Exercise is medicine? The cardiorespiratory implications of ultra-marathon.

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ABSTRACT

Regular physical activity decreases the risk of cardiovascular disease (CVD), type II diabetes, obesity, certain cancers, and all-cause mortality. Nevertheless, there is mounting evidence that *extreme* exercise behaviours may be detrimental to human health. This review collates several decades of literature on the physiology and pathophysiology of ultra-marathon running, with emphasis on the cardiorespiratory implications. Herein, we discuss the prevalence and clinical significance of post-race decreases in lung function and diffusing capacity, respiratory muscle fatigue, pulmonary edema, biomarkers of cardiac injury, left/right ventricular dysfunction, and chronic myocardial remodelling. The aim of this paper is to inform risk stratification for ultra-marathon, and to edify best-practice for personnel overseeing the events (i.e., race directors and medics).

Key Words: cardiac; cardiovascular; lung; marathon; respiratory; ultra-endurance.

1.0 INTRODUCTION

Physical activity, including structured exercise, is preventative in a myriad of lifestyle-related diseases, including cardiovascular disease (CVD), type II diabetes, obesity, certain cancers, and all-cause mortality (1–4). Guidelines from the US Department for Health and Human Services (HHS), agreed upon by the American Medical Association (AMA) and the World Health Organization (WHO), are to engage in at least 150 - 300 minutes (2.5 - 5 hours) of moderate-intensity aerobic physical activity per week, and to perform muscle-strengthening exercises on two-or-more days of the week (5). Long periods of sedentary behaviour (e.g., uninterrupted office work) has been independently associated with an increased risk of cardiovascular disease (6). Accordingly, a focus of recent study has been workplace interventions to reduce sitting time (7).

In 2010, approximately one-third of the world's population was classified as physically inactive (8). To combat the high prevalence of physical inactivity, and the associated health and financial burden, the AMA and the American College of Sports Medicine (ACSM) jointly-established the *Exercise is Medicine* initiative to elevate the status of physical activity in primary healthcare. The program called for the integration of basic physical activity and exercise prescription into the standard patient care process (9). The initiative further advocated that every patient receives an assessment for physical activity levels, counselling, exercise prescription, and a physical activity referral (e.g., to an exercise professional, physiotherapist, or wellness program). This concept characterizes exercise like a medication, with a "dose" that includes frequency, intensity, duration, and mode. As with all medicines, there is a minimum dose required to evoke a physiological benefit, an optimum range, and a maximum dose above which further benefits will not be obtained. There is also likely to be a dose above which any medication, including exercise, causes toxicity. For exercise training, the therapeutic ratio is high, but not infinite.

Indeed, paradoxical to the data concerning the harmful effects of physical inactivity, there is a growing body of work suggesting that *extreme* exercise behaviours may be detrimental to human health. The number of individuals participating in ultra-marathon has been steadily increasing for several decades (10). While an ultra-marathon is generally defined as a footrace that exceeds the marathon distance of 26.2 miles (42.2 km) (11), the actual distances contested in single-stage competition can be extreme and highly-variable, requiring exercise bouts lasting between 6 and 48 h; for example: Blackwater Trail in Florida, USA (31 miles/50 km); Comrades Marathon in Durban, South

Africa (56 miles/90 km); Western States Endurance Run in California, USA (100 miles/161 km); and Spartathlon in Athens, Greece (152 miles/245 km). The distances of multi-stage races can range from 150 miles/240 km (Marathon Des Sables in the Sahara Desert, Africa) to 3100 miles/4989 km (Self-Transcendence 3100 in New York, USA). The combined physiological stress evoked by race distance/duration, the remote locations, varying terrain, and extremes of temperature and altitude, has the potential to evoke pathological consequences for all body systems (12). Accordingly, there may be an upper-limit beyond which the risks of exercise engagement exceed the benefits. Moreover, if such an ‘upper-limit’ does exist, it is yet to be defined and remains a topic of contention among scientists and health professionals.

This review draws attention to the general physiology and pathophysiology of ultra-marathon running, with emphasis on the cardiorespiratory implications. The aim of the paper is to inform risk stratification for the sport, and edify best-practice for personnel overseeing the events (i.e., race directors and medics).

2.0 DISCUSSION

2.1 Physiological characteristics of ultra-marathon runners

Ultra-marathon runners generally contest their first race at the age of 36 y, following ~7 y of competition in running races of shorter distance (13). Relative to marathon or half-marathon, peak performance in ultra-marathon tends to occur at an older age, and the age of peak performance increases with race distance (Table 1.0) (12). There is broad variability in the physical characteristics of ultra-marathon runners. Nevertheless, a cohort of athletes contesting 24 h races were reported as having a mean body mass of ~73 kg (14), while elite runners contesting similar distances exhibited values of ~60 kg (15). Marathon running is thought to evoke ~75% $\dot{V}O_2$max and moderate-to-high levels of pulmonary ventilation (>80 L·min^{-1}) (16), but there is a paucity of equivalent data in ultra-marathon running. Given that ultra-marathon runners complete more miles at a slower velocity than marathon runners (17), it is reasonable to assume that ultra-marathon will generally evoke values below that reported in marathon. Maximal aerobic power and velocity at $\dot{V}O_2$max still appear to be important predictive variables in ultra-marathon performance (14,18). Surveys of >1,200 ultra-marathon runners show them as healthier than age-matched population norms, with rare instances of coronary heart disease (~0.7%), cancer (~4.5%), stroke (~0.7%), and diabetes (~0.7%) (19), although these data may be subject to selection bias. By contrast, allergies (~25%) and exercise-induced asthma (~13%) were reported as more prevalent in ultra-marathon runners (19). Finally, while the incidence of sudden cardiac arrest in runners is 0.54 per 100,000, it is significantly higher during marathons versus half-marathons (1.01 vs. 0.27 per 100,000), and higher in males versus females (0.90 vs. 0.16 per 100,000) (20). There are no data to this effect specific to ultra-marathon.

2.2 Influence of ultra-marathon on the respiratory system

In terms of the maximal capacity for ventilation, the respiratory machinery is thought to be overbuilt for the demands of exercise. Nevertheless, there are several mechanisms that potentially limit pulmonary performance, including: airflow limitation, narrowing/obstruction of the upper-airway, exercise-induced arterial hypoxemia owing to a widened alveolar-arterial O_2 pressure difference, and respiratory muscle fatigue (21,22). In a study of 110 endurance runners, lung function (spirometry) was negatively and independently associated with

marathon time (FVC; $r = -0.41$, $p < 0.001$: FEV_1; $r = -0.40$, $p < 0.001$: PEF; $r = -0.50$, $p = 0.005$) (23). While causation cannot be determined, these data offer an interesting insight into the potential impact of lung function on endurance performance. Most commonly determined via spirometry (the ability to inspire and expire volumes of air as a function of time), the lung function response to marathon running was studied in the 1920s (24), but equivalent data in ultra-marathon were not published until several decades later. The first study to assess changes in pulmonary function in response to a 100-km footrace (Lake Waramaug Ultra in Connecticut, USA) reported significant post-race decreases in FVC, FEV_1, and PEF in the region of 10–15% (25). The diminished lung function was attributed, at least in part, to small airway obstruction manifesting as a post-race decrease in maximal mid-expiratory flow at 50% FVC (MEF_{50}). These early data have since been replicated in footraces of longer distance; e.g., 110 km (26), 330 km (27), and 24-h running (28).

The aforementioned studies report inconsistent evidence of airway obstruction (for review, see [29]) and, therefore, the mechanisms that underpin the acute post-race decreases in lung function are not definitively known. Using the exhaled nitric oxide technique, airway inflammation and subsequent obstruction have been observed in non-asthmatics following marathon running (30). Others report a greater relative increase in pulmonary pro-oxidative levels (hydrogen peroxide and nitrogen dioxide) following marathon running when compared to half-marathon or the 10-km distance, suggesting that running time is positively associated with the magnitude of the acute post-exercise, pro-oxidative state (31). However, there are limited data to support this hypothesis in ultra-marathon. It is also likely that ultra-marathon evokes a degree of fatigue in the respiratory muscles, thereby reducing their force-generating capacity (see below). Despite numerous reports of pulmonary dysfunction following marathon and ultra-marathon, a recent reanalysis of the data using regression equations from the Global Lung Function Initiative (32) revealed that post-race parameters rarely fall below the lower-limits of normal, and that the post-race FEV_1/FVC ratio remains acceptable in all studies (range 0.78–0.85) (29). Thus, for most individuals (at least in the published literature), the post-race decreases in lung function following ultra-marathon are unlikely to be of clinical concern. Ultra-marathon may provoke more pronounced clinical manifestations in individuals with below-average baseline function, or in those with pre-existing respiratory disorders (e.g., asthma).

There are other important perturbations of the pulmonary system following prolonged running that warrant consideration. For instance, exercise-induced pulmonary edema – an abnormal accumulation of extravascular lung water (EVLW) – has been observed (via radiographic analysis) in 17% of marathon runners, although this finding did not associate with either lung function or marathon performance (33). Exposure to hypobaric hypoxia alone has been observed to evoke increased lung water in animal models (34). Accordingly, pulmonary edema could be expected to occur during long duration ultra-marathons performed at altitude, but this has only been recently investigated. In a series of studies, pulmonary function and edema were assessed in 75 ultra-marathon runners contesting 100 mile/160 km footraces at moderate-to-high altitude (Ultra-Trail du Mont-Blanc and the Hong Kong 100). The authors observed a mean post-race increase in the frequency of echocardiographic 'comet tails' – a sign of EVLW - with decreased lung diffusing capacity and alveolar-capillary membrane conductance (35). Extravascular lung water and gross decreases in alveolar-capillary membrane diffusion were more pronounced in a small subset of runners, suggesting that some individuals have an increased propensity for developing pulmonary edema under these conditions (35). Decreases in lung diffusing capacity also occurred congruent with reductions in right ventricular function (36). Given that right ventricular dysfunction following ultra-marathon is more prominent when compared to left ventricular dysfunction (37), these data indicate that there may be a disproportionate hemodynamic load on the pulmonary circulation (heart and lungs) compared to that of the periphery during ultra-endurance exercise (38). Moreover, it is likely that the most pronounced cardiopulmonary perturbations are mediated by the combined stimuli of exercise intensity, duration, and environmental factors (e.g., exposure to cold, dry, hypobaric hypoxic air) (39,40). These data, that mechanistically link transient dysfunction of the cardiac and pulmonary systems, are now enabling a more integrative and robust interpretation of the physiology and pathophysiology of ultra-marathon.

The main respiratory concerns of long-term participation relate to a mismatch between airway caliber and increased ventilation during exercise. There may also be chronic airway inflammation (exercise-induced asthma [EIA], exercise-induced bronchoconstriction [EIB], and airway hyperresponsiveness) particularly when training and competing in cold, dry conditions (22). In a sample of >1,200 ultra-marathon runners, EIA was reported in 13% (19), likely the result of chronic airway dehydration and subsequent damage and

inflammation (41), although this is far lower than that observed in Olympic athletes (20%) assessed using bronchodilator and bronchoprovocation tests (42). The self-reported 11% prevalence of asthma in ultra-marathon runners (19) is similar to 8% observed in the general population (43). Larger studies with longer follow-ups are required to further elucidate the chronic respiratory consequences of participation.

2.2.1 Respiratory muscle fatigue

Another widely-studied aspect of respiratory function during exercise is the behaviour of the muscles of respiration, specifically the diaphragm and major abdominals, which have important roles in ventilating the lungs and in postural control. Respiratory muscle fatigue is a phenomenon whereby muscles attached to the thoracic cage exhibit a reduced force-generating capacity relative to baseline measures, usually following exhaustive high-intensity exercise (21). Respiratory muscle fatigue has the potential to compromise exercise ventilatory capacity, exacerbate dyspnea, and compromise limb-locomotor blood flow via an exercise-induced metaboreflex (21).

Using mouth-pressure manoeuvres as a surrogate for respiratory muscle force output, several studies report evidence of respiratory muscle fatigue following ultra-marathon (for review, see [29]). Mouth-pressure manoeuvres involve maximal inspiratory/expiratory efforts against an occluded mouthpiece. The technique is non-invasive and generally reproducible, but limited in that the manoeuvres are volitional, subject to athlete motivation and a practice effect. Only one study has assessed inspiratory muscle fatigue objectively (using magnetic nerve stimulation) following ultra-marathon. By inducing action potentials in the phrenic nerves (those innervating the diaphragm), Wüthrich *et al*. provoked involuntary inspiratory muscle contractions in 16 runners following a 110-km ultra-marathon, observing a significant (19%) reduction in the post-race mouth twitch-pressure (26). Their data support the notion that inspiratory muscle fatigue following ultra-marathon is likely due to peripheral neuromuscular factors, as opposed to those which are centrally-mediated (Figure 1). Worthy of note is that the race of interest (The Ultra-Trail du Mont-Blanc, which begins in the French Alps) is characterized by moderate-to-high altitude, high elevation gain, strict qualifying standards, and necessitates runners of exceptional ability and experience. Thus, it is likely that the course induced substantial and sustained pulmonary ventilation above-and-beyond that observed in most other race types, thus, predicating the observed fatigue. The

clinical implications of respiratory muscle fatigue remain unclear, especially for athletic populations. Moreover, research is needed to explore the consequences for individuals who begin ultra-marathons with below-average function.

Accordingly, with extreme physical effort, the capabilities of the respiratory system may be exceeded acutely, resulting in a relative post-race dysfunction. Nevertheless, most parameters tend to recover within 24-48 h, and the respiratory system appears sufficiently robust to meet the body's metabolic needs in most instances. While there may be certain training-induced maladaptations in healthy subjects, chronic structural remodelling is more apparent in the cardiovascular system.

2.3 Influence of ultra-marathon on the cardiovascular system

Given the durations of ultra-marathons, and the associated dependence on aerobic energy transfer, much of the literature has focused on potential implications for the cardiovascular system. Acute functional and biochemical cardiac abnormalities are common following intense endurance exercise, although their clinical significance has been debated (44). As with most endurance events, concentrations of cardiac biomarkers (e.g., creatine kinase-MB, cardiac troponin I) increase following any given ultra-marathon (45–47), although observations of a training-induced increase in muscle CK-MB discount the notion that this indicates a significant degree of myocardial tissue damage (48). Higher absolute exercise intensities are generally associated with the greatest increases in troponin concentrations, and faster ultra-marathon runners tend to exhibit greater troponin concentrations relative to slower runners (49). While the appearance of myocardial biomarkers appears to be a common, transient response to ultra-marathon, more research is needed to elucidate its clinical implications, particularly in relation to ultra-marathon runners who rarely experience chronic myocardial injury.

In terms of functional cardiac changes, ultra-endurance exercise appears sufficient to acutely evoke both left ventricular (LV) and right ventricular (RV) dysfunction and/or fatigue. Impaired cardiac contractility and altered preload have been observed in finishers of the Hawaii Ironman Triathlon (50). Moreover, a 100-mile (160 km) ultra-marathon (Western States endurance Run in California, USA) evoked a decrease in stroke volume from 77 ± 12 mL at baseline to 64 ± 13 mL immediately post-race (51); values that approached the lower-limits of normal. Other studies performing transthoracic echocardiography have revealed

post-marathon decreases in both LV and RV systolic/diastolic function in amateur runners, but while systolic parameters were transient, diastolic abnormalities persisted at 1-month follow-up (52). The mechanisms responsible for diminished post-race stroke volume are incompletely understood, but may include RV dysfunction and horizontal RV-LV interaction, enhanced vagal reactivation (53), a downregulation of cardiac β-adrenoreceptors mediated by elevated catecholamines (54), disrupted biochemical homeostasis second to elevated free fatty acids (55), and abnormal calcium reuptake owing to a decrease in sarcoplasmic reticulum calcium ATPase (56).

Despite acute post-race LV dysfunction in some athletes, the response is generally transient and benign. Endurance-exercise-associated remodelling of the LV is actually thought to be a favourable adaptation to chronic training and, moreover, LV size is a predictive variable in ultra-marathon performance (57). Following ultra-endurance exercise, there is also a reduction in right ventricular ejection fraction (58) and, when compared to the left ventricle, right ventricle dysfunction may be more pronounced and less reversible (37). The notion that the magnitude of RV dysfunction may be congruent with exercise intensity and/or duration has been explored by La Gerche *et al.* (59). Echocardiography was performed on athletes contesting one-of-four races of varying duration: marathon (mean duration ~3 h); half-Ironman Triathlon (~5.5 h); Alpine cycling (~8 h); and Ironman Triathlon (~11 h). While LV function was retained across race type, there were significant post-race reductions in all metrics of RV function, including ejection fraction. Pertinently, RV stroke volume remained depressed at 1-week follow-up and, while acute recovery appeared complete, the authors observed chronic RV structural changes and myocardial fibrosis in a small subset of athletes who exhibited the longest competition history (Figure 2) (59).

Indeed, chronic RV remodelling is most commonly observed in highly-trained athletes who compete frequently in events of duration longer than marathon (60,61). In a study of lifelong, veteran male marathon and ultra-marathon runners undergoing cardiac magnetic resonance (CMR) imaging with late gadolinium enhancement, the athletes exhibited larger absolute and indexed LV and RV end-diastolic and systolic volumes, intraventricular septum thickness during diastole, posterior wall thickness during diastole, and reduced LV and RV ejection fractions relative to age-matched controls (62). Moreover, six-of-twelve athletes presented with evidence of myocardial fibrosis detected using late gadolinium enhancement, and this was positively associated with the

number of years training ($p < 0.001$), number of competitive marathons ($p < 0.001$), and ultra-marathons ($p < 0.007$) (62). Despite the small sample size, these data collectively suggest that chronic participation in ultra-endurance sport may result in pathological changes in myocardial structure and function; indeed, under such conditions, it is possible that an arrhythmogenic right ventricular cardiomyopathy (ARVC)-like phenotype may be acquired through intense exercise without an identifiable genetic predisposition (60).

An important consideration is whether or not chronic changes in cardiovascular structure and/or function – should they be reasonably replicated and shown in larger samples – result in an increased risk of mortality in otherwise healthy individuals, especially when considering the benefits of regular exercise in lowering CVD risk (3). Early research suggests protective effects of such training. Following nitroglycerin administration, ultra-marathon runners were found to have significantly greater coronary artery vasodilatory capacity when compared to age-matched, healthy controls, and a greater left ventricular mass index (152 vs. 116 g/m2) (63). Moreover, in a longitudinal study of >2,000 highly-active and healthy individuals, treadmill testing, coronary artery calcium (CAC) scanning, and a 10-y follow-up revealed that those with extraordinary levels of physical activity (>10,000 MET·min·wk^{-1}) exhibited no greater CAC scores, and no greater risk of mortality, when compared to the those who engaged in lower-levels of activity (64). Accordingly, these data question the notion that changes in cardiac morphology associated with extreme exercise behaviours represent a clinical concern, and such engagement may even bestow beneficial effects.

Worthy of consideration is that the extreme exercise behaviours studied (~35 h·wk^{-1} of moderate-intensity physical activity) are unlikely to evoke a similar physiological stress to that imposed by periodic participation in ultra-marathon competition; i.e., it may be repeated exposure to the stress of racing, rather than high-volume training, that leads to chronic cardiovascular abnormalities. Indeed, even ultra-marathon runners who devote many hours per week to accumulating a high weekly mileage, are unlikely to replicate in training the magnitude of stress/strain encountered during competition, the latter of which may exceed 24-h duration. As such, the demands and periodic stress of endurance *competition* may be an important independent risk factor that warrants closer study.

2.4 Additional considerations

A full discussion of the various facets underpinning ultra-marathon performance - such as hydration status, energy and electrolyte balance - is outside the scope of this manuscript (see [65] for further review). Nevertheless, further to the cardiorespiratory implications discussed, several issues deserve brief consideration owing to their substantial influence on ultra-marathon success. First, ultra-marathon runners must endure severe muscle damage, particularly in the course of racing. Creatine kinase concentrations following the Western States Endurance Run in California, USA (100 miles/161 km) increased from 117 U/l at baseline to 17,965 U/l (66), values which vastly-exceeded healthy norms. Others have observed whole-blood markers of muscle breakdown to be higher following ultra-marathons compared to marathons run at a relatively faster pace (67,68). These data suggest that race distance and/or duration may mediate muscle damage more than race intensity. Most ultra-marathons are contested on undulating and/or mountainous terrain, and the magnitude of muscle damage may be attributable, at least in part, to downhill running which itself is associated with greater joint flexion angles relative to level or uphill running. This exaggerates the eccentric component of impact-loading, thereby increasing muscle damage (69).

Second, a common cause of non-completion and/or reduced performance in ultra-marathon is gastrointestinal (GI) distress. A conservative estimate is that 30 - 50% of athletes experience GI-related issues during ultra-marathon (70), although others report values as high as 70 - 80% (71,72). The pathophysiology of GI distress in ultra-marathon is multifactorial, but is likely attributable to reduced mesenteric blood flow and a relative GI hypoperfusion (73). This is often predicated by dehydration, ingestion of highly-concentrated carbohydrates, and/or increased core temperature (65). Learning to mitigate both muscle damage and GI distress is an important component of the periodized training and nutrition program. These factors should be considered alongside the respiratory and cardiovascular responses to racing in order to provide integrated support to the ultra-marathon runner.

2.5 Implications and future considerations

There are a number of considerations in answering the primary question: *is ultra-marathon bad for health?* In short, while there are several studies in ultra-marathon that have failed to observe race-induced increases in cardiac troponin (45), or 12-lead ECG abnormalities (74), these findings are in the minority. In general, ultra-marathon running evokes an acute but substantial reduction in

both respiratory and cardiovascular function. Post-race changes include decreases in lung function, diffusing capacity, an apparent decrease in respiratory muscle contractile force, increased potential for pulmonary edema in certain individuals, and diminished systolic/diastolic function perhaps attributable to fatigue and/or injury to the left and right ventricles. Importantly, in most individuals and with the exception of certain metrics of RV function, these changes appear transient, and likely abate within 1-week of competition. Chronically, however, there is the potential for pathological airway remodelling (as with most endurance sports), and structural/functional cardiac abnormalities (including arrhythmias, hypertension, and myocardial fibrosis) which deserve closer scrutiny.

Subsequently, the other pertinent question is: *are such maladaptations clinically meaningful, and do they result in an increased risk of mortality?* This question continues to be debated (44,58,74), and more data are needed to draw definitive conclusions. Until then, attention must be focussed on identifying those individuals who may be at the highest risk for long-term damage. There are currently no proven screening strategies for detecting pathologic cardiovascular changes associated with extreme endurance exercise. Moreover, while use of post-competition ECG, cardiac imaging, and assessment of cardiac biomarkers have been suggested to help identify those individuals most susceptible to negative consequences (58), this is unlikely to be financially viable on a large scale (75). Accordingly, the notion of *shared decision making* (76) is pertinent for ultra-marathon runners; clinicians and athletes should work together to consider the evidence, and make balanced decisions on long-term participation that incorporate the risks/expected outcomes, and patient preferences and values.

Irrespective of the aforementioned research, when ultra-marathon runners were posed the question - *If you were to learn, with absolute certainty, that ultramarathon running was bad for your health, would you stop your ultramarathon training and participation?* – 74% of 1,349 runners responded that they would not (77). Interestingly, this group tended to exhibit higher personal goal achievement, higher ratings of psychological coping, and higher life-meaning scores on the Motivations of Marathoners Scales (77). These data suggest that the majority of runners prioritize continued participation in ultra-marathon over the potential health risks, likely compounded because, despite its popularity as a competitive sport, most ultra-marathon runners approach racing as a means of personal accomplishment (78). Ultra-marathon runners

also exhibit significantly greater exercise dependence relative to marathon runners or athletes contesting races of shorter distance (79). When collated with the research showing negative physiological outcomes with long-term participation, it is likely that ultra-marathon runners may be at a greater risk of exercise-induced pathology when compared to other exercising subgroups. Finally, while the risk of such pathology is likely minimal relative to the risks associated with chronic physical inactivity, there is a middle-ground which likely maximises the physical and psychological benefits of participation, while mitigating the possible contraindications of extreme endurance endeavours. An important, yet unexplored, question is to what extent the chronic structural/functional changes are attributable to exercise training or, instead, the cumulative stress of periodic racing.

3.0 Conclusions

The physiological, psychological, and sociological benefits of ultra-marathon running are extensive. Nevertheless, acute dysfunction of the respiratory and cardiovascular systems is highly-likely following any given competition, and chronic structural/functional abnormalities occur in a small subset of susceptible individuals. More data are needed to elucidate the clinical significance of these findings.

REFERENCES

1. Thompson PD, Eijsvogels TMH. New physical activity guidelines: A call to activity for clinicians and patients. *JAMA - Journal of the American Medical Association*. 2018;320(19):1983-1984. doi:10.1001/jama.2018.16070

2. Lee IM, Skerrett PJ. Physical activity and all-cause mortality: What is the dose-response relation? In: *Medicine and Science in Sports and Exercise*. Vol 33. ; 2001. doi:10.1097/00005768-200106001-00016

3. Kohl HW. Physical activity and cardiovascular disease: Evidence for a dose response. In: *Medicine and Science in Sports and Exercise*. Vol 33. ; 2001. doi:10.1097/00005768-200106001-00017

4. Chin SH, Kahathuduwa CN, Binks M. Physical activity and obesity: what we know and what we need to know. *Obesity Reviews*. 2016;17(12):1226-1244. doi:10.1111/obr.12460

5. Physical Activity Guidelines for Americans | HHS.gov. https://www.hhs.gov/fitness/be-active/physical-activity-guidelines-for-americans/index.html. Accessed January 27, 2020.

6. Henschel B, Gorczyca AM, Chomistek AK. Time Spent Sitting as an Independent Risk Factor for Cardiovascular Disease. *American Journal of Lifestyle Medicine*. September 2017:155982761772848. doi:10.1177/1559827617728482

7. Shrestha N, Kukkonen-Harjula KT, Verbeek JH, Ijaz S, Hermans V, Pedisic Z. Workplace interventions for reducing sitting at work. *Cochrane Database of Systematic Reviews*. 2018;2018(6). doi:10.1002/14651858.CD010912.pub4

8. Hallal PC, Andersen LB, Bull FC, et al. Global physical activity levels: Surveillance progress, pitfalls, and prospects. *The Lancet*. 2012;380(9838):247-257. doi:10.1016/S0140-6736(12)60646-1

9. Lobelo F, Stoutenberg M, Hutber A. The exercise is medicine global health initiative: A 2014 update. *British Journal of Sports Medicine*. 2014;48(22):1627-1633. doi:10.1136/bjsports-2013-093080

10. Hoffman MD, Ong JC, Wang G. Historical analysis of participation in 161km ultramarathons in North America. *International Journal of the History of Sport*. 2010;27(11):1877-1891. doi:10.1080/09523367.2010.494385

11. Nicolas M, Banizette M, Millet GY. Stress and recovery states after a 24 h ultra-marathon race: A one-month follow-up study. *Psychology of Sport and Exercise*. 2011;12(4):368-374. doi:10.1016/j.psychsport.2011.03.005

12. Knechtle B, Nikolaidis PT. Physiology and pathophysiology in ultra-marathon running. *Frontiers in Physiology*. 2018;9(JUN). doi:10.3389/fphys.2018.00634

13. Hoffman MD, Krishnan E. Exercise behavior of ultramarathon runners: Baseline findings from the ULTRA study. *Journal of Strength and Conditioning Research*. 2013;27(11):2939-2945. doi:10.1519/JSC.0b013e3182a1f261

14. Millet GY, Banfi JC, Kerherve H, et al. Physiological and biological factors associated with a 24 h treadmill ultra-marathon performance. *Scandinavian Journal of Medicine & Science in Sports*. 2011;21(1):54-61. doi:10.1111/j.1600-0838.2009.01001.x

15. Stellingwerff T. Competition nutrition practices of elite ultramarathon runners. *International Journal of Sport Nutrition and Exercise Metabolism*. 2016;26(1):93-99. doi:10.1123/ijsnem.2015-0030

16. Mahler DA, Loke J. The physiology of marathon running. *Physician and Sports Medicine*. 1985;13(1):84-97. doi:10.1080/00913847.1985.11708729

17. Rüst CA, Knechtle B, Knechtle P, Rosemann T. Comparison of anthropometric and training characteristics between recreational male marathoners and 24-hour ultramarathoners. *Open Access Journal of Sports Medicine*. 2012;2012:3-121. doi:10.2147/OAJSM.S37389

18. Davies CTM, Thompson MW. Aerobic performance of female marathon and male ultramarathon athletes. *European Journal of Applied Physiology and Occupational Physiology*. 1979;41(4):233-245. doi:10.1007/BF00429740

19. Hoffman MD, Krishnan E. Health and exercise-related medical issues among 1,212 ultramarathon runners: Baseline findings from the Ultrarunners Longitudinal TRAcking (ULTRA) Study. *PLoS ONE*. 2014;9(1). doi:10.1371/journal.pone.0083867

20. Kim JH, Malhotra R, Chiampas G, et al. Cardiac Arrest during Long-Distance Running Races. *New England Journal of Medicine*. 2012;366(2):130-140. doi:10.1056/NEJMoa1106468

21. Romer LM, Polkey MI. Exercise-induced respiratory muscle fatigue: Implications for performance. *Journal of Applied Physiology*. 2008;104(3):879-888. doi:10.1152/japplphysiol.01157.2007

22. Bussotti M, Marchese G, di Marco S. Respiratory disorders in endurance athletes – how much do they really have to endure? *Open Access Journal of Sports Medicine*. April 2014:47. doi:10.2147/oajsm.s57828

23. Salinero JJ, Soriano ML, Ruiz-Vicente D, et al. Respiratory function is associated to marathon race time. *Journal of Sports Medicine and Physical Fitness*. 2016;56(12):1433-1438.

24. Gordon B, Levine SA, Wilmaers A. Observations on a group of marathon runners: With special reference to the circulation. *Archives of Internal Medicine*. 1924;33(4):425-434. doi:10.1001/archinte.1924.00110280023003

25. Mahler DA, Loke J. Pulmonary dysfunction in ultramarathon runners. *The Yale Journal of Biology and Medicine*. 54(4):243-248. http://www.ncbi.nlm.nih.gov/pubmed/7324502. Accessed January 26, 2020.

26. Wüthrich TU, Marty J, Kerherve H, Millet GY, Verges S, Spengler CM. Aspects of respiratory muscle fatigue in a mountain ultramarathon race. *Medicine and Science in Sports and Exercise*. 2014;47(3):519-527. doi:10.1249/MSS.0000000000000449

27. Vernillo G, Rinaldo N, Giorgi A, et al. Changes in lung function during an extreme mountain ultramarathon. *Scandinavian Journal of Medicine and Science in Sports*. 2015;25(4):e374-e380. doi:10.1111/sms.12325

28. Warren GL, Cureton KJ, Sparling PB. Does lung function limit performance in a 24-hour ultramarathon? *Respiration Physiology*. 1989;78(2):253-263. doi:10.1016/0034-5687(89)90057-1

29. Tiller NB. Pulmonary and Respiratory Muscle Function in Response to Marathon and Ultra-Marathon Running: A Review. *Sports Medicine*. 2019;49(7):1031-1041. doi:10.1007/s40279-019-01105-w

30. Bonsignore MR, Morici G, Riccobono L, et al. Airway inflammation in nonasthmatic amateur runners. *American Journal of Physiology - Lung Cellular and Molecular Physiology*. 2001;281(3 25-3). doi:10.1152/ajplung.2001.281.3.l668

31. Araneda OF, Guevara AJ, Contreras C, Lagos N, Berral FJ. Exhaled breath condensate analysis after long distance races. *International Journal of Sports Medicine*. 2012;33(12):955-961. doi:10.1055/s-0032-1316314

32. Global Lung Function Initiative. https://www.ers-education.org/guidelines/global-lung-function-initiative.aspx. Accessed January 27, 2020.

33. Zavorsky GS, Milne ENC, Lavorini F, et al. Small changes in lung function in runners with marathon-induced interstitial lung edema. *Physiological Reports*. 2014;2(6). doi:10.14814/phy2.12056

34. Levine BD, Kubo K, Kobayashi T, Fukushima M, Shibamoto T, Ueda G. Role of barometric pressure in pulmonary fluid balance and oxygen transport. *Journal of Applied Physiology*. 1988;64(1):419-428. doi:10.1152/jappl.1988.64.1.419

35. Stewart G, Jorgenson C, Wheatley C, et al. Effect Of Ultra-endurance Exercise On Alveolar-Capillary Recruitment And Lung Diffusion. *Medicine & Science in Sports & Exercise*. 2019;51(Supplement):5. doi:10.1249/01.mss.0000560500.74973.02

36. Stewart G, Fermoyle C, Wheatley C, Ziegler B, Johnson B. Influence of ultra-endurance exercise on alveolar-capillary recruitment and lung diffusion. In: *European Respiratory Journal*. Vol 52. European Respiratory Society (ERS); 2018:PA2441. doi:10.1183/13993003.congress-2018.pa2441

37. la Gerche A, Connelly KA, Mooney DJ, MacIsaac AI, Prior DL. Biochemical and functional abnormalities of left and right ventricular function after ultra-endurance exercise. *Heart*. 2008;94(7):860-866. doi:10.1136/hrt.2006.101063

38. la Gerche A, Heidbüchel H, Burns AT, et al. Disproportionate exercise load and remodeling of the athlete's right ventricle. *Medicine and Science in Sports and Exercise*. 2011;43(6):974-981. doi:10.1249/MSS.0b013e31820607a3

39. Wheatley C, Stewart G, Fermoyle C, Ziegler B, Johnson B. Influence of an ultraendurance event on lung heath. In: *European Respiratory Journal*. Vol 52. European Respiratory Society (ERS); 2018:PA2440. doi:10.1183/13993003.congress-2018.pa2440

40. Stewart GM, Yamada A, Haseler LJ, et al. Influence of exercise intensity and duration on functional and biochemical perturbations in the human heart. *Journal of Physiology*. 2016;594(11):3031-3044. doi:10.1113/JP271889

41. Elers J, Pedersen L, Backer V. Asthma in elite athletes. *Expert Review of Respiratory Medicine*. 2011;5(3):343-351. doi:10.1586/ers.11.28

42. Dickinson JW, Whyte GP, McConnell AK, Harries MG. Impact of changes in the IOC-MC asthma criteria: A British perspective. *Thorax*. 2005;60(8):629-632. doi:10.1136/thx.2004.037499

43. Schiller JS, Lucas JW, Peregoy JA. Summary Health Statistics for U.S. adults: National Health Interview Survey, 2011. *Vital and Health Statistics, Series 10: Data from the National Health Survey*. 2012;10(256):1-80.

44. Whyte GP. Clinical significance of cardiac damage and changes in function after exercise. *Medicine and Science in Sports and Exercise*. 2008;40(8):1416-1423. doi:10.1249/MSS.0b013e318172cefd

45. Roth HJ, Leithäuser RM, Doppelmayr H, et al. Cardiospecificity of the 3rd generation cardiac troponin T assay during and after a 216 km ultra-endurance marathon run in Death Valley. *Clinical Research in Cardiology*. 2007;96(6):359-364. doi:10.1007/s00392-007-0509-9

46. Kim YJ, Shin YO, Lee JB, et al. The effects of running a 308 km ultra-marathon on cardiac markers. *European Journal of Sport Science*. 2014;14(SUPPL.1). doi:10.1080/17461391.2011.654267

47. Christensen DL, Espino D, Infante-Ramírez R, et al. Transient cardiac dysfunction but elevated cardiac and kidney biomarkers 24 h following an ultra-distance running event in Mexican Tarahumara. *Extreme Physiology & Medicine*. 2017;6(1):3. doi:10.1186/s13728-017-0057-5

48. Apple FS, Rogers MA, Casal DC, Sherman WM, Ivy JL. Creatine kinase-MB isoenzyme adaptations in stressed human skeletal muscle of marathon runners. *Journal of Applied Physiology*. 1985;59(1):149-153. doi:10.1152/jappl.1985.59.1.149

49. Khodaee M, Spittler J, Vanbaak K, Changstrom BG, Hill JC. Effects of Running an Ultramarathon on Cardiac, Hematologic, and Metabolic Biomarkers. *International Journal of Sports Medicine*. 2015;36(11):867-871. doi:10.1055/s-0035-1550045

50. Douglas PS, O'Toole ML, Hiller WDB, Hackney K, Reichek N. Cardiac fatigue after prolonged exercise. *Circulation*. 1987;76(6):1206-1213. doi:10.1161/01.CIR.76.6.1206

51. Scott JM, Esch BTA, Shave R, Warburton DER, Gaze D, George K. Cardiovascular consequences of completing a 160-km ultramarathon. *Medicine and Science in Sports and Exercise*. 2009;41(1):25-33. doi:10.1249/MSS.0b013e31818313ff

52. Neilan TG, Yoerger DM, Douglas PS, et al. Persistent and reversible cardiac dysfunction among amateur marathon runners. *European Heart Journal*. 2006;27(9):1079-1084. doi:10.1093/eurheartj/ehi813

53. Sztajzel J, Atchou G, Adamec R, Bayes De Luna A. Effects of extreme endurance running on cardiac autonomic nervous modulation in healthy trained subjects. *American Journal of Cardiology*. 2006;97(2):276-278. doi:10.1016/j.amjcard.2005.08.040

54. Hart E, Dawson E, Rasmussen P, et al. β-Adrenergic receptor desensitization in man: Insight into post-exercise attenuation of cardiac function. *Journal of Physiology*. 2006;577(2):717-725. doi:10.1113/jphysiol.2006.116426

55. Vanoverschelde JLJ, Younis LT, Melin JA, et al. Prolonged exercise induces left ventricular dysfunction in healthy subjects. *Journal of Applied Physiology*. 1991;70(3):1356-1363. doi:10.1152/jappl.1991.70.3.1356

56. Zile MR, Brutsaert DL. New concepts in diastolic dysfunction and diastolic heart failure: Part II. Causal mechanisms and treatment. *Circulation*. 2002;105(12):1503-1508. doi:10.1161/hc1202.105290

57. Nagashima J, Musha H, Takada H, Murayama M. Left ventricular chamber size predicts the race time of Japanese participants in a 100 km ultramarathon. *British Journal of Sports Medicine*. 2006;40(4):331-333. doi:10.1136/bjsm.2005.022673

58. O'Keefe JH, Patil HR, Lavie CJ, Magalski A, Vogel RA, McCullough PA. Potential adverse cardiovascular effects from excessive endurance exercise. In: *Mayo Clinic Proceedings*. Vol 87. Elsevier Ltd; 2012:587-595. doi:10.1016/j.mayocp.2012.04.005

59. la Gerche A, Burns AT, Mooney DJ, et al. Exercise-induced right ventricular dysfunction and structural remodelling in endurance athletes. *European Heart Journal*. 2012;33(8):998-1006. doi:10.1093/eurheartj/ehr397

60. la Gerche A, Robberecht C, Kuiperi C, et al. Lower than expected desmosomal gene mutation prevalence in endurance athletes with complex ventricular arrhythmias of right ventricular origin. *Heart*. 2010;96(16):1268-1274. doi:10.1136/hrt.2009.189621

61. Heidbüchel H, Hoogsteen J, Fagard R, et al. High prevalence of right ventricular involvement in endurance athletes with ventricular arrhythmias. Role

of an electrophysiologic study in risk stratification. *European heart journal*. 2003;24(16):1473-1480. doi:10.1016/s0195-668x(03)00282-3

62. Wilson M, O'Hanlon R, Prasad S, et al. Diverse patterns of myocardial fibrosis in lifelong, veteran endurance athletes. *Journal of Applied Physiology*. 2011;110(6):1622-1626. doi:10.1152/japplphysiol.01280.2010

63. Haskell WL, Sims C, Myll J, Bortz WM, st. Goar FG, Alderman EL. Coronary artery size and dilating capacity in ultradistance runners. *Circulation*. 1993;87(4):1076-1082. doi:10.1161/01.CIR.87.4.1076

64. Athletes Performing Extraordinary Physical Activity (>10,000 MET/min/wk) at No Greater Risk of All-Cause or Cardiovascular Disease Mortality. In: *American heart Association, scientific sessions.* https://www.abstractsonline.com/pp8/#!/7891/presentation/30918. Accessed March 4, 2020.

65. Tiller NB, Roberts JD, Beasley L, et al. International Society of Sports Nutrition Position Stand: Nutritional considerations for single-stage ultra-marathon training and racing. *Journal of the International Society of Sports Nutrition*. 2019;16(1):1-23. doi:10.1186/s12970-019-0312-9

66. Kupchak BR, Volk BM, Kunces LJ, et al. Alterations in coagulatory and fibrinolytic systems following an ultra-marathon. *European Journal of Applied Physiology*. 2013;113(11):2705-2712. doi:10.1007/s00421-013-2709-5

67. Shin KA, Park KD, Ahn J, Park Y, Kim YJ. Comparison of Changes in Biochemical Markers for Skeletal Muscles, Hepatic Metabolism, and Renal Function after Three Types of Long-distance Running. *Medicine (United States)*. 2016;95(20). doi:10.1097/MD.0000000000003657

68. Son HJ, Lee YH, Chae JH, Kim CK. Creatine kinase isoenzyme activity during and after an ultra-distance (200 km) run. *Biology of Sport*. 2015;32(3):267-272. doi:10.5604/20831862.1163384

69. Eston RG, Mickleborough J, Baltzopoulos V. Eccentric activation and muscle damage: biomechanical and physiological considerations during downhill running. *British Journal of Sports Medicine*. 1995;29(2):89-94. doi:10.1136/bjsm.29.2.89

70. de Oliveira EP, Burini RC, Jeukendrup A. Gastrointestinal complaints during exercise: Prevalence, etiology, and nutritional recommendations. *Sports Medicine*. 2014;44(SUPPL.1):79. doi:10.1007/s40279-014-0153-2

71. Riddoch C, Trinick T. Gastrointestinal disturbances in marathon runners. *British Journal of Sports Medicine*. 1988;22(2):71-74. doi:10.1136/bjsm.22.2.71

72. Stuempfle KJ, Hoffman MD. Gastrointestinal distress is common during a 161-km ultramarathon. *Journal of Sports Sciences*. 2015;33(17):1814-1821. doi:10.1080/02640414.2015.1012104

73. van Wijck K, Lenaerts K, van Loon LJC, Peters WHM, Buurman WA, Dejong CHC. Exercise-Induced splanchnic hypoperfusion results in gut dysfunction in healthy men. *PLoS ONE*. 2011;6(7). doi:10.1371/journal.pone.0022366

74. George KP, Warburton DER, Oxborough D, et al. Upper limits of physiological cardiac adaptation in ultramarathon runners. *Journal of the American College of Cardiology*. 2011;57(6):754-755. doi:10.1016/j.jacc.2010.05.070

75. Biffi A, Pelliccia A, Verdile L, et al. Long-term clinical significance of frequent and complex ventricular tachyarrhythmias in trained athletes. *Journal of the American College of Cardiology*. 2002;40(3):446-452. doi:10.1016/S0735-1097(02)01977-0

76. Bae JM. Shared decision making: relevant concepts and facilitating strategies. *Epidemiology and health*. 2017;39:e2017048. doi:10.4178/epih.e2017048

77. Hoffman MD, Krouse R. Ultra-obligatory running among ultramarathon runners. *Research in Sports Medicine*. 2018;26(2):211-221. doi:10.1080/15438627.2018.1431533

78. Hashimoto M, Hagura N, Kuriyama T, Nishiyamai M. Motivations and psychological characteristics of Japanese ultra-marathon runners using Myers-Briggs type indicator. *Japanese Journal of Health and Human Ecology*. 2006;72(1):15-24. doi:10.3861/jshhe.72.15

79. Pierce EF, McGowan RW, Lynn TD. Exercise dependence in relation to competitive orientation of runners. *The Journal of sports medicine and physical fitness*. 1993;33(2):189-193. http://www.ncbi.nlm.nih.gov/pubmed/8412056. Accessed January 28, 2020.

FIGURES AND TABLES

Table 1.0. The age of peak performance in ultra-marathon increases with race distance. From Knechtle and Nikolaidis (12).

Figure 1.0. Pre- to post-race changes in mouth twitch-pressure (n = 16), volitional maximum inspiratory pressure (MIP, n = 22), maximum expiratory pressure (MEP, n = 22), and voluntary activation (n = 16). Open circles depict individual data and closed circles depict mean values. *Significantly different relative to pre-race, $p < 0.01$. From Wüthrich *et al*. (26).

Figure 2.0. Duration-dependent increases in right ventricular dysfunction. Ejection fraction (A), fractional area change (B), and systolic strain rate (C) decreased in the post-race setting. There was a significant interaction between event type and time point (*p*-value) with greater functional declines in those completing the longest event (ultra-triathlon). From La Gerche *et al.* (59).