

The Impact of Gender-Affirming Hormone Therapy on Physical Performance

Ada S. Cheung,^{1,2} Sav Zwickl,¹ Kirsti Miller, Brendan J. Nolan,^{1,2} Alex Fang Qi Wong,¹ Patrice Jones,³ and Nir Eynon^{3,4}

¹Trans Health Research Group, Department of Medicine (Austin Health), The University of Melbourne, Melbourne 3084, Australia

²Department of Endocrinology, Austin Health, Heidelberg 3084, Australia

³Institute for Health and Sport (IHeS), Victoria University, Footscray 3011, Australia

⁴Australian Regenerative Medicine Institute, Monash University, Clayton 3800, Australia

Correspondence: Ada S. Cheung, MBBS (Hons), FRACP, PhD, The University of Melbourne, 145 Studley Road, Heidelberg, Victoria 3084, Australia.
Email: adac@unimelb.edu.au.

Abstract

Context: The inclusion of transgender people in elite sport has been a topic of debate. This narrative review examines the impact of gender-affirming hormone therapy (GAHT) on physical performance, muscle strength, and markers of endurance.

Evidence Acquisition: MEDLINE and Embase were searched using terms to define the population (transgender), intervention (GAHT), and physical performance outcomes.

Evidence Synthesis: Existing literature comprises cross-sectional or small uncontrolled longitudinal studies of short duration. In nonathletic trans men starting testosterone therapy, within 1 year, muscle mass and strength increased and, by 3 years, physical performance (push-ups, sit-ups, run time) improved to the level of cisgender men. In nonathletic trans women, feminizing hormone therapy increased fat mass by approximately 30% and decreased muscle mass by approximately 5% after 12 months, and steadily declined beyond 3 years. While absolute lean mass remains higher in trans women, relative percentage lean mass and fat mass (and muscle strength corrected for lean mass), hemoglobin, and VO_2 peak corrected for weight was no different to cisgender women. After 2 years of GAHT, no advantage was observed for physical performance measured by running time or in trans women. By 4 years, there was no advantage in sit-ups. While push-up performance declined in trans women, a statistical advantage remained relative to cisgender women.

Conclusion: Limited evidence suggests that physical performance of nonathletic trans people who have undergone GAHT for at least 2 years approaches that of cisgender controls. Further controlled longitudinal research is needed in trans athletes and nonathletes.

Key Words: transgender persons, testosterone, muscle, body composition, physical endurance, sport

Abbreviations: BMD, bone mineral density; DXA, dual x-ray absorptiometry; GAHT, gender-affirming hormone therapy; hs-cTn, high-sensitivity cardiac troponin.

Recently, the inclusion of transgender or gender diverse (trans) people in sport has encountered intense social and political debate. Common terminology used to describe gender is listed in Table 1. Sporting federations and organizations internationally are faced with pressure to determine policies for the eligibility of trans people to compete in sporting competitions. Yet, there is scant evidence describing the impact of gender-affirming hormone therapy (GAHT) on physical performance in nonathletes or trans athletes. The focus has been on the inclusion or exclusion of trans women and nonbinary individuals recorded male at birth within the female category due to potential physical performance advantages from prior male puberty.

Trans people comprise 0.5% to 3% of the general population and face significant barriers to health, well-being, and participating in society (1–6). Over 60% report a history of diagnosed depression or anxiety (7), and rates of death by suicide are over 2-fold greater than cisgender populations (8).

This is largely a result of marginalization and widespread discrimination in many social and institutional settings (9–12). Sport is no exception. A 2017 Human Rights Campaign Foundation study found that 68% of a national sample of all youth played on a sports team, but only 12% to 14% of trans youth played sport (13). Fear of discrimination from coaches or officials and a lack of inclusive policies are described barriers (13). Very few trans people have competed at the elite level despite trans people being eligible to compete at the Olympic Games since 2004.

Cisgender males have a performance advantage over cisgender females in multiple sports (14). Unequivocally, competitive sporting records for sports that are determined by maximal skeletal muscle or cardiac muscle performance demonstrate male advantage after the age of puberty (15). The difference between male and female performance differs depending on the sport. The lowest differences are seen in rowing, swimming, and running (11–13%), but the greatest

Table 1. Transgender glossary of terms

Term	Definition
Transgender, trans or trans and gender diverse	A person who has a gender that is different from what was recorded for them at birth. It is also used as an umbrella term to describe all people whose gender is different to what was recorded for them at birth which includes people with binary (male or female) and nonbinary identities. This manuscript uses the term trans as an umbrella term
Cisgender or cis	A person who is not transgender, and has a gender the same as their recorded sex at birth
Nonbinary	A person who has a gender that is not man or woman (binary) or not exclusively male or female. Some people identify as being somewhere on a spectrum from male to female, whereas others feel disconnected from such a spectrum entirely. Nonbinary people may also use GAHT
Trans man	A man who was recorded female at birth. Trans men may use testosterone therapy for gender affirmation
Trans woman	A woman who was recorded male at birth. Trans women may use feminizing hormone therapy with estrogens and antiandrogens for gender affirmation

Note that terminology differs across cultures and individuals may have their own definitions or preferences for language.

differences are seen in movements utilizing the upper body (16). For instance, there is a 20% male advantage for the fastest tennis serve and >50% difference in speed for baseball pitching (16). This is largely the result of pubertal testosterone concentrations in the male range of 7.7 to 29.4 nmol/L relative to 0.06 to 1.68 nmol/L in females. This results in taller height, higher hemoglobin, larger bones, lower body fat, and higher muscle mass and strength in postpubertal males (14, 17).

Serum testosterone concentrations are used to determine eligibility to compete in the female category. The cut-off level is heterogeneous between sports and no studies have definitively correlated performance in cisgender women with testosterone concentration. A double-blind randomized controlled trial of testosterone therapy attempted to evaluate the impact of testosterone in 48 cisgender women. The intervention group who achieved testosterone concentrations of 4.3 nmol/L for 10 weeks had an increase in running time to exhaustion but there were no differences observed in jump tests, knee extension torque, or anaerobic leg power compared with placebo (18). A longer duration of testosterone exposure may have had more marked effects.

While circulating testosterone is the main basis of sex differences in athletic performance, it may not be the only determinant, and there are genetic factors that may increase the likelihood of success in sporting competition (14, 19). Within people of the same age and sex, anthropometric proportions, body composition ratios, biomotor variables, and endocrine profile (including growth hormone, thyroid

hormone, etc.) may all play a role (20-23). Elite athletes are the most highly selected individuals in a population (Olympic athletes are 8-10 cm taller than the general population overall (24, 25)), and in themselves are statistically aberrant.

While it is reasonably clear that testosterone is the main driver of male performance advantage over females in the general population, what is less clear is the impact of GAHT on muscle strength and physical performance. It is also unknown whether trans women who have received GAHT have a definitive performance advantage once adjusted for height. As such, the aim of this narrative review is to examine the impact of GAHT on physical performance and influencing factors, including muscle mass, muscle strength, bone density, hemoglobin, and cardiorespiratory fitness.

Electronic databases were searched from inception to November 1, 2022. Ovid MEDLINE and Embase were searched using Medical Subject Headings (MeSH) terms and keywords: (“transgender persons”) AND (“gender-affirming hormone therapy” OR “hormone replacement therapy” OR “testosterone” OR “estradiol”) AND (“muscle” OR “body composition” OR “bone” OR “hemoglobin” OR “physical endurance” OR “sports” OR “exercise” OR “cardiorespiratory fitness”). Reference lists in relevant publications were additionally searched to identify further articles. All studies have involved adult trans people who began GAHT after puberty.

Gender-Affirming Hormone Therapy

GAHT (masculinizing or feminizing) is desired by many (but not all) trans people to induce physical characteristics of a person’s gender identity, embodiment goals, or both (26). Medically necessary GAHT is safe and effective at reducing gender incongruence or dysphoria, and can significantly improve psychological well-being and quality of life (26-28). Masculinizing hormone therapy with testosterone for trans men and nonbinary people recorded female at birth will commonly achieve serum testosterone concentrations in the male reference range (14, 26, 29, 30). This induces lowered voice, body and facial hair growth, menstrual cessation, as well as changes in body composition (increase in muscle mass and reduction in fat mass) (26, 29, 30). Common risks include acne, unmasking polycythemia (particularly in the setting of other conditions such as sleep apnea), infertility, androgenic alopecia, hypertension, reduced high-density lipoprotein cholesterol and an increased risk of myocardial infarction relative to cisgender women (26, 31).

Feminizing hormone therapy for trans women and nonbinary individuals recorded male at birth will typically achieve serum estradiol (100-200 pg/mL or 367-734 pmol/L) and testosterone concentrations (<2 nmol/L or <58 ng/dL or <2 nmol/L) in the female range (26, 29). Estradiol therapy is often paired with antiandrogen agents such as cyproterone acetate, spironolactone, bicalutamide, or gonadotropin-releasing hormone analogues for people with testes. Depending on the mechanism of action, peripheral androgen receptor antagonists such as spironolactone or bicalutamide may not lower testosterone concentrations but will block the action of testosterone at the receptor level (32, 33). Feminizing hormone therapy induces gynoid fat redistribution and breast growth, softens skin, and reduces muscle mass, body and facial hair growth, and libido (26, 29, 30). Voice

pitch and skeletal size do not change (26, 29, 30). Adverse effects include an increased risk of venous thromboembolism, infertility, weight gain, and hypertriglyceridemia as well as elevated risk of myocardial infarction and stroke relative to cisgender women and men in the setting of additional risk factors (26, 30, 31, 34).

Muscle Mass and Strength Changes With Gender-Affirming Hormone Therapy

In the general population, men have significantly higher skeletal muscle mass than women both in absolute terms and relative to body mass (men 38.4% vs women 30.6%) (35). Men have a greater proportion of muscle mass in the upper body (upper body muscle mass 42.9% in men vs 39.7% in women) than the lower body (lower body muscle mass in men 54.9% vs 57.7% in women) (35). Approximately 50% of the variance is explained by weight and height (35). Males also have a higher proportion of fast-twitch (type II) muscle fibers (36). The impact of GAHT on relative muscle mass distribution and muscle fiber composition of trans people is unclear, and inferences depend upon whether they are compared with cisgender men or women. The impact of GAHT on muscle mass and muscle strength will be reviewed below.

Muscle and Fat Mass

Given the challenges in undertaking randomized controlled trials in the field, uncontrolled longitudinal studies assessing muscle mass in nonathletic trans people commencing GAHT represent the best level of evidence, albeit low-moderate in quality (37). Studies have predominantly used dual x-ray absorptiometry (DXA) to estimate skeletal muscle size. DXA separates bone, fat, and lean mass (which includes muscle, connective tissue, water, and organs); however, lean mass is used as an estimate of muscle mass (38). Compared with gold-standard quantification of skeletal muscle size using magnetic resonance imaging or computed tomography, DXA is more accessible, easier to use, and cost effective (38). While DXA correlates well with skeletal muscle volume/size when measured by magnetic resonance imaging in cross-sectional studies, it is far more imprecise in detecting longitudinal changes in response to interventions (38-40).

For trans men, longitudinal studies examining lean mass using DXA have consistently shown a 10% increase over the first 12 months associated with a 10% decrease in fat mass (41-45). Muscle area (as opposed to mass) measured in a single-slice magnetic resonance imaging cross-section of the thigh found that muscle area increased in trans men by 19% over 3 years but most change had plateaued by 1 year (46). After a median of 44 months of GAHT, a cross-sectional analysis of 43 trans men showed that lean mass was 7.8 kg higher than cisgender women but fat mass was not statistically significantly different (47). Trans men had fat mass 29% with lean mass 68.3%, which was statistically significantly different to cisgender men (fat mass 19.7%, lean mass 77%, $P < .001$) (47).

Conversely, for trans women, longitudinal cohort studies show that reductions in absolute lean mass are modest, approximately 3% to 5% in the first 12 months (43, 45, 48-52). A longitudinal study in 179 trans women over the first 12 months of GAHT showed a decrease of total lean mass by 3% from baseline but fat mass increased by 28% (45). A

2-year study assessing relative lean mass percentage in trans women found reductions from 77.5% at baseline to 72.5% at 1 year and 71.7% at 2 years, whereas relative fat mass increased from 19% at baseline to 24.2% at 1 year and 25.6% at 2 years (51). A 3-year study assessing cross-sectional thigh muscle area in 19 trans women showed a decrease of 9% from baseline at 1 year and 12% from baseline at 3 years, although the loss between 1 to 3 years was statistically not significant (46). Muscle area in trans women remained statistically significantly greater than that measured in untreated trans men (used as the female comparison group), though with an almost complete overlap between the 2 groups. The authors noted that trans women were on average 10.7 cm taller than untreated trans men and in a linear regression model, height was a strong predictor of muscle area, even after correction for the effect of sex (46).

While longitudinal studies have followed trans women for relatively short durations, there have been 2 cross-sectional studies in nonathletic trans women that have aimed to describe the longer-term effects of GAHTs. After a mean 8 years of feminizing hormone therapy, 23 trans women were found to have 32% higher fat mass, 17% lower lean mass, 25% lower grip strength, 33% lower biceps peak torque, and 25% lower quadriceps peak torque relative to cisgender men (53). There was no cisgender female control group. Similarly, in another recent study designed to match participants for the same birth-recorded sex, 41 trans women (median 39 months GAHT) had a statistically significant 6.9 kg lower lean mass and 9.8 kg higher fat mass relative to cisgender men measured by DXA (47). Overall body composition in trans women (fat mass 32.3%, lean mass 65.0%) was similar to cisgender women (fat mass 32.8%, lean mass 64.5%, $P > .05$) (47), consistent with Alvares et al's cross-sectional analysis showing that fat mass percentage in trans women (median GAHT duration 14 years) was not statistically different to cisgender women (29.5% vs 32.9%, $P > .05$) (54). Lean mass corrected for height was also not statistically different between trans women and cisgender women (54). While the raw lean mass in trans women was higher than cisgender women, trans women were on average taller and as such, to compare body composition changes between groups, the percentage fat and lean mass may be a more appropriate comparison.

Higher muscle mass is a predictor of better physical performance, but fat mass adds significant implications (55). A systematic review has shown that higher fat mass, and higher muscle fat infiltration, is associated with poorer physical performance, especially in the lower extremities (55). Among healthy young military recruits, higher fat percentage was associated with poorer running performance and lower muscle strength (56). This may be a factor explaining the weak strength of the muscle mass and strength relationship. While muscle mass and area are positively correlated with muscle strength, population-based studies suggest that the strength of the linear relationship once adjusted for age and gender between skeletal muscle mass and muscle strength is weak, with a correlation coefficient between 0.22 and 0.365 (57, 58).

Muscle Strength

Studies assessing muscle strength have been few, and given the ease of use and accessibility of hand-grip dynamometry hand grip strength has been the main strength outcome used. Hand grip strength is partially related to lean body mass ($r = 0.469$)

but is dependent upon finger length, finger span, and hand perimeter (59, 60). Like height and skeletal size, hand dimensions do not change with GAHT. While hand grip strength has correlated with biomarkers of health in older adults, we need to be cautious in using grip strength alone as an indicator of overall strength or of athletic performance. The correlations between hand grip strength and individual sports are reviewed comprehensively in Cronin et al (61). Though maximum hand grip strength has a strong relationship with maximum upper or body strength in some movement patterns such as in powerlifting strength, there are weaker relationships with other movement patterns (61). There is evidence that hand grip strength is a poor correlate of knee flexion or extension strength (62) and is far more reliable as a marker of physical function if used together with lower limb strength (63, 64). Hand grip strength is more relevant for some physical performance activities such as rotational movements that transfer force and torque to the hand (ie, ball throwing), but shows poor correlation to movement patterns that require technical ability, physical capacity, aerobic fitness or tactical ability (ie, tennis stroke placement or cricket fielding performance) (61).

In trans men, a prospective controlled analysis found that 23 trans men had a mean 18% increase in hand grip strength over 12 months relative to 23 cisgender women (41). A larger longitudinal analysis of 278 trans men showed an increase in grip strength of 6.1 kg (18% from baseline) over 12 months (65). Interestingly, in trans men, the increase in grip strength was associated with an increase in lean body mass (per kg increase in grip strength: +0.010 kg, 95% CI +0.003; +0.017), while this was not statistically significant in trans women (per kg increase in grip strength: +0.004 kg, 95% CI -0.000; +0.009) (65). A cross-sectional study comparing hand grip in 19 trans men (mean 29 kg, 2 years after GAHT) with 19 cisgender men (mean 40 kg) showed that strength was considerably lower in the trans men (66). In a group of 12 trans men followed over the first 12 months of GAHT, knee flexion and extension strength increased, but, even when adjusted for height, remained lower than cisgender men (67).

In trans women, several uncontrolled longitudinal studies (42, 43, 51, 53, 54, 65, 67) and cross-sectional studies have made comparisons with cisgender men (53, 54). All assessed hand grip strength, except for 2 small studies that assessed knee extension/flexion (53, 67). Hand grip changes in trans women have shown variable results, with some studies demonstrating significant reductions of -4 to -7% over 12 months (51, 65) and smaller studies showing no significant change (42, 43). Mean hand grip strength if corrected for total lean mass has been shown to be no different in trans women compared with cisgender women, but was significantly lower than cisgender men (54).

In terms of lower-body strength, a cross-sectional analysis of 23 trans women (mean 8 years GAHT) showed knee extension was 25% lower than cisgender men (53). In contrast, a small longitudinal cohort study of 11 trans women over the first 12 months of GAHT found no statistically significant change in knee flexion/extension strength in trans women (67). While the study was small and the comparison group were not concurrently assessed, the findings suggest that 12 months of GAHT is insufficient to change knee flexion/extension strength to the level of cisgender women.

Overall, handgrip strength is limited as a proxy for overall strength. In trans men, absolute and relative muscle mass and

strength increases with GAHT and are higher than cisgender women but remain lower than cisgender men. Trans women after GAHT have higher absolute muscle mass, but their relative muscle and fat mass percentages and muscle strength corrected for lean mass are no different to cisgender women.

Bone Mineral Density Changes With Gender-Affirming Hormone Therapy

Estradiol and testosterone play crucial roles in bone modeling and remodeling and, as such, there are differences in bone size, shape, and density between sexes across various stages of life. While male puberty will induce irreversible effects on bone size and shape, changes in sex steroid concentrations with GAHT may impact on bone mineral density (BMD) (26). While not necessarily causative, higher BMD has been shown to be a good predictor of physical performance (55, 68).

Several systematic reviews and meta-analyses assessing areal BMD have produced inconsistent observations, particularly in trans women (69-71). Quality of evidence is low-moderate with no prospective controlled studies. Inferences are based on cross-sectional (72-75) or observational cohort studies (48, 76-82) mostly lacking cisgender control groups (48, 72, 73, 76, 77, 80-82). Moreover, studies have relied on areal BMD using DXA, but changes in body composition accompanying GAHT influence photon attenuation independent of bone matrix volume and introduce artifact which may explain variable results.

Bone microarchitecture measured by high-resolution peripheral quantitative computed tomography may overcome limitations of DXA and has been shown to improve fracture risk prediction (83, 84). A recent cross-sectional analysis involving 41 trans men and 40 trans women compared with cisgender comparison groups of the same birth-recorded sex found that trans women had compromised bone microarchitecture. There was lower total volumetric BMD (vBMD) with lower cortical and trabecular vBMD and higher cortical porosity relative to cisgender men (85). Prospective studies are required to confirm these findings, as previous research has shown that trans women have low areal BMD compared with cisgender men even before starting any hormonal therapy (86). Conversely, bone microarchitecture in trans men was preserved with higher total vBMD relative to cisgender women (85) but lower than that of cisgender men (66). These vBMD data are consistent with fracture data from a population-based study showing a higher percentage of fractures in trans women relative to cisgender men, but fracture risk in trans men was no different to cisgender women (87).

Hemoglobin Changes With Gender Affirming Hormone Therapy

Hemoglobin concentrations in men are higher than that for women in the general population (88). Increases in hemoglobin may contribute to enhanced performance of elite endurance athletes (89, 90). Interestingly, gene polymorphisms that regulate hemoglobin are more prevalent in endurance male cyclists (90). Androgens induce erythrocytosis via upregulating erythropoietin and downregulating ferritin and hepcidin concentrations (91), and it is not surprising that GAHT has marked and consistent effects on hemoglobin and hematocrit concentrations (92). In those on established GAHT, hemoglobin, hematocrit, and red blood cell count increases

to the male reference range in trans men (48, 49, 93, 94) and correspondingly decreases to the female reference range in trans women (49, 94-96) within 3 months (97). Such changes in erythrocytosis are likely to impact endurance (running times are discussed under “Physical Performance Changes With Gender-Affirming Hormone Therapy”).

Cardiorespiratory Function in Trans Women

The maximum rate of oxygen consumption attainable during intense maximal exercise is termed VO_2 max and is considered a gold-standard index of aerobic capacity and maximal cardiorespiratory function correlating strongly with performance in endurance-heavy sports such as running, swimming, or cycling, or long stop and start sports such as soccer or basketball (98, 99). VO_2 max is determined by various physiological determinants, predominantly stroke volume and cardiac output, and, as such, are approximately 10% higher in men than women (100, 101). While fat mass is not directly associated with VO_2 max (102), VO_2 max is strongly correlated with lean mass and hemoglobin (101, 103, 104). Dividing VO_2 max by lean mass is appropriate and important when making comparisons between different populations of individuals, particularly if they differ in body size (104-108).

The highest value of VO_2 attained in a high intensity exercise test is termed VO_2 peak, and while it is directly reflective of VO_2 max, it does not define an individual's maximal attainable value (109, 110). VO_2 peak reflects the integrated ability to transport oxygen to the mitochondria for cardiovascular and skeletal muscle oxidative functions (109, 110). VO_2 peak is an excellent predictor of overall mortality and cardiovascular disease, often used in the diagnosis of mitochondrial disease (111-113).

There has been only 1 cross-sectional study, assessing VO_2 peak in 15 trans women compared with 13 cisgender men and 14 cisgender women, and findings are summarized in Table 2 (54). While the trans women included had received GAHT for a mean of 14 years, the serum testosterone concentrations were widely distributed with mean 3.2 nmol/L (range 0.4-22.1) relative to cisgender women (Table 2). Trans women were taller than cisgender women and absolute values suggest that trans women appear to have muscle mass, strength, and VO_2 peak in between that of cisgender women and cisgender men. However, when VO_2 peak is corrected for weight or lean mass, there are no statistical differences between trans women and cisgender women, but are significantly lower than cisgender men (54).

Interestingly, Alvares et al noted that trans women had a lower VO_2 peak/lean mass index, and lower mean strength/lean mass index than both cisgender groups, suggesting that trans women produce less force per gram of muscle (54). Possible cellular dysfunction in the muscle of trans women following GAHT has been postulated (54). This notion is supported by animal models of androgen receptor knockout mice, which show impaired skeletal muscle function with reduced fast-twitch muscle mass and force production in male mice but not female mice (114). Gene expression in the muscle of these male mice suggested reduced polyamine biosynthetic enzymes and impaired myoblast differentiation.

Expiratory volume was also lower in trans women than in cisgender men, but there was no statistically significant difference compared with cisgender women (54). The authors hypothesized that there may be an effect of estradiol acting as

a potential bronchoconstrictor or respiratory muscle weakness (115, 116).

Although no direct studies have assessed cardiac size or function in trans people, high-sensitivity cardiac troponin (hs-cTn) concentrations are an indirect reflection of cardiac mass in healthy individuals (117-119). This likely explains the higher hs-cTn male reference range relative to females. A cross-sectional study assessing hs-cTn in trans people on GAHT for >12 months found that median concentrations of hs-cTn in trans men were similar to cisgender men, and trans women were similar to cisgender women (120). These findings are concordant with animal models demonstrating androgen deprivation in male mice induces metabolic remodeling of the heart with reduced cardiac mass and impaired cardiac output during stress (121).

Physical Performance Changes With Gender-Affirming Hormone Therapy

There have been very few published retrospective studies examining athletic performance. Running race times have been reported among 8 trans women distance runners both before and after commencing feminizing hormone therapy (122). Participants were recruited online and asked to self-select and self-report race times (5000 m to marathon) with times verified where possible. Collectively, the 8 runners reported times that were slower in the female category than when they competed in the male category, but their female age-grading percentage was almost identical to their male age-grading percentages. There are clear limitations of self-reported, recalled data among this small sample of nonelite trans women runners.

Two studies draw data from trans people undertaking fitness tests in the Air Force compared with cohorts of cisgender male and female service members under the age of 30 (summarized in Fig. 1) (123, 124). Roberts et al's initial report assessed sit-ups, push-ups, and running times (for 1.5 mile/2.4 km) in 29 trans men and 46 trans women in the first 2 years of GAHT, albeit with 13 assessments missing in trans men and 7 assessments missing in trans women during the follow-up period (123). Trans individuals were compared with cisgender means between 2004 and 2014 to establish when a trans person might gain or lose a competitive advantage relative to their gender (123).

More recent data from Chiccarelli et al have expanded the analysis with a larger cohort of 146 trans men and 228 trans women compared with cisgender mean aggregate scores in 2022 for Air Force members with an aim to guide fitness targets for their trans service members undergoing GAHT (124). There were 346 who dropped out from analysis, with only 28 trans individuals (15 trans women) completing follow-up to 4 years of GAHT (124). Dropouts are extremely important to consider in skewing results, given that those who remain in the military likely display a higher level of physical fitness or have better access to health care than those who leave.

Trans men service members prior to testosterone therapy performed 43% fewer push-ups and ran 1.5 miles 15% slower than cisgender men in the initial Roberts et al study (123). After commencing GAHT, there was progressive increase in push-ups and sit-ups performed and improvement in running times, and by 2 years, trans men were no different to cisgender men (123). In Chiccarelli's expanded analysis, while sit-ups achieved the level of cisgender men within 1 year, push-ups

Table 2. Summary of cardiorespiratory capacity and body composition data from Alvares et al (54) in nonathletic transgender women compared with cisgender women and men

	Transgender women (n = 15)	Cisgender women (n = 13)	Cisgender men (n = 14)
Age (years)	34.2	35.6	36.7
Height (m)	1.76	1.63 ^a	1.76 ^b
Weight (kg)	78.1	61.8 ^a	81.3 ^b
BMI (kg/m ²)	25.5	23.1	26.3 ^b
Mean testosterone concentration nmol/L	3.2 (range 0.4-22.1)	0.7 (range 0.4-1.4)	18.2
Fat mass percentage	29.5	32.9	20.2 ^{b,c}
Lean mass/height ² (kg/m ²)	18.3	15.8	20.5 ^{b,c}
VO ₂ peak (L/min)	2606	2167 ^a	3358 ^{b,c}
VO ₂ peak/weight (mL/kg/min)	33.5	35.7	42 ^{b,c}
VO ₂ peak/lean mass (L/min/kg)	47.3	53.3	52.4
Expired air volume (BTPS) (L/min)	102.3	87.4	128.8 ^{b,c}

VO₂ peak refers to the maximal oxygen consumption at time of peak exercise. Transgender women (mean duration of gender affirming hormone therapy 14 years) are the reference group in the first column.

Abbreviation: BMI, body mass index; BTPS, body temperature, pressure, water vapor saturated.

^aStatistically significant difference ($P < .05$) between cisgender women and transgender women.

^bStatistically significant difference ($P < .05$) between cisgender men and cisgender women.

^cStatistically significant difference ($P < .05$) between cisgender men and transgender women. Fat mass and lean mass (fat-free mass) were measured by bioelectrical impedance analysis.

and run times took 3 years to reach that of cisgender men (124). By 4 years, trans men appeared to exceed the average performance of cisgender men (124).

Trans women prior to feminizing hormone therapy performed 31% more push-ups, 15% more sit-ups in 1 minute, and ran 1.5 miles 21% faster than cisgender women in Roberts et al's study (123). It should be noted that height and size were not matched between trans women and cisgender women (Fig. 1). After 2 years of taking feminizing hormones, the push-ups and sit-ups performed in 1 minute significantly reduced and were no different to cisgender women (123). In Chiccarelli's analysis, the number of push-ups and sit-ups performed steadily declined over 4 years; however, although sit-ups were not statistically different to cisgender women at the 4 year time-point, push-ups performed remained statistically higher than cisgender women (albeit that 208 of 223 trans women dropped out over 4 years) (124). Run times slowed in both studies; however, statistical results were discrepant; Roberts et al found that trans women remained statistically faster than cisgender women at 2 years, but the larger Chiccarelli et al study found that run times among trans women were no different from cisgender women by 2 years of GAHT (123, 124).

Overall, trans men have improvements in physical performance after 1 to 2 years of testosterone therapy. In trans women, declines were seen in areas of physical performance but the discrepancy between statistical significance in Roberts et al and Chiccarelli et al may reflect a residual advantage in some parameters over cisgender women, or a type 1 error with survivorship bias influencing results given dropouts over time. Fitness test results must be interpreted in light of limitations. Tests have a minimum standard to pass, and, as such, are effort dependent and do not quantify maximal performance. Failure to pass a fitness test typically affects job prospects and requires service members to attend additional physical training sessions until they can meet the fitness requirements or leave military service. As such, there is survivorship bias across time with those remaining in the study likely

maintaining higher fitness levels. Moreover, test results are uncontrolled for lifestyle variables; the type and intensity of training of service members vary by occupation. Further prospective studies in trans people are needed.

Physical performance is dependent upon many factors that vary greatly depending on the needs of individual sports. There are no published research studies on the effect of GAHT on coordination, flexibility, cardiac size, lung function, maximal power output (W_{max}), anaerobic capacity, lactate threshold, exercise economy, efficiency, or factors such as W_{max}/body weight ratio that are an important marker of ability in competitive cyclists.

Summary and Conclusions

As trans people have been stigmatized for many decades, there is little research in the field and the evidence base is not definitive. Our understanding of the impact of GAHT on physical performance is based on retrospective data with no prospective longitudinal controlled studies. Further research is underway (125).

Existing studies in nonathletic trans men have shown that increases in muscle mass and strength occur with testosterone therapy, and physical performance appears to be no different to cisgender men by 1 to 3 years after GAHT.

Studies in nonathletic trans women after GAHT demonstrates no change in height, but have shown decreases in hemoglobin, bone density compromise, and decrease in muscle mass and strength, which continue to decline beyond 2 years. While absolute muscle mass is higher, their relative muscle and fat mass percentages and muscle strength corrected for lean mass are no different to cisgender women. Cross-sectional studies of trans women on GAHT for over 4 years show that relative percentages of muscle mass and fat mass as well as fitness as measured by VO₂ peak corrected for lean mass are no different to cisgender women and lower than that of cisgender men. Steady decrements are seen in physical performance of nonathletic trans women in the







	Before hormone therapy ^{a#}		After 2 years of hormone therapy ^{a#}		After 4 years of hormone therapy ^a	
	Compared with cis women	Compared with cis men	Compared with cis women	Compared with cis men	Compared with cis women	Compared with cis men
Trans Women						
Height	+11.9cm [^]	-1.9cm [^]	+11.9cm [^]	-1.9cm [^]		
Weight	+11kg [^]	-6.8kg [^]	+11kg [^]	-6.8kg [^]		
 Push-Ups	+31% [^] +66% [#]	-13% [^] -8% [#]	No difference [^] +31% [#]	-55% [^] -27% [#]	+18%	-35%
 Sit-Ups	+15% [^] +28% [#]	No difference ^{^#}	No difference [^] +17% [#]	-17% [^] -8% [#]	No difference	-15%
 1.5 Mile Run	+21% [^] +18% [#]	No difference ^{^#}	+12% [^] No difference [#]	No difference [^] -16% [#]	No difference	-22%
Trans Men						
Height	+1.2cm [^]	-12.7cm [^]	+1.2cm [^]	-12.7cm [^]		
Weight	+3.8kg [^]	-14kg [^]	+4.3kg [^]	-13.5kg [^]		
 Push-Ups	+13% [^] +25% [#]	-44% [^] -30% [#]	+46% [^] +61% [#]	No difference [^] -10% [#]	+89%	+15% (No difference at 3 years)
 Sit-Ups	+10% [^] +22% [#]	No difference [^] -4% [#]	+22% [^] +33% [#]	+10% [^] No difference [#]	+43%	+13% (No difference at 3 years)
 1.5 Mile Run	No difference [^] +5% [#]	-15% [^] -15% [#]	+20% [^] +12% [#]	No difference [^] -7% [#]	+79%	No difference

Figure 1. Summary of physical performance changes with gender-affirming hormone therapy. + indicates advantage (ie, faster run time or greater number of push-ups) and - indicates degree of disadvantage relative to cisgender comparison group. No difference refers to no statistically significant difference when compared with the cisgender comparison group. ^ indicates data from Roberts et al reporting Air Force fitness test times up to 2 years after GAHT. # indicates data from Chiccarelli et al that expanded analysis for up to 4 years after GAHT.

military, with no significant difference with cisgender women for running times by 2 years and sit-ups by 4 years after GAHT. An advantage in push-ups or upper body strength over cisgender women may remain at 4 years.

The limited existing research should be interpreted considering sports-specific factors; different combinations of physical capabilities including upper or lower body muscle strength, hand grip strength, endurance, power, flexibility, hand-eye coordination, communication with teammates, mindset, and strategy may or may not be relevant. Consideration of existing research will be part of the process in creating policies for the inclusion of trans people in elite sport. Reasonable accommodations for the inclusion of trans people are sport specific and could be based on the range of competitive advantages and abilities that are already accepted in the cisgender population.

Although prospective longitudinal controlled studies in trans athletes are needed, with so few trans athletes and extremely low participation of trans people in sport, recruitment into such research will be challenging. Future research should include larger sample sizes of trans people (nonathletes and athletes) to be compared with cisgender males and females with relevant outcomes adjusted for known confounders.

Acknowledgments

We would like to acknowledge Prof. David Handelsman and Dr. Julian Grace for their constructive comments about the

manuscript. The authorship team includes trans people with male, female, and nonbinary identities.

Funding

A.S.C. is supported by a NHMRC Investigator Grant (#2008956), B.J.N. is supported by a NHMRC Postgraduate Research Scholarship (#2003939), and N.E. is supported by a NHMRC Investigator Grant (#1194159).

Disclosures

A.S.C. and B.J.N. have received product (estradiol and progesterone) for investigator-initiated trials from Besins Healthcare. Besins Healthcare have not provided any monetary support nor had any input into the design and analysis of research studies or the writing of any manuscripts. A.S.C. is a member of the *Journal of Clinical Endocrinology and Metabolism* editorial board. This endocrine-focused narrative was an invited mini-review for the *Journal of Clinical Endocrinology and Metabolism*. Four authors (A.S.C., B.J.N., P.J., N.E.) additionally contributed to a separate narrative review (first author Moreland; PhD candidate in Eynon Lab, Institute for Health and Sport, PMID 37323162) with a greater focus on sports science, transgender participation in sport, and performance differences between sexes. Both manuscripts were written separately but we acknowledge some overlap in content.

Data Availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

References

- Spizzirri G, Eufrazio R, Lima MCP, *et al.* Proportion of people identified as transgender and non-binary gender in Brazil. *Sci Rep.* 2021;11(1):2240.
- Crissman HP, Berger MB, Graham LF, Dalton VK. Transgender demographics: a household probability sample of US adults, 2014. *Am J Public Health.* 2017;107(2):213-215.
- Kuyper L, Wijzen C. Gender identities and gender dysphoria in The Netherlands. *Arch Sex Behav.* 2014;43(2):377-385.
- Van Caenegem E, Wierckx K, Elaut E, *et al.* Prevalence of gender nonconformity in Flanders, Belgium. *Arch Sex Behav.* 2015;44(5):1281-1287.
- Åhs JW, Dhejne C, Magnusson C, *et al.* Proportion of adults in the general population of Stockholm County who want gender-affirming medical treatment. *PLoS One.* 2018;13(10):e0204606.
- Clark TC, Lucassen MF, Bullen P, *et al.* The health and well-being of transgender high school students: results from the New Zealand adolescent health survey (Youth'12). *J Adolesc Health.* 2014;55(1):93-99.
- Bretherton I, Thrower E, Zwickl S, *et al.* The health and well-being of transgender Australians: A national community survey. *LGBT health.* 2021;8(1):42-49.
- Boyer TL, Youk AO, Haas AP, *et al.* Suicide, homicide, and all-cause mortality among transgender and cisgender patients in the Veterans Health Administration. *LGBT health.* 2021;8(3):173-180.
- Chen R, Zhu X, Wright L, *et al.* Suicidal ideation and attempted suicide amongst Chinese transgender persons: national population study. *J Affect Disord.* 2019;245:1126-1134.
- Budhwani H, Hearld KR, Milner AN, *et al.* Transgender women's experiences with stigma, trauma, and attempted suicide in the Dominican Republic. *Suicide Life Threat Behav.* 2018;48(6):788-796.
- Zwickl S, Wong AFQ, Dowers E, *et al.* Factors associated with suicide attempts among Australian transgender adults. *BMC Psychiatry.* 2021;21(1):81.
- Marshall E, Claes L, Bouman WP, Witcomb GL, Arcelus J. Non-suicidal self-injury and suicidality in trans people: a systematic review of the literature. *Int Rev Psychiatry.* 2016;28(1):58-69.
- Johnson A, Miranda L, Lee M. *Play to Win: Improving the Lives of LGBTQ Youth in Sports.* Human Rights Campaign Foundation; 2017.
- Handelsman DJ, Hirschberg AL, Bermon S. Circulating testosterone as the hormonal basis of sex differences in athletic performance. *Endocr Rev.* 2018;39(5):803-829.
- Handelsman DJ. Sex differences in athletic performance emerge coinciding with the onset of male puberty. *Clin Endocrinol.* 2017;87(1):68-72.
- Hilton EN, Lundberg TR. Transgender women in the female category of sport: perspectives on testosterone suppression and performance advantage. *Sports Med.* 2021;51(2):199-214.
- Saez JM, Forest MG, Morera AM, Bertrand J. Metabolic clearance rate and blood production rate of testosterone and dihydrotestosterone in normal subjects, during pregnancy, and in hyperthyroidism. *J Clin Invest.* 1972;51(5):1226-1234.
- Hirschberg AL, Elings Knutsson J, Helge T, *et al.* Effects of moderately increased testosterone concentration on physical performance in young women: a double blind, randomised, placebo controlled study. *Br J Sports Med.* 2020;54(10):599-604.
- Ferguson-Smith MA, Bavington LD. Natural selection for genetic variants in sport: the role of Y chromosome genes in elite female athletes with 46, XY DSD. *Sports Med.* 2014;44(12):1629-1634.
- Zhao K, Hohmann A, Chang Y, Zhang B, Pion J, Gao B. Physiological, anthropometric, and motor characteristics of elite Chinese youth athletes from six different sports. *Front Physiol.* 2019;10:405.
- Mala L, Maly T, Zahalka F, *et al.* Body composition of elite female players in five different sports games. *J Hum Kinet.* 2015;45(1):207-215.
- Thuany M, Souza RF, Hill L, *et al.* Discriminant analysis of anthropometric and training variables among runners of different competitive levels. *Int J Environ Res Public Health.* 2021;18(8):8.
- Sonksen P. Determination and regulation of body composition in elite athletes. *Br J Sports Med.* 2018;52(4):219-229.
- Palmer D, Cooper DJ, Emery C, *et al.* Self-reported sports injuries and later-life health status in 3357 retired Olympians from 131 countries: a cross-sectional survey among those competing in the games between London 1948 and PyeongChang 2018. *Br J Sports Med.* 2021;55(1):46-53.
- Auld MC. Global country-level estimates of associations between adult height and the distribution of income. *Am J Hum Biol.* 2018;30(6):e23138.
- Coleman E, Radix AE, Bouman WP, *et al.* Standards of care for the health of transgender and gender diverse people, version 8. *Int J Transgend Health.* 2022;23(Suppl 1):S1-S259.
- van Leerdam TR, Zajac JD, Cheung AS. The effect of gender-affirming hormones on gender dysphoria, quality of life, and psychological functioning in transgender individuals: a systematic review. *Transgend Health.* 2021;8(1):6-21.
- Foster Skewis L, Bretherton I, Leemaqz SY, Zajac JD, Cheung AS. Short-term effects of gender-affirming hormone therapy on dysphoria and quality of life in transgender individuals: a prospective controlled study. *Front Endocrinol (Lausanne).* 2021;12:717766.
- Hembree WC, Cohen-Kettenis PT, Gooren L, *et al.* Endocrine treatment of gender-dysphoric/gender-incongruent persons: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab.* 2017;102(11):3869-3903.
- Safer JD, Tangpricha V. Care of transgender persons. *N Engl J Med.* 2019;381(25):2451-2460.
- Nota NM, Wiepjes CM, de Blok CJM, Gooren LJG, Kreukels BPC, den Heijer M. Occurrence of acute cardiovascular events in transgender individuals receiving hormone therapy. *Circulation.* 2019;139(11):1461-1462.
- Angus L, Leemaqz S, Ooi O, *et al.* Cyproterone acetate or spironolactone in lowering testosterone concentrations for transgender individuals receiving oestradiol therapy. *Endocr Connect.* 2019;8(7):935-940.
- Angus LM, Nolan BJ, Zajac JD, Cheung AS. A systematic review of anti-androgens and feminisation in transgender women. *Clin Endocrinol.* 2021;94(5):743-752.
- Getahun D, Nash R, Flanders WD, *et al.* Cross-sex hormones and acute cardiovascular events in transgender persons: a cohort study. *Ann Intern Med.* 2018;169(4):205-213.
- Janssen I, Heymsfield SB, Wang ZM, Ross R. Skeletal muscle mass and distribution in 468 men and women aged 18-88 yr. *J Appl Physiol.* 2000;89(1):81-88.
- Landen S, Hiam D, Voisin S, Jacques M, Lamon S, Eynon N. Physiological and molecular sex differences in human skeletal muscle in response to exercise training. *J Physiol.* 2023;601(3):419-434.
- Harper J, O'Donnell E, Sorouri Khorashad B, McDermott H, Witcomb GL. How does hormone transition in transgender women change body composition, muscle strength and haemoglobin? Systematic review with a focus on the implications for sport participation. *Br J Sports Med.* 2021;55(15):865-872.
- Tavoian D, Ampomah K, Amano S, Law TD, Clark BC. Changes in DXA-derived lean mass and MRI-derived cross-sectional area of the thigh are modestly associated. *Sci Rep.* 2019;9(1):10028.
- Tsukasaki K, Matsui Y, Arai H, *et al.* Association of muscle strength and gait speed with cross-sectional muscle area determined by mid-thigh computed tomography – a comparison with

- skeletal muscle mass measured by dual-energy X-ray absorptiometry. *J Frailty Aging*. 2020;9(2):82-89.
40. Hansen RD, Williamson DA, Finnegan TP, *et al*. Estimation of thigh muscle cross-sectional area by dual-energy X-ray absorptiometry in frail elderly patients. *Am J Clin Nutr*. 2007;86(4):952-958.
 41. Van Caenegem E, Wierckx K, Taes Y, *et al*. Body composition, bone turnover, and bone mass in trans men during testosterone treatment: 1-year follow-up data from a prospective case-controlled study (ENIGI). *Eur J Endocrinol*. 2015;172(2):163-171.
 42. Tack LJW, Craen M, Lapauw B, *et al*. Proandrogenic and antiandrogenic progestins in transgender youth: differential effects on body composition and bone metabolism. *J Clin Endocrinol Metab*. 2018;103(6):2147-2156.
 43. Auer MK, Ebert T, Pietzner M, *et al*. Effects of sex hormone treatment on the metabolic syndrome in transgender individuals: focus on metabolic cytokines. *J Clin Endocrinol Metab*. 2018;103(2):790-802.
 44. Pelusi C, Costantino A, Martelli V, *et al*. Effects of three different testosterone formulations in female-to-male transsexual persons. *J Sex Med*. 2014;11(12):3002-3011.
 45. Klaver M, de Blok CJM, Wiepjes CM, *et al*. Changes in regional body fat, lean body mass and body shape in trans persons using cross-sex hormonal therapy: results from a multicenter prospective study. *Eur J Endocrinol*. 2018;178(2):165-173.
 46. Gooren LJ, Bunck MC. Transsexuals and competitive sports. *Eur J Endocrinol*. 2004;151(4):425-429.
 47. Bretherton I, Spanos C, Leemaqz SY, *et al*. Insulin resistance in transgender individuals correlates with android fat mass. *Ther Adv Endocrinol Metab*. 2021;12:2042018820985681.
 48. Mueller A, Zollver H, Kronawitter D, *et al*. Body composition and bone mineral density in male-to-female transsexuals during cross-sex hormone therapy using gonadotrophin-releasing hormone agonist. *Exp Clin Endocrinol Diabetes*. 2011; 119(02):95-100.
 49. Wierckx K, Van Caenegem E, Schreiner T, *et al*. Cross-sex hormone therapy in trans persons is safe and effective at short-time follow-up: results from the European network for the investigation of gender incongruence. *J Sex Med*. 2014;11(8):1999-2011.
 50. Gava G, Cerpolini S, Martelli V, Battista G, Seracchioli R, Meriggola MC. Cyproterone acetate vs leuprolide acetate in combination with transdermal oestradiol in transwomen: a comparison of safety and effectiveness. *Clin Endocrinol*. 2016;85(2):239-246.
 51. Van Caenegem E, Wierckx K, Taes Y, *et al*. Preservation of volumetric bone density and geometry in trans women during cross-sex hormonal therapy: a prospective observational study. *Osteoporos Int*. 2015;26(1):35-47.
 52. Yun Y, Kim D, Lee ES. Effect of cross-sex hormones on body composition, bone mineral density, and muscle strength in trans women. *J Bone Metab*. 2021;28(1):59-66.
 53. Lapauw B, Taes Y, Simoens S, *et al*. Body composition, volumetric and areal bone parameters in male-to-female transsexual persons. *Bone*. 2008;43(6):1016-1021.
 54. Alvares LAM, Santos MR, Souza FR, *et al*. Cardiopulmonary capacity and muscle strength in transgender women on long-term gender-affirming hormone therapy: a cross-sectional study. *Br J Sports Med*. 2022;56(22):1292-1298.
 55. Shin H, Panton LB, Dutton GR, Ilich JZ. Relationship of physical performance with body composition and bone mineral density in individuals over 60 years of age: a systematic review. *J Aging Res*. 2011;2011:191896.
 56. Mattila VM, Tallroth K, Marttinen M, Pihlajamäki H. Physical fitness and performance. Body composition by DEXA and its association with physical fitness in 140 conscripts. *Med Sci Sports Exe*. 2007;39(12):2242-2247.
 57. Chen L, Nelson DR, Zhao Y, Cui Z, Johnston JA. Relationship between muscle mass and muscle strength, and the impact of comorbidities: a population-based, cross-sectional study of older adults in the United States. *BMC Geriatr*. 2013;13(1):74.
 58. Hayashida I, Tanimoto Y, Takahashi Y, Kusabiraki T, Tamaki J. Correlation between muscle strength and muscle mass, and their association with walking speed, in community-dwelling elderly Japanese individuals. *PLoS One*. 2014;9(11):e111810.
 59. Fallahi AA, Jadidian AA. The effect of hand dimensions, hand shape and some anthropometric characteristics on handgrip strength in male grip athletes and non-athletes. *J Hum Kinet*. 2011;29(2011):151-159.
 60. Visnapuu M, Jürimäe T. Handgrip strength and hand dimensions in young handball and basketball players. *J Strength Cond Res*. 2007;21(3):923-929.
 61. Cronin J, Lawton T, Harris N, Kilding A, McMaster DT. A brief review of handgrip strength and sport performance. *J Strength Cond Res*. 2017;31(11):3187-3217.
 62. Felicio DC, Pereira DS, Assumpção AM, *et al*. Poor correlation between handgrip strength and isokinetic performance of knee flexor and extensor muscles in community-dwelling elderly women. *Geriatr Gerontol Int*. 2014; 14(1):185-189.
 63. Sanderson WC, Scherbov S, Weber D, Bordone V. Combined measures of upper and lower body strength and subgroup differences in subsequent survival among the older population of England. *J Aging Health*. 2016;28(7):1178-1193.
 64. Fried LP, Tangen CM, Walston J, *et al*. Cardiovascular health study collaborative research G. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci*. 2001;56(3):M146-M156.
 65. Scharff M, Wiepjes CM, Klaver M, *et al*. Change in grip strength in trans people and its association with lean body mass and bone density. *Endocr Connect*. 2019;8(7):1020-1028.
 66. Andrade SRL, Mucida YM, Xavier JDC, Fernandes LN, Silva RO, Bandeira F. Bone mineral density, trabecular bone score and muscle strength in transgender men receiving testosterone therapy versus cisgender men. *Steroids*. 2022;178:108951.
 67. Wiik A, Lundberg TR, Rullman E, *et al*. Muscle strength, size, and composition following 12 months of gender-affirming treatment in transgender individuals. *J Clin Endocrinol Metab*. 2020;105(3):e805-e813.
 68. Locquet M, Beaudart C, Durieux N, Reginster JY, Bruyère O. Relationship between the changes over time of bone mass and muscle health in children and adults: a systematic review and meta-analysis. *BMC Musculoskelet Disord*. 2019;20(1):429.
 69. Singh-Ospina N, Maraka S, Rodriguez-Gutierrez R, *et al*. Effect of sex steroids on the bone health of transgender individuals: a systematic review and meta-analysis. *J Clin Endocrinol Metab*. 2017;102(11):3904-3913.
 70. Delgado-Ruiz R, Swanson P, Romanos G. Systematic review of the long-term effects of transgender hormone therapy on bone markers and bone mineral density and their potential effects in implant therapy. *J Clin Med*. 2019;8(6):784.
 71. Figuera TM, Ziegelmann PK, Rasia da Silva T, Spritzer PM. Bone mass effects of cross-sex hormone therapy in transgender people: updated systematic review and meta-analysis. *J Endocr Soc*. 2019;3(5):943-964.
 72. Ruetsche AG, Kneubuehl R, Birkhaeuser MH, Lippuner K. Cortical and trabecular bone mineral density in transsexuals after long-term cross-sex hormonal treatment: a cross-sectional study. *Osteoporos Int*. 2005;16(7):791-798.
 73. Wierckx K, Mueller S, Weyers S, *et al*. Long-term evaluation of cross-sex hormone treatment in transsexual persons. *J Sex Med*. 2012;9(10):2641-2651.
 74. Broulik PD, Urbánek V, Libanský P. Eighteen-year effect of androgen therapy on bone mineral density in trans(gender) men. *Horm Metab Res*. 2018;50(02):133-137.
 75. Chrisostomo KR, Skare TL, Chrisostomo HR, Barbosa EJJ, Nishihara R. Transwomen and bone mineral density: a cross-sectional study in Brazilian population. *Br J Radiol*. 2020;93(1111):20190935.

76. van Kesteren P, Lips P, Deville W, *et al.* The effect of one-year cross-sex hormonal treatment on bone metabolism and serum insulin-like growth factor-1 in transsexuals. *J Clin Endocrinol Metab.* 1996;81(6):2227-2232.
77. van Kesteren P, Lips P, Gooren LJ, Asscheman H, Megens J. Long-term follow-up of bone mineral density and bone metabolism in transsexuals treated with cross-sex hormones. *Clin Endocrinol.* 1998;48(3):347-354.
78. Turner A, Chen TC, Barber TW, Malabanan AO, Holick MF, Tangpricha V. Testosterone increases bone mineral density in female-to-male transsexuals: a case series of 15 subjects. *Clin Endocrinol.* 2004;61(5):560-566.
79. T'Sjoen G, Weyers S, Taes Y, *et al.* Prevalence of low bone mass in relation to estrogen treatment and body composition in male-to-female transsexual persons. *J Clin Densitom.* 2009;12(3):306-313.
80. Mueller A, Haeblerle L, Zollner H, *et al.* Effects of intramuscular testosterone undecanoate on body composition and bone mineral density in female-to-male transsexuals. *J Sex Med.* 2010;7(9):3190-3198.
81. Wiepjes CM, Vlot MC, Klaver M, *et al.* Bone mineral density increases in trans persons after 1 year of hormonal treatment: a multicenter prospective observational study. *J Bone Miner Res.* 2017;32(6):1252-1260.
82. Wiepjes CM, de Jongh RT, de Blok CJ, *et al.* Bone safety during the first ten years of gender-affirming hormonal treatment in transwomen and transmen. *J Bone Miner Res.* 2019;34(3):447-454.
83. Chapurlat R, Bui M, Sornay-Rendu E, *et al.* Deterioration of cortical and trabecular microstructure identifies women with osteopenia or normal bone mineral density at imminent and long-term risk for fragility fracture: a prospective study. *J Bone Miner Res.* 2020;35(5):833-844.
84. Samelson EJ, Broe KE, Xu H, *et al.* Cortical and trabecular bone microarchitecture as an independent predictor of incident fracture risk in older women and men in the bone microarchitecture international consortium (BoMIC): a prospective study. *Lancet Diabetes Endocrinol.* 2019;7(1):34-43.
85. Bretherton I, Ghasem-Zadeh A, Leemaqz SY, *et al.* Bone microarchitecture in transgender adults: a cross-sectional study. *J Bone Mineral Res.* 2022;37(4):643-648.
86. Van Caenegem E, Taes Y, Wierckx K, *et al.* Low bone mass is prevalent in male-to-female transsexual persons before the start of cross-sex hormonal therapy and gonadectomy. *Bone.* 2013;54(1):92-97.
87. Wiepjes CM, de Blok CJ, Staphorsius AS, *et al.* Fracture risk in trans women and trans men using long-term gender-affirming hormonal treatment: a nationwide cohort study. *J Bone Miner Res.* 2020;35(1):64-70.
88. Hawkins WW, Speck E, Leonard VG. Variation of the hemoglobin level with age and sex. *Blood.* 1954;9(10):999-1007.
89. Wehrlin JP, Zuest P, Hallén J, Marti B. Live high-train low for 24 days increases hemoglobin mass and red cell volume in elite endurance athletes. *J Appl Physiol.* 2006;100(6):1938-1945.
90. Zelenkova IE, Zotkin SV, Korneev PV, Koprov SV, Grushin AA. Relationship between total hemoglobin mass and competitive performance in endurance athletes. *J Sports Med Phys Fitness.* 2019;59(3):352-356.
91. Bachman E, Travison TG, Basaria S, *et al.* Testosterone induces erythrocytosis via increased erythropoietin and suppressed hepcidin: evidence for a new erythropoietin/hemoglobin set point. *J Gerontol A Biol Sci Med Sci.* 2014;69(6):725-735.
92. Cheung AS, Lim HY, Cook T, *et al.* Approach to interpreting common laboratory pathology tests in transgender individuals. *J Clin Endocrinol Metab.* 2021;106(3):893-901.
93. Fernandez JD, Tannock LR. Metabolic effects of hormone therapy in transgender patients. *Endocr Pract.* 2016;22(4):383-388.
94. SoRelle JA, Jiao R, Gao E, *et al.* Impact of hormone therapy on laboratory values in transgender patients. *Clin Chem.* 2019;65(1):170-179.
95. Colizzi M, Costa R, Scaramuzzi F, *et al.* Concomitant psychiatric problems and hormonal treatment induced metabolic syndrome in gender dysphoria individuals: a 2 year follow-up study. *J Psychosom Res.* 2015;78(4):399-406.
96. Roberts TK, Kraft CS, French D, *et al.* Interpreting laboratory results in transgender patients on hormone therapy. *Am J Med.* 2014;127(2):159-162.
97. Defreyne J, Vantomme B, Van Caenegem E, *et al.* Prospective evaluation of hematocrit in gender-affirming hormone treatment: results from European network for the investigation of gender incongruence. *Andrology.* 2018;6(3):446-454.
98. Bassett DR J, Howley ET. Limiting factors for maximum oxygen uptake and determinants of endurance performance. *Med Sci Sports Exercise.* 2000;32(1):70-84.
99. Butts NK, Henry BA, McLean D. Correlations between VO₂max and performance times of recreational triathletes. *J Sports Med Phys Fitness.* 1991;31(3):339-344.
100. Collis T, Devereux RB, Roman MJ, *et al.* Relations of stroke volume and cardiac output to body composition: the strong heart study. *Circulation.* 2001;103(6):820-825.
101. Joyner MJ. Physiological limits to endurance exercise performance: influence of sex. *J Physiol.* 2017;595(9):2949-2954.
102. Maciejczyk M, Więcek M, Szymura J, Szygula Z, Wiecha S, Cempla J. The influence of increased body fat or lean body mass on aerobic performance. *PLoS One.* 2014;9(4):e95797.
103. Khazraee T, Fararouei M, Daneshmandi H, Mobasheri F, Zamanian Z. Maximal oxygen consumption, respiratory volume and some related factors in fire-fighting personnel. *Int J Prev Med.* 2017;8(1):25.
104. Chantler PD, Clements RE, Sharp L, George KP, Tan LB, Goldspink DF. The influence of body size on measurements of overall cardiac function. *Am J Physiol Heart Circ Physiol.* 2005;289(5):H2059-H2065.
105. Ekelund U, Franks PW, Wareham NJ, Aman J. Oxygen uptakes adjusted for body composition in normal-weight and obese adolescents. *Obesity Res.* 2004;12(3):513-520.
106. Goran M, Fields DA, Hunter GR, Herd SL, Weinsier RL. Total body fat does not influence maximal aerobic capacity. *Int J Obes Relat Metab Disord.* 2000;24(7):841-848.
107. Toth MJ, Goran MI, Ades PA, Howard DB, Poehlman ET. Examination of data normalization procedures for expressing peak VO₂ data. *J Appl Physiol.* 1993;75(5):2288-2292.
108. Janz KF, Burns TL, Witt JD, Mahoney LT. Longitudinal analysis of scaling VO₂ for differences in body size during puberty: the Muscatine Study. *Med Sci Sports Exercise.* 1998;30(9):1436-1444.
109. Adachi H. Cardiopulmonary exercise test. *Int Heart J.* 2017;58(5):654-665.
110. Whipp BJ, Ward SA. Physiological determinants of pulmonary gas exchange kinetics during exercise. *Med Sci Sports Exercise.* 1990;22(1):62-71.
111. Ross R, Blair SN, Arena R, *et al.* Importance of assessing cardiorespiratory fitness in clinical practice: a case for fitness as a clinical vital sign: a scientific statement from the American Heart Association. *Circulation.* 2016;134(24):e653-e699.
112. Jeppesen TD, Schwartz M, Olsen DB, Vissing J. Oxidative capacity correlates with muscle mutation load in mitochondrial myopathy. *Ann Neurol.* 2003;54(1):86-92.
113. Blair SN, Kohl HW 3rd, Paffenbarger RS Jr, Clark DG, Cooper KH, Gibbons LW. Physical fitness and all-cause mortality. A prospective study of healthy men and women. *JAMA.* 1989; 262(17):2395-2401.
114. MacLean HE, Chiu WS, Notini AJ, *et al.* Impaired skeletal muscle development and function in male, but not female, genomic androgen receptor knockout mice. *FASEB J.* 2008;22(8):2676-2689.

115. Riffo-Vasquez Y, Ligeiro de Oliveira AP, Page CP, Spina D, Tavares-de-Lima W. Role of sex hormones in allergic inflammation in mice. *Clin Exp Allergy*. 2007;37(3):459-470.
116. Ambhore NS, Kalidhindi RSR, Loganathan J, Sathish V. Role of differential estrogen receptor activation in airway hyperreactivity and remodeling in a murine model of asthma. *Am J Respir Cell Mol Biol*. 2019;61(4):469-480.
117. de Lemos JA, Drazner MH, Omland T, *et al*. Association of troponin T detected with a highly sensitive assay and cardiac structure and mortality risk in the general population. *JAMA*. 2010;304(22):2503-2512.
118. Aw TC, Huang WT, Le TT, *et al*. Author correction: high-sensitivity cardiac troponins in cardio-healthy subjects: a cardiovascular magnetic resonance imaging study. *Sci Rep*. 2019;9(1):7686.
119. Neeland IJ, Drazner MH, Berry JD, *et al*. Biomarkers of chronic cardiac injury and hemodynamic stress identify a malignant phenotype of left ventricular hypertrophy in the general population. *J Am Coll Cardiol*. 2013;61(2):187-195.
120. Greene DN, Schmidt RL, Christenson RH, *et al*. Distribution of high-sensitivity cardiac troponin and N-terminal pro-brain natriuretic peptide in healthy transgender people. *JAMA Cardiol*. 2022;7(11):1170-1174.
121. Svedlund Eriksson E, Johansson I, Mårtensson AKF, *et al*. Castration of male mice induces metabolic remodeling of the heart. *J Endocr Soc*. 2022;6(11):bvac132. doi: [10.1210/endsol/bvac132](https://doi.org/10.1210/endsol/bvac132)
122. Harper J. Race times for transgender athletes. *J Sporting Cultures Identities*. 2015;6(1):1-9.
123. Roberts TA, Smalley J, Ahrendt D. Effect of gender affirming hormones on athletic performance in transwomen and transmen: implications for sporting organisations and legislators. *Br J Sports Med*. 2020:bjsports-2020-102329 [Online ahead of print]. doi: [10.1136/bjsports-2020-102329](https://doi.org/10.1136/bjsports-2020-102329)
124. Chiccarelli E, Aden J, Ahrendt D, Smalley J. Fit transitioning: when can transgender airmen fitness test in their affirmed gender? *Mil Med*. 2022:usac320 [Online ahead of print]. doi: [10.1093/milmed/usac320](https://doi.org/10.1093/milmed/usac320)
125. Jones PR, Voisin S, Nolan BJ, *et al*. Uncovering the effects of gender affirming hormone therapy on skeletal muscle and epigenetics: protocol for a prospective matched cohort study in transgender individuals (the GAME study). *BMJ Open*. 2022;12(5):e060869.