The effects of exercise on complement system proteins in humans: a systematic scoping review

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ABSTRACT

Background: The complement system is comprised of the classical, lectin and alternative pathways that result in the formation of: pro-inflammatory anaphylatoxins; opsonins that label cells for phagocytic removal; and, a membrane attack complex that directly lyses target cells. Complement-dependent cytotoxicity (CDC) – cell lysis triggered by complement protein C1q binding to the Fc region of antibodies bound to target cells – is another effector function of complement and a key mechanism-of-action of several monoclonal antibody therapies. At present, it is not well established how exercise affects complement system proteins in humans. Methods: A systematic search was conducted to identify studies that included original data and investigated the association between soluble complement proteins in the blood of healthy humans, and: 1) an acute bout of exercise; 2) exercise training interventions; or, 3) measurements of habitual physical activity and fitness. Results: 77 studies were eligible for inclusion in this review, which included a total of 10,236 participants, and 40 complement proteins and constituent fragments. Higher levels of exercise training and cardiorespiratory fitness were commonly associated with reduced C3 in blood. Additionally, muscle strength was negatively associated with C1q. Elevated C3a-des-Arg, C4a-des-Arg and C5a, lower C1-inhibitor, and unchanged C3 and C4 were reported immediately post-laboratory based exercise, compared to baseline. Whereas, ultra-endurance running and resistance training increased markers of the alternative (factor B and H), classical (C1s), and leptin (mannose binding lectin) pathways, as well as C3 and C6 family proteins, up to 72-h following exercise. Heterogeneity among studies may be due to discrepancies in blood sampling/handling procedures, analytical techniques, exercise interventions/measurements and fitness of included populations. Conclusions: Increased anaphylatoxins were observed immediately following an acute bout of exercise in a laboratory setting, whereas field-based exercise interventions of a longer duration (e.g. ultra-endurance running) or designed to elicit muscle damage (e.g. resistance training) increased complement proteins for up to 72-h. C3 in blood was mostly reduced by exercise training and associated with increased cardiorespiratory fitness, whereas C1q appeared to be negatively associated to muscle strength. Thus, both acute bouts of exercise and exercise training appear to modulate complement system proteins. Future research is needed to assess the clinical implications of these changes, for example on the efficacy of monoclonal antibody therapies dependent on CDC.

Keywords: acute exercise; aerobic fitness; exercise training; complement proteins; physical activity.

INTRODUCTION

The complement system is a fundamental component of the innate immune system, which constitutes more than 40 soluble and membrane-bound proteins, as well as constituent fragments (85, 86). Activation of the complement system is initiated by a cascade of reactions described as the classical, lectin or alternative pathways – all of which result in the cleavage of C3 (~187 kDa; Figure 1) (85). The central complement component C3, primarily of hepatic origin with a half-life of ~72-h in blood plasma (8, 31), is the pre-cursor to the formation of: pro-inflammatory anaphylatoxins (C3a and C5a; ~10 kDa) which enable the chemotaxis and activation of immune cells; opsonins (C3b, iC3b and C3d; 35-180 kDa) that label target cells for phagocytic removal; and, the membrane attack complex (MAC; C5b-9; ~1000 kDa) to elicit direct lysis of target cells (86).

The alternative complement pathway is constitutively activated by the spontaneous hydrolysis of C3 to form C3(H2O). C3(H2O) then binds to factor B (~86 kDa) and D (~27 kDa), which leads to the formation of a fluid-phase C3 convertase, C3bBb (~239 kDa; Figure 1). C3bBb, which is unstable due to spontaneous dissociation and thus has a brief half-life of ~90-s (103), facilitates the tick-over production of C3a and C3b in blood plasma. Under normal physiological conditions, complement activation through the alternative pathway is limited as C3b is only capable of binding to cell surfaces within ~60 nm of C3bBb, due to a short half-life of 60-µs and poor attachment efficiency of ~10% (73). To augment complement activation in response to pathogenic invasion, C3b – generated from carbohydrate-collectin and antigen-antibody interactions of the lectin and classical pathways, respectively – interact with properdin-stabilised C3bBb (37, 49), which induces anaphylatoxin-mediated recruitment of phagocytes and amplifies opsonisation of target cells that lack membrane-bound complement regulatory proteins (70).

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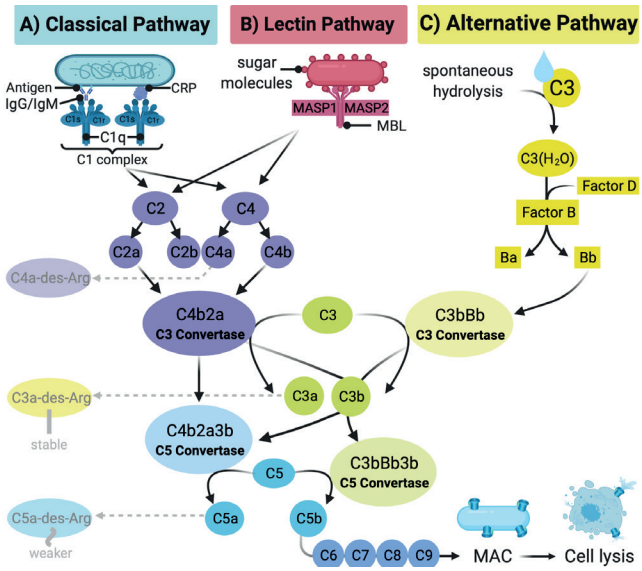

Figure 1. The classical, lectin and alternative pathways involved in the complement cascade. A) Activation of the classical pathway commences when C1q binds the Fc region of target cell bound antibody (either IgG or IgM), causing the serine proteases C1r and C1s to subsequently bind C1q, forming the C1 complex. C-reactive protein can also initiate the classical pathway by binding directly to C1q. C1r and C1s cleave C4 and C2 to form the C3 convertase (C4b2a); B) in the lectin pathway, activating recognition molecules (e.g. mannose-binding lectin [MBL], ficolins and collectins) converge with the classical pathway upon the cleavage of C4 and C2; C) the alternative pathway is initiated by spontaneous hydrolysis of C3 to form C3(H2O), which binds to Factor B and is cleaved into Bb and Ba by Factor D to form a different C3 convertase (C3bBb). Both C3 convertases cleave C3 into C3a and C3b. Complement C3b, is analogous to C3(H2O), and thus is capable of amplifying the alternative pathway; it is also a powerful opsonin that facilitates phagocytosis. With the additional binding of C3b to each of the C3 convertases, C5 convertases are formed (C4b2a3b from the classical and lectin pathways, and C3bBb3b from the alternative pathway). These enzymes cleave C5 into C5a and C5b. C5a is a pro-inflammatory anaphylatoxin along with C3a and C4a, while C5b recruits C6, C7, C8, and C9 to form the membrane attack complex (MAC), where the cascade ultimately results in cell lysis. Anaphylatoxins C3a, C4a and C5a are rapidly converted to C3a-des-Arg, C4a-des-Arg and C5a-des-Arg, respectively, by the cleavage of the arginine residue at the C-terminal. C5a-des-Arg has a weaker pro-inflammatory activity than its whole counterpart, while C3a-des-Arg has no pro-inflammatory activity and does not bind to the C3a receptor. However, C3a-desArg has been found to have additional functions that render it a more stable molecule than its whole counterpart. The function of C4a-des-Arg is not well characterised. This image was created with BioRender.com (Toronto, Canada).

Alternative pathway – as well as classical pathway – activation is also observed during tissue injury, and complement proteins have been implicated in the regeneration of ocular (60), hepatic (78, 133), skeletal (15, 137) and muscular (151, 158) tissues. For instance, rodent studies have demonstrated that the alternative pathway is activated during the early stages (<24-h) of cardiotoxin-induced muscle injury (158); potentially due to the necrotic cell releasing damage-associated markers (e.g. heat shock proteins and high mobility group box-1 proteins) (111, 124). Subsequently, the upregulation of C3a receptor (C3aR)-C3a signalling induces phosphorylation of protein kinase B and NF-κB that exacerbates the transcription of chemokines (e.g. CCL5), which facilitate monocyte trafficking (158). The differentiation of macrophages from an M1-like to M2-like phenotype is responsible for resolving such inflammation by expressing a plethora of anti-inflammatory cytokines (10). M2-like macrophages in muscle tissue are one of the major extra-hepatic sources of complement, which secrete C1q (410-461 kDa) that 'spills over' into circulation and peaks 2- to 4-days following muscle injury (151, 158). As such, interventions that cause muscle damage and inflammation in humans – such as resistance exercise (12), or exposure to unaccustomed, strenuous exercise (106) – could modulate complement activation via an extra-hepatic synthesis of C1q.

Modulating C1q may have wide-ranging clinical implications. Indeed, transient increases in C1q – such as those reported following muscle damage in rodent models (151, 158) – lead to the phagocytic removal and lysis of apoptotic myofibers, thus facilitating skeletal muscle regeneration through classical complement pathway activation, in a process likely mediated by C-Reactive Protein (CRP) and/or natural antibody (146). Moreover, due to its topology of six globular recognition domains and a collagen-like region (85), C1q is capable of binding to over 100 target molecules (61) and thus its secretion facilitates repair and restoration in a host of tissues. Importantly, C1q also binds to the Fc region of immunoglobulin G (IgG) during therapeutic monoclonal antibody treatment of several haematological and solid cancers (28, 59). For instance, rituximab is a chimeric IgG1 monoclonal antibody that targets CD20+ B cells, which is utilised during the treatment of non-Hodgkin's lymphoma and chronic lymphocytic leukaemia (110). Upon binding to CD20, the Fc portion of IgG1 binds the globular region of C1q, whilst the collagen-like region of C1q is bound to C1r and C1s to form the C1 complex on the target cell surface. Following this, the classical pathway is activated and the resultant MAC lyses the malignant cell through complement-dependent cytotoxicity (CDC) (141). As such, increasing the bioavailability of C1q in blood – via interventions that elicit muscle damage and inflammation – could improve the effectiveness of anti-cancer immunotherapies (62, 88).

At present, there is a lack of consensus regarding whether soluble complement proteins are modulated by an acute bout of exercise, exercise training, or in relation to habitual physical activity and fitness. Greater understanding of how exercise affects complement system proteins may yield insight into whether exercise can be harnessed to modulate complement proteins to improve health outcomes, for example during anti-cancer monoclonal antibody immunotherapy treatment. To date, it is well documented that a host of soluble proteins are released in response to exercise – in the presence and absence of muscle damage – including proteins that are directly implicated in complement activation, such as CRP (51, 138, 156). Contrarily, repeated bouts of exercise (i.e. exercise training) and greater fitness levels are associated with reduced complement-activating inflammatory proteins, such as CRP (38). However, the effects of exercise/physical activity on complement proteins themselves are not well understood; in part due to the complexities of complement regulation, as well as the vast number of different complement proteins and constituent fragments involved in the complement cascade.

This situation is complexed further by the likelihood that associations between complement proteins and exercise are likely to be heterogenous dependent upon: timing of the biological sample collection (e.g. during, immediately-post or days/weeks following exercise); the intensity and longevity of exercise; the extent of muscle damage and/or inflammation

caused by exercise; and, whether singular or repeated exercise bouts have been prescribed. As such, a scoping review was employed herein to enable a broad and more exploratory assessment of the effects of exercise on different complement system proteins (134), evaluated on a narrative basis. Whereas, a systematic review specifically assessing the quality of studies and aggregate quantitative data (e.g. meta-analysis) was deemed less suitable (93). The present systematic scoping review aimed to: 1) identify the soluble complement proteins in blood that have been studied in response to an acute bout of exercise, exercise training or in relation to measurements of habitual physical activity and/or fitness; 2) summarise the key findings regarding complement proteins and exercise in healthy humans; and, 3) determine the sources of heterogeneity in the investigation of soluble complement proteins and exercise (e.g. analytical techniques).

METHODS

This review adhered to the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) (136).

Eligibility criteria

Studies were included in the present review if they investigated the association between blood soluble complement proteins and: 1) an acute bout of exercise; 2) exercise training interventions; or, 3) measurements of habitual physical activity and/or fitness. Given that many acute and chronic health conditions affect complement proteins (20), eligible studies recruited healthy human participants. Furthermore, clinical studies were included if they contained a healthy control group who had not undergone an intervention other than those related to exercise. Studies which did not include human participants were excluded due to the substantial inter-species variation in complement function and structure (76, 85). Dissertations, conference abstracts, case studies and review articles, as well as studies which were not available in English or Spanish were excluded.

Literature search

Systematic searches of the PubMed, Embase and Web of Science databases were conducted on Tuesday 20th July 2021. Medical subject headings (MeSH) were searched for within the PubMed database, as follows: (“complement activation”[MeSH] OR “complement system proteins”[MeSH] OR complement[All Fields]) AND (exercise[All Fields] OR physical fitness[All Fields]). No limits on language, date or study type were included. A ‘human’ filter was used for these systematic searches of the PubMed and Embase databases. Additionally, reference lists from relevant review articles and original research studies that were included in the present review were hand-searched by authors to identify any additional studies.

Study selection

A two-stage screening process was completed independently by two review authors (DRR and AJC). After the removal of duplicates, all titles and abstracts were screened to identify whether the study met the eligibility criteria of the present review, with the exclusion of ineligible references. The full-text articles of the remaining studies were subsequently retrieved and compared to the eligibility criteria. All eligible studies were included in the scoping review (Tables 1-3).

Data extraction and synthesis

Data from selected papers were retrieved independently by two review authors (DRR and AJC). A review-specific form was used to extract information on the studies: design; aim; participants; exercise type, exercise intervention, habitual physical activity or fitness measures; sampling protocol and method of analysis; complement proteins measured; and, key findings. Findings from the systematic literature search were reported by thematic synthesis of the three main themes: acute bouts of exercise ( ), exercise training interventions (Table 2) and cross-sectional studies assessing measurements of habitual physical activity and/or fitness (Table 3).

RESULTS

Selection of studies

A flow diagram of the screening process is presented in Figure 2. Briefly, after removing n = 1065 duplicates and n = 5,374 citations by screening titles and abstracts, n = 157 full-texts were retrieved to determine whether studies were eligible. Of these, n = 66 studies were excluded and a further n = 14 were excluded because the full-text article could not be retrieved. Consequently, n = 77 studies were eligible, and these studies included a total of 10,236 participants and 40 complement proteins and/or constituent fragments.

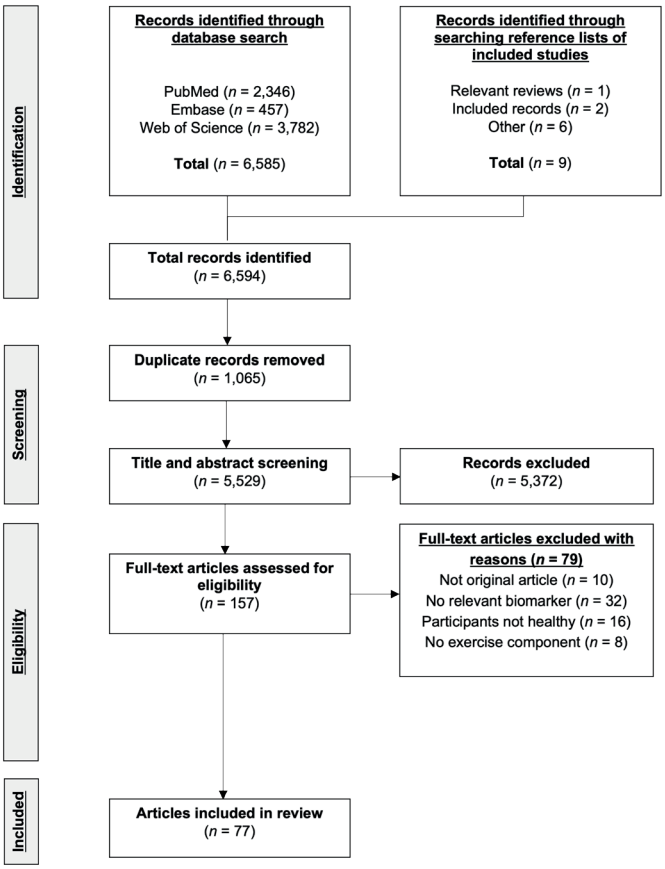

Figure 2. PRISMA flow chart of the study selection process.

Characteristics of studies

A summary of the characteristics of included studies are presented in Figure 3. Briefly, all studies were published between 1981 and 2021, and data were collected from 45 centres in Europe, 21 centres in Asia, five centres in North America, four centres in Africa, one centre in Oceania and one centre in South America. The majority of studies recruited adult participants only (n = 56; 72.7%), whilst paediatric cohorts were studied to a lesser extent (n = 20; 26.3%). Additionally, the majority of studies collected data from only men (n = 35; 46.1%) or a combination of men and women (n = 32; 42.1%); whereas n = 8 (10.4%) studies collected data in women only and n = 2 (2.6%) studies did not report the sex or gender of participants. (n = 10 proteins), were the topic of n = 64 (84.2%) studies. C5 family proteins were measured in n = 11 (14.5%) studies. Complement proteins that form the MAC (C6, C7, C8 and C9) were the topic of n = 5 (6.8%) studies, and the MAC itself was quantified in a further n = 3 (3.9%) studies. The other soluble proteins investigated were factor I (n = 2; 2.6% studies), factor H (n = 4; 5.3% studies), vitronectin (n = 1; 1.3% study) and clusterin (n = 2; 2.6% studies).

Complement proteins were most frequently measured in serum (n = 53; 69.7%) or plasma (n = 23; 29.9%), whilst n = 2 (2.6%) studies did not specify which blood component was analysed. Furthermore, n = 20 (26.3%) studies corrected complement concentrations for changes in plasma volume.

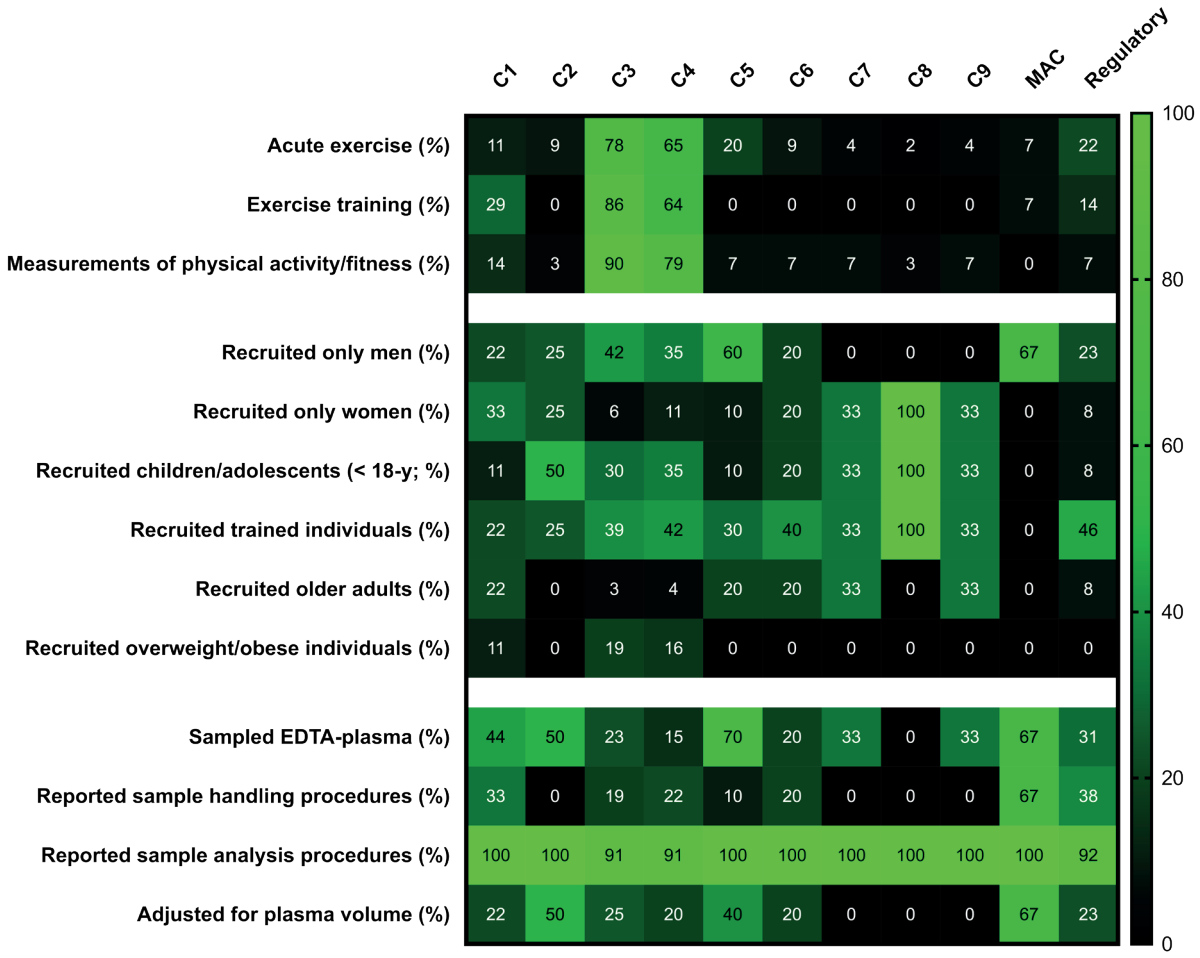

Figure 3. A heat map illustrating the characteristics of included studies. The top compartment demonstrates the percentage of studies that measured each complement protein within each exercise theme (e.g. 11% of studies that investigated the effects of acute exercise measured C1); the middle and bottom compartments demonstrates the percentage of studies that achieved each description within each complement protein (e.g. 22% of the studies that investigated C1 included only male participants).

Characteristics of complement proteins

A total of 40 soluble complement proteins were measured in blood, including five proteins from the classical (C1q, C1s, C1r, C1-inhibitor and C1rs-C1-inhibitor complex), two proteins from the lectin (mannose-binding lectin [MBL] and MBL-associated serine protease-2 [MASP-2]) and two proteins exclusively from the alternative (factor B and properdin) pathways. Convergence proteins of the classical and lectin pathways, the C2 and C4 family proteins (n = 7 proteins), were measured in n = 59 (77.6%) studies. Whereas the convergence proteins of all three pathways, the C3 family proteins Turbidimetry (n = 23; 30.2%), nephelometry (n = 20; 26.3%) and enzyme-linked immunosorbent assays (ELISA; n = 16; 20.8%) were the most commonly used methods of complement quantification. Less frequently used techniques were radial immunodiffusion (RID; n = 4; 5.3%), radioimmunoassay (RIA; n = 3; 3.9%), mass spectrometry (n = 2; 2.6%), electroimmunoassay (EIA; n = 1; 1.3%) and intermediate gel rocket electrophoresis (n = 1; 1.3%). Notably, n = 6 (7.9%) studies did not specify the methodology for quantifying complement.

Synthesis of results

Acute bouts of exercise

Soluble complement proteins in blood following an acute bout of exercise were the topic of n = 46 (60.5%) studies, and these studies included a total of 879 participants (Table 1). The most common modes of acute exercise were running (n = 21; 45.7%) and cycling (n = 15; 32.6%). Other modes of acute exercise were resistance exercises (n = 6; 13.0%), judo (n = 3; 6.5%) and swimming (n = 1; 2.2%). The duration of acute exercise used in studies ranged from brief (30-s Wingate tests) to multi-staged races (622.2-km over 6-days). The intensity of acute exercise ranged from moderate (e.g. 50% maximal oxygen uptake) to supramaximal (e.g. 'all-out' Wingate tests). Several studies also combined exercise interventions with exposure to heat (n = 2; 4.3%), hypoxia (n = 1; 2.2%) or dehydration (n = 1; 2.2%).

Soluble complement proteins in blood immediately following an acute bout of running exercise were the topic of n = 12 (26.1%) studies. C3 (66, 67, 116, 120), C3a-des-Arg (29), C3c (41), C4 (67, 116, 120), C4a-des-Arg (29) and C5a (17) were elevated; C1q (149), C1r (149), C3 (56, 57) and C4 (56, 57) were lower; and, C1-inhibitor (41, 84, 125), C3 (84, 119, 122), C3d (34), C4 (41, 84, 119, 125), C6 (125) and factor B (41) were unchanged immediately following running, compared to pre-exercise. Soluble complement proteins in blood during the recovery stage (5-mins to 10-h post-exercise) were also the topic of n = 8 (17.4%) studies. C1-inhibitor (125), C2 (65), C3 (97), C3a (65), C4 (65, 97, 125), C4a-des-Arg (29) and C5a (19) were elevated; C3 (65) and C4 (65) were lower; and, C3 (44, 97), C3a-des-Arg (30), C4 (44, 97), C4a-des-Arg (30), C5a (17) and C6 (125) were unchanged during the recovery from running (5-mins to 10-h post-exercise), compared to pre-exercise. C1-inhibitor (125), C3 (44, 56, 57), C4 (44, 56, 57, 125), C5a (19) and C6 (125) were unchanged 12-h to 6-days following the cessation of running, compared to pre-exercise, in n = 5 (10.9%) studies.

Soluble complement proteins in blood immediately following an acute bout of cycling exercise were the topic of n = 13 (28.3%) studies. C3a-des-Arg (18, 30), C4 (24), C4a-des-Arg (30) and C5a (16) were elevated; C3 (56, 57), C4 (56, 57) and C4a (109) were lower; and, C1q (94), C1/C1-inhibitor complex (94), C2 (94), C3 (24, 94), C3a (130), C3a-des-Arg (144), C3c (135), C3d (135), C4 (32, 94), C4a (98, 130), C4a-des-Arg (144), C4b binding protein (94), C4bc (94), C4d (94), C5a (130), C5a-des-Arg (144), MBL (155), MASP-2 (155), factor B (94), factor I (94), vitronectin (94), clusterin (94) and MAC (94) were unchanged immediately following cycling, compared to pre-exercise. Soluble complement proteins in blood during the recovery stage (30-mins to 6-h post-exercise) were the topic of n = 4 (8.7%) studies. C3 (24), C3a-des-Arg (18, 30), C4 (24), C4a-des-Arg (30) and C5a (16) were all unchanged during the recovery from cycling (30-mins to 6-h post-exercise), compared to pre-exercise. Furthermore, n = 2 (4.3%) studies demonstrated that C3 and C4 were unchanged 12- to 24-h following the cessation of cycling, compared to pre-exercise (56, 57). A single study demonstrated that reductions in C1-inhibitor in blood following cycling was only observed in females who were users of oral contraception (50). Additionally, combining cycling with severe normobaric hypoxia (ambient O2: 12%) increased the transient elevation of C3a-des-Arg, C4a-des-Arg and C5a-des-Arg immediately-post exercise, compared to pre-exercise at sea-level (ambient O2: 21%) (144).

Soluble complement proteins in blood immediately following ultra-endurance running were the topic of n = 3 (6.5%) studies. A 246-km running race with a mean duration of 32-h and 8-mins, immediately increased C1s subcomponent, C3, factor B and mannose-binding lectin (MBL), compared to pre-exercise (12). Whereas, factor H and the C4-B precursor were unchanged immediately following the 246-km running race, compared to pre-exercise (12). C3 and C4 were unchanged immediately following a 6-day run with an average completed distance of 622.2-km (35). C1-inhibitor, C3 and C4 were unchanged in the days following a 90-km run (126); whereas, C1s subcomponent (12), C3 (12), C6 (126), factor B (12, 126), factor H (12) and MBL (12) were elevated 24- to 72-h following 90-km (126) or 246-km (12) bouts of running exercise.

Soluble complement proteins in blood immediately following a single session of resistance exercise were the topic of n = 2 (4.3%) studies. C3 (101), C3b (101), C3d fragment (101) and clusterin (101) were elevated; and, C1rs-C1-inhibitor complex (114), C3b (114), C3bBbP (114), iC3b (114), C3c (114) and MAC (114) were unchanged immediately following resistance exercise, compared to pre-exercise. C3bc (105) and the MAC (105) were lower, whereas C3 (89) and C5a (55) were unchanged 1- to 96-h following resistance exercise, compared to pre-exercise. Furthermore, C3 (101), C3b (101), C3d fragment (101) and clusterin (101) were elevated 24-h following resistance exercise, compared to pre-exercise. C3 has been reported to increase (22), decrease (91) and remain unchanged (140) immediately following a judo training session; whereas, C4 was unchanged immediately following a judo training session, compared to pre-exercise (22, 91, 140). A single study also reported that C3d remained unchanged following swimming, compared to pre-exercise (33). Mild-to-severe dehydration calculated by changes in plasma volume (22) and an exercise training intervention (not corrected for changes in plasma volume) (91) appeared to blunt the transient post-exercise elevation of C3.

Exercise training interventions

Soluble complement proteins in blood in response to an exercise training intervention were the topic of n = 14 (18.2%) studies, and these studies included a total of 378 participants (Table 2). A training program comprising a combination of steady-state exercise, interval exercise, resistance exercise or judo training were the most studied interventions (n = 4; 28.6%). Other types of exercise interventions were resistance training alone (n = 2; 14.3%), a cross-country skiing, speed skating or volleyball season (n = 2; 14.3%), military training (n = 2; 14.3%), tai chi (n = 1; 7.1%), qigong (n = 1; 7.1%), stair climbing (n = 1; 7.1%) and cycling (n = 1; 7.7%). The duration of each exercise intervention ranged from 17-days to 20-months. Studies most frequently recruited college/university athletes (n = 5; 35.7%) professional athletes (n = 3; 21.4%) or military recruits (n = 2; 14.3%); whilst older adults (n = 1; 7.1%) and less active participants (n = 2; 14.3%) were also studied.

Soluble complement proteins in blood at rest, were investigated immediately following a training program that comprised of more than one mode of exercise by n = 4 (28.6%)

Table 1. Studies investigating the effects of acute exercise on complement proteins in blood.

Reference	Participants	Acute bout of exercise	Complement protein(s)	Key finding(s)
Balfoussia (2014) (12)	8 healthy adult men (median age: 43.2-years [range: 35 to 56-years]).	246-km running event completed in a mean completion time of 32-h and 8-mins.	Plasma C1s subcomponent, C3 precursor, C4-B precursor, factor B, factor H and MBL: venous blood samples were drawn into K_3EDTA tubes pre-, immediately post- and 48-h post-exercise cessation. Blood was centrifuged at room temperature at 1000 ×g for 10-mins and stored at −80°C. Proteins were identified by mass spectrometry. MBL was measured by immune-nephelometric assay.	C1s subcomponent (+323% vs. baseline), C3 (+3% vs. baseline), factor B (+134% vs. baseline) and MBL (+19% vs. baseline) were increased immediately after the completion of the race, whereas factor H was unchanged (+3% vs. baseline) and C4-B precursor was lower (−25% vs. baseline). C1s subcomponent (+300% vs. baseline), C4-B precursor (+30% vs. baseline), factor H (+97% vs. baseline), factor B (+67% vs. baseline) and MBL (+25% vs. baseline) were increased 48-h after the completion of the race, whereas C3 was lower (-47% vs. baseline).
Camus (1994) (16)	11 healthy male students (mean age: 23 ± 2-years).	Static cycle ergometry for 20-mins at a workload corresponding to 80% maximal oxygen uptake.	Plasma C5a: blood samples (n = 6) were collected at pre-exercise, after 10-mins of exercise, immediately post-, 5-mins post-, 10-mins post-, and 20-mins post-exercise. Samples were centrifuged within 5-mins of collection and plasma was stored at −70°C. C5a was identified by ELISA. Plasma C5a was adjusted for changes in plasma volume during and after exercise.	C5a increased after 20-mins of cycling (+76.6% vs. baseline). C5a returned to baseline values within 20-mins of recovery.
Camus (1997) (17)	18 male marathon runners (mean age: 41-years [range: 24 to 64-years]).	Marathon race.	Plasma C5a: blood was collected at rest, between 5 to 15-mins following race completion, and 1-h, and 24-h following race completion. Blood was collected into EDTA containing vacutainers and centrifuged at 2500 ×g for 10-mins. Plasma was stored at −70°C. C5a was identified by ELISA. Plasma C5a was adjusted for changes in plasma volume during and after exercise.	C5a increased immediately after the race (+437% vs. baseline). C5a returned to baseline values within 1-h of recovery.

Cannon (1994) (18)	21 less active participants with normal body mass index (9 women; age range: 20 to 72-years). All participants over the age of 60-years undertook 4-months of dietary fish oil supplementation prior to this study.	3x 15-mins intervals (separated by 5-mins rest) on a recumbent cycle ergometer (n = 5) or downhill (−16% gradient) running on a treadmill at an exercise intensity of 78 ± 6% and 77 ± 2% of maximal heart rate, respectively.	Plasma C3a-des-Arg: blood samples were taken immediately pre-exercise, immediately post-, 4-h post-, 8h post-, 5-d post-, and 12-d post-exercise. C3a-des-Arg was measured by RIA on once thawed samples. Changes in plasma volume during and after exercise were accounted for.	C3a-des-Arg was increased immediately post-exercise (+50.0% vs. baseline) and returned to near-baseline within 4-h. Between group comparisons indicated that increases in C3a-des-Arg with exercise were not attributed to age.
Castell (1996) (19)	18 male runners and 12 male non-exercise controls, who were aged 20- to 40-years (30 men).	The 1991 and 1993 Brussels marathons.	Plasma C5a: Blood samples (n = 4) were collected 30-mins pre-exercise, within 15-mins post-, 1-h post- and 16-h post-exercise. Blood samples were collected into EDTA tubes, the plasma was separated as soon as possible and frozen at −30°C. Plasma C5a was measured using EIA.	In 1991, there was an increase in C5a 5- to 15-mins following the marathon (+358% vs. baseline); however, C5a was not changed from baseline after 16-h (+25% vs. baseline). These results were replicated at the 1993 marathon.
Chishaki (2013) (22)	25 women judoists from a university judo team, were selected due to weight loss after a training session due to loss of body water. Of these, 17 participants experienced mild dehydration (mean age: 20.2 ± 0.7-years); 8 experienced severe dehydration (mean age: 19.8 ± 1.2-years).	2-h and 30-mins of judo training, including: 20-mins warm-up; 30-mins uchikomi; 5-mins rest; 65-mins standing randori; 5-mins rest; 20-mins sitting randori; 5-mins cool-down.	Serum C3 and C4: non-fasted blood samples were collected pre- and immediately post- exercise, and were centrifuged at 3000 rpm for 10-mins and frozen at −30°C. Serum C3 and C4 were both measured by turbidimetry. Both serum C3 and C4 were adjusted for changes in plasma volume during and after exercise.	C3 was increased post exercise (+4.0 ± 4.6% vs. baseline) in the mildly dehydrated cohort; however, there was no change in C3 in the severely dehydrated group (-0.3 ± 1.9% vs. baseline). C4 was not different post-exercise in the moderately (+2.9 ± 6.3% vs. baseline) or severely (-0.6 ± 4.2% vs. baseline) dehydrated groups.
Córdova (2010) (24)	12 male, professional volleyball players (mean age: 25.9 ± 2.6-years).	Incremental (25 W/min) cycling test until exhaustion, at the beginning and the end of a volleyball season.	Serum C3 and C4: fasted blood samples were collected 30-mins before exercise, immediately post-, and 30-mins post-exercise. Samples were analysed by nephelometry. Changes in plasma volume were determined; but it is unclear whether complement proteins were adjusted to account for changes.	At the beginning and end of a volleyball season, incremental exercise increased C4 (+21.3% and 14.1% vs. baseline, respectively), but changes in C3 were not different (+14.4% and 9.5% vs. baseline, respectively). Neither C3 or C4 were different from baseline following 30-mins of recovery.

Dufaux (1989) (29)	8 healthy male students aged between 20- and 28-years. Participants were moderately trained and habitually ran between 10- to 40-km/week.	Prolonged running race (2.5-h) at an average speed of 3.4 ± 0.4 m/s.	Plasma C3a-des-Arg, C4a-des-Arg and C5a-des-Arg: blood samples (n = 8) were collected 1-h pre-, during (1-h), immediately post-, immediately post-, 1-h post-, 3-h post-, 24-h post- and 48-h post-exercise. Blood was drawn into disodium-EDTA tubes and centrifuged at 2000 ×g, 4°C for 15-mins and frozen at −70°C for 2-weeks. C3a-des-Arg, C4a-des-Arg and C5a-des-Arg were measured by RIA and adjusted for changes in plasma volume during and after exercise.	C3a-des-Arg was higher during and immediately after exercise, compared to baseline. C4a-des-Arg was higher during, immediately after and during recovery (1 and 3-h). C5a-des-Arg was below the limit of detection at all time points.
Dufaux (1991) (30)	11 healthy, male, moderately trained students, aged between 19- to 25-years.	Incremental cycling test (10 W/min) until exhaustion.	Plasma C3a-des-Arg and C4a-des-Arg: blood samples (n = 5) were collected 30-mins before, immediately before, immediately post-, 30-mins post- and 60-mins post-exercise. Blood was drawn into disodium-EDTA tubes and centrifuged at 2000 ×g, 4°C for 15-mins and frozen at −70°C for 2 weeks. C3a-des-Arg and C4a-des-Arg were measured by RIA and adjusted for changes in plasma volume during and after exercise.	Both C3a-des-Arg and C4a-des-Arg were higher immediately following exercise (+43.7% and +35.7% vs. baseline, respectively), compared to baseline. However, both C3a-des-Arg and C4a-des-Arg returned to baseline within 30-mins
Ernst (1991) (32)	13 healthy male volunteers (mean age: 28.6 ± 2.0-years).	Incremental (50 W every 3-mins) cycling test using the Bruce protocol	Serum C4: blood samples (n = 4) were collected before (10-mins rest), immediately post-, 24-h post- and 72-h post-exercise. C4 was measured by nephelometry. Serum C4 data pre- and immediately post-exercise were normalised for haematocrit.	C4, normalised for haematocrit, did not increase following incremental exercise (+9.6% vs. baseline).
Espersen (1996) (33)	8 male, elite swimmers (mean age: 20-years [range: 18 to 22-years]) and 10 age- and sex-matched controls (mean age: 27-years [range: 22 to 40-years]).	A 5-km competition swim at 'maximal intensity'.	Plasma C3d: blood samples (n = 4) were collected pre-, immediately post-, 2-h post- and 24-h post-swimming. Blood was drawn into an EDTA-coated tube and plasma was frozen at −80°C within an 1-h of collection. Plasma C3d was measured by ELISA. Complement proteins were adjusted for changes in plasma volume with exercise.	C3d did not change immediately following the 5-km swim in swimmers (−3.4% vs. baseline) or controls (+3.4% vs. baseline). There was also no difference in C3d 1- or 2-h recovery compared to baseline.

Espersen (1991) (34)	11 male, elite or well-conditioned, long to middle distance runners (mean age: 28-years [range: 20- to 42-years]).	A 5-km running race (completion time range: 14.47-18.13-mins).	Plasma C3d: blood samples (n = 4) were collected 1-week prior the race, immediately post-, 2-h post- and 24-h post-exercise. Blood was drawn into an EDTA-coated tube and plasma was frozen at −80°C within an 1-h of collection. Plasma C3d was measured by ELISA. Correction for plasma volume did not change the results' significance.	C3d did not change immediately following the 5-km race.
Fallon (2001) (35)	8 healthy participants (7 men, 1 woman; mean age: 47 ± 7-years).	The 1996 Colac 6-day race (mean distance completed: 622.2-km).	Serum C3 and C4: blood samples (n = 8) were collected 30-mins pre-exercise, and then daily for the 6-days of the race, and within 15-mins of event completion. Blood was drawn in a seated position to Blood was drawn in a seated position to minimise changes in plasma volume, and samples were analysed within 18-h of collection. Serum C3 and C4 were measured by nephelometry. Serum C3 and C4 were adjusted for changes in plasma volume during and after exercise.	There were no changes in C3 or C4 at any time point during or immediately post-race (−12.1% and 0.0%, respectively) compared to baseline.
Gmünder (1990) (41)	16 runners (3 women; 13 men; median age of 2 groups: 28.0 and 33.0-years).	A 21-km run (run duration: 1-h 15-mins-1-h 50-mins).	Plasma C1-inhibitor, C3c, C4 and factor B: blood samples (n = 4) were collected the day before supplement intake began, 27-days after supplement intake at rest, within 2 to 5-mins of completion of the run, and 2-days following the run. Blood was collected into heparin vacutainers, immediately cooled on ice, centrifuged at 3500 ×g for 20-mins, and stored at −70°C.	C1-inhibitor, C4 and factor B were not different during or following the run, compared to baseline. However, C3c was higher after running (median: +13.6% vs. baseline), but not 2 days after the run (median: +3.0% vs. baseline).
Hanson (1981) (44)	6 male runners who trained 9.7-16.1-km/day (aged 27-40-years).	A 12.9-km run on a level pavement at an average velocity of 13-km/h and a work rate corresponding to 72% maximal oxygen uptake.	Plasma/serum C3 and C4: blood samples (n = 3) were collected 15-mins pre-exercise, 10-mins and 24-h post-exercise. Blood samples were measured by commercially available kits.	Neither C3 (+10.8% and +15.7%, respectively) or C4 (+3.7% and +3.7%, respectively) increased 10-mins or 24-h post exercise, compared to baseline.

Huisveld (1983) (50)	20 highly trained women cyclists; of which, 10 were (mean age: 25.6 ± 3.4-years) and 10 were not (mean age: 20.4 ± 4.3-years) users of oral contraception.	Stepwise incremental cycling test until exhaustion (mean duration: users of oral contraception, 11.1 ± 1.4 mins; non-users of oral contraception, 11.1 ± 2.7 mins).	Plasma C1-inhibitor: blood samples (n = 2) were collected pre-exercise and immediately post-exercise. Blood was drawn into a plastic tube containing 3.8% sodium citrate. Plasma C1-inhibitor was quantified by EIA and reported as a percentage of the amount present in 1 mL of a normal plasma pool of 40 healthy donors. Pre- and post-exercise data were corrected for haemoconcentration.	C1-inhibitor was lower immediately post-exercise in oral contraceptive users (−6.7% compared to baseline) but was not changed in non-users (−1.7% compared to baseline).
Kanda (2013) (55)	9 untrained healthy men (mean age: 24.8 ±1.3-years).	Calf-raise exercise (10 sets of 40 repetitions, with 3-mins rest between sets) at 0.5 Hz by the load corresponding to 50% body weight.	Plasma C5a: blood samples (n = 7) were collected pre-, 2-h post-, 4-h post-, 24-h post-, 48-h post-, 72-h post-, and 96-h post-exercise. Blood was collected into vacutainers containing EDTA and were centrifuged at 1000 ×g for 10-mins. Plasma was stored at −80°C and analysed by ELISA.	There were no differences in C5a 2-h (−5.3%), 4-h (−15.7%), 24-h (−13.2%), 48-h (−10.5%), 72-h (−7.9%) or 96-h (−7.9%), compared to baseline.
Karacabey (2005) (57)	40 sportswomen who played volleyball 3 times per week for at least 5-years and 20 healthy age-matched less active women.	Either 30-mins of treadmill running at a speed corresponding to 70% predicted maximal oxygen uptake (n = 20) or a 30-s maximal Wingate test (n = 20).	Serum C3 and C4: blood samples (n = 5) were collected pre-exercise, immediately post-, 4-h post-, 48-h post, and 5-days post-exercise. Blood samples were separated as soon as possible and stored at −80°C. C3 and C4 were measured by turbidimetry.	Aerobic exercise resulted in a decrease in C3 and C4 immediately after exercise (−35.4% and −56.0%, respectively), but no differences were observed 4-h (+2.4% and +12.0%, respectively), 48-h (+1.8% and −12.0%, respectively) or 120-h (+1.8% and −16.0%, respectively) after exercise, compared to baseline. Wingate exercise resulted in a decrease in C3 and C4 immediately after exercise (−31.3% and −50.0%, respectively), but no differences were observed 4-h (+1.2% and −4.2%, respectively), 48-h (+0.6% and −8.0%, respectively) or 120-h (−1.2% and −12.5%, respectively) after exercise, compared to baseline.

Karacabey (2005) (56)	40 elite male participants who played volleyball 3 times per week for at least 5-years and 20 healthy age-matched less active male controls.	Either 30-mins of treadmill running at a speed corresponding to 70% predicted maximal oxygen uptake (n = 20) or a 30-s maximal Wingate test (n = 20).	Serum C3 and C4: blood samples (n = 5) were collected pre-exercise, immediately post-, 4-h post-, 48-h post-, and 5-days post-exercise. Blood handling and analytical procedures were not clearly stated by authors.	Aerobic exercise resulted in a decrease in C3 and C4 immediately after exercise (−41.6% and −54.2%, respectively), but no differences were observed 4-h (−5.1% and +4.2%, respectively), 48-h (−2.8% and −8.3%, respectively) or 120-h (−5.1% and −12.5%, respectively) after exercise, compared to baseline. Wingate exercise resulted in a decrease in C3 and C4 immediately after exercise (−39.9% and −61.1%, respectively), but no differences were observed 4-h (−5.2% and −11.1%, respectively), 48-h (−1.2% and −5.6%, respectively) or 120-h (−6.4% and −9.3%, respectively) after exercise, compared to baseline.
Kostrzewa-Nowak (2020) (65)	51 physically active men with a mean age of 16-years (range: 15 to 21-years).	Either an 'aerobic' 20-m shuttle-run test or an 'anaerobic' repeated speed ability test.	Serum C3 and C4, but plasma C2, C3a, iC3b: blood samples (n = 3) were collected pre-exercise, within 5-mins of exercise cessaion, and 1-h post-exercise. Blood was collected into S-Monovette tubes for serum separation. Serum C3 and C4 were measured by a colorimetric assay. Plasma C2, C3a and iC3b were measured by ELISA. Changes in plasma volume were calculated by haemoglobin and haematocrit values.	The 'aerobic' exercise decreased C3 (−24.7 to −48.1%) 5-mins post exercise, whereas C3a (+65.4 to +77.3%) and C4 (+5.9 to + 158.9%) were elevated. After 60-mins of recovery from the 'aerobic' exercise, iC3b (+35.7 to +49.2%) and C2 (+11.5 to +18.4%) were increased, compared to pre-exercise. Anaerobic exercise only decreased C2 (−7.5 to −16.6%; during recovery) and C4 (−31.2 to −45.6%; 5-mins post-exercise), but increased C3a (+18.5 to +29.6%; during recovery), compared to pre-exercise.
Kumae (1994) (66)	18 healthy men (mean age: 19.8 ± 1.9-years) who had never participated in any regular exercise training.	A 1500-m run at maximal exertion in a playground, both before and after a 10-weeks of Japanese Military Training (3-4-h of daily training, consisting of: 1-h in the morning; 1-2-h in the afternoon; and, 1-h in the evening).	Serum C3: blood samples (n = 2) were collected before and immediately post-exercise. Blood was allowed to clot, centrifuged then stored at −70°C. Serum C3 was measured by nephelometry. Changes in plasma volume were calculated by haemoglobin and haematocrit values.	C3 was higher immediately following the 1500-m run, compared to baseline (+25.0%), both before and after 10-weeks of military training.
Kumae (1987) (67)	26 healthy male students (mean age: 22.6-years [range: 18 to 30-years]).	A 1500-m run in a playground (mean completion time 398.6 ± 42.0 s).	Serum C3 and C4: blood samples (n = 2) were collected before and immediately post-exercise. Blood was allowed to clot, centrifuged then stored at −70°C. C3 and C4 were measured by nephelometry.	C3 (+24.3%) and C4 (+16.0%) were higher immediately following the 1500-m run, compared to baseline.

McKune (2009) (84)	15 active, but untrained, men (range: 18 to 22-years).	Downhill running on a treadmill (−13.5% decline) for 60-mins at 75% maximal oxygen uptake.	Serum C1-inhibitor, C3 and C4: blood samples (n = 9) were collected pre-, immediately post-, 3-h post-, 6-h post-, 9-h post-, 12-h post-, 24-h post-, 48-h post- and 72-h post-exercise. Blood was collected into SST-vacutainers and allowed to clot for 30-mins, centrifuged at 2000 ×g for 10-mins and stored at −80°C. C1-inhibitor, C3 and C4 were measured by nephelometry.	C1-inhibitor, C3 and C4 did not change post-exercise, compared to pre-exercise.
Milias (2005) (89)	13 healthy, recreationally active men (mean age: 27.5 ± 3.8-years).	36 (6 sets of 6 repetitions) maximal elbow flexors of the non-dominant arm on a motorised dynamometer. Each repetition was separated by 10-s and each set was separated by 1-mins.	Plasma C3: blood samples (n = 6) were collected immediately pre-, 2-h post-, 24-h post-, 48-h post-, 72-h post-, and 96-h post-exercise. Citrated blood was drawn from the non-exercised arm and stored at room temperature until fibrinogen analysis was performed. Plasma C3 was measured by nephelometry.	C3 was not different from baseline 2-h (+0.8%), 24-h (0.0%), 48-h (−4.2%) or 72-h (−4.2%) after the eccentric exercise intervention; however, C3 was lower 96-h post-exercise compared to baseline (−5.0%).
Miura (2005) (91)	56 male judoists who had practised judo for at least 3-years; but, had not participated in judo exercise for 3-months prior to the study (mean age: 18.0 ± 0.1-years).	A judo session, consisting of: 15-mins preparation; 20-mins of uchikomi; 5x 10-mins sessions of randori; and, a 15-mins cool-down. Participants then enrolled on an intensive 6-month training programme (see Table 2).	Serum C3 and C4: fasted blood samples (n = 2) were collected pre- and immediately post-judo exercise. Blood was allowed to clot for 30-mins at room temperature and centrifuged at 1000 ×g for 10-mins. Samples were stored at −80°C and analysed by nephrometry.	Prior to the 6-month training programme, a single session of judo reduced C3 (−4.2% vs. baseline) immediately following exercise; but, C4 was not different (−4.8% vs. baseline). Furthermore, following 6-months of intensive training, neither C3 (−2.2%) or C4 (−2.3%) were different immediately following a single judo training session compared to baseline.
Mochizuki (1999) (92)	15 athletes (11 cross country skiers; 4 speed skaters; 2 women; 13 men; age range: 16-18-years).	Incremental treadmill test until exhaustion at the following time-points: at baseline prior to the athletic season; during the athletic season; and, after the athletic season (see Table 2).	Serum C3 and C4: blood samples (n = 3) were collected pre-, immediately post-, and 1-h post-exercise. Blood was allowed to clot for 30-mins at room temperature and centrifuged at 1000 ×g for 10-mins. Samples were frozen at −80°C and analysed by nephelometry. Serum C3 and C4 were corrected for changes of plasma volume.	C3 was not different immediately post-exercise before the competitive season (−1.9% vs. baseline); however, C3 was lower immediately post-exercise during (−6.9% vs. baseline) and after (−3.1% vs. baseline) the competitive season. C4 was not different immediately post-exercise before (−1.7% vs. baseline) or after (-0.7% vs. baseline) the competitive season; however, C4 was lower immediately post-exercise during (−7.2% vs. baseline) the competitive season.

Navarro-Sanz (2013) (120)	10 healthy, elite middle-distance runners (5 women; 5 men; mean age: 28.7 ± 4.7-years).	3x 800-m sprints on an open-aired running track at maximal speed, interspersed by 30-s recovery periods.	Serum C3 and C4: blood samples (n = 2) were collected before and immediately after the last sprint. Blood was collected into serum-gel vacutainers and allowed to clot for 30-mins, centrifuged at 4000 rpm and immediately analysed for C3 and C4 by nephelometry.	Both C3 (+42%) and C4 (+29%) were elevated immediately post-exercise, compared to pre-exercise. Strong positive correlations were observed between the increase in C3 and C4 and changes in creatine kinase and post-exercise lactate, respectively.
Nielsen (1995) (94)	7 'normal' controls (6 women; 1 male).	A cycling test at a heart rate of 150 bpm (women) or 170 bpm (male), until they reached a Borg score of 17. This took 10 to 15-mins for women and 15 to 20-mins for men.	Serum C1q, C1-inhibitor, C2, C3, C3a, C3bc, C4, C4bc, C4d, C4b binding protein, C5a, factor I, factor B, vitronectin, clusterin and MAC: blood samples (n = 4) were collected before exercise, immediately after, 2-h and 4-h after the start of cycling. Blood was drawn into a Terumo plastic syringe and analysed as follows; C1q, C2, factor B, factor I, C4d and C4b binding protein by enzyme immunoassays; C3 and C4 by nephelometry. Complement proteins were corrected for changes in plasma volume due to exercise.	C1/C1-inhibitor complexes were not changed by exercise in the normal controls; furthermore, exercise had no effect on any other complement proteins.
Nieman (1989) (97)	11 marathon runners, who had completed at least 3 marathons (11 men; mean age: 42.7 ± 2.1-years) and 9 less active age- and gender-matched controls (mean age: 44.2 ± 1.2-years).	Incremental running exercise until exhaustion.	Serum C3 and C4: fasted blood samples were collected before, during (every 5-mins) and 5-mins, 10-mins, 15-mins, 30-mins, and 45-mins after exercise. Samples were drawn from a catheter and analysed by nephelometry.	Both C3 and C4 were higher 5-mins post-exercise compared to baseline in marathon runners (+15.3% and +11.3%, respectively) and less active controls (+17.1% and +14.2%, respectively). There were no changes in C3 or C4 30-mins post-exercise.
Nijs (2010) (98)	22 healthy and less active women (mean age: 38.9 ± 15.0-years).	Submaximal incremental cycling until achieving 75% age-predicted heart rate maximum; and, self-paced and physiologically limited cycling at a heart rate corresponding to 80% of the anaerobic threshold.	Plasma C4a: blood samples (n = 2) were collected before and immediately after exercise. Blood was collected into EDTA-tubes and analysed by ELISA.	C4a was not changed post-exercise in either submaximal (−13.0%) or self-paced (−11.9%) exercise, compared to pre-exercise.
Oberbach (2011) (101)	15 healthy lean men, aged 20 to 35-years.	60-mins of resistance circuit training at 80% maximal power. The session consisted of 3 repetitions at different stations with 30-s rest.	Serum C3, C3b, C3d fragment and clusterin: fasted blood samples (n = 3) were collected before exercise, immediately after, and 24-h after exercise. Samples were centrifuged at 2500 ×g and 4°C for 10-mins and stored in liquid nitrogen. clusterin and C3 were measured by ELISA.	C3 (+16.3 to 28.9% and +16.3 to 25.6%), C3b (+12.8 to 21.7% and +16.0 to 17.9%), C3d fragment (+19.0% and +21.3%) and clusterin (+23.5% and +12.4%) were 'upregulated' immediately and 24-h post-exercise compared to baseline, respectively.

Paulsen (2005) (105)	11 healthy male students (mean age: 25.7 ± 4.0-years).	300 unilateral, maximal, isokinetic eccentric actions with m. quadriceps. The intervention lasted 35-mins and consisted of 30 sets of 10 repetitions, with 30-s rest between sets.	Plasma C3bc and MAC: blood samples (n = 6) were collected 1.5-h before exercise, 1-min, 0.5-h, 1-h, 6-h and 23-h after exercise. Blood was drawn into tubes containing EDTA and centrifuged at 1500 ×g for 15-mins at 4°C. Plasma was then re-centrifuged at 11000 ×g for 5-mins at 4°C and stored at −80°C. Complement proteins were measured by EIA.	C3bc (−21 ± 2%) and MAC (−30 ± 3%) were lower 1-h after exercise compared to baseline; but, returned to baseline within 6-h. C3bc was also lower (−15 ± 2%) 23-h after exercise compared to baseline.
Polli (2019) (109)	22 healthy and less active women (mean age: 38.9 ± 15.0-years).	Submaximal incremental cycling until achieving 75% age-predicted heart rate maximum; and, self-paces and physiologically limited cycling at a heart rate corresponding to 80% of the anaerobic threshold.	Plasma C4a: blood samples (n = 2) were collected before and after exercise. Blood was collected into EDTA-tubes, centrifuged at 1500 ×g for 10-mins and stored at −80°C. Samples were analysed by ELISA.	C4a was lower following both submaximal (median change: −17.7%) or self-paced (median change: −8.6%) exercise, compared to pre-exercise samples.
Risøy (2003) (114)	7 men who had performed recreational strength training for at least 2-years (mean age: 26.0 ± 4.0-years).	Squats, front-squats and knee extensions at an intensity of 100% 6-repition maximum (3 sets of 6 repetitions, with 3-mins rest between all exercise and 8-mins rest between squat and front-squat).	Plasma C1rs-C1-inhibitor complex, C3bBnP, C3b, iC3b, C3c and MAC: blood samples (n = 9) were collected 30-mins before, 25-mins into, and 5-mins, 20-mins, 35-mins, 50-mins, 65-mins, 5-h and 23-h after exercise. Blood was drawn into vacutainers containing EDTA, placed on ice and centrifuged within 30-mins at 1000 ×g at 4°C for 10-mins. Samples were stored at −20 °C. Enzyme immunoassays were used for analysing complement proteins. Changes in plasma volume were calculated from changes in the plasma total protein concentration.	There was no evidence of systemic complement activation in the hours after heavy strength exercise.
Romeo (2008) (116)	22 healthy men (mean age: 21.27 ± 1.83-years).	A treadmill warm-up for 5-mins at 40% maximal aerobic speed; followed by 60-mins at 60% maximal aerobic speed; and, 5-mins at 30% maximal aerobic speed to cool-down. Laboratory conditions were 35°C and 60% relative humidity.	Serum C3 and C4: fasted blood samples (n = 2) were collected immediately before and 10-mins after running. Samples drawn into SST-vacutainers, centrifuged at 3000 rpm at 22-24°C for 15-mins and frozen at −80°C. Complement proteins were measured by immuno-turbidimetry.	C3 (+4%) and C4 (+4.3%) were increased immediately-post exercise, compared to baseline.

Saito (2003) (119)	24 male marathon runners (mean age: 22.9-years) who train an average of 17.4 ± 4.1-h/wk (175 ± 33.8-km).	A 30-km run, which was completed in an average time of 1-h 48-mins and 27-s ± 3-mins 23-s.	Serum C3 and C4: blood samples (n = 2) were collected before and after the run. Blood samples were centrifuged at 2000 ×g for 10-mins and stored at −60°C. Complement C3 was measured by turbidimetry. Data were corrected for changes in haematocrit.	C3 (-0.9%) or C4 (−1.1%) were unchanged immediately post-exercise, compared to baseline.
Sarichter (1995) (121)	36 healthy men aged 21- to 25-years.	70 eccentric contractions (7 sets separate by 3-mins of rest) of the quadricep femoris. Furthermore, a subgroup of participants underwent concentric contractions on a dynamometer one day before and 2, 24, 48, 76, 152, 216-h after eccentric loading.	Serum C3c and C4: blood samples (n = 7) were collected before and 2-h, 1-day, 2-days, 3-days, 6-days, and 9-days after exercise. Blood was collected into serum tubes and measured by turbidimetry.	C3c or C4 remained within the given reference range in all samples from both groups.
Sawka (1989) (122)	5 'fit' male participants who were acclimated to exercising in hot conditions (mean age: 33 ± 2-years).	2 heat-stress tests, which were 120-mins (2 repeated of 15-mins rest and 45-mins exercise on the treadmill) in 35°C and 70% relative humidity. Notably, one test was conducted hypohydrated and one test was conducted euhydrated.	Plasma C3: blood samples (n = 3) were collected at rest and 15-mins, and 40-mins during exercise. Blood samples were collected from a standing position. Changes in plasma volume were calculated by haemoglobin and haematocrit values.	C3 was not altered by exercise; however, hypohydration resulted in a greater C3 compared to euhydration.
Semple (2004) (126)	11 experienced ultramarathon athletes (6 men; 5 women; mean age: 43 ± 9-years).	A 90-km running ultramarathon.	Serum C1-inhibitor, C3, C4, C6 and factor B: blood samples (n = 5) were collected 24-h before their predicted finishing time, immediately after the run and 3-h, 24-h, and 72-h after the run. Blood was allowed to clot for 15-mins, centrifuged at 1000 ×g for 10-mins and stored at −80°C. C1-inhibitor, C3 and C4 were measured by nephelometry. C6 and factor B were measured by RID. Complement protein concentrations were corrected for changes in plasma volume due to exercise.	C3, C4 and C1-inihibitor showed no differences up to 72-h post-ultramarathon. C6 was elevated at 24-h post ultramarathon (+7.8% vs. baseline) and remained elevated at 72-h post. Factor B was elevated at 72-h post-ultramarathon (+12.8% vs. baseline) only.

Semple (2011) (125)	11 active, but untrained, healthy men (mean age: 19.7 ± 0.4-years).	2 bouts of downhill running (−13.5% decline) on a treadmill for 60-mins at 75% maximal oxygen uptake, spaced 14-days apart.	Serum C1-inhibitor, C4 and C6: blood samples (n = 20) were collected at baseline, immediately after exercise and 1-h, 2-h, 3-h, 4-h, 5-h, 6-h, 7-h, 8-h, 9-h, 10-h, 11-h, 12-h, 24-h, 48-h, 72-h, 96-h, 120-h, and 144-h after exercise. Blood was allowed to clot for 30-mins, centrifuged at 1000 ×g for 20-mins and stored at −70°C. C1-inhibitor and C4 were measured by nephelometry. C6 was measured by RID.	C1-inhibitor was elevated 9- and 10-h post-exercise, compared to pre-exercise, with concentrations being up to 7% higher during the second exercise bout. C1-inhibitor was back to pre-exercise levels 24-h post-exercise. C4 was elevated 7- and 9-h post-exercise, compared to pre-exercise, with concentrations being up to 17% higher during the second exercise bout. C4 was back to pre-exercise levels 24-h post-exercise. Post-exercise C6 was not different from pre-exercise at any time point, but were up to 4% higher during the second exercise bout.
Sorensen (2003) (130)	29 healthy controls, who were sedentary to moderately active (women:male ratio: 2.5:1; 18 to 45-years).	A submaximal, steady-state cycling for 20-mins at 70% predicted workload.	Plasma C1-inhibitor, C1q, C1r, C1s, C2, C3, C4, C5, C6, C7, C9, factor B, factor H, factor I, C3a-des-Arg, C4a-des-Arg and C5a-des-Arg: blood samples (n = 5) were collected immediately before, immediately after and 1-h, 6-h, and 24-h after exercise. Blood was collected into EDTA-containing tubes were centrifuged at 4°C and store at −70°C. Plasma C1-inhibitor, C1q, C1r, C1s, C2, C3, C4, C5, C6, C7, C9, factor B, factor H and factor I were measured by radioimmunodiffusion. Plasma C3a-des-Arg, C4a-des-Arg and C5a-des-Arg were measured by ELISA.	In the control group, exercise did not alter C3a, C4a or C5a at any time-point. Authors did not report the effect of exercise on C1-inhibitor, C1q, C1r, C1s, C2, C3, C4, C5, C6, C7, C9, factor B, factor H and factor I.
Thomsen (1992) (135)	14 healthy, untrained male students, aged 20 to 29-years.	60-mins of cycling at a work rate corresponding to ~75% maximal oxygen uptake.	Plasma C3c and C3d: blood samples (n = 4) were collected before exercise, during exercise and 2-h, and 24-h after exercise. Blood was collected into EDTA-tubes and stored at −80°C within 2-h of collection. C3 split products were measured by intermediate gel rocket immunoelectrophoresis.	Cycling did not induce changes in C3c or C3d.

Umeda (2008) (140)	22 male university judoists (mean age: 19.1 ± 0.8-years).	A 2-h judo session (consisting of: 15-mins warm-up; 20-mins of uchikomi; 70-mins of randori; and, 15-mins cool-down), in 28.2 ± 0.4°C.	Serum C3 and C4: fasted blood samples (n = 2) were collected immediately before and immediately after the judo session. Blood samples were drawn from a supine position, centrifuged at 3000 rpm for 10-mins and stored at −30°C. Complement proteins were measured by turbidimetry. Post-exercise complement concentrations were corrected for changes in plasma volume.	Compared to baseline, there were no changes in C3 (+1.7%) or C4 (+1.3%) immediately after 2-h of judo training.
Wang (2009) (144)	15 healthy sedentary men (mean age: 23.7 ± 1.5-years).	Cycling at an incremental workload until exhaustion (strenuous) or a work rate corresponding to 50% maximal oxygen uptake (moderate) at several levels of graded normobaric hypoxia with O_2 concentrations of 12% (~4460-m), 15% (2733-m) and 21% (sea-level).	Plasma C3a-des-Arg, C4a-des-Arg and C5a-des-Arg: blood samples (n = 3) were collected before, immediately after and 2-h after exercise. Blood samples were collected into EDTA-polypropylene tubes, centrifuged at 10000 ×g at 4°C for 30-mins. Complement split products were measured by ELISA.	Moderate exercise has no effect on complement cleavage products in any of the hypoxic conditions. C3a-des-Arg, C4a-des-Arg and C5a-des-Arg were elevated 2-h after strenuous exercise, but not immediately-post exercise. The combination of severe hypoxia and strenuous exercise were the only conditions to increase C3a-des-Arg, C4a-des-Arg and C5a-des-Arg immediately-post exercise.
Wolach (1998) (149)	Participants were prepubertal girls that were elite gymnasts (n = 7) and untrained controls (n = 6), aged 10- to 12-years.	20-mins of treadmill running at a heart rate of 170-180 beats per minute.	Serum C1q, C1r, C1s, C2, C3, C4, C5, C6, C7, C8, C9, factor B and properdin: fasted heparinized blood samples (n = 3) were collected before, immediately after, and 24-h after the run. Samples allowed to clot at room temperature for 30-mins, centrifuged at 4°C and stored at −80°C. Complement proteins were measured by RID.	C1q (trained: −5.2%; untrained: −6.4%) and C1r (trained: −3.0%; untrained: −3.5%) were reduced immediately-post exercise; whereas, C4 was elevated in untrained participants only immediately post-exercise (+9.9%). C1q (trained: −11.2%; untrained: −9.2%), C1r (trained: −4.0%; untrained: −2.3%) and C7 (untrained: −6.2%) were lower 24-h post-exercise compared to baseline; whereas C4 was elevated (+4.9%) 24-h post exercise in untrained participants only. Other complement proteins were not different between time-points.
Ytting (2007) (155)	14 healthy adults (10 women; 4 men; median age: 49-years [range: 35- to 64-years]).	An incremental cycling test until participants reached 70% to 80% predicted heart rate maximum. The total cycling time was 25-mins.	Serum MBL and MASP-2: blood samples (n = 4) were collected before exercise, immediately after and 1-h, and 3-h after exercise. Blood samples were collected in endotoxin-free siliconized glass tubes. Samples were allowed to clot at room temperature for 1-h, centrifuged at 2500 ×g at 4°C for 10-mins and stored at −80°C. Samples were analysed by time-resolved immune-fluorometric assays.	No changes in MBL or MASP-2 were detected between the pre- and post-exercising samples.

Table 2. Studies investigating the effects of exercise training interventions on complement proteins.

Reference	Participants	Exercise intervention	Complement protein(s)	Key finding(s)
Chen (2021) (21)	30 obese, sedentary women (mean age: 65.4 ± 6.6-years).	Either ascending (n = 15) or descending (n = 15) stair walking training in a 10-story building (110 stairs = 1 repetition) two times a week for 12 weeks. Exercise volume was gradually increased by doubling the number of repetitions every 2-weeks.	Plasma C1q: blood samples taken at baseline and after the 12-week intervention were drawn into EDTA vacutainers. Samples were centrifuged at 2000 rpm for 10-mins and plasma stored at -80°C until further analysis by ELISA.	After the 12-week intervention, plasma C1q concentrations decreased by 51% in the descending stair walking group, compared to baseline. No differences in C1q were seen in the ascending stair walking group.
Córdova (2010) (24)	12 professional volleyball players (mean age: 25.9 ± 2.6-years).	An incremental (25 W/min) cycling test until exhaustion. Samples were taken at the start of and following the 4-month professional volleyball season.	Serum C3 and C4: fasted blood samples were collected 30-mins before exercise, immediately after, and 30-mins after exercise. Protein concentrations were measured by nephelometry. Plasma volume changed were measured; but it was unclear whether complement proteins were corrected.	Resting (+1.7% and +11.3% vs. pre-season, respectively), immediately-post incremental exercise (−2.7% and +4.7% vs. pre-season, respectively) and 30-mins recovery (−12.5% and +1.9% vs. pre-season, respectively) C3 and C4 were not different at the beginning of a volleyball season compared to the end of a 4-month season.
Jia (2016) (53)	60 Chinese male military recruits (mean age: 18.8 ± 1.7-years).	3-months of basic military training.	Serum C3 and C4: fasted blood samples were collected immediately after each military training session, drawn into procoagulation tubes, allowed to clot for 30-mins at 37°C and then centrifuged at 1760 ×g for 15-mins at 37°C. Samples were stored at −20°C and analysed by nephelometry.	Neither C3 (-0.9% vs. baseline) or C4 (+3.8% vs. baseline) were different following 3-months of basic military training.
Kumae (1994) (66)	18 healthy men (mean age: 19.8 ± 1.9-years) who had never participated in any regular exercise training.	1500-m run at a maximal exertion, both before and after a 10-weeks of Japanese Military Training (3-4-h of daily training, consisting of: 1-h in the morning; 1-2-h in the afternoon; and, 1-h in the evening).	Serum C3: blood samples were collected before and immediately after the exercise. This was done both at the start of the training period and after. Blood was allowed to clot, centrifuged then stored at −70°C. Serum C3 was measured by nephelometry. Complement proteins were adjusted for changes in plasma volume with exercise.	C3 was reduced following 10-weeks of military training (−23.5%).
Manzaneque (2004) (77)	29 healthy psychology students, aged 18 to 21-years (14 men; 15 women), were allocate to a control (n = 13) or experimental (n = 16) group.	Qigong training for 30-mins per day for 1 month. Each qigong sequence contained 8 movements, which were repeated 8 times, equating 64 movements per session.	Serum C3 and C4: blood samples were collected before the training began, and 1-month after the qigong training. Blood samples were collected into a vacutainer tube and centrifuged at 3500 rpm. Complement proteins were measured by nephelometry.	After 1-month of qigong training, C3 was lower in the experimental group compared to the control group (98.89 vs. 109.74 mg/dL, respectively); however, there was no difference in C4 (16.51 vs. 18.02 mg/dL, respectively).

Mashiko (2004) (83)	25 college male rugby players (mean age: 20.2-years).	A training camp for 6-h/day (3-h in the morning and 3-h in the afternoon) for 17-days.	Serum C3 and C4: fasted blood samples were collected immediately before the start of the training camp, and immediately after training camp completion. Samples were centrifuged at 3000 ×g for 15-mins and stored at −80°C. Complement proteins were measured by turbidimetry.	C4 (+22.5%) was increased immediately following the 17-day training camp; whereas, C3 was unchanged from baseline (+1.0%).
Miura (2005) (91)	56 male judoists who had practised judo for at least 3-years; but, had not participated in judo exercise for 3-months prior to the study (mean age: 18.0 ± 0.1-years).	A 6-month training programme, consisting of: 2x interval sprint running sessions per week; 2x resistance exercise sessions per week; 2x 30-mins runs with intermittent sprints per week; 6x judo training sessions per week; and, 1x rest day per week.	Serum C3 and C4: fasted blood samples were collected before and after the training period, both taken immediately following the judo exercise. Blood samples were allowed to clot for 30-mins at room temperature and centrifuged at 1000 ×g for 10-mins. Samples were stored at −80°C until being analysed by nephelometry.	Neither resting C3 (−3.5%) or C4 (−6.2%) were different pre- and post-6 months of intensive judo training.
Mochizuki (1999) (92)	15 athletes (11 cross country skiers; 4 speed skaters; 2 women; 13 male; age range: 16 to 18-years).	Participants underwent: *a)* athletic pre-season, characterised by extensive endurance training and leg-power training; *b)* during the season, characterized by similar training as pre-season to maintain fitness but with additional technical training; and, *c)* post-season, characterised by one months of rest following the final event of the season.	Serum C3 and C4: blood samples were collected before, immediately after, and 1-h after the test during pre-season, peri-season, and post-season. Blood was allowed to clot for 30-mins at room temperature and centrifuged at 1000 ×g for 10-mins. Samples were frozen at −80°C and analysed by nephelometry. Serum C3 and C4 were corrected for changes of plasma volume.	C3 was not different between the pre-season (103 ± 13 mg/dL) and during-season (101 ± 14 mg/dL) measurements; however, C3 was lower following 1-month of rest (−5.8%). C4 was lower during the season (−16.0%) and after 1-months rest (−20.4%), compared to pre-season.
Risøy (2003) (114)	17 male students who had performed recreational strength training for at least 2-years (mean age: 25.9-years).	4-weeks of normal resistance training, followed by an additional 2-week period of heavy leg extensor training in a subgroup of participants (n = 10).	Plasma C1rs-C1-inhibitor complex, C3bBbP, C3b, iC3b, C3c and terminal complement complex: blood samples were collected 30-mins before, after 25-mins of exercise and 5-mins, 20-mins, 35-mins, 50-mins, 65-mins, 5-h and 23-h after each exercise session. Blood was drawn into vacutainers containing EDTA, placed on ice and centrifuged within 30-mins at 1000 ×g at 4°C for 10-mins, samples were stored at −20°C. Complement proteins were corrected for changes of plasma volume.	There was no evidence of systemic complement activation after the resistance training intervention.

Semple (2006) (127)	17 professional cyclists (mean age: 28 ± 1-years).	The Vuelta a Espańa, which is a 2956-km cycling race that is conducted over 21 consecutive days.	Serum C1-inhibitor, C3 and C4: fasted blood samples were collected before the race began (0-km), on the first rest day (194-km), and at 164-km. Blood samples were allowed to clot in serum separator tubes at room temperature, centrifuged at 2000 ×g at 4°C for 20-mins and stored at −80°C. C3 and C4 were measured by nephelometery.	C3 and C1-inhibitor were not different after stage 10 (−1.2% and +2.5%, respectively) or stage 19 (+1.2% and +1.4%, respectively); whereas, C4 was elevated after stage 10 (+12.5%), but not stage 19 (0.0%), compared to baseline.
Umeda (2004) (139)	49 male college judoists, who had not participated in judo for 14-days prior to the intervention.	A 20-month training programme, consisting of: 2x interval sprint running sessions per week; 2x resistance exercise sessions per week; 2x 30-mins runs with intermittent sprints per week; 6x judo training sessions per week; and, 1x rest day per week. 38 athletes combined the training camp with calorie restriction.	Serum C3 and C4: fasted blood samples were collected 20-days, 4-days, and 1-day before the competition, and 7-days after the competition. Samples were centrifuged at 3000 rpm for 15-mins and stored at −30°C. C3 and C4 were measured by turbidimetry.	Neither C3 or C4 were altered by pre-competition judo training for 16 (−2.0% and +5.8%, respectively) or 19 (−1.5% and +1.4%, respectively) days. However, complement C3 (−8.5%), but not C4 (−6.2%), was lower 7-days post-competition. Calorie restriction did not affect the response of C3 or C4 to exercise in judoists.
Watanabe (2015) (145)	11 men aged 60- to 81-years.	Resistance training 3 times per week, on alternate days, for 12-weeks. The starting weight used during exercise was 70% of the participants' 1-repition maximum for 3 sets of 10 repetitions using leg curl and extension machines. The rest period between sets was 3-mins.	Serum C1q: fasted blood samples were collected at least 48-h after exercise, both at the beginning and at the end of the study period. Samples were centrifuged immediately at 1500 ×g at 4°C for 15-mins and stored at −80°C. C1q was measured by ELISA.	C1q was reduced (−44.5%) by the resistance training intervention, compared to baseline. The reduction in C1q was associated with an increased thigh cross-section area following resistance training.
Yaegaki (2007) (152)	16 women university judoists, who had rested for 2-weeks prior to the intervention.	A 20-day training programme, consisting of: 2x interval sprint running sessions per week; 2x resistance exercise sessions per week; 2x 30-mins runs with intermittent sprints per week; 6x judo training sessions per week; and, 1x rest day per week. 8 athletes combined the training camp with weight reduction.	Serum C3 and C4: blood samples were collected on the first and last days of a 20-day training period, before the judo competition. Blood samples were measured by nephelometry.	Neither C3 (−12.6%) or C4 (−3.3%) were altered by 20-weeks of intensive judo training.
Yang (2010) (153)	23 healthy adult participants (11 women; 12 men; mean age: 52.1 ± 2.2-years).	12 weeks of tai chi chuan exercise, which consisted of 37 standardised movements that lasted 60-mins (including a 10-mins warm-up and 10-mins cool-down).	Serum C1-inhibitor, C1r subcomponent precursor, C3 precursor, factor H and factor B: blood samples were collected before and after the intervention. Serum was analysed by mass spectroscopy (n = 3) and validated by western blot (n = 20)	Factor H and C3 precursor were upregulated, whereas factor B, C1r subcomponent precursor and protease C1-inhibitor were downregulated, compared to baseline.

Table 3. Studies investigating the relationship between measurements of habitual physical activity and fitness, and complement proteins in blood.

Reference	Participants	Measurement of physical activity or fitness	Complement protein(s)	Key finding(s)
Agostinis-Sobrinho (2020) (1), LabMed Physical Activity Study	406 healthy adolescents (212 girls, 194 boys, mean age 14.4 ± 1.7-years).	Cardiorespiratory fitness by a 20-m shuttle run test.	Serum C3 and C4: Fasted blood samples were stored for up to 4-h at 4-8°C and analysed by turbidimetry.	There were no statistical analyses conducted that determined the association between cardiorespiratory fitness and complement proteins.
Agostinis-Sobrinho (2018) (3), LabMed Physical Activity Study	529 healthy adolescents (267 girls, 262 boys, mean age 14.3 ± 1.7-years).	Upper body isometric strength by hand-grip dynamometry; lower body explosive strength by a standing long-jump test; cardiorespiratory fitness by a 20-m shuttle run test.	Serum C3 and C4: Fasted blood samples were stored for up to 4-h at 4-8°C and analysed by turbidimetry.	There was no relationship found between fitness and C3 or C4.
Agostinis-Sobrinho (2018) (2), LabMed Physical Activity Study	529 adolescents (267 girls, 262 boys, mean age 14.3 ± 1.7-years).	Cardiorespiratory fitness by a 20-m shuttle run test.	Serum C3 and C4: Fasted blood samples were stored for up to 4-h at 4-8°C and analysed by turbidimetry.	There were no statistical analyses conducted that determined the association between cardiorespiratory fitness and complement proteins.
Agostinis-Sobrinho (2017) (4), LabMed Physical Activity Study	529 adolescents (267 girls, 262 boys, mean age 14.3 ± 1.7-years).	Cardiorespiratory fitness by a 20-m shuttle run test.	Serum C3 and C4: Fasted blood samples were stored for up to 4-h at 4-8°C and analysed by turbidimetry.	The 'fit' group had lower C3 and C4, compared to the 'unfit' group.
Almeida-de-Souza (2018) (7), LabMed Physical Activity Study	412 adolescents (216 girls, 196 boys, mean age 14.9-years [range: 12.6 to 15.7-years]). Notably, 7.5% of the studied cohort were obese and 22.1% were overweight.	Physical activity was assessed by accelerometery.	Serum C3 and C4: Fasted blood samples were stored for up to 4-h at 4-8°C and analysed by turbidimetry.	There were no statistical analyses conducted that determined the association between physical activity and complement proteins.
Almeida-de-Souza (2018) (6), LabMed Physical Activity Study	329 adolescents (184 girls, 145 boys, mean age 15.0-years [range: 13.0 to 16.0-years]). Notably, 7.9% of the studied cohort were obese and 22.8% were overweight.	Physical activity was assessed by accelerometery.	Serum C3 and C4: Fasted blood samples were stored for up to 4-h at 4-8°C and analysed by turbidimetry.	There were no statistical analyses conducted that determined the association between physical activity and complement proteins.
Artero (2014) (11), Healthy Lifestyle in Europe by Nutrition in Adoles- cence (HELENA) Study	639 adolescents (343 girls, 296 boys, mean age 14.9 ± 1.2-years). Of which, 0.8% of the studied cohort were obese and 2.3% were overweight.	Upper body isometric strength by hand-grip dynamometry; lower body explosive strength by a standing long-jump test; cardiorespiratory fitness by a 20-m shuttle run test.	Serum C3 and C4: Fasted blood samples were analysed by nephelometry.	C3 was negatively correlated with upper body isometric strength, lower body explosive strength and cardiorespiratory fitness. Additionally, C4 was negatively correlated with upper body isometric strength, lower body explosive strength and cardiorespiratory fitness. Regression analysis revealed muscular fitness was negatively associated with C3 and C4 after adjusting for sex, age and pubertal status.

Chen (2021) (21)	30 obese, sedentary women (mean age: 65.4 ± 6.6 years).	Maximal voluntary isometric contraction (MVIC) of the right knee extensors; and performance of functional fitness tests for senior adults (30-s chair stand, 2-min step, 6-m walk, 6-m tandem walk, and balance).	Plasma C1q: blood samples taken at baseline and after the 12-week intervention were drawn into EDTA vacutainers. Samples were centrifuged at 2000 rpm for 10 min and plasma stored at -80°C until further analysis by ELISA kits.	After 12-weeks of descending stair walking training (n=15), the decreased normalised changes in C1q concentrations were associated with MVIC strength, and the 6-m walk fitness tests.
Delgado-Alfonso (2018) (27), UP&DOWN Study	503 children and adolescents (mean age 11.3 ± 3.4-years).	Cardiorespiratory fitness was assessed by a 20-m shuttle run test; muscular fitness was assessed by measuring maximum handgrip strength and the standing long jump; motor ability was assessed by a 4x 10-m shuttle run test.	Serum C3 and C4: fasted blood samples drawn into dried gel and sodium citrate, centrifuged and frozen at −80°C. C3 and C4 was measured by turbidimetry.	In children, 20-m shuttle run, handgrip strength, standing long jump, motor ability and global fitness were predictors of C3 and C4, respectively. In adolescents, only 20-m shuttle run, standing long jump and global fitness were predictors of C4 and no parameters were predictors of C3. C3 and C4 were lower in children with the highest global fitness compared to the least fit tertile; whereas only C3 was lower in adolescents with the highest global fitness compared to the least fit tertile.
Espersen (1996) (33)	8 male, elite swimmers (mean age: 20-years [range: 18 to 22-years]) and 10 age- and sex-matched controls (mean age: 27-years [range: 22 to 40-years]).	A case-control comparison between trained and untrained individuals.	Plasma C3d: blood samples (n = 4) were collected before, immediately after and 2-h, and 24-h after exercise in both athletes and aged-matched controls. Blood was drawn into an EDTA-coated tube and plasma was frozen at −80°C within an hour of collection. Plasma C3d was measured by ELISA.	C3d was not different between elite swimmers and their age- and sex-matched controls.
González-Gil (2018) (42), Healthy Lifestyle in Europe by Nutrition in Adoles- cence (HELENA) Study	659 adolescents (295 boys; 364 girls), of which 127 were overweight or obese and 383 were classified as metabolically healthy.	Physical activity by the International Physical Activity Questionnaire for Adolescents.	Serum C3 and C4: fasted blood samples were drawn and centrifuged at 3500 ×g for 15-mins. Samples were analysed by nephelometry.	There were no statistical analyses conducted that determined the association between physical activity and complement proteins.
González-Gil (2017) (43), Healthy Lifestyle in Europe by Nutrition in Adoles- cence (HELENA) Study	543 adolescents (251 boys; 292 girls).	'Ideal' levels of physical activity were classified as participating in more than 60-mins of self-reported moderate to vigorous exercise per day.	Serum C3 and C4: fasted blood samples were analysed for C3 and C4 by nephelometry.	There were no statistical analyses conducted that determined the association between physical activity and complement proteins.

Karacabey (2005) (57)	40 sportswomen who have played volleyball 3 times per week for at least 5-years and 20 healthy age-matched less active women were enrolled.	A case-control comparison between trained and untrained individuals.	Serum C3 and C4: blood samples were collected once from untrained individuals and five samples were taken in the trained individuals (before exercise and immediately, 4-h, 2-days, and 5-days after exercise). Blood samples were separated as soon as possible and stored at −80°C. C3 and C4 were measured by turbidimetry.	There were no differences in resting C3 or C4 between sportswomen and their healthy age-matched less active controls.
Karacabey (2005) (56)	40 elite male participants who have played volleyball 3 times per week for at least 5-years and 20 healthy-age matched less active male controls.	A case-control comparison between trained and untrained individuals.	Serum C3 and C4: blood samples were collected once from untrained individuals and five samples were taken in the trained individuals (before exercise and immediately, 4-h, 2-days, and 5-days after exercise). Blood handling and analytical procedures were not clearly stated by authors.	There were no differences in resting C3 or C4 between elite men and their healthy age-matched less active controls.
Labayen (2009) (69), The EYHS Study	145 children (74 girls; 71 boys) and 118 adolescents (65 girls; 53 boys) who were 'apparently' healthy, of which 9.9% were overweight or obese.	Cardiorespiratory fitness was determined by an incremental cycling test.	Serum C3 and C4: fasted blood samples were taken from participants in the supine position. Samples were stored at −80°C.	There were no statistical analyses conducted that determined the association between cardiorespiratory fitness and complement proteins.
Lin (2017) (74)	12 older adults who could walk independently or with aids (6 women; 6 men; mean age: 77.6 ± 1.2-years).	Handgrip strength was measured by a handheld dynamometer; cardiorespiratory fitness was assessed by the 6-mins walk test.	Serum C1s subcomponent, C4b-binding protein α chain, C5, C6, C7, C9, factor B and factor H: fasted blood samples were collected into vacutainers containing an anticoagulant, centrifuged at 1500 ×g for 15-mins and stored at −80°C. Serum protein concentrations were measured by mass spectrometry.	There were no statistical analyses conducted that determined the association between cardiorespiratory fitness/handgrip strength and complement proteins.
Martinez-Gomez (2012) (80), The AFINOS Study	183 adolescents (95 boys; 88 girls; mean age: 14.8 ± 1.3-years), of which 24.6% were overweight or obese.	Sedentary time, time spent watching television and physical activity was quantified by 7-days of accelerometery and self-report.	Serum C3 and C4: blood samples were measured by turbidimetry.	C3 and C4 were not associated with sedentary time or television viewing time, when models were adjusted for age, sex, pubertal status, moderate to vigorous physical activity or body mass index.

Martinez-Gomez (2012) (82), Healthy Lifestyle in Europe by Nutrition in Adoles- cence (HELENA) Study	1025 adolescents (476 boys; 549 girls)	Physical activity was measured objectively by accelerometery and subjectively by the International Physical Activity Questionnaire for Adolescents; cardiorespiratory fitness was assessed by the 20-m shuttle test; muscle fitness was measured using a hand-grip strength and a standing long jump; muscular fitness was assessed by a 4x10-m shuttle-run test.	Serum C3 and C4: fasted blood samples were drawn and measured by nephelometry.	Objectively measured vigorous physical activity was negatively associated with C3, independent of body mass index. Furthermore, objectively measured fitness was negatively associated with C3 and C4, independent of body mass index.
Martinez-Gomez (2010) (81), The AFINOS Study	192 adolescents (98 boys; 94 girls; mean age: 14.8 ± 1.3-years), of which 19% were overweight or obese.	Physical activity was quantified by accelerometery; cardiorespiratory fitness was assessed by a 20-m shuttle-run test.	Serum C3 and C4: fasting blood samples were collected, allowed to clot for 1-h, centrifuged and stored at −80°C. C3 and C4 were measured by turbidimetry.	C3 and C4 were not correlated with total, moderate, vigorous, or moderate to vigorous physical activity. However, both C3 and C4 were negatively correlated with cardiorespiratory fitness. C3 and C4 were adjusted for age, sex and pubertal status.
Nieman (1989) (97)	11 male marathon runners, who had completed at least 3 marathons (mean age: 42.7 ± 2.1-years) and 9 less active male age-matched controls (mean age: 44.2 ± 1.2-years).	A case-control comparison between trained and untrained individuals.	Serum C3 and C4: fasted blood samples were collected before, during (every 5-mins) and 5-mins, 10-mins, 15-mins, 30-mins, and 45-mins after exercise, for both trained and untrained. Samples were drawn from a catheter and analysed by nephelometry.	Resting C3 and C4 were lower in athletes compared to non-athletes, respectively. C3 and C4 were not correlated with training load or marathon performance time.
Phillips (2017) (108), The Cork and Kerry Diabetes and Heart Disease Study	396 adults (46% male; mean age: 59.58 ± 5.46-years), of which 317 were overweight or obese.	Physical activity was measured by accelerometery.	Plasma/serum C3: fasted blood samples were collected at baseline and after a 7.5-year follow-up period. Samples were analysed by turbidimetry.	The most sedentary tertial had higher C3 compared to the least sedentary tertile. C3 were lower in the tertiles performing the most light and moderate to vigorous physical activity duration, compared to the tertile that performed the least respective form of physical activity. Once adjusted for age and gender, isotemporal modelling analysis revealed that replacing 30-mins of daily sedentary time with 30-mins of moderate to vigorous physical activity reduced C3.
Puchau (2009) (112)	100 healthy participants (79 women; 21 men; mean age: 20.7 ± 2.7-years), of which 20.4% were overweight.	Physical activity was determined by self-reported time spent practicing sports and whether the participants considered themselves active.	Serum C3: fasted blood samples were immediately centrifuged at 3500 rpm and 4°C for 15-mins and stored at −80°C. C3 was measured by turbidimetry.	Participants with low C3 (<1.085 g/L) were more likely to self-report regular participation in sport (54.9% vs. 30.6%), more time spent practicing sport (3.0 ± 6.5 vs. 1.0 ± 1.9-h per week) and consider themselves active (84.3 vs. 67.3%), compared to participants with high C3 (>1.085 g/L), respectively.

Ruiz (2008) (117), The AVENA Study	416 adolescents, aged 13.0-18.5-years (230 boys; 186 girls; mean age: 15.4 ± 1.4-years), of which 26% were overweight or obese.	Cardiorespiratory fitness was measured by a 20-m shuttle run; muscle strength was measured by a handgrip strength test and the standing broad jump test.	Serum C3 and C4: fasted blood samples were separated and stored at −80°C. C3 and C4 were measured by turbidimetry.	After controlling for sex, age, pubertal status, weight, height, socioeconomic status and cardiorespiratory fitness, C3 was associated with muscle strength; however, no association was evident for C4.
Ruiz (2007) (118), The European Youth Heart Study	142 children (74 boys; 68 girls; mean age: 9.5 ± 0.4-years).	Physical activity was measured by accelerometery; cardiovascular fitness was measured by an incremental cycling test to exhaustion.	Serum C3 and C4: fasted samples were drawn with the participant in a supine position, separated and stored at −80°C. C3 and C4 were measured 'with kits from DakoCytomation'.	After controlling for age, sex and pubertal status, C3 was associated with cardiovascular fitness, but not physical activity. C4 was not associated with physical activity cardiovascular fitness.
Saygin (2006) (123)	15 less active controls (mean age: 22.2 ± 2.7-years), 15 volleyball players (mean age: 20.9 ± 2.2-years) and 15 long distance running athletes (mean age: 21.6 ± 1.9-years).	Cardiorespiratory fitness was estimated by a 20-m shuttle run test; q case-control comparison between trained and untrained individuals.	Serum C3 and C4: blood was measured by turbidimetry.	Long distance running athletes has lower C3, compared to volleyball players and less active controls. Whereas volleyball players had lower C4 compared to less active controls and long-distance runners.
Volp (2012) (142)	157 healthy adults (91 women; 66 men; mean age: 23.3 ± 3.5-years), of which 13.4% were overweight/obese.	A questionnaire on lifestyle habits was used to determine: participation in sports; physical activity patterns; and, a metabolic equivalent index.	Serum C3: fasted blood samples were centrifuged at 2465 ×g at 5°C for 15-mins and stored at −80°C. Serum C3 was measured by turbidimetry.	There were no correlations between C3 and physical activity level.
Watanabe (2015) (145)	131 healthy participants (62 women; 69 men), aged 20 to 81-years.	Muscular strength was measured by knee extensor and flexor dynamometry.	Serum C1q: fasted blood samples were collected at least 48-h after exercise both at the beginning and at the end of the study period. Samples were centrifuged immediately at 1500 ×g at 4°C for 15-mins and stored at −80°C. C1q was measured by ELISA.	Negative correlations were observed between C1q and both isometric peak knee extension power and isometric peak knee flexion power.
Wolach (1998) (149)	Participants were prepubertal elite women gymnasts ($n = 7$) and untrained women ($n = 6$), aged 10 to 12-years.	A case-control comparison between trained and untrained individuals; Participants underwent 20-mins of treadmill running at a heart rate of 170-180 beats per minute.	Serum C1q, C1r, C1s, C2, C3, C4, C5, C6, C7, C8, C9, factor B and properdin: fasted heparinized blood samples were collected before, immediately after, and 24-h after the run in both trained and untrained individuals. Blood was allowed to clot at room temperature for 30-mins, centrifuged at 4°C and stored at −80°C. All complement proteins were measured by RID.	When resting serum was expressed as a ratio of pooled normal sera, resting C1r was elevated in trained compared to untrained girls; whereas C2 (0.81 ± 0.11 vs. 0.98 ± 0.08) and C3 (0.89 ± 0.09 vs. 1.06 ± 0.15) was lower in trained compared to untrained girls. These differences were maintained immediately and 24-h post-exercise. C1q, C1s, C4, C5, C6, C7, C8, C9, factor B nor properdin were not different between groups.
Zhang (2020) (157), China Hainan Centenarian Cohort Study	943 older adults among the longevous population in Hainan, China (81.4% female; mean age: 102.9 ± 2.8-years).	Physical activity was estimated by the Barthel Index of activities of daily living. A case-control comparison between physically dependent and physically independent older adults.	Serum C3 and C4: measured by turbidimetry.	There was no difference in C3 or C4 between the physically dependent and independent groups. When all data was pooled, there was no correlation between C3 or C4 and physical activity. However, C3 was negatively and C4 was positively associated with physical activity in a model that was adjusted for sex, age, body mass index, education, smoking, alcohol consumption, depressive syndromes, and visual and auditory impairments.

studies. C4 was elevated following a training camp in college rugby players (83); whereas, C3 (83, 91, 139, 152) and C4 (91, 139, 152) were unchanged following training intervention that combined more than one type of exercise, compared to baseline. A single (7.1%) study also demonstrated that C3 was lower, and C4 was unchanged, 7-days following the completion of an interval, resistance and judo exercise training intervention (139). Soluble complement proteins in blood at rest collected before and following a military training intervention were the topic of n = 2 (14.3%) studies. C3 was lower following 10-weeks of military training in n = 1 (7.1%) study (66); whereas, opposing findings demonstrated that both C3 and C4 were unchanged following 3-months of military training (53). A single (7.1%) study reported that weight loss during an interval, resistance and judo exercise training intervention did not affect resting C3 or C4 (139).

With training interventions that incorporated only a single type of exercise, n = 2 (14.3%) studies reported soluble complement proteins in blood at rest, following a resistance exercise intervention. C1q was lower following 12-weeks of both resistance exercise (145) or descending stair walking (21); whereas, C1rs-C1-inhibitor complex, C3b, iC3b, C3bBbP, C3c and MAC were unchanged following 4-weeks of resistance exercise (114). A strong negative correlation demonstrated that reductions in C1q were associated with increased muscle cross sectional area following 12-weeks of resistance exercise (145). 21-days of cycling did not alter resting C1-inhibitor, C3 or C4 in professional cyclists; however C4 was elevated after 10-days of the intervention (127). One-month of daily qigong training lowered C3, but not C4, in healthy young students (77). Whereas, 12-weeks of tai chi (3 times per week) elevated C3 precursor and factor H, but reduced C1-inhibitor, C1r subcomponent precursor and factor B, in university judoists (153).

Soluble complement proteins in blood measured at different stages of an athletic season were the topic of n = 2 (14.3%) studies. C3 (24, 92) and C4 (24) were unchanged throughout the athletic season; whereas, a single study reported lower C4 during the season in cross country skiers and speed skaters (92). The latter study also reported lower C3 and C4 one-month following the completion of an athletic season (92).

Habitual physical activity and fitness

The association amongst soluble complement proteins in blood and measurements of habitual physical activity/fitness were the topic of n = 29 (37.7%) studies, and these studies included 9,284 participants (Table 3). The most studied assessments of habitual physical activity/fitness were cardiorespiratory fitness (n = 14; 48.3%) and habitual physical activity levels (n = 13; 46.4%). Assessments of muscular strength (n = 8; 27.6%), a case-control comparison of active and less active controls (n = 7; 25.0%) and assessments of motor ability (n = 2; 7.1%) were also studied. Overweight or obese participants were recruited by n = 12 (41.4%) studies, and a further n = 5 (17.9%) studies exclusively recruited well trained or elite athletes. Whilst all included studies measured habitual physical activity/fitness alongside soluble complement proteins in blood, n = 8 (28.6%) studies did not perform statistical analyses to inform the present review.

Soluble complement proteins in blood between cohorts with different habitual physical activity levels were the topic of n = 3 (10.7%) studies. C3 was lower in participants who engaged in more habitual physical activity, compared to their less active counterparts (108, 112). It was reported that C3 was negatively associated with higher habitual physical activity levels (82); whereas, n = 5 (17.9%) studies reported no correlation between habitual physical activity levels and C3 (80, 81, 118, 142, 157) or C4 (80, 81, 118, 157). A single (3.6%) study employed isotemporal modelling analysis to demonstrate that replacing less active time with 30-mins of moderate to vigorous physical activity would reduce resting C3 in blood at the time of sampling (108).

Soluble complement proteins in blood between cohorts with different fitness and training statuses were the topic of n = 9 (32.1%) studies. C3 and C4 were lower in 'fit' (predicted maximal oxygen uptake ≥42 or 35 mL•kg•min-1 for boys and girls, respectively) compared to their 'unfit' (predicted maximal oxygen uptake <42 or 35 mL•kg•min-1 for boys and girls, respectively) counterparts (4, 27). Whereas, both C3 and C4 were not different between physically dependent and physically independent older adults (157). C2 (149), C3 (97, 123, 149) and C4 (97, 123) were lower in athletes compared to non-athletic controls; whereas, C1q (149), C1s (149), C3 (56, 57), C3d (33), C4 (56, 57, 149), C5 (149), C6 (149), C7 (149), C8 (149), C9 (149), factor B (149) and properdin (149) were not different between athletes and non-athletic controls. C3 (11, 81, 82, 118) and C4 (11, 81, 82) were negatively associated with cardiorespiratory fitness; whereas, C1q (145), C3 (11, 117) and C4 (11) were negatively associated with muscle strength. Both C3 (3) and C4 (3, 118) were not associated with fitness in n = 2 (7.1%) studies, and a single (3.6%) study reported that C4 was not associated with muscular strength (117). The association between fitness and C4 appears to be weakened by the progression from childhood to adolescence (27).

DISCUSSION

The purpose of this scoping review was to comprehensively explore the relationship between complement proteins in blood and acute bouts of exercise, exercise training, or measurements of habitual physical activity/fitness (Figure 4). n = 77 eligible studies were identified, and these studies included a total of 10,236 participants and 40 complement proteins. Firstly, the C3 and C4 family proteins were the most studied, yet studies investigating proteins that are upstream of these proteins – and therefore exclusive to the classical, lectin or alternative pathways – were less common. Secondly, it appeared that complement was transiently activated immediately following an acute bout of exercise, and complement proteins were also upregulated up to 72-h following resistance exercise and ultra-endurance running, perhaps reflecting muscle-damage induced activation of the classical and alternative complement pathways. On the other hand, exercise training and cardiorespiratory fitness were more commonly associated with a downregulation of C3 family proteins. Lastly, diversity in the sampling procedures, analytical methodologies, exercise intervention and measurements of habitual physical activity/fitness likely contributed to heterogeneity in the findings observed between different studies.

It is well established that an acute bout of strenuous or unaccustomed exercise causes a profound alteration in various plasma proteins (51, 71, 102, 131, 132, 138, 156), yet inconsis-

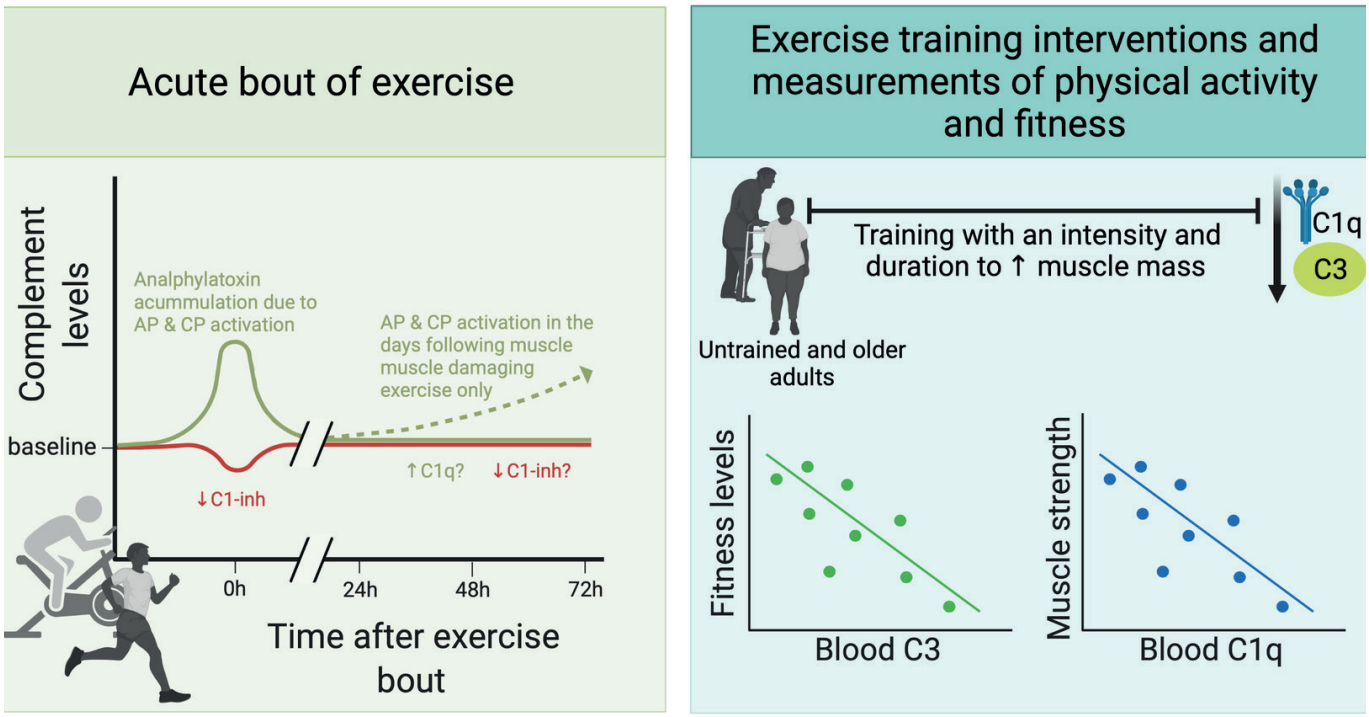

Figure 4. A theoretical graphical summary of the findings of the present systematic scoping review which evaluated the relationship between complement proteins in blood and acute bouts of exercise, exercise training, or measurement of physical activity/fitness among 76 eligible studies, which including 10,206 participants. Firstly (left panel), a consistent finding was that anaphylatoxins (e.g. C3a-des-Arg, C4a-des-Arg and C5a) were increased immediately following an acute bout of exercise in a laboratory setting – potentially due to a transient reduction in the C1-inhibitor (C1-inh), which prevents the formation of both fluid-phase and membrane bound C3 convertases. Whereas ultra-endurance running and resistance exercise – but not exercise which fails to induce muscle damage – increased complement proteins specific to- or downstream- of the classical and alternative pathways (e.g. C1s, factor b, and the C3 and C6 family proteins) for up to 72-h, which may be a result of muscle damage and coincided with a concurrent elevation in the complement activator, CRP. It remains unclear in humans whether other complement proteins specific to the alternative and classical pathways (e.g., C1q) are secreted in excess after muscle-damage, as reported in animal studies (151, 158). Separately (right), C3 in blood was reduced by exercise training and associated with increased fitness, whereas C1q appeared to be negatively associated to muscle strength. This image was created with BioRender.com (Toronto, Canada).

tencies between studies means it remains unclear whether exercise modulates soluble complement proteins in humans (Table 1). One such inconsistency between studies, was the observation that proteins of the classical (C1q and C1-inhibitor), lectin (MBL) and alternative (factor B) pathways were reported to be elevated, lower and unchanged immediately-following an acute bout of exercise (12, 41, 50, 84, 94, 114, 125, 126, 149, 155). More consistent results were reported by studies that employed an acute bout of exercise in a laboratory setting and corrected soluble complement proteins for changes in plasma volume; whereby, the 6 studies which satisified these criterion reported that C3a-des-Arg, C4a-des-Arg and C5a were elevated (16, 18, 30), whereas C3 and C4 were unchanged (32, 92), and C1-inhibitor were lower (50) immediately-post exercise. Reductions in the C1-inhibitor – which prevents the formation of both the membrane-bound (C4b2a) and fluid-phase (C3bBb) C3 convertase (54, 85) and thus is considered a pan-complement inhibitor – could be a mechanism contributing to anaphylatoxin accumulation immediately following an acute bout of exercise in a laboratory setting. Anaphylatoxin accumulation may be further explained by a pH-dependent modulation of the alternative pathway C3 convertase, C3bBb, which is upregulated by lactic acidosis (39, 45, 129). It may alternatively be the case that increased C3a-des-Arg, C4a-des-Arg, and C5a-des-Arg immediately post-exercise reflects muscle-damage induced activation of the classical pathway, albeit at a modest level as many of these laboratory studies did not explicitly seek to induce muscle damage per se (16, 18, 30). Lastly, elevated C4a-des-Arg may arise due to lectin pathway activation (30) – which is in keeping with the observation of increased MBL following ultra-endurance running (12) – though the mechanisms of this process are less clear but could involve changes to gut homeostasis (40). Taken together, it may be that all three pathways can be activated during/immediately after exercise, and further research is needed to elucidate the stimuli for such activation.

While activation of all three complement pathways may occur during or immediately following an acute bout of exercise, release and 'spill over' of C1q from inflammatory/repair responses in muscle (e.g., by macrophages) is likely responsible for the activation of complement – via the classical pathway – for up to 2- to 4-days post-exercise in a muscle damage-dependent manner (151, 158). Indeed, it was consistently demonstrated that an acute bout of cycling or running (duration range: 30-s to 60-mins) did not result in complement secretion or activation – as indicated by unchanged C1-inhibitor, C3, C4, C5a and C6 – 12-h to 6-days following exercise cessation (19, 44, 56, 57, 125). Whereas exercise of a longer duration (e.g. ultra-endurance running) or designed to elicit muscle damage (e.g. resistance training) increased markers of the classical (C1s), as well as C3 and C6 family proteins, up to 72-hours following exercise cessation (12, 101, 126). Notably, no studies included in the present review have investigated the association between complement activation following muscle-damaging exercise and complement activatory proteins, such as CRP (51, 138, 156). However, a single study observed

a similar time-course between increases in the classical complement protein C1s and CRP following a 246-km run (12). Additionally, it was shown that alternative pathway factor B was also increased in the days after ultra-endurance exercise (12, 126). Given that proteins of both the classical and alternative pathways were modulated following ultra-endurance and resistance exercise (12, 101, 126), which coincided with elevated CRP (12), it is plausible that both pathways are involved in skeletal muscle regeneration. This would be in keeping with rodent models which show that regeneration is facilitated by classical complement pathway activation in a factor-B dependent manner (151, 158). Separately, it was observed that a marker of the leptin pathway (MBL) is elevated in the days following ultra-endurance running, and as outlined earlier, the mechanisms underpinning this response are unclear, but could reflect changes to gut homeostasis (40).

In contrast to an acute bout of exercise, exercise training is known to reduce both complement-activating inflammatory proteins (e.g. CRP) and cells capable of secreting complement system proteins (e.g. monocytes) (38, 100). Whilst the majority of studies reported that circulating C3 and C4 were unchanged (24, 53, 77, 83, 91, 92, 127, 139, 152), several studies also reported that C3 or C4 were lower or elevated following exercise training (66, 77, 83, 92, 139). A source of heterogeneity resulted from the duration of exercise intervention. For instance, a 4-week resistance exercise intervention in well-trained young men did not change resting C1 or C3 family proteins in blood (114). Whereas a progressive intervention of resistance training over 12-weeks in older adults lowered C1q, which is a precursor of the classical pathway; an effect that was associated with greater muscle cross-sectional area (145). A reduction of C1q in blood following resistance exercise training is, at first glance, somewhat surprising, as previous research demonstrated that 12-weeks of endurance cycling training increased the intramuscular presence of C1q-secreting M2-like macrophages after an acute bout of resistance exercise (143). However, observations of reduced C1q in blood following resistance exercise could support the notion that C1q is utilised during muscle regeneration – in the presence of the classical complement pathway activator, CRP – through promoting the lysis and removal of damaged myofibers (151, 158), as opposed to being released into circulation. Nonetheless, this emphasises the need for further research to determine whether an acute bout of muscle damaging exercise or a resistance training intervention result in an excessive secretion of C1q by tissue-resident M2-like macrophages, sufficient to increase serum bioavailability – this could have clinical implications, particularly regarding the effectiveness of immunotherapy induced CDC.

A possible further source of heterogeneity amongst included studies that investigated the effects of exercise training on complement system proteins was the fitness of participants at study entry. For instance, complement proteins in blood were unchanged following an exercise intervention in 7/8 (87.5%) studies who recruited participants who were well-trained at baseline (24, 83, 91, 92, 114, 127, 139, 152). Whereas, exercise training interventions modulated soluble complement proteins in 4/4 (100%) studies that recruited untrained or older adult participants (66, 77, 145, 153). As such, exercise training interventions, incorporating sufficient intensity and duration to improve muscle mass, have the potential to modulate complement proteins that are implicated in inflammation or muscle regeneration in untrained or older adult participants.

This notion is supported further by the findings from studies assessing the relationship between complement proteins and measurements of habitual physical activity. The present review found that 5/6 (83.3%) studies found no correlation between habitual physical activity and complement proteins (80, 81, 118, 142, 157); whereas, 3/5 (60%) studies reported that athletes, who were likely to undertake intensive physical activity regularly, were reported to have lower C3 in blood compared to their non-athletic counterparts (97, 123, 149). However, two studies which reported comparable C3 in athletes and controls provided incomplete blood handing/analysis procedures (56, 57). We also found that 5/6 (83.3%) studies reported a negative association between circulating C3 and measures of cardiorespiratory fitness or muscle strength in healthy humans (11, 81, 82, 117, 118). Whereas the majority of studies reported no association between physical activity/fitness and C4 in blood (3, 56, 57, 80, 81, 117, 118, 149, 157). Furthermore, only two studies reported the association between physical activity/fitness and soluble complement proteins other than C3 or C4 (145, 149). As such, future research is required to investigate the association between habitual physical activity, fitness and complement proteins exclusive to specific pathways and/or the MAC.

Areas for further research

Research to date has demonstrated that exercise may enhance anti-cancer immunotherapy through the mobilisation of immune cells (72, 79, 147), modulation of immune checkpoints (13) and vascularisation of the tumour (14). Given that numerous therapeutic monoclonal antibodies used for the treatment of cancers exert cell killing via CDC in a C1q-dependent manner (28, 59), it is promising that an acute bout of exercise may be a means of increasing complement proteins downstream of C1q, which may indicate that exercise can be harnessed to increase the bioavailability of C1q in blood (63). Although complement activation during or immediately following an acute bout of exercise is likely a result of alternative and classical pathway activation (16, 18, 30), complement proteins downstream of C1q are upregulated 12- to 72-hours following resistance and ultra-endurance exercise, perhaps reflecting a dependence on muscle damage and CRP (12, 101, 126), which can be more feasibly achieved in clinical populations using eccentric and/or resistance exercise. These findings are in keeping with rodent models, which have recently demonstrated that C1q is secreted by M2-like macrophages during the resolution of muscle injury, with peak serum C1q occurring 2- to 4-days post-injury (151, 158). However, future research is required to confirm whether the observed complement activation 12- to 72-hours following exercise cessation in healthy humans is the result of increased C1q in blood, which may have clinical implications – for example by augmenting the efficacy of immunotherapy-induced CDC against cancer cells.

The dysregulation of soluble complement proteins is also the feature of numerous chronic health conditions, including diabetes mellitus (5), cardiovascular disease (148), Rheumatoid arthritis (48) and cancer (113). For example, the proliferation of skin and breast cancer cell lines were exacerbated in the presence of pro-inflammatory anaphylatoxins, C3a and C5a, due to upregulated Wnt-β catenin-Sox2 mediated vascu-

lar endothelial growth factor (VEGF) secretion and Akt mediated response gene to complement (RGC)-32 expression, respectively (36, 75). As such, strategies to prevent long-term exposure to anaphylatoxins, such as the C5 targeting monoclonal antibody eculizumab (150), have shown promise and the potential for long-term exercise training to modulate soluble complement proteins is of clinical interest. Whilst studies included in the present review suggested that higher levels of habitual physical activity and cardiorespiratory fitness were associated with reduced C3 in blood (11, 81, 82, 117, 118), no studies determined whether there was an association with fragments of complement (e.g. C3a-des-Arg or C5a-des-Arg), which are indicative of inflammation and complement activation (99). Therefore, future research is warranted to determine whether exercise training elicits an anti-inflammatory effect through the modulation of complement activation, which may have important implications for the prevention and management of chronic diseases associated with complement dysregulation. Nonetheless, it is unknown whether the complement system responds in a similar manner between healthy people and those who have been diagnosed with chronic diseases and/or undergoing treatment that affect complement system proteins (e.g. anti-coagulative therapy; 9). Therefore, future research that investigates the response of soluble complement proteins to exercise training in the context of chronic health conditions is warranted.

Technological advances have also allowed improved biochemical profiling of plasma proteins, which have been successfully used to identify distinct plasma proteomes in states of health and disease in both humans (23, 25, 26, 52, 101) and animal models (90). Global proteomic analyses involve reliable techniques that can produce a large-scale characterisation of the plasma proteome profile whereby protein-protein interactions can be predicted, and therefore serve to provide a broader view of human physiology (47, 107). A proteomics approach could therefore help undercover the mechanisms behind complement changes in response to exercise as this most likely involves several pathways and protein interactions, which are harder to observe in single-targeted protein studies. Recent studies have applied these global proteomic techniques in the context of exercise training and further support the profound alterations that exercise has on the plasma proteome profile (12, 64, 68, 87, 95, 96, 104, 115, 153). Indeed, several studies have demonstrated that the volume of exercise conducted is positively associated with the magnitude of change to the plasma proteome profile and, in turn, the accumulation of complement system proteins (87, 95, 96). While the authors conclude that these changes to complement system proteins are indicative of 'overreaching', for reasons highlighted earlier in this review, it may rather reflect ongoing muscle damage/repair and the associated inflammation.

Limitations

Several sources of heterogeneity were identified amongst included studies, which may contribute to the conflicting evidence that currently exists regarding soluble complement proteins in blood and exercise in healthy humans. It was concluded that the primary sources of heterogeneity were discrepancies in blood sampling, handling and analytical procedures. For instance, ethylenediaminetetraacetic acid (EDTA), but not citrate or heparin, is the only anticoagulant to completely inhibit complement activation ex vivo and, therefore, EDTA-plasma is the preferable biological specimen to measure complement concentrations or activation fragments (99, 154). However, 52 of 76 (68.4%) studies measured complement levels and/or activation products in serum. Furthermore, polymer surfaces, including plastics, are established activators of complement ex vivo (46, 128). Despite this, only 1 of 76 (1.3%) studies reportedly used glass laboratory equipment. Lastly, it is well established that exercise expands plasma volume in a modality- and intensity-dependant manner and, therefore, interpreting complement within blood pre- and post-exercise without correction for such expansion could lead to erroneous results (58). For instance, an increased concentration of complement proteins in blood in the presence of an expansion of plasma volume immediately post-exercise could be reported as the complement protein being unchanged from baseline. Nonetheless, only 20 of 76 (26.3%) studies corrected soluble complement proteins for changes in plasma volume pre-, during- or post-exercise (Figure 3). Therefore, it is important that future studies consider these limitations in blood sampling, handling and analytical procedures.

Conclusions

This review demonstrated that C3 and C4 family proteins were the most commonly studied soluble complement proteins in prior research which has investigated the effects of an acute bout of exercise, exercise training or habitual physical activity levels and/or fitness on complement system proteins. There is consistent evidence indicating that long-term exercise training, and the concomitant augmentation of muscle mass and fitness, seems to downregulate C3 family proteins in blood of healthy humans, which is in keeping with the notion that regular exercise exerts anti-inflammatory effects and may have implications for the prevention and treatment of diseases associated with inflammation and complement dysregulation. In addition, it was reported that anaphylatoxins were transiently increased immediately following an acute bout of exercise in healthy humans, likely a result of alternative and classical pathway activation. Whereas soluble complement proteins downstream of the classical complement pathway precursor, C1q, were elevated 12- to 72-hours following resistance and ultra-endurance exercise. Therefore, it may be the case that exercise-induced muscle damage in humans results in elevated C1q secretion from muscle by immune cells. Future studies should explore whether this process can be harnessed to improve the efficacy of cancer immunotherapies that are reliant on CDC as a primary mechanism-of-action.

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