Lin Zhangyuan

Does Running Really Make Us Healthier?

Introductions and Motivations

Requiring almost no extra, additional equipment outside of what most people already have, running has always been a popular and highly accessible sport. With the current COVID-19 pandemic limiting the ability of people not within the same family from gathering outside, especially during the Circuit Breaker implemented just months ago, running and jogging has seemingly become even more popular, as locals seek to find effective ways to exercise alone. This observation was not limited to Singapore, as an ongoing study by ASICS showed a 62% spike in the number of people going for a weekly run worldwide [1]. For many of the runners, the surge could be attributed to the mental benefits running offers, such as the ability of running in helping them cope mentally during stressful situations (such as during a lockdown), as well as the ability of running in helping them feel "saner and more in control" and in clearing their mind [1].

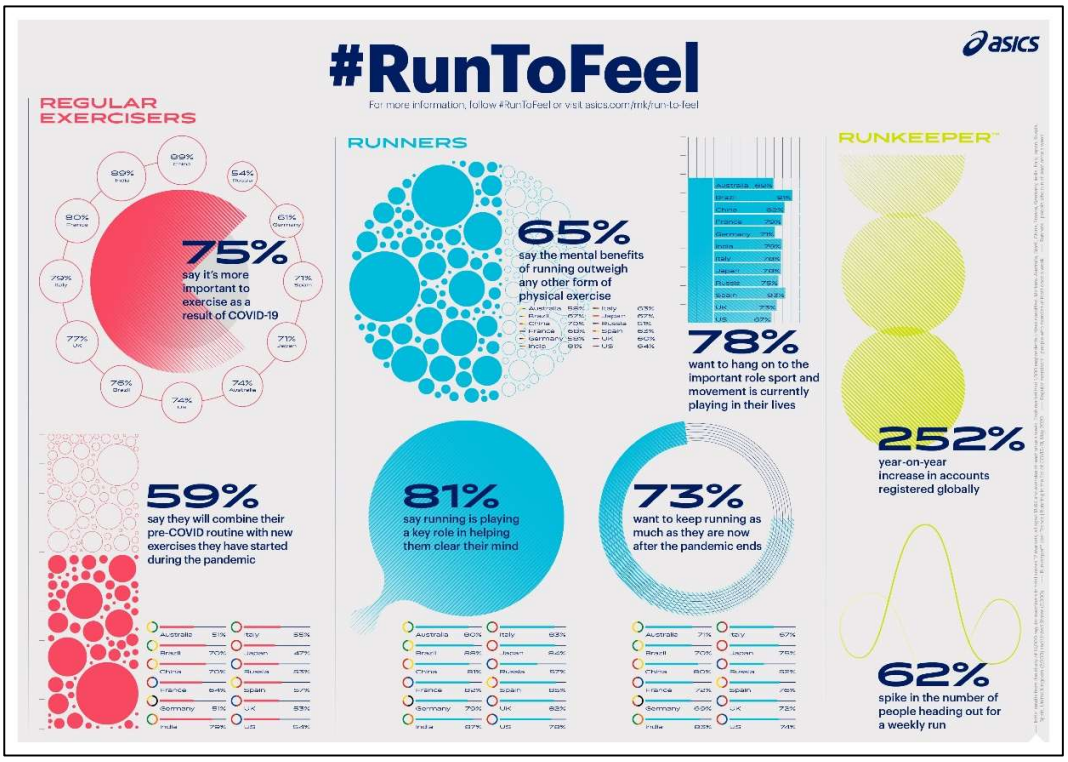

Figure 1, Brief summary of study from ASICS [1]

Even before the COVID-19 pandemic, running has been a popular sport, with over 50million runners every year in the United States alone [2], and over 25000 running events each year in the United States from 2012 to 2016 [3]. Consequently, it is also a sport where the gears and apparels held a global market size of USD 9.8 Billion in 2016, expected to grow to USD 22.53 billion in 2023, at a compounded annual growth rate of 12.97% [4].

With all these in mind and considering the rising popularity of running as a form of exercise, especially during the current COVID-19 pandemic, it provides an incentive for us to look deeper into running, and

whether this popular and accessible sport is really all it claims to be, and if it is indeed a suitable sport to pursue during the current COVID-19 pandemic.

Main Body

History of running

While running is an activity enjoyed by many in the modern times, few might be aware of its historical backgrounds.

In the days of the early humans, it was thought humans developed into endurance runners from the need to forage and reach carcasses early, as well as the practice of the persistent hunting of animals -- chasing the prey until it becomes too exhausted to flee [5]. This was a practice possible due in part to the ability of humans to keep their bodies cool by sweating while running, as well as the ability of humans to tolerate heat stresses well above a theoretical critical thermal limit of 41.6-42°C [5]. The need for thermoregulation due to such foraging and hunting practices likely shaped human evolution, which resulted in distinct human characteristics such as bipedalism, loss of functional body hair, and an increase in body size linearly [5].

Moving and skipping along in the timeline, we arrived at 776BC, where the first Olympic Games began, and the first event was a foot race [6]. During this era, running was a need in wars as a method not only to hone warriors for battle, but also for developing a network of highly trained runners which was often needed for communication purposes [7]. Competitions such as the Olympics then modified the needs and motivation for running – in allowing the warriors and athletes to keep up their skill levels [7]. However back then, there were no marathon events, and the furthest distance was the 'Dolichos' event, ranging between 7 to 24 'Stades' which were typically distances of 200m each [8]. The marathon was only added in 1896, when organizers decided to honour the Greek soldier Pheidippides, who was said to have died after running from Marathon to Athens, Greece, roughly 25miles, to deliver news of a military victory in 490BC [9]. From then on, endurance running in the West was mostly the specialty of athletes who participated in competitions and marathons.

Today, in places and times where the relevant communications and transport facilities are unavailable, running then serves as a means of transport and communication [7]. However, this is probably not the reason for modern humans, especially those of developed countries, for choosing to get into running.

Why do people nowadays get into running?

In some countries and places, running might be a need due to the physical tests and standards set by various organizations and governments as a method to ensure and keep the fitness level of the population in check. For instance, in Singapore, children in the Primary to Junior College level are often required to participate in mandatory "National Physical Fitness Award/Assessment" (NAPFA) tests, as part of the Ministry of Education's efforts in ensuring the fitness and health of all school children so as to boost their learning potential. Meanwhile, in the Singapore Armed Forces, the Singapore Police Force and the Singapore Civil Defence Force, a similar in concept but different 'Individual Physical Proficiency Test' (IPPT) is used to assess and ensure the physical fitness and skills of the members are kept up to standards.

Outside of being forced to run as a punishment or for training in schools or military service, the reason the lay-person runs often varies. In a study done by Running USA, while the majority of the runners get into running out of desire to exercise, a large percentage of runners also started running out of weight and health concerns, including mental health concerns such as in relieving stress, as shown in figure 2 below [10]. Additionally, the largest motivation for existing runners continuing to run was also indicated as due to desires to stay healthy, stay in shape, and in relieving stress, as shown in figure 3 below [11].

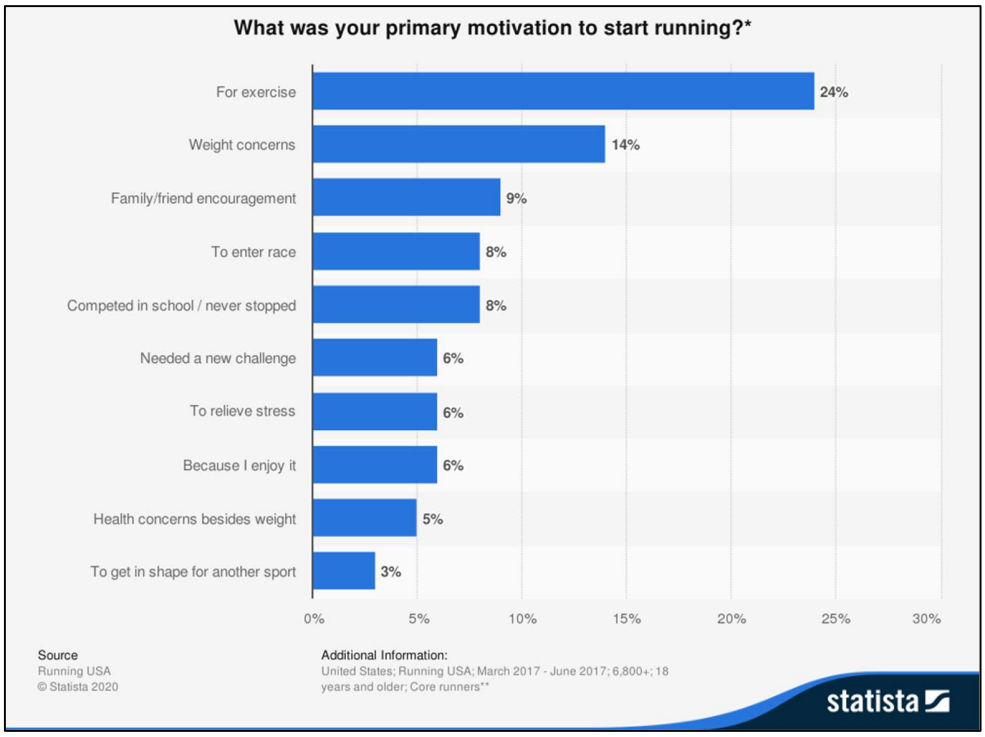

Figure 2, Motivations for people to get into and start running [10]

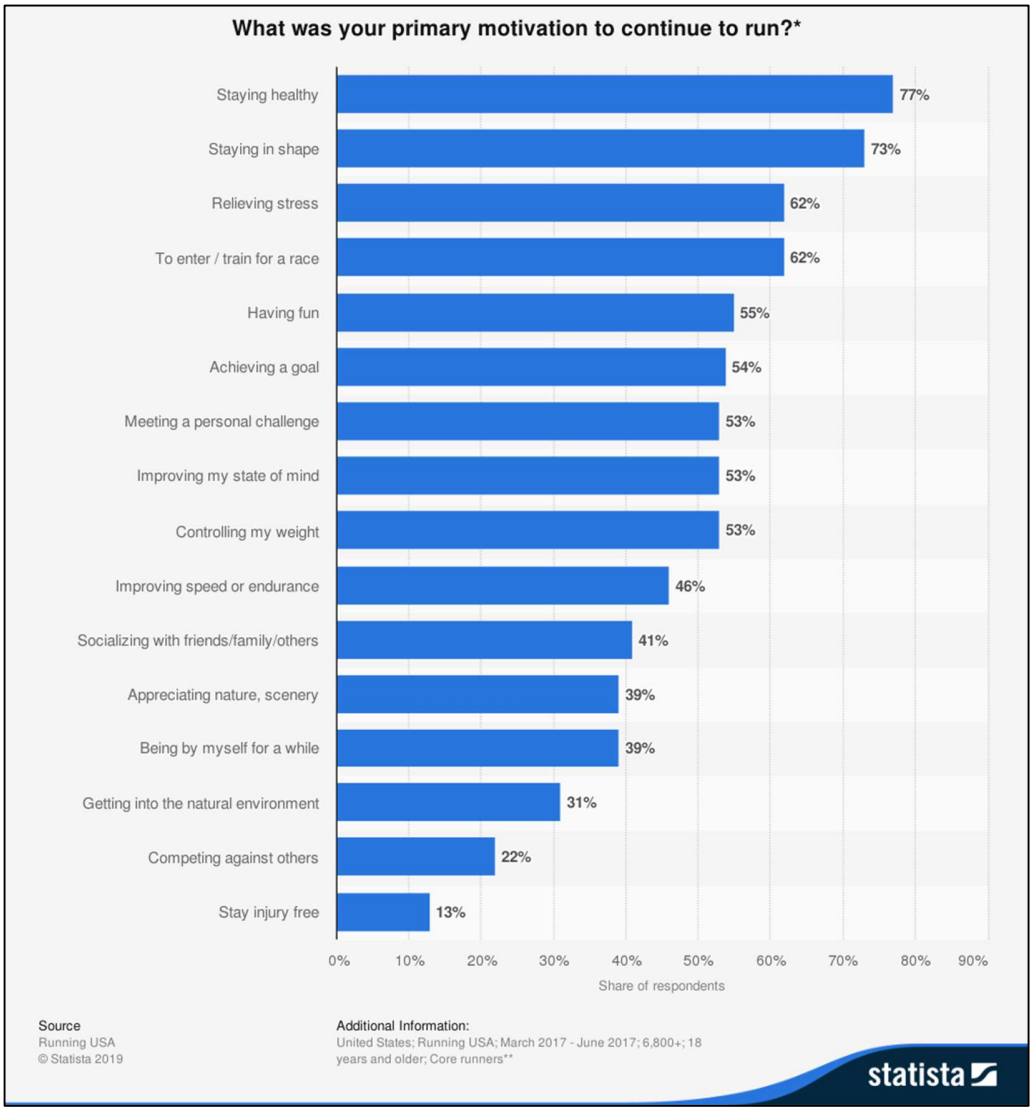

Figure 3, Motivations for existing runners to continue running [11]

Popular believes of running and its impacts on human health, and their truths

Clearly, a major motivation and reason for people who got into and continued to stay in the sport of running are due to health concerns and the impacts of running on human health, both physically and mentally.

Physical impacts

Among the many impacts of running on physical health, perhaps most notable includes its effects on weight and obesity. For instance, running, as an exercise is well known to be capable of burning calories, increasing insulin sensitivity and lowering cholesterol levels. However, on top of that, researchers have also found that its effects reach the subcellular level as well, where the mitochondria of the runners

become more efficient at burning off fatty fuel. This effect could then reduce our likely hood to develop other age-related diseases, such as diabetes, heart disease, and even Parkinson's and Alzheimer's [12].

In addition to the effects on weight and obesity, the effects of running on the cardiovascular system are also noted. According to one study, a person's risk of non-fatal myocardial infarction decreased linearly with greater cardiorespiratory fitness, as determined by running performance. Additionally, regular running was also associated with a reduction in cardiovascular disease related mortality by as much as 57% [13]. In fact, due to this lowered risk of fatal coronary heart disease, there have been records of the implementation of running training for patients recovering from heart attacks in some rehabilitation centres in Toronto and Honolulu [14].

Moreover, running was also found to have benefits on the respiratory system and brain function. Running training was also shown to be positively related with improved pulmonary function, in particular due to the increased strength of respiratory muscles [15]. Brain function wise, running was also found to increase cell proliferation and neurogenesis, possibly improving hippocampus-dependent memory [16]. Additionally, runners were also found to have higher sleep efficiency, with an increased proportion of deep stage 3 and REM sleep [14].

Furthermore, running was also found to reduce the risk of stroke by 12% in men and 11% in women, while also reducing the risk of cancers such as kidney cancer, breast cancer, and brain cancer [13]. On top of that, running was also associated with a reduced risk of osteoarthritis and need for hip replacement compared to non-runners by as much as 35% [13].

While the physical benefits are well documented, it is worth noting that there are limits to those benefits, and additional risks on physical health as well. Although studies have proven that regular running provides the physiological benefits of an increased life expectancy, it is worth noting that participating in such activities at an extreme, and frequent level provides a risk of cardiotoxicity and development of cardiomyopathy as well, although these risks and abnormalizes appeared to resolve quickly within weeks of the extreme activity [13]. Additionally, running also poses a possible risk of medical conditions including musculoskeletal problems, exercise-induced gastrointestinal and respiratory issues, as well as heat exhaustion, particularly if the activity is done at a high intensity level. However, it is also noted that further increased training reduces the risk of such issues, and that frequent runners are less prone to these issues than novices as their bodies adapt to the regular training [14].

Psychological impacts

On top of the effects on physical health, running was found to provide a list of benefits to mental health as well. For instance, running was observed to result in the release of endorphins from the brain, which subsequently produces a calming effect that also puts one in a euphoric state, commonly well known as a "runner's high" [14]. Additionally, the action of achieving a previously set goal (such as in running and other exercises) is also known to give a feeling of empowerment as well as increasing self-esteem [14]. This combined with a healthier external appearance due to the beneficial physical effects of running can then increase one's potential physical attractiveness, and thereby build on to one's self-confidence [14]. Lastly, running was also noted as a possible intervention and method in countering depression [17], as well as in helping one mitigate chronic stress and stress due to stressful stimuli and events [18].

Lin Zhangyuan

Effects of running on microbes

While the gross physical and mental effects on our body due to running have been described above, less thought about are the effects on the microbes on our skin and inside our body. With the huge diversity of microbes on our skins, as well as the well-known and important relationship between gut-microbes and the human body [19], this could be a potentially interesting area to look into as well, particularly under the current COVID-19 pandemic, where there is a greater public emphasis and awareness of microbes.

Effects of running on the immune system

It is commonly been believed that regular, moderate exercise (including running) improves immune function compared to those who remain sedentary. Out of the difficulty of predicting the overall effects of small to moderate changes in the host's immune system, the incidence of respiratory symptoms and Upper Respiratory Tract Infections (URTI) is commonly used as an indicator in many studies [20].

Indeed, many studies indicate that those who engage in moderate exercise on a regular basis, do carry a reduced incidence of respiratory symptoms compared to those less physically active. A community study done between 1994 to 1997 found that both men and women who engaged in moderate physical activity had a 29% reduction in incidence rate of URTI [21]. Meanwhile, another study done in 1989 on athletes also found that those who ran over 15miles per week had a reduced incidence of respiratory symptoms compared to those who trained with shorter distances [21].

Mortality wise, a study done in Hong Kong during 1998 also shown that a moderate frequency of exercise even reduces the risk of influenza-associated mortality compared to those who were sedentary [21].

Additionally, animal studies on mice also shown that mice assigned to the moderate exercise groups post infection to influenza strain A/Puerto Rico/8/34 also carried a significantly lower mortality rate when compared with the control, non-exercising group [21]. Which indicates that even moderate exercise initiated after infection but before symptom onset could have a beneficial effect on susceptibility to respiratory pathogens as well [21].

The reasons for the above observations were thought to be due to a few causes and mechanisms. Firstly, a prominent mechanism suggests that moderate intensity exercises increases salivary Immunoglobin A (IgA), which binds to and marks foreign organisms and microbes for phagocytosis by other immune cells, providing protection against respiratory symptoms [21][22]. Other causes include a shift in immune responses from an inflammatory to anti-inflammatory response which was associated with improved outcomes following infections and a reduction in morbidity and mortality [21]; and also due to increases in CD4-T-Cells [23].

Effects of running too hard on the immune system

While it has been demonstrated that moderate exercise and running is beneficial for the immune system, many studies have also found that excessive running and training at a high intensity, such as in marathon running and training, could have adverse effects on the immune system instead, in particular increasing the risk of URTIs.

A study which examined athletes participating in the 2000 Los Angeles Marathon showed that runners who trained more than 97km per week had twice the risk of developing URTIs compared to those who trained less than 32km per week [21]. The same study also showed that runners who completed the marathon had an increased risk of URTI in the week following the race by as much as 6 times compared to those who trained but did not participate [21]. Another study done in 2006 also suggested that a strenuous bout of exercise performed after an initial infection also potentially increases the risk of subsequent infections [21].

In the animal study where mice were infected with influenza strain A/Puerto Rico/8/34 pre-exercise mentioned earlier, mice placed in the prolonged exercise group was also observed to suffer from a greater percentage of mortality compared to the non-exercising control group [21].

These observations were thought to be due to the immune system of the host being overwhelmed by the combined psychological and physiologic stress of the activity [24]. In particular, immune cells numbers and function have been constantly reported to decrease immediately following intense activity, with natural killer cells, neutrophils and macrophages exhibiting the greatest change in response to the activity [25].

All these changes are then thought to be associated with a immunosuppressive effect, temporarily decreasing in host protection, providing an “open window” which might last between 3 to 72 hours for infections to occur [25]. However, it was also noted that some of the symptoms consistent with URTI might not be due to microbes, but due to other immune system related phenomena such as allergic reactions and other idiopathic causes including airway hypersensitivity [21]. Additionally, it was also observed that the modulation of nutrition and diet can also potentially reduce such intense exercise related URTIs. For instance, the consumption of supplements such as vitamin C and probiotics appears to reduce the rate of URTIs, and the consumption of carbohydrate-rich beverages appears to be able to reduce the adverse, immunosuppressive effects of the intense activity as well [20].

From an evolutionary point of view, the differences in immune system response between moderate and intense exercise and running is possibly due to the “fight or flight” response, and the need to escape from stressors and predators [21]. The benefits of moderate activity on the immune system was believed to be a response by the body in preparing the immune system for potential challenges due to the predator and stressors, while the converse, adverse effects of intense activity was due to the need to conserve energy when coping with the stressor [21].

The combination of these observations can then be plotted as a “J-Shaped graph” of infection risk against intensity and dosage of exercise, as seen in figure 4 below [21]. These suggest that just like foods, although it is important for us to exercise and run, it is also important that we do so in moderation. Still, in the human studies, it was also observed that subjects who exercised demonstrated shorter episodes and number of days of symptoms compared to those who were sedentary, suggesting a possible overall positive effect on the body after all [21].

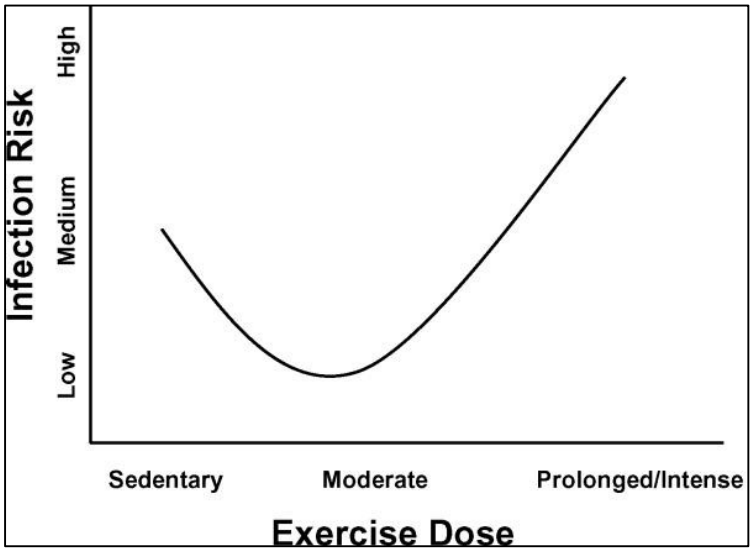

Figure 4, "J-Shaped graph" of infection risk against intensity and dosage of exercise [21]

How running can change gut microbes

The importance of the gut-microbes and human body has been well noted in multiple studies [19]. Interestingly, there are studies suggesting that exercise can alter gut microbiota as well via multiple potential mechanisms.

For instance, at the immune and cellular level, it was suggested that exercise can alter the expression of the immune cells in the gut responsible for the maintenance of the gut microbiome [26]. This was demonstrated in animal studies, where according to Hoffman-Goetz et al., it was found that "exercise alters the gene expression of intraepithelial lymphocytes, downregulating pro-inflammatory cytokines and upregulating anti-inflammatory cytokines and antioxidant enzymes" [26]. Additionally, it was believed that exercise might also affect the structure and integrity of the gut mucus lining, which serves to keep some microbes from attaching to the gut epithelium, while serving as an important substrate for other bacteria [26].

Physically, exercise is also known to raise body temperature, resulting in heat stress; and reduce the intestinal blood flow by more than 50% as the body redirects blood to the more vital areas, resulting in temporary ischemia, especially in high intensity exercise [26]. As the gut epithelial cells utilize oxidative metabolism, the combination of both exercise induced heat stress and ischemia could then result in a temporarily impaired gut barrier function, resulting in more direct contact between the gut microbes and the gut immune system which might then result in an altered gut microbiota [26].

Additionally, the effects of exercise on the nervous system can also result in the acceleration of substances moving through the gut, potentially reducing the amount of time food spends in the gut and hence reducing the amount of nutrients available to the gut microbes [26]. Combined with the mechanical forces present while running and exercising, they could then also potentially affect the biofilm structure and formation in the gut, hence altering the gut microbiota [26].

Lastly, it was discovered that exercise could also alter and increase the secretion of bile acids by the liver [26]. Given that bile acids are potent regulators of the gut microbiota, changes in the level of secretion could then serve as another mechanism in the altering of gut microbiota as well [26].

The mechanisms described above, while not comprehensive, describes some of the potential ways in which exercise and running can alter gut microbiota.

How these gut microbes can change our attitudes and performance in running

It is understood that the changes in gut microbiota can impact various bodily functions [19][26], including our brain function and hence impacting our attitudes and behaviours such as stress, anxiety and depression via the gut-brain axis [27]. Hence, we shall also look at a few possible ways gut microbes can alter and improve our performance in running and exercise.

Apart from the methods and mechanisms mentioned above describing how exercise and running can modify gut microbiota, another possible way is through the consumption of probiotics, which usually contain live microorganisms, with common ones being lactic acid bacteria. While probiotics are commonly used to protect the host's guts against other harmful microbes, as well as strengthen the immune system, improve digestibility and metabolic disorders [28]; studies suggest probiotics such as lactic acid bacteria could have beneficial impacts on exercise performance as well. In a study by Chen et al. published in 2016 on mice, it was shown that the supplementation of a specific, *Lactobacillus plantarum* TWK10 (LP10) was able to increase muscle mass, grip strength, improve energy production and exercise performance by the production of lactic acid in the gut, which could be used by other bacteria, forming adenosine triphosphate (ATP) - the "energy currency" of a cell [29]. Additionally, the LP10 supplement was also able to provide antifatigue effects and reduce inflammation through the reduction in levels of "serum lactate, ammonia, and creatine kinase" [29].

Most recently in 2019 [30], a study of *Veillonella atypica (V.atypica)*, usually more abundant in the guts and fecal matter of endurance runners compared to non-endurance runners, provided another insight as to how gut microbes can impact and improve running performance. In the study, it was discovered that *V.atypica* uses lactate, a byproduct of muscle metabolism associated with fatigue; as a main food source. Subsequently during mice studies, after fecal containing *V.atypica* was transplanted int the guts of mice, it was observed that the mice was able to outperform non-*V.atypica* transplanted mice. Further studies observed *V.atypica* in the gut being able to break down the exercise induced lactate which could pass from bloodstream into the gut, due to the temporary impaired gut barrier function triggered by exercise. The breakdown of lactate, forming propionate was thought to be able to increase heart rate and oxygen consumption, while also regulating blood pressure. This observation, thought to be the main mechanism for the improved exercise performance due to *V.atypica* then raised the possibility of using *V.atypica* in fecal transplant procedures or as a probiotic to improve running performance [30].

Conclusions and Reflections

From the research done so far, it is clear that running, as a form of sport and exercise, does confer a whole list of benefits on the runner. Starting from the numerous physical benefits, to the psychological benefits, running offers more than just simple benefits on body weight. On top of that, running appears to even confer immunological benefits against microbes as well, seemingly boosting our immune systems and

protecting us against microbes, respiratory symptoms and URTIs, which would be extremely beneficial in the current COVID-19 pandemic posed by the SARS-COV-2 virus which spreads mainly through respiratory means.

With many countries affected by COVID-19, and the need for people to continue staying active even during lock downs and pandemics, running then appears to offer a viable alternative to other group sports such as soccer and basketball that might not be as suitable in the current situation. However, with the evidence and research on the immunosuppressive effects posed by intense, excessive running, runners should probably take note and lower their training intensity appropriately in contrast to the pre-COVID-19 days, as well as watch their diet and nutrition requirements.

However, even after the COVID-19 pandemic in the future, running can still remain and be pursued as a popular sport enjoyed by many, especially considering the numerous benefits posed on the body. Additionally, with the research on gut microbes, and how certain microbes can actually boost our performance, it appears the running scene and sport will be an exciting one to look out for in the future. This will be especially so if and when humans start taking more notice and effort in what they eat, and in preserving and altering their gut microbes, which might eventually contribute to and result in human limits being continuously broken thanks to those microbes. Perhaps, one day those gut microbes mentioned above can even be taken by the layperson as a probiotic, and the results and impacts on those compulsory and dreaded IPPT and NAPFA tests will then be another interesting area to look at.

As an avid runner in a varsity Cross Country team, the research done into this topic has opened my perspective about running, especially with the discovery of the numerous benefits and possibilities the sport can confer, which myself and most people were not even aware of. The discovery of these benefits will and has definitely increased my teammate's and my attraction towards the running sport and hobby, especially as we realise that there is something more than the relentless pounding of the ground and the endless panting that most people observe and think of during training. However, perhaps most valuable to my team and I will be the discovery of the negative, immunosuppressive effects due to excessive, intense running, which happens during most of the training programme. With this information, it will better aid my peers and I in maintaining and keeping our bodies healthy and infection free even after an intense training and workout, which combined with the benefits of running, can help to further improve our training efforts, and more importantly, our academic life.

References

[1] Asics, “NEW STUDY EXPLORES THE WORLD'S NEW-FOUND LOVE OF RUNNING: ASICS South Africa.” [Online]. Available: https://www.asics.com/za/en-za/blog/article/new-study-explores-the-world's-new-found-love-of-running. [Accessed: 04-Nov-2020].

[2] P. by S. Lock and J. 31, “Running/jogging participants US 2006-2017,” *Statista*, 31-Jul-2019. [Online]. Available: https://www.statista.com/statistics/190303/running-participants-in-the-us-since-2006/. [Accessed: 04-Nov-2020].

[3] C. Gough, “Number of running events United States 2012-2016,” *Statista*, 29-Aug-2018. [Online]. Available: https://www.statista.com/statistics/280485/number-of-running-events-united-states/. [Accessed: 04-Nov-2020].

[4] “Running Gear Market by Share, Size, Growth and Forecast – 2023: MRFR,” *Running Gear Market by Share, Size, Growth and Forecast – 2023 | MRFR*. [Online]. Available: https://www.marketresearchfuture.com/reports/running-gears-market-4346. [Accessed: 04-Nov-2020].

[5] Louis Liebenberg and C. T. Conservation, “Persistence Hunting by Modern Hunter-Gatherers,” *Current Anthropology*, 01-Dec-2006. [Online]. Available: https://www.journals.uchicago.edu/doi/10.1086/508695. [Accessed: 04-Nov-2020].

[6] “'Run Leonidas Run': meet the stars of the track at the Ancient Olympic Games,” *International Olympic Committee*, 20-Dec-2018. [Online]. Available: https://www.olympic.org/ancient-olympic-games/running. [Accessed: 04-Nov-2020].

[7] C. Egan-Wyer, “The Sellable Self: Exploring endurance running as an extraordinary consumption experience,” *The Sellable Self - Lund University*, 30-Aug-2019. [Online]. Available: https://portal.research.lu.se/portal/en/publications/the-sellable-self(3e119423-2545-49c1-a619-2009ed6536c6).html. [Accessed: 04-Nov-2020].

[8] “Ancient Olympic Sports - running, long jump, discus, pankration,” *International Olympic Committee*, 20-Dec-2018. [Online]. Available: https://www.olympic.org/ancient-olympic-games/the-sports-events. [Accessed: 04-Nov-2020].

[9] E. Nix, “Why is a marathon 26.2 miles?,” *History.com*, 29-Oct-2014. [Online]. Available: https://www.history.com/news/why-is-a-marathon-26-2-miles. [Accessed: 04-Nov-2020].

[10] C. Gough, “Motivation to start running as a sport 2017,” *Statista*, 29-Aug-2018. [Online]. Available: https://www.statista.com/statistics/558667/motivation-to-start-running-as-a-sport/. [Accessed: 04-Nov-2020].

[11] C. Gough, “Motivation to continue running as a sport 2017,” *Statista*, 29-Aug-2018. [Online]. Available: https://www.statista.com/statistics/608651/motivation-to-continue-running-as-a-sport/. [Accessed: 04-Nov-2020].

[12] "Best medicine: the science of exercise shows benefits beyond weight loss." *Harvard Heart Letter*, July 1, 2013. *Gale Academic OneFile* (accessed November 4, 2020). https://link.gale.com/apps/doc/A335728499/AONE?u=nuslib&sid=AONE&xid=f05b9795.

[13] Lavie, Carl J. et al., "Effects of Running on Chronic Diseases and Cardiovascular and All-Cause Mortality," *Mayo Clinic Proceedings*, Volume 90, Issue 11, 1541 - 1552

[14] "Long-Distance Running: An Investigation Into its Impact on Human Health," *Long-Distance Running: An Investigation Into its Impact on Human Health | The People, Ideas, and Things (PIT) Journal*. [Online]. Available: https://pitjournal.unc.edu/article/long-distance-running-investigation-its-impact-human-health. [Accessed: 04-Nov-2020].

[15] Akhade, Varsha. (2014). "The effect of running training on pulmonary function tests," *National Journal of Physiology, Pharmacy and Pharmacology*. 4. 1. 10.5455/njppp.2014.4.151220131.

[16] van Praag, H., Kempermann, G. & Gage, F. Running increases cell proliferation and neurogenesis in the adult mouse dentate gyrus. *Nat Neurosci* **2,** 266–270 (1999). Available: https://doi-org.libproxy1.nus.edu.sg/10.1038/6368 [Accessed: 04-Nov-2020].

[17] F. R. Kruisdijk, I. J. M. Hendriksen, E. C. P. M. Tak, A. T. F. Beekman, and M. Hopman-Rock, "Effect of running therapy on depression (EFFORT-D). Design of a randomised controlled trial in adult patients [ISRCTN 1894]," *BMC public health*, 19-Jan-2012. [Online]. Available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3299590/. [Accessed: 04-Nov-2020].

[18] "Running helps brain stave off effects of chronic stress," *ScienceDaily*, 14-Feb-2018. [Online]. Available: https://www.sciencedaily.com/releases/2018/02/180214093823.htm. [Accessed: 04-Nov-2020].

[19] S. M. Jandhyala, R. Talukdar, C. Subramanyam, H. Vuyyuru, M. Sasikala, and D. Nageshwar Reddy, "Role of the normal gut microbiota," *World journal of gastroenterology*, 07-Aug-2015. [Online]. Available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4528021/. [Accessed: 04-Nov-2020].

[20] A. Moreira, L. Delgado, P. Moreira, and T. Haahtela, "Does exercise increase the risk of upper respiratory tract infections?," *OUP Academic*, 31-Mar-2009. [Online]. Available: https://academic.oup.com/bmb/article/90/1/111/324145. [Accessed: 04-Nov-2020].

[21] S. A. Martin, B. D. Pence, and J. A. Woods, "Exercise and respiratory tract viral infections," *Exercise and sport sciences reviews*, Oct-2009. [Online]. Available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2803113/. [Accessed: 04-Nov-2020].

[22] Nehlsen-Cannarella SL;Nieman DC;Jessen J;Chang L;Gusewitch G;Blix GG;Ashley E; "The effects of acute moderate exercise on lymphocyte function and serum immunoglobulin levels," *International journal of sports medicine*. [Online]. Available: https://pubmed.ncbi.nlm.nih.gov/1917224/. [Accessed: 04-Nov-2020].

[23] S. Schlabe *et al*, "Moderate endurance training (marathon-training) - effects on immunologic and metabolic parameters in HIV-infected patients: the 42 KM cologne project," *BMC Infectious Diseases,* vol. 17, 2017. Available: http://libproxy1.nus.edu.sg/login?url=https://www-proquest-

com.libproxy1.nus.edu.sg/docview/1934571371?accountid=13876. DOI: http://dx.doi.org.libproxy1.nus.edu.sg/10.1186/s12879-017-2651-y.

[24] Nieman DC;Berk LS;Simpson-Westerberg M;Arabatzis K;Youngberg S;Tan SA;Lee JW;Eby WC; "Effects of long-endurance running on immune system parameters and lymphocyte function in experienced marathoners," *International journal of sports medicine*. [Online]. Available: https://pubmed.ncbi.nlm.nih.gov/2599719/. [Accessed: 04-Nov-2020].

[25] Nieman, D.C. Marathon Training and Immune Function. *Sports Med* **37,** 412–415 (2007). https://doi-org.libproxy1.nus.edu.sg/10.2165/00007256-200737040-00036 [Accessed: 04-Nov-2020].

[26] 1D. of N. Sciences, "Exercise and the Gut Microbiome: A Review of the Evidence,... : Exercise and Sport Sciences Reviews," *LWW*. [Online]. Available: https://journals.lww.com/acsm-essr/fulltext/2019/04000/Exercise_and_the_Gut_Microbiome__A_Review_of_the.4.aspx?fbclid=IwAR0Q3CTLWukI-pRgi2Owjax9SOWH3dXbeyXrj7aRcu1_XxCRVVP2oNGUGBE. [Accessed: 04-Nov-2020].

[27] M Hasan Mohajeri, Giorgio La Fata, Robert E Steinert, Peter Weber, Relationship between the gut microbiome and brain function, *Nutrition Reviews*, Volume 76, Issue 7, July 2018, Pages 481–496, https://doi.org/10.1093/nutrit/nuy009

[28] D. Zielińska and D. Kołożyn-Krajewska, "Food-Origin Lactic Acid Bacteria May Exhibit Probiotic Properties: Review," *BioMed Research International*, 01-Oct-2018. [Online]. Available: https://www.hindawi.com/journals/bmri/2018/5063185/. [Accessed: 04-Nov-2020].

[29] V. Monda, I. Villano, A. Messina, A. Valenzano, T. Esposito, F. Moscatelli, A. Viggiano, G. Cibelli, S. Chieffi, M. Monda, and G. Messina, "Exercise Modifies the Gut Microbiota with Positive Health Effects," *Oxidative medicine and cellular longevity*, 2017. [Online]. Available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5357536/. [Accessed: 04-Nov-2020].

[30] "How Running a Marathon Changes Your Gut Microbes," *Inside Science*. [Online]. Available: https://insidescience.org/news/how-running-marathon-changes-your-gut-microbes. [Accessed: 04-Nov-2020].