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NUTRITION, EXERCISE AND LIFESTYLE (S SHAPSES AND R DALY, SECTION EDITORS)

Bone Tissue Responsiveness To Mechanical Loading—Possible Long-Term Implications of Swimming on Bone Health and Bone Development

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Abstract

Purpose of Review To revisit the bone tissue mechanotransduction mechanisms behind the bone tissue response to mechanical loading and, within this context, explore the possible negative influence of regular swimming practice on bone health, particularly during the growth and development period.

Recent Findings Bone is a dynamic tissue, responsive to mechanical loading and unloading, being these adaptative responses more intense during the growth and development period. Cross-sectional studies usually report a lower bone mass in swimmers compared to athletes engaged in weigh-bearing sports. However, studies with animal models show contradictory findings about the effect of swimming on bone health, highlighting the need for longitudinal studies.

Summary Due to its microgravity characteristics, swimming seems to impair bone mass, but mostly at the lower limbs. It is unkown if there is a causal relationship between swimming and low BMD or if other confounding factors, such as a natural selection whithin the sport, are the cause.

Keywords Bone tissue · Mechanotransduction · Signaling pathway · Swimming · Non-weight bearing exercise

Introduction

Bone tissue can respond to mechanical stimulation promoted by ground reaction forces (GRFs) or by direct tension elicited by skeletal muscle contraction, and adapt itself to these stimuli [1]. This occurs because bone cells, in particular osteocytes, can identify mechanical stimuli, translate them into biochemical second messengers and activate signaling pathways that coordinate the differentiation and activity of osteoblasts and osteoclasts [2, 3]. Several mechanisms are involved in the detection of mechanical loading by osteocytes, namely tension exerted on components of the cytoskeleton such as actin filaments, microtubules and intermediate filaments, deformation of the osteocyte dendrites cell membrane, stresses exerted on focal adhesion molecules, changes in gap junctions structure, deformation of primary cilia and opening of voltage, or mechanodependent ion channels [4•] (see Fig. 1).

When mechanically stimulated, osteocytes increase the expression of several intracellular second messengers such as ionized calcium [5] adenosine triphosphate (ATP) [6], nitric oxide (NO) [7], and prostaglandins (PGE2) [8], which trigger anabolic signaling pathways on osteoblast precursors [7, 9], inducing thereby osteoblastogenesis and new bone formation.

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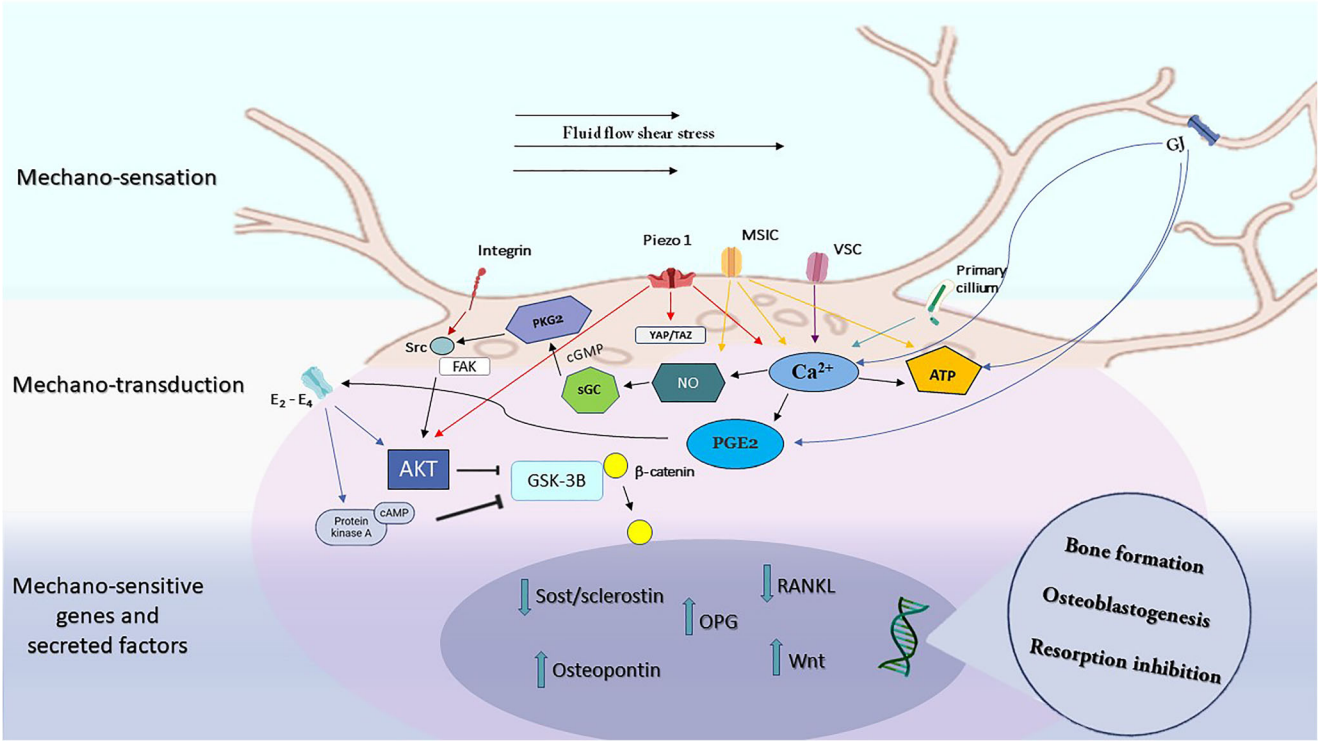

Fig. 1 Osteocyte molecular response to fluid flow shear stress forces and bone tissue deformation. Mechanosensation: In response to the fluid flow shear stress (FFSS) promoted by bone tissue deformation and generation of pressure gradients within osteocytes canaliculi, mechanosensors, such as mechanosensitive ions channels (MSIC), namely, Piezo channels, voltagesensitive calcium channels (VSC), primary cilium, Gap junctions (GJs), and integrins are activated. Mechanotransduction: One of the first responses to mechanical stimulation is the increase of intracellular calcium concentrations through MSCI, Piezo channel, VSC, GJs, and primary cilium. This leads to intracellular increase in ATP levels and prostaglandins (PGE2) and nitric oxide (NO) synthesis and release. Intracellular increase in PGE2 can also occur due to GJs response to mechanical stimulation. By connecting to E2-E4 receptors, PGE2 (mediated by AKT) leads to glycogen synthase kinase-3β (GSK-3β) inhibition, increasing free β-catenin content. This GSK-3β lock mechanism also happens through NO/cGMP/PGK2 pathway, which culminates in Src activation, and consequently, AKT phosphorylation. YAP/TAZ and src/FAK pathways can also be activated by Piezo channels and integrins, respectively. Mechanosensitive genes and secreted factors: With the increase in β-catenin stabilization and nuclear translocation, the activation of genes related with osteoblast differentiation and secretory activity is stimulated. In opposition, secreted factors related with bone resorption and osteoclastic activity or differentiation, such as RANKL and sclerostin, will be downregulated in order to favor bone formation.

Conversely, lack of a sufficient amount of loading also triggers signaling pathways, namely an increase in sclerostin expression [10], that reduce bone formation and increase bone resorption, leading to bone loss such as in cases of long-term immobilization [11], bed rest [12], or spaceflight [13].

The volume and type of mechanical loading to which bones are exposed to, or the lack of thereof, are therefore pivotal for shaping its geometry, microarchitecture, and mechanical properties. Nevertheless, the importance of mechanical stimulation in shaping bone structure is not the same throughout the lifespan [14]. Bone response to loading is more expressive during the peripubertal years [15] making this period a window of opportunity to enhance bone mass, geometry, and strength [16]. There is also evidence that these beneficial adaptations are maintained long term until late adulthood, contributing to postpone the detrimental effects of age-related bone loss such as osteoporosis and fragility fractures [17•].

Weight bearing physical activities have been recommended as the optimal strategy to enhance bone formation, namely during growth [18, 19], whereas non-weight bearing activities have been suggested to not be sufficiently effective to stimulate an adequate bone formation response [20••, 21, 22]. This can be appreciated by comparing bone mass in athletes from sports with high loading magnitudes and loading rates, such as volleyball, basketball, and gymnastics, with athletes from non-impact sports, such as swimming [23–26].

However, there is an important caveat here since most of these comparisons result from cross-sectional studies and, therefore, they are unable to determine if there is, in fact, a causal relationship between swimming and the swimmer's tendency to display a lower bone mass [23, 27]. Further, studies performed with rats and mice usually report positive effects of swimming on bone health, which contrast with most of the available evidence from humans [28]. Considering the mechanisms underlying bone tissue adaptation to mechanical loading

discussed previously and the available evidence suggesting that swimmers tend to display a lower bone mass compared to athletes from other impact sports and even physically inactive counterparts, the aim of this review is to discuss how bone tissue responds to different types of mechanical stimulation and to determine if regular swimming practice can be, or not, prejudicial to bone mass acquisition during growth [21].

Variations in the Bone Formation Response to Different Physical Exercise Stimuli

Bone tissue does not perceive all types of mechanical loading the same way. Some types of loading elicit very expressive adaptations while others elicit no response [29]. Mechanical stimuli considered as osteogenic tends to have high loading rates, inducing mechanical stresses of greater magnitude and therefore a higher degree of bone tissue deformation, triggering thereby the osteocyte mechanisms involved in mechanical loading detection, such as pulsatile fluid flow within the canalicular network [4•] culminating consequently in greater skeletal adaptations [30••, 31]. Further, bone tissue adapts more efficiently when loading is fragmented into small bouts interspersed with resting periods, in opposition as when it is delivered continuously in a single bout or continuous exercise [29]. This concept is well demonstrated in studies showing 80% greater bone formation in the tibia of animal models, subjected to four bouts of 90 cycles of loading compared to a single continuous bout of 360 cycles [32]. Thus, merely increasing the number of loading cycles without interruptions quickly leads to saturation of the bone anabolic response, reflected by the "diminishing returns" principle [33]. Bone tissue also responds more efficiently to loading stimulus applied in multiple directions [34] and less well to monotonous and cyclical loading patterns. Therefore, the optimal mechanical stimulation pattern to stimulate osteogenesis is dynamic strains, with high magnitude joint or GRFs, high loading rate, and short duration interspersed with resting periods [29]. These characteristics are mostly found in land based intermittent exercises involving jumps, rapid changes in direction and lifting weights.

In contrast, physical activities that do not involve weight bearing or high loading rates, with static or monotonous strains, such as swimming [35] and cycling [36], are considered as having a reduced osteogenic effect compared to other exercises [20••, 21, 22, 23, 24, 37, 38] or even to the effects of physical inactivity [27, 39–42]. Therefore, these non-weight bearing activities have not been recommended as a strategy to promote increases in bone mass [43, 44], especially during the period of growth and development. A review [30••] comparing the effect of different exercise protocols on bone quality in experimental animals, such as treadmill running, wheel running, swimming, resistance exercise and vertical whole-body vibration, reported that swimming, the only non-weight bearing activity included in the study, was associated with the highest percentage of negative effects on bone microarchitecture, specifically a lower trabecular number (Tb.N) and a higher trabecular separation (Tb.Sp), among all exercise protocols studied.

However, one study reported these detrimental effects on tibia proximal metaphysis only when compared with a baseline, and thus younger, control group [45]. Further, trabecular microarchitecture was impaired when rats performed a much more vigorous swimming protocol (6h/day, 5 days/week) than usual (2h/day, 5 days/week), exposing them to a higher hypogravity duration [46] or to exceedingly demanding metabolic conditions [47]. Another review with small animals exposed to low-impact loading exercise protocols, such as swimming and treadmill running, also showed positive increases in Tb.N and slight increases in Tb.Th, whereas high-impact loading exercises, such as jumping, were mostly associated with increases in Tb.Th [48••]. These findings suggest that different mechanical loading stimulus can lead to different patterns of trabecular microarchitecture adaptation.

Studies carried out with humans also suggest that activities with higher impacts tend to favor bone health outcomes [49, 50]. For instance, higher bone stiffness is found in children and adolescents regularly engaged in exercise with high mechanical impacts [51•]. Participation in high-intensity jumping exercises for seven months also enhanced lumbar spine and femoral neck BMC, and lumbar spine aBMD, as well as bone area at the femoral neck in prepubertal children [52]. Engaging in weight-bearing intermittent sports with dynamic loading profiles, such as soccer and volleyball, can also increase at least 10% male aBMD in the femoral neck, compared with mean growth values [53••].

Most of the available data therefore suggest that sports or exercises with a high loading rate and high frequency loading, such as running and jumping [16, 54], as well as activities with significant overload and adequate periods of recovery [31] are the best suited to increase bone mass and to favor beneficial long term geometrical adaptations in adolescents. However, the question remains if other types of exercises that do not comply with the principles of bone tissue adaptation to mechanical loading [29] could be merely suboptimal for leading adolescents to achieve their full genetic potential in terms of bone mass and strength or, in opposition, could even have a (long lasting) detrimental effect on bone health.

Bone Tissue Responses to Unloading and Microgravity Environments

Gravity has a crucial influence on cell functionality and bone tissue homeostasis [55•] and changes in local and systemic bone metabolism during unloading conditions can significantly contribute to the impairment of the musculoskeletal system [55•, 56]. In animal models, hindlimb suspension can promote

significant decreases in BMD, trabecular bone volume fraction (BV/TV), Tb.Th and bone formation [57]. In humans, only 17 weeks of bed rest lead to a decrease in lumbar spine, pelvis and legs BMD [58]. In other experiments, 60 days of bed rest negatively affected not only BMD [59], but also bone microarchitecture and geometry [60]. Similarly, space missions can lead to BMD losses between 2 and 9% [61], or even higher than 10% [62], with skeletal regions such as the lumbar spine, femoral neck and hip, losing over 1% BMD per month [63]. Therefore, weight bearing skeletal sites have been described as the anatomical regions most severely affected by microgravity conditions [56].

Resistance exercise protocols during spaceflight missions seem to only attenuate bone mass losses but not to effectively prevent them [64, 65] probably because, due to the lack of GRFs, muscle contraction seems to be the unique mechanism to induce bone tissue strain on space. Nevertheless, in the lower limbs, which are responsible for weight-bearing function, it is hard to appreciate the isolated effect of muscle contraction on bone. In this regard, some studies have assessed the effect of muscle contraction elicited by electrical stimulation in the bone of hindlimb suspended animal models. Electrically stimulated suspended limbs can exhibit a higher tibia BMD and bone formation [66], as well as an increased cross-sectional area and bone volume [67], compared to the non-stimulated contralateral limb.

Despite some evidence showing that an effective adaptative bone response to muscle contraction can occur even in the absence of gravitational forces [68], this effect is typically not observed in astronauts, even after four months performing an exercise protocol (2–3 h/day, 4 d/week) with cycle ergometer or treadmill with bungee cords to promote a gravitational force about 0.6 times the body weight on earth, as well as resistance training with elastic bands [63]. Nevertheless, muscle contractions elicited during these exercise protocols led astronauts to present with lower lean mass losses compared to bedridden subjects without any exercise intervention [58, 69]. Curiously, astronauts still present higher bone mass losses [58], suggesting that even though skeletal muscle contraction has an important role in bone mass maintenance, the lack of GRFs can still significatively impair bone health, making them probably the most important factor for inducing bone mass gains during exercise.

Bone Response to Mechanical Stimulation During the Period of Growth and Peak Bone Mass Attainment

During childhood and adolescence, the skeletal system is more sensitive and responsive to mechanical stimulation than during adulthood [49, 50, 54] due to the intense bone metabolism during the period of growth and development [15] with a greater number of actively bone forming cells and a more favorable hormonal context [70], such as adequate estrogen [16, 26] testosterone and somatotrophin levels [71]. All these factors make this period a "window of opportunity" for bone accrual, favoring net bone gains during remodeling and a favorable bone modeling adaptation [72•].

Peak bone mass (PBM) is considered as the largest amount of bone mass accumulated at the end of the growth period and is an important determinant of bone strength and bone health [70, 73]. Despite the importance of genetic factors, environmental and behavioral factors, such as nutrition and physical activity, influence between 20 and 40% of the PBM attained [72•, 74]. The precise age at which PBM is reached remains, nevertheless, uncertain [15]. Some authors report that the PBM is completely achieved around the age of 20 [75–77], while others argue that it can be reached until the third decade of life [15, 78, 79]. More specifically, it is around the two years before and after peak height velocity (PHV), that one third of the maximum bone mineral content (BMC) can be attained, which corresponds to an approximate age of 12 years for girls and 14 years for boys [80].

Bone growth and BMC are sex-independent until about 13 years of age; however, at 15 years, boys can present a 13% higher BMC than girls [53••]. During pubertal maturation, increases in cortical thickness in boys are mostly related with greater periosteal bone apposition, whereas in girls, it is mostly the result of endosteal bone apposition [81]. The periosteum growth leads not only to a higher bone strength to bending and torsion, but can also be a good predictor of future bone health since bone resorption in the periosteal surface is extremely rare during adulthood [82]. When periosteum expansion matches marrow cavity expansion, cortical thickness remains unaltered during growth. However, asymmetries in these processes lead to the "modelling drift", and to changes in bone geometry [83]. The coordinated communication between endosteal resorption and periosteal expansion can be regulated by many mechanisms, including mechanosensing of external loading by osteocytes, adapting bone shape to its loading needs [84]. Sex differences during bone growth can also be explained by the later puberty timing in male adolescents in comparison with females. The longer maturational period allows males to further increase bone mass and size, reaching larger bone sizes, as can be evidenced by their higher bone area and endocortical area [85]. Accordingly, in young adulthood, men can display a 35–42% larger bone area than women. The smaller bone size attained by women at their peak bone mass age, as well as a lower trabecular and cortical volumetric bone mineral density are contributing factors to the higher fracture risk seen in elderly women [86].

The amount and type of mechanical loading experienced by the skeleton during the peripubertal years is pivotal in determining the bone mass and geometry attained at early adulthood. For instance, adolescents who started practicing

sports in a period close to PHV were shown to have a similar BMD compared to children who were actively engaged in sports since childhood [87]. This clearly shows that those early years of exercise contributed far less than the peripubertal years for the adolescents' bone mass. In the two years around PHV, moderate to vigorous physical activity was able to elicit greater adaptations in bone strength determinants, specifically to the total area and cortical porosity of the tibia [88]. Another strong evidence is the higher difference in BMC and bone area displayed by the dominant *vs* non-dominant arm of peri-pubertal tennis players (from 11 to 13 years) compared to that of pre-pubertal (from 7 to 9 years) players [89]. All these data support that mechanical stimulation seems to be particularly important in the years surrounding the PHV.

In addition, many of the bone adaptations acquired in this age period, both in terms of bone mass and specially, geometry and microarchitecture, are mostly maintained throughout life [90, 91]. Studies with animal models show that improvements in bone mass and strength attained during the early period of life are maintained, even after detraining, during most of the animal's lifespan. In particular, early life geometrical adaptations seem to be well preserved thought life and to have a long lasting significant contribution to bone strength [92]. Further, a cross-sectional study conducted among professional baseball players also demonstrated that the effect elicited by exercise during youth on the humerus geometry and estimated strength was maintained throughout life, even long after the cessation of regular exercise practice [90]. Physically inactive men, but who were actively engaged in sports during growth, also tend to have higher cortical cross-sectional area, cortical thickness, and cortical periosteal circumference at the tibia compared to subjects that were inactive at younger ages [91]. Together, this evidence suggest that bone adaptations elicited by mechanical stimulation during childhood and adolescence, both in bone mass and specially, geometry and microarchitecture, seem to be maintained at long term and to impact bone health during adulthood, raising thereby concern regarding the potential negative consequences of performing non-osteogenic activities during the most sensitive period of bone development. Considering that, theoretically, the higher the PBM reached the lower the risk of developing osteopenia, osteoporosis and, bone fractures [49, 72•, 78], several authors have considered osteoporosis as a disorder with pediatric roots, whose prevention should be particularly promoted during the years of the growth spurt [54, 74].

Effects of Regular Swimming on Bone Development and Concerns About Its Long-Term Bone Health

Swimming has traditionally been considered as a non-osteogenic physical activity since it does not offer any weight bearing or GRFs type of loading, promoting a neutral [93], or even a negative [35, 94••] influence on bone health. Although swimming might elicit bone strain mostly through muscle contraction forces, as previously discussed, this type of strain, in the absence of significant GRFs, seems to not be sufficiently effective to improve bone mass [94••]. Moreover, the mechanical stimulation promoted by swimming does not follow the optimal mechanical loading characteristics to induce an osteogenic response [29], since swimming induces low magnitude peak strains, low loading rate due to the absence of rapid accelerations or decelerations, the absence of GRFs related impacts (apart from turns and starts), and the higher number of repetitive cycles per session, favoring osteogenic signal saturation [95]. Thus, engaging in this sport during youth could raise some concerns, since the lack of adequate amounts of loading could compromise the attainment of an adequate PBM and, thereby, compromise long-term bone health [18].

The daily training history of several years in a hypogravity environment, which can promote a negative impact on bone health, could explain the low BMD identified in many swimmers [23]. In addition, a lower amount of daily time performing other moderate to vigorous physical activities was documented in swimmers [96]. Nevertheless, the lack of an adequate training characterization, years of practice, or even the simultaneous engagement in other exercise activities is a major limitation of most studies which hinders understanding the isolated effect of swimming on bone health [96].

Several studies show that swimmers tend to have a similar [18, 22–25, 38, 93, 97, 98] or even smaller BMD [27, 35, 39, 99, 100] when compared to physically inactive counterparts. Further, two meta-analyses were carried out, one with children and adolescents [26], and other with adults aged 18–30 years [18] and both studies reported lower BMD values at the lumbar vertebrae, femoral neck and whole-body in swimmers compared to other athletes, but similar values compared to non-athletic controls. Therefore, these findings can be observed not only in the maturational [21, 22, 25, 38, 101], but also in the post maturational period. In fact, engaging in swimming during growth could be a possible explanation for the lower BMD observed in adult swimmers [18, 53••]. Nevertheless, to ascertain if this low BMD is the result of not reaching an optimal PBM, longitudinal studies are needed to follow these athletes from childhood into adulthood, assessing the effect of swimming on bone outcomes [15, 49, 102].

The differences found in the femoral neck and lower limbs BMD between swimmers and other athletes reinforce the notion that the impact promoted by weight bearing activities is a key factor for the increase in local BMD, and that the bone response to mechanical stimulation is type- and site- dependent [27]. The hypogravity elicited by the aquatic environment can partially explain the decreased BMD in swimmers'

lower limbs. Even though lower limbs are subjected to some GRFs during turns and block starts in a competitive race [103, 104], their main function during swimming is to stabilize the body in water [102], as can also be evidenced by the low fatigue index in the lower limbs muscles assessed through electromyography during swimming [105].

Contrarily, the upper limbs are responsible for most of the mechanical work needed for propulsion and swimming velocity, and thus are more exposed to internal forces resulting from muscle contraction, which could elicit substantial mechanical strains on bone structures [106]. Consequently, when upper and lower limbs BMD are compared between swimmers and weight-bearing sports athletes, or non-athletes, interesting patterns can be observed related to a site-dependent response to swimming exercise (Table 1). Most studies showed lower BMC and BMD on swimmers' lower limbs when compared with weight bearing sports athletes [21, 38, 100, 107–110]. In comparison with non-athletic controls, no differences were observed in most of the studies except two, which found either higher [111] or lower [42] values for swimmers, respectively. Nevertheless, for upper limbs/arms BMC and BMD, most of the studies found no differences between swimmers and other athletic groups [21, 38, 100, 107, 108, 110, 112] or non-athletic controls [38, 95, 100, 107, 108, 110, 113]. Still, some studies also observed higher upper limbs BMD in swimmers compared to physically active controls [42, 109, 111, 112].

Considering only the studies evaluating swimmers of elite or national competition level [21, 38, 100, 110, 113, 114], this pattern can be even more evident, with all lower limbs related outcomes presenting lower and similar values for swimmers in comparison with weight-bearing athletic groups and non-athletes, respectively. Moreover, for the upper limbs, all the comparisons evidenced no differences between swimmers and other athletes' BMD, BMC or bone area, and for BMC and bone area between swimmers and non-athletes.

These findings might suggest that muscle contractions on the upper limbs elicited during swimming may represent a sufficiently high stimulus to induce bone formation in the non-weight bearing limbs, reducing thereby the effect of the hypogravity environment in this region. Nevertheless, in anatomical regions related to weight bearing, such as the lower limbs and hip, daily GRFs seems to be the most important mechanical stimulus to induce bone formation, since despite the existence of muscle contraction during swimming, lower bone formation is observed in these regions. In accordance, during spaceflight, upper limbs bone mass tends to not be impaired by the lack of gravitational forces, which is in opposition to what is observed in the lower limbs [63], where bone losses occur even despite exercise stimulation [64]. Therefore, as bone tissue adaptations to loading are mainly local and not systemic, swimming, like any other sport, can have distinct effects on bone according to the different anatomical regions analyzed [102].

A recent review comparing the effect of swimming with other sports during growth, reported that beyond the lower lumbar and leg aBMD and distal tibia Tb.Th, swimmers also presented lower arms aBMD and distal radius Tb.Th. compared to other athletes [53••]. These results are somewhat contradictory with findings that swimming may not negatively affect upper limbs, but it opens a discussion to the plausible hypothesis that "natural selection" might also justify the lower BMD profile typically observed in swimmers. It is possible that subjects with a predisposition for a lower BMD may have some competitive advantage in swimming, particularly due to their greater horizontal buoyancy. This hypothesis could also explain the higher prevalence of adult swimmers with lower bone mass, since these would tend to have a higher competitive success and, consequently, to display lower attrition rates and to remain for a longer time in this sport, as well as to reach higher competitive levels. However, this hypothesis is unable to be adequately addressed in any cross-sectional study carried out in swimmers [23, 27].

Studies with laboratory animal models, with the same genetic background, could offer some advantages for answering natural selection hypothesis. Unlike human studies [28], swimming protocols lasting between eight and 12 weeks with rats between four and 12 weeks-age [28, 43, 115–117] tend to show, in general, positive effects on bone mass. Nevertheless, some interventions have also demonstrated that swimming protocols can lead to smaller bone formation and inferior biomechanical properties [45] or to cause trabecular bone loss in the lumbar vertebrae and distal femur [46], leading to an inconclusive overall interpretation. Different follow-ups duration may also explain these results discrepancy, since some protocols may have an insufficient length to promote significant adaptations in these animals bone structure [116]. Also, the absence of protocols that follow these animals during the whole period of growth and development is another major limitation [116, 118].

A possible explanation for different effects of swimming on humans and small animals' bone is that, as GFRs are related with body weight, it seems that in humans it might produce a higher mechanical stimulation on bone than only muscle contraction [28], and thus, this could be the major responsible for bone strain in human bone cells. Possible evidence of this is an experimental study with rats that assessed different jumping phases, the "take-off", usually related to muscle contraction, and the "landing phase", theoretically more osteogenic due to higher GRFs involved. Interestingly, the rats exposed only to the "take off" phase presented better bone microarchitecture responses, namely in BV/TV and Tb.Th compared to the take-off plus landing group [119]. Similarly, in another study with rats submitted to hindlimb unloading and daily sessions of jumping (only the take-off phase), there was an increase in lower limbs Tb.Th and a suppression of Tb.N reduction [120]. Interestingly, micro-

Table 1 General characteristics of the studies comparing swimmers bone outcomes in the upper and lower limbs and identification of differences between swimmers and other athletes and non-athletes (control group), using dual-energy X-ray absorptiometry (DXA)

Author (Year)	Sample characteristics Sports and control groups	Training or physical activity data information	Main findings
Gomez-Bruton et al. (2019) [95]	Swimmer (SW): *n*=34 ♀; age=13.9 ± 1.9 *n*=31 ♂; age=15.1 ± 1.5. Non-athletes (N-A): *n*=51 ♀; age=14.2 ± 2.3. *n*= 68 ♂; age=14.9 ± 2.3	Training session (hours/week): At least 6 h/week Previous experience: At least 3 years of training and competition in regional levels	Legs BMC (g) ♂ SW: 404.7 ± 93.5 *vs* N-A: 402.0 ± 119.2: *d*= 0.025 ♀ SW:283.8 ± 66.7 *vs* N-A:318.5 ± 75.1; *d*= 0.488 Arms BMC (g) ♂ SW: 135.2 ± 33.4 *vs* N-A: 121.5 ± 41.4; *d*= 0.364 ♀ SW: 99.2 ± 25.8 *vs* N-A:101.7 ± 26.9; *d*= 0.094
Maillane-Vanegas et al. (2018)	Swimmer (SW): *n*=13♀, 29 ♂; age=13.6 ± 1.8. Basket: *n*= 0 ♀, 35 ♂; age=13.7 ± 1.3. Soccer: *n*= 0 ♀, 106 ♂; age=14.9 ± 1.8. Karate: *n*=20 ♀, 13 ♂; age=12.6 ± 1.4. Judo: *n*=18 ♀, 35 ♂; age=13.1 ± 1.8. Kung Fu: *n*=17 ♀, 32 ♂; age=13.8 ± 1.7. Non-athletes (N-A): *n*=61♀, 50♂; age=13.1 ± 1.6;	Training session: nr Previous experience: At least 6 months of training and competition Resistance training (%) SW: 59.5% Basket: 82.9% Soccer: 15.1% Karate: 97.0% Judo: 83.0% Kung Fu: 95.9%	Lower limbs BMD (g/cm^2) SW: 1.143 ± 0.131 *vs*: Soccer: 1.450 ± 0.176; *d*= 1.97* Basket: 1.362 ± 0.163; *d*=1.48* Karate: 1.146 ± 0.147; *d*=0.021 Judo: 1.161 ± 0.164; *d*=0.121 Kung Fu: 1.189 ± 0.171; *d*=0.152 N-A: 1.138 ± 0.127; *d*= 0.038 Upper limbs BMD (g/cm^2) SW: 0.795 ± 0.107 *vs*: Soccer: 0.876 ± 0.144; *d*=0.638 Basket: 0.811 ± 0.094; *d*=0.158 Karate: 0.714 ± 0.078; *d*=0.865 Judo: 0.789 ± 0.169; *d*=0.042 Kung Fu: 0.780 ± 0.116; *d*=0.134 N-A: 0.731 ± 0.088; *d*= 0.653
Vlachopoulos et al. (2018) [108]	Swimmer (SW): *n*= 37 ♂; age=13.5 ± 1.0 Soccer: *n*= 37 ♂; age=12.9 ± 0.9 Cycling: *n*= 28 ♂; age=13.2 ± 1.0. Non-athletes (N-A): *n*=14 ♂; age=12.3 ± 0.5.	Training session (hours/week): SW: 9.4 ± 5.1 Soccer: 10.0 ± 2.3 Cycling: 5.2 ± 2.1 Previous experience (years): SW: 5.2 ± 2.5 Soccer: 7.5 ± 2.3 Cycling: 3.9 ± 1.3 Moderate to vigorous physical activity (min/day): SW: 85.0 ± 30.9 Soccer: 119.8 ± 29.7 Cycling: 106.5 ± 33.7 N-A: 83.2 ± 26.8	Legs BMC (g)[a] SW: 215.6 ± 27.4 *vs*: Soccer: 253.7 ± 27.9; *d*=1.377* Cycling: 223.0 ± 25.8; *d*=0.278 N-A: 216.3 ± 27.8; *d*=0.025 Arms BMC (g)[a] SW: 209.2 ± 19.6 *vs*: Soccer: 207.2 ± 19.4; *d*= 0.102 Cycling: 211.9 ± 18.4; *d*=0.142 N-A: 193.4 ± 19.5; *d*=0.808
	Swimmer (SW):	Training session (session/year):	Lower limbs BMC (g)

Table 1 (continued)

Author (Year)	Sample characteristics Sports and control groups	Training or physical activity data information	Main findings
Valente- Dos- Santos et al. (2018) [21]	*n*=20 ♀; age=15.71 ± 0.93 Volley: *n*=26 ♀, age=16.20 ± 0.77	SW: 298 ± 34 Volley: 115 ± 26 Previous experience (years): SW: 8.9 ± 3.9 Volley: 4.1 ± 1.8 Competition in national levels	SW: 781.0 ± 106.0 *vs* Volley: 928.0 ± 164.0; *d*= 1.06* Lower limbs BMD (g/cm^2) SW: 1.155 ± 0.103 *vs* Volley: 1.235 ± 0.123; *d*= 0.71* Upper limbs BMC (g) SW: 290.0 ± 36.0 *vs* Volley: 300.0 ± 64.0; *d*= 0.192 Upper limbs BMD (g/cm^2) SW: 0.801 ± 0.049 *vs* Volley: 0.812 ± 0.066; *d*= 0.189
Agostinete et al. (2017) [100]	Swimmer (SW): *n*=15 ♂; age=15.9 ± 2.1 Basket: *n*=18 ♂; age=14.5 ± 0.9 Non-athletes (N-A): *n*= 20♂; age=13.0 ± 1.3	Training session (min/week): SW: 1152 ± 387.6 Basket: 1072 ± 122.9 Previous experience (years): SW: 7.2 ± 2.9 Basket: 4.3 ± 2.3 Clubs registered in national federations	Lower limbs BMC (g)[a] SW: 1002.0 ± 263.3 *vs*: Basket: 1250.0 ± 284.2; *d*= 0.905* N-A: 1238.0 ± 379.3; *d*= 0.722 Lower limbs BMD (g/cm^2) [a] SW: 1.257 ± 0.19 *vs*: Basket: 1.397 ± 0.21; *d*= 0.699* N-A: 1.350 ± 0.30; *d*=0.370 Upper limbs BMC (g)[a] SW: 375.0 ± 89.1 *vs:* Basket: 387.0 ± 97.6; *d*=0.128 N-A: 359.0 ± 138.6; *d*=0.137 Upper limbs BMD (g/cm^2) [a] SW: 0.862 ± 0.14 *vs*: Basket: 0.895 ± 0.16; *d*=0.219 N-A: 0.875 ± 0.23; *d*=0.068
Vlachopoulos et al. (2017) [111]	Swimmer (SW): *n*= 41 ♂; age=13.4 ± 1.0 Soccer: *n*= 37 ♂; age=12.8 ± 0.9 Cycling: *n*= 29 ♂; age=13.2 ± 1.0. Non-athletes (N-A): *n*=14 ♂; age=12.3 ± 0.5.	Training session (hours/week): SW: 9.5 ± 5.1 Soccer: 10.0 ± 2.3 Cycling: 5.1 ± 2.1 Previous experience (years): At least three years Moderate to vigorous physical activity (min/day): SW: 85.0 ± 30.9 Soccer: 119.8 ± 29.7 Cycling: 106.5 ± 33.7 N-A: 83.2 ± 26.8 Vigorous physical activity (min/day): SW: 11.9 ± 7.3 Soccer: 22.5 ± 9.0 Cycling: 18.5 ± 12.8 N-A: 8.9 ± 4.0	Legs BMC (g) SW: 779.0 ± 141.6 *vs*: Soccer: 747.8 ± 175.0; *d*=0.196 Cycling: 745.4 ± 179.2; *d*=0.208 N-A: 612.2 ± 179.7; *d*= 1.031* Legs BMD (g/cm^2) SW: 1.091 ± 0.010 *vs:* Soccer: 1.124 ± 0.106; *d*=0.438 Cycling: 1.077 ± 0.116; *d*=0.170 N-A: 0.975 ± 0.103; *d*=1.585* Arms BMC (g) SW: 244.9 ± 64.8 *vs*: Soccer: 188.3 ± 48.0; *d*=0.992* Cycling: 212.9 ± 59.2; *d*=0.515 N-A: 155.9 ± 40.6; *d*=1.645* Arms BMD (g/cm^2) SW: 0.784 ± 0.071 *vs*:

Table 1 (continued)

Author (Year)	Sample characteristics Sports and control groups	Training or physical activity data information	Main findings
			Soccer: 0.736 ± 0.047; *d*=0.00* Cycling: 0.747 ± 0.069; *d*=0.00 N-A: 0.690 ± 0.049; *d*=1.54*
Agostinete et al. (2016) [112]	Swimmer (SW): *n*= 16 ♂; age=13.5 ± 1.5 Basket: *n*= 14 ♂; age=13.4 ± 1.2 Soccer: *n*= 18 ♂; age=12.4 ± 1.9 Judo: *n*= 12 ♂; age=13.1 ± 1.5 Karate: *n*= 9 ♂; age=13.1 ± 1.8 Non-athletes (N-A): *n*=13 ♂; age=11.9 ± 2.2	Training session (min/week): nr Previous experience (months): SW: 57.1 ± 32.1 Basket: 32.2 ± 22.2 Soccer: 41.5 ± 43.8 Judo: 47.6 ± 39.3 Karate: 41.1 ± 37.4 Resistance training (%) SW: 62.5% Basket: 35.7% Soccer: 38.9% Judo: 33.3% Karate: 22.2%	Lower limbs BMD (g/cm^2) SW: 1.180 ± 0.117 *vs:* Basket: 1.352 ± 0.126; *d*=1.414 Soccer: 1.201 ± 0.174; *d*=0.141 Judo: 1.186 ± 0.132; *d*=0.048 Karate: 1.259 ± 0.142; *d*=0.607 N-A: 1.080 ± 0.157; *d*= 0.722 Upper limbs BMD (g/cm^2) SW: 0.803 ± 0.084 *vs:* Basket: 0.789 ± 0.060; *d*=0.191 Soccer: 0.728 ± 0.095; *d*=0.836 Judo: 0.784 ± 0.136; *d*=0.168 Karate: 0.765 ± 0.098; *d*=0.416 N-A: 0.679 ± 0.083; *d*=1.485*
Ribeiro dos Santos (2016) [113]	Swimmer (SW): *n*=10 ♀; age=13.1 ± 2.1 *n*=16 ♂; age=12.7 ± 2.1. Non-athletes (N-A): *n*=16 ♀; age=13.1 ± 2.1 *n*= 13 ♂; age=12.7 ± 2.1	Training session (min/week): SW: 1,051.9 ± 315.75 Previous experience (months): At least 9 months of training and competition in national levels	Lower limbs BMD (g/cm^2) [a] ♂ SW: 1.104 ± 0.09 *vs* N-A: 1.175 ± 0.09; *d*=0.788 ♀ SW:1.061 ± 0.15 *vs* N-A:1.106 ± 0.035; *d*=0.413 Upper limbs BMD (g/cm^2) [a] ♂ SW: 0.752 ± 0.05 *vs* N-A: 0.743 ± 0.05; *d*=0.18 ♀ SW:0.701 ± 0.09 *vs* N-A:0.726 ± 0.08; *d*=0.293
Gomez-Bruton et al. (2014) [42]	Swimmer (SW): *n*=23 ♀; age=13.77 ± 2.07 *n*=23 ♂; age=14.96 ± 1.91. Non-athletes (N-A): *n*=23 ♀; age=13.87 ± 2.57. *n*= 29 ♂; age=14.37 ± 2.57	Training session (hours/week): ♀ SW: 10.02 ± 2.18 ♂ SW: 10.31 ± 2.09 Previous experience (years): At least three years of training and competition in regional levels	Legs BMD (g/cm^2) ♂ SW: 1.065 ± 0.019 *vs* N-A: 1.068 ± 0.170; *d*= 0.024 ♀ SW:0.962 ± 0.093 *vs* N-A:0.959 ± 0.157; *d*= 0.023 Legs BMD (g/cm^2)[a] ♂ SW: 1.020 ± 0.089 *vs* N-A: 1.104 ± 0.086; *d*= 0.94* ♀ SW:0.951 ± 0.067 *vs* N-A:0.970 ± 0.067; *d*= 0.283 Legs BMC (g) ♂ SW: 392.6 ± 87.5 *vs* N-A: 371.3 ± 116.8; *d*= 0.206 ♀ SW: 287.2 ± 59.8 *vs* N-A:292.6 ± 87.6; *d*= 0.072 Legs BMC (g)[a] ♂ SW: 353.3 ± 46.7 *vs* N-A: 402.5 ± 54.3; *d*= 1.07* ♀ SW:277.5 ± 32.2 *vs* N-A:302.4 ± 32.2; *d*= 0.77* Arms BMD (g/cm^2) ♂ SW: 0.724 ± 0.065 *vs* N-A: 0.678 ± 0.090; *d*= 0.89*

Table 1 (continued)

Author (Year)	Sample characteristics Sports and control groups	Training or physical activity data information	Main findings
			♀ SW:0.646 ± 0.064 *vs* N-A:0.607 ± 0.084; *d*=0.522 Arms BMD (g/cm^2)[a] ♂ SW: 0.692 ± 0.040 *vs* N-A: 0.703 ± 0.039; *d*= 0.278 ♀ SW: 0.641 ± 0.029 *vs* N-A: 0.612 ± 0.029; *d*=0.45* Arms BMC (g) ♂ SW: 135.1 ± 34.3 *vs* N-A: 116.3 ± 41.8; *d*= 0.491 ♀ SW:100.2 ± 22.2 *vs* N-A:96.1 ± 30.4; *d*= 0.154 Arms BMC (g)[a] ♂ SW: 119.1 ± 14.0 *vs* N-A:128.9 ± 13.6; *d*= 0.70* ♀ SW: 97.8 ± 10.4 *vs* N-A: 98.5 ± 10.4; *d*=0.067
Maimoun et al. (2013a) [109]	Swimmer (SW): *n*=20 ♀; age=14.1 ± 1.8 Artistic Gymnastics (AG): *n*=20 ♀; age=13.8 ± 2.0 Rhythmic Gymnastics (RG): *n*=20 ♀; age=13.8 ± 2.2 Non-athletes (N-A): *n*=20 ♀; age=13.7 ± 2.0.	Training session (hours/week): SW: 14.5 ± 5.9 AG: 20.3 ± 4.2 RG: 21.1 ± 4.4 Previous experience (age at start training): SW: 6.5 ± 1.8 AG: 5.6 ± 1.7 RG: 6.6 ± 1.2	Legs BMD (g/cm^2) SW: 0.992 ± 0.074 *vs:* AG: 1.094 ± 0.148; *d*=0.871* RG: 1.028 ± 0.153; *d*=0.299 N-A: 0.979 ± 0.094; *d*=0.153 Legs BMD (g/cm^2)[a] SW: 0.951 ± 0.014 *vs:* AG: 1.090 ± 0.014; *d*=9.92* RG:1.059 ± 0.013; *d*=7.99* N-A: 0.993 ± 0.014; *d*=3.0 Arms BMD (g/cm^2) SW: 0.695 ± 0.016 *vs:* AG: 0.751 ± 0.088; *d*=0.88* RG: 0.651 ± 0.072; *d*=0.84 N-A: 0.653 ± 0.060; *d*=0.956 Arms BMD (g/cm^2) [a] SW: 0.673 ± 0.010 *vs:* AG: 0.748 ± 0.010; *d*=7.5* RG: 0.666 ± 0.010; *d*= 0.7 N-A: 0.923 ± 0.013; *d*=21.5
Maimoun et al. (2013b) [114]	Swimmer (SW): *n*=10 ♀; age=14.9 ± 0.9 Non-athletes (N-A): *n*=21 ♀; age=15.6 ± 1.6.	Training session (hours/week): SW: 17.0 ± 5.2 N-A: 1.8 ± 1.2 Previous experience (age at start training): SW: 7.1 ± 2.3 N-A: 8.3 ± 2.3 Elite athletes	Lower limbs BMD (g/cm^2) SW: 1.070 ± 0.021 *vs* N-A: 1.060 ± 0.015; *d*= 0.547 Upper limbs BMD (g/cm^2) SW: 0.748 ± 0.013 *vs* N-A: 0.707 ± 0.009; *d*=3.667*
Dias Quitério et al. (2011) [110]	Swimmer (SW): *n*= 20 ♂; age=16.4 ± 2.5.	Training session (hours/week): SW: 19.1 ± 6.2	Lower limbs BMC (g) SW: 434.4 ± 93.5 *vs*:

Table 1 (continued)

Author (Year)	Sample characteristics Sports and control groups	Training or physical activity data information	Main findings
	Basket + Handball + Gymnastics (B+H+G): *n*= 34 ♂; age=15.7 ± 1.6. Non-athletes (N-A): 26 ♂; age=15.9 ± 2.8.	B+H+G: 12.8 ± 8.7 Previous experience (age at start training): SW: 8.7 ± 2.8 B+H+G: 8.0 ± 3.8 Athletes at regional, national, and international levels	B+H+G: 540.1 ± 134.2; *d*=0.91* N-A: 423.8 ± 142.9; *d*= 0.087 Lower limbs BMD (g/cm^2) SW: 1.178 ± 0.171 *vs*: B+H+G:1.352 ± 0.195; *d*=0.94* N-A: 1.167 ± 0.208; *d*= 0.057 Upper limbs BMC (g) SW: 150.4 ± 39.8 *vs*: B+H+G: 171.3 ± 42.7; *d*=0.50 N-A: 140.1 ± 48.7; *d*= 0.231 Upper Limbs BMD (g/cm^2) SW: 0.751 ± 0.090 *vs*: B+H+G:0.795 ± 0.098; *d*=0.46 N-A: 0.728 ± 0.124; *d*= 0.212
Duncan et al. (2002) [38]	Swimmer (SW): *n*=15 ♀; age=16.7 ± 1.3 Running: *n*= 15 ♀; age=17.8 ± 1.4 Cycling: *n*= 15 ♀; age=16.5 ± 1.4 Triathlon: *n*= 15 ♀; age=17.7 ± 1.1 Non-athletes (N-A): *n*= 15 ♀; age=16.9 ± 0.9	Training session (hours/week): SW: 15.0 ± 4.8 Running: 8.4 ± 1.2 Cycling: 15.0 ± 4.9 Triathlon: 16.2 ± 4.7 Previous experience (years): SW: 6.1 ± 2.7 Running: 5.1 ± 1.6 Cycling: 3.1 ± 1.8 Triathlon: 2.5 ± 1.2 Athletes at state or national levels	Legs BMD (g/cm^2) [a] SW:1.15 ± 0.09 *vs*: Running:1.31 ± 0.09; *d*=1.77* Cycling: 1.18 ± 0.09; *d*=0.33 Triathlon: 1.24 ± 0.09; *d*=1.0* N-A: 1.22 ± 0.09; *d*=0.77 Arms BMD (g/cm^2) [a] SW:0.94 ± 0.09 *vs*: Running: 0.98 ± 0.09; *d*=0.44 Cycling: 0.93 ± 0.09; *d*=0.11 Triathlon: 0.94 ± 0.09; *d*=0.0 N-A: 0.92 ± 0.06; *d*=0.26

The studies included are from a search performed on Pubmed and Scopus database, that attend the following inclusion criteria: (i) participants were female or male adolescents' swimmers (ii) assesses upper and lower limbs (or arms and legs) *aBMD*, BMC and bone area with DXA (iii) included a comparator group: other sports groups or a non-athletic control group. *BMC* bone mineral content; *BMD* bone mineral density; *N-A* non-athletes; *nr* not reported; *SW* swimmers. ♀= female groups; ♂= male groups. * $p < 0.05$ significant differences compared with swimmer group; [a] comparisons adjusted to confounders

finite element analysis evidenced that some structural parameters, such as lacunae volume and osteocytes shape and size, can influence the strain detected by bone cells [121]. Thus, it is possible that some differences between larger and small mammals bone tissue, such as differences in the number of osteons and Haversian channels, can somehow, interfere with osteocytes sensibility to mechanical loading, leading to different adaptative responses. However, there is a gap in the literature regarding how these micro-structural differences could interfere with changes in the mechanosensation process between humans and rats, making this hypothesis speculative and highlighting the need of further investigation.

Conclusions

Bone tissue is a very plastic structure that can adapt itself to the usual mechanical forces that are applied to it, being this responsiveness considerably higher during childhood and adolescence. Therefore, adequate stimulation of bone structures during this age period is critical for reaching the highest PBM possible and to prevent the premature onset of bone disorders associated with increased fracture risk. Considering that bone tissue is mostly sensitive to mechanical loading induced by gravitational GRFs and vigorous muscle contractions, a reduced amount of weight-bearing activities, such as in swimming, seems to be detrimental for bone health, and may explain the low BMD phenotype typically displayed by swimmers, especially in the lower limbs.

Nevertheless, and despite the mechanistic evidence supporting this hypothesis, considering that most evidence on athletes is cross-sectional, it is not possible to establish a definitive causal relationship between regular swimming and low bone mass. In addition, studies performed with experimental animal models show contradictory findings about the effects of swimming on bone health. Consequently, longitudinal studies encompassing a substantial part of the developmental period are necessary to fully elucidate whether lower BMD typically observed in swimmers, in particular at the lower limbs, is causally related with the hypogravity water environment to which they are chronically exposed to, or if it is more plausible that these differences could be attributed to attrition and a selection effect within the sport.

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Data Availability Not applicable.

Code Availability Not applicable.

Declarations

Conflict of Interest The authors declare no conflict of interest.

Humans and Animal Rights All reported studies/experiments with human or animal subjects performed by the author have been previously published and complied with all applicable ethical standards (including the Helsinki Declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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