Böning D[1], *Riveros-Rivera A*[1,2]

Why are the Tarahumara Amerindians in Mexico such Powerful Mountain Runners?

Warum sind die Tarahumara-Indianer in Mexiko so leistungsfähige Gebirgslangstreckenläufer?

REVIEW

ACCEPTED: December 2020

PUBLISHED ONLINE: March 2021

Böning D, Riveros-Rivera A. Why are the tarahumara amerindians in mexico such powerful mountain runners? Dtsch Z Sportmed. 2021; 72: 47-53. doi:10.5960/dzsm.2020.472

1. CHARITÉ-UNIVERSITÄTSMEDIZIN BERLIN, *Institut für Physiologie, Berlin, Germany*
2. PONTIFICIA UNIVERSIDAD JAVERIANA BOGOTÁ, *Department of Physiological Sciences, Bogotá, Colombia*

Summary

- **The Tarahumara Amerindians** in Mexico are extremely potent runners on long mountain trails. We have analyzed publications to find causes. Traditionally the Tarahumara live alternating at altitudes between 2400 m and 800 m. Distances from homes to fields and village centers are large and covered on foot since childhood. Men and women take part in running competitions often with kickballs.
- **Investigated runs** lasted on average 8:42 h (78 km without ascent) and 6:58 h (63km), respectively. The intensity during the short race amounted to 70% of estimated $\dot{V}O_2$max (ranging between 41 and 70 ml/(kg*min)), energy expenditure reached 21000 kJ. People run barefoot or with thin sandals resulting in increased forefoot impact and storage of elastic energy. This and the slim frame with little subcutaneous fat reduce energy consumption. The vegetarian nutrition contains many carbohydrates and plant proteins, little fat and cholesterol. Hemoglobin concentration tends to increased values. Noncoding beta-chain variants possess no importance for oxygen affinity. The hearts are not enlarged like in endurance athletes. Genes show little European admixture. Gene enrichment in musclerelated pathways suggests a contribution to physical resistance.
- **Conclusions:** Explanations for the extreme endurance are favorable biomechanical conditions and physical training beginning during childhood. Running on slopes and changing living sites between 800 and 2400 m play an additional role. Standard exercise tests and genetic investigations are necessary in future.

KEY WORDS:
Altitude, Hypoxia, Long Distance Running, Genetics

Zusammenfassung

- **Die Tarahumara-Indianer** sind extrem leistungsfähige Läufer auf langen Gebirgsstrecken. In einer Literaturanalyse wurden mögliche Ursachen untersucht. Die Tarahumara leben abwechselnd auf Höhen zwischen 2400 m und 800 m. Die Wege von den Wohnplätzen zu Feldern und Dorfmittelpunkten sind bis zu 50 km lang und werden von klein auf zu Fuß zurückgelegt. Männer und Frauen nehmen an Wettläufen (häufig mit Bällen) teil.
- **Die untersuchten Läufe** dauerten im Mittel 8:42 h (78 km ohne Steigung) bzw. 6:58 h (63 km). Die Intensität während der Läufe betrug etwa 70% der indirekt bestimmten maximalen Sauerstoffaufnahme (zwischen 41 und 70 ml/(kg*min)). Der Energieumsatz beim kurzen Rennen erreichte 21000 kJ. Da barfuß oder mit Sandalen gelaufen wird, kommt es zum Vorfußlauf mit geringeren Stoßkräften und elastischer Energiespeicherung. Dies und der schlanke Körperbau mit dünnem Unterhautfett senken den Energieumsatz. Die überwiegend vegetarische Ernährung enthält viele Kohlehydrate und pflanzliche Eiweiße, wenig Fett und Cholesterin. Die Hämoglobinkonzentration tendiert zu erhöhten Werten. Nichtkodierende Varianten in den Beta-Ketten haben keine Bedeutung für die Sauerstoffaffinität. Die Herzen sind nicht im Sinn eines Sportherzens vergrößert. In den Genen findet sich wenig europäische Beimischung. Genanreicherungen in muskelbezogenen Stoffwechselwegen haben möglicherweise Bedeutung für die Ausdauer.
- **Schlussfolgerungen:** Erklärungen für die extreme Ausdauer sind günstige biomechanische Bedingungen und Training von der Kindheit an. Training auf Steigungen und wechselnde Wohnhöhen zwischen 800 und 2400 m könnten eine zusätzliche Rolle spielen. Bei zukünftigen Untersuchungen sind Standardergometrien und weitere Genanalysen notwendig.

SCHLÜSSELWÖRTER:
Höhe, Hypoxie, Langlauf, Genetik

Introduction

The members of the Amerindian tribe Tarahumara in Mexico are extremely good runners on long mountain tracks (60-300 km) according to many press and scientific reports. We have analyzed available scientific publications in the search for possible causes.

Carl Lumholtz (30) described already in 1902 the great endurance of the Tarahumara. He noticed, how a young man transported 50 kg per 180 km in 70 hours consuming only pinole (a gruel of parched corn meal and water).

The Tarahumara (Raramuri – Fleet Foot – in their own language) have lived as farmers seasonally changing altitude between 2400 m and 800 m in the Sierra Madre Occidental in Mexico since at least 1700 AD (4). At the lower altitude they stay in canyons (Barrancas). The distances between houses and fields or villages are long (up to 50 km) but are always covered running by adults and children. In former times the Tarahumara like the Bushmen in Africa pursued deer or horses until the animals were exhausted. ›

CORRESPONDING ADDRESS:
Univ. Prof. a. D. Dr. med. Dieter Böning
Institut für Physiologie, Campus Mitte
Charité – Universitätsmedizin Berlin
Virchowweg 6, 10117 Berlin
✉: dieter.boening@charite.de

Table 1

Comparison of performances in investigated competitions and a similar competition in the Alps. "Real running velocity higher resulting from interruption because of logistic issues; *=Median; #=Mean Value.

COMPETITION	ALTITUDE m	DISTANCE km	MEAN RUNNING TIME h:min	LONGEST RUNNING TIME h:min	BEST RUNNING TIME h:min	MAX. VELOCITY km/h	REFERENCE
Barranca del Cobre	800-2100	64			06:18	10.16"	4
Investigation run without slopes	2400	78	08:42*	11:41:00	06:43	12.01	13
Ultramaraton de los Canones	600-2400	63	06:58#	08:05	05:51	10.77	14
Mountainman Trüebsee-Pilatus 2017	712-2149	61	10:40#	13:24	07:48	7.82	35

Table 2

Clinical Data of Tarahumara Runners

QUANTITY	UNIT	MEAN VALUE	SD
GROUP A (14): 10 RUNNERS			
Age	Years	29.9	6.6
Height	cm	162	10
Body Mass	kg	54.2	5.7
Body Mass Index	kg/m²	21.2	1.7
Body Fat	%	10.6	1.5
Blood Pressure systolic	mmHg	105	9
Blood Pressure diastolic	mmHg	64	7
Hemoglobin	g/dl	15.7	1.5
Hematocrit	%	47.2	4.8
HbA1c	%	5.7	0.2
GROUP B (13): 10 RUNNERS			
Age	Years	38	12
Height	cm	163	4
Body Mass	kg	60.2	5.9
Body Mass Index	kg/m²	22.7	1.8
Blood Pressure systolic	mmHg	122	14
Blood Pressure diastolic	mmHg	73	10
Hemoglobin	g/dl	14.8	1.8

Perhaps the most striking of their athletic customs is the game *ralá hipa* (ralá: foot, hipa: throw) where men must kick an oak root ball 4 cm in diameter for a race that can be up to 48 hours or 270 km long (30). Women also have a similar activity, although of less duration (maximally 40 km), called *arihueta* or *rohuémala.* A little hoop (rohué = ring) is thrown using a stick (28, 29). There are also runs for the whole population (Figure 1).

Many members of the tribe especially those no longer living in the mountains have abandoned the traditional life, move rarely, eat Western diet and often suffer from metabolic syndrome (12). A problem for all Tarahumara is drug commerce because the Mafia forces them to collaborate. As these problems and rather frequent infections (e. g. bowel parasites) are not topic of this review, the corresponding publications are not included.

Methods

A search using keywords "Tarahumara OR Raramuri" was conducted in three databases: Pubmed, Embase and Lilacs on April 20, 2020. A complementary search in Google Scholar with "Tarahumara OR Raramuri AND Exercise OR Endurance" did not add significant results (except for a conference paper and a book chapter). There was no restriction by date or language. Articles not available in full text were excluded. A total of 200 papers were collected (Pubmed=90; Embase=101; Lilacs=9). RSI files (a standardized format of references) were uploaded in the online version of the software SRA-DM and a deduplication protocol removed 81 papers (39). The remaining 119 titles were screened to find physiological or clinical information related to exercise performance or endurance. 74 full-text articles were read. Two additional papers identified from references were added. Finally, 22 studies referring immediately to the Tarahumara were included and results grouped as follows: Exercise Physiology and Related Data, Biomechanics, Miscellaneous and Genetics. Thirty one papers treating questions of importance for this paper were added. The data are presented usually as means±standard deviation.

Exercise Physiology and Related Data

Table 1 presents the running performances during scientific investigations in Tarahumara males (4, 13, 14) and in a similar competition in the European Alps (Mountainman ultramarathon 2017 (35)). Kickballs were used only in the Barranca del Cobre run, probably cause for the longer running time than in the Ultramaratón de los Canones in spite of less altitude differences. The Amerindians were volunteers, not always those with highest performance capacity. Therefore mean running times were much longer than those of the winners. In Marathon races the Tarahumara do not win often. Causes might be the relatively low $\dot{V}O_2$max compared to high level marathon runners as well as "life-long adaptation to long distance running at low absolute intensity"(13).

Table 2 shows additional data for the 2 groups of Tarahumara taking part in the runs mentioned in Table 1 (13, 14). The runners are small and light with little body fat. The BMI does

not reveal this, because the square of body length decreases more than proportionally for low values. Tarahumara consuming a Western diet show values of approximately 28 kg/m² (12). Blood pressure is low in Group A, glycated Hb normal. The Hb concentration varies between 12.4 and 18.0 g/dl, the values are increased in part compared to sea level.

The only (transcutaneous) measurements of arterial oxygen hemoglobin saturation (92±3 %) were performed within 30 min after the race without slopes at 2400 m of altitude (13). The values are similar to those in Colombian highlanders (93±4 %) at rest,at 2600 m above sea level (9).

Unfortunately there were also no real maximal tests of oxygen uptake $\dot{V}O_2$, but only submaximal exercise tests with heart rate measurements (32). The exercise consisted in stepping up and down a bench at 2 different frequencies; the corresponding $\dot{V}O_2$ were calculated from heart rates and body mass and extrapolated to the age-related maximal heart rate. These estimated values varied between 41 and 70 ml/(kg*min) in men aged 29.9 ± 6.6 SD years (14). These are values of untrained and very well trained males, respectively, at an altitude of 2400 m (8). Mean intensity during the competition reached 70% of the maximal value. This is markedly lower than the highest values (85% $\dot{V}O_2$max) during marathon races in the plain (25). Energy turnover during the race amounted to 18278 kJ/4373 kcal (14). Maximal consumption values of 46000 kJ/24 hours were reached during races over 100 miles/161km (4).

Already in 1971 Aghemo et al. (1) published similar measurements at 2300 m of altitude. Males on average 30 years old reached a $\dot{V}O_2$max of 63±7 ml/(min*kg), the highest value was 81 ml/(min*kg). Rivera-Morales et al. (40) applied the method in males aged 16.9±1.2 years in Guachochi (2400 m): Traditionally living Tarahumara presented significantly (p=0.007) higher values (54.2±8.6 ml/(min*kg)) than nontraditionally living (47.3±7.6 ml/(min*kg)) and Mestizos (46.2±8.9 ml/(min*kg).

The superiority of aerobic performance compared to a control population is already evident in children (48). Maximal aerobic power determined by the Margaria method was higher in 10-year-old Tarahumara boys than in Mestizos (53.2±9.3 vs 48±8.7 ml/(min*kg)). These differences persist when controlling for body composition (65.7±11.3 vs 60.1±9.7 ml/(min*kg fat free mass) (37). The general problem of all these studies is that maximal heart rate varies markedly by approximately 30/min in each age group due to genetics and motivation (48). Christensen et al. (14) assume±12% deviation from the results of indirect calorimetry.

Only few blood quantities were measured. After the race (14) the Creatine kinase increase was marked, but not extreme (mean value 2737 units/l). Sodium concentration in plasma decreased on the average from 138 to 128 mmol/l obviously caused by sweating and inappropriately high consumption of water. A concomitant potassium increase is explainable by loss from muscle tissue. Apparently lactate concentration was never measured.

Figure 1

A group of women paced by some men playing Ariweta (a traditional race for women running and throwing a ring made of wood and cloth) in Urique, Chihuahua, Mexico. Picture: IMAGO / MarcosxFerro.

Biomechanics

The Tarahumara run either barefoot or wear very thin sandals, leading to forefoot running with increased impact and probably good storage of elastic energy (24, 51) with consequently slightly reduced O_2-consumption (20, 46). Groom (18) describes their gait as "rhythmic and swinging, moderate, but unrelenting". This is favored by a stiffer plantar arch and stronger toe abductors (23). These characteristics are beginning to change as the Tarahumara adopt the use of conventional running shoes. Lieberman et al (28) found that the rearfoot strike is more predominant in the Tarahumara wearing conventional shoes (75% vs 30%), correlated with higher strike type index (2.69±0.59 vs 2.04±0.71) and angle of incidence (-6.27±5.28° vs -1.42±4.46°). Whether this change in the type of shoes and consequently the foot strike pattern modifies their physical performance, remains to be studied. It has to be mentioned, however, that the test in this study was performed on a short flat trackway not really corresponding to conditions in the mountains. Additionally, a review based on five studies concluded that this pattern as sole factor does not explain changes in running economy (36). Notwithstanding, and considering the type of terrain in which the Tarahumara run, neurodynamic factors such as step frequency or proprioception could confer them advantages. Additionally the slim body with very thin subcutaneous fat (18) reduces energy need.

Similar advantages have been shown in Kenyans. Gastrocnemius muscle and Achilles tendon store much energy by stretching during hopping (44). Kangaroos can even increase their hopping velocity with minimal rise of energy turnover (27).

Additionally running downhill (negative exercise) on half the distance in most Tarahumara competitions costs very little energy (31). A minimum was measured at a slope of -10%. An uptake of usable energy by the muscle during braking (e. g. ATP-synthesis) was already suggested by Hill (21) and never disproved (7).

Miscellaneous

Nutrition

The mainly vegetarian traditional diet contains many carbohydrates (corn) and vegetable proteins (beans), little fat (mainly unsaturated) and cholesterol (4, 11, 33). As mentioned ›

Table 3

Genetic Investigations in the Tarahumara

GENES	TARAHUMARA	REFERENCE
Y-chromosome	Small European admixture	38
Mitochondrial genes	No European or African admixture	43
Beta-Hemoglobin	5' Haplotype 1 and 3' Haplotype C most frequent	10
Human leukocyte antigens	Similar like in Bolivian and Brasilian Amerindians	15
Methylenetetrahydrofolate reductase *C677T* (neural tube defects)	Frequency low contrasting to other tribes in Mexico	11
***CYP2C19*2* -*CYP2C19*3*(poor drug metabolism, connected to muscular blood flow)**	Frequency high contrasting to other tribes in Mexico	42
Exon 3-VNTR of the DRD4 (Behavior)	Frequency high contrasting to other tribes in Mexico	2
KIR genes (function of killer cells)	Frequency high contrasting to Caucasian and Mestizo	19
Collagen and extracellular matrix in muscle and tendons	Enrichment in contrast to Mestizos	41

above, part of the tribe now eats Western diet and consumes too much with consequent health problems (11). Christensen et al. (12) detected 71.9 % obesity, 28,8% hypertension and 3.3% diabetes in a crossectional study in 64 subjects from 5 rural communities.

The lifestyle of the Tarahumara conditions their body composition. A study evaluating urban versus rural Tarahumara children in boarding schools (5) showed lower body fat percentage (19.73 ± 5.61% vs 13.55 ± 6.62%, p<0.01), even when caloric intake was equal during the weekdays. The authors suggest that during the weekend at home the intake decreases considerably in rural children and that their levels of general physical activity are higher than that of urban children (5). This rural-urban distribution observed also in adults is not seen in all rural Tarahumara. While the BMI was normal in 67.2% of rural males, the percentage reached only 35% in females (p =0.002, (34)). The possible cause is that most women end racing after birth of the first child (29). Gender differences did not exist in town inhabitants.

Cardiovascular and Respiratory System

The hearts are not enlarged as in endurance athletes (18). After the Ultramaratón de los Canones (14) most cardiac functions (echocardiographic and electrocardiographic measures) normalized within 6 hours. Blood pressure was initially low in young runners (see Table 2) and was slightly decreased for at least 24 h after the race.

The Tarahumara do not hyperventilate at the end of a 4-hour-race, but frequently moan about muscle soreness (4). However, "the lack of panting at the end of a race may reflect only that they were running below their aerobic threshold" (29).

Erythrocyte and Plasma Volume

Because of the regular stay at high altitude and the partly increased [Hb] as well as the regular physical training one should expect a rise of the red cell volume (9), but no measurements in the Tarahumara exist. According to investigations in subjects regularly changing between highland and lowland in Chile the Hb mass remains increased, while the plasma volume decreases after each ascent (45).

Genetics

There are many genetic investigations in the Tarahumara and other Ameroindians, but few concerning performance capacity and altitude. A selection of interesting papers is presented in Table 3. The European admixture amounts to 15% for the Y-chromosome (38). Since fathers contribute less than half of total base pairs, this means maximally 7% of the genome. The mitochondrial genes show no such admixture and indicate pure female Amerindian descent (43). *Avila-Arcos* et al (3) describe that the gene *BCL2* like 13 encoding for a mitochondrial protein is highly expressed in the muscles of the Tarahumara.

Some gene variations (HLA class I and class II) are equal as in the Aymara, a population in the Andes (15). The most frequent haplotypes of the beta hemoglobin chain genes (5' Haplotype 1 and 3' Haplotype C) are similar to those in North China and in the Aché tribe in Paraguay (10). But these DNA variants are non-coding (located in intron 2 or in the flanking regions of the adult beta-globin gene). None of those DNA changes would alter the beta-chain amino acid sequence and they would have no effect on the functional properties of Hb (47).

The only genetic analysis carried out specifically in Tarahumara runners showed a striking enrichment in genes related to the production of the extracellular matrix of tendons and muscles in a gene ontology analysis (41). This genetic profile could provide the mechanical advantages for the foot strike that we mentioned above.

There is a relatively high frequency of the alleles *CYP-2C19*2-CYP2C19*3* in the Tarahumara population, which are associated with poor metabolizers of many drugs (42). If this has any relation to Tarahumara endurance, should be evaluated in the future. Together with nitric oxide synthase (NOS) this protein complex has been shown to participate in the regulation of muscular blood flow during physical activity (22).

One haplotype for a dopamine receptor *(DRD4)* has been found in the Tarahumara (2). The repercussions that such a polymorphism may have on physical performance, are merely speculative. However, it should be noted that another polymorphism in the expression of the dopamine D4 receptor (R7) has been linked to longevity due to its ability to regulate behavioral responses to the environment, such as changes in levels of physical activity. It would not be surprising, if the Tarahumara's high motivation for engaging in physical activities had to do with genetically inherited behavioral modifications (16).

Finally, although a direct connection between killer cell immunoglobulin-like receptors (KIR) and physical endurance has not been determined, natural killer cells (NKC) are the mostly modulated immune cells during exercise. Probably immunological benefits of physical activity are due to them (50). The heterogeneity of the responses to intense physical exercise, for example during marathons, suggests that differential epigenetic processes can provide advantages, especially in recovery times (6, 26, 53). The advantage of epigenetic adaptations which may last for generations is their velocity: the distribution of changes

in a population needs only few years instead of at least centuries for mutations (26). Remarkably, it has been found that physical training in hypoxia can upregulate NKC activating molecules (52). And indeed, the activator gene, *KIR2SD5*, has a differential expression among the Tarahumara (19).

Conclusions

Astonishingly little is known about exercise physiology in the Tarahumara. Obviously standard maximal ergometric tests or lactate measurements have never been performed. Probable explanations for the high-performance capacity of the Tarahumara are similarly like in Kenyans favorable biomechanical conditions and regular physical training beginning in early childhood. Running on steep paths and changing living altitudes between 800 and 2400 m might play an additional role. Some investigators believe that genetic properties are less important for endurance capacity of highlanders than acclimation since childhood (4, 17, 49). Epigenetic mechanisms, i. e. living and training for generations at high altitude, have recently came into the focus (26).

However, the roles of genetic properties or epigenetic effects as well as standard exercise physiology remain a challenge for future research.

Conflict of Interest

The authors have no conflict of interest.

References

(1) **AGHEMO P, PINERA LIMAS F, SASSI G.** Maximal aerobic power in primitive Indians. Int Z Angew Physiol. 1971; 29: 337-342.

(2) **AGUIRRE-SAMUDIO AJ, CRUZ-FUENTES CS, GONZÁLEZ-SOBRINO BZ, GUTIÉRREZ-PÉREZ V, MEDRANO-GONZÁLEZ L.** Haplotype and nucleotide variation in the exon 3-VNTR of the DRD4 gene from indigenous and urban populations of Mexico. Am J Hum Biol. 2014; 26: 682-689. doi:10.1002/ajhb.22581

(3) **ÁVILA-ARCOS MC, MCMANUS KF, SANDOVAL K, RODRÍGUEZ-RODRÍGUEZ JE, VILLA-ISLAS V, MARTIN AR, LUISI P, PEÑALOZA-ESPINOSA RI, ENG C, HUNTSMAN S, BURCHARD EG, GIGNOUX CR, BUSTAMANTE CD, MORENO-ESTRADA A.** Population history and gene divergence in native Mexicans inferred from 76 human exomes. Mol Biol Evol. 2020; 37: 994-1006. doi:10.1093/molbev/msz282

(4) **BALKE B, SNOW C.** Anthropological and physiological observations on Tarahumara endurance runners. Am J Phys Anthropol. 1965; 23: 293-301. doi:10.1002/ajpa.1330230317

(5) **BENITEZ-HERNANDEZ ZP, HERNANDEZ-TORRES P, CABANAS MD, TORRE-DIAZ MDLDL, LOPEZ-EJEDA N, MARRODAN MD, CERVANTES-BORUNDA M.** Body composition, nutritional status and diet in rural and urban Tarahumara schoolchildren in Chihuahua, Mexico. Nutr Clín Diet Hosp. 2014; 34: 71-79.

(6) **BERK LS, NIEMAN DC, YOUNGBERG WS, ARABATZIS K, SIMPSON-WESTERBERG M, LEE JW, TAN SA, EBY WC.** The effect of long endurance running on natural killer cells in marathoners. Med Sci Sports Exerc. 1990; 22: 207-212.

(7) **BÖNING D, MAASSEN N, STEINACH M.** The efficiency of muscular exercise. Dtsch Z Sportmed. 2017; 68: 203-214. doi: 10.5960/dzsm.2017.295

(8) **BÖNING D, ROJAS J, SERRATO M, REYES O, COY L, MORA M.** Extracellular pH defense against lactic acid in untrained and trained altitude residents. Eur J Appl Physiol. 2008; 103: 127-137. doi:10.1007/s00421-008-0675-0

(9) **BÖNING D, ROJAS J, SERRATO M, ULLOA C, COY L, MORA M, GOMEZ J, HÜTLER M.** Hemoglobin mass and peak oxygen uptake in untrained and trained residents of moderate altitude. Int J Sports Med. 2001; 22: 572-578. doi:10.1055/s-2001-18530

(10) **CASAS-CASTAÑEDA M, IBARRA B, RIZO-DE LA TORRE LC, SANCHEZ-LOPEZ JY, MAGANA-TORRES MT.** 5´ and 3´ beta-globin haplotypes in Purepechas and Tarahumaras, two Mexican indigenous groups. Am J Hum Biol. 2015; 27: 697-703. doi:10.1002/ajhb.22691

(11) **CERQUEIRA MT, FRY MM, CONNOR WE.** The food and nutrient intakes of the Tarahumara Indians of Mexico. Am J Clin Nutr. 1979; 32: 905-915. doi:10.1093/ajcn/32.4.905

(12) **CHRISTENSEN DL, ALCALA-SANCHEZ I, LEAL-BERUMEN I, CONCHAS-RAMIREZ M, BRAGE S.** Physical activity, cardio-respiratory fitness, and metabolic traits in rural Mexican Tarahumara. Am J Hum Biol. 2012; 24: 558-561. doi:10.1002/ajhb.22239

(13) **CHRISTENSEN DL, ESPINO D, INFANTE-RAMIREZ R, ESPINO D, INFANTE-RAMÍREZ R, BRAGE S, TERZIC D, GOETZE JP, KJAERGAARD J.** Normalization of elevated cardiac, kidney, and hemolysis plasma markers within 48 h in Mexican Tarahumara runners following a 78 km race at moderate altitude. Am J Hum Biol. 2014; 26: 836-843. doi:10.1002/ajhb.22607

(14) **CHRISTENSEN DL, ESPINO D, INFANTE-RAMÍREZ R, CERVANTES-BORUNDA MS, HERNÁNDEZ-TORRES RP, RIVERA-CISNEROS AE, CASTILLO D, WESTGATE K, TERZIC D, BRAGE S, HASSAGER C, GOETZE JP, KJAERGAARD J.** Transient cardiac dysfunction but elevated cardiac and kidney biomarkers 24 h following an ultra-distance running event in Mexican Tarahumara. Extrem Physiol Med. 2017; 6: 3. doi:10.1186/s13728-017-0057-5

(15) **GARCÍA-ORTIZ JE, SANDOVAL-RAMÍREZ L, RANGEL-VILLALOBOS H, MALDONADO-TORRES H, COX S, GARCÍA-SEPÚLVEDA CA, FIGUERA LE, MARSH SG, LITTLE AM, MADRIGAL JA, MOSCOSO J, ARNAIZ-VILLENA A, ARGÜELLO JR.** High-resolution molecular characterization of the HLA class I and class II in the Tarahumara Amerindian population. Tissue Antigens. 2006; 68: 135-146. doi:10.1111/j.1399-0039.2006.00636.x

(16) **GRADY DL, THANOS PK, CORRADA MM, BARNETT JC JR, CIOBANU V, SHUSTAROVICH D, NAPOLI A, MOYZIS AG, GRANDY D, RUBINSTEIN M, WANG GJ, KAWAS CH, CHEN C, DONG Q, WANG E, VOLKOW ND, MOYZIS RK.** DRD4 genotype predicts longevity in mouse and human. J Neurosci. 2013; 33: 286-291. doi:10.1523/JNEUROSCI.3515-12.2013

(17) **GREKSA LP, SPIELVOGEL H, PAREDES-FERNANDEZ L.** Maximal exercise capacity in adolescent European and Amerindian high-altitude natives. Am J Phys Anthropol. 1985; 67: 209-216. doi:10.1002/ajpa.1330670306

(18) **GROOM D.** Cardiovascular observations on Tarahumara Indian runners - the modern Spartans. Am Heart J. 1971; 81: 304-314. doi:10.1016/0002-8703(71)90099-8

(19) **GUTIÉRREZ-RODRÍGUEZ ME, SANDOVAL-RAMÍREZ L, DÍAZ-FLORES M, MARSH SG, VALLADARES-SALGADO A, MADRIGAL JA, MEJÍA-ARANGURE JM, GARCÍA CA, HUERTA-ZEPEDA A, IBARRA-CORTÉS B, ORTEGA-CAMARILLO C, CRUZ M.** KIR gene in ethnic and Mestizo populations from Mexico. Hum Immunol. 2006; 67: 85-93. doi:10.1016/j.humimm.2005.11.007

(20) **HANSON NJ, BERG K, DEKA P, MEENDERING JR, RYAN C.** Oxygen cost of running barefoot vs. running shod. Int J Sports Med. 2011; 32: 401-406. doi:10.1055/s-0030-1265203

(21) **HILL AV.** Production and absorption of work by muscle. Science. 1960; 131: 897-903. doi:10.1126/science.131.3404.897

(22) **HILLIG T, KRUSTRUP P, FLEMING I, OSADA T, SALTIN B, HELLSTEN Y.** Cytochrome P450 2C9 plays an important role in the regulation of exercise-induced skeletal muscle blood flow and oxygen uptake in humans. J Physiol. 2003; 546: 307-314. doi:10.1113/jphysiol.2002.030833

(23) **HOLOWKA NB, WALLACE IJ, LIEBERMAN DE.** Foot strength and stiffness are related to footwear use in a comparison of minimally- vs. conventionally-shod populations. Sci Rep. 2018; 8: 3679. doi:10.1038/s41598-018-21916-7

(24) **HRYVNIAK D, DICHARRY J, WILDER R.** Barefoot running survey: Evidence from the field. J Sport Health Sci. 2014; 3: 131-136. doi:10.1016/j.jshs.2014.03.008

(25) **JOYNER MJ, COYLE EF.** Endurance exercise performance: the physiology of champions. J Physiol. 2008; 586: 35-44. doi:10.1113/jphysiol.2007.143834

(26) **JULIAN CG.** An Aptitude for Altitude: Are Epigenomic Processes Involved? Front Physiol. 2019; 10: 1397. doi:10.3389/fphys.2019.01397

(27) **KRAM R, DAWSON TJ.** Energetics and biomechanics of locomotion by red kangaroos (Macropus rufus). Comp Biochem Physiol B Biochem Mol Biol. 1998; 120: 41-49. doi:10.1016/S0305-0491(98)00022-4

(28) **LIEBERMAN DE.** Strike type variation among Tarahumara Indians in minimal sandals versus conventional running shoes. J Sport Health Sci. 2014; 3: 86-94. doi:10.1016/j.jshs.2014.03.009

(29) **LIEBERMAN DE, MAHAFFEY ME, QUIMARE SC, HOLOWKA NB, WALLACE IJ, BAGGISH AL.** Running in Tarahumara (Rarámuri) culture. Persistence hunting, footracing, dancing, work, and the fallacy of the athletic savage. Curr Anthropol. 2020; 61: 3.

(30) **LUMHOLTZ C.** Unknown Mexico. New York: Charles Scribner's Sons, 1902.

(31) **MARGARIA R.** Positive and negative work performances and their efficiencies in human locomotion. Int Z Angew Physiol. 1968; 25: 339-351. doi:10.1007/BF00699624

(32) **MARGARIA R, AGHEMO P, ROVELLI E.** Indirect determination of maximal O2 consumption in man. J Appl Physiol. 1965; 20: 1070-1073. doi:10.1152/jappl.1965.20.5.1070

(33) **MCMURRY MP, CERQUEIRA MT, CONNOR SL, CONNOR WE.** Changes in lipid and lipoprotein levels and body weight in Tarahumara Indians after consumption of an affluent diet. N Engl J Med. 1991; 325: 1704-1708. doi:10.1056/NEJM199112123252405

(34) **MORENO-ULLOA J, MORENO-ULLOA A, MARTINEZ-TAPIA M, DUQUE-RODRIGUEZ J.** Comparison of the prevalence of metabolic syndrome and risk factors in urban and rural Mexican Tarahumara-foot runners. Diabetes Res Clin Pract. 2018; 143: 79-87. doi:10.1016/j.diabres.2018.06.015

(35) **MOUNTAINMAN.** Complete results. 2017. https://www.webscorer.com/race?raceid=109833 [18th January 2020].

(36) **NICHOLS R, GERMANO C, BURKE M, NOLAN K, YOUNGS-GRAND K, GIRARD J.** The effects of foot strike on running economy in distance runners: a narrative review. Phys Ther Rev. 2016; 21: 32-37. doi:10.1080/10833196.2016.1193970

(37) **PASQUET P, BALCAZAR-QUINTERO M, RODRIGUEZ MF, HINOJOSA M, DESANTIAGO S.** Relationship between physical activity, aerobic capacity and body composition in school children from the Sierra Tarahumara, Mexico. In: Proceedings of the 18 International Congress of Nutrition, edited by Vorster HH, Blaauw, R., Dhansay, M.A., Kuzwayo, P.M.N., Moeng, L., Wentzel-Viljoen, E. Durban, South Africa: 2005.

(38) **RANGEL-VILLALOBOS H, MUNOZ-VALLE JF, GONZALEZ-MARTIN A, GOROSTIZA A, MAGANA MT, PAEZ-RIBEROS LA.** Genetic admixture, relatedness, and structure patterns among Mexican populations revealed by the Y-chromosome. Am J Phys Anthropol. 2008; 135: 448-461. doi:10.1002/ajpa.20765

(39) **RATHBONE J, CARTER M, HOFFMANN T, GLASZIOU P.** Better duplicate detection for systematic reviewers: evaluation of Systematic Review Assistant-Deduplication Module. Syst Rev. 2015; 4: 6. doi:10.1186/2046-4053-4-6

(40) **RIVERA-MORALES J, SOTUYO S, VARGAS-GUADARRAMA LA, DE SANTIAGO S, PASQUET P.** Physical activity and cardiorespiratory fitness in Tarahumara and Mestizo adolescents from Sierra Tarahumara, Mexico. Am J Hum Biol. 2020; 32: e23396. doi:10.1002/ajhb.23396

(41) **ROMERO-HIDALGO S, OCHOA-LEYVA A, GARCÍARRUBIO A, ET AL.** Demographic history and biologically relevant genetic variation of Native Mexicans inferred from whole-genome sequencing. Nat Commun. 2017; 8: 1005. doi:10.1038/s41467-017-01194-z

(42) **SALAZAR-FLORES J, TORRES-REYES LA, MARTÍNEZ-CORTÉS G, RUBI-CASTELLANOS R, SOSA-MACÍAS M, MUÑOZ-VALLE JF, GONZÁLEZ-GONZÁLEZ C, RAMÍREZ A, ROMÁN R, MÉNDEZ JL, BARRERA A, TORRES A, MEDINA R, RANGEL-VILLALOBOS H.** Distribution of *CYP2D6* and *CYP2C19* polymorphisms associated with poor metabolizer phenotype in five Amerindian groups and western Mestizos from Mexico. Genet Test Mol Biomarkers. 2012; 16: 1098-1104. doi:10.1089/gtmb.2012.0055

(43) **SANDOVAL K, BUENTELLO-MALO L, PEÑALOZA-ESPINOSA R, AVELINO H, SALAS A, CALAFELL F, COMAS D.** Linguistic and maternal genetic diversity are not correlated in Native Mexicans. Hum Genet. 2009; 126: 521-531. doi:10.1007/s00439-009-0693-y

(44) **SANO K, ISHIKAWA M, NOBUE A, DANNO Y, AKIYAMA M, ODA T, ITO A, HOFFRÉN M, NICOL C, LOCATELLI E, KOMI PV.** Muscle-tendon interaction and EMG profiles of world class endurance runners during hopping. Eur J Appl Physiol. 2013; 113: 1395-1403. doi:10.1007/s00421-012-2559-6

(45) **SCHMIDT W.** Effects of intermittent exposure to high altitude on blood volume and erythropoietic activity. High Alt Med Biol. 2002; 3: 167-176. doi:10.1089/15270290260131902

(46) **SQUADRONE R, GALLOZZI C.** Biomechanical and physiological comparison of barefoot and two shod conditions in experienced barefoot runners. J Sports Med Phys Fitness. 2009; 49: 6-13.

(47) **STORZ JF.** Hemoglobin: Insights into Protein Structure, Function, and Evolution. Oxford University Press, 2019.

(48) **TAKKEN T, BONGERS BC, VAN BRUSSEL M, HAAPALA EA, HULZEBOS EHJ.** Cardiopulmonary exercise testing in pediatrics. Ann Am Thorac Soc. 2017; 14: S123-S128. doi:10.1513/AnnalsATS.201611-912FR

(49) **TERBLANCHE JS, TOLLEY KA, FAHLMAN A, MYBURGH KH, JACKSON S.** The acute hypoxic ventilatory response: testing the adaptive significance in human populations. Comp Biochem Physiol A Mol Integr Physiol. 2005; 140: 349-362. doi:10.1016/j.cbpb.2005.01.016

(50) **TIMMONS BW, CIESLAK T.** Human natural killer cell subsets and acute exercise: a brief review. Exerc Immunol Rev. 2008; 14: 8-23.

(51) **WALLACE IJ, KOCH E, HOLOWKA NB, LIEBERMAN DE.** Heel impact forces during barefoot versus minimally shod walking among Tarahumara subsistence farmers and urban Americans. R Soc Open Sci. 2018; 5: 180044. doi:10.1098/rsos.180044

(52) **WANG JS, WENG TP.** Hypoxic exercise training promotes antitumour cytotoxicity of natural killer cells in young men. Clin Sci (Lond). 2011; 121: 343-353. doi:10.1042/CS20110032

(53) **ZIMMER P, BLOCH W, SCHENK A, ZOPF EM, HILDEBRANDT U, STRECKMANN F, BEULERTZ J, KOLIAMITRA C, SCHOLLMAYER F, BAUMANN F.** Exercise-induced natural killer cell activation is driven by epigenetic modifications. Int J Sports Med. 2015; 36: 510-515. doi:10.1055/s-0034-1398531