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Review

Gender-affirming hormone therapy, mental health, and surgical considerations for aging transgender and gender diverse adults

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***Abstract*:** As the transgender and gender diverse (TGD) population ages, more transfeminine and transmasculine individuals present to clinic to initiate or continue their gender-affirming care at older ages. Currently available guidelines on gender-affirming care are excellent resources for the provision of gender-affirming hormone therapy (GAHT), primary care, surgery, and mental health care but are limited in their scope as to whether recommendations require tailoring to older TGD adults. Data that inform guideline-recommended management considerations, while informative and increasingly evidence-based, mainly come from studies of younger TGD populations. Whether results from these studies, and therefore recommendations, can or should be extrapolated to aging TGD adults remains to be determined. In this perspective review, we acknowledge the lack of data in older TGD adults and discuss considerations for evaluating cardiovascular disease, hormone-sensitive cancers, bone health and cognitive health, gender-affirming surgery, and mental health in the older TGD population on GAHT.

Keywords: aging, bone health, cancer, cardiovascular disease, cognitive health, gender diverse, gender-affirming hormone therapy, gender-affirming surgery, mental health, transgender

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Introduction

Gender-affirming care may include gender-affirming hormone therapy (GAHT), gender-affirming surgery, and gender-affirming mental health care, depending on the individual goals of each transgender and gender diverse (TGD) person. Most data informing our knowledge about TGD medical, mental health, and surgical outcomes come from large European cohorts with a small proportion of older adults. The Amsterdam Gender Clinic, which has provided gender-affirming care since 1972, reportedly had 700 of 4432 (16%) transfeminine (i.e. person with male sex recorded at birth who has a female/feminine gender identity) and 250 of 2361 (11%) transmasculine (i.e. person with female sex recorded at birth who has a male/masculine gender identity) adults reach the age of 60 years or above in 2015.[1] The European Network for the Investigation of Gender Incongruence (ENIGI) has published many cross-sectional and prospective results on a variety of topics related to gender-affirming care. In 2016, Dekker *et al.*[2] described the ENIGI Endocrine protocol, which has included TGD persons since 2010, as monitoring cohorts with relatively young median ages but a wide range of ages among transfeminine ($n = 333$, median age = 30 years, range = 16–65) and transmasculine ($n = 343$, median age = 24 years, range = 16–51) adults. By 2022, ENIGI had 1261 transfeminine and 1411 transmasculine patients in its cohort, as reported by Cocchetti *et al.*,[3] with a growing proportion of older TGD adults being followed. Data from ENIGI are currently representative of a younger TGD population but hold promise for future studies assessing older TGD adults and age-related differences in health outcomes impacted by gender-affirming care.

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In addition, there are US cohorts with significant proportions of older TGD adults.[4] According to Brown and Jones,[5] the average age of 5135 TGD Veterans within the US's Veterans Health Administration (VHA) was 55.8 years [standard deviation (SD) = 13.5] between 1996 and 2013. Quinn *et al.*[6] described the US's Study of Transition Outcomes and Gender (STRONG) cohort, which identified 3475 transfeminine (16% were aged 46–55 years and 14% were aged >55 years at study enrollment) and 2892 transmasculine (7.6% were aged 46–55 years and 4.2% were aged >55 years at study enrolment) adults to investigate health outcomes compared with presumed cisgender (henceforth referred to as cisgender) men and women [e.g. cardiovascular disease (CVD), diabetes, cancers].

As it is vital to provide gender-affirming care to older TGD persons in a safe and comfortable environment that aligns with individual goals, we aimed to write this perspective review to offer considerations based on existing data while recognizing the above limitations. We review current masculinizing and feminizing GAHT factors surrounding CVD and metabolic diseases, cancer, bone health, and cognitive impairment, highlighting several conditions impacted by advancing age. We also provide discussion of mental health care and gender-affirming surgery in older TGD adults.

Masculinizing GAHT

In most studies, the mean age of transmasculine adults initiating care at gender clinics is younger than transfeminine adults. The prevalence of transmasculine adults over 50 years at the Amsterdam Gender Clinic was 9.7 out of 100,000 persons compared with 37.6 out of 100,000 transfeminine adults.[7] This lower number of older transmasculine adults included in the currently available literature may lead to uncertainty in discussing GAHT-related risk when older transmasculine individuals present for gender-affirming care. Ideally, masculinizing GAHT can be tailored to the patient's goals, the risk/benefit ratio of the treatment, and co-occurring morbidities, while taking into account possible social and economic issues.[8]

Masculinizing GAHT is usually continued lifelong to maintain virilization independent of genital surgery. There is currently no available literature on specific treatment regimens or the need for dose-tapering or cessation of GAHT in aging transmasculine adults.[1] In cisgender women, menopause usually occurs between ages 40 and 60 years old, with a median age of about 52 years old.[9] The menopause transition leads to reduced estrogen production, although the postmenopausal ovaries continue to produce some androgens.[10] Aromatization of those androgens results in levels of estrogens much lower than during the premenopausal years. In TGD persons who undergo gender-affirming oophorectomy, the main source of endogenous androgens is removed. Previous research in a large sample of transmasculine individuals of all ages who received testosterone therapy, however, showed no difference in serum estradiol levels in people with *versus* without gonads.[11] This is likely due to aromatization of exogenous testosterone into estrogens. The serum estradiol levels in this transmasculine population were higher than those observed in a control group of men and those described in postmenopausal women. Again, it remains to be determined whether this is also the case for older transmasculine adults initiating masculinizing GAHT in whom menopause may have already occurred.

CVD and metabolic risk in transmasculine adults

CVD and most of its risk factors are diseases of aging. In general, CVD occurs up to 10 years earlier in cisgender men compared with cisgender women.[12] This is often attributed to several factors: higher blood pressures in men, historically more prevalent smoking among men, and sex hormone differences – in addition to CVD being understudied, underdiagnosed, and undertreated in women.[12–14] Whether these changes increase the risk of CVD and CVD risk factors in older transmasculine adults have yet to be determined. Currently available literature is reassuring, however. There does not appear to be a significant increase in CVD-related mortality or cardiovascular events based on large cohort data, regardless of compared reference population (e.g. general population, cisgender population). de Blok *et al.*[15] reported mortality trends in TGD adults between 1972 and 2018 and found <10 of 1641 transmasculine individuals [median age of the cohort 23 years, interquartile range (IQR) = 20–32] died from CVD, as well as no significant difference in CVD-related mortality compared with the general population of men and women.

Regarding cardiovascular events, Nota *et al.*[16] described nonsignificant standardized incidence ratios (SIRs) for venous thromboembolism (VTE) and ischemic stroke in transmasculine adults compared with the general population of men and women. There, however, was a significantly higher SIR for myocardial infarction (MI) among 1358 transmasculine adults (median age = 23 years) compared with the general population of women [3.69, 95% confidence interval (CI) = 1.94 to 6.42] but not compared with the general population of men (1.00, 95% CI = 0.53 to 1.74). Analyses of self-reported Behavioral Risk Factor Surveillance System (BRFSS) survey data in the United States have shown conflicting results for transmasculine individuals. Nokoff *et al.*[17] found no significant differences in history of MI, angina/coronary heart disease, or stroke in transmasculine respondents compared with cisgender men or women respondents from 2015. Alzharani *et al.*[18] analyzed 2014–2017 BRFSS data and calculated higher odds of self-reported MI among transmasculine adults compared with cisgender men [odds ratio (OR) = 2.53, 95% CI = 1.14 to 5.36] and women respondents (OR = 4.90, 95% CI = 2.21 to 10.90) after adjusting for age, diabetes mellitus, chronic kidney disease, smoking, hypertension, hypercholesterolemia, and exercise. In contrast, Caceres *et al.*[19] did not find significantly higher odds of MI (nor angina/coronary heart disease, stroke, or any CVD) among transmasculine adults compared with cisgender men and women respondents after adjusting for state of residence, survey year, age, race/ethnicity, income, education, marital status, employment status, body mass index, and diabetes.

Reports on the effect of testosterone on systolic and diastolic blood pressure (SBP and DBP, respectively) are inconclusive[20–23] or often nonsignificant,[24–27] with the caveat that most studies have been conducted with younger groups of transmasculine individuals. Banks *et al.*[28] recently reported SBP and DBP changes after initiating masculinizing GAHT in 223 transmasculine patients (mean age = 26.1 years, SD = 7.1) at a Federally Qualified Health Center and an academic center in the United States serving a more racially and ethnically diverse population compared with European cohorts. Results showed that mean SBP remained in the normal range but increased by 2.6 mmHg (95% CI = 0.28 to 4.99) in the first 2–4 months and that increase was maintained throughout the 57-month follow-up. There was no significant change in DBP. Overall, masculinizing GAHT does not appear to have a clinically meaningful effect on blood pressure.

Initiating testosterone therapy in transmasculine adults usually results in modestly increased low-density lipoprotein–cholesterol (LDL-C) and triglycerides, possible increased total cholesterol, and decreased high-density lipoprotein–cholesterol (HDL-C) depending on the time of monitoring.[23,29,30] A systematic review and meta-analysis by Maraka *et al.*[30] found that masculinizing GAHT was associated with statistically significant increases at ⩾24 months in LDL-C (17.8 mg/dl, 95% CI = 3.5 to 32.1) and triglycerides (21.4 mg/dl, 95% CI = 0.14 to 42.6) but not total cholesterol. At ⩾24 months, masculinizing GAHT was associated with a statistically significant decrease in HDL-C (−8.5 mg/dl, 95% CI = −13.0 to −3.9).

Additional available metabolic outcome data include the effects of masculinizing GAHT on diabetes and body composition. Wierckx *et al.*[31] reported an increased incidence of type 2 diabetes mellitus in all TGD people prior to GAHT initiation, although this may be biased by endocrine screening during the first visit at the clinic. van Velzen *et al.*[32] recently reported that transmasculine individuals ($n = 1514$; median age = 32 years, IQR = 24–49) had no difference in type 2 diabetes mellitus incidence compared with individuals of the same birth-assigned sex (i.e. general population of women). The STRONG cohort, reported by Islam *et al.*,[33] also found no significant difference in prevalent or incident type 2 diabetes mellitus among the transmasculine cohort ($n = 131$; 28.3% aged >55 years) compared with cisgender men or women. Klaver *et al.*[34] recently reported that 1 year of masculinizing GAHT resulted in decreased total body fat (2.8 kg, 95% CI = 2.2 to 3.5), unchanged visceral fat, and increased visceral adipose tissue/total body fat ratio (14%, 95% CI = 10 to 17) in 162 transmasculine adults (median age = 24 years, IQR = 21–33); there were no associations with changes in lipids or insulin sensitivity. Spanos *et al.*[35] conducted a systemic review of 26 studies, concluding that masculinizing GAHT increases lean mass, decreases fat mass, and has no impact on insulin resistance.

Another consideration surrounding exogenous testosterone use and CVD risk is secondary erythrocytosis or polycythemia. Defreyne *et al.*[36]

reported a significant increase in hematocrit between baseline and 36 months in 192 transmasculine adults from ENIGI (median age = 22.5 years, range = 17–62) after initiating testosterone (linear regression $p < 0.001$); however, only 11.5% developed a hematocrit ⩾50%. They also revealed that shorter-acting testosterone esters were associated with a larger increase in hematocrit compared with longer-acting testosterone undecanoate. Among transmasculine adults from the Amsterdam Gender Clinic ($n = 1073$; median age at GAHT start 22.5 years, IQR = 18.4–31.8), that had hematocrit measured twice during 20 years of follow-up, 11% had hematocrit >50%, 3.7% had hematocrit >52%, and 0.5% had hematocrit >54%, as published by Madsen *et al.*[37] In that study, tobacco use, long-acting testosterone undecanoate, older age at GAHT initiation, higher body mass index, and pulmonary conditions were all associated with higher odds of elevated hematocrit. Antun *et al.*[38] assessed 424 transmasculine STRONG cohort participants (9.4% aged 46–55 years, 2.4% aged >55 years), reporting a higher rate of erythrocytosis compared with cisgender men [defined as hematocrit >52%; hazad ratio (HR) = 7.4, 95% CI = 4.1 to 13.4] and cisgender women (defined by hematocrit >48%, HR = 83.1, 95% CI = 36.1 to 191.2). Nolan *et al.*[39] reported on the prevalence of polycythemia (defined by hematocrit >50%) in their Australian cohort of 180 relatively young transmasculine adults (mean age = 28.4 years, SD = 8.8) taking testosterone undecanoate *versus* testosterone enanthate *versus* transdermal testosterone. There was a significantly lower proportion of patients with polycythemia in the group on transdermal testosterone (0%, $n = 24$) compared with the group on intramuscular testosterone enanthate (23%, $n = 31$), but not compared with the group on intramuscular testosterone undecanoate (15%, $n = 125$). Finally, Oakes *et al.*[40] reported that the prevalence of hematocrit >50% among 519 transmasculine individuals in the United States with available pre-/post-testosterone labs (ages not reported) was 20%. The rate of thromboembolic events was 0.9%, which was higher than the 2016–2017 US National Inpatient Sample that reported 7 of 4141 (0.17%) erythrocytosis in TGD individuals and 1 of 4141 (0.02%) had a concurrent venous thromboembolic event. Although it appears the rate of vascular complications from secondary erythrocytosis from masculinizing GAHT is reassuringly very low, the clinical significance of erythrocytosis after initiating masculinizing GAHT requires more research.

Unfortunately, most studies on cardiometabolic risk in TGD individuals report on relatively young cohorts, whereas the peak incidence of cardiometabolic morbidity occurs at older ages.[13] Smoking and alcohol use are also higher among TGD individuals compared with non-TGD individuals.[41,42] With an aging TGD population and more TGD adults seeking care at all ages, there is an urgent need for more studies of cardiometabolic risk associated with GAHT while also taking into account other independent CVD risk factors.

Cancer risk in transmasculine adults: breast, cervical, endometrial, and ovarian

Cancer also increases with age. Given the lack of specific guidelines on cancer risk in TGD adults taking masculinizing GAHT, guidelines often recommend an organ system inventory approach to cancer screening.[43] If an organ or tissue is present, individuals should be included in preventive screening strategies for the respective organ or tissue. It is, however, possible that the cancer risk in TGD adults for certain organ systems differs from cisgender adults. For instance, de Blok *et al.*[44] showed that breast cancer risk appears to be lower in transmasculine adults ($n = 1{,}229$; median age at GAHT initiation 23 years, IQR = 19–31; median duration of GAHT 15 years, IQR = 2–17) compared with age-matched cisgender women (SIR = 0.2, 95% CI = 0.1 to 0.5), although this may change as the TGD population ages. Hormonal factors may impact this risk, although lifestyle factors should not be overlooked. Research in cisgender adults has described breast cancer associations with dietary patterns, alcohol intake, physical inactivity, hormonal contraception, and childbearing.[45,46] Breast cancer screening recommendations should follow local/regional guidelines, with an understanding that some breast tissue often remains present after gender-affirming chest masculinizing surgery and the best modality for screening in this circumstance has yet to be determined.

The presence of human papilloma virus (HPV) increases the risk for cervical cancer.[47] The prevalence of cervical high-risk HPV infection in the

overall transmasculine adult population is unknown, but Reisner *et al.*[48] detected a 16.0% prevalence by provider-collection in their cohort of 131 participants (age range = 21–50 years) and 71.4% concordance by self-collection. They also reported over 90% of participants surveyed preferred the self-collected over the provider-collected swab. A recent systematic review did not identify any studies on the impact and effectiveness of HPV vaccine in TGD individuals, highlighting significant gaps in knowledge.[49] In addition, due to the lack of TGD adults in HPV vaccination studies, it remains difficult to identify and address barriers to and facilitators for HPV vaccination in this population.[50]

Testosterone may also have an independent role in cervical cancer risk. Free testosterone has been positively associated with cervical cancer in premenopausal women, whereas in menopausal women, there was a positive association with total testosterone.[51] Whether the exogenous testosterone in masculinizing GAHT is associated with an increased risk for cervical cancer in transmasculine adults remains unknown to date, and only a few case reports of transmasculine adults diagnosed with cervical cancer have been published.[52–54] Current screening recommendations for transmasculine adults are to follow local/regional guidelines as long as cervical tissue is present (i.e. not removed as part of gender-affirming hysterectomy).

Testosterone levels have been linked to endometrial cancer in postmenopausal women.[55] Testosterone can be aromatized to estradiol and thereby stimulate endometrial and ovarian epithelium proliferation. Testosterone, however, can also be converted into dihydrotestosterone (DHT). Both DHT and testosterone can promote endometrial and ovarian epidermal growth, although DHT may also halt proliferation of endometrial and ovarian cells, thereby leading to a decreased cancer risk.[51] The oral contraceptive pill appears to have a long-lasting effect on the prevention of ovarian and endometrial cancer, and childbearing decreases the risk of ovarian, endometrial, and breast cancer but increases the risk of cervical cancer.[46] It remains to be determined whether exogenous testosterone therapy will result in increased ovarian and endometrial cancer risk, in contrast to the oral contraceptive pill, or whether these effects are mediated by anovulation, which occurs in most transmasculine adults on testosterone therapy.

In the current literature, reports on transmasculine individuals on testosterone therapy experiencing endometrial cancer[54,56] or ovarian cancer[53,57–59] are scarce. Data on the endometrial effects of testosterone administration in transmasculine adults are mixed and limited to younger adults. Perrone *et al.*[60] investigated testosterone use for at least 1 year and found endometrial histology consistent with inactive endometrium. In contrast, a more recent study by Grimstad *et al.*[61] found almost 70% of patients on testosterone for an average of 3 years before hysterectomy were found to have active (predominantly proliferative) endometrium on histopathology despite amenorrhea. Hawkins *et al.* reported 40% with proliferative endometrium and 50% with atrophic endometrium in their recent study in transgender and gender nonbinary adults using gender-affirming testosterone for a median of 4 years (IQR = 2–7). Just as for cisgender women, there are no recommendations for endometrial or ovarian cancer screening, but counseling on abnormal uterine bleeding is encouraged in transmasculine adults taking testosterone.[62] Care can be discussed on an individual basis or deemed unnecessary after gender-affirming hysterectomy and oophorectomy.

Cancer screening recommendations for TGD individuals who are *BRCA1* or *BRCA2* mutation carriers follow cisgender guidelines, as do recommendations for testing for *BRCA* mutations, although longer-term prospective studies are needed to inform the impact of exogenous GAHT and duration of GAHT on cancer risk independent of mutation status. As noted by Bedrick *et al.*,[63] having a *BRCA* mutation may reduce insurance barriers to receiving gender-affirming care (including surgery) that aligns with a person's gender affirmation.

The effect of long-term masculinizing GAHT on cancer risk in aging TGD individuals has not been well-studied, and transmasculine adults in published studies are relatively young. Therefore, it remains inconclusive if long-term GAHT will lead to increased cancer risk in transmasculine adults, although current research with limited follow-up duration shows no significantly increased breast, cervical, endometrial, or ovarian cancer risk compared with cisgender women.

Bone health in transmasculine adults

Advanced age is also a risk factor for osteoporosis and fragility fractures. Bone density in transmasculine adults appears to be similar to the general population at baseline and after taking GAHT.[64,65] Although testosterone initiation often leads to cessation of menses and thus a relative deficiency in estradiol, several studies, including a meta-analysis by Singh-Ospina *et al.*,[66] have shown stable bone mineral density (BMD) in transmasculine adults on GAHT. Testosterone use by transmasculine adults alters body composition by increasing muscle mass, decreasing fat mass and also likely has direct action on the bone.[64] Longitudinal data from 543 transmasculine (median age = 25 years, IQR = 21–34) adults from Wiepjes *et al.*[67] found only 4.3% had low BMD for age at baseline (defined as *Z*-score less than −2.0). Of these adults, 70 had duel-energy X-ray absorptiometry (DXA) reassessed after 10 years on masculinizing GAHT, and while BMD was not significantly changed, lumbar spine *Z*-scores improved. The subgroup with the greatest gains was individuals over 40 years of age at the time of GAHT initiation, raising the question as to whether there may have been an age-related relative estrogen deficiency driving the benefit in this older cohort. There was no association with testosterone levels, *per se*, however, larger increases were seen in those with lower luteinizing hormone (LH) levels, indicating LH suppression may be an indicator of adequate presence of sex steroids for bone health.

Fortunately, no increased fracture risk has been observed across the lifespan, something important to consider for the aging TGD adult, although fracture data remain limited. Recent data from Wiepjes *et al.*[68] found that 1.7% of transmasculine adults experienced a fracture compared with 3.0% of age-matched cisgender men (OR = 0.57, 95% CI = 0.35 to 0.94) and 2.2% of age-matched cisgender women (OR = 0.79, 95% CI = 0.48 to 1.30). In a relatively young adult cohort, Bretherton *et al.*[69] assessed bone architecture using high-resolution peripheral quantitative computed tomography (HR-pQCT) in 41 transmasculine adults with median age = 28.6 years (IQR = 24.6–30.9) and median duration of masculinizing GAHT 42.5 months (IQR = 21.4–65.0). In comparison with 71 cisgender women controls, the transmasculine cohort had higher volumetric bone mineral density (vBMD) and thicker cortices, although cortical vBMD and cortical porosity did not differ. Overall, data in transmasculine adults are reassuring in that despite their relative reduction in estradiol levels with masculinizing GAHT, skeletal health is preserved. Accordingly, guidelines suggest screening bone densities should mainly be done in individuals who undergo gonadectomy, stop GAHT or have other risk factors for low BMD.[43]

Feminizing GAHT

Current guidelines for and publications about feminizing GAHT provide ranges of estrogen and antiandrogen dosages to achieve physiologic levels of serum estradiol and testosterone seen in premenopausal cisgender women.[70–75] Notably, these dosages are higher than those used in the management of symptoms associated with postmenopausal status in cisgender women, in whom estradiol levels are lower. Concerns have arisen regarding long-term use of menopausal hormone therapy in cisgender women due to elevated risk of CVD, VTE, and breast cancer, with the caveats that risk appears to be higher with concomitant progestin use compared with estrogen alone and when hormone therapy is initiated several years after menopause.[76,77] Whether dosages of estrogen need to be lowered or discontinued in older TGD adults on feminizing therapy have not yet been determined.

Aside from safety, other aspects of feminizing GAHT among older TGD adults that need to be considered and balanced with risks include feminizing effects, satisfaction with feminization, and reduction of gender dysphoria. Can older TGD individuals achieve their feminization goals on lower, often considered 'safer', dosages of estrogen (e.g. transdermal), or with lower serum levels of estradiol? Conversely, are higher dosages of estrogen and serum estradiol safe and more effective at feminization in older TGD adults? These and other questions remain. Predictors of feminization or satisfaction/dissatisfaction have yet been identified but deserve more investigation.

CVD and metabolic risk in transfeminine adults

As mentioned above, estrogen has been thought to have protective cardiovascular and metabolic effects in cisgender women as CVD prevalence is lower prior to the menopause transition compared with age-matched cisgender men, yet increases to match cisgender men after menopause.[78] Data

among TGD cohorts, however, have revealed concerning higher rates of CVD-related conditions among transfeminine adults on feminizing GAHT compared with both age-matched men and women from the general population. Starting with mortality, de Blok *et al.*'s Amsterdam Gender Clinic data showed that 50 of 2927 transfeminine adults (median age of cohort 30 years, IQR = 24–42) died from CVD between 1972 and 2015, more than compared with the general population of women [SMR (standardized mortality ratio) = 2.6, 95% CI = 1.9 to 3.4] and possibly men (SMR = 1.4, 95% CI = 1.0 to 1.8). CVD mortality among transfeminine adults was driven by MI (when compared with men) and other cardiovascular events (when compared with men and women) but not VTE. In addition, a subgroup analysis for overall mortality that only included transfeminine adults who took ethinyl estradiol revealed similar SMRs as the overall cohort.

Regarding cardiovascular events, Nota *et al.*[16] calculated significant SIRs for VTE (compared with the general population of women: 5.52, 95% CI = 4.36 to 6.90; compared with the general population of men: 4.55, 95% CI = 3.59 to 5.69) and ischemic stroke (compared with women: 2.42, 95% CI = 1.65 to 3.42; compared with men: 1.80, 95% CI = 1.23 to 2.56) among 2517 transfeminine adults (median age = 30 years). Transfeminine adults also had higher incidence of MI compared with the general population of women (SIR = 2.64, 95% CI = 1.81 to 3.72) but not men (SIR = 0.79, 95% CI = 0.54 to 1.11). In a subgroup analysis that excluded transfeminine adults who used ethinyl estradiol, the SIR for VTE improved but remained elevated [compared with women: 3.92 (CI not reported); compared with men: 3.39 (CI not reported)]. Similar to data for transmasculine adults, US BRFSS analyses show conflicting results for transfeminine individuals. Nokoff *et al.*[17] found transfeminine individuals had higher odds of self-reporting a history of MI compared with cisgender women (OR = 2.87, 95% CI = 1.55 to 5.34) but not cisgender men, and no increased odds of angina/coronary heart disease or stroke compared with either. Alzharani *et al.*'s[18] 2014–2017 BRFSS analyses found higher odds of self-reported MI among transfeminine adults compared with cisgender women (OR = 2.56, 95% CI = 1.78 to 3.68) but not men (OR = 1.32, 95% CI = 0.92 to 1.90). Similarly, Caceres *et al.*[19] found significantly higher odds of MI (as well as angina/coronary heart disease and stroke) among transfeminine adults compared with cisgender women but not men respondents. In the latter analyses, transfeminine adults also had higher odds of reporting any CVD compared with both men (OR = 2.24, 95% CI = 1.65 to 3.06) and women (OR = 1.38, 95% CI = 1.01 to 1.88). Again, the differences in results may be related to adjusting for different covariates in the above analyses as described in the previous section on CVD and masculinizing GAHT.

Data from the STRONG cohort, as reported by Getahun *et al.*,[79] found a higher risk of VTE among transfeminine adults compared with cisgender men [adjusted hazard ratio (aHR) = 1.9, 95% CI = 1.4 to 2.7] and women (aHR = 2.0, 95% CI = 1.4 to 2.8), after adjusting for history of any acute cardiovascular event, body mass index, smoking status, blood pressure, and total cholesterol. Caveats to interpreting the STRONG cohort data include no adjustments for age at initiation of GAHT, duration, type, or route of administration. While the increased VTE risk among transfeminine adults compared with cisgender populations appears more conclusive, it is reassuring that absolute rates remain very low. A systematic review and meta-analysis by Khan *et al.*[80] estimated the incidence rate of VTE in transfeminine adults prescribed estrogen to be 2.3 per 1000 person-years, with significant heterogeneity of studies. The authors suggested this may be an overestimate of risk because the number of studies in the meta-analysis was too small to allow for subgroup analyses, including determining the impact of older studies that utilized ethinyl estradiol on the overall estimate. Previously reported higher rates of VTE may have been related to the use of ethinyl estradiol, which is no longer recommended in GAHT because it is associated with elevated VTE risk compared with other currently available estrogens.[81,82]

The effects of feminizing GAHT on SBP and DBP need to consider whether spironolactone (an antihypertensive) was the antiandrogen used along with estrogen. Like masculinizing GAHT, most studies have been conducted in younger groups of transfeminine adults. According to Gooren *et al.*,[83] among European cohorts that used estrogen plus cyproterone acetate, an antiandrogenic progestin, blood pressures have not been affected or had slight increases after initiating feminizing GAHT. Banks *et al.* recently reported blood pressure changes after initiating feminizing GAHT

(estrogen plus majority spironolactone) in 247 transfeminine patients (mean age = 29.3 years, SD = 10.1). In contrast to the small rise in SBP after initiating masculinizing GAHT, feminizing GAHT was associated with a significant decrease in mean SBP within 2–4 months (−3.99 mmHg, 95% CI = −6.20 to −1.77) that was sustained throughout the 57-month follow-up. There was no significant change in DBP. It is reassuring from a CVD perspective that feminizing GAHT does not appear to be associated with negative effects on blood pressures.

Regarding lipids, the systematic review and meta-analysis by Maraka *et al.*[30] found that feminizing GAHT (mainly oral estrogen) was associated with a statistically significant increase at ⩾24 months in triglycerides (31.9 mg/dl, 95% CI = 3.9 to 59.9) but not LDL-C, HDL-C, or total cholesterol. Whether changes in other lipid-related proteins (e.g. lipoprotein (a), apolipoproteins) impact overall CVD risk in transfeminine adults remain to be determined.

There have been a few studies on diabetes and body composition related to feminizing GAHT. van Velzen *et al.*[32] recently reported that transfeminine individuals ($n = 2585$; median age = 48 years, IQR = 33–58) had no difference in type 2 diabetes mellitus incidence compared with individuals of the same birth-assigned sex (i.e. general population of men). In contrast, Islam *et al.*'s[33] recent type 2 diabetes mellitus analyses of data from the STRONG cohort showed that prevalent (OR = 1.3, 95% CI = 1.1 to 1.5) and incident (HR = 1.4, 95% CI = 1.1 to 1.8) diabetes were more common among the transfeminine cohort ($n = 287$; 41.8% aged >55 years) compared with cisgender women but not men. Klaver *et al.*[34] recently described how, among 179 transfeminine adults (median age = 29 years, IQR = 23–43), 1 year of feminizing GAHT resulted in increased total body fat (4.0 kg, 95% CI = 3.4 to 4.7), unchanged visceral fat, and increased visceral adipose tissue/total body fat ratio (17%, 95% CI = 15 to 19) without any associations with changes in lipids or insulin sensitivity. In the systematic review by Spanos *et al.*,[35] feminizing GAHT (i.e. estrogen with or without antiandrogen) decreased lean mass, increased fat mass, and possibly worsened insulin resistance.

The fact that absolute rates of cardiovascular events (especially among transfeminine adults) appear to be low is reassuring; however, it is unknown how these rates may change as TGD adults initiate and continue GAHT as they age. As stressed above, most published studies have been conducted in relatively younger aged adults, and therefore, it remains uncertain what implications those results have for older-aged TGD adults. Another area of research interest is whether vascular endothelial function changes with GAHT (independent of known changes with increasing age), and if so, identifying the mechanisms mediating such changes.[84,85] We also lack data to inform how CVD risk (e.g. 10-year atherosclerotic CVD risk) should be calculated in TGD adults, including those younger than 40 years of age, and whether we should be screening and intervening earlier based on the data above, especially for transfeminine adults. Some guidelines suggest routine screening based on your local/regional guidelines, using the risk calculator for the sex assigned at birth or gender identity (perhaps whichever duration has been longer; related to duration of exposure to endogenous *versus* exogenous sex hormones), or an average of the two.[43]

Despite the concerning CVD mortality and events among transfeminine adults compared with cisgender men and women, we lack data to suggest which CVD risk factors are contributing (and contributing the most) to increased CVD risk. As recently emphasized, more TGD individuals need to be included in CVD-related research. In addition, there needs to be a better understanding of the intersectional transgender multilevel minority stress model linking various aspects of identity (including age) with stigmatization, resilience-promoting factors, and psychosocial, behavioral, and clinical CVD risk factors.[85] More research in these areas will provide us with an increased, well-rounded knowledge base to better inform our understanding of CVD risk in transfeminine adults and develop ways to mitigate that risk while continuing to provide life-saving GAHT.

Cancer risk in transfeminine adults: breast and prostate

Estrogen and increasing age are risk factors for breast cancer.[86] Therefore, increasing attention has been paid to the relevance of long-term feminizing GAHT to potential breast cancer risk. As mentioned in the previous section on cancer risk

in transmasculine adults, organ-specific screening is recommended for organs or tissues for which routine screening exists for the general population. With the development of breast tissue after the initiation of estrogen, studies on breast cancer risk have thus far been reassuring. de Blok *et al.*[44] showed that breast cancer risk was higher in transfeminine adults ($n = 2260$; median age at GAHT initiation 31 years, IQR = 23–41; median duration of GAHT 18 years, IQR = 7–37) compared with age-matched cisgender men (SIR = 46.7, 95% CI = 27.2 to 75.4), but there was lower incidence compared with cisgender women (SIR = 0.3, 95% CI = 0.2 to 0.4). Although future data in older transfeminine adults who have longer durations of estrogen exposure may change breast cancer incidence, current data have informed some TGD-specific guidelines to begin breast cancer screening at age 40–50 = years (depending on your location or clinical setting) in addition to at least 5 years of estrogen exposure.[43]

Aging is also a risk factor for prostate cancer. The aging transfeminine individual, depending on their goals for feminization, may have suppressed testosterone and physiologic female-range estradiol levels. As the prostate is usually retained in transfeminine adults regardless of gender-affirming surgical status, the hormonal milieu in this setting raises questions about prostate cancer risk. van Kesteren *et al.*[87] found that estrogen use led to prostate atrophy in transfeminine adults. Among Dutch transfeminine adults, de Nie *et al.*[88] calculated a lower prostate cancer risk compared with the general population of men (SIR = 0.20, 95% CI = 0.08 to 0.42). The STRONG cohort, as reported by Silverberg *et al.*,[89] was found to have a prostate cancer incidence in transfeminine adults of 72 per 100,000 person years (95% CI = 36 to 145), also significantly lower than that found in cisgender men (aHR = 0.4, 95% CI = 0.2 to 0.9) after adjusting for birth year, race, location of care, smoking, and body mass index. Thus far, we do not have adequate evidence to inform routine prostate cancer screening guidelines for transfeminine individuals, but screening should be performed through shared decision-making.

We lack other cancer screening recommendations for transfeminine adults for organs and tissues that may be affected by feminizing GAHT. The long-term cohort studies mentioned above will provide more valuable information about cancer risk in older-aged transfeminine adults and individuals who have been taking feminizing GAHT for many decades. With those results, we may be able to develop transfeminine-specific cancer screening guidelines if necessary.

Bone health in transfeminine adults

Sex steroids, particularly estrogen, play a key role in bone health and prevention of osteoporosis. Thus, it is important to understand the effect of feminizing GAHT on the skeleton. It is clear from animal models and human case reports that mutations affecting estrogen production and estrogen receptors interfere with closure of epiphyseal plates with a subsequent deleterious effect on attainment of peak bone mass, even in the face of normal to high testosterone levels.[90,91] Estrogen acts on osteoblasts, osteoclasts, and osteocytes to maintain bone formation and decrease resorption. Estrogen deficiency influences both the rapid decline in BMD seen in postmenopausal cisgender women as well as the more gradual loss seen with aging in cisgender men.

In transfeminine adults, numerous studies show low BMD prior to the initiation of feminizing GAHT. Similar findings were reported in TGD youth, with lower *Z*-scores seen particularly in transfeminine youth, even prior to any hormonal treatments.[92,93] The etiology is unclear, but data suggest lower physical activity, vitamin D deficiency, and tobacco use may play a role.[64,65] Rates of sport participant and overall minutes of physical activity were reported to be lower in TGD youth compared with their cisgender peers.[94] In addition, TGD student respondents were more likely to be bullied for their weight or size and to be overweight.[94] Questions have also been raised as to whether there could be intrauterine factors leading to bone density alterations in transfeminine youth prior to GAHT initiation, as postulated by a whole-exome sequencing study that identified variants in estrogen receptor-activated pathways that may also influence bone mineralization.[93,95] Of additional concern are recent data showing that even once GAHT is initiated in TGD youth post puberty blockade, despite BMD increases, they do not seem to 'catch up' to their peers' *Z*-scores.[93] More data will be needed; however, exercise should be strongly encouraged at all stages of life, including at older age, as should calcium, vitamin D, and avoidance of excess alcohol and tobacco.

After initiation of feminizing GAHT with estrogen and antiandrogens, bone density increases, despite increases in fat mass and decline in muscle mass. A meta-analysis by Singh-Ospina *et al.*[66] of 13 studies that included 392 transfeminine adults reported increases in lumbar spine, but not hip, BMD at 1 and 2 years after initiating feminizing GAHT. The longest study to date is a 10-year cohort study of 711 transfeminine adults (median age = 35 years, IQR = 26–46) from Amsterdam, published by Wiepjes *et al.*[67] At the start, 21.9% had low bone density (defined as *Z*-score < -2.0 using reference male population) even prior to initiation of feminizing GAHT or orchiectomy. After 10 years of feminizing GAHT, DXA was reassessed in 102 transfeminine adults (14%) and there was a significant increase in *Z*-score, but not lumbar spine BMD. An association between estradiol level and lumbar spine BMD was seen; transfeminine adults with the highest tertile of estradiol levels (mean = 443 pmol/l or 121 pg/ml) had an observed increase in lumbar spine BMD, while those in the lowest tertile (mean = 118 pmol/l or 32 pg/ml) had a decrease in lumbar spine BMD. There was no association with LH or degree of testosterone suppression.[67]

Despite these benefits, a recent retrospective study by Wiepjes *et al.*,[68] of ~2000 transfeminine adults, reported an elevated fracture risk in those aged 50 and older ($n = 934$; mean age = 60 years, SD = 8). Fractures were experienced by 4.4% of the cohort, in contrast to 2.4% of age-matched cisgender men (OR = 1.90, 95% CI = 1.32 to 2.74). The fracture rates in transfeminine adults were more comparable to cisgender women, in which 4.2% experienced a fracture (OR = 1.05, 95% CI = 0.75 to 1.49).

While etiology is not known, recent HR-pQCT data from Bretherton *et al.*[69] suggest ongoing altered bone microarchitecture in transfeminine adults, even in those on feminizing GAHT. Forty transfeminine adults, with median age of 37.6 years (IQR = 26.3–52.7) and median duration of GAHT of 39.1 months (IQR = 21.8–60.5 months), were compared with 52 cisgender male controls and were found to have lower total vBMD, lower cortical thickness, and increased cortical porosity. Trabecular bone volume was also lower with greater trabecular separation. Although estradiol levels were assessed as a single measurement, the reported median was 335.0 pmol/l (IQR = 157.0–468.0) which would be consistent with typical goals for feminizing GAHT. Owing to these concerns, the Endocrine Society guidelines advocate for consideration of screening BMD in transfeminine adults at baseline and otherwise at age 60 years or in the setting of GAHT noncompliance.[70] Other guidelines also suggest assessing BMD postgonadectomy, particularly if GAHT is stopped, and in those over age 50 years with other risk factors for low BMD.[43] All transfeminine adults should be asked about risk factors for low BMD, and consideration for nonpharmacologic measures and medications should be prescribed as clinically appropriate.

Cognitive health in TGD adults

Currently, a link between impaired cognition and GAHT has not been described in the available literature. The brains of TGD adults, however, appear to differ in some respects from cisgender adults, including the axonal organization of the white matter,[96,97] the rate of diffusion of molecules and water in the brain,[98] the frontal and parietal lobes,[99] and the left and right hemispheres.[100] Research on cognitive tasks that have established sex differences in spatial rotation and verbal fluency and on brain architecture has also reported a change in transgender adults toward that of their gender identity after initiating GAHT.[101] A recent meta-analysis by Karalexi *et al.*[102] subdivided the available literature by birth-assigned sex and described an enhancement in visuospatial ability 3–12 months after initiating GAHT. The meta-analysis did not reveal any significant changes in verbal memory, reasoning or working memory, computation, or motor coordination. Whether all these changes play a role in the aging process of cognitive health among older TGD adults remain to be determined.

Age-related dementia has been linked to lifestyle factors including smoking, dietary choices, and alcohol consumption.[103] Although there has not been any published research on cognitive decline as it relates to lifestyle factors in TGD adults, the prevalence of smoking,[104] alcohol use,[105] and low levels of physical activity[106] is higher in TGD adults compared with cisgender adults. Whether these factors contribute to age-related dementia in TGD warrant further study. Given the scarcity of related literature, it is advised that TGD adults are encouraged to lead healthy lifestyles and referred for cognitive assessments when specific work up and interventions are considered necessary.

Mental health and aging

It is well documented that TGD individuals have higher rates of mental health conditions, including depression, suicidality, and anxiety, compared with the general population.[107–110] Rates of clinically significant depressive symptoms in older TGD adults have been reported to be as high as 48%,[111] significantly higher than the 6–8% prevalence reported in the general population of older adults.[112,113] It has been hypothesized that one of the most significant factors in the development of these conditions among TGD individuals is the impact of minority stress.[114] Minority stress is defined as the excess stress experienced by individuals in a marginalized and stigmatized social category.[115] The gender minority stress model provides a clear outline of the psychological processes that lead to the development of these mental health conditions.[116] Distal stressors experienced by TGD individuals include gender-based victimization, gender-based rejection, gender-based discrimination, and nonaffirmation of their gender identity. Chronic exposure to these stressors leads to 'proximal' stressors that include negative expectations for future events, nondisclosure of gender identity, and internalized transphobia.[115,116] This internalization of negative societal attitudes toward TGD individuals contributes to the higher risk of mental health conditions.[117] For older TGD adults, including those who are beginning their transition journey, the impact of having experienced decades of distal stressors (whether they were 'out' as TGD or not) and the resulting development of internalized proximal stressors only compounds the risk for mental health concerns.

Older TGD individuals, particularly those who are only beginning their gender transition, also must deal with the stressors associated with aging and agism. Potential loss of social support from friends and family after coming out or transitioning only worsens the social isolation already experienced by many elderly individuals. Individuals who have spent most of their life concealing their gender identity may not have developed strong social support and TGD community connectedness.[118,119] Finding such resources and relationships may be particularly difficult for an older TGD individual who may not fully feel comfortable in their identity or feel comfortable with the younger TGD population. This is particularly important, however, as these positive TGD social connections and supports have been shown to counter gender minority stresses.[120] In addition, TGD individuals pursuing transition at an older age also face a unique form of transphobic agism, namely, an attitude from others of 'Why bother now?'. This reaction, from both within and outside the TGD community, only serves to reinforce the negative thoughts and beliefs that have likely played a role in the individual's postponement of transitioning, including fears of not passing as their identified gender and doubts about whether someone their age needs different genitals. Individuals, however, who have a solid sense of 'time left to live' as their identified gender and 'time served' as their sex assigned at birth, or who have worked on countering their internalized stigma and adopted a resilience mind-set, likely navigate aging in a more positive and healthy manner overall.[121,122]

Given this, the role of the mental health professional in the holistic care of older TGD individuals in general, and particularly older TGD individuals initiating their transition, must include comprehensive mental health assessment and treatment of any existing psychiatric conditions. Additional roles may include providing psychoeducation both to the individual and possibly their family members, support in navigating and accessing other gender-affirming care, providing therapy to address internalized transphobia and develop resiliency to related social stressors, and advocacy.[123]

Gender-affirming surgeries and aging

With the rapid growth of the elderly population along with greater life expectancy, it is not surprising that individuals are undergoing all types of surgery at older ages, and this includes gender-affirming surgery. Age remains a risk factor for postoperative morbidity and mortality, not only in the United States, but around the world.[124–129] In addition, postoperative length of stay is often longer with older surgical patients than in younger patients.[130,131] Without a doubt, the aging process produces physiological and anatomical changes within the major organs systems of the body as well as cognitive changes. Despite this, many centers report outcomes in older patients that are comparable to the general population. Encouraging results have been reported for complex operations such as pancreaticoduodenectomy, hepatectomy, gastrectomy, and aortic arch replacement.[132–137] More importantly, studies have shown that the

quality of life in the elderly can be maintained or improved after surgery.[138–141]

Older TGD adults frequently ask if there is an age cut-off for eligibility for gender-affirming surgery. Although gender-affirming surgery techniques are still being refined, they follow the same principles as most other surgeries. As for every patient, it is essential to perform a thorough preoperative evaluation and carefully review comorbid conditions. Although the data around this topic are very limited, there are several factors that must be considered, including the presence of comorbid conditions (both generally and specifically in areas that would impact gender-affirming surgical outcomes), use and route of GAHT, patient-specific surgical goals and expectations, and postoperative recovery and support.

Importantly, aging alone does not alter perioperative risk, but rather its effect in association with age-related comorbidities. For example, transfeminine adults undergoing vaginoplasty who have had prior treatment for prostate cancer, whether surgery or radiation, have scarring in the retro-prostatic space, and thus a higher risk of injury to the rectum with subsequent fistula formation.[142] Surgeons have recommended minimal depth vaginoplasty as opposed to full depth vaginoplasty in individuals with previous radical prostatectomy or pelvic radiation and conditions such as congestive heart failure, stroke, or unprovoked deep vein thrombosis.[19] In addition, conditions such as joint problems are usually observed in older individuals and may preclude patient self-care and performance of necessary postoperative functions such as dilations after vaginoplasty. Even if such conditions are well-controlled, they may represent situations with high risk for poor patient outcomes. Such a detailed approach promotes decisions based on functional age rather than chronologic age and on each TGD patient as an individual. Moreover, one should explore areas likely to affect the elderly such as social support during the postoperative period, polypharmacy, cognition, frailty and functionality, nutrition, and social support. Risk calculators exist for some surgical populations, such as the American College of Surgeons Risk Calculator, and perhaps a similar risk calculator can be established for patients undergoing gender-affirming surgeries to enhance surgeons' ability to gauge the perioperative risk for the older TGD population.

Questions remain as to whether GAHT should be discontinued preoperatively. Historically due to concerns about the postoperative hypercoagulable state, patients were asked to hold GAHT for several weeks prior to and following surgery. This practice, however, has recently been called into question due to the lack of data as to whether this effectively reduces clotting risk, as well as patient reports of significant dysphoria during the time of withholding hormones. In a recent retrospective chart review by Kozato *et al.*[143] including 407 vaginoplasty cases in transfeminine patients, 190 patients stopped estrogen for a week, while in 212 patients remained on feminizing GAHT. One patient, who held hormones, presented with VTE postoperatively. The average age in this study, however, was 35.6 years, and there was variation in routes of feminizing GAHT prescribed, both of which may impact VTE risk. There were no VTE cases among 329 transmasculine surgeries, and all patients continued testosterone during the perioperative period. Boskey *et al.*[144] conducted a systematic review which concluded that current evidence does not support the need to discontinue testosterone perioperatively. In a more recent review, Haveles *et al.*[145] identified seven studies examining the incidence of VTE in transfeminine patients undergoing gender-affirming surgeries. They found heterogeneity in protocols for perioperative management of feminizing GAHT and concluded that there are insufficient data to support that continuing feminizing GAHT elevates VTE risk. It should be noted that the risk of postoperative VTE is higher in older individuals and as such, the Caprini risk factor assessment increases to 2 points for patients between 60 and 74 years old and 3 points for patients older than 75 years. It may be more appropriate to consider GAHT discontinuation in this group of older TGD adults, but this should ultimately be a shared decision-making process between the patient and the surgeon.[146]

Older TGD adults may also have different goals and expectations related to the outcome of surgery. It is critical to discuss these goals early on to navigate the discussion in the appropriate direction. Previous authors have shown that age can influence sexual attraction or preferences, as well as sexual activity. Zavlin *et al.*[147] previously explored the role of a dichotomous distribution of age at gender dysphoria onset in transfeminine individuals. In this study, following surgery, the

younger transfeminine individuals (mean age at surgery = 32.7 years, SD = 10.9) were predominantly attracted to men (52.6%), whereas individuals who were diagnosed with gender dysphoria at a later age preferred women or both men and women (85.7%) as sexual partners ($p = 0.010$). In addition, younger TGD individuals were more frequently sexually active than older TGD adults (73.7% *versus* 42.9%, respectively, $p = 0.049$). Thus, with older TGD individuals, as with all patients undergoing consultations for feminizing genital reconstruction, it is important to discuss whether they desire penetrative intercourse or to maintain a vaginal canal with frequent dilations as it may impact the choice of full depth *versus* minimal depth vaginoplasty.

Postoperative recovery and support are extremely important for all TGD patients undergoing gender-affirming surgery. The approach to postoperative care for older TGD patients may have another layer of complexity not only because recuperation is usually longer but also because other factors must be controlled. Such factors may include joint problems, decreased hearing, fall risk, and pressure sore risk. Immediate postoperative care in the hospital may require additional measures to minimize the risk of complications. In addition, postoperative protocols as they relate to timing of restrictions and timing of supervision or need for a support network may have to be adjusted for elderly TGD patients.

In summary, gender-affirming surgeries in older TGD patients have become increasingly common and will only become more so in the future. Therefore, we should continue to utilize the most well-vetted best practice guidelines to optimize perioperative care, but also develop guidelines specific to gender-affirming surgery.

Conclusion

Currently available guidelines on gender-affirming care can help inform care for older TGD populations, but the studies informing these guidelines frequently are developed from data on younger individuals. As we age, the incidence of CVD, cancer, and osteoporosis increases, and our patients on GAHT will need screening for conditions over the life span. We need more comprehensive data on older TGD adults to better understand whether there is a need to tailor recommendations for GAHT, screening studies, mental health care, and surgery, and, if so, how best to do this safely while keeping the individual goals of our patients in mind.

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Consent for publication

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Author contributions

Sean J. Iwamoto: Conceptualization; Project administration; Supervision; Writing – original draft; Writing – review & editing.

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Robert D. Davies: Writing – original draft; Writing – review & editing.

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