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] Graduate Program in 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.

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.

_____

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.

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 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, or 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

Table 1. Characteristics of the studies included.

First Author, Year	Species	Age	Sex		Exercise time-point	Intensity category/ protocol	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% V̇O2 max.	Running (treadmill)	30 min/ 3 d			
Brown, 2007 (5)	Mice	7 wk	F	HSV-1 (Intranasal)	Before inoculation	EF/ 70–80% V̇O2 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% V̇O2 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; $VO_{2\,max}$ 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 21th day was meta-analysed in order to maintain consistency between studies.

(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.

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).

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 me-

ta-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.
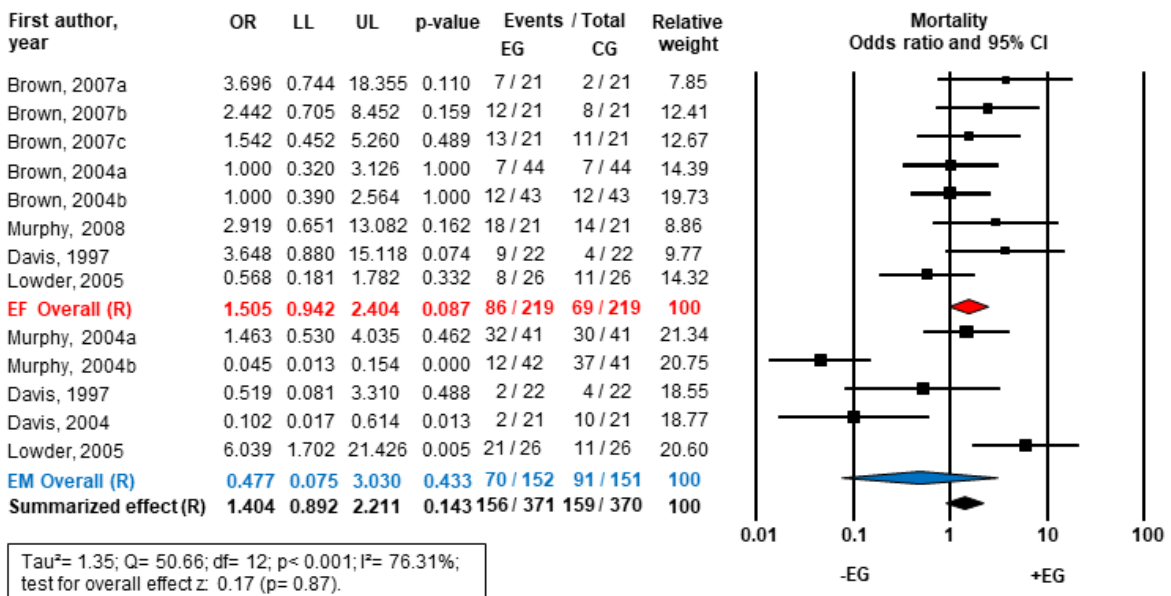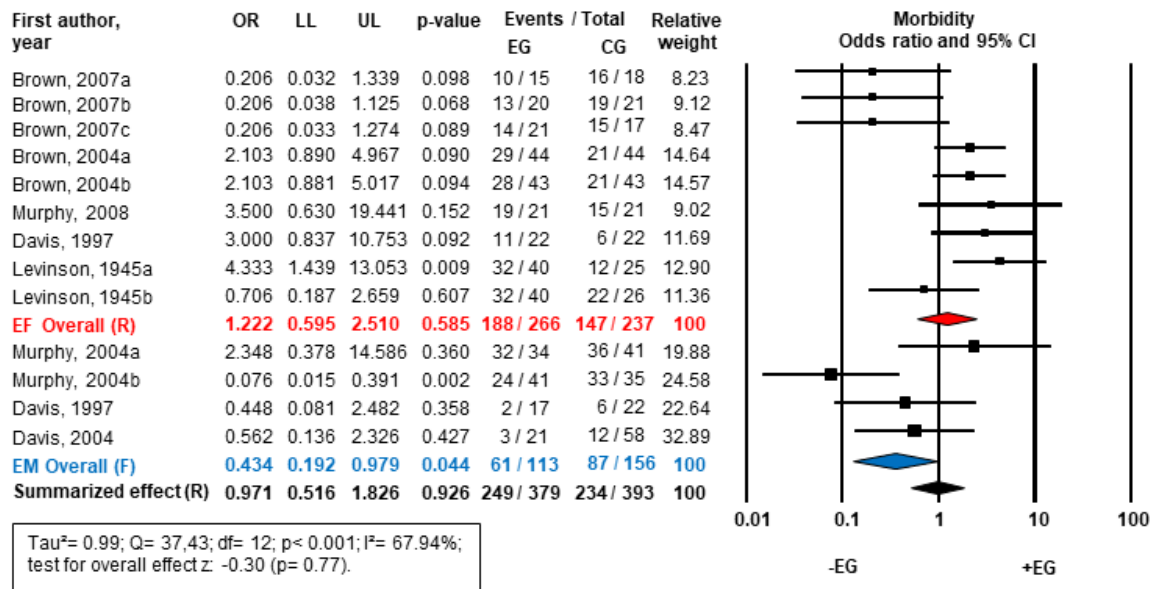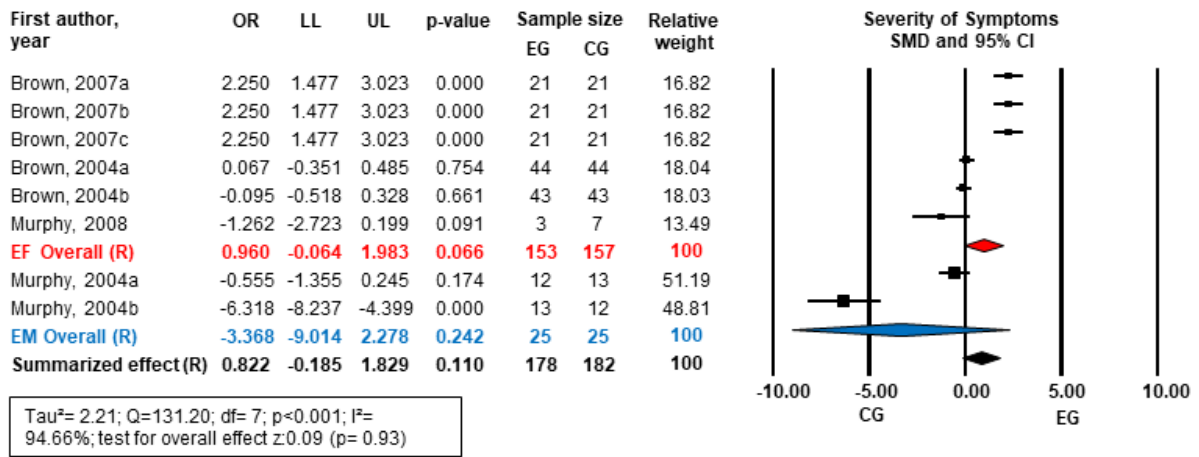
DISCUSSION

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

Considering that the studies in the meta-analysis were performed in previously healthy, young animals, the effect of exercise during infections in a high-risk population such as older animals or humans remains to be determined. The only two studies testing exercise effects during infection in humans were in healthy young adults but showed that moderate exercise did not alter symptom severity (55, 56). As these adults would have

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; I²: 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.

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	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	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).

highly functional immune systems, the benefits of exercise may be more marked in an older population with compromised immunity (16).

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

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

In conclusion, while exercise to fatigue trended to increase symptom severity and mortality during infections in animals, moderate exercise did not and significantly 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.

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.

REFERENCES

1. Agha NH, Mehta SK, Rooney B, Laughlin MS, Markofski MM, Pierson DL, Katsanis E, Crucian BE, Simpson RJ. Exercise as a countermeasure for latent viral reactivation during long duration space flight. FASEB J 34: 2869–2881, 2020. doi: 10.1096/fj.201902327R.

2. Alibegovic AC, Højbjerre L, Sonne MP, Van Hall G, Stallknecht B, Dela F, Vaag A. Impact of 9 days of bed rest on hepatic and peripheral insulin action, insulin secretion, and whole-body lipolysis in healthy young male offspring of patients with type 2 diabetes. Diabetes 58: 2749–2756, 2009. doi: 10.2337/db09-0369.

3. Bay ML, Pedersen BK. Muscle-Organ Crosstalk: Focus on Immunometabolism. Front Physiol 11: 1–8, 2020. doi: 10.3389/fphys.2020.567881.

4. Brown AS, Davis JM, Murphy EA, Carmichael MD, Carson JA, Ghaffar A, Mayer EP. Susceptibility to HSV-1 infection and exercise stress in female mice: Role of estrogen. J Appl Physiol 103: 1592–1597, 2007. doi: 10.1152/japplphysiol.00677.2007.

5. Brown AS, Davis JM, Murphy EA, Carmichael MD, Carson JA, Ghaffar A, Mayer EP. Susceptibility to HSV-1 infection and exercise stress in female mice: Role of estrogen. J Appl Physiol 103: 1592–1597, 2007. doi: 10.1152/japplphysiol.00677.2007.

6. Brown AS, Davis MM, Murphy EA, Carmichael MD, Ghaffar A, Mayer EP. Gender differences in viral infection after repeated exercise stress. Med Sci Sports Exerc 36: 1290–1295, 2004. doi: 10.1249/01.MSS.0000135798.72735.B3.

7. Campbell JP, Turner JE. Debunking the myth of exercise-induced immune suppression: Redefining the impact of exercise on immunological health across the lifespan. Front Immunol 9: 1–21, 2018. doi: 10.3389/fimmu.2018.00648.

8. Cavalcante PAM, Gregnani MF, Henrique JS, Ornellas FH, Araújo RC. Aerobic but not Resistance Exercise Can Induce Inflammatory Pathways via Toll-Like 2 and 4: a Systematic Review. Sport Med - open 3: 42, 2017. doi: 10.1186/s40798-017-0111-2.

9. Chen C, Nakagawa S, An Y, Ito K, Kitaichi Y, Kusumi I. The exercise-glucocorticoid paradox: How exercise is beneficial to cognition, mood, and the brain while increasing glucocorticoid levels. Front Neuroendocrinol 44: 83–102, 2017. doi: 10.1016/J.YFRNE.2016.12.001.

10. Chodzko-Zajko WJ, Proctor DN, Fiatarone Singh MA, Minson CT, Nigg CR, Salem GJ, Skinner JS. American College of Sports Medicine position stand. Exercise and physical activity for older adults. Med Sci Sports Exerc 41: 1510–1530, 2009. doi: 10.1249/MSS.0b013e3181a0c95c.

11. Davis JM, Kohut ML, Colbert LH, Jackson DA, Ghaffar A, Mayer EP. Exercise, alveolar macrophage function, and susceptibility to respiratory infection. J Appl Physiol 83: 1461–1466, 1997. doi: 10.1152/jappl.1997.83.5.1461.

12. Davis JM, Murphy EA, Brown AS, Carmichael MD, Ghaffar A, Mayer EP. Effects of moderate exercise and oat β-glucan on innate immune function and susceptibility to respiratory infection. Am J Physiol - Regul Integr Comp Physiol 286: 366–372, 2004. doi: 10.1152/ajpregu.00304.2003.

13. Demangel R, Treffel L, Py G, Brioche T, Pagano AF, Bareille M-P, Beck A, Pessemesse L, Candau R, Gharib C, Chopard A, Millet C. Early structural and functional signature of 3-day human skeletal muscle disuse using the dry immersion model. J Physiol 595: 4301–4315, 2017. doi: 10.1113/JP273895.

14. Dhabhar FS. Effects of stress on immune function: the good, the bad, and the beautiful. Immunol Res 58: 193–210, 2014. doi: 10.1007/s12026-014-8517-0.

15. Dorneles GP, da Silva IM, Santos MA, Elsner VR, Fonseca SG, Peres A, Romão PRT. Immunoregulation induced by autologous serum collected after acute exercise in obese men: a randomized cross-over trial. Sci Rep 10: 1–16, 2020. doi: 10.1038/s41598-020-78750-z.

16. Duggal NA, Niemiro G, Harridge SDR, Simpson RJ, Lord JM. Can physical activity ameliorate immunosenescence and thereby reduce age-related multi-morbidity? Nat Rev Immunol 19: 563–572, 2019. doi: 10.1038/s41577-019-0177-9.

17. Duggal NA, Pollock RD, Lazarus NR, Harridge S, Lord JM. Major features of immunesenescence, including reduced thymic output, are ameliorated by high levels of physical activity in adulthood. Aging Cell 17, 2018. doi: 10.1111/acel.12750.

18. Eichner ER. Infection, Immunity, and Exercise. Phys Sportsmed 21: 125–135, 1993. doi: 10.1080/00913847.1993.11710319.

19. Gerdes EOW, Vanichkachorn G, Verdoorn BP, Hanson GJ, Joshi AY, Murad MH, Rizza SA, Hurt RT, Tchkonia T, Kirkland JL. Role of senescence in the chronic health consequences of COVID-19. .

20. Gleeson M, Bishop N WN. Exercise immunology. 1st Editio. London: August 14, 2013, 2013.

21. Gleeson M, Bishop NC, Stensel DJ, Lindley MR, Mastana SS, Nimmo MA. The anti-inflammatory effects of exercise: mechanisms and implications for the prevention and treatment of disease. Nat Rev Immunol 11: 607–615, 2011. doi: 10.1038/nri3041.

22. Grande AJ, Keogh J, Silva V, Scott AM, AJ G, Keogh J. Exercise versus no exercise for the occurrence, severity, and duration of acute respiratory infections (Review). Cochrane Database Syst Rev , 2020. doi: 10.1002/14651858.CD010596.pub3.www.cochranelibrary.com.

23. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schünemann HJ. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 336: 924–926, 2008. doi: 10.1136/bmj.39489.470347.AD.

24. Haugen F, Norheim F, Lian H, Wensaas AJ, Dueland S, Berg O, Funderud A, Skålhegg BS, Raastad T, Drevon CA. IL-7 is expressed and secreted by human skeletal muscle cells. Am J Physiol - Cell Physiol 298, 2010. doi: 10.1152/ajpcell.00094.2009.

25. Hooijmans CR, Rovers MM, De Vries RBM, Leenaars M, Ritskes-Hoitinga M, Langendam MW. SYRCLE's risk of bias tool for animal studies. BMC Med Res Methodol 14: 1–9, 2014. doi: 10.1186/1471-2288-14-43.

26. Jaworski CA, Rygiel V. Acute Illness in the Athlete. Clin Sports Med 38: 577–595, 2019. doi: 10.1016/j.csm.2019.05.001.

27. Kakanis MW, Peake J, Brenu EW, Simmonds M, Gray B, Hooper SL, Marshall-Gradisnik SM. The open window of susceptibility to infection after acute exercise in healthy young male elite athletes. Exerc Immunol Rev 16: 119–137, 2010.

28. Kawai T, Akira S. Toll-like Receptors and Their Crosstalk with Other Innate Receptors in Infection and Immunity. Immunity 34: 637–650, 2011. doi: 10.1016/j.immuni.2011.05.006.

29. Krüger K, Alack K, Ringseis R, Mink L, Pfeifer E, Schinle M, Gindler K, Kimmelmann L, Walscheid R, Muders K, Frech T, Eder K, Mooren F-C. Apoptosis of T-Cell Subsets after Acute High-Intensity Interval Exercise. Med Sci Sports Exerc 48: 2021–2029, 2016. doi: 10.1249/MSS.0000000000000979.

30. Krüger K, Lechtermann A, Fobker M, Völker K, Mooren FC. Exercise-induced redistribution of T lymphocytes is regulated by adrenergic mechanisms. Brain Behav Immun 22: 324–338, 2008. doi: 10.1016/j.bbi.2007.08.008.

31. Levinson SO, Milzer A, Lewin P. Effect of fatigue, chilling and mechanical trauma on resistance to experimental poliomyelitis. Am J Epidemiol 42: 204–213, 1945. doi: 10.1093/oxfordjournals.aje.a119037.

32. Lowder T, Padgett DA, Woods JA. Moderate exercise protects mice from death due to influenza virus. Brain Behav Immun 19: 377–380, 2005. doi: 10.1016/j.bbi.2005.04.002.

33. Mooren FC, Krüger K. Apoptotic lymphocytes induce progenitor cell mobilization after exercise. J Appl Physiol 119: 135–139, 2015. doi: 10.1152/japplphysiol.00287.2015.

34. Murphy EA, Davis JM, Brown AS, Carmichael MD, Van Rooijen N, Ghaffar A, Mayer EP. Role of lung macrophages on susceptibility to respiratory infection following short-term moderate exercise training. Am J Physiol - Regul Integr Comp Physiol 287: 1354–1358, 2004. doi: 10.1152/ajpregu.00274.2004.

35. Murphy EA, Davis JM, Carmichael MD, Gangemi JD, Ghaffar A, Mayer EP. Exercise stress increases susceptibility to influenza infection. Brain Behav Immun 22: 1152–1155, 2008. doi: 10.1016/j.bbi.2008.06.004.

36. Nieman DC, Henson DA, Fagoaga OR, Utter AC, Vinci M. Change in salivary IgA following a competitive marathon race. Int J Sports Med 23: 69–75, 2002. doi: 10.1055/s-2002-19375.

37. Nieman DC, Wentz LM. The compelling link between physical activity and the body's defense system. J Sport Heal Sci 8: 201–217, 2019. doi: 10.1016/j.jshs.2018.09.009.

38. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. Syst Rev 5: 1–10, 2016. doi: 10.1186/s13643-016-0384-4.

39. Pascoe AR, Fiatarone Singh MA, Edwards KM. The effects of exercise on vaccination responses: a review of chronic and acute exercise interventions in humans. Brain Behav Immun 39: 33–41, 2014. doi: 10.1016/j.bbi.2013.10.003.

40. Pedersen BK. Anti-inflammatory effects of exercise: role in diabetes and cardiovascular disease. Eur J Clin Invest 47: 600–611, 2017. doi: 10.1111/eci.12781.

41. Pedersen L, Idorn M, Olofsson GH, Lauenborg B, Nookaew I, Hansen RH, Johannesen HH, Becker JC, Pedersen KS, Dethlefsen C, Nielsen J, Gehl J, Pedersen BK, Thor Straten P, Hojman P. Voluntary Running Suppresses Tumor Growth through Epinephrine- and IL-6-Dependent NK Cell Mobilization and Redistribution. Cell Metab 23: 554–562, 2016. doi: 10.1016/j.cmet.2016.01.011.

42. Ried-Larsen M, Aarts HM, Joyner MJ. Effects of strict prolonged bed rest on cardiorespiratory fitness: systematic review and meta-analysis. J Appl Physiol 123: 790–799, 2017. doi: 10.1152/japplphysiol.00415.2017.

43. Rinnov A, Yfanti C, Nielsen S, Akerström TCA, Peijs L, Zankari A, Fischer CP, Pedersen BK. Endurance training enhances skeletal muscle interleukin-15 in human male subjects. Endocrine 45: 271–278, 2014. doi: 10.1007/s12020-013-9969-z.

44. Sardeli AV, Mori MA, Lord JM. Effect of exercise on acute senescent lymphocyte counts: a systematic review and meta-analysis. 2021.

45. Sardeli AV, Mori MA, Lord JM. Effect of Exercise on Acute Senescent Lymphocyte Counts: A Systematic Review and Meta-Analysis. .

46.   Sardeli AV, Tomeleri CM, Cyrino ES, Fernhall B, Cavaglieri CR, Chacon-Mikahil MPT. Effect of resistance training on inflammatory markers of older adults: A meta-analysis. Exp Gerontol 111: 188–196, 2018. doi: 10.1016/j.exger.2018.07.021.

47.   Sarin H, Gudelj I, Honkanen J, Ihalainen JK, Vuorela A, Lee JH, Jin Z, Terwilliger JD, Isola V, Ahtiainen JP, Häkkinen K, Jurić J, Lauc G, Kristiansson K, Hulmi JJ, Perola M. Molecular pathways mediating immunosuppression in response to prolonged intensive physical training, low-energy availability, and intensive weight loss. Front Immunol 10, 2019. doi: 10.3389/fimmu.2019.00907.

48.   Shamliyan T, Talley KMC, Ramakrishnan R, Kane RL. Association of frailty with survival: a systematic literature review. Ageing Res Rev 12: 719–736, 2013. doi: 10.1016/j.arr.2012.03.001.

49.   Shek P, Sabiston B, Buguet A, Radomski M. Strenuous Exercise and Immunological Changes. Int J Sports Med 16: 466–474, 1995. doi: 10.1055/s-2007-973039.

50.   Shephard RJ. Adhesion molecules, catecholamines and leucocyte redistribution during and following exercise. Sport Med 33: 261–284, 2003. doi: 10.2165/00007256-200333040-00002.

51.   Shephard RJ. Aging, Persistent Viral Infections, and Immunosenescence: Can Exercise "Make Space"? Yearb Sport Med 2011: 144–146, 2011. doi: 10.1016/j.yspm.2011.03.027.

52.   Simpson RJ, Boßlau TK, Weyh C, Niemiro GM, Batatinha H, Smith KA, Krüger K. Exercise and adrenergic regulation of immunity. Brain Behav Immun 97: 303–318, 2021. doi: 10.1016/j.bbi.2021.07.010.

53.   Simpson RJ, Campbell JP, Gleeson M, Krüger K, Nieman DC, Pyne DB, Turner JE, Walsh NP. Can exercise affect immune function to increase susceptibility to infection? Exerc Immunol Rev 26: 8–22, 2020.

54.   Simpson RJ, Hussain M, Baker F, Bigley AB, Peek MK, Stowe RP. Cardiorespiratory fitness is associated with better control of latent herpesvirus infections in a large ethnically diverse community sample: Evidence from the Texas City Stress and Health Study. Brain Behav Immun 66: e35, 2017. doi: 10.1016/J.BBI.2017.07.128.

55.   Weidner T, Schurr T. Effect of exercise on upper respiratory tract infection in sedentary subjects. Br J Sports Med 37: 304–306, 2003. doi: 10.1136/bjsm.37.4.304.

56.   Weidner TG, Cranston T, Schurr T, Kaminsky LA. The effect of exercise training on the severity and duration of a viral upper respiratory illness. Med Sci Sports Exerc 30: 1578–1583, 1998. doi: 10.1097/00005768-199811000-00004.

57.   Wilson MG, Hull JH, Rogers J, Pollock N, Dodd M, Haines J, Harris S, Loosemore M, Malhotra A, Pieles G, Shah A, Taylor L, Vyas A, Haddad FS, Sharma S. Cardiorespiratory considerations for return-to-play in elite athletes after COVID-19 infection: A practical guide for sport and exercise medicine physicians. Br J Sports Med 54: 1157–1161, 2020. doi: 10.1136/bjsports-2020-102710.

58.   Xu J, Wan CS, Ktoris K, Reijnierse EM, Maier AB. Sarcopenia Is Associated with Mortality in Adults: A Systematic Review and Meta-Analysis. Gerontology: 1–16, 2021.

59.   Zhu W. Should, and how can, exercise be done during a coronavirus outbreak? An interview with Dr. Jeffrey A. Woods. J. Sport Heal. Sci. 9: 105–107, 2020.

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.
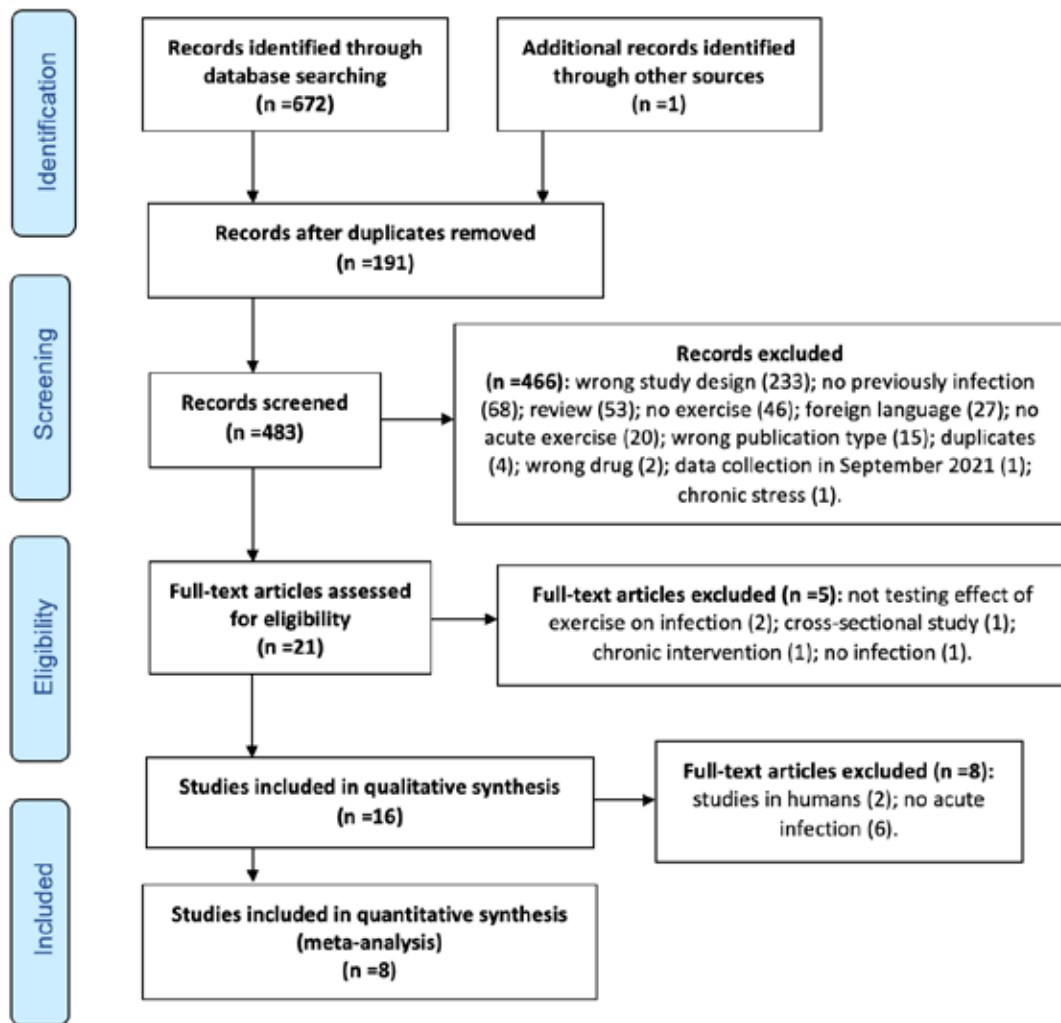
Supplementary Table 1. SYRCLE Risk of Bias in the studies included.
Legend: 1: allocation sequence adequately generated and applied; 2: similar groups at baseline or adjusted for confounders in the analysis; 3: group allocation adequately concealed; 4: animals randomly housed during the experiment; 5: 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.

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