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Transgender health and the impact of aging and menopause

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ABSTRACT

Gender affirming hormone therapy (GAHT) is used by many transgender people to reduce gender incongruence and improve psychological functioning. As GAHT shares many similarities with menopausal hormone therapy, clinicians supporting people through menopause are ideally placed to manage GAHT. This narrative review provides an overview of transgender health and discusses long-term effects of GAHT to consider when managing transgender individuals across the lifespan. Menopause is less relevant for transgender individuals who take GAHT (often given lifelong) to achieve sex steroid concentrations generally in the range of the affirmed gender. For people using feminizing hormone therapy, there is an elevated risk of venous thromboembolism, myocardial infarction, stroke and osteoporosis relative to cisgender individuals. For trans people using masculinizing hormone therapy, there is an increased risk of polycythemia, probable higher risk of myocardial infarction and pelvic pain which is poorly understood. Proactive mitigation of cardiovascular risk factors is important for all transgender people and optimization of bone health is important for those using feminizing hormones. With a lack of research to guide GAHT in older age, a shared decision-making approach is recommended for the provision of GAHT to achieve individual goals whilst minimizing potential adverse effects.

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Introduction

Given that menopausal hormone therapy shares many similarities with gender affirming hormone therapy (GAHT), clinicians who support cisgender women through menopause are well placed to support transgender and gender diverse individuals. Transgender and gender diverse, or simply the umbrella term ‘trans’, refers to someone who has a gender different from that presumed for them at birth and includes binary (male or female) and non-binary (i.e. gender fluid, agender) identities. Population-based samples suggest approximately 0.5–3% of the general population are trans [1–6]. The visibility of trans people differs markedly across countries worldwide due to complex social and cultural factors, laws and availability of healthcare services for trans people.



There are many ways in which a trans person may affirm their gender; changing names, pronouns or gender expression, voice therapy, hair removal, using hormone therapy and/or surgery – all of which can significantly improve mental health, gender dysphoria and quality of life [7–11].

Research on the effects and adverse effects of GAHT is evolving and in its infancy. Much of our understanding of the

effects and adverse effects of GAHT has been gained from well-characterized retrospective analyses and observational cohort studies from North America and Europe, often compared to population samples which will be summarized in this review. Long-term adverse effects are not definitive and become more relevant as individuals age and develop co-occurring medical conditions. This narrative review aims to provide an overview of transgender health with a focus on masculinizing and feminizing GAHT for clinicians experienced in menopausal hormone therapy and discuss implications of aging when managing trans adults across the lifespan.

Transgender health

Trans people as a whole face significant marginalization worldwide, including in health care. Difficulty accessing basic medical as well as gender affirming care are frequently reported [12]. Even when being able to access gender affirming care, there remains low-quality evidence to guide the medical treatment of trans people overall and health provider knowledge of trans health remains frequently suboptimal [13,14]. Healthcare avoidance because of fear of misgendering, discrimination and mistreatment is extremely

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common, which contributes to poor health. Moreover, the experience of widespread social stressors (social isolation, violence and hate crimes, unemployment) resulting in economic and legal marginalization leads to minority stress, in turn exacerbating poor physical and mental health outcomes [15–17].

It is not surprising that trans people have an elevated risk of many chronic health conditions compared to their cisgender counterparts, including chronic obstructive pulmonary disease, depression, hepatitis, HIV, schizophrenia, substance use disorders as well as obesity and other liver conditions [18,19]. More than 60% report a history of diagnosed depression or anxiety [20] and over 40% have attempted suicide [21–24]. Rates of death by suicide are more than two-fold greater than for cisgender populations [25] and significant disparities exist for all-cause mortality, especially among trans people presumed male at birth (with feminine or non-binary identities) and trans people of color [26–28]. The health inequity faced by trans people globally is a major public health concern.

In 2019, the World Health Organization in its International Classification of Diseases 11th Revision (ICD-11) redefined and reclassified ‘Gender Incongruence’ from the ‘Mental Health’ chapter into a newly established ‘Sexual Health’ chapter, reflecting modern understanding of gender identity [29]. Gender diversity is not a mental health condition, and reclassification sought to reduce stigma and aid access to gender affirming health care. ‘Gender Incongruence of Adolescence and Adulthood’ is defined as a marked and persistent incongruence between an individual’s experienced gender and the assigned sex, which often leads to a desire to ‘transition’, in order to live and be accepted as a person of the experienced gender, through hormonal treatment, surgery or other healthcare services to make the individual’s body align, as much as desired and to the extent possible, with the experienced gender [29].

Given the marked vulnerability of the trans community, many with experiences of trauma in healthcare settings, respectful and culturally sensitive health care which uses language tailored to what is most comfortable for the individual (including names and pronouns) is essential. A consultation for gender affirming care is often an opportunity to holistically address social, medical and mental healthcare needs.

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 affirmed gender. Commencement of hormone therapy is typically a highly considered decision after balancing potential benefits on psychological functioning with potential medical and social risks [8,30]. GAHT can significantly improve mental health, gender dysphoria and quality of life [7,8,30].

Masculinizing hormone therapy

Trans people presumed female at birth who commence masculinizing hormone therapy will generally achieve serum

testosterone concentrations in the typical cisgender male reference range [11,31]. Testosterone therapy is given in the same manner as that for hypogonadal cisgender men. This induces lowered voice, body and facial hair growth, as well as changes in body composition with increase in muscle mass and reduction in fat mass. Non-binary individuals may desire a more androgynous appearance and may use low-dose testosterone therapy for more gradual effects, often achieving testosterone concentrations above the cisgender female reference range but not necessarily in the cisgender male reference range [32]. Adverse effects of testosterone therapy include polycythemia, reduced high-density lipoprotein cholesterol, androgenic alopecia, acne, gynecological effects such as pelvic pain and genital dryness, and cardiovascular effects as discussed further in the following [33].

Feminizing hormone therapy

Trans people presumed male at birth who commence feminizing hormone therapy will generally achieve serum estradiol and testosterone concentrations in the cisgender female range [11,31]. This most often involves estradiol with anti-androgen agents such as cyproterone acetate, spironolactone or gonadotropin-releasing hormone analogues for people who do not undergo orchiectomy. Depending on the mechanism of action, peripheral androgen receptor antagonists such as spironolactone or bicalutamide may not necessarily lower the testosterone concentrations [34,35]. Feminizing hormone therapy induces breast growth, increases in fat mass and redistribution to a gynoid pattern, reduction in muscle mass, reduction in body and facial hair growth and reduction in sexual function. Some physical characteristics induced by male puberty do not change, such as lowered voice pitch and bone structure [11]. Adverse effects include an increased risk of venous thromboembolism (VTE), weight gain, compromised bone structure and cardiovascular disease (CVD) relative to cisgender women and men [33,36].

Aging and menopause

Aging trans adults have unique challenges. Fear of mistreatment in older care, isolation and loneliness exacerbated by trans identity, increased vulnerability to financial stressors, perceived lack of agency, and healthcare system and provider inclusivity are major concerns [37,38]. This is compounded by a need for increased healthcare provider interaction with the multiple chronic disease burden exacerbated with aging [19]. Alzheimer’s disease and related dementia diseases may be more prevalent among trans people [39], but the impact of GAHT on cognitive functioning remains unclear [40].

The term menopause whereby oocyte production and menstruation ceases is framed around cisgender women and is relevant only for older trans people presumed female at birth who do not use GAHT. There has only been one study published examining trans women’s experiences and beliefs about menopause [41]. Sixty-seven trans women of mean age 49 years expressed positive views about GAHT, including

treatment importance and personal and mental health benefits, but also concerns about long-term effects. Most expected to use GAHT indefinitely and 96% were taking GAHT at the time of the study. As such, trans women did not feel menopause was relevant [41]. No studies have been undertaken with trans people using testosterone therapy, but from a clinical perspective, many would continue therapy lifelong.

For trans people who take GAHT, whether it be testosterone or estradiol, there remain minimal data on how to manage GAHT with aging, whether there are higher risks with commencement in older age or whether the dose needs to be reduced over time. There is no age at which GAHT is absolutely contraindicated, and in fact, trans people who commence GAHT in older age report higher quality of life scores compared to younger individuals [42]. In trans people using testosterone therapy, there is a complete absence of data, so an individualized approach is needed. In trans people using feminizing hormone therapy, a retrospective chart review of 296 individuals compared estradiol formulations and serum estradiol concentrations in those aged ≥ 45 years ($n = 55$) and < 45 years ($n = 241$) in Australia [43]. Despite recommendations for transdermal estradiol in individuals aged ≥ 45 years [44], oral estradiol was the predominant estradiol formulation used by 58% of those aged ≥ 45 years. However, the median oral estradiol valerate dose was lower (4 mg vs. 6 mg, $p = 0.01$), and a higher proportion of individuals aged ≥ 45 years used transdermal estradiol (31% vs. 8%, $p < 0.01$). There was no difference in serum estradiol concentration between groups (300 pmol/l vs. 328 pmol/l, $p = 0.22$). Notably, it is unclear whether the recommendations from the menopausal hormone therapy literature are applicable to trans individuals who are typically treated with higher oral and transdermal estradiol doses, and further research is needed.

Venous thromboembolism

VTE is a rare but serious side-effect of exogenous oral estrogens including oral contraceptives and menopausal hormone therapy [45]. Estradiol therapy used in GAHT is no exception. No elevated risk of VTE has been observed with masculinizing hormone therapy and, as such, this section will focus on the risk of VTE with feminizing hormones [33,36].

Two large cohort studies from the USA and the Netherlands comparing trans people to reference cisgender men and women in the general population have consistently demonstrated a two-fold to five-fold elevated risk of VTE in trans people using feminizing hormone therapy relative to reference populations [33,36]. Retrospective cohort studies report a 0–5% incidence of VTE during feminizing hormone therapy [46–48]. The largest cohort from the Netherlands of 816 individuals using oral (ethinyl estradiol) and transdermal estradiol followed for a total of 10,152 patient-years found that 0.4% had a VTE [47]. The highest risk of VTE appears to occur in the first year of treatment, in those aged > 40 years, with ethinyl estradiol use, smoking and obesity [47,48]. Based on these studies, transdermal estradiol has been

recommended for those with risk factors, and the use of oral ethinyl estradiol is no longer recommended [11,31]. However, trans people on feminizing hormone therapy have hypercoagulable global coagulation assays relative to cisgender men, but there was no difference between those on oral compared to transdermal estradiol [49]. Whilst this was a very small pilot study, the hypercoagulability seen with transdermal therapy is different to menopausal hormone therapy [50], potentially because of higher doses of transdermal estradiol used in GAHT (typically 100–200 $\mu\text{g}/24$ h estradiol patches) [48,49].

In trans people over the age of 40 years, an individualized shared decision-making approach to estradiol therapy is needed, taking into consideration comorbidities, medication adherence and, importantly, goals of care. Despite knowledge of an elevated risk of VTE, many trans people elect to use oral estradiol therapy due to an inability to tolerate transdermal therapy or for quality of life benefits [43].

In those who have had a VTE on GAHT, treatment with therapeutic anticoagulation should be based on current guidelines for cisgender individuals [51]. There are no specific data to guide treatment of VTE in trans people, nor are there data to guide cessation or continuation of estradiol during an acute VTE event.

Similarly, there are minimal data to guide the perioperative use of feminizing hormone therapy. A single-center retrospective review of 407 trans people having vaginoplasty found no VTE events in those who continued estradiol therapy, with a mean postoperative follow-up of 285 days [52]. Previous reviews have not found any evidence to support or refute routine discontinuation of estradiol therapy prior to surgery (which may carry negative psychological consequences) [53–55]. The physical and mental health benefits of estradiol therapy may outweigh the risk of VTE [56]. Overall, treatment decisions for the formulation, dose, duration and route of hormone therapy should be individualized.

Cardiovascular disease

Many early studies described a higher risk of cardiovascular morbidity and mortality in trans women, but many earlier studies utilized ethinyl estradiol which is no longer used as GAHT [48,57–60]. More recently, larger cohort studies and registry studies with population-based comparison groups have been more informative, but not all are entirely consistent.

One of the largest studies reviewed medical records of all 6793 trans individuals attending the Amsterdam Gender Clinic over a 43-year period [33]. It was found that trans women had an elevated incidence of stroke and myocardial infarction relative to cisgender women, and an elevated incidence of stroke relative to cisgender men. Trans men had an elevated risk of myocardial infarction relative to cisgender women but not cisgender men [33]. Findings were almost entirely consistent with Getahun et al.'s analysis of US Kaiser Permanente's electronic medical record data which found that trans women had an elevated risk of ischemic stroke (adjusted hazard ratio 1.9; 95% confidence interval [CI] 1.3–2.6) and myocardial infarction (adjusted hazard ratio 1.8; 95%

CI 1.1–2.9) relative to cisgender women but not cisgender men [36]. For trans men, the evidence was insufficient to draw conclusions about cardiovascular events [36]. These retrospective chart reviews were limited in not being able to completely account for potential confounders such as smoking, HIV status or minority stress.

In an attempt to control for potential confounding cardiovascular risk factors, two separate analyses of the Behavioral Risk Factor Surveillance System data from 2014 to 2017 were used to evaluate the odds of being trans and myocardial infarction [61,62]. Multivariable analyses adjusted for CVD risk factors including age, diabetes mellitus, hypertension, hypercholesterolemia, chronic kidney disease, smoking and exercise. Trans women had a more than two-fold increase in the rate of myocardial infarction compared with cisgender women (odds ratio, 2.56; 95% CI 1.78–3.68; $p < 0.01$) but not compared with cisgender men [61]. Trans women also had a higher rate of angina/coronary heart disease (adjusted odds ratio 1.90, 95% CI 1.34–2.68) and stroke (adjusted odds ratio 1.88, 95% CI 1.16–3.03) relative to cisgender women and any CVD than cisgender men (adjusted odds ratio 1.38, 95% CI 1.01–1.88) [62].

Data on trans men remain conflicting, with no elevated risk of myocardial infarction or CVD reported in some studies [36,62], but an elevated risk of myocardial infarction relative to cisgender women but not cisgender men in others [33]. Alzahrani et al. showed an increased rate of myocardial infarction relative to both cisgender men and women of more than two-fold [61].

Two national registry studies from Sweden and Denmark have attempted to analyze the mediating effect of GAHT on CVD [63,64]. Due to the young age of included participants, both studies used very broad definitions of CVD which included conduction disorders. Both studies demonstrated an elevated risk of CVD in trans men and in trans women relative to cisgender counterparts. Testosterone therapy in trans men was shown to explain part of the elevated risk of CVD [63]. In contrast, Karalexi et al. found similar results whether trans people were on GAHT or not on GAHT, suggesting that CVD risk is mediated by factors unrelated to hormonal therapy [64].

Mechanistically, several studies have tried to explain the potential increased CVD risk in trans women. In cisgender men, elevated estradiol concentrations and testosterone deprivation have been shown to be associated with elevated CVD risk [65–68]. In trans women, increased body fat and insulin resistance, compromised endothelial function [69], altered biomarkers such as advanced glycation end products associated with systemic inflammation and CVD [70] as well as platelet activation and increased concentrations of coagulation markers and inflammation markers [71] may all potentially contribute. In trans men, several studies have shown unfavorable lipid changes with increased total cholesterol, triglycerides and low-density lipoprotein and decreased high-density lipoprotein [72–74] as well as increased high-sensitivity C-reactive protein [71]. Moreover, hematocrit rises with testosterone therapy [75], and it is unclear if higher hematocrit, which is associated with venous and arterial thrombosis risk and long-term mortality in the general

population, may account for increased CVD risk in trans men [76–79]. Higher intima-media thickness in the carotid artery has also been observed in trans men [73]. Increasing research has revealed that cardiovascular risk factors at the individual level do not fully account for the increased cardiovascular risk, and minority stress itself is associated with higher odds of CVD and behaviors such as smoking, poor sleep and inadequate nutrition [80,81].

Screening for cardiometabolic derangements and risk reduction are important for all aging individuals but even more so for both trans women and men across the lifespan.

Bone health

Given the importance of sex steroid concentrations in bone remodeling, bone health is an area of concern for aging trans individuals. Only one nationwide cohort study of >3000 trans people has examined fractures (obtained from emergency department visit data) compared to reference men and women [82]. Fracture risk was higher in older trans women (occurring in 4.4%) compared to age-matched reference men (odds ratio 1.90, 95% CI 1.32–2.74) but not to reference cisgender women. Fracture risk was lower in trans men compared to reference cisgender men (odds ratio 0.57, 95% CI 0.35–0.94) but the numbers of fractures were small ($n = 18$) [82]. Fracture type and lifestyle risk factors were not available.

Consistent with the fracture data are cross-sectional bone microarchitecture data measured by high-resolution peripheral quantitative computed tomography, an imaging modality which predicts fracture risk better than standard dual X-ray absorptiometry [83]. Trans women on feminizing hormone therapy for a median of 39 months had compromised bone microarchitecture relative to cisgender men with lower total volumetric bone mineral density (BMD), higher cortical porosity, lower trabecular density and number as well as greater trabecular separation. Trans men conversely had preserved bone microarchitecture with higher total volumetric BMD, and higher trabecular thickness compared to cisgender women [83].

Compromised bone density appears inherent even prior to commencement of GAHT. Trans women have lower areal BMD at baseline relative to cisgender men. In addition, lower hand grip strength, lower forearm muscle area and lower 25-hydroxyvitamin D concentrations suggest that lower areal BMD may be related to lifestyle factors such as less physical activity or social isolation [84].

Estradiol concentrations achieved with GAHT are also important. Trans women with low estradiol (<182 pmol/l) have significant reductions in areal BMD over time [85] and increased bone remodeling markers [86]. In trans men who started GAHT aged <50 years, bone remodeling markers increased, but in those aged >50 years (presumed postmenopausal) bone remodeling markers decreased over the first 12 months of testosterone therapy [86].

Concerns regarding compromised bone microstructure and fracture risk appear to be relevant for trans women only and lifestyle factors may reduce attainment of peak bone mass [84]. In young trans people, the role of routine measurement of BMD is not clear. However, all trans women

should be encouraged to optimize their bone health through engaging in regular weight-bearing exercise, smoking cessation, optimization of vitamin D levels and ensuring adequate dosing of GAHT to achieve estradiol concentrations >182 pmol/l.

Pelvic pain with testosterone use

Masculinizing hormone therapy induces significant genital and reproductive system changes, including menstrual cessation, clitoral enlargement, vulvovaginal atrophy and increase in libido [30]. Trans people using testosterone also frequently report pelvic pain, which is most often described as cramping in nature, and occurring in the suprapubic region or less occasionally the right and left iliac regions [87–89]. The cause of this pelvic pain is poorly understood.

While menstrual cessation typically occurs within the first 6 months of masculinizing therapy [90], breakthrough bleeding is not uncommon, and some may experience persistent menstruation [91]. Persistent menstruation along with pain with orgasm are both associated with an increased likelihood of pelvic pain [87]. The association between pelvic pain and pain with orgasm also indicates the possibility of bladder neck contractions, uterine neuro-inflammation, uterine contractions and/or pelvic floor musculature dystonia [92,93]. The pelvic floor muscles are enriched with androgen receptors and exquisitely androgen-sensitive, with androgens causing anabolic effects on pelvic floor muscles [94]. It is therefore plausible that masculinizing hormones may affect the pelvic floor and perineal muscles, and it is hypothesized that pelvic floor muscle dysfunction may contribute to pelvic pain.

Many trans people seek hysterectomy and/or oophorectomy but effects on pelvic pain are inconsistent, with some small studies reporting improvements and little to no change in pelvic pain [87,95].

Without a clear understanding of the causes of pelvic pain in people using masculinizing hormones, a multidisciplinary biopsychosocial approach is required. This may include simple analgesia with paracetamol and non-steroidal anti-inflammatory drugs and pelvic floor physical therapy with release of myofascial trigger points which has been used in cisgender individuals [96]. There also appears to be a link between pelvic pain and current or previous post-traumatic stress disorder diagnosis [87], highlighting the need for trauma-informed approaches to address possible psychological factors [97].

Summary

Provision of safe, affirming healthcare environments is essential to reduce health disparity and optimize health outcomes for trans people. GAHT has significant mental health, physical health and quality of life benefits regardless of age at commencement and is often continued lifelong. With aging, the mitigation of cardiovascular risk factors is important for all individuals, and optimization of bone health through ensuring adequate vitamin D levels, dietary calcium intake and

regular weight bearing exercise is additionally important for trans people on feminizing hormone therapy. Given a lack of research on the management of GAHT with aging, a shared decision-making approach is recommended to ensure individual goals are attained whilst minimizing potential medical risks.

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References

- Spizzirri G, Eufrásio 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, et al. 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.
- Foster Skewis L, Bretherton I, Leemaqz SY, et al. 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.
- 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. *Transgender Health*. 2023;8(1):6–21.
- Baker KE, Wilson LM, Sharma R, et al. Hormone therapy, mental health, and quality of life among transgender people: a systematic review. *J Endocr Soc*. 2021;5(4):bvab011.
- Javier C, Crimston CR, Barlow FK. Surgical satisfaction and quality of life outcomes reported by transgender men and women at least one year post gender-affirming surgery: a systematic literature review. *Int J Transgend Health*. 2022;23(3):255–273.
- Coleman E, Radix AE, Bouman WP, et al. Standards of care for the health of transgender and gender diverse people, version 8. *Int J Trans Health*. 2022;23(sup1):S1–S259.
- Safer JD, Coleman E, Feldman J, et al. Barriers to healthcare for transgender individuals. *Curr Opin Endocrinol Diabetes Obes*. 2016;23(2):168–171.
- Ortiz-Martínez Y, Ríos-González CM. Need for more research on and health interventions for transgender people. *Sex Health*. 2017;14(2):196–197.

- [14] Safer JD. Research gaps in medical treatment of transgender/non-binary people. *J Clin Invest*. 2021;131(4):e142029.
- [15] Bockting WO, Miner MH, Swinburne Romine RE, et al. Stigma, mental health, and resilience in an online sample of the US transgender population. *Am J Public Health*. 2013;103(5):943–951.
- [16] Meyer IH. Prejudice, social stress, and mental health in lesbian, gay, and bisexual populations: conceptual issues and research evidence. *Psychol Bull*. 2003;129(5):674–697.
- [17] Scandurra C, Amodeo AL, Valerio P, et al. Minority stress, resilience, and mental health: a study of Italian transgender people. *J Soc Issues*. 2017;73(3):563–585.
- [18] Hughes L, Shireman TI, Hughto J. Privately insured transgender people are at elevated risk for chronic conditions compared with cisgender counterparts. *Health Aff (Millwood)*. 2021;40(9):1440–1448.
- [19] Dragon CN, Guerino P, Ewald E, et al. Transgender medicare beneficiaries and chronic conditions: exploring fee-for-service claims data. *LGBT Health*. 2017;4(6):404–411.
- [20] 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.
- [21] Zwickl S, Wong AFQ, Dowers E, et al. Factors associated with suicide attempts among Australian transgender adults. *BMC Psychiatry*. 2021;21(1):81.
- [22] 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.
- [23] 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.
- [24] Marshall E, Claes L, Bouman WP, et al. Non-suicidal self-injury and suicidality in trans people: a systematic review of the literature. *Int Rev Psychiatry*. 2016;28(1):58–69.
- [25] 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.
- [26] Hughes LD, King WM, Gamarel KE, et al. Differences in all-cause mortality among transgender and Non-Transgender people enrolled in private insurance. *Demography*. 2022;59(3):1023–1043.
- [27] Hughes LD, King WM, Gamarel KE, et al. US Black-White differences in mortality risk among transgender and cisgender people in private insurance, 2011–2019. *Am J Public Health*. 2022;112(10):1507–1514.
- [28] Wiepjes CM, den Heijer M, Bremmer MA, et al. Trends in suicide death risk in transgender people: results from the Amsterdam cohort of gender dysphoria study (1972–2017). *Acta Psychiatr Scand*. 2020;141(6):486–491.
- [29] World Health Organization. International classification of diseases eleventh revision (ICD-11). Geneva: World Health Organization; 2022.
- [30] Cheung AS, Wynne K, Erasmus J, et al. Position statement on the hormonal management of adult transgender and gender diverse individuals. *Med J Aust*. 2019;211(3):127–133.
- [31] 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.
- [32] Cheung AS, Leemaqz SY, Wong JWP, et al. Non-binary and binary gender identity in Australian trans and gender diverse individuals. *Arch Sex Behav*. 2020;49(7):2673–2681.
- [33] Nota NM, Wiepjes CM, de Blok CJM, et al. Occurrence of acute cardiovascular events in transgender individuals receiving hormone therapy. *Circulation*. 2019;139(11):1461–1462.
- [34] 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.
- [35] Angus LM, Nolan BJ, Zajac JD, et al. A systematic review of anti-androgens and feminisation in transgender women. *Clin Endocrinol (Oxf)*. 2021;94:743–752.
- [36] 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.
- [37] Ettner R. Care of the elderly transgender patient. *Curr Opin Endocrinol Diabetes Obes*. 2013;20(6):580–584.
- [38] Adan M, Scribani M, Tallman N, et al. Worry and wisdom: a qualitative study of transgender elders' perspectives on aging. *Transgender Health*. 2021;6(6):332–342.
- [39] Guo Y, Li Q, Yang X, et al. Prevalence of Alzheimer's and related dementia diseases and risk factors among transgender adults, Florida, 2012–2020. *Am J Public Health*. 2022;112(5):754–757.
- [40] van Heesewijk JO, Dreijerink KMA, Wiepjes CM, et al. Long-term gender-affirming hormone therapy and cognitive functioning in older transgender women compared with cisgender women and men. *J Sex Med*. 2021;18(8):1434–1443.
- [41] Mohamed S, Hunter MS. Transgender women's experiences and beliefs about hormone therapy through and beyond mid-age: an exploratory UK study. *Int J Transgend*. 2019;20(1):98–107.
- [42] Cai X, Hughto JMW, Reisner SL, et al. Benefit of gender-affirming medical treatment for transgender elders: later-life alignment of mind and body. *LGBT Health*. 2019;6(1):34–39.
- [43] Balcerak MI, Nolan BJ, Brownhill A, et al. Feminizing hormone therapy prescription patterns and cardiovascular risk factors in aging transgender individuals in Australia. *Front Endocrinol (Lausanne)*. 2021;12:667403.
- [44] Dekker MJ, Wierckx K, Van Caenegem E, et al. A European network for the investigation of gender incongruence: endocrine part. *J Sex Med*. 2016;13(6):994–999.
- [45] Rosendaal FR, Helmerhorst FM, Vandenbroucke JP. Female hormones and thrombosis. *Arterioscler Thromb Vasc Biol*. 2002;22(2):201–210.
- [46] Ott J, Kaufmann U, Bentz EK, et al. Incidence of thrombophilia and venous thrombosis in transsexuals under cross-sex hormone therapy. *Fertil Steril*. 2010;93(4):1267–1272.
- [47] van Kesteren PJ, Asscheman H, Megens JA, et al. Mortality and morbidity in transsexual subjects treated with cross-sex hormones. *Clin Endocrinol (Oxf)*. 1997;47(3):337–342.
- [48] Wierckx K, Elaut E, Declercq E, et al. Prevalence of cardiovascular disease and cancer during cross-sex hormone therapy in a large cohort of trans persons: a case-control study. *Eur J Endocrinol*. 2013;169(4):471–478.
- [49] Lim HY, Leemaqz SY, Torkamani N, et al. Global coagulation assays in transgender women on oral and transdermal estradiol therapy. *J Clin Endocrinol Metab*. 2020;105(7):dgaa262.
- [50] Bagot CN, Marsh MS, Whitehead M, et al. The effect of estrone on thrombin generation may explain the different thrombotic risk between oral and transdermal hormone replacement therapy. *J Thromb Haemost*. 2010;8(8):1736–1744.
- [51] Ortel TL, Neumann I, Ageno W, et al. American Society of Hematology 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism. *Blood Adv*. 2020;4(19):4693–4738.
- [52] Kozato A, Fox GWC, Yong PC, et al. No venous thromboembolism increase among transgender female patients remaining on estrogen for gender-affirming surgery. *J Clin Endocrinol Metab*. 2021;106(4):e1586–e1590.
- [53] Boskey ER, Taghinia AH, Ganor O. Association of surgical risk with exogenous hormone use in transgender patients: a systematic review. *JAMA Surg*. 2019;154(2):159–169.
- [54] Haveles CS, Wang MM, Arjun A, et al. Effect of cross-sex hormone therapy on venous thromboembolism risk in male-to-female gender-affirming surgery. *Ann Plast Surg*. 2021;86(1):109–114.
- [55] Nolan BJ, Cheung AS. Estradiol therapy in the perioperative period: implications for transgender people undergoing feminizing hormone therapy. *Yale J Biol Med*. 2020;93(4):539–548.
- [56] Arrington-Sanders R, Connell NT, Coon D, et al. Assessing and addressing the risk of venous thromboembolism across the spectrum of gender affirming care: a review. *Endocr Pract*. 2022 Dec 17;1530-891X(22)00898-9. DOI:10.1016/j.eprac.2022.12.008

- [57] Defreyne J, Van de Bruaene LDL, Rietzschel E, et al. Effects of Gender-Affirming hormones on lipid, metabolic, and cardiac surrogate blood markers in transgender persons. *Clin Chem*. 2019; 65(1):119–134.
- [58] 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.
- [59] Gooren LJ, Wierckx K, Giltay EJ. Cardiovascular disease in transsexual persons treated with cross-sex hormones: reversal of the traditional sex difference in cardiovascular disease pattern. *Eur J Endocrinol*. 2014;170(6):809–819.
- [60] Gooren LJ, Giltay EJ, Bunck MC. Long-term treatment of transsexuals with cross-sex hormones: extensive personal experience. *J Clin Endocrinol Metab*. 2008;93(1):19–25.
- [61] Alzahrani T, Nguyen T, Ryan A, et al. Cardiovascular disease risk factors and myocardial infarction in the transgender population. *Circ Cardiovasc Qual Outcomes*. 2019;12(4):e005597.
- [62] Caceres BA, Jackman KB, Edmondson D, et al. Assessing gender identity differences in cardiovascular disease in US adults: an analysis of data from the 2014–2017 BRFSS. *J Behav Med*. 2020;43(2): 329–338.
- [63] Glintborg D, Rubin KH, Petersen TG, et al. Cardiovascular risk in Danish transgender persons: a matched historical cohort study. *Eur J Endocrinol*. 2022;187(3):463–477.
- [64] Karalexi MA, Frisell T, Cnattingius S, et al. Cardiovascular outcomes in transgender individuals in Sweden after initiation of gender-affirming hormone therapy. *Eur J Prev Cardiol*. 2022; 29(15):2017–2026.
- [65] Luria MH, Johnson MW, Pego R, et al. Relationship between sex hormones, myocardial infarction, and occlusive coronary disease. *Arch Intern Med*. 1982;142(1):42–44.
- [66] Abbott RD, Launer LJ, Rodriguez BL, et al. Serum estradiol and risk of stroke in elderly men. *Neurology*. 2007;68(8):563–568.
- [67] Saigal CS, Gore JL, Krupski TL, Urologic Diseases in America Project, et al. Androgen deprivation therapy increases cardiovascular morbidity in men with prostate cancer. *Cancer*. 2007;110(7): 1493–1500.
- [68] Tsai HK, D'Amico AV, Sadetsky N, et al. Androgen deprivation therapy for localized prostate cancer and the risk of cardiovascular mortality. *J Natl Cancer Inst*. 2007;99(20):1516–1524.
- [69] Gulanski BI, Flannery CA, Peter PR, et al. Compromised endothelial function in transgender men taking testosterone. *Clin Endocrinol (Oxf)*. 2020;92(2):138–144.
- [70] Lake JE, Wang R, Barrett BW, et al. Trans women have worse cardiovascular biomarker profiles than cisgender men independent of hormone use and HIV serostatus. *AIDS*. 2022;36(13):1801–1809.
- [71] Schutte MH, Kleemann R, Nota NM, et al. The effect of transdermal gender-affirming hormone therapy on markers of inflammation and hemostasis. *PLoS ONE*. 2022;17(3):e0261312.
- [72] Cocchetti C, Castellini G, Iacuanelli D, et al. Does gender-affirming hormonal treatment affect 30-Year cardiovascular risk in transgender persons? A two-year prospective European study (ENIGI). *J Sex Med*. 2021;18(4):821–829.
- [73] Aranda G, Mora M, Hanzu FA, et al. Effects of sex steroids on cardiovascular risk profile in transgender men under gender affirming hormone therapy. *Endocrinol Diabetes Nutr (Engl Ed)*. 2019; 66(6):385–392.
- [74] Maraka S, Singh Ospina N, Rodriguez-Gutierrez R, et al. Sex steroids and cardiovascular outcomes in transgender individuals: a systematic review and meta-analysis. *J Clin Endocrinol Metab*. 2017;102(11):3914–3923.
- [75] 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.
- [76] Sorlie PD, Garcia-Palmieri MR, Costas R Jr, et al. Hematocrit and risk of coronary heart disease: the Puerto Rico Health Program. *Am Heart J*. 1981;101(4):456–461.
- [77] Gagnon DR, Zhang TJ, Brand FN, et al. Hematocrit and the risk of cardiovascular disease—the Framingham study: a 34-year follow-up. *Am Heart J*. 1994;127(3):674–682.
- [78] Paul L, Jeemon P, Hewitt J, et al. Hematocrit predicts long-term mortality in a nonlinear and sex-specific manner in hypertensive adults. *Hypertension*. 2012;60(3):631–638.
- [79] Braekkan SK, Mathiesen EB, Njolstad I, et al. Hematocrit and risk of venous thromboembolism in a general population. The Tromso study. *Haematologica*. 2010;95(2):270–275.
- [80] Poteat TC, Divsalar S, Streed CG Jr, et al. Cardiovascular disease in a population-based sample of transgender and cisgender adults. *Am J Prev Med*. 2021;61(6):804–811.
- [81] Streed CG Jr, Beach LB, Caceres BA, et al. Assessing and addressing cardiovascular health in people who are transgender and gender diverse: a scientific statement from the American Heart Association. *Circulation*. 2021;144(6):e136–e148.
- [82] 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.
- [83] Bretherton I, Ghasem-Zadeh A, Leemaqz SY, et al. Bone micro-architecture in transgender adults: a cross-sectional study. *J Bone Miner Res*. 2022;37(4):643–648.
- [84] 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.
- [85] 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.
- [86] Vlot MC, Wiepjes CM, de Jongh RT, et al. Gender-affirming hormone treatment decreases bone turnover in transwomen and older transmen. *J Bone Miner Res*. 2019;34(10):1862–1872.
- [87] Zwickl S, Burchill L, Wong AFQ, et al. Pelvic pain in transgender people using testosterone therapy. *LGBT Health*. 2023 Jan 4. DOI:10.1089/lgbt.2022.0187
- [88] Grimstad FW, Boskey E, Grey M. New-Onset abdominopelvic pain after initiation of testosterone therapy among trans-masculine persons: a Community-Based exploratory survey. *LGBT Health*. 2020;7(5):248–253.
- [89] Moussaoui D, Elder CV, O'Connell MA, et al. Pelvic pain in trans-masculine adolescents receiving testosterone therapy. *Int J Trans Health*. 2022;1–9. DOI:10.1080/26895269.2022.2147118
- [90] Defreyne J, Vanwonderghem Y, Collet S, et al. Vaginal bleeding and spotting in transgender men after initiation of testosterone therapy: a prospective cohort study (ENIGI). *Int J Transgend Health*. 2020;21(2):163–175.
- [91] Grimstad F, Kremen J, Shim J, et al. Breakthrough bleeding in transgender and gender diverse adolescents and young adults on long-term testosterone. *J Pediatr Adolesc Gynecol*. 2021;34(5): 706–716.
- [92] Barnas JL, Pierpaoli S, Ladd P, et al. The prevalence and nature of orgasmic dysfunction after radical prostatectomy. *BJU Int*. 2004; 94(4):603–605.
- [93] Yong PJ. Clinical conundrum: a 33-year-old with pain post-orgasm and a history of endometriosis. *J Obstet Gynaecol Can*. 2020;42(5):625–628.
- [94] Ho MH, Bhatia NN, Bhasin S. Anabolic effects of androgens on muscles of female pelvic floor and lower urinary tract. *Curr Opin Obstet Gynecol*. 2004;16(5):405–409.
- [95] Hillis SD, Marchbanks PA, Peterson HB. The effectiveness of hysterectomy for chronic pelvic pain. *Obstet Gynecol*. 1995;86(6): 941–945.
- [96] van Reijn-Baggen DA, Han-Geurts IJM, Voorham-van der Zalm PJ, et al. Pelvic floor physical therapy for pelvic floor hypertonicity: a systematic review of treatment efficacy. *Sex Med Rev*. 2022;10(2): 209–230.
- [97] Grinberg K, Sela Y, Nissanholtz-Gannon R. New insights about Chronic Pelvic Pain Syndrome (CPPS). *IJERPH*. 2020;17(9):3005.