in response to an infection in subjects with a fully functioning immune system.

The cumulative effects of long-term training at high loads and intensity were observed in a decline in immune protection over time. Pretraining or preseason lower salivary-IgA concentrations were shown to be associated with the increase in episodes of ARill/ARinf, symptom duration[34 35] and severity in elite swimmers.[60 81] A 65% reduction in salivary-IgA concentration was reported 1–2 weeks before the appearance of a suspected ARinf in rugby union players.[82] Similarly, in a cohort of elite yacht racing sailors, low individual relative salivary-IgA values (<40% drop) suggested a 48% chance of an ARill within 3 weeks.[83] In elite swimmers, an additional infection was observed for each 10% drop (slope) of pretraining salivary-IgA level over time (per month).[46] In recreationally active individuals (various sports), low salivary-IgA (<5.5 µg/mL) and reduced secretion rate (>30%) was associated with ARill in the week following a competition.[40] The reductions in salivary-IgA concentration

and secretion rates may have been the result of increments in training load[83 84] or inadequate recovery time between training sessions.[80 85]

Strengths and limitations

The quality of the studies included in this review and the variables explored as risk factors for ARill/ARinf provides some direction on the topic, specifically for elite/high performance athletes. A strength of this review is that it followed a systematic approach for inclusion and although a meta-analysis could not be performed, studies were reviewed for the quality assessment and risk of bias using a modified Downs and Black tool.[25]

However, this review has some limitations. First, while a consensus of the research group was used to reduce inclusion/exclusion bias, we acknowledge that the selected criteria may have (to a certain extent) led to selection bias. For example, the inclusion of studies in the English Language might have resulted in language restriction bias. There are other possible biases not considered by the selected appraisal tool in this study, which have the potential to affect study outcomes. For example, measurement bias could result from selected studies reporting self-reported symptoms only, without clinical verification by a physician. Additionally, residual confounding bias could result from studies which did not adequately consider adjustments of the confounders when reporting the strength of association. Further, sparse data bias,[86] may have arisen in studies which had fewer participants, subsequently influencing the OR and relative risk outcomes, with considerable upward biases when there were minimal athletes at key combinations of the outcome, exposure and covariates.

Second, the focus on statistically positive findings ($p<0.05$) may result in researchers losing results reporting some evidence that could be a clinically relevant factor associated with ARill. Third, the differences in methodological design, definitions of ARill/ARinf, outcome measures within diagnostic methodologies and heterogeneity of athletes' levels of performance and sports codes made it difficult to interpret the magnitude of each risk factor. Also, the approach we adopted might be considered "reductionist' in the identification and stratification of risk factors. Indeed, there is considerable complexity of these identified risk factors and their interaction with other risk factors for example, the interactions of training variations and dietary changes on immune function. Fourth, only a few studies identified the infections by clinical assessment and confirmed with laboratory diagnosis. Fifth, asthma, atopy and allergy were excluded as a risk factor for ARill. Sixth, this review considered research published only in the English language, such that relevant studies conducted in non-English languages were overlooked.

The broad search strategy provided a degree of confidence that, within the inclusion criteria of risk factors for respiratory infections/illnesses, the studies were of a high level of quality. Interpretation of findings should consider that there are potentially other influences on the risks for ARill/ARinf than those examined. Future studies would need to standardise diagnostic methods, and outcome measurements to allow comparisons between studies, variables and to enable a future meta-analysis.

What is already known?

⇒ Acute respiratory illnesses (ARill), especially respiratory tract infections, are the most common acute illnesses affecting athletes.
⇒ ARill can result in time loss from training and competition.
⇒ Individual studies have reported that strenuous exercise-induced immunosuppression, mental stress, nutritional restrictions, air travel, human crowding, housing with other athletes, low temperature with low humidity and competition all potentially increase the risk for ARill.

What are the new findings?

⇒ Increased training load, monotony, endurance training programmes, lack of tapering, training during winter and at altitude, and international travel were reported to increase the risk of acute respiratory infections (ARinf).
⇒ It is important for clinicians working with athletes to consider vitamin D deficits, particularly those prone to repeated acute respiratory illness (ARill)/ARinf.
⇒ Biomarkers for monitoring athletes at a higher risk of ARill/ARinf include low tear-(SIgA) and low salivary-(IgA).

SUMMARY AND CONCLUSIONS

The review identified several modifiable risk factors that could be considered by sports coaches when preparing training programmes, particularly for athletes who experience recurrent episodes of ARill/ARinf and those at a less competitive level (table 5). Risk factors included increased training monotony, endurance training programmes, lack of tapering, training during winter and at altitude, and international travel. It is also important for clinicians working with athletes to consider vitamin D deficits, particularly those prone to repeated ARill/ARinf. Biomarkers for monitoring athletes at a higher risk of ARill/ARinf included: low tear-SIgA concentration and low salivary-IgA concentrations. While other possible risk factors for ARill/ARinf were identified in this review, conflicting evidence limits conclusions to be draw. Further research in these areas is therefore warranted.

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PRISMA Checklist: Risk factors associated with infective acute upper respiratory illnesses in athletes: A systematic review (Supplementary information not included in paper)

Online Supplementary File:

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstract's checklist.	3, see below for abstract checklist
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	5
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	5
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	5-6, Online supplementary S1 for generic, below for full string for each database
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	5-6
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	5-7
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	6-7, see below for further details
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	6-7, further details below
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	7-8
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	6-8 (no sub-group analysis was performed)
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	5-8, see below for further information
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	5-8
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the	6-8 (no meta-

PRISMA Checklist: Risk factors associated with infective acute upper respiratory illnesses in athletes: A systematic review (Supplementary information not included in paper)

Section and Topic	Item #	Checklist item	Location where item is reported
		model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	analysis was performed)
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	-
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	(no subgroup analysis was performed)
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	7-8, see below for further details
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	7-8
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	8, Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	See below for details.
Study characteristics	17	Cite each included study and present its characteristics.	8-9, Table 2, Tables 3a-3c, & online supplementary S3.
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	37, Online supplementary S4
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Table 2, Tables 3a-c, online supplementary S4
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	8, see below for further details
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	8, no subgroup analysis was performed
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	8-9
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	No sub-group analysis was performed
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	No subgroup analysis performed
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	8-9

PRISMA Checklist: Risk factors associated with infective acute upper respiratory illnesses in athletes: A systematic review (Supplementary information not included in paper)

Section and Topic	Item #	Checklist item	Location where item is reported
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	9-14
	23b	Discuss any limitations of the evidence included in the review.	13-14
	23c	Discuss any limitations of the review processes used.	13-14
	23d	Discuss implications of the results for practice, policy, and future research.	14-15
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	3 & 5
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	5
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	See below for details
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	17
Competing interests	26	Declare any competing interests of review authors.	17
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Online supplementary S1-4

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

PRISMA Checklist: Risk factors associated with infective acute upper respiratory illnesses in athletes: A systematic review (Supplementary information not included in paper)

PRISMA abstract checklist:

Section and Topic	Item #	Checklist item	Reported (Yes/No)
TITLE			
Title	1	Identify the report as a systematic review.	Y
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	Y
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	Y (some) See paper for the rest
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	Y
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	No, within the paper
Synthesis of results	6	Specify the methods used to present and synthesise results.	Y (some)
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	Y
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	Y (no meta-analyses done)
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	Y (some)
Interpretation	10	Provide a general interpretation of the results and important implications.	Y
OTHER			
Funding	11	Specify the primary source of funding for the review.	No, within the paper
Registration	12	Provide the register name and registration number.	Y

7. Present the full search strategies for all databases, registers and websites, including any filters and limits used.

PubMed: (Rhinovirus OR Parainfluenza OR Adenovirus OR coronavirus OR "human metapneumovirus" OR enterovirus OR "respiratory syncytial virus" OR "bordetella pertussis" OR "Chlamydophila pneumoniae" OR "mycoplasma pneumoniae" OR Rhinitis OR influenza OR "common cold" OR flu OR sinusitis OR "rhino sinusitis" OR "acute pharyngitis" OR tonsillitis OR pharyngitis OR epiglottitis OR laryngitis OR pneumonia OR bronchitis OR "lung disease" OR "Respiratory tract disease*" OR "Respiratory illness*" OR "Respiratory tract infection*" OR "respiration disorder*" OR "respiratory system disease*" OR "upper respiratory tract illness*" OR "upper respiratory tract disease*" OR "Lower respiratory tract illness*" OR "Lower respiratory tract disease*" OR "Viral disease*" OR tuberculosis) AND (athlete* OR sport* OR exercis*) AND (risk factor*) NoT (asthma) NoT (COPD OR "chronic obstructive pulmonary disease" OR cancer OR animal* OR HIV OR "human immunodeficiency virus" OR AIDS OR "acquired immunodeficiency syndrome" OR post-operative) Filters: Journal Article, Humans, English, MEDLINE, from 1990-July 2020

PRISMA Checklist: Risk factors associated with infective acute upper respiratory illnesses in athletes: A systematic review (Supplementary information not included in paper)

EbscoHost: (Rhinovirus OR Parainfluenza OR Adenovirus OR coronavirus OR "human metapneumovirus" OR enterovirus OR "respiratory syncytial virus" OR "bordetella pertussis" OR "Chlamydophila pneumoniae" OR "mycoplasma pneumoniae" OR Rhinitis OR influenza OR "common cold" OR flu OR sinusitis OR "rhino sinusitis" OR "acute pharyngitis" OR tonsillitis OR pharyngitis OR epiglottitis OR laryngitis OR pneumonia OR bronchitis OR "lung disease" OR "Respiratory tract disease*" OR "Respiratory illness*" OR "Respiratory tract infection*" OR "respiration disorder*" OR "respiratory system disease*" OR "upper respiratory tract illness*" OR "upper respiratory tract disease*" OR "Lower respiratory tract illness*" OR "Lower respiratory tract disease*" OR "Viral disease*" OR tuberculosis) AND (athlete* OR sport* OR exercis*) AND (risk factor*) NoT (asthma) NoT (COPD OR "chronic obstructive pulmonary disease" OR cancer OR animal* OR HIV OR "human immunodeficiency virus" OR AIDS OR "acquired immunodeficiency syndrome" OR post-operative) Scholarly (Peer Reviewed) Journals; Published Date: 19920101-20201231; Document Type: Article; Language: English, Species: Human

Web of Science: TOPIC: (Rhinovirus OR Parainfluenza OR Adenovirus OR coronavirus OR "human metapneumovirus" OR enterovirus OR "respiratory syncytial virus" OR "bordetella pertussis" OR "Chlamydophila pneumoniae" OR "mycoplasma pneumoniae" OR Rhinitis OR influenza OR "common cold" OR flu OR sinusitis OR "rhino sinusitis" OR "acute pharyngitis" OR tonsillitis OR pharyngitis OR epiglottitis OR laryngitis OR pneumonia OR bronchitis OR "lung disease" OR "Respiratory tract disease*" OR "Respiratory illness*" OR "Respiratory tract infection*" OR "respiration disorder*" OR "respiratory system disease*" OR "upper respiratory tract illness*" OR "upper respiratory tract disease*" OR "Lower respiratory tract illness*" OR "Lower respiratory tract disease*" OR "Viral disease*" OR tuberculosis) AND (athlete* OR sport* OR exercis*) AND (risk factor*) NoT (asthma) NoT (COPD OR "chronic obstructive pulmonary disease" OR cancer OR animal* OR HIV OR "human immunodeficiency virus" OR AIDS OR "acquired immunodeficiency syndrome" OR post-operative): Refined by DOCUMENT TYPES: (ARTICLE), LANGUAGES: (ENGLISH), SPECIES: (HUMANS) Time span: 1990-2020. Indexes: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC.

10a. List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.

All studies included in the review reported the overall domain of risk factors for ARill and ARinf (undiagnosed and diagnosed). The small number of studies assessing each risk factor or biomarker made it difficult to draw consensus conclusions for most risks. Furthermore, the differences in the methodologies for classifying respiratory illnesses/infections further impaired comparisons.

10b. List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.

All details of variables are reported in the paper. No assumptions were made, however risk association was determined based on the types of statistical tests performed and whether this took confounders into account or not as well as whether the statitiscal test was a multi-variable analaysis or not.

13b. Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.

Not all papers performed an analysis to determine risk association, risk association and strength of association was determined based on a 4 level metric to classify the type and strength of an association between a risk factor and ARill and ARinf as follows: no association (0, 00 or 000), some association (+), good association (++) or strong association (+++). For more details please review paper.

14. Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).

The domains from the modified Downs and Black tool that assessed risk of bias were (yes, no or unable to determine):

If any of the results of the study were based on "data dredging", was this made clear?
Were the statistical tests used to assess the main outcomes appropriate?
Were the main outcome measures used accurate (valid and reliable)?
Were losses of patients to follow-up taken into account?

These 4 questions were part of the quality assessment. It must be noted that this review is not on RCTs, so the bias is not as clear as in reviews of RCTs, and therefore this was not specifically taken into consideration when performing the synthesis. The overall quality of article was assessed as per guidelines (including this risk of bias, however was used as an overall measure).

PRISMA Checklist: Risk factors associated with infective acute upper respiratory illnesses in athletes: A systematic review (Supplementary information not included in paper)

16b. Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.

We cite studies on asthma and allergy that appeared to meet the inclusion criteria but were excluded after IOC consensus subgroup 1 meeting which resolved that asthma and allergy were being covered by another IOC sub-group as such they should be removed from this study.

20a. For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.

As mentioned above, that this review is not on RCTs, so the bias is not as clear as in reviews of RCTs, and therefore this was not specifically taken into consideration when performing the synthesis. The overall quality of article was assessed as per guidelines (including this risk of bias, however as an overall measure). Therefore for each synthesis the bias was not reported, this was further validated as no studies were rated as ”poor” with all 48 studies rated as either excellent or good.

21. Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.

There was no meta-analysis performed for this study and no studies with missing data were included in the review, therefore no assessment of risk of bias due to missing results (arising from reporting biases are presented in this review.

24c. Describe and explain any amendments to information provided at registration or in the protocol.

The protocol was amended by the following:
-The search period was extended by 7 months from 2019 to July 2020, due to the COVID-19-related delay of the IOC consensus meeting.
-The exclusion criteria were revised to exclude studies that only included non-infective acute respiratory illnesses such as asthma and allergy.

ONLINE SUPPLEMENTARY S2

Risk factor: Variable associated with an increased risk of disease or infection.[109]

Odds ratio: An odds ratio (OR) is another measure of association that quantifies the relationship between exposure with two categories and health outcome.[110]

Risk: The probability or chance, as measured by the occurrence of new cases of disease in a defined population over a defined period. Risk relates to the number of newly observed cases.

Risk ratio/relative risk: A risk ratio (RR), also called relative risk, compared the risk of a health event (disease/illness, injury, risk factor, or death) among one group with the risk among another group.

Level of athlete performance: Studies were categorized according to the level of performance of the athletes participating in the study and included: elite/professional, amateur, trained/competitive, recreational or a combination thereof.

Pathological classification (main and subgroups) of acute respiratory illness (ARill) and infections (ARinf) by diagnostic method.

Pathological classification		**Methods to diagnose ARill**	**Description**
Main group	**Subgroup**		
General (undiagnosed) acute respiratory illness (ARill)		• Self-reported symptoms of ARill only • Self-reported symptoms combined with an algorithm at least partially validated for ARill • Self-reported symptoms of an ARill reviewed by a physician, but without clinical or laboratory evaluation • Clinical diagnosis of an ARill by a physician, based on history and clinical examination	• General symptoms of an ARill where the pathology could not be attributed specifically to an infection • ARill studies could include illnesses that are due to either infective or non-infective causes but were not specified in the study design
Acute respiratory infection (ARinf)	Suspected acute respiratory tract infection (ARinf)	• Self-reported symptoms combined with an algorithm that has been validated for ARinf • Self-reported symptoms of an ARinf reviewed by a physician, but without clinical or laboratory evaluation • Clinical diagnosis of an ARinf by a physician, based on history and clinical examination	• General symptoms and/or physical signs suggestive of an ARinf, but where the specific pathology of an infection was not confirmed • The validated questionnaires that were used included the Wisconsin Upper Respiratory Symptom Survey (WURSS-21®); the Jackson Cold Scale (JCS); or other questionnaires in which the severity of the symptoms were scored to provide a quantitative assessment (AIS Symptom log).[21]
	Confirmed acute respiratory tract infection (ARinf)	• Clinical diagnosis of ARinf by a physician that was confirmed by laboratory investigation to identify a specific pathogen utilising polymerase chain reaction (PCR) testing on specimen(s), culture of an	• In some studies, the identified pathogen was associated with a viral outbreak in a sporting team. The incidence rates in these studies may not reflect the rates of ARinf in general studies monitoring for ARinf in athletes.

		organism from specimen(s), or serology (e.g. rise in antibody titres)	

ONLINE SUPPLEMENTARY S3

Study characteristics (sorted alphabetically by sport): Study design, sport, level of training (category), number of participants, age (years) and gender (♀, female; ♂, male - reported separately where specified) and period of study (duration).

Study	Study design	Sport	Category	Participants	Age (years)	Period
Fahlman[27]	Prospective study Longitudinal cohort	American Football	Trained	75	♂ 20.5 ± 1.5	12 months
Edouard et al.[28]	Prospective study	Athletics	Elite	12594	-	11 competitions (59 days)
Matthews et al.[29]	Prospective study Longitudinal cohort	Athletics (Endurance)	Elite	12	31.8 ± 4.0	31 days
Fricker et al.[30]	Prospective study Longitudinal cohort	Athletics (Endurance)	Elite	20	♂ 24.2 ± 3.1	4 months
Cox et al.[31]	Prospective study Longitudinal cohort	Athletics (Endurance)	Well trained	18	♂ 31.2 ± 8.2	3 sessions (3 days)
Ihalainen et al.[32]	Prospective study	Athletics (Endurance)	Trained	25	♂ 34.6 ± 1.3	12 weeks
Ansley et al.[33]	Prospective study	Athletics (Endurance)	Recreational	201	♂ 37.4 ± 9.6; ♀ 40.3 ± 10.9	1 day (in-competition)
Moreira et al.[34]	Prospective study Longitudinal cohort	Basketball	Elite	15	♂ 19.0 ± 0.6	4 weeks
Svendsen et al.[35]	Retrospective study	Cross-country skiers	Elite	39	-	8 seasons (2007 – 2015)
Dressendorfer et al.[36]	Prospective study Longitudinal cohort	Cycling	Competitive	9	♂ 24.7 ± 2.1	14 weeks
Spence et al.[10]	Prospective study Longitudinal cohort	Cycling / Triathlon	Elite and Competitive	63	Elite: 22.5 ± 3.8 Recreational: 25.2±3.6	4 months
Hanstock et al.[37]	Prospective study Randomised control trial	Cycling / Triathlon	Trained	27	♂ 29.9 ± 9.1	4 weeks
Schwellnus et al.[38]	Prospective study	Paralympic athletes	Elite	3565	30.9 ±9.2 (13 to 61)	14 days
Leicht et al.[39]	Prospective study Longitudinal cohort	Paralympic athletes (tetraplegic)	Elite	14	33 ± 5	4 months
Furusawa et al.[40]	Prospective study Longitudinal cohort	Paralympic athletes (Endurance)	Trained	21	42.0 ± 1.7	6 weeks
Fowler et al.[41]	Prospective study	Rugby League	Elite	18	♂ 24.2 ± 3.3	10 days
Thornton et al.[42]	Prospective study	Rugby League	Professional	32	26.0 ± 4.8	29 weeks (14-18 competitions)
Cunniffe et al.[43]	Prospective study	Rugby Union	Elite	31	♂ 26.8 ± 0.9	11 months
Schwellnus et al.[44]	Prospective study	Rugby Union	Elite	259	-	16 weeks
Schwellnus et al.[45]	Prospective study	Rugby Union	Elite	259	-	16 weeks
Tiernan et al.[46]	Prospective study	Rugby Union	Elite	19	♂ 19.7 ± 1.1	10 weeks
Yamauchi et al.[47]	Prospective study	Rugby Union	Trained	32	♂ 20.4 ± 1.4	7 weeks
Neville et al.[48]	Prospective study Longitudinal cohort	Sailors	Elite	38	♂ 36 ± 7	18 months
Nakamura et al.[49]	Prospective study	Soccer	Well trained	12	♂ 19 to 21	33 days
Milanez et al.[50]	Prospective study	Soccer (Futsal)	Elite and Competitive	13	♀ 22.1 ± 4.2	5 weeks
Gleeson et al.[51]	Prospective study Longitudinal cohort	Swimmers	Elite	25	16 to 24	7 months
Hellard et al.[13]	Prospective study Longitudinal cohort	Swimmers	Elite	28	16 to 30	4 years
Gleeson et al.[52]	Prospective study Longitudinal cohort	Swimmers	Elite	25	16 to 24	7 months
Gleeson et al.[53]	Prospective study Longitudinal cohort	Swimmers	Elite	14	♂ 21.4 ± 2.3	30 days
Rama et al.[54]	Prospective study Longitudinal cohort	Swimmers	Elite	19	♂: 17.2 ± 1.8 ♀: 15,8 ± 0,8	13 weeks
Hellard et al.[55]	Prospective study Longitudinal cohort	Swimmers	Elite	18	19 to 30	2 years
Brisola et al.[56]	Prospective study Longitudinal cohort	Swimmers (Water polo)	Elite	25	♀ 15.7 ± 1.3	15 weeks
Novas et al.[57]	Prospective study Longitudinal cohort	Tennis	Elite	17	♀ 14 to 21	12 weeks

Novas et al.[58]	Prospective study Longitudinal cohort	Tennis	Elite, Trained and Recreational	31	♀ 16 ± 2	12 weeks
He et al.[59]	Prospective study Longitudinal cohort	Triathlon	Recreational to Elite	225	♂ 22 ± 3	4 months (winter)
Hausswirth et al.[60]	Prospective study Randomized control trial	Triathlon	Trained	27	37 ± 6	6 weeks
Zehsaz et al.[61]	Retrospective study	Various (Endurance)	Elite	100	♂ 24.0 ± 5.9	2 years
Reid et al.[62]	Prospective study	Various (Endurance)	Elite and Competitive	41	12 to 56	12 months URS (Clinical study)
Gleeson et al.[63]	Prospective study Longitudinal cohort	Various (Endurance)	Highly trained	16	♂ 32.5 ± 8.1	9 months
Gleeson et al.[9]	Prospective study Longitudinal cohort	Various (Endurance)	Trained	75	22.5 ± 4.0	4 months
He et al.[64]	Prospective study Longitudinal cohort	Various (Endurance)	Recreational	210	21 ± 3	16 weeks (winter)
Gleeson et al.[65]	Prospective study Longitudinal cohort	Various (Endurance)	Recreational to Elite	80	♂ -22.5 ±4.0	4 months (winter)
Ikonen et al.[66]	Prospective study Longitudinal cohort	Various (Military)	Highly trained	53	♂ 19.6 ± 0.3	8 weeks
Scullion et al.[67]	Prospective study Cross sectional	Various (Rugby/Rowing)	Elite	53	22.9 ± 3.2	6 months
Blume et al.[68]	Prospective study Longitudinal cohort	Various (Youth)	Trained	274	13.8 ± 1.5	4 years
Cox et al.[69]	Prospective study	Various	Elite	70	19.3 ± 2.6	Single session (Clinical study)
Cox et al.[70]	Retrospective study	Various	Elite	170	25.4 ± 8.6	12 months URS
Hanstock et al.[71]	Prospective studyRepeated measures crossover trial	Various	Recreational	40 (sub-cohort: n=13)	♂: 22 ± 4; ♀: 22 ± 6; ♂ sub-cohort: 24 ± 4	3 weeks (winter)

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Modified Downs and Black[25] Quality assessment scores and 2009 OCEBM[26] classifications for studies included.

Included studies	Downs and Black Question															OCEBM
	1	2	3	4	5	6	7	8	9	10	11	12	13	Total score	Quality of study	Study level
Fahlman[27]	1	1	1	1	1	1	1	1	1	0	1	1	1	12	Excellent	1b
Edouard et al.[28]	1	1	0	1	1	1	0	1	1	0	1	1	1	10	Good	2b
Matthews et al.[29]	1	1	1	1	1	1	1	0	1	0	1	1	1	11	Excellent	1b
Fricker et al.[30]	1	1	1	1	1	1	1	0	1	0	1	1	1	11	Excellent	1b
Cox et al.[31]	1	1	1	1	1	1	1	0	1	0	1	1	1	11	Excellent	1b
Ihalainen et al.[32]	1	1	1	1	1	1	1	1	1	0	1	1	1	12	Excellent	2b
Ansley et al.[33]	1	1	1	1	0	1	1	0	0	0	1	1	1	9	Good	3b
Moreira et al.[34]	1	1	1	1	1	1	0	0	1	0	1	1	1	10	Good	3b
Svendsen et al.[35]	1	1	1	1	1	1	0	0	1	0	1	1	1	10	Good	2b
Dressendorfer et al.[36]	1	1	1	1	1	1	1	0	1	0	1	1	1	11	Excellent	3b
Spence et al.[10]	1	1	1	1	1	1	1	1	1	0	1	1	1	12	Excellent	1b
Hanstock et al.[37]	1	1	1	1	1	1	1	0	1	0	1	1	1	11	Excellent	1b
Schwellnus et al.[38]	1	1	1	1	1	1	0	1	1	0	1	1	1	11	Excellent	3b
Leicht et al.[39]	1	1	1	1	1	1	1	1	1	0	1	1	1	12	Excellent	1b
Furusawa et al.[40]	1	1	1	1	1	1	1	0	1	0	1	1	1	11	Excellent	3b
Fowler et al.[41]	1	1	1	1	1	1	0	0	1	0	1	1	1	10	Good	1b
Thornton et al.[42]	1	1	1	1	1	1	1	0	1	0	1	1	1	11	Excellent	1b
Cunniffe et al.[43]	1	1	1	1	1	1	1	0	1	0	1	1	1	11	Excellent	1b
Schwellnus et al.[44]	1	1	0	1	1	1	1	1	1	0	1	1	1	11	Excellent	1b
Schwellnus et al.[45]	1	1	1	1	1	1	0	1	1	0	1	1	1	11	Excellent	3b
Tiernan et al.[46]	1	1	1	1	1	1	1	0	0	0	1	1	1	10	Good	1b
Yamauchi et al.[47]	1	1	1	1	1	1	1	1	1	0	1	1	1	12	Excellent	1b
Neville et al.[48]	1	1	1	1	1	1	0	0	1	0	1	1	1	10	Good	1b
Nakamura et al.[49]	1	1	1	1	1	1	0	1	1	0	1	1	1	11	Excellent	3b
Milanez et al.[50]	1	1	1	1	1	1	1	0	1	0	1	1	1	11	Excellent	2b
Gleeson et al.[51]	1	1	1	1	1	1	1	0	1	0	1	1	1	11	Excellent	1b
Hellard et al.[13]	1	1	1	1	1	1	1	0	1	0	1	1	1	11	Excellent	1b
Gleeson et al.[52]	1	1	1	1	1	1	1	1	1	0	1	1	1	12	Excellent	1b
Gleeson et al.[53]	1	1	1	1	1	1	1	0	1	0	1	1	1	11	Excellent	1b
Rama et al.[54]	1	1	1	1	1	1	1	0	1	0	1	1	1	11	Excellent	3b
Hellard et al.[55]	1	1	1	1	1	1	1	1	1	0	1	1	1	12	Excellent	1b
Brisola et al.[56]	1	1	1	1	1	1	1	0	1	0	1	1	1	11	Excellent	1b
Novas et al.[57]	1	1	1	1	1	1	1	1	1	0	1	1	1	12	Excellent	1b
Novas et al.[58]	1	1	1	1	1	1	1	0	1	0	1	1	1	11	Excellent	1b
He et al.[59]	1	1	1	1	1	1	1	1	1	0	1	1	1	12	Excellent	1b
Hausswirth et al.[60]	1	1	1	1	1	1	1	1	1	0	1	1	1	12	Excellent	2b
Zehsaz et al.[61]	1	1	1	1	1	1	1	1	1	0	1	1	1	12	Excellent	1b
Gleeson et al.[63]	1	1	1	1	1	1	1	0	1	0	1	1	1	11	Excellent	1b
He et al.[64]	1	1	1	1	1	1	1	1	1	0	1	1	1	12	Excellent	1b
Gleeson et al.[65]	1	1	1	1	1	1	1	1	1	0	1	1	1	12	Excellent	1b
Ikonen et al.[66]	1	1	1	1	1	1	1	0	1	0	1	1	1	11	Excellent	3b
Scullion et al.[67]	1	1	1	1	1	1	1	1	1	0	1	1	1	12	Excellent	1b
Gleeson et al.[9]	1	1	1	1	1	1	0	1	1	0	1	1	1	11	Excellent	1b
Blume et al.[68]	1	1	1	1	1	1	1	1	1	0	1	1	1	12	Excellent	1b
Cox et al.[69]	1	1	1	1	1	1	0	0	1	0	1	1	1	10	Good	2b
Cox et al.[70]	1	1	1	1	1	1	1	1	1	0	1	1	1	12	Excellent	3b
Reid et al.[62]	1	1	1	1	0	1	0	0	1	0	1	1	1	9	Good	1b
Hanstock et al.[71]	1	1	1	1	1	1	1	0	1	0	1	1	1	11	Excellent	1b

Note: 1, Is the hypothesis/aim/objective of the study clearly described?; 2, Are the main outcomes to be measured clearly described in the Introduction or Methods section?; 3, Are the characteristics of the patients included in the study clearly described; 4, Are the main findings of the study clearly described?; 5, Does the study provide

estimates of the random variability in the data for the main outcomes?; 6, Have the characteristics of patients lost to follow-up been described?; 7, Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?; 8, Were the subjects asked to participate in the study representative of the entire population from which they were recruited?; 9, Were those subjects who were prepared to participate representative of the entire population from which they were recruited?; 10, If any of the results of the study were based on "data dredging", was this made clear?; 11, Were the statistical tests used to assess the main outcomes appropriate?; 12, Were the main outcome measures used accurate (valid and reliable)?; 13, Were losses of patients to follow-up taken into account?.