Higher risk of upper respiratory tract infection post marathon running: when physical exercise becomes a threat to the immune system

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ABSTRACT

Background: Several studies have reported that marathon runners have a higher risk of upper respiratory tract infections (URTI) post marathon than non-exercising controls. However, other studies did not find a higher risk of URTI in the same participants before and after a marathon, precluding a conclusive consensus. Besides the between-subjects effects, another important confounding factor in these results is the different pre and post follow-up time to track URTI.

Objectives: Identify by meta-analysis whether a marathon running increases the risk of URTI, adjusting the follow-up time to track URTI.

Data sources: We searched for articles using MEDLINE (PubMed), Embase, Scopus, Web of Science, the Cochrane Library, and EBSCOhost, combining the marathon and respiratory infection descriptor synonyms, on 1st December 2022.

Eligibility criteria: The PICOS framework included human population, comparison between pre and post marathon running, of URTI symptoms (assessed from one to 4 weeks), in non-controlled intervention studies.

Data Synthesis: Because follow-up was longer before the marathon in many studies, we adjusted the number of subjects with infections before marathon to the equivalent post-marathon follow-up duration. There was 18% higher incidence of URTI post-marathon (OR 1.18 95%CI [1.05-1.33], p= 0.005) in a very consistent meta-analysis (I^2 = 0%, p = 0.69), with no risk of publication bias (Egger test p-value = 0.82) for the 7 studies included. The main issues in the quality of the studies were bias in measuring the outcome, bias in classification of intervention (participation in the marathon) and time-varying confounding (corrected for analysis), and therefore the quality of evidence was moderate (GRADE approach = 3).

Limitations: The need for follow-up time adjustment is a limitation, since the number of URTI recorded could be different if the original studies had used the same follow-up time pre and post marathon. The subjectivity of the URTI self-assessments is another limitation in this field.

Conclusions: There is an increased risk of URTI post marathon running and research on this topic to understand mechanisms might support runners to find efficient interventions to reduce this risk.

Protocol registration on in the International Prospective Register of Systematic Reviews (PROSPERO): CRD42022380991

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INTRODUCTION

There is no doubt that regular physical activity improves human health outcomes (1), including improved immune responses (2,3). Although there is no strong evidence of exercise training reducing risk of acquire upper respiratory infections, there is evidence that exercise training reduces the severity of upper respiratory tract infection (URTI) and the number of symptom days in adults (4,5). During a viral infection, moderate exercise training can reduce morbidity in animals (6), although exhaustive exercise in this condition trends towards an increase in mortality and severity of symptoms (6). The volume and intensity of exercise undertaken may therefore determine the impact on infections and the immune response to them.

Researchers have proposed that under healthy conditions, there is a potential for immunological suppression after an exhaustive physical exercise session, a phenomenon called "open window" (7). In support of the open window theory, there are animal studies showing that exhaustive exercise just preceding or immediately after virus injections leads to worse outcomes including death (8,9). In humans, immunological alterations observed after exhaustive exercise or after intensified periods of training with poor recovery have been interpreted as immunosuppressive. For example, very high exercise workloads are associated with transient immune impairment, inflammation, oxidative stress and muscle damage (7,10).

An extreme challenge type of exercise is the marathon. A Marathon is a road race of 42.195 km distance, and a more extreme event is the ultramarathon, that encompasses any distance above the marathon distance, such as the Comrades Ultramarathon in South Africa which is 88 km. During prolonged exercise we continuously increase the energetic demand for active muscles (11). There is a general negative association between exercise volume and intensity, to allow the body to meet its energetic needs, especially at high intensity (speed or pace in the case of the marathon) or volume (distance in the case of the marathon). Marathon runners cover 42.195 km at steady-state oxygen consumption, corresponding to 94% of their maximal capacity (12), making the marathon extremely challenging for the body. Thus, if the open window theory is true, the marathon will be a perfect combination of extremely high intensity and volume, to test whether the potential immunosuppression can be converted to a real increase in the risk of URTI.

In fact, after a marathon running, there is a reduction in the salivary immunoglobulin A levels (13,14), T cell proliferation (15), antigen presentation by macrophages (16), counts of natural killer and T cells (17), granulocyte oxidative burst (18), neutrophils (18) and changes in cytokines and stress hormones (18–20). Furthermore, the energy depletion during a marathon (11), could at least partially contribute to immune suppression considering the immune processes required to fight infections have a high energy cost (10,21).

Despite this literature there is no consensus whether excessive exercise, such as a marathon, could lead to an increased risk of URTI (10,22). Most of the evidence supporting the harmful effects of exercise in humans have been from studies in athletes from different modalities, and athletes undergo many other types of stress besides the exercise load (14,23,24). For example, they are often exposed to crowds or lower hygienic environments when accommodated with too many other team members, and therefore undergo higher exposure to pathogens, what is especially evident in a marathon run setting (23,25). Also, athletes can often be calorie restricted, sleep deprived, or subjected to high climate or altitude variations when traveling to competitions; and they undergo a very high psychological stress since they are always chasing perfection and improvement in performances (23).

URTI are very common in adults, occurring 1 to 3 times a year (26). The risk of URTI in marathon studies is usually assessed by common cold symptoms and it may result from viral infection of the upper respiratory tract, but could be also confounded with sinusitis, tonsillitis and laryngitis depending of the way it is assessed (26). Studies investigating the effects of marathon running have generally tested URTI by the incidence of self-reported symptoms or infectious episodes using a variety of criteria for the definition of URTI (13,27–30). Some of these studies have reported that marathon runners had higher frequency of symptoms of URTI than non-exercising controls (4,5) and that higher intensity running leads to even higher incidence of URTI (31). On the other hand, other studies have not found a higher risk of URTI comparing the same participants before and after a marathon, including para-athletes (13,27–30). It is not clear why these studies have divergent results, but besides the individual differences in studies comparing different groups of people for in each condition, another confounding factor might be the time of follow-up to assess URTI before and after a marathon in those studies.

To bring consensus to this conflicting literature, we carried out a meta-analysis with studies that compared the same subjects in longitudinal study designs, measuring the incidence of URTI before and after a marathon run with adjusted times of follow-up.

METHODS

Protocol and registration

Details of the systematic review can be found in the International Prospective Register of Systematic Reviews (PROSPERO, CRD42022380991).

Eligibility Criteria

The PICOS framework encompassed studies with humans of any sex, race, age or health condition (Population), running a marathon or ultramarathon (intervention/effect), with assessments before (comparator) the marathon and after the marathon run, to identify the number of individuals with URTI symptoms (outcome) in a certain period of follow-up in each time-point, in non-controlled intervention studies (study type).

Search and Study selection

We first did an exploratory comprehensive search encompassing any type of exercise protocol to conclude the URTI symptoms

were most frequent after a marathon run. Then, the new search focused only on this type of extreme exercise. The new search was conducted on PubMed/MEDLINE, Scopus, EMBASE, Web of Science, Cochrane, EBSCOhost for CINAHL and SPORTDiscus 1st December 2022, with no data or language restrictions. The search combined the marathon and the respiratory tract infection synonyms, including abbreviations on title, abstract and keywords. as detailed on PROSPERO (CRD42022380991). The retrieved studies were transferred to the Rayyan Systematic Reviews system (32), which automatically removes obvious duplicates. Two independent and experienced reviewers, then screened the articles using the Rayyan-Systematic Reviews system, excluding less obvious duplicates, non-original data studies (reviews, book chapters, conference papers, case study, protocols), cross-sectional studies, studies that did not assess URTI before the marathon and studies that did not assess number of participants with URTI. Next the two reviewers fully read the studies retrieved to confirm they had data to be extracted. Conflicts were solved by further discussion between the two reviewers and the opinion of the third reviewer was sought when defining the specific outcomes to answer the main question.

Data collection and items

Data was collected in duplicate and confirmed by automatic excel software check, as well as revised by both reviewers in case of conflict. We extracted basic characteristics of the studies such as age, place of marathon and supplementations tested if any. The main data collected for meta-analysis were the time of follow-up to assess URTI before and after the marathon, the total number of participants running the marathon and the number of participants with reported infection in each of the follow-up periods. Because a few studies tested the effect of supplementation on marathon-induced URTI, we extracted this information for analysis.

Risk of bias assessment

The Cochrane ROBINS-I-tool to assess risk of bias in non-randomized studies of interventions was selected here considering the Marathon running was an acute intervention with or without supplementation, where pre-post assessments were conducted without a control (non-marathon running group). The tool judged bias due to confounding, in selection of participants, in classification of interventions, due to deviations from intended interventions, due to missing data, in measurement of outcomes, and in selection of the reported result. For each of these items a series of questions needed to be answered to attribute a final score for each study (33).

Summary measures and Statistical analysis

The meta-analysis was performed using the software Comprehensive meta-analysis version 4.0. The outcome selected was the number of participants with URTI, excluding studies assessing for example number of symptom days or numbers of symptoms within the whole cohort. Because in many studies the URTI assessment period was longer before the marathon, we adjusted the number of subjects with URTI before marathon to the equivalent post-marathon follow-up duration (URTI pre/ [days pre/days post]). Next, the odds ratio (OR) and 95% confidence interval was calculated comparing the ratio of individuals reporting URTI before with the ratio of individuals reporting URTI after the marathon. Egger test was performed to identify risk of publication bias. In all tests we considered significant the $p \leq 0.05$. Additionally, we assessed heterogeneity by percentage of inconsistency between studies, in which we considered lower than 25% as low, between 25 and 75% as moderate, and above 75% as high (34).

Risk of bias across studies

The GRADE approach (35) was used to identify the quality of the evidence in which interventional studies start with maximal score (4 = high) and have one or two points removed if they show severe or very severe risk of publication bias, low quality of studies included, imprecision, inconsistency of results and indirect evidence.

Results

The new search was very specific to marathon running and thus only 132 were retrieved before we selected the final 7 studies. Three of these studies had 2 subgroups each, with a supplementation and placebo group which were included as an individual study for analysis, since they analysed different participants in each group.

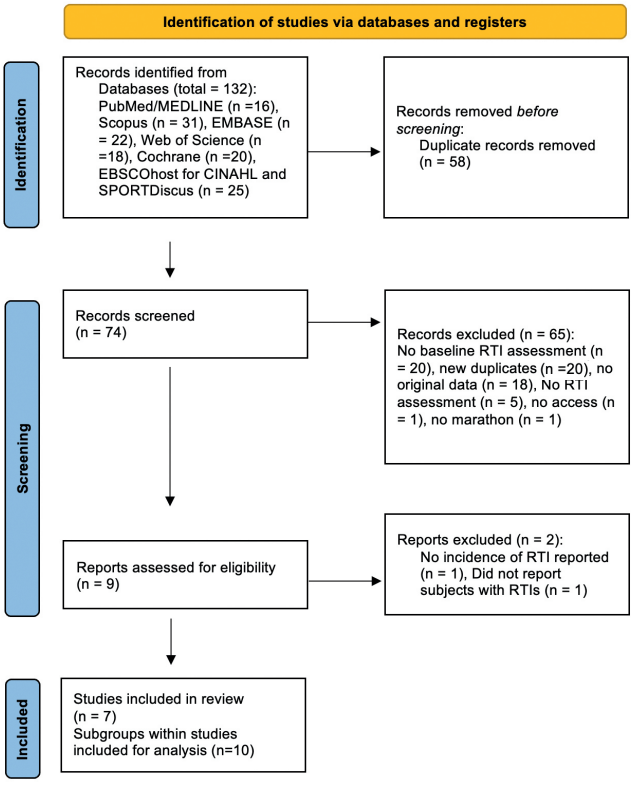

Figure 1. Flowchart of studies selection.
From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/.

STUDY CHARACTERISTICS

The main features of the analysed studies (13,27–29,36–38) are described on Table 1. The studies were performed in males and females, with a wide age range (20-69 years), with naturally acquired URTI. URTI was assessed by questionnaires, self-reported symptoms or self-reported infection episode, telephone interview and daily registration of symptoms in previously healthy individuals. In general, they did not define a criterion or how many symptoms would be enough to confirm a URTI and their results were presented as a binary variable (number of individuals with and without URTI in a given time-point). The comparator was the same individuals before and after the period in which the symptoms of infection was tracked. In general, there was longer follow-up before (15-84 days) than after the marathon run (7-21 days). ROBINS-I showed a few indications of low risk of bias (Supplementary Table 1), such as bias in measuring the outcome, bias in classification of intervention (participation in the marathon) and time-varying confounding, although this last one was corrected for analysis.

FIRST AUTHOR, YEAR	SAMPLE SIZE (SEX)	AGE	MARATHON	URTI ASSESSMENT
Ekblom, 2006	1694 (1354♂/340♀)	29-59y	2000 Stockholm Marathon (Sweden)	Self-reported infection episodes.
Furusawa, 2007	21 ♂	20-67y	1998 Oita International Wheelchair Marathon (Japan)	Self-reported any symptoms (sore throat, cough, fever, runny nose, sneezing) for more than 2 days and separated by at least 1 week from a previous episode.
Harden, 2004	L-methionine Supplement 11 (9♂/2♀) and Placebo 10 (8♂/2♀)	35- 36y	Comrades Ultramarathon (South Africa)	Minimum of 3 symptoms for cold (cough, sore throat, running nose, sneezing) or influenza (fever, aches and pains in joints or muscles, cough sore throat) such that they did not train, or they consulted a doctor for treatment.
Himmelstein, 1998	Vitamin C 30, Placebo 14, 44 total (33♂/11♀)	25-40y	1994 Duke City Marathon (USA)	Self-reported runny nose, cough, or sore throat.
Kekkonen, 2007	LGG Supplement 70 (62♂/8♀), Placebo 71 (63♂/8♀)	22-69y	2003 Helsinki City Marathon (Finland)	Any self-reported symptoms (fever, rhinitis, sore throat, cough, wheezing, earache) for at least 2 days in a row and if there were at least 3 days until the next symptoms appeared.
Nieman, 1990	(1702♂/300♀)	35-38y	1987 Los Angeles Marathon (USA)	Self-reported infectious episodes (yes or no).
Nieman, 2002	98 (86♂/12♀)	21-72y	1999 Charlotte Marathon (USA) and 2000 Grandfather Mountain Marathon (USA)	Self-report cold symptoms (runny, stuffy nose, sore throat, coughing, sneezing, coloured discharge) or flu symptoms (fever, headache, general aches and pains, fatigue and weakness, chest discomfort, cough) for at least 2 days in a row.

Legend: ♀: Women; ♂: Men; y: years old; LGG: Lactobacillus rhamnosus GG.

Table 1. Characteristics of the selected studies.

EVIDENCE SYNTHESIS

Figure 1 reveals a higher incidence of URTI post-marathon (OR 1.18 95%CI [1.05-1.33], p= 0.005) in a very consistent meta-analysis (I^2 = 0%, p = 0.69), with no risk of publication bias (Egger test p-value = 0.82) for the 7 studies included. The GRADE approach led to moderate quality of evidence (score 3) with the removal of one point due to low quality of the studies; while no point was removed from risk of publication bias, inconsistency, indirect evidence, or imprecision.

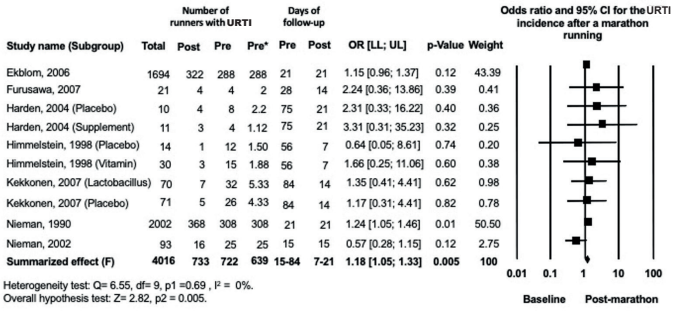

Figure 2. Forest plot for URTI incidence (odds ratio) before and after marathon running.
OR: Odds ratio; F: fixed effect; LL: Lower Limit; UL: Upper limit; CI: confidence interval; Q: Q-value for heterogeneity test (observed heterogeneity); df: degrees of freedom (expected heterogeneity); p1: p-value for heterogeneity test; I^2: inconsistency between studies; Z: Z-value for hypothesis test; p2: p-value for hypothesis test (difference of URTI incidence before and after marathon); URTI: Upper Respiratory Tract Infections; *adjusted to equivalent post-marathon follow-up duration.

Because there was no significant heterogeneity (p=0.69, I^2=0%) and most papers did not assess the major outcome (URTI) separately by confounding factors (e.g.: age, sex, training intensity, training load, marathon performance and supplementation), we were not able to run subgroup analysis to explore the mediators of outcome heterogeneity.

Discussion

We confirmed that a marathon can increase the risk of URTI, however the different magnitude of effects across studies suggests it deserves further investigation. Therefore, in the next paragraphs we are going to discuss the possible influence of the following confounding factors: climate conditions, age, sex, training load and carbohydrate supplementation. We will also consider the potential physiological mechanisms underpinning our results.

Climate condition

Periods of low temperatures coincide with epidemics of many respiratory viruses and it is known that URTI are more prevalent during the autumn and winter (~70%) than spring and summer (~30%) (39,40), which could influence the results. Nevertheless, a majority of the marathons in this review were performed in the summer and spring seasons and with temperatures varying from 50 to 77°F, whether they were in South Africa (36), Japan (27), Finland (37), Sweden (29), or in USA (13,28,38). In addition, since our control was the risk of URTI in the same individuals before the marathon, the possible differences in temperatures in different marathons within the studies will be controlled for by this internal comparison. Unfortunately, there was no control of the individuals that could be traveling from regions with different climate conditions just for the marathon.

Age

With regard to age, we observed there was a higher risk of URTI post marathon in younger participants in two studies with very large sample sizes of 2002 (38), and 1694 (29). This is despite the fact that pre-marathon there is a higher risk of URTI in older marathon runners (28), suggesting the older marathon runners might have the same impaired immune system seen in older adults in general, as we have shown previously (2,41). Indeed, Nieman, (38) showed age did not influence post marathon URTI for individuals who had a URTI before the marathon, while young male and female individuals (<30 years) had significantly higher post marathon URTI when compared between individuals who had no URTI before marathon. Another possibility is that older marathon runners are usually more experienced with marathon running, its training progression, diet etc compared to the younger ones who may not be as well prepared.

Sex

Only two studies reported separate results for men and women, limiting the investigation of this confounding factor in our analysis. At baseline there was a higher odds ratio of URTI in female marathon runners than males (OR 3.059, 95% CI 1.0 - 9.6, p-value 0.05)(28). However, one large study, n=1694, reported that the marathon did not increase the risk of URTI more in women than men (29).

Training load

Higher training speed and volume has been associated with higher risk of URTI post-marathon (27,28), which could be related to higher energetic depletion with higher exercise loads, or norepinephrine release that is commonly beneficial for immunosurveillance in shorter exercise bouts, but in prolonged exposure may lead to suppression of effector functions (42). During exercise, there is also an increase in cortisol, and its anti-inflammatory action can jeopardize the immune response after long exposure (43). In fact, the higher volume of the only study testing the ultramarathon (36), showed a much higher OR for URTI than marathon studies. However, the low sample size generated very high imprecision in this study, preventing a fair comparison with other studies and reducing the weight of this study in the overall meta-analysis results. In contrast, two studies identified that lower training volume was associated with higher URTI risk post-marathon (28,38), but the same studies suggested this contradictory finding might be explained by the opposing cause-effect, in which the previous URTI influenced the reduction of training volume.

Carbohydrate supplementation

There is considerable evidence showing that carbohydrate supplementation before, during and after exercise reduces inflammation, neutrophilia and monocytosis (22), and prevents decreases in granulocyte and monocyte phagocytosis, and cytokines in the circulation (44–49). The intake of food or beverages restores glucose levels, leading to reestablishment of normal stress hormone levels (epinephrine and cortisol) that are known to regulate immune function and also support the immune cell metabolic capacity (10,22,50), which ultimately regulate

immune cells function (21,51). Specifically after a high intensity run, carbohydrate supplementation attenuates leucocytosis and influences neutrophil and monocyte numbers (52,53). In contrast, exercising under glycogen-depleted conditions has been shown to amplify exercise-induced immune alterations, which might, in some cases, be detrimental to training adaptations (54,55). Here, just one of the studies included, tested carbohydrate supplementation, showing that within the 16 runners reporting URTI after a marathon, ten had consumed placebo and six had consumed carbohydrate (13), which did not led to a conclusive finding. Other supplements tested in the included studies were not meant to restore energetic depletion, and they did not affect URTI incidence in those studies (28,36,37), in agreement with previous reviews showing lack of evidence to support recommendation of other supplements (7,45).

Physiological mechanisms underpinning the effect of marathon running on URTI

The higher risk of URTI observed post-marathon, could be affected by the reduction in several types of lymphocytes in the circulation (naïve and memory CD4 helper T cells, activated CD8 cytotoxic T cells, NK, NKT, and B1 cells), reduction in delayed-type hypersensitivity response, salivary immunoglobulin A, T cell proliferation, antigen presentation by macrophages (by suppression of MHC II expression), natural killer cell activity, granulocyte oxidative burst, higher neutrophil/lymphocyte ratio and changes in cytokines and stress hormones that are known to change after this type of strenuous exercise (15,17,22). It is debatable to what extent these changes increase susceptibility to infection, but exhaustive exercise reduces cytokine production in response to antigen stimulation and increases mortality in animals with ongoing infection (6,56).

There is increasing evidence to suggest that the main trigger of immunosuppression with strenuous exercise is the lack of energy for the immune cells to exert their functions. For example, strenuous exercise has been shown to lead to reduced proliferative capacity (57), migration (58), and cytotoxicity in T lymphocytes and other immune cells (44), which are highly energy consuming functions. CD4+ T cells, important against respiratory infections, undergo metabolic stress during strenuous exercise (which does not happen with moderate intensity exercise) which influences their ability to metabolize ATP into adenosine leading to an immunosuppressive phenotype (59). A reduction in T cell proliferation in response to Concanavalin A (a T cell mitogen that can activate immune responses) also occurs after exercise (57,60) and there is a greater reduction when exercise lasts longer than one hour, regardless of exercise intensity (57) highlighting the influence of energy expenditure in this response. One review has detailed the evidence for exercise modulating peripheral lymphocytes metabolism and how it can be jeopardized with strenuous exercise (51).

Another mechanism that deserves more investigation is the effect of exercise induced endotoxemia during a marathon (61), that could be caused by an increase in gut permeability by the common use of Iboprufen by marathon runners, or by direct effects of high intensity exercise (62). However, this is more likely to lead to more severe types of infections rather than URTI.

Limitations

The need for follow-up time adjustment is a limitation in our study, since the number of URTI participants could be different if the original studies had used the same URTI assessment time pre and post marathon. Another limitation in URTI studies is the subjectivity of the assessments that do not absolutely define URTI, for example using a nasal swab and tests for an infection. Specifically, the studies with higher weight in our analysis, including the ones with higher significant increase in URTI, were the ones allowing the participants to define their infection episode without specifying how many symptoms, or days of symptoms, for example. Nevertheless, since we only included studies testing URTI in the same participants before and after a marathon and the main effect is based on each study difference between time those points, we had this confounding factor controlled in our analysis. Next studies need to repeat those experiments with high sample size and rigorous methodological control, and controlling variables such as sleep quality, stress and nutrition.

CONCLUSIONS

Our analysis shows that a marathon run increases the risk of a URTI by 18% over a period of 7-21 days post-marathon. The physiological mechanisms by which this type of exercise would increase susceptibility to respiratory tract infections is unclear and more research is needed to identify mechanisms to target to reduce this risk for runners.

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