# Exercise effect on symptom severity, morbidity and mortality in viral infections

Araujo, Rafaela; Chacon-Mikahil, Mara Patrícia Traina ; Lord, Janet; Veiga Sardeli, Amanda

# Exercise effect on symptom severity, morbidity and mortality in viral infections: a systematic review and meta-analysis.

Rafaela Bertini de Araujo[a], Mara Patrícia Traina Chacon-Mikahil[a,b], Janet M. Lord[c,d], Amanda Veiga Sardeli[a,b, c, d]

[a] Laboratory of Exercise Physiology (FISEX), School of Physical Education, University of Campinas, Campinas, Brazil.

[b] Post Graduate Program Gerontology, Faculty of Medical Sciences, University of Campinas, Campinas, Brazil.

[c] MRC-Versus Arthritis Centre for Musculoskeletal Ageing Research, Institute of Inflammation and Ageing, University of Birmingham, Birmingham, UK.

[d] NIHR Birmingham Biomedical Research Centre, University Hospital Birmingham and University of Birmingham, Birmingham, UK.

Corresponding Author: Amanda Veiga Sardeli, Institute of Inflammation and Ageing, Queen Elizabeth Hospital, Mindelsohn Way, Birmingham, West Midlands, B15 2WB, UK, E-mail: a.veigasardeli@bham.ac.uk.

**Short running head:** Exercise effects during virus infections.

**Abstract**

There is a knowledge gap regarding the consequences of exercise during acute infections in humans and contradictory findings in animal studies, compromising public health advice on the potential benefits of physical activity for immunity. Here, we carried out a meta-analysis of studies of the effects of moderate exercise (ME) and exercise until fatigue (EF) on symptom severity, morbidity and mortality during viral infection in animal models. The systematic review on PubMed, Scopus, Embase, Web of Science, Cochrane and EBSCOhost (CINAHL and SPORT Discus) identified 8 controlled studies, with 15 subgroups within them. The studies exposed the animals (mice [7 studies] and monkeys [1 study]) to exercise immediately before or after viral inoculation (HSV-1, H1N1 influenza and B.K. virus) with follow-up for 21 days. ME significantly reduced morbidity (OR 0.43 [0.19; 0.98], P = 0.04) with no change for symptom severity (SMD -3.37 [-9.01; 2.28], P = 0.24) or mortality (OR 0.48 [0.08;3.03], P = 0.43). In contrast, EF gave a trend towards increased symptom severity (SMD 0.96 [-0.06; 1.98], P = 0.07) and mortality (OR 1.47 [0.96;2.28], P =0.08) with no change in morbidity (OR 1.22 [0.60;2.5], P = 0.58). We conclude that in animals moderate exercise during infection is advantageous, whilst exercise until fatigue should be avoided. Further research is required to determine if moderate exercise may also be beneficial in humans during infection.

**Keywords:** Immunity, Virus Infection, Physical Activity, Exercise, Survival.

## Introduction

There is a considerable literature supporting the benefits of exercise for human health in general (10) and for the immune system in particular (7, 16, 21). The positive effects of exercise include an enhanced response to vaccination (39), improved immune surveillance mediated by redistribution of immune cells to tissues following exercise (30, 52), increased apoptosis of senescent T cells potentially rejuvenating the immune system (33, 51), and with maintained physical activity in to old age there is evidence that the negative effects of age upon immune phenotype and immune responses can be reduced (17, 46). Regards effect of exercise on occurrence, severity and duration of acute respiratory infections, a comprehensive meta-analysis showed exercise reduced the severity of symptoms and the number of symptom days (22). However, the benefits of exercise during an acute infection have received less attention and some of the data concerning the immune response to acute exercise, such as temporary lymphopenia (45, 49, 50) and reduced salivary immunoglobulin A levels (36), have been interpreted as indicating immune suppression (27). Whilst alternative interpretations of the exercise immunology literature have been made (7), recommendations for conservative exercise protocols, and even exercise restriction at times of infection persist (20, 26). Crucially, as there is also good evidence that exercising skeletal muscle is a major positive regulator of immune function (3, 16), it is also possible that exercise could enhance the immune response against viruses and bacteria and reduce the burden of latent viral infections (1, 22, 54). In the absence of infection, exercising skeletal muscle is the major producer of a range of cytokines including IL-6 which in this context has anti-inflammatory actions (3), for example induction of IL-10, and IL-1RA production by macrophages (40). Muscle also produces

cytokines such as IL-7 and IL-15 which support the function of the thymus and enhance the survival and function of immune cells (24, 43).

Opinions, reviews and practical guidelines discussing the risk of acute exercise during infection in humans, including the recent COVID-19 pandemic, are based largely on indirect evidence (18, 20, 57, 59) and only two controlled trials in humans have been reported that directly tested exercise effects on symptom severity during infections (55, 56). In the first, rhinovirus 16 was inoculated into moderately fit young adults who then underwent 40 minutes of aerobic exercise at 70% of their reserve heart rate for the following 7 days (56). There was no difference in the scores for the number of symptoms or the symptom severity measure between the exercise and control groups during the 10 day follow-up (56). However in this study symptom severity was assessed only by weighing the mucus (nasal secretion) instead of a more robust and/or sensitive method to confirm the duration of infection (56). A second study by the same group assigned non-physically active young adults with a naturally acquired upper respiratory tract infection to either 30 minutes aerobic exercise at 70% of target heart rate for five days, or control period with no exercise (55). The study found no difference between mean symptom score and mean number of days with symptoms (55). Although these studies do not make a case for the benefits of exercise during infection, in healthy young individuals, they also do not support the school of thought that exercise is detrimental at times of infection.

In contrast to the lack of human studies, studies in animals, including mice and primates, have considered the influence of exercise on infection outcomes (11, 31). These studies have shown negative effects of exercise carried out before virus inoculation, with increased symptom severity, morbidity and mortality in mice and monkeys compared to controls (11, 31). These apparent differences in outcome

between humans and animals could be caused by the differences in volume and intensity of exercise performed in animals, as some studies have used exercise with exhaustive protocols (11). In fact, after a marathon race, humans undergo some reduction in delayed-type hypersensitivity response, salivary IgA, T cell function, NK cell activity, macrophage function, granulocyte oxidative burst together with increase in neutrophil/lymphocyte ratio, cytokines and stress hormones that would lead to transient immune dysfunction (37).

To address the discordance between studies and attempt to come to some consensus regarding exercise and the response to viral infections, we aimed to carry out a meta-analysis of the effects of moderate exercise (ME) and exercise until fatigue (EF) on symptom severity, morbidity and mortality during viral infection in animal studies.

## Methods

All details of the review protocol can be seen on PROSPERO (CRD42021277401). We searched on PubMed (MEDLINE), adapted to Embase Scopus, Web of Science, Cochrane, and EBSCOhost, April 19, 2021, for controlled studies testing the effect of any type of exercise in animals during infection. They could be purposely or naturally exposed to infection by any virus, and they needed to report the impact on morbidity, symptom severity, and mortality in the exercise and control groups. Duplicates were automatically removed using the Mendeley reference manager system and the selection of studies was done by two independent reviewers on the Rayyan-Systematic Reviews system (38).

Morbidity was assessed as the percentage of sick animals on the last day of follow up which was at day 21; symptom severity was assessed by scales that would

consider different symptoms such as ruffled fur, inactivity, hunched back, and redness around eyes, nose, or mouth; mortality was assessed by percentage of deaths during the study period. Thus, morbidity and mortality were assessed as odds ratio (OR and 95% CI), according to the following equation OR = (n events in EXERCISE / n total in EXERCISE) / (n events in CONTROL/ n total in CONTROL). The symptom severity was calculated as the standardized mean difference (SMD) and 95% CI between exercise and control means at a given day.

The three meta-analyses were performed using Comprehensive Meta-Analysis software, version 3.3.070. When there was statistical significance for heterogeneity, randomized effect models were selected and when there was no significant heterogeneity, fixed effects were applied. The inconsistency between studies was reported as a percentage ($I^2$), based on difference between expected heterogeneity (df) and true heterogeneity (Q-value). The subgroups within studies were clustered according to exercise protocols performed until fatigue (EF) or protocols of moderate intensity (ME). Although, one of the studies described its exercise group as prolonged exercise, it was analyzed as EF (32). Q tests were applied to group comparisons, considering 95% confidence. Egger's tests were performed to check the risk of publication bias in each meta-analysis.

**Results**

Supplementary figure 1 details the flowchart of selection of studies that led to inclusion of 8 controlled studies, with 15 subgroups within them. The characteristics of the studies are summarized on table 1.

****Please insert Table 1 here***

The meta-analysis of morbidity included 249 animals in the EXERCISE and 393 animals in the CONTROL. Since some studies had more than one group of intervention and control (e.g.: males and females), each controlled intervention was included as a separated study for analysis (4, 6, 31, 34). The overall hypothesis test showed the meta-analysis was not significant (OR 0.90 [0.46; 1.77], P = 0.77), with significant heterogeneity and inconsistency across studies (P < 0.001; $I^2$= 67.94%), and significant risk of bias (Egger test, P = 0.02). Figure 1a shows EF did not alter morbidity compared to CONTROL (OR 1.22 [0.60;2.5], P = 0.58), while ME significantly reduced morbidity in comparison to CONTROL (OR 0.43 [0.19; 0.98], P = 0.04).

The meta-analysis of symptom severity included 178 animals in the EXERCISE and 182 animals in the CONTROL. The days that each study reported the severity peak of symptoms were included for analysis, except for one study that reported the first day of symptoms rather than its severity peak (6). The overall hypothesis test showed there was no significant difference between the EXERCISE and CONTROL groups (SMD 0.05 [-1.04; 1.14], P = 0.93), with significant heterogeneity and inconsistency across studies (P < 0.001; $I^2$= 94.66%), and non-significant risk of bias (Egger test, P = 0.75). Figure 1b shows EF trended towards a higher severity of symptoms compared to CONTROL (SMD 0.96 [-0.06; 1.98], P = 0.07), with no difference between ME and CONTROL (SMD -3.37 [-9.01; 2.28], P = 0.24).

The meta-analysis of mortality included 371 animals in the EXERCISE and 370 animals in the CONTROL. The overall hypothesis test showed the meta-analysis was not significant (OR 1.07 [0.51; 2.21], P = 0.17), with significant heterogeneity and inconsistency across studies (P < 0.001; $I^2$= 76.31%), and non-significant risk of bias (Egger test, P = 0.94). Figure 1c shows EF trended towards higher mortality than

CONTROL (OR 1.47 [0.96; 2.28], P = 0.08), while ME was no different from CONTROL (OR 0.48 [0.08; 3.03], P = 0.43).

****Please insert figure 1 a, b and c here****

SYRCLES`s risk of bias tool (25) showed low quality within the primary studies, in which the large majority of them did not report whether group allocation was adequately concealed, whether caregivers and outcome assessors were blinded; whether the animals were selected at random for outcome assessment, and incomplete outcome were not reported (Supplementary Table 1). At last, there was low quality of evidence (score 2) for the severity of symptoms and Mortality meta-analyses, whilst there was very low quality of evidence (score 1) for the morbidity meta-analysis assessed by the GRADE approach (23). In summary, the three meta-analyses lost two points due to its considerable inconsistency and low quality in their primary studies (score between 4 and 5 on SYRCLES); only the morbidity meta-analysis lost one more point due to its significant risk of publication bias; and all three led to precise results by direct evidence.

## Discussion

Eichner (18) first questioned why someone should exercise during an infection if the workout intensity will be suboptimal to increase performance or skills. However, the loss of strength, muscle mass, and cardiorespiratory capacity are remarkable after a few days of de-training, such as during bed rest with or without an infection (2, 13, 42). An argument therefore could be made for maintaining exercise routines during an infection to avoid deconditioning. This may be even more important in older individuals

who are already at increased risk of sarcopenia and frailty (48, 58). Older adults also have compromised immune systems which increase their risk of infections and of succumbing to more severe symptoms, as demonstrated in the COVID-19 pandemic (19).

Here we showed that moderate exercise could be a tool to boost immune responses as we found a significant reduction in morbidity in animal studies of viral infection using such exercise programmes. Many physiological mechanisms could be mediating such benefits. Acute exercise sessions repeated over several weeks increase antibody production and cell-mediated responses during vaccination (39) and transiently enhance immune system features such as reducing the number of senescent lymphocytes in the circulation (29, 44), increasing in blood counts for neutrophils, lymphocytes, monocytes, and natural killer cells (37). Through the increase in cortisol and adrenaline, and possibly also increased blood and lymph circulation, exercise stimulates leukocyte circulation, release of cytokines, chemokines, in turn facilitating antigen recognition, processing, and presentation, as well as cell migration to lymph nodes and cell differentiation (39, 41).

In contrast, we found that exercise to fatigue trended towards an increase in the severity of symptoms and mortality. The exact mechanism that explains the differences between types of exercise are unknown. However, the exercise to fatigue could affect different pathways that contribute to reduced immune responses. For example, the generation of Damage Associated Molecular Patterns (DAMPs) from damaged muscle which is then recognized by TLR receptors and could lead to immune paresis (8, 28). Production of immune suppressive stress hormones such as cortisol would also impact on immunity and reduction in energy availability with these longer duration exercise protocols could compromise lymphocyte proliferation which

222 is highly energy dependent (15, 37, 47). It is worth noting that animals who are forced
223 to perform exercise would be more stressed than during voluntary exercise, which
224 would trigger a negative immune response (9, 14, 53).

225 Considering that the studies in the meta-analysis were performed in previously
226 healthy, young animals, the effect of exercise during infections in a high-risk population
227 such as older animals or humans remains to be determined. The only two studies
228 testing exercise effects during infection in humans were in healthy young adults but
229 showed that moderate exercise did not alter symptom severity (55, 56). As these
230 adults would have highly functional immune systems, the benefits of exercise may be
231 more marked in an older population with compromised immunity (16).

232 The main limitation of this study was the high inconsistency and low quality of
233 evidence in each analysis suggesting that more studies will be necessary to identify
234 the potential causes of heterogeneity between studies. Also, since most of the
235 analyses were heterogeneous, we believe the difference between studies might be
236 caused by a variety of factors such as: type and dose of pathogen; the mode, duration
237 and intensity of exercise; and timing of virus administration in relation to exercise
238 treatment.

239 Another potential limitation was the inclusion of two exercise interventions to
240 fatigue in monkeys (31) in the meta-analysis assessing morbidity. However, we ran a
241 separate analysis without these interventions and confirmed the same results as the
242 analysis with all studies included (OR 1.056 [0.448; 2.489], P = 0.901)

243 In conclusion, while exercise to fatigue trended to increase symptom severity
244 and mortality during infections in animals, moderate exercise did not and significantly
245 reduced mortality. Future studies should test the effect of moderate intensity exercise

during infections in humans as a potential therapy to reduce symptom burden and accelerate recovery.

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**Statement of Ethics**

An ethics statement is not applicable as this study is based exclusively on published literature.

**Conflict of Interest Statement**

The authors have no conflicts of interest to declare.

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## Figures and Tables

**Table 1.** Characteristics of the studies included.

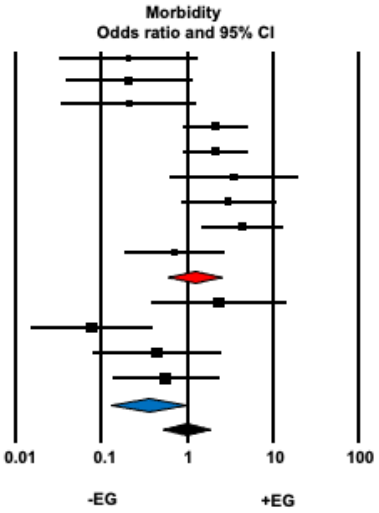
| First Author, Year | Species | Age | sex | | Exercise time-point | Intensity category/ exactly | Type | Volume/Duration | Morbidity | Mortality | Symptoms Severity |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Levinson, 1945 (31) | Monkeys (Macaca mulatta) | NR | M/F | BKV (intracerebrally) | Post inoculation | EF/ Fatigue | Swimming | 2-3 hours/ 4 d | Yes (days 11-14) | - | Yes * |
| Davis,1997 (11) | Mice | 4 wk | M | HSV-1 (Intranasal) | Before inoculation | EF/ Fatigue | Running (treadmill) | 2.5–3.5 hours/ 3 d | Yes (day 21); | Yes (day 21) | - |
| | | | | | | ME/ NR | Running (treadmill) | 30 minutes/ 3 d | | | |
| Brown, 2004 (6) | Mice | ~60 d | M/F | HSV-1 (Intranasal) | Before inoculation | EF/ 70–80% V̇O2 max. | Running (treadmill) | 135 ± 5 min/ 3 d | Yes (day 21) | Yes (day 21) | Yes (1° day of symptom) |
| Davis, 2004 (12) | Mice | 4 wk | M | HSV-1 (Intranasal) | Post inoculation | ME/ 68-78% V̇O2 max. | Running (treadmill) | 1 hour/ 6 d | Yes (day 21); | Yes (day 21) | |
| Murphy, 2004 (34) | Mice | 4 wk | M | HSV-1 (Intranasal) | Post inoculation | ME/ 75-90% V̇O2 max. | Running (treadmill) | 1 hour/ 6 d | Yes (day 21); | Yes (day 21) | Yes (day 7) |
| Lowder, 2005 (32) | Mice | 20-24 wk | M | H3N2 (Intranasal) | Post inoculation | EF/ 65-70% V̇O2 max. | Running (treadmill) | 2.5 hours/ 3 d; | Yes (day 21); | Yes** (day 21) | |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | ME/ 65-70% $\dot{V}O_2$ max. | Running (treadmill) | 30 min/ 3 d | | | |
| Brown, 2007 (5) | Mice | 7 wk | F | HSV-1 (Intranasal) | Before inoculation | EF/ 70–80% $\dot{V}O_2$ max. | Running (treadmill) | 20 min/ 3 d, | Yes (day 21); | Yes (day 21) | Yes (days 12, 16-21) |
| Murphy, 2008 (35) | Mice | 4 wk | M | H1N1 (Intranasal) | Post inoculation | EF/ 70–80% $\dot{V}O_2$ max. | Running (treadmill) | 20 min/ 3 d | Yes (day 21); | Yes (day 21) | Yes (day 7) |

**Legend:** BKV: BK virus; d: days; EF: Exercise-fatigue; ME: moderate exercise; F: Female; H1N1: Influenza A virus subtype H1N1; HSV-1: herpes simplex virus 1; M: Male; Min: Minutes; NR: Not report; $\dot{V}O_{2\ max}$ refers to the maximum amount of oxygen you can utilize during exercise; wk: weeks;* Assessed by incidence of paralysis and degree of involvement (not included in the meta-analysis); **The animals were followed up for 30 days, but the $21^{th}$ day was meta-analysed in order to maintain consistency between studies.

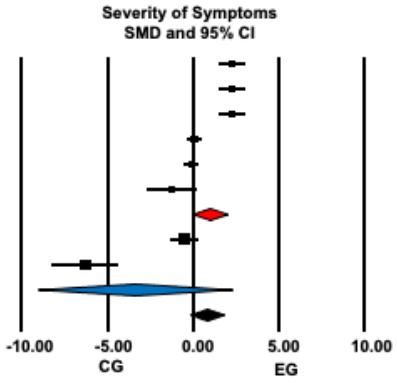
| First author, year | OR | LL | UL | p-value | Events / Total EG | Events / Total CG | Relative weight |
|---|---|---|---|---|---|---|---|
| Brown, 2007a | 0.206 | 0.032 | 1.339 | 0.098 | 10 / 15 | 16 / 18 | 8.23 |
| Brown, 2007b | 0.206 | 0.038 | 1.125 | 0.068 | 13 / 20 | 19 / 21 | 9.12 |
| Brown, 2007c | 0.206 | 0.033 | 1.274 | 0.089 | 14 / 21 | 15 / 17 | 8.47 |
| Brown, 2004a | 2.103 | 0.890 | 4.967 | 0.090 | 29 / 44 | 21 / 44 | 14.64 |
| Brown, 2004b | 2.103 | 0.881 | 5.017 | 0.094 | 28 / 43 | 21 / 43 | 14.57 |
| Murphy, 2008 | 3.500 | 0.630 | 19.441 | 0.152 | 19 / 21 | 15 / 21 | 9.02 |
| Davis, 1997 | 3.000 | 0.837 | 10.753 | 0.092 | 11 / 22 | 6 / 22 | 11.69 |
| Levinson, 1945a | 4.333 | 1.439 | 13.053 | 0.009 | 32 / 40 | 12 / 25 | 12.90 |
| Levinson, 1945b | 0.706 | 0.187 | 2.659 | 0.607 | 32 / 40 | 22 / 26 | 11.36 |
| **EF Overall (R)** | **1.222** | **0.595** | **2.510** | **0.585** | **188 / 266** | **147 / 237** | **100** |
| Murphy, 2004a | 2.348 | 0.378 | 14.586 | 0.360 | 32 / 34 | 36 / 41 | 19.88 |
| Murphy, 2004b | 0.076 | 0.015 | 0.391 | 0.002 | 24 / 41 | 33 / 35 | 24.58 |
| Davis, 1997 | 0.448 | 0.081 | 2.482 | 0.358 | 2 / 17 | 6 / 22 | 22.64 |
| Davis, 2004 | 0.562 | 0.136 | 2.326 | 0.427 | 3 / 21 | 12 / 58 | 32.89 |
| **EM Overall (F)** | **0.434** | **0.192** | **0.979** | **0.044** | **61 / 113** | **87 / 156** | **100** |
| **Summarized effect (R)** | **0.971** | **0.516** | **1.826** | **0.926** | **249 / 379** | **234 / 393** | **100** |

Tau²= 0.99; Q= 37,43; df= 12; p< 0.001; I²= 67.94%; test for overall effect z: -0.30 (p= 0.77).




| First author, year | OR | LL | UL | p-value | Sample size EG | Sample size CG | Relative weight |
|---|---|---|---|---|---|---|---|
| Brown, 2007a | 2.250 | 1.477 | 3.023 | 0.000 | 21 | 21 | 16.82 |
| Brown, 2007b | 2.250 | 1.477 | 3.023 | 0.000 | 21 | 21 | 16.82 |
| Brown, 2007c | 2.250 | 1.477 | 3.023 | 0.000 | 21 | 21 | 16.82 |
| Brown, 2004a | 0.067 | -0.351 | 0.485 | 0.754 | 44 | 44 | 18.04 |
| Brown, 2004b | -0.095 | -0.518 | 0.328 | 0.661 | 43 | 43 | 18.03 |
| Murphy, 2008 | -1.262 | -2.723 | 0.199 | 0.091 | 3 | 7 | 13.49 |
| **EF Overall (R)** | **0.960** | **-0.064** | **1.983** | **0.066** | **153** | **157** | **100** |
| Murphy, 2004a | -0.555 | -1.355 | 0.245 | 0.174 | 12 | 13 | 51.19 |
| Murphy, 2004b | -6.318 | -8.237 | -4.399 | 0.000 | 13 | 12 | 48.81 |
| **EM Overall (R)** | **-3.368** | **-9.014** | **2.278** | **0.242** | **25** | **25** | **100** |
| **Summarized effect (R)** | **0.822** | **-0.185** | **1.829** | **0.110** | **178** | **182** | **100** |

Tau²= 2.21; Q=131.20; df= 7; p<0.001; I²= 94.66%; test for overall effect z:0.09 (p= 0.93)




| First author, year | OR | LL | UL | p-value | Events / Total EG | Events / Total CG | Relative weight |
|---|---|---|---|---|---|---|---|
| Brown, 2007a | 3.696 | 0.744 | 18.355 | 0.110 | 7 / 21 | 2 / 21 | 7.85 |
| Brown, 2007b | 2.442 | 0.705 | 8.452 | 0.159 | 12 / 21 | 8 / 21 | 12.41 |
| Brown, 2007c | 1.542 | 0.452 | 5.260 | 0.489 | 13 / 21 | 11 / 21 | 12.67 |
| Brown, 2004a | 1.000 | 0.320 | 3.126 | 1.000 | 7 / 44 | 7 / 44 | 14.39 |
| Brown, 2004b | 1.000 | 0.390 | 2.564 | 1.000 | 12 / 43 | 12 / 43 | 19.73 |
| Murphy, 2008 | 2.919 | 0.651 | 13.082 | 0.162 | 18 / 21 | 14 / 21 | 8.86 |
| Davis, 1997 | 3.648 | 0.880 | 15.118 | 0.074 | 9 / 22 | 4 / 22 | 9.77 |
| Lowder, 2005 | 0.568 | 0.181 | 1.782 | 0.332 | 8 / 26 | 11 / 26 | 14.32 |
| **EF Overall (R)** | **1.505** | **0.942** | **2.404** | **0.087** | **86 / 219** | **69 / 219** | **100** |
| Murphy, 2004a | 1.463 | 0.530 | 4.035 | 0.462 | 32 / 41 | 30 / 41 | 21.34 |
| Murphy, 2004b | 0.045 | 0.013 | 0.154 | 0.000 | 12 / 42 | 37 / 41 | 20.75 |
| Davis, 1997 | 0.519 | 0.081 | 3.310 | 0.488 | 2 / 22 | 4 / 22 | 18.55 |
| Davis, 2004 | 0.102 | 0.017 | 0.614 | 0.013 | 2 / 21 | 10 / 21 | 18.77 |
| Lowder, 2005 | 6.039 | 1.702 | 21.426 | 0.005 | 21 / 26 | 11 / 26 | 20.60 |
| **EM Overall (R)** | **0.477** | **0.075** | **3.030** | **0.433** | **70 / 152** | **91 / 151** | **100** |
| **Summarized effect (R)** | **1.404** | **0.892** | **2.211** | **0.143** | **156 / 371** | **159 / 370** | **100** |

Tau²= 1.35; Q= 50.66; df= 12; p< 0.001; I²= 76.31%; test for overall effect z: 0.17 (p= 0.87).

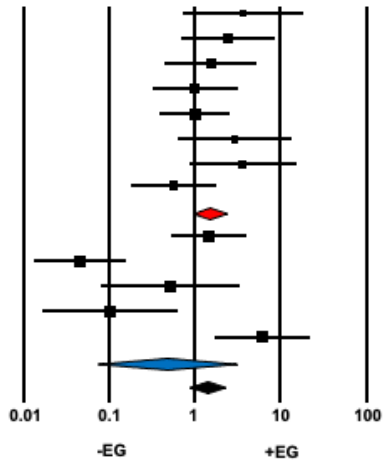
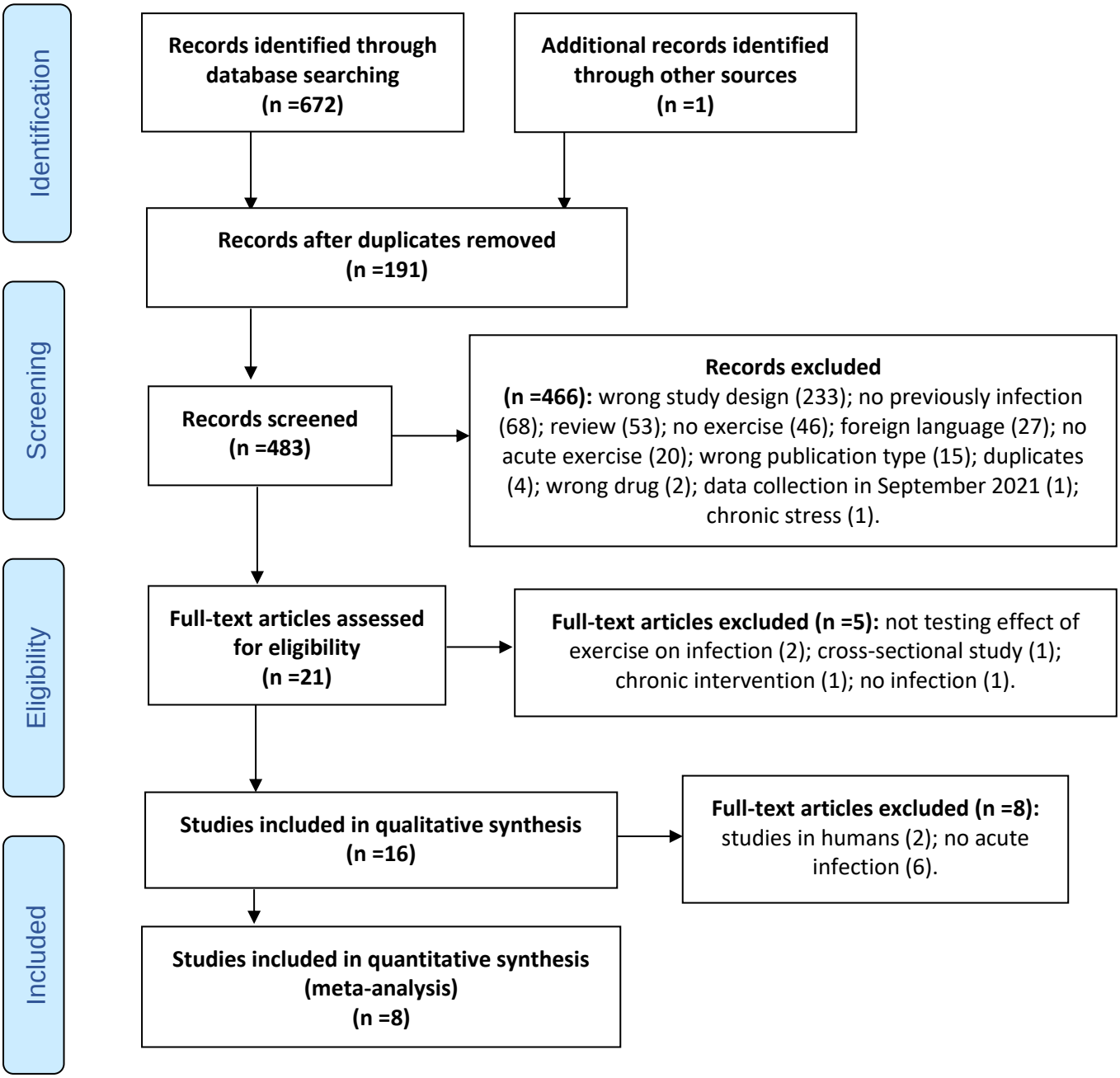


**Figure 1. Forest plots of the effect of acute exercise on symptom severity (a), morbidity (b) and mortality (c) during acute virus infections.** CG: control group; CI: confidence interval; df: degrees of freedom; EG: exercise group; F: fixed effect; $I^2$: percentage of inconsistency between studies; LL: Lower limit; OR: Odds ratio; PBS: PBS liposomes; Q: true heterogeneity; R: random effect; SMD: standardized mean difference; UL: Upper limit; Brown, 2007a: intact (Sham) group; Brown, 2007b: ovariectomized group; Brown, 2007c: ovariectomized and estrogen-supplemented group; Brown, 2004a: female group; Brown, 2004b: male group; Levinson, 1945a: Cage control group; Levinson, 1945b: Water control group; Murphy, 2004a: clodronate encapsulated liposomes intranasally administered group; Murphy, 2004b: PBS liposomes intranasally administered group.

## Supplementary Figures and Tables




**Supplementary Figure 1.** The flowchart of selection of studies. Of note the final analysis did not include the 2 human studies and the focus was on the 8 animal studies.

**Supplementary Table 1.** SYRCLE Risk of Bias in the studies included.

| **First author, year** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **Total** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Levinson, 1945 | Yes | Yes | NR | Yes | No | NR | NR | NR | Yes | No | **4** |
| Davis,1997 | Yes | Yes | NR | Yes | No | NR | NR | NR | Yes | No | **4** |
| Brown, 2004 | Yes | Yes | NR | Yes | No | NR | NR | NR | Yes | No | **4** |
| Davis, 2004 | Yes | Yes | NR | Yes | No | NR | NR | NR | Yes | No | **4** |
| Murphy, 2004 | Yes | Yes | NR | Yes | No | NR | NR | NR | Yes | No | **4** |
| Lowder, 2005 | Yes | Yes | NR | Yes | No | NR | NR | NR | Yes | No | **4** |
| Brown, 2007 | Yes | Yes | NR | Yes | No | NR | NR | NR | Yes | No | **4** |
| Murphy, 2008 | Yes | Yes | NR | Yes | No | NR | NR | Yes | Yes | No | **5** |

**Legend:** 1: allocation sequence adequately generated and applied; 2: similar groups at baseline or adjusted for confounders in the analysis; 3: group allocation adequately concealed; 4: animals randomly housed during the experiment; 5: caregivers blinded; 6: animals selected at random for outcome assessment; 7:outcome assessor blinded; 8: incomplete outcome data adequately addressed; 9: Reports of the study free of selective outcome reporting; 10: apparently free of other risk of bias; NR: Not Reported.