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Letter to the editor

Team sport, power, and combat athletes are at high genetic risk for coronavirus disease-2019 severity

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Dear editor,

As government restrictions put in place to slow the acceleration of the coronavirus disease-2019 (COVID-19) pandemic start to ease, many people, including elite athletes, will begin to return back to their normal daily activities. Although the majority of risk factors for severe COVID-19—hypertension, respiratory system disease, obesity, older age, and cardiovascular disease[1]—are exceptionally rare in elite athletes, when athletes train in groups or common training areas, they are not immune from contracting the illness; and, although the subsequent risk of death is low, it is not zero.

It has been estimated that 22% of the global population are at increased risk of severe COVID-19 if infected.[2] Precisely because elite athletes are generally young, fit, and healthy, the identification of high-risk individuals within this cohort is likely to be difficult, requiring a multidisciplinary approach. One area with potential early promise is that of genetic testing,[3] with a number of genetic variants tentatively associated with an increased susceptibility to, and an increased chance of complications from, contracting COVID-19.[4,5]

So far, 4 studies[4–7] have shown that at least 6 DNA polymorphisms might be implicated in COVID-19 severity, with the ABO blood group (*ABO*) rs657152 A, angiotensin I converting enzyme (*ACE*) D, apolipoprotein E (*APOE*) rs429358 C, leucine zipper transcription factor like 1 (*LZTFL1*) rs11385942 GA, transmembrane protein 189-ubiquitin-conjugating enzyme E2 variant 1 (*TMEM189-UBE2V1*) rs6020298 A, and transmembrane serine protease 2 (*TMPRSS2*) rs12329760 C alleles being considered as risk factors (Supplementary Table 1). According to the UK Biobank cohort, these risk alleles are also associated with immune system disorders (*ABO*, *LZTFL1*, *TMEM189-UBE2V1*), thrombosis (*ABO*), hypertension (*ACE*, *TMPRSS2*), dementia (*APOE*), obesity (*ACE*, *APOE*), respiratory disorders (*ABO*, *TMPRSS2*), and dyslipidemia (*APOE*) (Supplementary Table 1). Interestingly, these risk alleles are also associated with performance-related traits (Supplementary Table 2), with 4 risk alleles showing favorable effects on endurance and/or power.

It is well-established that genetic and phenotypic variations may have pleiotropic effects. For example, a high percentage of type II muscle fibers is positively correlated with power performance, but is considered as a risk factor for the development of obesity, diabetes, and hypertension,[8] which explains why former endurance athletes have lower rates of coronary heart disease and obesity compared with power athletes.[9] This can be considered a result of natural selection due to the pleiotropic effect of genes, rather than a negative effect of power performance on the health of athletes.

We thus hypothesized that polygenic risk scores for COVID-19 severity based on 6 DNA polymorphisms may vary across different sporting groups (endurance and power

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oriented). Using the 1000 Genomes database and our own data of 802 Russian elite athletes and 224 controls (Supplementary Table 3 and Supplementary Methods), we first identified the proportion of subjects with increased risk in each population. For this, we classified all subjects according to the number of risk alleles they possessed (e.g., carriers of *ABO* CC, *ACE* II, *APOE* TT, *LZTFL1* GG, *TMEM189-UBE2V1* GG, and *TMPRSS2* TT genotypes had zero risk alleles, and subjects with *ABO* AA, *ACE* DD, *APOE* CC, *LZTFL1* GA/GA, *TMEM189-UBE2V1* AA, and *TMPRSS2* CC genotypes had 12 risk alleles). About one-half of Russian controls (47.3%) were carriers of 5 or more risk alleles. This value therefore was considered as a threshold for further analysis.

Long-distance athletes had the lowest proportion of subjects with genotype scores (i.e., ≥5 alleles) indicative of increased risk (odd ratio (OR) = 1.07, $p = 0.802$ compared to controls). In comparison, other athletes had a greater proportion of individuals with high risk genotype scores. Specifically, middle-distance (OR = 1.58, $p = 0.04$), combat (OR = 1.63, $p = 0.048$), and power (OR = 1.74, $p = 0.0036$) athletes, as well as team sport players (OR = 1.89, $p = 0.0005$) had a significantly higher proportion of subjects with increased genetic risk compared to controls (Table 1). Interestingly, the polygenic risk scores show a significant geographical variation, putting some countries at greater risk than others (Table 1).

Table 1
Proportion of subjects with increased risk for COVID-19 severity.

Group	*n*	Proportion of subjects with high number of risk alleles (%)
Russian cohorts		
Russian long-distance athletes	90	48.9
Russian middle-distance athletes	126	58.7*
Russian combat athletes	96	59.4*
Russian power athletes	228	61.0*
Russian team sport players	262	63.0*
Russian controls	224	47.3
Other populations		
Americans (African ancestry)	61	68.9
Americans (European ancestry)	99	59.6
Bangladesh	86	59.3
Barbados	96	82.3
British	91	53.8
Chinese	301	28.6
Colombian	94	54.3
Finnish	99	60.6
Gambian	113	80.5
Indian	205	56.6
Italian	107	71.0
Japanese	104	41.3
Kenyan	99	81.8
Mexican	64	45.3
Nigerian	207	82.1
Pakistani	96	56.3
Peruvian	85	52.9
Puerto Rican	104	53.8
Sierra Leone	85	89.4
Spanish	107	59.8
Sri Lankan	102	51.0
Vietnamese	99	38.4

*p <0.05, statistically significant differences between Russian athletes and controls.
Abbreviation: COVID-19 = coronavirus disease-2019.

In conclusion, we identified that team sport, power, and combat athletes possess a higher genetic risk for COVID-19 severity than untrained subjects or endurance athletes. We suggest that genetic testing, alongside more well-established health-related information like vitamin D status,[10] might be useful to determine the individual risk profiles of each athlete.

Authors' contributions

IIA conceived and designed the study, performed analysis, and drafted the manuscript; OVB and EVG carried out data collection, interpreted data, and critically revised the manuscript; EAS, ONA, and LBA performed analysis and critically revised the manuscript; CP performed analysis and drafted the manuscript. All authors have read and approved the final version of the manuscript, and agree with the order of presentation of the authors.

Competing interests

The authors declare that they have no competing interests.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jshs.2020.07.010.

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