COVID-19 SYMPTOMS AND ANTIBODY FORMATION IN COMPETITIVE CROSS-COUNTRY SKIERS

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ABSTRACT

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The COVID-19 pandemic set the whole world in front of a relatively new situation. Knowledge of the new infection, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was sparse and people in every industry started to rethink their habits and guidelines. Acute respiratory illnesses and infections are a major burden to competitive athletes and some guidelines considering avoiding infections and return to sport already exist. However, proper scientific based guidelines were and are still missing, especially considering return to sport. The purpose of this thesis was to enhance the understanding of respiratory viral infections in athletes and to describe the nature COVID-19 in a cohort of Finnish cross-country skiers.

15 cross-country skiers who had been infected with SARS-CoV-2 in spring 2020, were interviewed two months and 13 months after symptoms onset. Symptoms, training status and subjective evaluation of performance were asked in the interviews. Blood samples were collected three months and 14.5 months after symptoms onset. Samples were analysed for antibodies against SARS-CoV-2 nucleoprotein (N) and spike glycoproteins RBD (spike receptor-binding domain) and SFL (full-length spike protein) IgG concentration, and neutralizing antibody titres against the wildtype virus.

All athletes had mild symptoms and none of the athletes required hospital care. The most common symptoms were alterations in sense of taste and/or sense of smell, abnormal fatigue, muscle soreness, runny nose or nasal congestion, fever and headache. Mean symptom duration was 10 days, symptom severity on scale one to three was 1.6, number of symptoms 5 and mean days to return to training happened 9 days from the symptom's onset. All athletes developed measurable positive antibody responses. In serum samples collected three months after the infection, all athletes had values over the line of positivity in IgG anti-N, IgG anti-RBD and IgG anti-SFL. At the same time 13 out of 15 athletes microneutralization test (MNT) titre was positive.

Finding in this thesis supports the previous knowledge that athletes experience mostly mild COVID-19 and can successfully return to training and competitions. Athletes develop measurable antibody response and vaccination seems to strengthen the response after natural COVID-19 infection. The cohort of this thesis was small, including only one sport discipline and interpretation of these results should be made with caution. Guidelines to return to training still varies after a few years of the COVID-19 pandemic and thus, more information and updated guidelines are required to ensure athletes safe return to play regarding not only COVID-19 infection but also of other viral respiratory infections.

Keywords: COVID-19, SARS-CoV-2, Antibody, Athlete, Cross-country skiing.

TIIVISTELMÄ

Laatikainen-Raussi, V. 2022. COVID-19-INFEKTION SAIRASTANEIDEN KILPAMAASTOHIIHTÄJIEN OIREKUVA, HARJOITTELUUN PALAAMINEN JA VASTA-AINEMUODOSTUS. Liikuntatieteellinen tiedekunta, Jyväskylän yliopisto, Liikuntafysiologian pro gradu -tutkielma. 54 s.

COVID-19 pandemia asetti uudenlaisia haasteita ympäri maailmaa. Tieto uudesta taudista, COVID-19-infektiosta ja sitä aiheuttavasta viruksesta, SARS-CoV-2:sta, oli aluksi niukkaa. Pandemia onkin saanut ihmiset ja organisaatiot pohtimaan uudelleen hygieniakäytäntöjä ja -ohjeistuksia ehkäistäkseen hengitystieinfektioita. Hengitysteiden akuutit sairaudet ovat haaste kilpaurheilijoille. Jo ennen koronapandemiaa urheilijoille on ollut ohjeistuksia tartuntatautien välttämiseksi ja urheiluun palaamiseksi taudin jälkeen. Pandemia on kuitenkin vauhdittanut tätä työtä merkittävästi. Tämän opinnäytetyön tarkoituksena on lisätä ymmärrystä urheilijan hengitysteiden virusinfektioista ja kuvata COVID-19-infektion sairastaneiden maastohiihtäjien taudinkuvaa, vasta-ainemuodostusta ja paluuta harjoitteluun.

Opinnäytetyössä tutkittiin 15:tä maastohiihtäjää, jotka sairastivat COVID-19-infektion vuoden 2020 keväällä. Maastohiihtäjät haastateltiin kahdesti: kaksi ja 13 kuukautta ensimmäisten oireiden ilmaannuttua. Oireet, kuvaus harjoittelusta ja subjektiivinen arvio suorituskyvystä selvitettiin haastatteluin. Urheilijoilta kerättiin lisäksi verinäytteet kolme ja 14,5 kk oireiden alkamisesta. Verinäytteiden seerumista analysoitiin vasta-aineiden pitoisuudet SARS-CoV-2 pintaproteiinille (N) ja piikkiproteiineille (RBD ja SFL). Lisäksi seerumeista analysoitiin neutraloivia vasta-aineita villityypin virusta vastaan.

Kaikki tutkittavina olleet urheilijat sairastivat taudin lievänä, eikä yksikään tarvinnut sairaalahoitoa. Yleisimmät oireet olivat, haju- tai makuaistin muutokset, poikkeava väsymys, lihassärky, vuotava tai tukkoinen nenä, kuume ja päänsärky. Oireet kestivät keskimäärin 10 päivää, oireiden keskimääräinen voimakkuus oli 1,6 asteikolla yhdestä kolmeen, oireita oli keskimäärin viittä erilaista ja paluu harjoitteluun tapahtui keskimäärin yhdeksässä päivässä. Kaikki urheilijat kehittivät positiivisen vasta-ainevasteen. IgG tyypin vasta-aineet viruksen pinta- ja piikkiproteiineja vastaan ylittivät kaikilla urheilijoilla positiivisuuden rajan kolmen kuukauden verinäytteissä. Samoista näytteistä analysoidut, neutraloivien vasta-aineiden pitoisuudet ylittivät positiivisuuden raja-arvon 87 %:lla urheilijoista.

Opinnäytetyön tulokset tukevat aiempaa tietoa urheilijoiden pääosin lievästä COVID-19 taudinkuvasta ja onnistuneesta paluusta harjoitteluun ja kilpailemiseen. Urheilijat kehittävät mitattavan ja positiivisen vasta-ainevasteen COVID-19-infektiota vastaan ja urheilijan rokotevaste vaikuttaa olevan normaali. Tämän opinnäytetyön otoskoko oli pieni ja sisälsi vain yhden lajin urheilijoita, joten tuloksia on syytä tulkita suuntaa antavina. Tulevaisuudessa tulee pyrkiä kehittämään tutkittuun tietoon perustuvia ohjeistuksia harjoitteluun palaamisesta virusinfektioiden jälkeen.

Avainsanat: COVID-19, SARS-CoV-2, Vasta-aineet, Urheilija, Maastohiihto.

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1 INTRODUCTION

The novel coronavirus SARS-CoV-2 has brought a huge challenge to health care systems all over the world. Sport is no exception, and professional leagues, recreational sports and even the Olympic Games have been put on pause or postponed. To date, thousands of studies have been released concerning SARS-CoV-2 and COVID-19 but studies on athletes are still not widely available. In fact, the relationship between viral respiratory infections and athletic performance is still a relatively unexplored area in research, despite their high prevalence.

Acute infections are a major burden to athletes and proper management of infections is one part of long-term success in competitive sports. Acute infections may decrease performance through impaired coordination and body temperature regulation (Schwellnus et al. 2016). Performance may decrease during incubation time and remain at lower levels even after the symptoms are already gone. Viral infections tend to affect performance in many selective ways (Smith 1990). Knowledge of the prevalence, causes and symptoms of respiratory infections is vital in their treatment and prevention.

Despite the fact that efficient antiviral drugs have been developed only for influenza (Waris et al. 2017), and now some promising experiments have been done for SARS-CoV-2 (Smith & Gill 2021), the clinical legitimacy for viral testing on respiratory symptoms comes from the following reasons: the need to decrease antibiotic use (Waris et al. 2017), development of vaccines (Ginocchio & McAdam 2011) and development of new antiviral drugs (Adamson et al. 2021). Virus recognition also gives more information on the symptom profile of different virus diseases (Waris et al. 2017) and thus helps to evaluate optimal forms of treatment. Optimal treatment shortens the time of hospitalization and reduces unnecessary investigations and costs of the treatment (Loeffelholz & Chonmaitree 2010). From an exercise physiology point of view, the clinical importance of recognizing the cause of respiratory symptoms can, in the best scenario, save an athlete's competition event and prevent possible pathogens spreading within the team (Valtonen et al. 2019). An additional benefit for viral pathogen testing in sports is that medical personnel are able to give athletes more specific instructions to manage the respiratory

illness episode. It may be necessary for the athlete to take a few days, or a few weeks, of total rest and it is valuable to know, how this may affect their performance in the acute phase and in the long-term.

The return of sport from the break caused by novel coronavirus includes decision making concerning actions to prevent spreading of SARS-CoV-2 and evaluation of how the chosen actions worked. Return to sports protocols after the corona break seem to work, at least when taking into consideration whether protocols successfully identify acute COVID-19 infections (Shah et al. 2021) and thus prevent spreading of the virus. At least in outdoor sports, spreading of the viruses have been minor between the athletes (England et al. 2021). However, athletes may share the same locker room, travel in same vehicle and to be in same accommodation, and thus, to be at risk to spread the viruses outside the field (Jones et al. 2021).

In indoor sports, more alarming findings have been published. Jang et al. (2020) reported 112 infections in 24 days in fitness dance classes in 12 different facilities in South Korea. Brlek et al. (2020) reported five COVID-19 infections linked to playing squash in Slovenia. In the latter study, the data shows possibility of indirect transmission of the virus by contaminated surfaces or aerosolization. According to more recent studies, the transmission via contaminated surfaces seems to be minor at least with standard cleaning procedures (Mondelli et al. 2021; Pitol & Julian 2021) and the main route of transmission of SARS-CoV-2 to be via respiratory transmission (Meyerowitz et al. 2020).

The break in sport caused by the corona pandemic has also caused disruption to athletes' physical condition. In the Major League Baseball season of 2020, which was dramatically interrupted by corona pandemic, twice as many injuries were recorded compared to seasons 2019 and 2018. This is possibly due to insufficient or irregular preparations prior to the start of the season. (Platt et al. 2021)

In addition to physical challenges concerning COVID-19, athletes may face also psychological and economic challenges as a direct consequence of the corona pandemic. It seems that canceled or postponed major events like the Olympic Games and Paralympic Games might have

an impact in athlete's psychological welfare and create a burden concerning the continuity of their career. An unstable situation and possible changes in everyday life may lead to prolonged distress and have a significant impact on those in low economic status. (Håkansson et al. 2020)

The purpose of this Master's Thesis was to describe symptoms of COVID-19, health, antibody formation, return to sport (RTS) and subjective evaluation of performance in competitive cross-country skiers infected with SARS-CoV-2. The athletes had COVID-19 infection in spring 2020 and the last blood samples and interviews were performed in spring and summer 2021.

2 VIRUSES AND UPPER RESPIRATORY INFECTIONS

Upper respiratory track symptoms are one of the most common reasons to visit medical care in the general population (Finley et al. 2018) and among athletes (Gleeson & Pyne 2016). Research up to this point has often failed to reliably report the cause of respiratory symptoms and use of terms upper respiratory symptoms (URS) and upper respiratory tract infection (URTI), especially in older studies, might mislead the reader on the true cause of the symptoms. Recent research in athletes and in the general population shows that most URTIs are caused by common respiratory viruses (Byington et al. 2015; Tang et al. 2019; Valtonen et al. 2019). The rest of the symptoms are most likely caused by drying of the airways, local inflammation, transmission of cytokines, high amount of pro-inflammatory substances, asthma, allergy, or reactivation of Epstein-Barr virus. (Walsh et al. 2011a)

There is a lot of variation in pathogens detection between studies reporting the cause of URS. Valtonen et al. (2019) reported detected pathogens causing 75 % of the symptomatic upper respiratory illness cases in athletes, Byington et al. (2015) reported that detected pathogens caused 60 % of the symptomatic cases in community study and Tang et al. (2019) reported pathogens causing 30.5 % of the symptoms in patients with fever and influenza-like symptoms. The detection of the pathogens from a sample is dependent on the existent of the pathogens, but also the specimen collection method (Spencer et al 2019), transportation of the sample (Loens et al. 2009) and analyzing methods (Lambert et al. 2008). The amount of the viral material in patient's respiratory tract is influenced by the age of the patient so that in children the viral load is greater than in adults (Waris et al. 2017). Nucleic acid amplification tests (NAATs) are sensitive methods to detect all viruses (Loens et al. 2009) but, for example, Karhu et al. (2014) reported that some commercial polymerase chain reaction (PCR) tests fail to properly detect the most common symptoms causing respiratory virus rhinovirus.

Viral respiratory infections are mostly self-limiting infections known also as the common colds. Respiratory viral infections mostly generate only mild to moderate symptoms (Zoorob et al. 2012) but can generate a wide spectrum of symptoms and severities and can also be fatal in some instances (Leung 2021) like in older people (Jacobs et al. 2013) or when combined with

intense exercise (Schwellnus et al. 2016). The most common symptoms in mild infection include cough, sneezing, sore throat, and nasal discharge (Heikkinen & Järvinen 2003). More severe episodes include symptoms like high fever, neck stiffness and rash (Worrall 2011). The average URTI lasts seven to ten days and symptoms peak during the second and third day. However, symptoms can in some instances last over three weeks. (Heikkinen & Järvinen 2003) Respiratory viruses should disappear in healthy individuals' respiratory tract in a relatively short period, but in patients with immune system alterations, shedding of virus can be prolonged. Shedding of virus in respiratory tract and infection symptoms seems to correlate. (Peltola et al. 2013) However, a person can be already infectious before experiencing any symptom and thus, symptoms can occur with a delay comparing to shedding of the virus (Johansson et al. 2021). Viral pathogen detection in patient, however, does not necessarily mean symptoms, and asymptomatic persons can also spread viruses (Johansson et al. 2021).

Byington et al. (2015) reported that of all viral pathogen detection episodes 56 % were associated with symptoms and Waris et al. (2017) report that viral respiratory pathogens can be found on 60 % of asymptomatic children. It needs also to be remembered that finding pathogens with PCR-testing does not necessarily tell that the pathogens are infectious (Peltola et al. 2013). Finding of multiple viruses in one sample is also possible and may interfere with the interpretation of the result. Several PCR-tests give a cycle threshold (Ct) value that represents the time when the pathogenic material during the test exceeds the available control point (point of positivity). Thus, Ct values represent the amount of viral material in the sample. The full clinical meaning of Ct values is still not known. Some studies show a strong positive correlation between Ct and severity of the symptoms, but the results are contradictory and there are still some questions to answer considering that association. (Waris et al. 2017; Rabaan et al. 2021)

2.1 Most common respiratory viruses

There are several virus clusters that cause most of the upper respiratory infections (table 1). Rhinoviruses are the most common viruses that cause URTIs, causing approximately half of the infections (Jacobs et al. 2013). Seasonal variation can raise the proportion of rhinoviruses even to 80 % of all URTIs (Arruda et al. 1997). Rhinoviruses are most common cause of viral

respiratory infections during the spring, summer, and autumn but in winter months influeza viruses and respiratory syntical viruses cause the most cases (Jacobs et al. 2013). The cause of the infection cannot be known alone by the symptoms because all respiratory viruses can generate similar symptoms (Waris et al. 2017). However, there are some typical findings and small differences between pathogens. Byington et al. (2015) reported that influenza A, human metapneumovirus and coronaviruses HKU1 and OC43 were more frequently reported with symptoms than infections caused by bocavirus and rhinovirus, and bronchiolitis caused by respiratory syntical virus, tonsillitis caused by adenovirus and laryngitis caused by parainfluenza are examples of typical findings in URTIs (Waris et al. 2017).

Neither differentiation of virus subtypes nor the multiple virus findings in one sample are clinically meaningful (Waris et al. 2017), but in future if new antivirals are developed, differentiation of the predominant virus in the sample might be useful (Heikkinen & Järvinen 2003). In those cases, defining the Ct values of the samples might be helpful to differentiate the predominant virus, because it seems that viruses tend to act differently in coinfections (Martin et al. 2011). For those virus clusters with high volume of subtypes makes it more difficult or even impossible to develop effective antiviral drug or vaccine (McLean 2014). Rhinovirus, with over three different species and more than 167 subtypes, is one good example of that (Jacobs et al. 2013). More recently found viruses like bocavirus and humanmetapneumovirus reminds also that new pathogens might yet to be found and regular identifications of viruses in patients is necessary (Heikkinen & Järvinen 2003; Jartti et al. 2008).

TABLE1. Incidence of different virus clusters causing illness episodes in different articles. Studies that present 100 % sums are describing a specific virus clusters' presence in all positive samples. Other studies describe a specific virus clusters' presence in all symptomatic cases.

Article	Mäkelä et al. (1998)	Heikkinen & Järvinen (2003) *review*	Byington et al. (2015)	Spence et al. (2007)	Valtonen et al. (2019)	Valtonen et al. (2021)
Data collection	October 1994 – November 1995	Multiple	August 2009– August 2010	December - April	January – February 2018	February – March 2019
Country	Finland	Multiple	United states	Australia	South Korea	Austria
Subjects	Students at university of Turku	Multiple variety	University of Utah campus community	Elite triathletes and cyclists, recreationally competitive and sedentary controls	Nordic sports athletes and team staff members	Nordic sports athletes and their team staff members, and controls
Rhinoviruses	52.5 %	30–50 %	53.1 %	16 %	5 %	42 %
Coronaviruses	8.5 %	10–15 %	13.8 %	-	36 %	37 %
Influenza viruses	6 %	5–15 %	6 %	-	14 %	-
Adenoviruses	1 %	< 5 %	1.3 %	5 %	-	-
Metapneumoviruses	-	Unknown	1.5 %	-	12 %	-
Parainfluenzaviruses	3.5 %	5 %	2.2 %	3 %	-	-
Bokaviruses	-	-	19.3 %	-	-	5 %
Respiratory syntical viruses	2 %	5 %	2.2 %	-	14 %	16 %
Enteroviruses	0.5 %	< 5 %	0.6 %	-	-	-

Viruses also have slightly different shedding times and differ from each other regarding the optimal specimen type for viral testing. Viral shedding is the highest within the first two days and decreases after that. Investigation of the optimal specimen type and viral shedding gives the possibility to optimally detect the viral pathogens from respiratory tract. (Memish et al.

2014) Interestingly, Lambert et al. (2008) found that the collection of the sample from the onset of symptoms was not meaningful to the positivity of the sample, but delay of two or more days in analyzing of the sample did decrease the rate of positivity of the sample (table 2). (Lambert et al. 2008) It seems that the form of the virus's genetic material has impact on the shedding so that RNA viruses have usually quite short (one to two weeks) shedding, whereas DNA virus shedding times seem to vary a bit more (Peltola et al. 2013).

TABLE 2. Swab positivity for any virus by delay from onset to collection, and collection to testing (Lambert et al. 2008).

Delay from onset of ARI to specimen collection (days)	Delay from specimen collection to test (days)			
	≤ 1	2	≥ 3	Total
≤ 1	41/58 (71 %)	40/53 (75 %)	48/61 (79 %)	129/172 (75 %)
2–3	45/60 (75 %)	47/63 (75 %)	39/57 (68 %)	131/180 (73 %)
4–5	25/34 (74 %)	15/22 (68 %)	31/40 (78 %)	71/96 (74 %)
≥ 6	35/45 (78 %)	20/32 (63 %)	23/38 (61 %)	78/115 (68 %)
Total	146/197 (74 %)	122/170 (72 %)	141/196 (72 %)	409/563 (73 %)

Respiratory specimens from the nasopharynx have been considered the most sensitive method to identify viral pathogens in influenza patients (Spencer et al. 2019) but in general, nasopharyngeal aspirate is held as the optimal specimen type for virus detection especially with only rapid tests available (Loens et al. 2009). The high sensitivity nucleic acid amplification tests, like PCR, enable less invasive and easier methods to be applied in detection of all viruses (Loens et al. 2009). From a clinical perspective, a combination of several less invasive methods (like nasal and throat swabs) can possibly replace more invasive methods and give an optional method to collect samples with reliable results. (Spencer et al. 2019)

2.2 Consequences of infection and recovery

Because respiratory viral infections are mostly self-limiting illnesses, most of the cases do not need health care, and the majority of cases thus stay out of normal health care calculations of prevalence of respiratory infections (Middeldorp et al. 2020). The same phenomenon has been reported during the COVID19 pandemic (Caini et al. 2020). The COVID-19 pandemic has increased the official numbers of respiratory infection cases in Finland (THL 2021). However, making direct conclusions about the absolute number of respiratory illnesses by numbers reported via health care is not meaningful, at least during pandemic, because pathogen testing is concentrated to SARS-CoV-2 testing and not for other viruses. Recommendations in mild URS cases were at some point in Finland to stay home because testing was overburdened. Social distancing as well as other actions to prevent spreading of the SARS-CoV-2 has also impacted the spreading of other viruses (Solomon et al. 2020).

During mild acute respiratory infections, the recommendation for individuals in general, is to stay home and thus to prevent spreading of the pathogens to others and to rest (Purushothama & Chien 1996). Staying isolated immediately from the onset of the first symptoms at least until the reduction of the symptoms is justified because the infectiousness is at its highest usually on the first day of symptoms but can already peak a few days before the of the first symptoms onset (He et al. 2020). In addition to the individual level, acute respiratory infections make up a considerable portion of work absenteeism and influence on-the-job productivity and thus effectiveness of work and creates significant economic burden to organizations and countries (Bramley et al. 2002). During the COVID-19 pandemic the true national and global meaning of that has been made clear.

Acute respiratory illnesses caused absences from work in 14 % of the illness episodes in the study of Middeldorp et al. (2020). In these cases, the employees missed on average 19 hours of work per illness episodes and self-estimated work efficacy tend to be a bit lower during illness episode. (Middeldorp et al. 2020) Palmer et al. (2010) reported that in cases where a person was absent from work due to illness episode, the efficacy of their work was declined even after recovery from the illness. In addition to the individual's own illness, the respiratory illness of a

child or other member of the same household affects the presence of the individual in work (Palmer et al. 2010).

The clinical symptom descriptions of most mild to moderate viral respiratory infections are similar, but the incubation time between different viruses varies from under one day to a week. Symptoms tend to decrease two to three days after the start of the symptoms. Because there are several different viral clusters that can cause respiratory infections and lack of efficient antivirals, managing of typical respiratory viral infection concentrates on managing the symptoms like nasal congestion, fever, and cough. In some cases, viral infections can predispose to bacterial infections and dramatically change the direction of the illness episode and prolong healing. Asthma and other respiratory medical conditions can exacerbate the course of respiratory viral infection. (Heikkinen & Järvinen 2003)

Some viruses tend to stay in human organs and to stay inactive until reactivation. Epstein-Barr virus is one of these viruses and reactivation of the virus has presented to explain a portion of the respiratory symptoms reported in follow-up studies (Walsh et al 2011a). However, the role of the Epstein-Barr virus reactivation in respiratory illness episodes is contradictory. Cox et al. (2004) reported patients with a former Epstein-Barr episode to have same number of respiratory illness episodes in the follow up than patients without a former episode. Besides long-term effects of some viruses via reactivation, it is possible that viruses may cause permanent symptoms via complications like development of asthma following viral respiratory infections (Achten et al. 2022).

2.3 Prevention of respiratory illnesses

Spreading of viruses generally happens via four mechanisms: direct or indirect contact, by large droplets or by small aerosols in the air. Viruses differ from each other in their most effective spreading route and transmissibility. (Heikkinen & Järvinen 2003; Leung 2021) Good hand hygiene, avoiding of crowded places and infected people, avoiding nutrient deficiencies and excess stress, good sleep quality and quantity (Walsh et al. 2011a) and vaccination (Vos et al. 2020) are ways to avoid URTIs.

Prevention of illness episodes and infections lies mostly on these behavioral actions, but additional benefits can be gained with use of vitamin D and C. The usefulness of other preventive means lacks good quality proof. (Short et al. 2017) It is also good to remember that there might not be any additional benefits from vitamin D supplementation if person does not already suffer from a deficiency (Scullion et al. 2019).

2.4 Immune response and antibodies

The immune system is an organism's defense system against the broad and constantly evolving spectrum of different pathogenic microbes, allergenics and toxins trying to enter the host, for example, via mucosal surfaces. The immune system has highly sensitive mechanisms to differentiate its own particles from non-self-particles, which is key to its proper function. The mammalian immune system can be separated into two mechanisms which detect and eliminate pathogenic microbes: innate and adaptive immunity. These systems are tightly connected to each other to create functional immune responses. The innate system is fast and non-specific including features supporting epithelial health and cleaning, and proteins and molecules responsible of cytokine and chemokine excretion. Adaptive immunity is a highly specific system built to respond to specific, known threats, and it includes mostly T-cells and B-cells. Antibody responses are induced by B-cells, with the help of T-helper cells, and are thus part of adaptive immunity. (Chaplin 2010)

Both innate and adaptive immunity use a model of recognizing the non-self-particle's structural feature to differentiate it from their own cells. The first line of defense of the immune system is normally the innate immune system. It has a large number of cells with broad recognition of pathogenic microbes and thus, is able to act immediately. The adaptive immune system includes a small number of cells specific to individual pathogens. That means that the specific cells must

proliferate to actuate a proper response to the pathogens, and for that reason the adaptive immune system usually presents the latter phase of immune response. (Chaplin 2010)

Antibodies, also known as immunoglobulins (Ig) are proteins that function as a part of the immune system. Antibodies serve mostly two different purposes: recognizing and neutralizing pathogens or recognizing pathogens and activation of other immunological cascades. Antibodies can be classified into five different isotypes: IgM, IgG, IgA, IgD and IgE. IgG antibodies are the most investigated, most prevalent and longest-lasting isotype of antibodies. IgG isotypes antibodies participate in both complementary cascade activation and to direct immune responses by neutralizing pathogens. (Schroeder & Cavacini 2010) Antibodies can be used to evaluate patients immunocompetence and ability to stand against reinfections by the same specific pathogens (Khoury et al. 2021).

Antibodies' ability to activate complementary systems and the effect of the whole immunological cascade might not always be positive phenomenon. Newton et al. (2016) reported that the host's immune system response might be responsible for the most injury incurred from the viral infection rather than the injury presented by the proliferation of the pathogens. Interindividual differences like high cytokine expression (Gleeson et al. 2017) and deficits in IgG isotype concentrations (Popa et al. 1993) might also affect susceptibility to infections and the severity of them. Regular, at least moderate physical activity is associated with decreased risk of community-acquired infectious diseases by 31 % and decreased mortality to infectious diseases by 37 %. Physical activity strengthens the first line defense systems of the immune system via better mucosal immune response and higher CD4 T-cell concentration. Regular physical activity can also enhance the effect of vaccines. (Chastin et al. 2021)

Antibody detection is traditionally done via serum samples but can be done also by saliva samples. The clinical meaning of antibody detection in acute infection is questionable because there are other better ways (like NAAT) to detect acute viral pathogens from a patient, and the detection of antibodies onset of acute infection might be difficult. IgG antibody detection does not affect a patient's acute management, so the purpose of antibody testing is based mostly on vaccine efficacy control and epidemiological surveys. (Loeffelholz & Chonmaitree 2010) In recent

antibody test research Shibata et al. (2020) reported that for the SARS-CoV-2 antibody tests, there might be high incidence of false positive results due to possible cross-antigenity with human common cold coronaviruses. This might have been due to a past coronavirus episode, but this sort of cross reactivity is potentially one limitation to immunoassays and effects their reliability. (Shibata et al. 2020)

3 VIRUSES AND UPPER RESPIRATORY SYMPTOMS IN ATHLETES

Athletes in general do not differ from the normal population in the number of the causative agents of respiratory symptoms during a calendar year (Walsh et al. 2011a). However, URSs in athletes seems to concentrate in the pre-competition season, competition season and during competitions. That is why athletes should pay a special attention in previously mentioned strategies to avoid infections during those times. (Walsh et al. 2011a; Svendsen et al. 2016) Svendsen et al. (2016) reported that URS tend to appear after competitions but not after competition-like trainings in cross-country skiers. Thus, it seems that illness episodes could be more likely to appear due to other factors related to competitions, like increase of social contacts and psychological stress (Svendsen 2016; Campbell & Turner 2018; Walsh 2018) than the physical performance itself. However, it remains under debate whether very high level of physical activity or elite sports itself alters to higher risk of URS (Simpson et al. 2020).

Wide spread of competitions around the world usually means a lot of air traveling. Intercontinental air traveling is one recognized risk factor for athlete to be exposed to infections (Svendsen et al. 2016). Proper management on training load should also be focused on athletes to avoid infections (Schwellnus et al. 2016). These factors combined with psychological stress seems to be a mixture of factors that predispose athletes to infections (Walsh et al. 2011a). However, research methods differ broadly between studies and number of good quality studies on athletic population is still small (Derman et al. 2022). Additionally, research often lacks a long-term design.

A classical presentation between URTI and physical activity is a Nieman's (1994) J-shaped curve that presents association between low activity and increased risk of URTI compared to moderate activity level. In that model, high physical activity like elite sports is presented even higher risk to URTIs than low activity. Malm (2006) has suggested that the curve should continue and generate a shape of letter S. In this model high physical activity is still presented as high risk of URTIs but the very top of elite sports is separated to have a lower prevalence of URTIs (figure 1). Svendsen et al. (2016) reported less symptomatic days on the top athletes than other athletes and Hellard et al. (2015) reported less URTI episodes on top athletes. This

exception could be explained by better function of the immune system on top athletes (Malm 2006) and better choices in daily life, better life and training load control and better hygiene practices (Walsh et al. 2011b).

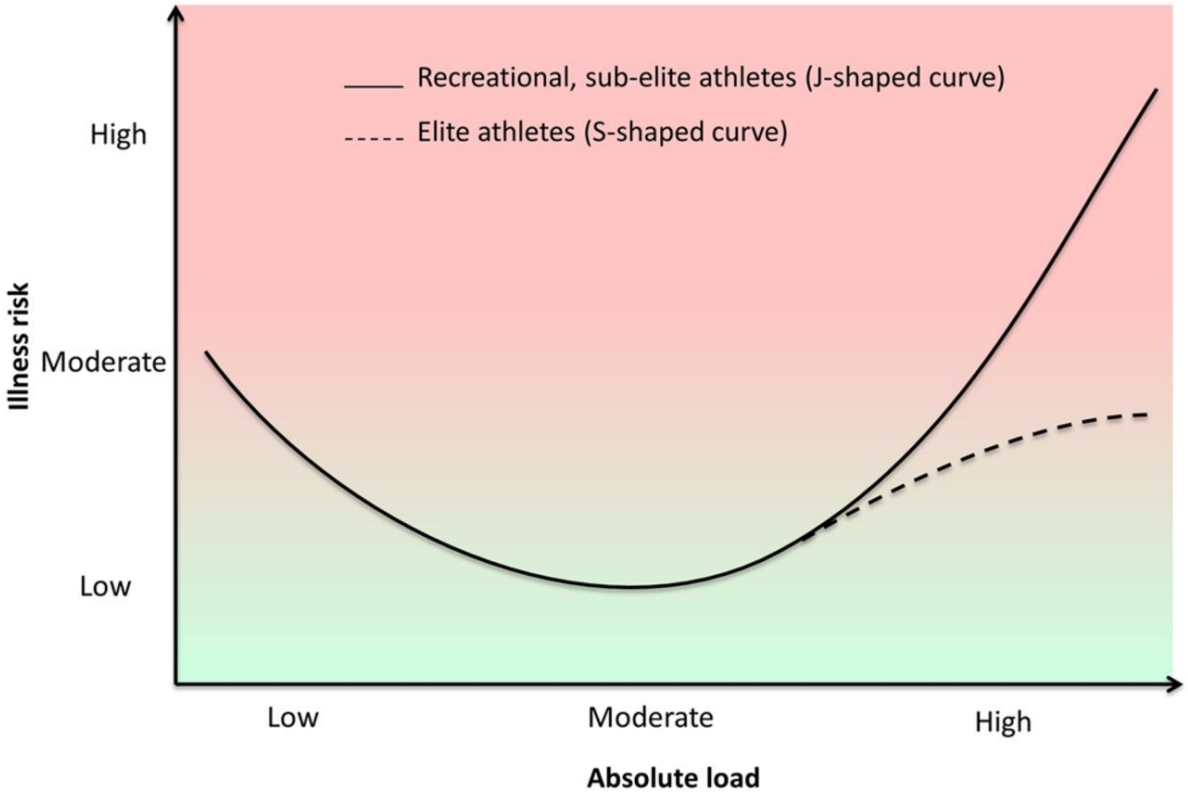

FIGURE 1. Traditional J-shaped curve and additional S-shaped curve (dashed line) on exercise intensity and risk of illness (Schwellnus et al. 2016).

A small number of athletes are reported to experience recurrent URS. Recognizing of these cases and proper evaluation of the health status is needed. Recurrent URS might be due un-treated asthma or allergy or imbalance in their treatment. Life and training load management should also be considered on athletes with recurrent URS. (Gleeson & Pyne 2016) Some sports disciplines predispose athletes to greater amount of allergenic and cold air and expose athletes to allergenic or exercise induced rhinitis. This on the other hand might impair performance and recovery and expose to a greater risk to develop asthma. (Gałązka-Franta et al. 2016)

3.1 Endurance athletes and cross-country skiers

Although athletes in general seem to have same amount of URS episodes during a year, some sports disciplines might be more prone to respiratory symptoms and infections. Cox et al. (2004) reported a slightly increased URS episodes in elite distance runners compared to the general population, but the study period was only four months long and does not necessarily represent the annual appearance of URS. The study group discussed that more frequent URSs in elite runners might be due to excessive breathing and drying of the airways. (Cox et al. 2004)

Prevalence of URS seems to be higher in events during winter season (Schwellnus et al. 2016). Valtonen et al. (2019) and Svendsen et al. (2015) reported high prevalence of URS in elite cross-country skiers during and after major competitive event. Valtonen et al. (2019) reported that 71 % of the Finnish skiers experienced URS in 2018 winter Olympics but only one athlete needed to skip a single competition. Svendsen et al. (2015) reported 48 % of the Norwegian skiers participated into the Tour de Ski experienced URS during or within 10 days of the event.

Temperature developed acute stress might be greater in athletes with low or high temperature sports discipline, but it seems not to be a risk factor of immune suppression with clinical consequences. It is still unsure how long-term exposure to cold air affects the epithelia of the airways (Walsh et al. 2011b), but Kennedy et al. (2016) reported increased inflammation of respiratory tract and cough during winter months in female skiers, while Boulet and O'Byrne (2015) reported winter sport athletes' respiratory tract to be more sensitive than in population generally. Lennelov et al. (2019) reported 23 % of young Swedish skiers to have asthma and Mäki-Heikkilä et al. (2020) reported 26 % of the Finnish skiers to have asthma, which is greater number than in the general Finnish population. Interestingly the prevalence of asthma in Mäki-Heikkilä's et al. (2020) study was greater in the most successful quartile with 56 % of those skiers having asthma.

3.2 Recovery from infection and return to sport

Viral infections can cause multiple variations of symptoms and symptom durations and thus, making simple universal guidelines to return to sport is impossible and unmeaningful. Viral respiratory infections usually take no more than a day to return to training in athletes (Snyders et al. 2021) and short viral shedding times are reported (Valtonen et al. 2021), but on the other hand, infection can also in some instances influence the whole season or career as seen during COVID-19 pandemic. Consideration of return to training in respiratory illnesses is based mostly on the symptom's region and severity. Traditional neck check, which take in consideration whether the symptoms are superior or below neck level, is a widely used method, but the scientific evidence behind it is missing. (Derman et al. 2022)

Strenuous exercise during respiratory infection or fever may be hazardous and can lead into serious health complications (Frieman & Wesslén 2000; Derman et al. 2022). Current data is limited and more information on athletes' illnesses and infection is needed to develop evidence-based guidelines for return to sport. One of the most vital gaps in the knowledge of athletes' illnesses is the cause of the symptoms. Snyders et al. (2021) highlights in their systematic review the need of pathogen specific data on respiratory infections.

4 SARS-COV-2

Novel coronavirus SARS-CoV-2, the virus causing COVID-19 infections, started to spread in late 2019 from Wuhan, China. The new virus was localized strongly with local seafood market (Chen et al. 2020) and is assumed to be zoonotic origin with natural selection in animal host before transfer in humans or natural selection in human following zoonotic transfer (Andersen et al. 2020). The SARS-CoV-2 is one addition to SARS-CoV and MERS on coronaviruses that can cause severe disease in humans. The other four coronaviruses (HCoV-NL63, -229E, -OC43 and -HKU1) that are known to infect humans cause only mild infections. (Corman et al. 2018) Spreading of the virus was quick and during early 2020 the World Health Organization (WHO) classified the disease as a pandemic. While writing on this master's thesis over half a billion cases are confirmed around the world and over 6 million deaths are confirmed relating SARS-CoV-2. (WHO 2022)

Dominant transmission of SARS-CoV-2 is via respiratory transmission with intensity of ventilation and proximity to infectiousness person playing major role in the risk of transmission. Infectiousness of people seems to vary so that most of the people does not infect the virus to others whereas some individuals cause multiple secondary infections. Infectiousness seems to be highest the day before symptoms onset and to decline within a week of the beginning of the symptoms. (Meyerowitz et al. 2020) All over the world actions against transmission of the virus have been put in place to suppress the pandemic. The most crucial actions include good hand hygiene, avoiding mucous membrane touching and use of facial masks (Ma et al. 2020), social distancing (Cowling et al. 2020; Nouvellet et al. 2021), testing to recognize the cases, isolating the cases and contacts and border entry restrictions (Cowling et al. 2020).

Symptoms of acute COVID-19 infections include fever, cough, diarrhea, vomiting (Larsen et al. 2020) and myalgia (Robbiani et al. 2020). COVID-19 has some symptoms in common with other human coronaviruses, and it is notable that COVID-19 acute infections can be more likely to include fever at first symptom than other infective respiratory viruses like influenza. Another feature that might be helpful of distinguish SARS-CoV-2 from other viruses like SARS-CoV or MERS is diarrhea. (Larsen et al. 2020) One must keep in mind that all respiratory viruses

tend to degenerate same kind of symptoms and distinguishing of viruses via only symptoms is not effective nor precise (Waris et al. 2017).

4.1 Long-term effects

According to NICE (National Institute for Health and Care Excellence) guidelines for long-COVID, a patient with symptoms still after 4 – 12 weeks from the start of the acute symptoms is classified as an ongoing COVID-19 infection and a patient with symptoms after 12 weeks is classified as a postacute-COVID-19-syndrome case (Venkatesan 2021). A Norwegian study by Blomberg et al. (2021) reported that over half of the home-isolated young adults with mild infection experienced symptoms after 6 months of the infection. Symptoms included taste or smell changes, fatigue, dyspnea, and cognitive issues. "The high prevalence of persistent fatigue in patients with COVID-19 is striking and appears higher than observed after common infections, such as influenza, Epstein–Barr virus mononucleosis and dengue" (Blomberg et al. 2021). Long lasting symptoms of hospitalized patients are known to be common (Carfi et al. 2020; Sykes et al 2021), but more data is needed to identify the possible nature of long-COVID in patients with mild acute COVID-19 infection (Blomberg et al. 2021). Symptoms of long-COVID or post-COVID-19-syndrome can include at least chronic cough, chest sensations, shortness of breath, cognitive problems, and fatigue (Venkatesan 2021). Long lasting symptoms seem to be more common in female patients (Blomberg et al. 2021; Sykes et al. 2021). It is possible that residual symptoms could be partially explained by biopsychosocial factors linked to new and poorly understood disease (Sykes et al. 2021). The possibility for a person to create long-COVID is still not well understood but there is evidence that a severity of acute COVID-19 infection can be one predictive factor (Sudre et al. 2020).

None of the athletes with acute or prior COVID-19 infection reported recurrent symptoms in Shah et al. (2021) study following the returning to training. Also, symptoms considering cardiovascular problems were not found from the athletes at any point. However, in this study cardiac MRI was not used to detect abnormalities of the heart and due to a low case number of COVID-19 infections this study may not be optimal to consider the possible health issues following COVID-19 infection in athletes.

4.2 Immune response and antibodies for COVID-19

According to Shirin et al. (2020) IgG type antibodies against SARS-CoV-2 antigens are recorded in all cases including mild symptoms, but only in 45 % of asymptomatic cases. Krzywański et al. (2022) reported that 88 % of athletes develop symptoms in COVID-19. Antibody formation seems to correlate well with the severity of symptoms so that more severe infection seems to lead into higher amounts of antibodies (Marklund et al. 2020; Krzywański et la. 2022), and severity of COVID-19 seems to correlate with more rapid antibody formation (Marklund et al. 2020). Highest concentration of IgG and IgA antibodies against SARS-CoV-2 are recorded within three to four weeks of infection and IgM antibodies are measurable within five to seven days symptoms onset (figure 2) (Denning et al. 2020).

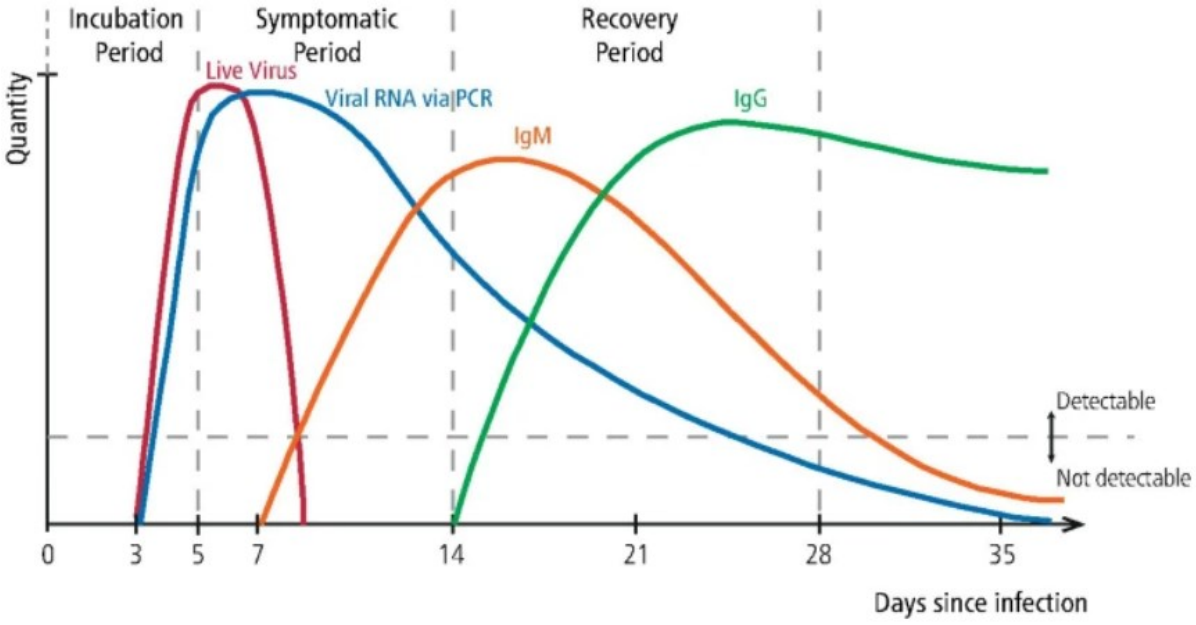

FIGURE 2. Persistence of antibody isotypes and presence of living virus and PCR testing (Denning et al. 2020).

COVID-19 was recognized, at the beginning, as a specific respiratory disease, but further observations and studies revealed the role of SARS-CoV-2's receptor binding domain (RBD) spike (S) protein feature to bind in hosts angiotensin-converting enzyme 2 (ACE2) and thus,

the ability of SARS-CoV-2 to cause multiorgan disorders (Lopes-Pacheco et al. 2021). Neutralizing antibodies (NAb) against SARS-CoV-2 aim to interfere of the binding of SARS-CoV-2's S-protein to the hosts ACE2. NAb levels are thus a recognized marker of protection against SARS-CoV-2. NAbs are reported to persist in most individuals at least half year after infection. IgG1 and IgA type antibodies are suggested to mostly mediate the neutralizing activity against SARS-CoV-2, but only IgG type antibodies are relevant in long-term protection against the disease and thus, are more relevant in serological studies. (Haveri et al. 2021)

4.3 Consideration for athletes

The most obvious considerations include the predominant hygiene habits presented earlier to avoid the possibility exposure, taking vaccines to avoid the illness or at least the more severe disease, and arranging everyday life together with sports to manage the total amount of stressors and stress. More specific considerations include applying safety protocols even in outdoor training, although some studies have reported that in outdoor sports spreading of the SARS-CoV-2, even in contact sports (Jones et al. 2021), is most likely low (England et al. 2021).

Return to sports should happen with caution and possible alterations to performance and coordination should take into consideration. For example, Crameri et al. (2020) reported a significant decrease in aerobic performance in subjects with symptomatic COVID-19 infection after two months onset of the infection. Strength abilities were remained despite COVID-19 infection. (Crameri et al. 2020). Reduction of aerobic performance is visible even without infection no matter what causes the detraining, and already two to four weeks of continuous detraining can impair aerobic performance significantly (Neufer 1989; Sousa et al. 2019). So, acknowledgement of the possibility of overloading post infection should be in athlete's and supporting teams' minds while returning to training.

5 RESEARCH QUESTIONS AND HYPOTESIS

The purpose of this thesis was to describe the symptoms and severity of SARS-CoV-2 caused COVID-19 in competitive cross-country skiers, and to observe possible long-term effects and antibody formation. Blood samples were collected two times after infection to observe the antibody response of the athletes.

Research question 1: How severe is athletes' COVID-19 and are athletes able to return training and competitions without any additional or long-term symptoms?

Hypothesis 1: Athletes COVID-19 infections are mostly mild and return to training happens without any major trouble. Multiple previous research show that an athlete's infection of SARS-CoV-2 is mostly mild (Costello et al. 2022; Hull et al. 2022; Krzywański et al. 2022) and return to training is successful. However, some athletes might experience long lasting or long-term symptoms (Hull et al. 2022; Krzywański et al. 2022).

Research question 2: Do athletes produce measurable antibody responses after COVID-19 infection, is antibody response related to training before infection, and does athletes' antibody response somehow differ from nonathletes' response?

Hypothesis 2: Athletes produce a measurable antibody response, and it does not differ from antibody responses measured from nonathletic population. Krzywański et al. (2022) reported that most athletes degenerate measurable antibody response to SARS-CoV-2 infection and Grande et al. 2020 concluded that exercise do not have influence in number of illness episode or symptom days, nor blood markers related to immune function, but might be beneficial in lowering the severity of illness. Knowing, that severity of illness is one indicator of the antibody formation (Marklund et al. 2020; Krzywański et la. 2022), it could be possible that athletes produce less antibodies than inactive and sedentary people. Training before vaccines has been reported to be beneficial for antibody formation (Whitham & Blannin 2003) and thus training before infection could in theory work in the same way. However, evidence of that is still missing. Even so, it is clear that habitual as well as one single bout of acute exercise, excluding

exercise with extreme intensity or prolonged duration, improves immunity pathways (Nieman & Wentz 2019).

6 METHODS

Data of this thesis was collected from 15 national and international level cross-country skiers exposed to and later infected with SARS-CoV-2 in spring 2020. All athletes had symptoms after exposure and 11 of the athletes were tested with PCR-test in local health care. The remaining, four athletes were not tested in the acute phase of the disease in accordance with the recommendations of the national and regional testing protocols that were based partially on the severity of the symptoms. Nine of the PCR tests were positive, but since the clear exposure and symptoms after exposure were present, diagnoses of COVID-19 were done, like normally in that time, and all athletes despite negative PCR-test result or not testing at all were included in the data collection. Data collection was performed under the Communicable Diseases Act 1227/2016 (2016).

6.1 Interviews

All athletes were interviewed two and 13 months after symptoms onset. Athletes were interviewed at two months by two different physicians. The physicians had same prescheduled interview protocol which aimed to get answers regarding the following: symptoms of the acute phase of the infection, severity of the symptoms (excluding alterations in palate and/or sense of smell, fever and diarrhoea), durations of the symptoms (those that excluded from the severity), date of birth, sex, chronic illnesses, non-prescription medical treatments, annual training hours (2019–2020), annual high intensity training percent, exposure date, first symptom day, result of the PCR-test, used medication for the infection, training hours of the week before first symptomatic day, high intensity training week before first symptomatic day, first training day after first symptoms onset and evaluation of the first day without symptoms.

The second interview, at 13 months after symptoms onset, was aimed to collect information about health status of the athletes regarding the past year after COVID-19 infection via prescheduled questions. Following questions were asked: How would you describe your health at the moment on scale 1–5 (1 = bad, 5 = excellent)? Have you had any changes in your health status or medication after the first interview? How many respiratory symptom episodes have

you had after the first interview? Have you still ongoing, continuous, symptoms after the COVID-19 infection? What was the number of training hours of the past season (2020-2021)? How would you describe your training at the past season on scale 1–5 (1 = did not go as planned, 5 = succeeded in line with objectives)? Did you compete at the past season? How would you describe your performances in competitions in the past season on scale 1–5 (1 = did not go as planned, 5 = succeeded in line with objectives)? Are you satisfied with your performance, if not why?

6.2 Serum samples and antibodies

Blood samples were collected from all the athletes after the first possible day after the first interview. The second blood samples were collected from 15 athletes after the first possible day after the second interview. After the second blood sample collection athletes were asked if they had received SARS-CoV-2 vaccinations, and which vaccination they have received. Serum was separated from the plasma after the collection of the blood samples. All serum samples were sent to be analysed at The Finnish Institute of Health and Welfare (THL), with their in-house fluorescent multiplex immunoassay (FMIA) developed to simultaneously recognize antibodies against SARS-CoV-2 nucleoprotein and spike glycoprotein. The method is fully described in the Solastie et al. (2021) article. Briefly: SARS-CoV-2 RBD (product codes REC31849), SFL (REC31868), and N (REC31812; Native Antigen Company, Oxford, United Kingdom) antigens were conjugated on the surfaces of MagPlex-C superparamagnetic carboxylated microspheres by carbodiimide reaction. The microspheres were added onto black 96-well plates with diluted sera and reference and control samples and incubated at room temperature with shaking at 600 rpm in the dark for 1 h. The unbound particles were washed away with a magnetic plate and R-phycoerythrin-conjugated AffiniPure goat anti-human IgG, IgA, or IgM Fcγ fragment-specific detection antibodies (Jackson ImmunoResearch, Cambridge, United Kingdom) were added to the wells. The plates were incubated for 30 min and then washed again. The median fluorescence intensity (MFI) was measured with the MAGPIX system (Luminex). MFI values were automatically converted into antibody concentration (FMIA U/mL) via interpolation from 5-parameter logistic curves created from serially diluted (1:400 to 1:1,638,400) in-house reference serum. The 1:400 dilution of the standard was given an arbitrary concentration of 100 FMIA U/mL. (Solastie et al. 2021) Sample was considered positive for anti-S antibodies when

concentrations were ≥ 0,388 and ≥ 0,712 (FMIA U/ml) for SFL and RBD respectively. On natural infections without vaccination the sample was considered positive for anti-N antibodies when the concentration was ≥ 1,71 (FMIA U/ml). The MNT-titres were also done by THL with the method fully described in Solastie et al. (2021) study. Briefly described: "…the MNT was performed using Vero E6 cells and true duplicates of sera diluted serially from 1:4. After 4 days the cells were fixed with 30 % formaldehyde, and the cytopathic effect (CPE) was measured. The viral strains used were hCoV-19/Finland/1/2020 (FIN-1) (GISAID accession ID EPI_ISL_407079) and hCoV-19/Finland/FIN-25/2020 (FIN-25) (GISAID accession ID EPI_ISL_412971) in the analysis of positive- and negative-serum panels. A sample was considered positive when the NAb titer was ≥ 6 for at least one virus and negative when titers for both viruses were < 4. A sample was considered borderline if its highest titer was 4. Negative samples were given a titer value of 2 for statistical analyses. In cases where the titers of the two viruses differed, the titer of the sample was defined as the highest of the two." (Solastie et al. 2021) FMIA has reported to be highly sensitive for anti-spike IgG antibodies (100% specificity and sensitivity for samples collected 13 to 150 days post onset of symptoms, DPO) and for anti-nucleoprotein IgG antibodies (100% specificity and 98 % sensitivity for samples collected 52 to 150 DPO) (Solastie et al. 2021).

6.3 Statistics

All data was collected into a spreadsheet program (Microsoft Excel for Office 365 MSO, Microsoft Corporation, Redmond, Washington, US). Data analyses were performed with the spreadsheet program and with SPSS-program (IBM SPSS Statistics, versio 26.0, IBM Corporation, Armonk, New York, US). On the chronic illnesses only asthma and seasonal allergy was included in the analysis. All unclear answers to the questions at the interviews and questions that athletes could not answer were set as blank. Data was handled as abnormally distributed due to the small sample size.

Related-samples Wilcoxon signed rank test was used to identify possible change in IgG antibodies from 3 months to 14.5 months on those who had not got vaccinated or did not present over 30 % elevation in any IgG antibodies in line with study of Haveri et al. (2021). Differences

between independent samples were analysed by Mann Whitney U-test. Associations between incubation time, symptoms (acute and long-term), antibodies and subjective evaluation of performance and training on the season following COVID-19 were searched and identified by Spearman's correlation test. With antibodies, possible outliers were also identified, and correlation tests were done also with the exclusion of the outliers. Exclusion criteria was set to values outside mean ± 2*SD, which is widely used in studies (Berger & Kiefer 2021). In all tests level of significance was set to $p < 0,05$.

7 RESULTS

Data analyses include 15 cross-country skiers (8 woman and 7 men) with average age of 24.3 years (table 3). Eight athletes had asthma and three athletes had seasonal allergies. All athletes were interviewed the first time two months after the symptoms onset (June 2020) and the second time 13 months after the symptoms onset (April 2021). Blood samples were collected on average with 86 ± 14 days (n = 15) and 436 ± 6 days (n = 11) days after the symptom's onset. Four athletes got their first vaccine dose (Comirnaty, Pfizer-BionTech) (mean 28 days, range 23-39) before the second serum sample collection. None of the athletes reported to have a recurrent SARS-CoV-2 infection before the second serum sample.

TABLE 3. Basic characteristics of the athletes and their training of the week before the COVID-19 infection.

	N	Mean	SD	Range
Age (years)	15	24.3	4.8	19–35
Annual training hours (2019–2020)	15	645	165	200–900
Annual training hours (2020–2021)	15	688	160	300–940
Training hours week before infection	13	13.2	5.8	6–25
Intensive training week before infection (YES)	10 out of 13	-	-	-

All athletes had mild symptoms and none of the athletes required hospital care. Symptoms lasted on average 10 ± 7 days (range 3–30). Mean severity of the symptoms (excluding alterations on sense of taste and/or sense of smell, fever and diarrhoea) were 1.6 ± 0.5 on scale one to three, and athletes had on average 5 (range 1–8) different symptoms. Eleven athletes were treated with nonsteroidal anti-inflammatory drug or/and paracetamol, three athletes increased the dosage of inhalable corticosteroids or beta2-agonists (related to asthma treatment), three

athletes used decongestants and one athlete was treated with antibiotics. Having non-prescription medical treatments did not have significant impact on the severity, duration, or number of symptoms. Most common symptoms were alterations of palate and/or sense of smell, abnormal fatigue, muscle soreness, runny nose or nasal congestion, fever (≥ 37.5 C˚) and headache (table 4).

TABLE 4. Symptoms of the acute phase of SARS-CoV-2 infection. Alterations of the palate and/or sense of smell, fever (≥ 37.5 C˚) and diarrhoea are presented as days and other symptoms as a severity on scale 1–3.

Symptom	N	%	Mean duration	Range	Mean severity (1–3)	SD	Range
Alterations of sense of taste and/or sense of smell	13	87	12	7–21	-	-	-
Abnormal fatigue	12	80	-	-	1.8	0.62	1–3
Muscle soreness	9	60	-	-	1.7	0.71	1–3
Runny nose or nasal congestion	8	53	-	-	1.4	0.52	1–2
Fever (≥ 37.5 C˚)	8	53	5	2–11	-	-	-
Headache	7	47	-	-	2.0	1.00	1–3
Chest sensation	4	27	-	-	1.0	-	1
Cough	3	20	-	-	1.3	0.58	1–2
Sore throat	3	20	-	-	1.0	-	1
Skin sensitivity	2	13	-	-	2.5	0.71	2–3
Eye sensation/pain	2	13	-	-	2.0	-	2
Joint ache	2	13	-	-	2.0	-	2
Vomiting	1	7	-	-	2.0	-	2
Diarrhoea	1	7	7	-	-	-	-
Dizziness	1	7	-	-	2.0	-	2
Sneezing	1	7	-	-	-	-	-

There was no significant difference on any marker regarding asthma. Those without seasonal allergies were more likely to be satisfied with their performance in the latter interview in April 2021 than athletes with allergies. There were no significant differences between sexes in any marker, although a slight trend was noticed proposing that men could develop higher anti-N IgG antibodies ($p = 0.094$). Athletes had on median one ± 1.5 (range 0–6) URS-episodes between COVID-19 infection and 13 months interview. Mean duration of return to training was 9 ± 5 days (range 0–21) and athletes reported to be fully recovered within mean of 22 ± 12 days (range 7–48).

7.1 Antibodies

In the 3-month serum samples, anti-N IgG and combined anti-RBD IgG and anti-SFL IgG antibody concentrations exceeded the limit of positivity in all athletes ($n = 15$). MNT titre was positive in 13 of 15 (87 %) athletes. Anti-spike IgG antibody concentrations, anti-RBD and anti-SFL, had strong positive association with each other and with MNT titre (figure 3), whereas anti-N IgG had significant association only with anti-RBD IgG (figure 4).

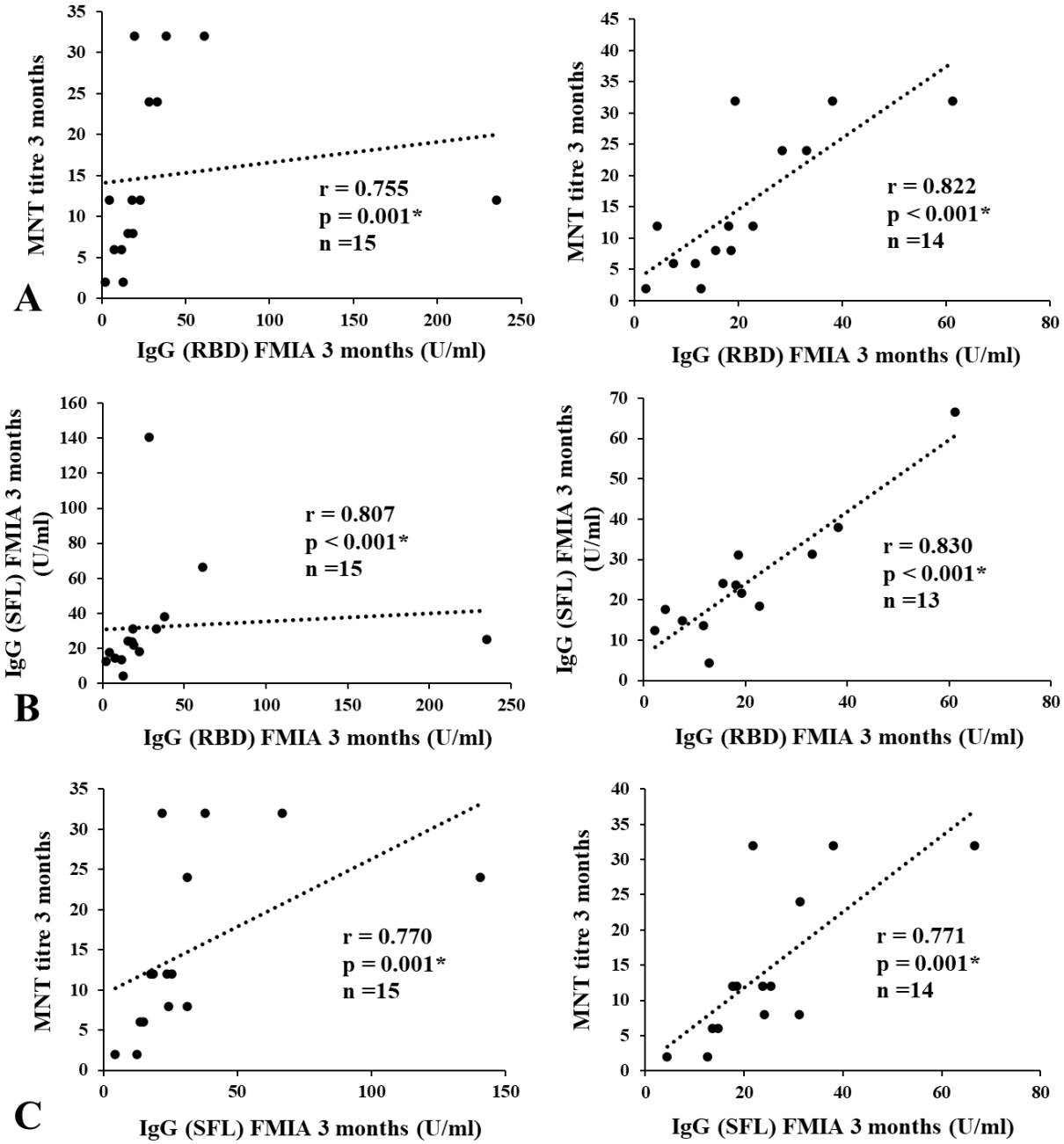

FIGURE 3. IgG anti-RBD, IgG anti-SFL and MNT titre associations by Spearman's correlation test. On the left side with all participants and on the right side with exclusion of outliers (< or > of mean ± 2*SD).

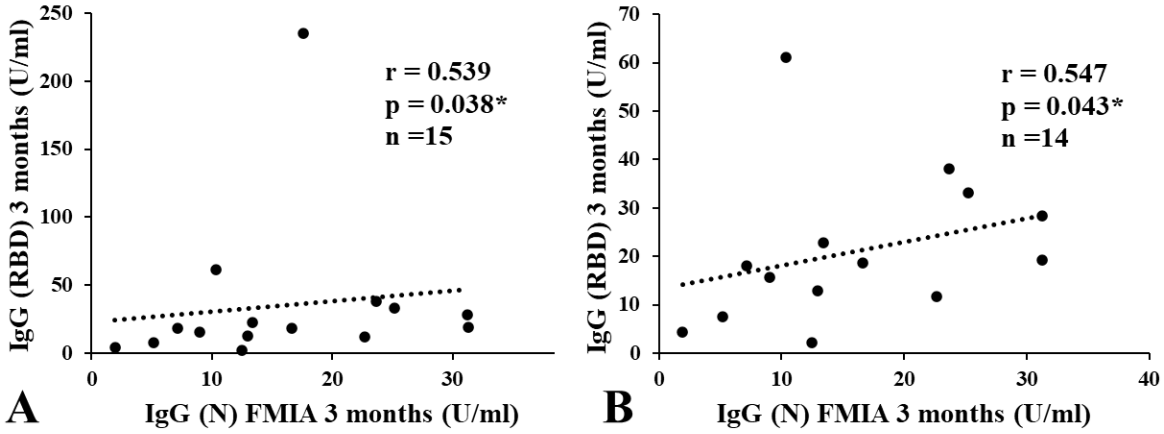

FIGURE 4. Anti-N IgG and anti-RBD IgG antibodies association by Spearman's correlation test. On the left side with all participants and on the right side with exclusion of outliers (< or > of mean ± 2*SD).

Athletes who had received their first vaccine before the second serum sample collection (n = 4) had developed significantly more anti-RBD IgG (p = 0.006), anti-SFL IgG (p = 0.006) antibodies in the 14.5 months samples and their MNT titre was significantly higher (p = 0.012) compared to those who had not been vaccinated before the serum sample collection (figure 5).

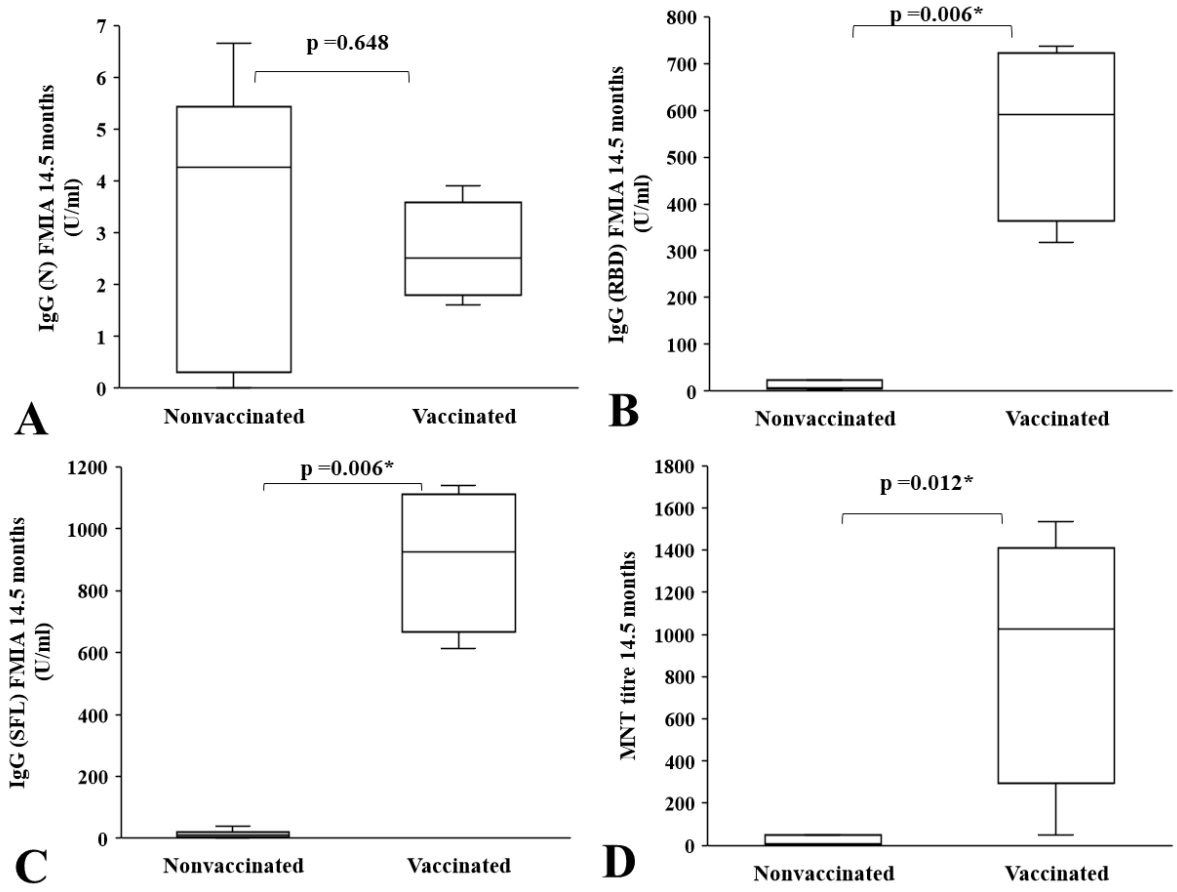

FIGURE 5. Differences in serum anti-N IgG (A), anti-RBD IgG (B), anti-SFL IgG (C) antibodies and MNT titre (D) of vaccinated and nonvaccinated athletes at 14.5 months after symptoms onset.

The seven athletes who had not been vaccinated recorded a significant decrease in anti-N IgG ($p = 0.018$), anti-RBD IgG ($p = 0.028$) and anti-SFL IgG ($p = 0.018$) antibodies, while there was no significant difference in MNT titres between the two timepoints (figure 6). One athlete's concentration of anti-RBD was higher in the latter serum sample and in three athletes MNT titre was higher from the latter serum sample, whereas all athletes recorded a drop in anti-N and anti-SFL IgG antibodies between the two time points. Nonetheless, anti-S IgG, and anti-N IgG antibodies, and MNT titre was positive in 7/7, 5/7 and 5/7 of nonvaccinated athletes at 14.5 months symptoms onset respectively.

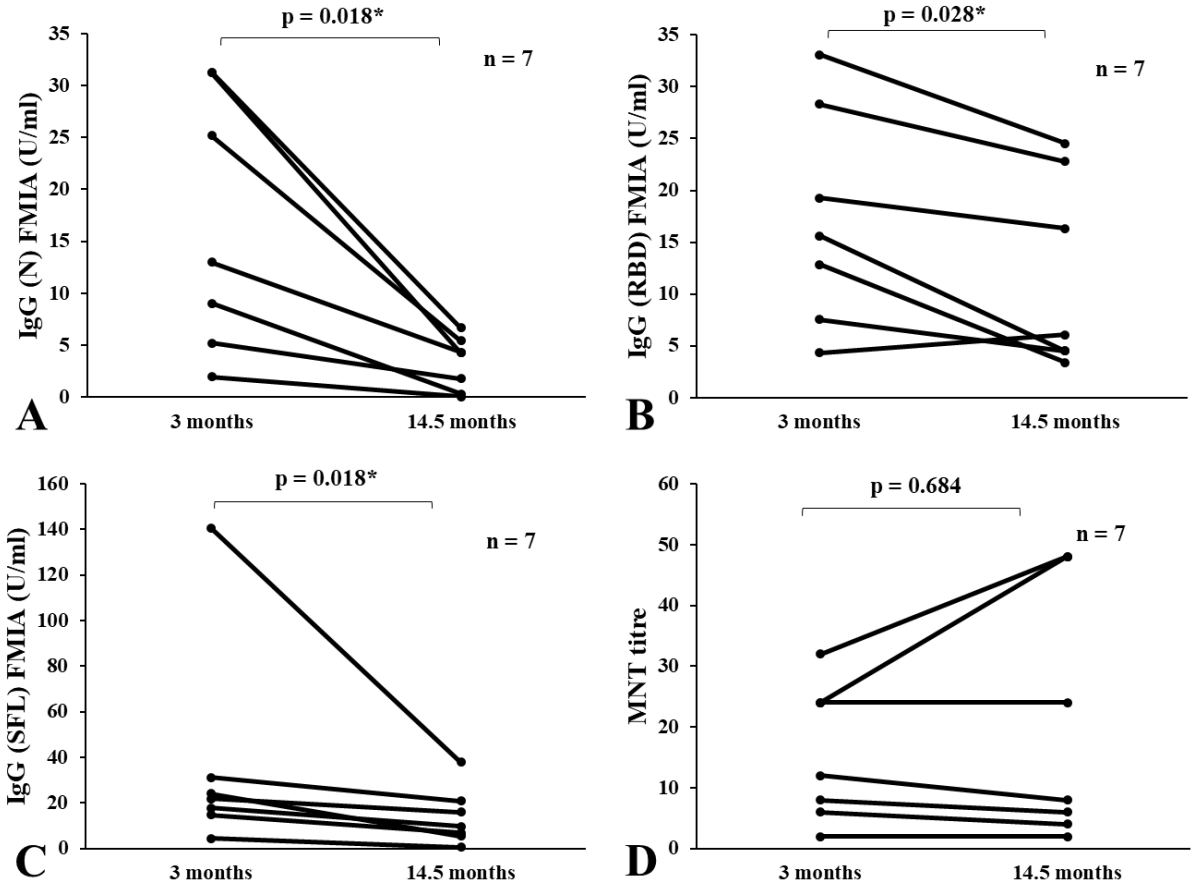

FIGURE 6. Individual changes in anti-N IgG, anti-RBD IgG, anti-SFL IgG concentrations and MNT titres from 3 months to 14.5 months in nonvaccinated athletes.

7.2 Associations between symptoms, antibody concentrations and training

Incubation time did not have association with the acute phase symptoms or any antibody concentrations. Number of symptoms had positive association with age ($p = 0.036$) and with days to start training after symptoms onset ($p = 0.006$). Number of days with fever had positive association with the days after subjective feeling of full recovery ($p = 0.05$) and with anti-N IgG antibody concentration in 3 months serum sample ($p = 0.015$). Symptoms mean severity and symptoms duration was not associated with any marker measured.

Training load (sum of hours or presence of intensity trainings) on the past week before infection was not associated with any symptom marker or antibody concentration. Training hours in the

week before infection was associated positively with annual training sum in 2019-2020 ($p < 0.001$) and in 2020–2021 ($p = 0.002$), whereas presence of intensity training week before the infection was associated with the training hours of the week before infection ($p = 0.004$) and annual training sum in 2019–2020 ($p = 0.007$) and in 2020–2021 ($p = 0.027$); in other words, those with intensity training on past week before infection trained annually more. Presence of intensity training on the past weeks of infection was also associated the with days to start training after symptoms onset ($p = 0.020$) so, that those who had intensity trainings on the week before infection returned to training sooner ($p = 0.028$ by Mann-Whitney U-test).

Number of URS-episodes on the years after COVID-19 was associated with presence of non-prescription medical treatment of acute phase of the infection ($p = 0.046$) so, that those who used non-prescription medication on COVID-19 had more URS-episodes, although by the Mann-Whitney U-test the two group did not show a significant difference ($p = 0.078$). Number of URS-episodes was associated also with presence of long-term symptoms ($p = 0.008$); two athletes with long-term symptoms (alterations on palate) had more URS-episodes. This difference was also recognized with Mann-Whitney U-test ($p = 0.019$). Satisfaction to own performance on 13 months interview was associated with wellbeing on 13 months interview ($p < 0.001$); those who were satisfied with their performance reported better wellbeing ($p = 0.026$ on Mann-Whitney U-test).

8 DISCUSSION

All athletes infected with COVID-19 experienced the disease as a mild infection. None of the athletes required hospital care and return to training was successful after the acute phase of the infection. Two athletes reported to have alterations in the sense of taste in the interview 13 months after symptoms onset. Serum samples at three months after infection were positive in anti-S IgG and anti-N IgG in all athletes. 14.5 months after symptoms onset four athletes had received their first dose of vaccine and those athletes differed from nonvaccinated athletes significantly. Athletes with first vaccination had larger concentration of antibodies and bigger MNT titre than nonvaccinated athletes.

8.1 Symptoms and return to training

During the COVID-19 cases presented in this thesis, knowledge of the disease was sparse, and athletes were treated concerning the clinical symptoms. In some athletes, the PCR results reached the athlete and medical staff when the symptoms were mostly gone. And thus, the treatment of the athletes did not make meaningful exception comparing other viral URTIs. The athletes made a self-initiated return to training in quite early stage compared to the guidelines of RTP presented lately (Goergen et al. 2021; Krzywański et al. 2022) and interestingly, the return to training happened on average one day before the symptoms of the acute phase ended. However, duration and severity of the symptoms was not different in these athletes compared with other studies including athletes with mild COVID-19 infection (Hull et al. 2022; Krzywański et al. 2022). Also, long-term symptoms in the annual interview were only presented in two athletes and concerned only alterations in the sense of taste. Additionally, presence of antibody formation was comparable to the 111 Polish elite athletes presented by the study Krzywański et al. (2022).

Those athletes that had more symptoms started training later and logically, athletes with more fever days experienced to be fully recovered later. Interestingly, a higher age was associated with higher number of symptoms. Same kind of result is presented in the study of Krzywański et al. (2022) who reported asymptomatic individuals to be younger, and athletes over 26 years

to be more prone to develop symptoms. Presence of intense training on the week before COVID-19 was associated with earlier return to training and thus, intense training cannot be seen as a decelerating factor in return to sports in this cohort. Amount of training week before COVID-19 or relative annual intense training amount was not associated with antibody formation and annual amount of training did not affect the antibody concentrations. Although the level of training was quite high in all participating athletes, and all represented the same sports discipline. Thus, the same kind of kinetics as can be seen in research comparing sedentary and exercising cohorts might not be visible in studies including only athletes.

Some athletes are reported to be more prone to illness episodes and prolonged symptoms than others (Walsh et al. 2011a; Svendsen et al 2016). That can also be seen in this thesis, with those two (13 % of all) athletes reporting long-term symptoms also reported the most respiratory illness episodes on the year following COVID-19. None of the other athletes experienced more than one respiratory illness episode and five athletes (33 %) had not a single URS-episodes between COVID-19 and 13 months interview. Asthma was not related to any symptom marker in this thesis. Previous studies have not shown a clear answer whether asthma is a risk factor of severe disease or not (Terry et al. 2021) and updated information of that is still needed.

8.2 Antibodies

Considering the high sensitivity and specificity of the FMIA, the antibody results from the serum samples presented in this thesis can be considered as a relative strong proof of antibody formation and some sort of immunity against the virus. Although the sample size was small and during the spring 2020 prevalence of COVID-19 cases in Finland can be considered as rather rare, and thus possibility of antibody cross reactions should be in mind while interpreting these results (Caini et al. 2020). It is good to keep in mind that antibody levels do not necessarily correlate with other immune factors like concentration of T-cells, and thus do not represent alone the whole variety of immunity to certain pathogens (Dan et al. 2021).

Haveri et al. (2021) presented that FMIA tested anti-S IgG antibodies persist at least 13 months after infection in 97 % of the subjects and anti-N IgG antibodies persisted in 36 % of the subjects. Additionally, MNT titre against WT SARS-CoV-2 was positive in 89 % of the subject 13 months after the infection. (Haveri et al. 2021) On those seven athletes in the present thesis that have not got vaccine before 14.5 months serum sample collection anti-S IgG, anti-N IgG and MNT titer was positive in 7/7 (100 %), 5/7 (71 %) and 5/7 (71 %) respectively. Thus, it can be concluded that athletes at least in this cohort maintain their antibodies in the same way than in population generally. In the seven athletes who were under comparison of the change in antibodies from 3 months to 14.5 months, the fall in anti-S IgG and anti-N IgG antibodies were 43 % and 78 % respectively, which is larger compared to the fall in same antibodies from 8 months to 13 months reported by Haveri et al. (2021). That is also to be expected, as IgG antibodies are usually at their highest during the first months after infection (Denning et al. 2020; Wang et al. 2021) and start to fall evenly after that (Wang et al. 2021). Haveri et al. (2021) and Blomberg et al. (2021) reported higher concentrations in serum antibody with more severe infection, but that was not seen in this thesis, which might be due to data with homogeneous severity of the infection. Additionally, anti-N IgG antibody concentration was associated with the number of days with fever in this thesis. This is in line with the information that antibody formation is associated to the severity of symptoms (Marklund et al. 2020; Krzywański et la. 2022) and anti-N IgG antibody formation is greatest during the acute phase of the infection (Fenwick et al. 2021).

8.3 Limitations

The mutations of the virus and different variants make the interpreting of different studies hard. Studies on different time points include different variants of the SARS-CoV-2 virus and many studies on athletes ignore the classification of the variants present, including this thesis. For that reason, comparing of the exact symptoms and possible long-term impacts to other studies is not

that meaningful than the overall impact of the infection to athletes' health and life. The size of the cohort in this thesis was small. That is a major limitation of the interpretation of the results presented. Although the results seem to match with previous knowledge quite well and the major result of athlete's successful return to training and competition is valuable and needed.

Variation in symptom severity, duration, and number of symptoms in the present cohort was small. This may have impact on the correlations and significances between the markers under reviewed. Homogeneity of the cohort and absence of untrained controls make it hard to directly compare the antibody formation between athletes and non-athletes. Additionally, retrospective collection of the data, especially, in the interviews has its challenges. Patients may not remember all the symptoms and/or training, or they can remember it wrong due to subjective evaluation. This could have been avoided by collecting the training data straight from the training monitors or electronic training diaries that athletes normally use and collecting symptom diaries from the acute phase of the infection.

8.4 Conclusions and practical applications

The results of the present thesis highlight the general observation that athletes are able to return training and competitions without any major implications. Some athletes might experience long-term symptoms, but those symptoms are not necessarily related to training or competition successfulness. All the athletes developed measurable antibody formation against COVID-19 which is in line with previous studies in symptomatic individuals.

There is much to learn from the COVID-19 pandemic concerning viruses and preventing illnesses at general. Proper hygiene habits, management of training load and stressors in daily life and in competitions, sport specific considerations such as traveling, and return to training protocols should be in mind when dealing with athletes and sports organizations. Future consideration in the study of sports and physical activity should consider the role of different pathogens while studying respiratory illnesses and their impact on performance and wellbeing.

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