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SYSTEMATIC REVIEW

Performance and Side Effects of Supplementation with *N*-Acetylcysteine: A Systematic Review and Meta-Analysis

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Abstract

Background *N*-Acetylcysteine (NAC) is a promising antioxidant supplement with potential as an acute strategy to enhance performance in elite sport, but there are concerns about its side effects with high doses.

Objective To review the current literature and evaluate the effects of NAC supplementation on sport performance and the risk of adverse effects.

Methods The literature up to May 2016 was searched on MEDLINE (PubMed), EMBASE, SPORTDiscus, Google Scholar and Scopus databases to identify all studies investigating the effects of NAC supplementation on exercise performance and/or side effects experienced. Performance outcomes from each study were converted to the percent effect equivalent to mean power output in a time trial. All pooled analyses were based on random-effects models generated by Review Manager (RevMan) [Computer program], version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, 2014).

Results A total of seven studies met criteria for inclusion in the sport performance meta-analysis, and 17 for inclusion in the side effects meta-analysis. The typical daily dose of NAC reported was 5.8 $g \cdot d^{-1}$; with a range between 1.2 and 20.0 $g \cdot d^{-1}$. The mean increase in performance was 0.29% (95% confidence interval −0.67 to 1.25). The difference in the odds ratio of side effects on NAC compared with placebo was 1.11 (95% confidence interval 0.88–1.39). The sub-analysis of NAC dose suggested an increase in side effects as the dosage of NAC increased; however, this observation requires further investigation.

Conclusions Despite initial research publications reporting positive performance effects with NAC, at this stage it cannot be recommended further. The risk of side effects from NAC supplementation also remains unclear owing to significant variations in effects. Suboptimal reporting and documentation in the literature creates difficulties when meta-analysing outcomes and generating conclusions.

Key Points

N-Acetylcysteine (NAC) has the capacity to influence redox-regulated exercise responses via modulating the redox environment.

NAC supplementation in the range of 1.2–20 g per day produced varied performance effects from beneficial to trivial to harmful, and the true performance effect of NAC remains unclear. The extent to which NAC causes side effects is also unclear.

There is a need for further research in the area of NAC supplementation and sports performance so that clear conclusions can be drawn before NAC can be advocated for use in elite sport.

1 Introduction

During physical exercise, contracting skeletal muscle fibres generate reactive oxygen species (ROS) via a number of different sources and pathways. A review of these

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pathways is discussed elsewhere [1, 2], but can be summarised as mitochondrial ROS leakage secondary to elevated oxygen consumption and metabolic rate, generation of ROS by the sarcoplasmic reticulum and t-tubule systems, electron transfer across the plasma membrane through the nicotinamide adenine dinucleotide phosphate oxidase complex and activation of phospholipase A2, resulting in a cascade of enzymes and increased ROS production [1].

ROS production during exercise may have dual effects for the athlete: high levels of ROS produced during high-intensity strenuous exercise are harmful as they induce cellular damage and impair muscle function; however, low-to-moderate or transient high levels of ROS have been proven to play a protective role in enhancing skeletal muscle adaptations to training, and are essential for optimal muscle force production [1, 3]. Indeed, there seems to be an optimal physiological redox state within muscle that can be achieved by matching the rates of ROS production with the capacity at which cellular antioxidants can buffer [4].

Skeletal muscle fibres contain a network of endogenous antioxidant defence mechanisms that work to 'mop up' ROS to help achieve and maintain this optimal redox balance within cells and reduce the risk of oxidative damage occurring [5]. During high-intensity, strenuous or prolonged exercise, such as during competitions or tournaments, the rate of free radicals and ROS produced within skeletal muscle fibres exceeds the buffering capacity of the endogenous system, resulting in the accumulation of ROS [1, 2, 4, 6]. High levels of muscle-derived ROS are detrimental, as they initiate cellular damage through various cellular processes and contribute to exercise-induced muscle damage, immune dysfunction and fatigue [7]. The metabolic changes that occur within skeletal muscle during exercise can also exert direct negative effects on exercise and sport performance [8]. It is in situations such as these where there has been a substantial amount of interest in whether pre-treating skeletal muscle with dietary antioxidants may help to re-establish an optimal balance between the ratio of ROS to antioxidants within cells, and as a result reduce the risk of oxidative damage occurring and improve performance [9].

In more recent years, there has been an increasing amount of research investigating the performance effects of the antioxidant called *N*-Acetylcysteine (NAC). NAC has long been used in various clinical settings via intravenous (IV) infusion for the prevention of haemorrhagic cystitis, as an emergency treatment for acetaminophen and carbon monoxide poisoning, and as a mucolytic agent for various pulmonary diseases including chronic obstructive pulmonary disease. However, its use by athletes in the sporting environment has not been widely adopted [10]. The biological and metabolic properties of NAC certainly make it an attractive antioxidant supplement for potential use among athletes as a means of improving recovery and enhancing athletic performance; NAC is an effective non-specific antioxidant and reduced thiol donor that potentially reduces the harmful effects of exercise-induced ROS by direct scavenging and by supplying cysteine for synthesis of glutathione [11–13]. Glutathione is an important and abundant cellular antioxidant that works to maintain an ideal redox state by serving as a substrate for glutathione peroxidase in the removal of hydrogen peroxide, and by direct scavenging of ROS [1]. Proposed mechanisms of NAC action include enhancement of potassium homeostasis, preservation of the Na^+/K^+ pump activity within skeletal muscle and the inhibition of calcium ATPase oxidation at the sarcoplasmic reticulum [21]. If the damage caused by exercise-induced ROS could be attenuated by an acute dose of NAC before or after exercise, then recovery may be quicker, and the ability of the athlete to back up performance during periods of extensive anaerobic energy turnover such as in competition and tournament settings may be improved [14, 15].

A number of previous studies have claimed varying degrees (2–32%) of performance benefits with NAC in the laboratory; however, differences in studies' methodology, documentation and reporting of results raise difficulties in making a clear judgement on the true ergogenic potential of NAC [11, 15–19]. Whether these results will be transferred to a field-based sports setting has also not yet been investigated. Although exercise protocols performed in the laboratory provide a controlled environment in which performance can be accurately measured, elite sport is very different to the laboratory, and there are a number of variables that can influence the performance of an individual or team [20]. To our knowledge, there have only been two published studies that have used practical exercise protocols that closely simulate physiological responses to actual sport performed to evaluate the performance effect of NAC [5, 6]. There are a limited number of studies that have tested the efficacy of NAC in athletes at the top elite level. Many studies involve 'trained' athletes, but when the hours of training and fitness of the individuals are taken into consideration, these subjects are incorrectly described as 'elite'. The literature to date also lacks conclusions around whether NAC should be used in training or competition settings.

The lack of comprehensive research and information regarding the optimal dose and timing of NAC supplementation also limits its use in elite sport, and the potential it has to cause harmful or adverse effects [10, 21, 22]. For elite athletes, the tolerability of a supplement is a key consideration when deciding whether or not to consume a supplement, no matter how effective that supplement may claim to be. This is because uncomfortable side effects can

hugely disrupt an elite athlete's usual routine in the days or hours leading up to an important race, event or training, and can consequently result in worsened performance. The most common side effects of NAC include diarrhoea, vomiting and headache [23], and unfortunately we do not currently have a detailed analysis of the extent to which these side effects occur with different doses and administration of NAC supplementation. This shortfall of comprehensive evaluation and clear consensus of the effectiveness, safety and tolerability of NAC means that coaches, trainers and sports dietitians cannot yet confidently advocate the use of NAC supplements for athletes.

It is therefore apparent that we lack a clear consensus of the ergogenic effect of NAC supplementation, and the side effects it may cause. Current literature also lacks studies that comprehensively research NAC supplementation within practical sport settings, or with elite athletes as the study subjects. This has left many researchers, athletes, coaches and their support staff unsure and confused as to whether NAC supplementation should be used as a performance enhancement strategy in elite sport.

The aim of this review is to evaluate the current literature investigating the effect of NAC supplementation on exercise performance, and also its safety and tolerability, using a meta-analytical approach.

2 Methods

2.1 Search Strategy and Study Selection

Figures 1 and 2 summarise the study selection process for the performance and side effect data, respectively. An electronic search was conducted for all studies investigating the effects of NAC supplementation on exercise performance via MEDLINE (PubMed), EMBASE, SPORTDiscus, Google Scholar and Scopus databases. The search period was not restricted by year of publication (up to May 2016). Additional studies were manually identified by cross checking reference lists in relevant studies, articles and citations in review papers. The titles of each study were initially screened during the electronic search to exclude irrelevant studies from the database list. Pre-specified inclusion and exclusion criteria were applied to the abstracts of remaining studies. The full texts were then assessed for eligibility, and those that met inclusion criteria were critically appraised and quality checked to reach a final decision. Two authors (KR, AB) carried out the search independently, and then resolved any disagreements. A second search using the same process but with different keywords was independently conducted to search for all studies reporting the side effects of NAC. A number of studies reporting the side effects of NAC were also manually identified through the Natural Medicines database [23].

2.2 Eligibility Criteria

Table 1 summarises criteria used to select studies for performance and side effects data.

2.3 Risk of Bias Assessment in Included Studies

The risks of bias for all included studies were independently assessed using the guidelines and criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions [24]. The major sources chosen to assess were random sequence generation (selection bias), allocation concealment (selection bias), blinding (performance bias and detection bias) and selective reporting (reporting bias), as recommended by the Cochrane Handbook [25]. Each study was also checked for bias through the involvement of a conflict of interest by manually checking the acknowledgements and funding source of each study. The risk for each major source of bias was defined as either 'low risk', 'unclear risk' or 'high risk' for each included trial, and a risk of bias table was generated. The assessment of risk for each study was then independently entered into Review Manager (RevMan 5.3) to generate a risk of bias summary, which is reported alongside the meta-analysis results.

2.4 Statistical Methods and Data Extraction

2.4.1 Performance Data Aadjustments

To make comparisons between studies, the performance effects of NAC supplementation from all included studies must be expressed in a common metric [26]. The effects on performance from each study were adjusted to the equivalent percent effect on mean power output in a time trial. The adjusted performance effects for each included study are presented in Table 2.

The performance adjustments can be explained as follows. If the performance test was a time to fatigue at constant power, the percent effect was divided by 15 to convert it to the effect on mean power in a time trial. Performance in a time trial was also converted by multiplying the percent effect by the following: running, 1; cycling on a Monark ergometer, 1; swimming, 2; cycling on Kingcycle and Velotron ergometers, 2.5; rowing and kayaking, 3. Where individual change scores in performance were available, these were used to calculate the percent performance effect rather than group mean scores, such as for Bailey et al. [15]. The converted performance effect reported for Corn and Barstow [17] in the results was

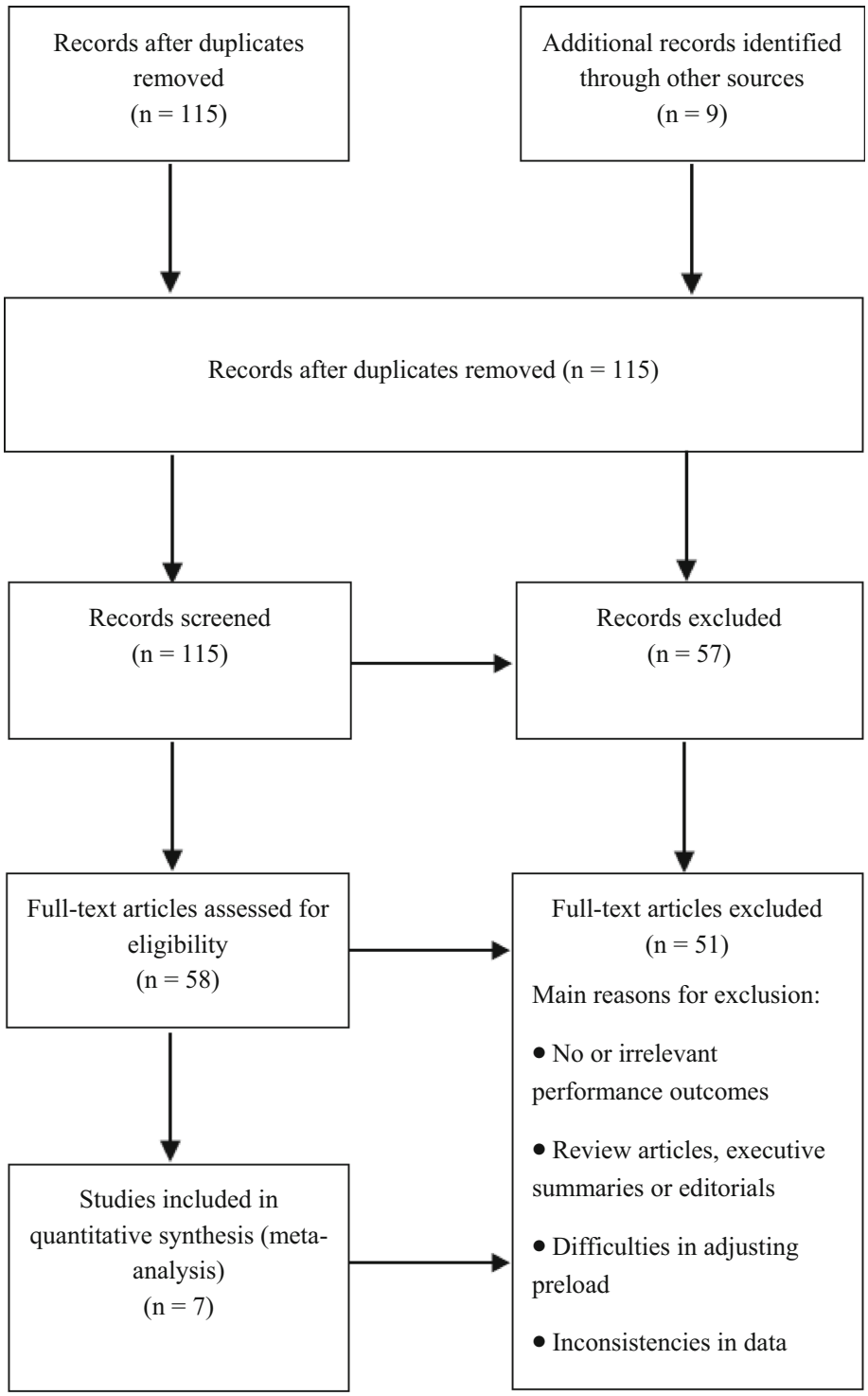

Fig. 1 Flow diagram describing the study selection for performance data

calculated by using the reported performance effect at 80% maximal power.

Converted performance effects for incremental tests to fatigue or tests with a preload were calculated as an assumed fraction at which the test started. In the study by Trewin et al. [26], subjects' mean power outputs during 30 min of high-intensity exercise repetitions were similar to their mean power outputs during the 10-min time trial (82 vs. ~80%, respectively); therefore, the 30-min exercise preload was considered part of the performance test, and the overall performance effect was divided by a factor of 4.

In terms of the significance of the performance effect reported in each study, when exact *p* values were given, this was reported in the results. For studies reporting a

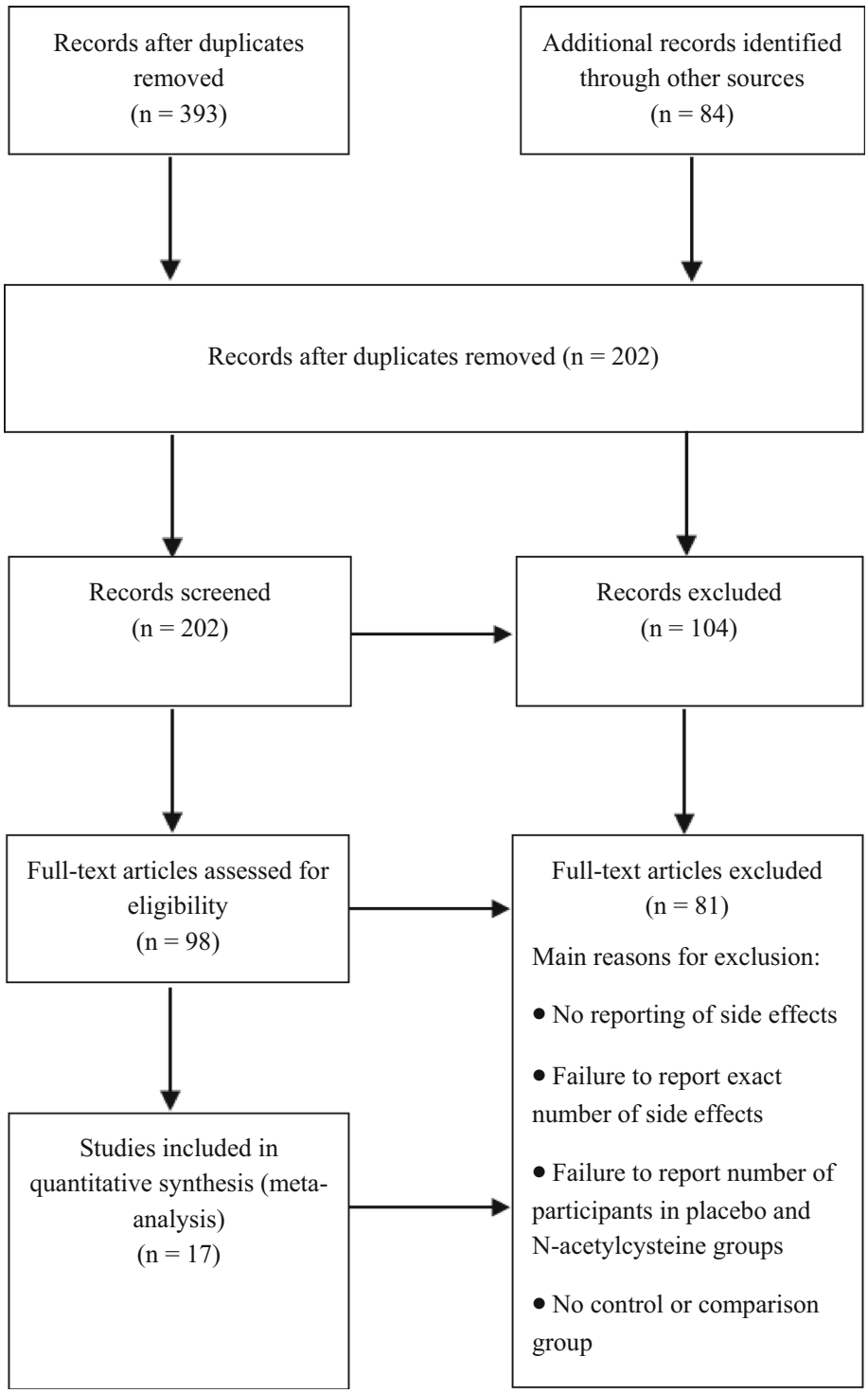

Fig. 2 Flow diagram describing the study selection for side effects data

'significant' effect but not an exact *p* value, we have stated a *p* value of "<0.05", and vice versa. Four studies [16, 27–29] did not report exact *p* values; however, we were able to impute a *p* value by using the "sample size for magnitude-based inferences excel spreadsheet" to calculate the standard error (SE) by assuming the typical error in time trials is ~±2% [29, 30].

2.4.2 Side Effects Data Extraction

Outcomes were reported as the mean difference in symptom count per subject between the NAC and placebo groups for each included study. Side effect events were reported as the total number of episodes over the entire supplementation period, regardless of severity. For studies

Table 1 Criteria used to select studies for performance and side effects data

Performance data	Side effects data
Inclusion	Inclusion
Randomised control or cross-over design	Any study that administered NAC to its study participants with clear reporting of the number of episodes of side effects
Reports effects of a maximal performance test and clear performance outcome measures (typically time to fatigue or time in a time trial)	Human studies
No restrictions were placed on the timing, dose, form of administration (IV or oral), or frequency of supplementation	Studies written in English
Human studies	Published studies
Studies written in English	No restrictions were placed on the timing, dose, form of administration (IV or oral), or frequency of supplementation
Published studies	Any type of study participants: people of any age, sex and level of athletic ability (i.e. trained or untrained)
Any type of study participants: people of any age, sex and level of athletic ability (i.e. trained or untrained)	
Exclusion	Exclusion
Animal studies	Animal studies
Exercise protocols that required subjects to exercise at their submaximal performance or for a fixed period of time were excluded, unless followed by a maximal performance test	Studies that fail to report the exact number of side effects in each of the NAC and control groups
Studies exclusively reporting VO_{2max} as the only performance outcome measure, given the large error of measurement inherent in testing [1]	Studies that fail to report the number of participants in each of the NAC and control groups
Studies reporting indirect measures of performance (e.g. blood markers of muscle fatigue)	Studies that had no control or comparison group
Unreliable performance tests	

IV intravenous, *NAC* *N*-acetylcysteine, VO_{2max} maximum volume of oxygen

that reported zero episodes of side effects for both NAC and placebo groups, the number of side effects was changed to 0.5 in the assumption that both groups may have been on the verge of showing one side effect, and if the study were to be repeated then a side effect would have been observed. This meant that a SE could then also be calculated for these studies. The total daily dose of NAC supplementation was calculated as the average daily dose given across the entire supplementation period. For studies using IV administration of NAC, if the authors reported the actual total dose administered in the results, then this dose was used instead of the intended dose reported in their methods. Categories for small, moderate and large doses of NAC were set at <2, 2–5 and >5 g of NAC per day, respectively.

2.4.3 Meta-Analysis of Performance and Side Effects Data

Effect estimates (% performance change and symptom count difference) and their SEs for each included study were independently entered into RevMan 5.3. The data were analysed using the random-effects model for generic inverse variance to generate an overall test statistic. Outcome measures are reported as an odds ratio, and confidence intervals (CIs) are set at 95%. The outcome was considered clear (or statistically significant/$p < 0.05$), if the 95% CI did not include 1.0. Forest plots were also visually assessed to determine 'trends' in the data. A subgroup analysis was conducted for the effect of NAC dose (small, moderate or large) on side effect symptom count.

2.4.4 Assessment of Heterogeneity

Assessment of heterogeneity between included studies was evaluated by the Higgins score (I^2). Values of I^2 were interpreted using the guidelines outlined in the Cochrane Handbook for Systematic Reviews of Interventions, where 0–40% might not be important; 30–60% may represent moderate heterogeneity; 50–90% may represent substantial heterogeneity and 75–100% may represent considerable heterogeneity [24].

3 Results

3.1 Results of Search

3.1.1 Performance Data

Figure 1 summarises the search process for performance data. A total of 167 articles were identified through searching databases and nine through other sources. Following removal of duplicates, 115 articles remained. After screening by title and abstract, 58 full-text articles

Table 2 Details of NAC studies included in the performance meta-analysis

Study	Subjects; design	NAC treatment	Timing of final dose	Performance protocol	Performance outcome[a]
Bailey et al. [15]	8 male individuals (non-athletes); crossover	Initial, 125 $mg.kg^{-1}\cdot h^{-1}$ for 15 min; during 25 $mg\cdot kg^{-1}\cdot h^{-1}$ (IV)	Before and during test	Cycle time to fatigue after a preload (12.9 min)	↑13% NS [↑1.0%]
Zembron-Lancy et al. [16]	15 male physical activity students (non-athletes), crossover	1.2 g daily for 8 days (oral)	2 h before test	Cycle time to fatigue (17 min)	↑1.6% $p = 0.03$[b] [↑1.6%]
Corn and Barstow [17]	7 male individuals (non-athletes); crossover	70 $mg\cdot kg^{-1}$ for 9 days (oral)	1 h before test	Peak power during a cycle time to fatigue (6.7 min)	↑21%[b] $p = 0.03$ [↑1.4%]
Miltenberger et al. [27]	18 male college students (non-athletes); crossover	A one-off dose of 70 $mg\cdot kg^{-1}$ (oral)	1.5 h before test	Mean sprint time during repeated sprints (5 min)	↑0.2% NS [↑0.2%]
Nielsen et al. [28]	19 male rowers (athletes), crossover	6 g daily for 3 days (oral)	2 h before test	Total power (W) produced during a maximal rowing test (6 min)	↓0.3% $p = 0.82$[b] [↓0.3%]
Da Silva et al. [29]	10 male individuals with intermittent claudication (non-athletes); crossover	1.8 g daily for 4 days (oral), followed by 2.7 g on testing day	1 h before test	Maximal walking time during a graded treadmill test (9 min)	↓0.8% NS [↓0.8%]
Trewin et al. [26]	9 elite male cyclists (athletes); crossover	500 $mg\cdot kg^{-1}$ over 2 days (oral)	1 h before test	Mean power during a 10-km cycle time trial after a preload (10 min)	↓4.9% NS [↓1.2%]

IV intravenous, *NAC* *N*-acetylcysteine, *NS* non-significant, ↑ increased, ↓ decreased

[a] [..] = converted performance effects

[b] Calculated from results presented in the paper

remained. Following the application of specific inclusion and exclusion criteria, critical appraisal and quality checking of full-text articles, seven were deemed acceptable for inclusion in the performance effects quantitative synthesis. The primary reasons for exclusion were failure to adequately report performance outcomes, or reporting of unclear performance outcomes [17, 19, 32–36]. Three review articles were excluded; however, these were valuable for elucidating antioxidant status, mechanistic actions and side effects of NAC [1, 2, 21]. Two further studies were excluded because of difficulties in adjusting for the preload [5, 6].

Three studies completed by Medved and colleagues [11, 37, 38] were excluded because of inconsistencies with other published data, in particular, regarding the reliability of their performance test. One study [37] reported a mean typical error (TE) of 7.4, which was calculated from two preliminary constant power trials to fatigue. In other investigations of reliability of time-to-exhaustion tests of similar duration, TEs of at least 15% were usually observed, and ~2% in time trials [30]. The study also used a considerable preload, which usually increases the error of measurement in a subsequent performance test. In another study by Medved et al. [11], an even lower TE of 5.6 between the two preliminary constant power trials was reported. In this study, Medved and colleagues also failed to provide any explanation as to why their subjects fatigued after only 5 min of cycling at 92% maximal oxygen consumption. Endurance-trained healthy men should typically be able to exercise at 92% maximal oxygen consumption for 30 min before they reach exhaustion. Another study identified from the literature search [18] appears to use the same performance data set as one of the papers by Medved and colleagues [11] and was therefore excluded. Another study published by Medved and colleagues [38] was excluded because they also reported a low TE (2.4%) between two reliability constant power trials to fatigue.

3.1.2 Side Effects Data

Figure 2 summarises the search process for side effects data. A total of 477 articles were identified through searching databases and other sources. Following the removal of duplicates, 202 articles remained. After

screening by title and abstract, 98 full-text articles remained. Following the application of specific inclusion and exclusion criteria, critical appraisal and quality checking of full-text articles, 17 studies were deemed acceptable for inclusion in the side effects data. The primary reason for exclusion was failure to report side effects at all [8, 13, 16–18, 28, 32, 39] followed by failure to report the exact number of side effect episodes [40, 43]. Another common reason was failure to report the number of participants in each of the NAC and placebo groups, and having no comparison or control group.

3.2 Description of Included Studies

3.2.1 Performance Data

Table 2 summarises the seven studies deemed acceptable for inclusion in the performance meta-analysis. Among the included studies, one administered an IV form of NAC (16), and the remaining studies administered oral NAC. The total daily dose of NAC ranged from 1.2 to 20 g, and the period of NAC supplementation varied from acute (minutes to hours prior to the performance test) to 8 days. Of the seven studies, two used trained athletes as their study participants [26, 28], and five used non-athletes [15–17, 27, 29]. All studies used a cross-over design, and reported the effect of NAC on either walking, sprinting, cycling or rowing performance.

3.2.2 Side Effects Data

Table 3 summarises the 17 studies included in the side effects meta-analysis. Among the included studies, nine administered oral NAC, and eight administered NAC via IV infusion. The total daily dose of NAC ranged from 600 to 20,000 mg, and the period of NAC supplementation varied from acute (one-off dose) to chronic (1 year). The majority of studies had a cross-over design; however, some parallel and randomised control trials were also included.

3.3 Risk of Bias in Included Studies

3.3.1 Performance Data

Whilst there were some gaps in the reported methods of included studies, there was an overall low risk that the true performance effect of NAC had been influenced by bias from included studies. The risk of bias assessment for all included studies ranged from low risk to unclear risk, with no studies displaying a high risk of bias (see Fig. 3). All studies failed to report how allocation sequences were generated, or their method of concealing allocation of NAC assignment, and thus the risk of allocation concealment bias for all studies remained unclear.

3.3.2 Side Effects Data

Overall, there seemed to be low risk that the true effect of NAC to produce side effects had been influenced by bias (see Fig. 4). Again, the risk of allocation concealment bias was generally unclear across all included studies, with the exception of two studies where the methods of allocation concealment were adequately stated [33, 44]. One study showed a high risk of performance, detection and reporting bias [36].

3.4 Meta-Analysis Results

3.4.1 NAC and Its Effect on Performance

The performance effect of NAC vs. placebo during exercise was investigated in seven studies. The random-effects model was used for the meta-analysis and it calculated the mean percent effect of NAC on performance to be 0.29 (95% CI −0.67 to 1.25, $p = 0.55$), which is unclear (see Fig. 3). There was evidence of heterogeneity among studies ($I^2 = 56\%$, $\text{tau}^2 = 0.86$, $p = 0.03$).

3.4.2 NAC and the Risk of Side Effects

The extent to which NAC results in side effects compared with placebo was investigated in 17 studies. The random-effects model was used to meta-analyse the difference in side effects between the NAC and control treatment, and the outcome was unclear with a pooled mean effect of 1.11 (95% CI 0.88–1.39, $p = 0.37$). There was no evidence that the mean effect was influenced by the heterogeneity among studies ($I^2 = 0\%$, $\text{tau}^2 = 0.00$, $p = 0.91$) [see Fig. 4]. Although unclear, there was a trend of increasing side effects as the dosage of NAC increased from small to moderate to large, with a pooled mean effect of 1.03 (95% CI 0.77–1.37, $p = 0.86$), 1.20 (95% CI 0.65–2.20, $p = 0.57$) and 1.28 (95% CI 0.82–2.01, $p = 0.28$), respectively.

3.4.3 Comment on Worthwhile Excluded Studies

Two studies could not be meta-analysed as they contained a complicated pre-load or exercise protocol, and thus it was too difficult to convert the performance effects to an equivalent effect in a time trial [5, 6]. However, we believe that these studies provided results that are worthy of scrutiny and discussion. A study by Cobley et al. [5] reported a significant increase in Yo-Yo intermittent recovery test level 1 (YYIRT-L1) performance with NAC

Table 3 Details of NAC studies included in the side effects meta-analysis

Study	*n*	NAC treatment	TDD NAC (mg)	Incidence of adverse events in NAC group			Incidence of adverse events in placebo group			Difference in count per person
				Mild	Moderate	Severe	Mild	Moderate	Severe	
Ferreira et al. (dose 3) [33]	2	35 mg·kg (oral)	2800	6 Upset stomach: 2, stomach or intestinal gas: 2, sleepiness: 1, metallic taste: 1			7 Stomach or intestinal gas: 2, sleepiness: 3, lightheadedness: 1, redness of the eye, face, or hands: 1	1 Metallic taste		−1.0
Ferreira et al. (dose 4) [33]	2	70 mg·kg (oral)	5600	11 Upset stomach: 2, stomach or intestinal gas: 1, sleepiness: 3, metallic taste: 3, lightheadedness: 1, cough: 1	1 Upset stomach	1 Stomach or intestinal gas	7 Stomach or intestinal gas: 2, sleepiness: 3, lightheadedness: 1, redness of the eye, face, or hands: 1	1 Metallic taste		1.5
Tse et al. [52]	120 COPD subjects	600 mg·d for 1 year (oral)	600	4 GERD symptoms: 1, diarrhoea: 1, dry mouth: 1, joint pain and muscle pain: 1			5 GERD symptoms: 3, dry mouth: 1, increase in cough: 1			−0.3
Bailey et al. [15]	8	125 mg·kg^{-1}·h^{-1} for 15 min followed by 25 mg·kg^{-1}·h^{-1} until the termination of exercise	3500	0			0			0.0
Kelly et al. [44]	8	1800 mg (oral)	1800	0			0			0.0
Kersick et al. [53]	30	1800 mg (oral)	1800	0			0			0.0
Michailidis et al. [35]	10	20 mg·kg for 8 days (oral)	1600	0			0			0.0
Slattery et al. [6]	8	1200 mg	1350	0			0			0.0
Trewin et al. [26]	8	500 mg·kg over 48 h (oral)	20,000	1 GI disturbances						0.11

Table 3 continued

Study	*n*	NAC treatment	TDD NAC (mg)	Incidence of adverse events in NAC group			Incidence of adverse events in placebo group			Difference in count per person
				Mild	Moderate	Severe	Mild	Moderate	Severe	
Artsall et al. [54]	27	20 mg·min IV for the first hour, then 10 mg/min for the subsequent 23 h (IV)	15,000	7 Haemorrhage: 3, headache: 4		1 Extreme sinus bradycardia				0.40
Reid et al. [36]	130	150 mg·kg (IV)	12,000	65[a] Conjunctival irritation: 11, dysphoria: 8, sleepiness: 7, cough: 7, lightheadedness: 6, palmar erythema/sweating: 6, facial erythema: 5, dyspepsia: 5, nausea: 4, pruritus: 3, metallic taste: 3			9 Sleepiness: 8, metallic taste: 1[a]			0.43
Medved et al. [11]	8	Initial, 125 $mg \cdot kg^{-1} \cdot h^{-1}$ for 15 min; 25 $mg \cdot kg^{-1} \cdot h^{-1}$ for 20 min (IV)	3200	10 Erythema: 2, swelling: 1, flushing: 2, coughing: 1, sweating: 3, itchy skin: 1			6 Flushing:1, sweating: 4, itchy skin: 1			0.50
Brown et al. [50]	24	Initial, 125 $mg \cdot kg^{-1} \cdot h^{-1}$ for 15 min; 25 $mg \cdot kg^{-1} \cdot h^{-1}$ for 35 min and during exercise (IV)	4473	32 Nausea: 1, local erythema: 10, local edema: 14, flushing: 4, rash: 2, coughing: 1	1 Vomiting		12 Nausea/vomiting: 1, local erythema: 7, flushing: 1, rash: 2, coughing: 1			0.88
Travaline et al. [55]	4	150 mg·kg (IV)	12,000	4 Nausea: 2, transient skin flushing and pruritus: 2						1.0
Medved et al. [38]	8	Initial, 125 $mg \cdot kg^{-1} \cdot h^{-1}$ for 15 min; 25 $mg \cdot kg^{-1} \cdot h^{-1}$ during exercise (2 min) [IV]	3450	24 Vomiting: 1, erythema: 2, swelling: 7, flushing: 1, rash: 2, altered moods: 2			6 Vomiting:1, erythema: 3, rash: 1, coughing: 1			1.13
Medved et al. [37]	7	Initial, 125 $mg \cdot kg^{-1} \cdot h^{-1}$ for 15 min; 25 $mg \cdot kg^{-1} \cdot h^{-1}$ for 20 min and during exercise (IV)	5090	13 Erythema: 6, swelling: 6, flushing: 1	1 Nausea		5 Erythema: 4, rash:1			1.29

Table 3 continued

Study	*n*	NAC treatment	TDD NAC (mg)	Incidence of adverse events in NAC group			Incidence of adverse events in placebo group			Difference in count per person
				Mild	Moderate	Severe	Mild	Moderate	Severe	
Cobley et al. [5]	12	50 mg·kg^{-1} (oral) daily for 6 days	4000	9 Diarrhea: 5, indigestion: 4		1 Diarrhea	1 Indigestion			1.50
Ferreira et al. (dose 1) [33]	2	2 × 300-mg capsules (oral)	600	5 Upset stomach: 2, nausea: 1, stomach or intestinal gas: 1, cough: 1			1 Stomach or intestinal gas			2.0
Ferreira et al. (dose 2) [33]	2	2 × 600-mg capsules (oral)	1200	7 Upset stomach: 1, nausea: 1, stomach or intestinal gas: 2, sleepiness: 2, metallic taste: 1			1 Stomach or intestinal gas			3.0
Matuszczak et al. [19]	18	150 mg·kg (oral)	11,000	58 Sweating: 1, erythema: 4, conjunctivitis: 4, pruritus: 3, lightheadedness : 10, drowsiness:4, dysphoria: 2, metallic taste: 1, nausea: 6, dyspepsia: 6, flatulence: 9, diarrhea: 8			0			3.22
Ferreira et al. (dose 5) [33]	2	140 mg·kg (oral)	11,200	17 Upset stomach: 5, nausea: 3, stomach or intestinal gas: 2, sleepiness: 2, metallic taste: 4, lightheadedness: 1	5 Upset stomach: 1, stomach or intestinal gas: 4		7 Stomach or intestinal gas: 2, sleepiness: 3, lightheadedness: 1, redness of the eye, face, or hands: 1	1 Metallic taste		4.50

COPD chronic obstructive pulmonary disorder, *GERD* gastroesophageal reflux disease, *GI* gastrointestinal, *IV* intravenous, *NAC* *N*-acetylcysteine, *NS* non-significant

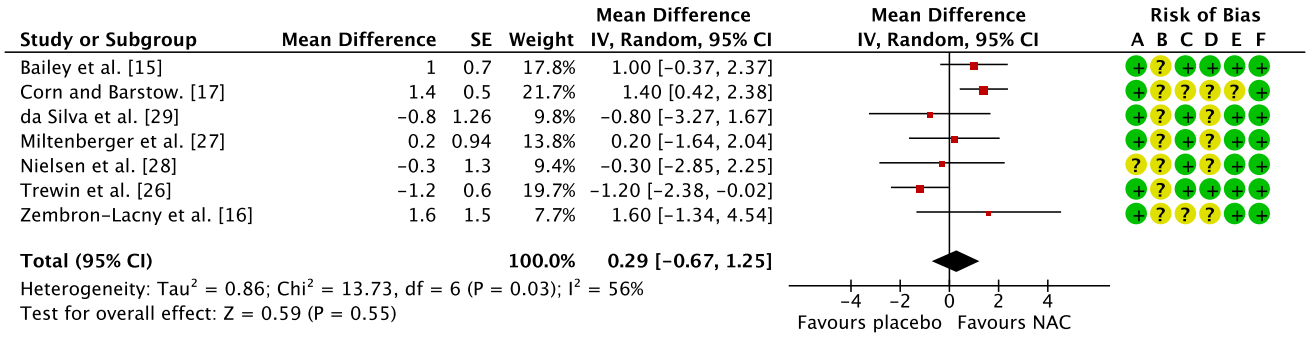

Fig. 3 Forest plot showing the mean difference in performance with NAC compared with placebo, and the risk of bias summary. Performance results are expressed as mean differences, and 95% confidence intervals (CI). *IV* intravenous, *NAC* *N*-acetylcysteine, *SE* standard error, + indicates low risk, ? indicates unclear risk

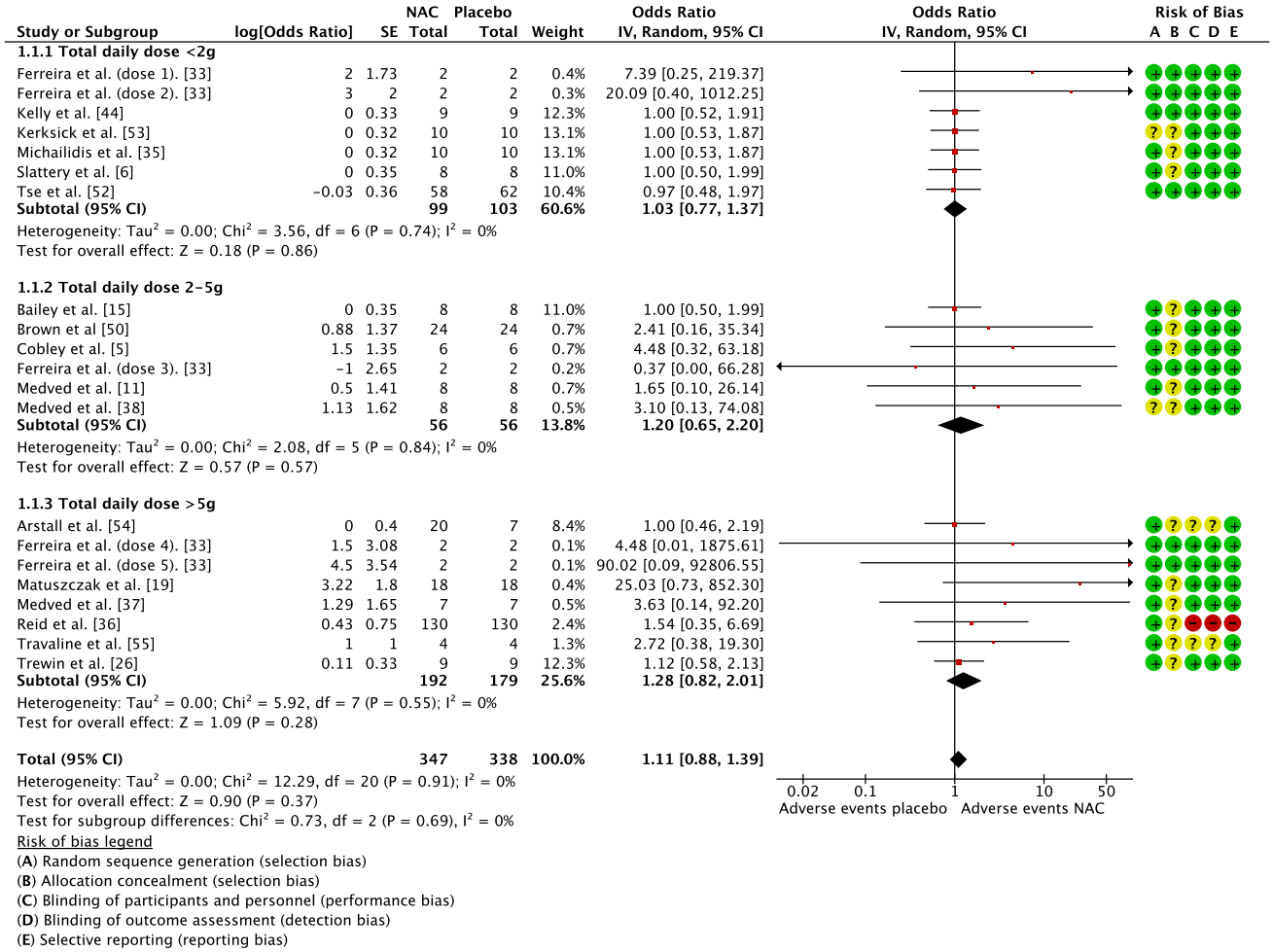

Fig. 4 Forest plot of side effects with small (<2 g), moderate (2–5 g) and large (>5 g) doses of NAC compared with placebo. Results are expressed as mean differences, and 95% confidence intervals (CI). *IV* intravenous, *NAC* *N*-acetylcysteine, *SE* standard error

over three separate testing sessions, and a significant decrease in performance for those on placebo ($p \leq 0.0005$). By the third testing session, YYIRT-L1 performance was 50% greater with NAC compared with placebo. Another study reported a significant improvement in sprint performance with NAC during a cycle ergometer race simulation during the 5-, 10- and 15-s efforts ($p < 0.001$), but no difference in mean power during each steady-state time trial effort between NAC and placebo trials [6].

4 Discussion

4.1 NAC and its Effect on Performance

The literature to date is characterised by many inconsistencies regarding the ergogenic potential of NAC. Previous research carried out in the laboratory has shown that NAC is effective in prolonging time to fatigue during cycling tests at constant power [17] with one study claiming a dramatic increase in time to fatigue of 26% with NAC [10]. Several recent studies demonstrated that this performance benefit may even transfer to settings outside of the laboratory, such as in a practical sport setting. For example, Cobley and colleagues [5] supplemented recreationally trained men with 50 $mg \cdot kg^{-1}$ oral NAC for 6 days and observed performance enhancements of up to $\sim$50% with NAC during high-intensity intermittent shuttle runs. Slattery and colleagues [6] also observed improved sprint performance in trained athletes with a lower dose of oral NAC (1200 $mg \cdot day^{-1}$) during an exercise protocol that was designed to mimic the physiological demands of a cycle race.

However, not all studies have demonstrated performance benefits with NAC supplementation, particularly during steady-state time trials. Whilst Slattery et al. [6] reported significant improvements in repeated sprint performance with NAC, there was no change in performance during steady-state time trials of 2 and 5 min duration. Work by Nielsen et al. [28] also reported no effect of 6 g oral NAC on the mean power produced by male oarsmen during a 6-min rowing ergometer time trial. One study has even reported a 4.9% decrement in well-trained cyclists' mean power output during a 10-min cycle time trial with a large oral dose of NAC (20 g) [26] A number of studies have also failed to demonstrate improvements in cycle time to fatigue [15, 16, 37], or high-intensity cycling bouts to fatigue in non-trained individuals [38].

Collectively, it seems that there is large variability across previous literature regarding the effectiveness of NAC, and the results from this meta-analysis certainly support this. There does however seem to be a recurring trend of NAC supplementation being most effective when exercise is performed in a fatigued state, and previous investigators have claimed that the incorporation of fatiguing submaximal exercise prior to the exercise test or maximal bout is needed to precipitate the effects of NAC [5, 11]. A landmark study by Cobley et al. [5] was one of the first studies to demonstrate that NAC can reverse fatigue in untrained individuals. These investigators required their subjects to perform a 60-min Loughborough Intermittent Shuttle Test (LIST), which involves jogging, running and sprinting. After the completion of the LIST, the subjects then completed an YYIRT-L1. This meant that the LIST was performed by subjects in a fresh and non-fatigued state, but caused the subjects to be fatigued prior to performing the YYIRT-L1. There seemed to be no evidence of an effect of supplementation with 50 mg/kg oral NAC on 20-m sprint time during the LIST; however, the subjects' YYIRT-L1 performance increased over time, with the greatest performance enhancement seen in the last testing session. Slattery et al. [6] also observed the greatest enhancements in sprint performance for the 15-s sprints performed nearer to the end of the 9-min cycle race simulation test (when subjects are likely to be more fatigued), compared with the 5- and 10-s sprints performed nearer to the start of the test. This suggests that NAC is effective in settings when exercise is performed in a fatigued state, and the greater the extent of fatigue, the greater the benefit from NAC. Despite this evidence, we are still unsure of the optimal setting in which NAC supplementation is most effective.

4.2 Documentation of Methods and Reporting of Results

Differences in study design are likely to explain the large range of performance effects reported. The heterogeneity calculated from the performance meta-analysis is reflected in the large variability of performance outcomes. The Higgins score for the performance meta-analysis was calculated as 56%, which is deemed as a substantial amount of heterogeneity according to the guidelines and criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions [24]. Differing exercise protocols, documentation of methods and results, supplementation regimes, subjects' training status and individual responsiveness to NAC are likely to have contributed to such substantial heterogeneity [11].

Previous studies have claimed large performance enhancements with NAC that are giving athletes, coaches, support personnel and researchers potentially misleading information and unrealistic beliefs regarding the effectiveness of NAC [11, 17]. A study mentioned in Sect. 3.1.1 reported a 26.3 $\pm$ 9.1% enhancement in time to fatigue

with IV infusion of 125 $mg \cdot kg^{-1} \cdot h^{-1}$ for 15 min followed by 25 $mg \cdot kg^{-1} \cdot h^{-1}$ during exercise [11]. However, if the considerable preload performed [45 min at 71% maximum volume of oxygen (VO_{2max})] and the fact that the test was performed at constant power (92% VO_{2max}) are taken into account, the performance improvement of NAC would be ~1%, at best. An important consideration that many people overlook is that performance measures in laboratory tests are often different outcomes (e.g. VO_{2max}, power output sprint time) to those of competitive performance. This lack of understanding of how to best interpret and report changes in an athlete's performance and then apply them to actual sport performance has resulted in a wide range of reported performance benefits with NAC and confusion around the true effect of NAC on performance.

Many studies fail to adequately describe or document aspects of their study design, rendering difficulties in conducting accurate meta-analyses. Common examples of suboptimal reporting include failure to describe the exercise protocol used, or how study participants were allocated to either NAC or placebo groups. As previously mentioned, we also found many inconsistencies among reported results within and across published studies. Suboptimal reporting, errors in reporting and a lack of high-quality reliable studies hinder the accumulation of evidence and make it difficult to accurately meta-analyse current literature. Hopkins et al. [45] provide advice and their view of best practice for measuring, analysing and documenting outcomes in sport and exercise studies. We recommend that future researchers use these guidelines, along with the guidelines outlined in the Cochrane Handbook for Systematic Reviews of Interventions to ensure adequate and clear documentation of their study design and procedures [24]. This would give researchers a better idea of the true bias of studies, and hopefully a clearer understanding of the true effectiveness of NAC.

4.3 Type and Duration of Exercise Tests

With regard to the type and duration of exercise tests, it appears those of shorter duration (<4 min) rely on anaerobic pathways to generate energy in the form of adenosine triphosphate, whereas energy demands during exercise tests of longer duration (>10 min) are met through aerobic metabolism [46]. This means during short-duration exercise, i.e. sprinting, performance is limited by reduced energy generated though anaerobic pathways, rather than the accumulation of ROS that occurs during longer duration exercise. Based on this, NAC is only likely to benefit performance for exercise tests >~6 min duration. A study by Medved et al. [38] supports this theory as they reported no effect of NAC supplementation on repeated sprints of 45 s duration. In a study by Corn and Barstow [17], the investigators demonstrated the relationship between the duration of exercise and the ability of NAC to enhance performance through a critical power model. The model showed that the longer the duration of the exercise, the greater the performance effect with NAC [17]. Unfortunately, our meta-analysis was unable to provide sufficient evidence to delineate this link between exercise duration and the effectiveness of NAC.

Differences in the duration of exercise protocols may however contribute to the large variability in performance outcomes in this current meta-analysis. The duration of the exercise test in included studies ranged from 5 to 17 min. Currell and Jeukendrup [20] state that exercise tests of longer duration can result in higher variation and lower reliability compared with tests of shorter duration for a number of reasons; because prolonged exercise (>10 min) generates adenosine triphosphate through the aerobic and glycolytic systems, it can be greatly influenced by an individual's training routine and diet. It has also been suggested that the motivation of the exercising subject can influence performance during longer duration exercise tests (22). It may be that the true performance effect of NAC in the studies using longer exercise tests may have been influenced by these variables compared with studies using shorter tests, and thus contributed to the overall heterogeneity between included studies.

4.4 Individual Responsiveness to NAC and Training Status

Individual responsiveness to NAC and training status may account for the discrepancies between previous literature and the findings of this meta-analysis. There are two important points to consider: (1) the level of NAC absorbed by the body will vary between individuals and (2) the extent to which the body's endogenous antioxidant system has been developed will also vary between individuals [47]. These two points mean that both within and between studies, individuals will have different sensitivities to NAC, resulting in a large range of reported performance effects of NAC in the literature [17]. Several studies have even reported on the individual variability in the response to NAC supplementation. Bailey et al. [15] found no significant differences in mean performance between placebo and NAC-supplemented groups. However, when the individual changes scores were analysed, the investigators found large inter-subject variability in the effectiveness of NAC: four subjects experienced performance decrements of 4, 8, 11 and 14%, and four subjects experienced performance enhancements of 24, 24, 40 and 69%. The level of total plasma sulfhydryl groups (i.e. the level of NAC absorbed) also varied between study subjects, and a direct positive relationship was observed between the change in

total plasma sulfhydryl groups and the change in exercise performance [15]. This study provides evidence that NAC will have different effects on different individuals, which may explain why such a large range of performance effects with NAC have been reported.

A number of earlier studies [11, 37, 38] completed by Medved and colleagues suggested that NAC supplementation may only be effective for enhancing performance in trained individuals (i.e. athletes). Through a number of studies, the investigators demonstrated that IV infusion of 125 $mg \cdot kg^{-1} \cdot h^{-1}$ NAC for 15 min followed by 25 $mg \cdot kg^{-1} \cdot h^{-1}$ is effective in prolonging time to fatigue during cycling exercise in endurance-trained subjects, but not in untrained subjects [11, 37, 38]. It has been proposed that athletes possess the ability to work harder and generate greater ROS during exercise when compared with lesser trained individuals, therefore resulting in a more effective response to antioxidant supplementation [15]. Medved and colleagues suggested that NAC supplementation may result in greater increases in force production (and thus performance) in fitter individuals owing to higher proportions of slow-twitch muscle fibres in comparison to lesser trained individuals [37]. However, in this current meta-analysis, we found performance decrements for the two studies that used trained individuals as their study participants [26, 28] and performance benefits for four of the five studies that used untrained individuals [15–17, 19]. This may be because athletes possess highly developed endogenous antioxidant defence systems, and the exercise protocols performed may not have produced enough ROS to stress the endogenous antioxidant system [26]. It therefore seems we still lack an understanding of whether NAC is more effective in trained or untrained individuals. Future studies should focus on evaluating the individual effectiveness of NAC supplementation in individuals with differing training status. Future studies should also endeavour to use large sample sizes to reduce the variability arising from differences in individual responsiveness to NAC [47].

4.5 Supplement Regimes

In this review, we conducted a sub-analysis on the timing, dose and type of administration of NAC as all these factors have the potential to influence the efficacy of NAC [21]. This analysis found a large variation in the dosage of NAC administered in each included study, with total daily doses (TDDs) ranging from small (1.2 g) to very large (20 g). The analysis also showed that larger doses did not necessarily result in greater performance benefits. In fact, the opposite trend was typically observed. The studies that supplemented with the two largest TDDs of NAC (20 and 6 g) both displayed performance decrements of −1.2 and −0.3%, respectively [26, 28]. Studies that supplemented with smaller TDDs of NAC (1.2, 3.5 g) displayed the largest performance effects of 1.6 and 1.4%, respectively [16, 17]. These results are in line with the hypothetical model proposed by Reid in 2001, which describes the effects of the cellular redox state on isometric force. This model suggests that there is an optimal intracellular redox state for muscle force production, and deviations either side of this optimum result in the loss of force and a decrease in performance [48]. Antioxidants (endogenous and exogenous) and ROS produced during exercise "act on the relationship in different directions" [17]. Therefore, when NAC is administered as an exogenous antioxidant, the aim is to supplement with a moderate dose to create an optimal redox state for force production and performance (which according to previous studies is deemed as NAC ∼1.2 to 5 mg/day) [5, 6, 15–17]. It is possible that the larger doses of NAC supplementation have buffered cellular oxidants to a point where there are insufficient levels of oxidants to facilitate normal force production, resulting in the loss of muscle force production and impaired performance. Conversely, smaller doses of NAC are effective in mopping up just enough oxidants to maintain an optimal redox state, resulting in enhanced muscle force production and performance.

The duration of supplementation ranged from a one-off acute dosage to 8 days, which had little influence on performance. This is most likely owing to the fast rate of clearance of NAC (∼6 h post ingestion) [10]. Previous research suggests that antioxidant supplementation for longer durations can negatively affect performance by reducing physiological responses and adaptations to training [2, 21]. One study included in the meta-analysis supplemented oral NAC 1.2 g over an 8-day loading period; thus, there was some concern that this duration was long enough to reduce adaptive responses to training and subsequently impair performance. However, this was not the case, as we found a performance enhancement of 1.6% (−1.34 to 4.54) for this study, and the authors did not report an increase in the markers of oxidative stress after 8 days of NAC supplementation [16]. Another study suggested that supplementation with oral NAC 1.2 g over 9 days actually promotes physiological adaptations after a cycle race simulation test. The study reported a significantly greater increase in the activation of a redox-sensitive transcription factor, nuclear factor-κB, 2 h post-exercise with NAC compared with placebo. Nuclear factor-κB plays an important role in the regulation of genes involved in the antioxidant system, and is a key player in promoting the adaption of physiological responses to exercise [6]. These findings suggest that supplementation of NAC for durations up to 9 days is not likely to reduce physiological adaptations to training or negatively affect performance. On the contrary, one study demonstrated that NAC infusions

during cycling exercise attenuated nuclear factor-κB p65 phosphorylation at fatigue by 14% ($p < 0.05$) [39]. Further research is required to establish the true effect of NAC supplementation on signalling pathways and the genes involved in exercise adaptation.

The timing of the final dose of NAC was similar across included studies and did not appear to influence the performance test effect. In all studies, NAC was administered to the participants between 1 and 2 h prior to performing the exercise test. NAC undergoes extensive first-pass metabolism in the liver and intestine, and then undergoes deacetylation to yield cysteine. Once NAC has been metabolised, cysteine concentrations typically peak within 1–2 h post-ingestion, with a half-life of 2.3–2.4 h [10]. Therefore, to get the best performance effect of NAC, it makes sense to administer the supplement 1–2 h prior to exercise.

4.6 NAC and Its Potential Side Effects

The overall effect of NAC on side effect symptoms was unclear, and there was a large range of reported side effects across studies. Despite this, the Higgins score was calculated at 0%, indicating that the heterogeneity across included studies did not influence the overall outcome. The fact that we still have no idea whether or not NAC causes side effects is partially owing to inadequate measuring and reporting of side effects in studies. For many of the studies investigating the effects of NAC supplementation on exercise performance, side effects are typically secondary or additional outcome measures. The symptom outcomes tend to be poorly measured and documented, thus making it difficult for other researchers to draw conclusions from these studies. Studies that are more vigilant in the monitoring and reporting of side effects will report a higher frequency of side effects with NAC compared with studies that are less attentive. Different methods of monitoring and measuring side effects may also yield different results, making it difficult to make sound comparisons between studies.

Although a number of studies reported single sentences stating that no side effects were experienced from NAC, many studies failed to mention the absence or presence of side effects at all [8, 13, 16–18, 28, 32, 39]. It is important to remember that the absence of documentation of side effects should not be interpreted as indicating that the NAC supplemented in that study is well tolerated or safe. It is somewhat surprising that investigators are failing to adequately measure or report the side effects of NAC because information regarding the safety and tolerability of a supplement is of the highest importance for athletes, coaches and their support staff. No matter how effective a supplement may claim to be, if it causes uncomfortable side effects for athletes then ethically, it should not be recommended. We advocate that all future studies administrating NAC to their study participants should include rigorous monitoring of the type and frequency of side effects experienced throughout the entire study duration, followed by complete documentation of such side effects in published reports. This will hopefully generate greater data and evidence so that researchers can provide a clear answer as to whether or not NAC causes side effects.

Although unclear, there was a trend of increasing side effects with increasing doses of NAC compared with placebo. However, the smallest doses of NAC were typically administered orally, and larger doses of NAC intravenously. Thus, we are unsure whether this trend of increasing side effects with increasing dosage is caused by a direct effect of NAC supplementation, or an artefact of IV infusion. Anaphylactic reactions to NAC have been previously reported with IV administration, but rarely reported with oral administration. Symptoms may include pruritus, rash, angioedema, bronchospasm, tachycardia, hypotension, nausea and vomiting, and generally occur within 30 min post-infusion of the loading dose of NAC [49]. Previous studies have also found that larger doses of IV NAC have resulted in a greater number of side effects, and also more severe side effects [49, 50].

Studies supplementing with IV NAC typically measured and reported side effects more vigilantly than studies that supplemented with oral NAC; however, doping issues preclude the use of IV administration of NAC in sport. It is therefore of high importance that future studies supplementing with oral NAC accurately monitor and report their subjects' side effects so that the information is available for athletes, coaches and their support staff. Studies by Cobley et al. [5] and Ferreira and Reid [33] provide detailed documentation regarding the occurrence, type and severity of side effects with oral NAC. Ferreira and Reid even reported side effects with titrated doses of NAC. There is a need for more studies designed in this way so that researchers can determine the optimal dose of NAC that is effective, yet does not result in uncomfortable side effects.

4.7 Limitations

At present, there is a sparse amount of literature in the area of NAC supplementation and sports performance, and unfortunately many of these sport performance studies are poorly documented. Because of this, we were only able to identify seven studies that were deemed acceptable for inclusion in the performance meta-analysis. Such a small sample size limited the type of analyses and conclusions that we could reach, thus there is a real need for further research to be conducted in the area of NAC supplementation and sport performance so that clear outcomes can be determined.

One weakness of this meta-analysis is that whilst we have adjusted the performance effect of each included

study to a common metric for analysis, differences among studies still remain that we have not adjusted for. These include the sex, age and training status of the study subjects, the way in which NAC was administered (IV vs. oral), the dose and duration of supplementation, and the timing of the final dose. There is a possibility of bias arising from such inconsistencies across included studies. Future research should endeavour to determine whether or not these variables affect the ergogenic potential of NAC.

We used Review Manager (RevMan) to analyse statistical data and conduct each meta-analysis. RevMan allowed us to conduct a subgroup analysis for the effect of NAC dose on side effects; however, it did not allow us to conduct other sophisticated subgroup analysis such as adjusting for other possible confounding factors previously mentioned (e.g. age, sex). It is possible that adjustment for such confounding factors could be conducted using other analytical methods.

5 Conclusions

Our first meta-analysis suggests that NAC supplementation in the range of 1.2–20 g/day produces a range of performance effects from beneficial to trivial to harmful, and the true performance effect of NAC remains unclear. Our second meta-analysis suggests that the extent to which NAC causes side effects is also unclear; however, larger doses of NAC (>5 g) may produce more side effects than smaller doses of NAC (<2 g), but further evidence is needed to confirm these findings. Our findings suggest that in general, there is a need for further research in the area of NAC supplementation and sports performance so that clear conclusions can be drawn. Future studies should aim to follow best-practice guidelines for sports performance research and adequately document their methodology and results. Further research should focus on applying NAC supplementation in practical and elite sport settings, and ensuring adequate monitoring and reporting of side effects.

Compliance with Ethical Standards

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Conflict of interest Kate Rhodes and Andrea Braakhuis declare they have no conflicts of interest relevant to the content of this review.

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