Exercise as a Drug for Mental Health and Longevity

Annabel Kuhn, M.D., Yenifer Aponte, M.D., David Puder, M.D.

Dr. Seiler, Dr. Kuhn, Dr. Aponte and Dr. Puder have no conflicts of interest.

In this episode, Dr. Puder speaks with Dr. Stephen Seiler about the connection between mental health and physical activity.

Dr. Seiler grew up in Texas and Arkansas. As a child, Dr. Seiler was so passionate about science that he set up a laboratory under the staircase of his parents' home. Meanwhile, the young Dr. Seiler also loved sports. When he was 15 years old, he stumbled upon a book chapter titled "The Scientist of Sport"; it was then that he realized his two passions can coexist. Now, Dr. Seiler is known as one of the top exercise physiologists in the world and works in Norway.

Physical activity has been shown to reduce stress reactivity and reduce all cause mortality. Physical activity also results in decreased psychosocial stress. Today we explore this intersection and discuss the significance of incorporating physical exercise as a part of a robust mental health care plan.

Physical activity reduces all-cause mortality

A study from 2018 explored the association between cardiorespiratory fitness and long-term mortality. The study followed a group of 122,000 patients over 8.4 years, and it demonstrated that performance on a treadmill test predicted all-cause mortality. Of the 120,000 patients, 13,637 died by 8.4 year follow up. Of those that died, 23.7% (6,904) were in the "low performance" group on the treadmill test, and only 2.6% (93) were in the "elite" group on the treadmill test. Being an elite performer as opposed to a low performer resulted in a raw 10-fold reduction in all-cause mortality. The hazard ratio going from elite performance to low was 5.04, meaning there would be a 500% increase in risk of death if an elite performer became a low performer. To highlight how significant of a risk this truly is, in this study the hazard ratio for smoking was 1.41, which would mean that smoking causes a 40% increase risk in all-cause mortality.

Table 1. Patient Demographics[a]

Demographic	All Patients (N = 122 007)	Performance Group Low (n = 29 181)	Below Average (n = 27 172)	Above Average (n = 31 897)	High (n = 30 187)	Elite (n = 3570)
Age, mean (SD), y	53.4 (12.6)	53.7 (12.5)	53.2 (12.7)	53.3 (12.5)	53.5 (12.6)	53.3 (12.6)
Male	72 173 (59.2)	17 496 (60.0)	15 333 (56.4)	19 040 (59.7)	18 073 (59.9)	2231 (62.5)
Maximum No. of METs, mean (SD)	9.0 (2.7)	6.1 (1.7)	8.2 (1.6)	9.6 (1.7)	11.4 (1.8)	13.8 (1.5)
Estimated METs, mean (SD), %	101.2 (27.1)	68.0 (15.4)	92.5 (8.6)	107.6 (10.3)	128.0 (15.7)	155.9 (23.5)
BMI, mean (SD)	28.7 (5.8)	31.7 (7.3)	29.8 (5.5)	28.0 (4.6)	26.2 (3.9)	24.5 (3.4)
CAD	19 197 (15.7)	6472 (22.2)	4411 (16.2)	4409 (13.8)	3551 (11.8)	354 (9.9)
CABG or PCI	10 735 (8.8)	3975 (13.6)	2393 (8.8)	2350 (7.4)	1843 (6.1)	174 (4.9)
Diabetes	14 115 (11.6)	6387 (21.9)	3537 (13.0)	2590 (8.1)	1514 (5.0)	87 (2.4)
Hypertension	53 307 (43.7)	16 820 (57.6)	12 998 (57.8)	12 693 (39.8)	9846 (32.6)	2620 (26.6)
Hyperlipidemia	32 953 (27.0)	7323 (25.1)	7114 (26.2)	8552 (26.8)	8836 (29.3)	1128 (31.6)
ESRD	1385 (1.1)	900 (3.1)	251 (0.9)	148 (0.5)	79 (0.3)	7 (0.2)
Current or prior smoker	55 577 (45.6)	16 522 (56.6)	13 292 (48.9)	13 732 (43.1)	11 014 (36.5)	1017 (28.5)
Medication use						
Aspirin	40 680 (33.3)	11 353 (38.9)	9137 (33.6)	10 055 (31.5)	9051 (30.0)	1084 (30.4)
β-Blocker	29 620 (24.3)	10 975 (37.6)	6770 (24.9)	6476 (20.3)	4957 (16.4)	442 (12.4)
Statin	32 000 (26.2)	8617 (29.5)	7177 (26.4)	7991 (25.1)	7360 (24.4)	855 (24.0)
Follow-up, median (IQR), y	8.4 (4.3-13.4)	7.9 (3.8-13.1)	9.0 (4.5-14.2)	8.9 (4.6-14.1)	8.2 (4.3-12.8)	7.1 (3.8-10.7)
Death (all-cause)	13 637 (11.2)	6904 (23.7)	2888 (10.6)	2340 (7.3)	1412 (4.7)	93 (2.6)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CABG, coronary artery bypass grafting; CAD, coronary artery disease; ESRD, end-stage renal disease; IQR, interquartile range; METs, metabolic equivalents; PCI, percutaneous coronary intervention.

[a] Data are presented as number (percentage) of patients unless otherwise indicated. $P < .001$ for all categories.

Table 1 from Mandsager 2018

Dr. Seiler states that this 2018 study is representative and reinforces most or all of the research that has been done on physical activity and physical wellbeing. The London Transport Workers Study (published in 1953) was one of the first studies to explore the connection between physical activity and overall health. The study explored differences in health between tour bus drivers and tour bus guides. The bus drivers sat most of the day, whereas the guides are constantly getting off and on the bus. The guides demonstrated greater overall health. We have 60-70 years worth of studies and data that proves that human bodies are meant to be physically active.

One does not have to fall into the “elite performer” category to achieve health benefits. Dr. Seiler says that a reasonably consistent physical activity plan is beneficial, even if it is not extremely intense. Increasing the duration of moderate exercise is a great way to achieve the health benefits.

Mind-Body Connection During Exercise

Progressive physiologic stress helps us handle psychological stress. When we exercise, the brain is receiving an amazing amount of information from the body. This is known as afferent feedback–the body tells the brain where our limbs are in space and tells us about the chemical state around the muscles. There is also the perception of effort that occurs in a feed-forward and feed-back loop. The feed-forward arm involves the brain's awareness of how much muscle it is recruiting to do the physical action. Feedback signals from the muscles doing the work influence the brain and inform how much energy is being expended.

Signaling during movement and exercise promotes a conversation between mind and body, where the brain and body are asking one another, "How do I feel?", or "How much longer can I go at this intensity?". Teleoanticipation is defined as "the anticipation of the end of a physical task that allows more efficient expenditure of energy". Ask yourself to find a fairly difficult running pace that you could maintain for an hour. The brain learns quite rapidly about the body and is usually able to find this pace within 5-8 minutes of exercise. The brain is projecting out some rate of fatigue. The brain is learning to build physical courage, and you become more comfortable with the discomfort. In anticipation of fatigue, the brain develops strategies to handle or resist the negative feedback from the muscles. Thus, long-term athletes develop not only better ways for their bodies to physiologically process stress, but also develop ways to psychologically process discomfort.

Exercise Decreases Stress Reactivity

Stress reactivity is defined as the magnitude of the reaction to acute mental stress (Mücke 2018). Mucke and colleagues found 7 out of 12 studies showed that higher fitness levels had less adrenocortical stress reactivity. A 2010 meta-analysis demonstrated that a higher stress reactivity was associated with higher risk of subsequent cardiovascular complications. Fortunately, there is a way to reduce stress reactivity. One can increase physical activity in order to reduce stress reactivity and therefore reduce risk of cardiovascular complications. A meta-analysis from 2006 found that study participants with increased cardiorespiratory fitness levels showed lower cardiovascular reactivity. Specifically, they reported point estimates of -1.84 ($p < 0.005$) for HR, and - 3.69 ($p<0.001$) for systolic blood pressure. These findings suggest that higher fitness levels are associated with a blunted stress reactivity.

How do elite athletes exercise?

Dr. Seiler and his colleagues published a study in 2006 which quantified the daily distribution of training intensity in a group of well-trained junior cross-country skiers. This paper studied twelve male cross country skiers between ages 17-18. The athletes performed a continuous treadmill test to voluntary exhaustion to determine a heart rate and VO_2 corresponding to ventilatory thresholds (VT_1, VT_2), maximal oxygen consumption (VO_{2max}), and maximum heart rate. VT_1 and VT_2 as well as blood lactate measurements were used to delineate three intensity zones.

In our podcast, Dr. Seiler describes zone 1 as a “talking pace” level of aerobic exercise. Zone 2 is a “threshold zone”, in which the intensity is too difficult to hold a conversation. Zone 3 represents a high intensity of exercise at which individuals fatigue quickly.

Let’s first explore the zones in terms of lactate concentration. Zone 1 corresponds to ≤2.0mM lactate, zone 2, >2.0 and <4.0mM lactate, and zone 3, ≥4.0mM lactate. Seiler’s 2006 study analyzed 60 consecutive training sessions of athletes, 71% were performed with ≤2.0mM blood lactate, 7% between 2 and 4mM, and 22% with over 4mM (mean=9.5±2.8mM).

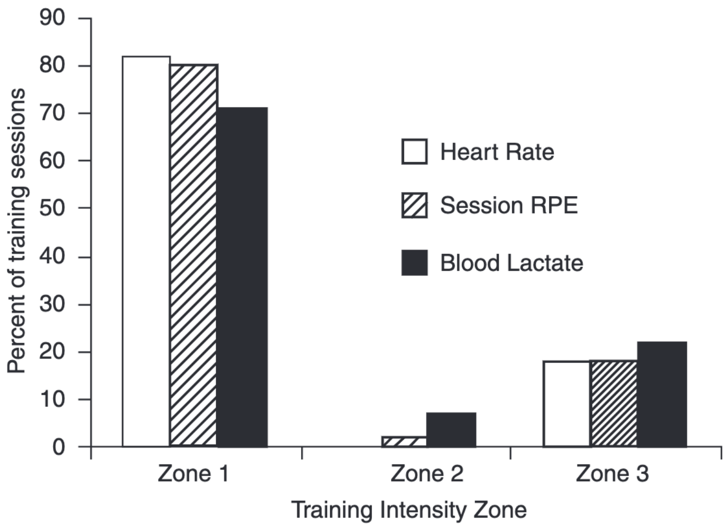

Fig. 4. Training intensity distribution for a continuous subset of 60 training sessions where heart rate, session RPE and blood lactate were recorded. There were no significant differences in intensity distribution among the three analysis methods. The heart rate bar is absent for zone 2 because none of the 60 sessions were identified in this zone based on heart rate.

Figure 4 from [Seiler 2006]

Next, let’s examine fitness zones in terms of heart rate. Intensity distribution across endurance training sessions (*n*=318) was similar when based on heart rate analysis (75±3%, zone 1; 8±3%, zone 2; 17±4%, zone 3) or session RPE (76±4%, zone 1; 6±5%, zone 2; 18±7%, zone 3).

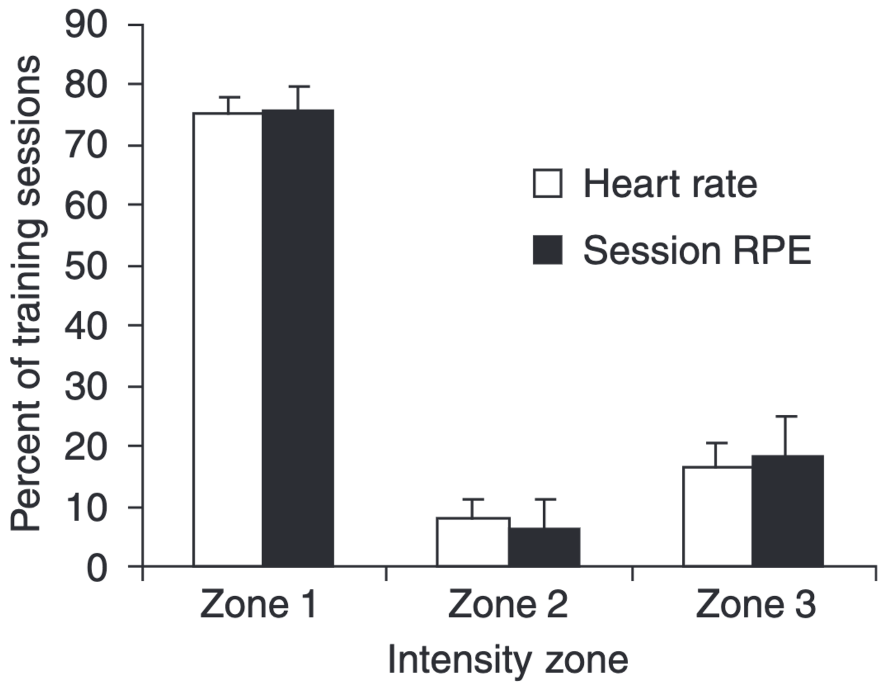

Figure 3 from Seiler 2006: “Training intensity distribution in 318 training bouts where heart rate records were complete and session RPE was recorded. There was no significant difference in intensity distribution between session-goal heart rate analysis and session RPE.”

It might surprise you that elite endurance athletes train primarily in zone 1. According to Dr. Seiler, for elite athletes, 80% to 90% of training sessions are actually spent in zone 1 where there is purposeful but reasonably comfortable intensity. There are indeed times when elite athletes train in zones 2 and 3, and those sessions are important, but the ratio of maintaining a high percentage of zone 1 exercise to zones 2 and 3 seems to be important for physical fitness.

In Seiler’s 2010 review he concludes that frequent, low intensity (≤2.0mM blood lactate), longer duration training is effective in stimulating physiological adaptations.

Measuring Maximum Heart Rate

As discussed above, it is useful to know your own maximum heart rate. Many people believe 220 minus your age is equivalent to a maximum heart rate; however, this is not accurate on an individual level. More accurate and personalized measures of maximum heart rate can be calculated based on an individual's own factors, such as their actual heart rate at maximum exercise. Dr. Seiler says that maximum heart rate does not have correlation with performance. Dr. Seiler says that it is also useful to know your resting heart rate. When you have your maximum and resting heart rate, now you know your range. If you want to stay at 65% of your maximum aerobic capacity, you multiply the range by .65. This will give you a number that you add to your resting heart rate. For example, Dr. Puder's maximum heart rate is 170 and his resting heart rate is 50, so his range is 170-50 = 120. Then multiplying .65 X 120 = 78, which you add to his resting heart rate of 50. So Dr. Puder's 65% of his maximum aerobic capacity is a heart rate of 128. Endurance athletes spend 80-90% of their workouts at a heart rate that is 60-70% of their aerobic capacity. For Dr. Puder this would be training around 122-134 beats per minute. You can check your resting heart rate by measuring your heart rate first thing in the morning. You can check your maximum heart rate with a heart rate monitor and do an intensive workout (like a treadmill with increasing the intensity every 1 minute till you can't go any longer) or going to an exercise laboratory test. As always, consult your physician before attempting something like this!

How Consistent Exercise Changes Our Physiology

I. San-Millán, G. A. Brooks

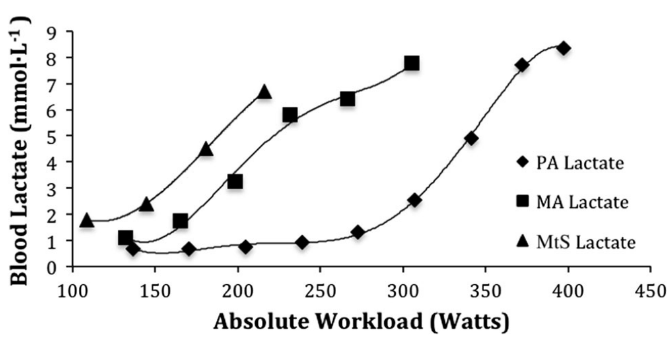

Fig. 1 Relationships between average blood lactate levels and exercise power outputs in international-level PAs, MAs, and individuals with MtS. *PAs* professional endurance athletes, *MAs* moderately active healthy individuals, *MtS* metabolic syndrome

Fig. 1 from San-Millán 2018

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San-Millán et al,, 2018 compared blood lactate levels (in millimoles per liter) and workload (in Watts) during bicycle exercise. The paper explored three groups, the first group was composed of individuals with diabetes mellitus or metabolic syndrome, the second group was made of individuals who are moderately active (three hours of exercise per week), and the third group was professional endurance athletes. Let's compare the absolute workload of the three groups at a blood lactate of 2 mmol/L. On average, individuals with metabolic syndrome produce around 125 Watts. On average, moderately active individuals produce 175 watts. Professional endurance athletes produce 275-300 watts, which is a phenomenal difference from the other two groups. What is happening on a cellular level?

Endurance exercise promotes mitochondrial proliferation. Muscle fibers synthesize more mitochondria and more mitochondrial enzymes that aerobically metabolize and use fuel to produce ATP. Essentially, you pack muscle fibers with more mitochondria and they become much more efficient at processing fats and carbohydrates. Mitochondria becomes particularly efficient at metabolizing carbohydrates because lactate is not produced.

Lactate is a small molecule that the body can use to essentially "transport" energy sources around the body. Lactate produced in one muscle fiber can be transported into another fiber where it can be converted into pyruvate and finally transported into the mitochondria of a cell in the muscle fiber. There is a beautiful interplay of fuel sources across fibers and in athletes with a high mitochondrial density there is a significant amount of lactate transportation and conversion into energy. Energy utilization is more efficient within the fibers because of the increased mitochondrial density.

There are three main energy sources that our muscles use: fat, carbohydrates, and stored carbohydrates (known as glycogen). Muscles use all three sources for energy during exercise. The muscles of a professional endurance athlete are optimized to use fat, glycogen, and glucose ***without*** an excessive lactate production. The combination is that high performance athletes have very flat lactate curves (as seen above in Fig. 1 from San-Millán 2018), where the intensity of exercise continues to increase, but the blood lactate level remains low. Finally, at 300 Watts, the lactate begins to increase. 300 Watts is the maximum capacity of most individuals, at which their blood lactate levels might be around 10 millimoles per liter, whereas an endurance athlete's blood lactate would be 3 millimolars per liter at this absolute workload. This phenomenal difference is a result of tremendous levels of low basic ("level 1") aerobic exercise over time.

After doing prolonged low intensity training, individuals become more efficient at using fat as a fuel source. This is a valuable adaptation. Let's say you are running a marathon (42.195km or 26.219 miles). Many people will "hit a wall", often at about the 30km mark or 18.64 miles. This occurs due to the muscle running out of glycogen as a fuel source. Every individual will "hit a wall" at some point when exercising, but the more experienced athletes will get to such a point much later than others. This is because endurance athletes spare their glycogen by using more fat for fuel.

Date	Time (minutes)	Absolute workload (Watts)	Average HR (BPM)	Lactic Acid (mg/dL)	Lactic Acid (mmol/L)	Notes
1/26/2022	5	177	118	22	1.22	
	5	209	126	24	1.33	
	4	247	147	75	4.17	
1/27/2022	5	210	128	30	1.67	
	5	219	136	41	2.28	
	5	219	136	32	1.78	Hard time getting poke, took 3 times trying
	10	200	137	35	1.94	

Dr. Puder rowed on his ergometer, took his average heart rate, average watts and measured his lactate every 5 minutes. His goal was to understand his corresponding heart rate for his lactate blood level of 2 mmol/L.

Dr. Seiler states that the first two data points on 1/26/22 are clear indicators that Dr. Puder is in a nice aerobic zone (zone 1) with no increase in blood lactate. There is a clear change from 209 to 247 watts, where Dr. Puder’s blood lactate is now 4.17 mmol/L (the beginning of zone 3). In order for Dr. Puder to achieve optimal aerobic exercise, he should aim for a maximum absolute workload of 215 Watts, at which point his blood lactate will be below 2 until he fatigues. This is consistent with his goal of 60-70% HR zone (122-134) which would be a lactate level just below 2 mmol of lactic acid. Over time the hope would be to produce more watts at a lower heart rate while producing less lactic acid. Optimizing the body's health will impact both longevity, mental wellness and cognitive function.

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Conclusion

Optimizing our bodies ability to perform in exercise increases longevity, wellness and decreases our stress reactivity. Most of us think that we need to enter into the red zone every workout to achieve results, whereas elite performers only do that around 10% of the time. With my personal training program, I enter into a heart rate zone of 60-70% for the majority of my workouts to optimize long-term performance enhancements. This optimal zone occurs when we produce less than 2 mmol lactic acid. We should be able to talk, but not sing, during this zone 1 training level. I prescribe exercise in this zone to clients along with strength training for optimization of mood and total wellness. Ideally, some of this time is spent in nature and out of a gym.

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