Bone health in transgender people

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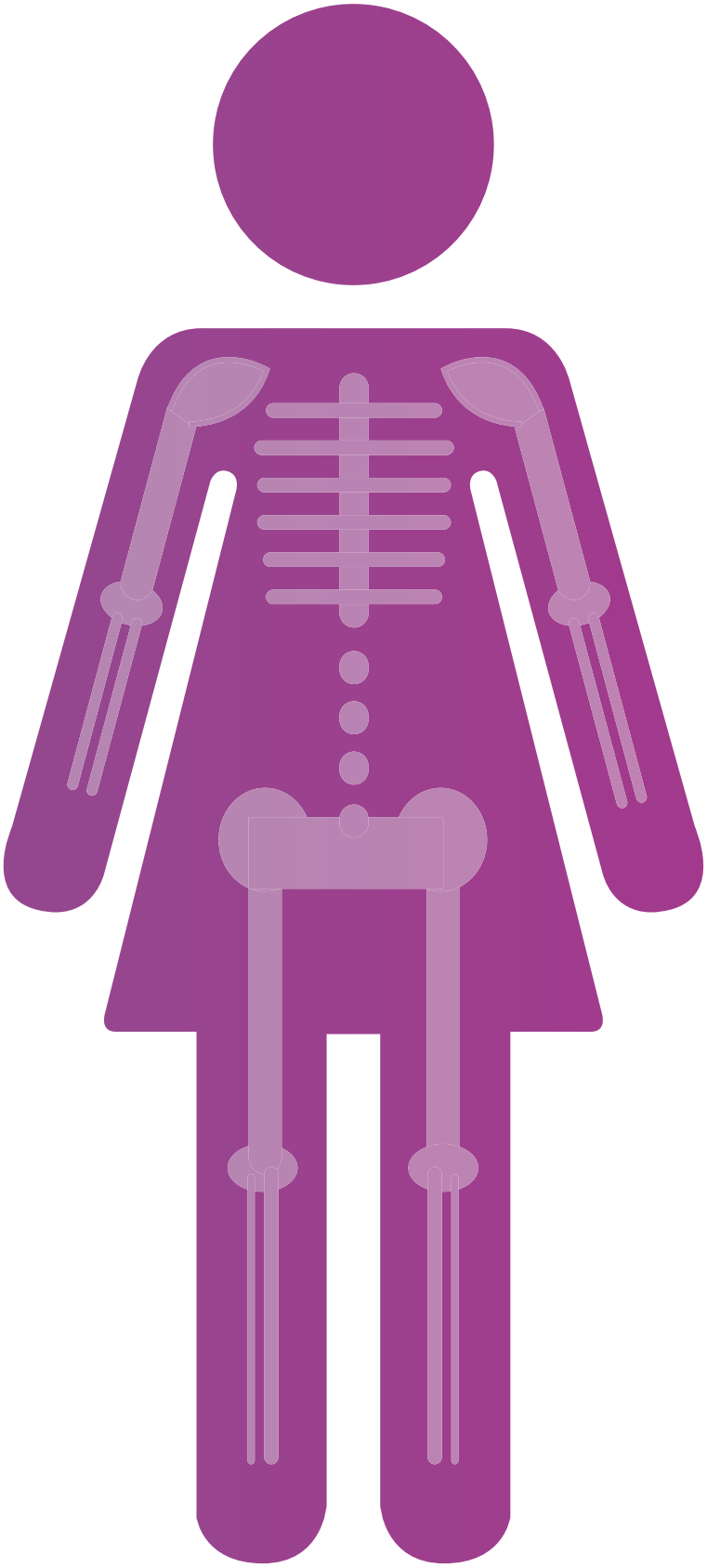
2020

document version
Publisher's PDF, also known as Version of record



Chapter 9

Fracture risk in trans women and trans men using long-term gender-affirming hormonal treatment: a nationwide cohort study

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J Bone Miner Res. 2020;**35**(1):64-70

Abstract

Concerns about bone health in transgender people using gender-affirming hormonal treatment (HT) exist, but the fracture risk is not known. In this nationwide cohort study, we aimed to compare the fracture incidence in transgender people using long-term HT with a control population. All adult transgender people who started HT before 2016 at our gender identity clinic were included and were linked to a random population-based sample of 5 age-matched control men and 5 age-matched control women per person. Fracture incidence was determined using diagnoses from visits to hospital emergency rooms nationwide between 2013-2015. A total of 1,089 trans women <50 years (mean 38±9) and 934 trans women ≥50 years (mean 60±8) using HT for median 8 (IQR 3-16) and 19 (IQR 11-29) years, respectively, were included. 2.4% of the trans women <50 years had a fracture, while 3.0% of the control men (OR 0.78, 95%CI 0.51; 1.19) and 1.6% of the control women (OR 1.49, 95%CI 0.96; 2.32) experienced a fracture. In trans women ≥50 years, 4.4% experienced a fracture, compared with 2.4% of the control men (OR 1.90, 95%CI 1.32; 2.74) and 4.2% of the control women (OR 1.05, 95%CI 0.75; 1.49). A total of 1,036 trans men (40±14 years) using HT for median 9 (IQR 2-22) years were included. Fractures occurred in 1.7% of the trans men, 3.0% of the control men (OR 0.57, 95%CI 0.35; 0.94), and 2.2% of the control women (OR 0.79, 95%CI 0.48; 1.30). In conclusion, fracture risk was higher in older trans women compared with control men. In young trans women, fracture risk tended to be increased compared with control women. Fracture risk was not increased in trans men.

Introduction

Transgender people can receive gender-affirming hormonal treatment (HT) to change the physical characteristics belonging to their experienced gender. Trans women (birth-assigned males, female identity) receive estrogens to induce feminization, resulting for example into breast growth [1] and changes in body composition.[2] Trans men (birth-assigned females, male identity) are treated with testosterone, which among others stimulates lowering of the voice [3] and growth of body hair.[4] Besides changes in physical characteristics, HT also influences bone mineral density (BMD).

Earlier studies found either a maintenance [5-9] or increase [5-7,10-15] in BMD in both adult trans women and trans men after short-term HT. Long-term effects of HT have been investigated in a few small-sample cross-sectional studies in which trans women were compared with control men, and trans men with control women. Contradictory results were obtained from these studies: higher [16,17], similar [17,18], and lower [19] BMD than controls were found. One follow-up study found no change in BMD in trans women and trans men during the first ten years of HT.[20] However, before the start of HT, trans women were found to have relatively low BMD, possibly due to co-existing vitamin D deficiency and a different life style, leading to decreased muscle mass and therefore decreased mechanical loading on bone.[21]

In clinical practice there are concerns about bone health in transgender people, particularly regarding the low initial BMD in trans women and the lack of fracture data. A few studies described no increased fracture risk before the start of HT in trans women [13,21] and trans men.[9] In short-term follow-up studies, no fractures were observed in trans women [13], trans men [9], or their controls. In studies after long-term HT, no increased fracture risk was found in both trans women [19] and trans men.[22] However, all these studies had a small sample size (n<50) or were using questionnaires to define fractures.

Therefore, the aim of this study is to investigate the fracture incidence in a large cohort of adult trans women and trans men after long-term HT, based on diagnoses from visits to the hospital emergency rooms nationwide, and to compare this incidence with an age-matched male and female control population. In addition, we aimed to study whether the types of fractures differed between the transgender population and their control groups, and whether BMD or other characteristics were different in the transgender population with fractures compared to those without fractures.

Materials and Methods

Study design and population

This study is part of the Amsterdam Cohort of Gender Dysphoria study [23], including all 6,793 people who once visited the gender identity clinic of the Amsterdam University Medical Center, the Netherlands, between 1972 and 2016. Study design and population have been described previously.[23] In short, the medical files of these people were reviewed and clinical data were retrieved. For the current study, only people who started with HT and were not deceased at time of data collection were included. The cohort was linked to a random control sample of 5 age-matched males and 5 age-matched females per transgender person, provided by the Statistics Netherlands (Central Bureau of Statistics) based on the National Civil Record Registry. The study was approved by the Medical Ethics Committee of the Amsterdam University Medical Centers, location VUmc, and necessity for informed consent was waived due to the retrospective design and the absence of interventions.

Treatment

After the diagnostic process, people could start with HT when the diagnosis gender dysphoria was confirmed.[24] In trans women, HT consists of anti-androgens, which were usually continued until orchiectomy, in combination with estrogens. In trans men, HT consisted of testosterone only. After at least one year of HT and after the age of 18 years, surgery could be performed, including vaginoplasty with orchiectomy in trans women and hysterectomy with oophorectomy in trans men.

Fracture data

The total population of transgender people and their 10 age-matched controls were linked to a database from Statistics Netherlands, which stores all diagnoses made by medical doctors from visits to the hospital emergency rooms nationwide based on Diagnosis-Treatment-Combination trajectories (DTCs) for specialized medical care. These DTCs are used to calculate the insurance claim, which is sent to the individual's medical insurance company. Health insurance is obligatory for every inhabitant of the Netherlands. The diagnoses were available for the years 2013, 2014, and 2015.

Dual-energy X-ray absorptiometry (DXA)

BMD was regularly measured during patient care using a DXA Hologic Delphi. This densitometer was updated in July 2004 and replaced in February 2011 by a Hologic Discovery A (Hologic Inc., Bedford, MA, USA). For both machines, the coefficient of variation (CV) was <1%. Phantom calibration allowed for comparison of the absolute BMD values. Absolute BMD values (g/cm^2) of the lumbar spine (LS) were obtained and T-scores were calculated, based on the birth-assigned sex reference values of the

National Health and Nutrition Examination Survey (NHANES). If more than one BMD measurement was available, the most recent measurement was used for analysis. BMD measurements were available for 77% of the trans women and 84% of the trans men.

Laboratory measurements

Blood samples were frequently obtained during patient care. When improved quality assays were available, these were implemented and conversion formulas for comparison of the concentrations were generated. Until January 2010, estradiol was measured using a radioimmunoassay (Diasorin, Saluggia, Italy) with an inter-assay CV of 10% and a lower limit of quantitation (LOQ) of 18 pmol/L. Between January 2010 and July 2014, a competitive immunoassay (Delfia, Wallac, Turku, Finland) was used (inter-assay CV 10%, LOQ 20 pmol/L). For conversion, the formula Delfia=1.267*Diasorin–28.87 was used. Since July 2014, LC-MS/MS (VUmc, Amsterdam, the Netherlands) was used (inter-assay CV 7%, LOQ 20 pmol/L) and the formula LC-MS/MS=1.60*Delfia–29 was used for conversion. Testosterone was measured using a radioimmunoassay (RIA; Coat-A-Count, Siemens, USA) until January 2013 (inter-assay CV 7-20%, LOQ 1 nmol/L), hereafter a competitive immunoassay (Architect, Abbott, USA) was used (inter-assay CV 6-10%, LOQ 0.1 nmol/L). Two formulas were used for conversion: Architect=1.1*RIA+0.2 for testosterone concentrations <8 nmol/L; Architect=1.34*RIA–1.65 for testosterone concentrations >8 nmol/L. Luteinizing hormone (LH) was measured using an immunometric assay (Delfia, Wallac, Turku, Finland) until June 2011 (inter-assay CV <7%, LOQ 0.5 U/L). After June 2011, an immunometric assay (Architect, Abbott, USA) was used (inter-assay CV <6%, LOQ 2 U/L), using the formula Architect=0.91*Delfia–0.01 for conversion. Mean estradiol, testosterone, and LH concentrations per person were calculated by averaging the results from the measurements performed during HT. Laboratory measurements were available for 66% of the trans women and 72% of the trans men.

Statistical analysis

Characteristics of the transgender population are presented as mean with standard deviation (SD), median with inter quartile range (IQR), or percentages. First, the fracture incidence was calculated in trans women, trans men, and their age-matched control men and women. Thereafter, logistic regression analyses were performed to calculate odds ratios (OR) with 95% confidence intervals (CI), as an approximation of the relative risk for fractures. As age affects the risk of fractures, the trans women group was divided into two groups (<50 years and ≥50 years), and the analyses were repeated for both age groups separately. Fractures were divided into two groups: hip, spine, forearm, and humerus fractures (which are all an approximation of osteoporotic fractures), and other fractures [25]. Chi-square tests were performed to investigate whether the type of fractures differed

between the groups. To investigate whether age in 2015, age at start of HT, body mass index (BMI), smoking habits, T-score of the LS, estradiol concentrations, testosterone concentrations, and LH concentrations were associated with fracture risk, multivariable logistic regression analyses were performed in the transgender population. To protect the anonymity of the population, data are only shown if more than 10 individuals were present in each group. Subgroup analyses were therefore not performed if less than 20 individuals were present in one group. Analyses were performed using STATA Statistical Software (Statacorp, College Station, Texas, USA), version 14.2.

Results

Study population

Of the 6,793 people who are included in the total cohort, 2,726 people were excluded for this study because they did not start with any treatment (yet), 442 started with treatment during adolescence, 15 received alternating testosterone and estradiol treatment, 319 could not be linked to the Statistics Netherlands database (e.g. because they were not registered in the Netherlands), and 232 people were deceased. This led to a total study population of 3,059 people, consisting of 2,023 trans women and 1,036 trans men. The characteristics are shown in Table 1.

Table 1. Characteristics of the study population.

	Trans women <50 years	Trans women ≥50 years	Trans men
Number of people	1,089	934	1,036
Age in 2015, yr	38 (9)	60 (8)	40 (14)
Age at start HT, yr	26 (22 – 33)	40 (31 – 48)	25 (21 – 33)
Duration HT, yr	8 (3 – 16)	19 (11 – 29)	9 (2 – 22)
BMI, kg/m^2 (n=2,756)	23.9 (4.2)	25.7 (4.6)	25.8 (4.9)
Smoking, % yes (n=2,614)	44.7	49.0	47.8
Gonadectomy, % yes	57.8	80.9	69.8
Laboratory *			
Estradiol, pmol/L	211 (132 – 308)	241 (138 – 391)	147 (102 – 205)
Testosterone, nmol/L	1.2 (0.7 – 1.4)	1.3 (1.0 – 1.3)	25.0 (17.1 – 36.5)
LH, IU/L	2.2 (0.2 – 9.7)	3.2 (0.3 – 8.4)	3.6 (0.9 – 11.5)

Characteristics are shown as mean with standard deviation, median with inter quartile range, or percentage. Associations are shown as odds ratios (OR) with 95% confidence intervals (CI). # Laboratory measurements were available of 66% of the trans women and 72% of the trans men. Abbreviations: yr=years, HT = hormonal treatment, BMI = body mass index, LH = luteinizing hormone

Trans women

Fractures occurred in 3.3% of the trans women (n=67) in the 3-year time period, while 2.7% of the control men (n=275) and 2.8% of the control women (n=283) had a fracture. The overall fracture incidence was not increased in trans women compared with control men (OR 1.23, 95%CI 0.93; 1.61) nor with control women (OR 1.19, 95%CI 0.91; 1.56). 41.8% of all fractures in trans women was a hip, spine, forearm, or humerus fracture, compared with 26.6% in control men (p=0.014) and 36.0% in control women (p=0.381).

After age stratification, trans women ≥50 years (n=934) had an increased fracture risk (4.4%, n=41) compared with control men ≥50 years (2.4%, n=110, OR 1.90, 95%CI 1.32; 2.74), but a similar fracture risk compared with control women ≥50 years (4.2%, n=195, OR 1.05, 95%CI 0.75; 1.49) (Figure 1). Trans women <50 years (n=1,089) did not have an increased fracture risk (2.4%, n=26) compared with control men <50 years (3.0%, n=165, OR 0.78, 95%CI 0.51; 1.19), but tended to have a higher fracture risk compared with control women <50 years (1.6%, n=88, OR 1.49, 95%CI 0.96; 2.32) (Figure 1).

In Table 2, the differences in characteristics between trans women with and without fractures are shown. In the multivariable analysis, age in 2015 (per year: OR 1.05, 95%CI 1.02; 1.08) and T-score of the lumbar spine (per 1.0 point: OR 0.75, 95%CI 0.59; 0.96) were associated with fracture risk. Smoking tended to be associated with a higher fracture risk (yes vs no: OR 1.68, 95%CI 0.93; 3.04), while mean BMI (per point: OR 1.04, 95%CI 0.97; 1.11) and age at start of HT (per year: OR 0.98, 95%CI 0.95; 1.01) were not associated with an increased fracture risk. Laboratory measurements were not included in this multivariable analysis, due to the smaller number of individuals with laboratory measurements available. However, in univariable analyses, no associations were found between estradiol (per 10 pmol/L: OR 0.99, 95%CI 0.97; 1.02), testosterone (per 1 nmol/L: OR 1.03, 95%CI 0.96; 1.10), and LH (per 1 IU/L: OR 1.00, 95%CI 0.97; 1.04) concentrations and fracture risk.

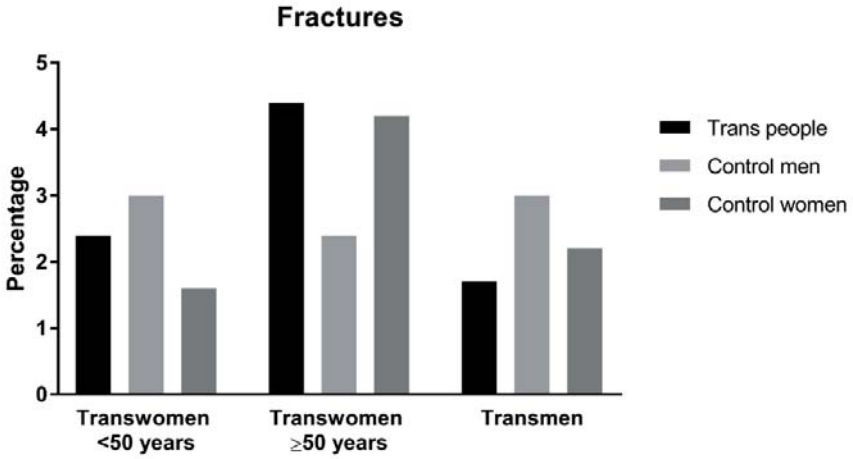

Figure 1.
Fracture incidence during the years 2013, 2014, and 2015 in the transgender population and control groups. Data is shown as percentages separately for trans women <50 years, trans women ≥50 years, trans men, and their age-matched control men and women. Due to the low number of fractures in trans men, no stratification for age could be performed.

Trans men

Eighteen trans men experienced a fracture (1.7%) in the 3-year time period, while 3.0% of the control men (n=155) and 2.2% of the control women (n=114) had a fracture (Figure 1). The fracture risk was similar to control women (OR 0.79, 95%CI 0.48; 1.30), but lower compared with control men (OR 0.57, 95%CI 0.35; 0.94). Table 2 displays the differences in characteristics between trans men with and without fractures. In the multivariable analyses, no associations were found between fracture risk and age in 2015 (per year: OR 1.02, 95%CI 0.97; 1.07), age at start of HT (per year: OR 1.00, 95%CI 0.93; 1.07), mean BMI (per point: 0.92, 95%CI 0.80; 1.06), smoking (yes vs no: OR 1.44, 95%CI 0.48; 4.30), and T-score of the LS (per 1.0 point: 0.99, 95%CI 0.62; 1.59). Due to the smaller number of individuals with laboratory measurements, these were not included in the multivariable analyses. However, in the univariable analyses it was found that estradiol concentrations were associated with fracture risk (per 10 pmol/L: OR 0.89, 95%CI 0.80; 0.99), but testosterone (per 1 nmol/L: 0.98, 95%CI 0.93; 1.02) and LH (per 1 IU/L: OR 1.03, 95%CI 0.98; 1.08) concentrations were not.

Due to the low number of fractures in trans men, no stratification for age or type of fracture could be performed.

Table 2. Differences in characteristics in the transgender population with and without fractures.

	Trans women		Trans men	
	No fracture	**Fracture**	**No fracture**	**Fracture**
Number of people	*1,956*	*67*	*1,018*	*18*
Age in 2015, yr	48 (14)	55 (13)	40 (14)	45 (14)
Age at start HT, yr	31 (24 – 41)	33 (26 – 45)	25 (21 – 33)	25 (21 – 34)
BMI, kg/m^2 (n=1,785)	24.6 (4.4)	25.8 (5.1)	25.8 (4.9)	24.4 (3.5)
Smoking, % (n=1,714)	46	63	48	56
T-score lumbar spine	-1.02 (1.28)	-1.34 (1.40)		
Laboratory #				
Estradiol, pmol/L	220 (135 – 337)	172 (116 – 299)	148 (103 – 206)	84 (65 – 133)
Testosterone, nmol/L	1.3 (0.8 – 1.3)	1.3 (0.9 – 2.2)	25 (17 – 37)	22 (17 – 29)
LH, IU/L	2.5 (0.3 – 9.3)	2.8 (0.7 – 9.6)	3.6 (0.9 – 11.4)	10.1 (2.2 – 15.2)

Characteristics are shown as mean with standard deviation, median with inter quartile range, or percentage.
* Laboratory measurements were available of 66% of the trans women and 72% of the trans men.
Abbreviations: HT = hormonal treatment, BMI = body mass index, LH = luteinizing hormone

Discussion

In this study, we found that fracture risk was higher in older trans women using long-term HT compared with control men but similar to control women. In young trans women, fracture risk tended to be increased compared with control women but not compared with control men. In addition, the type of fractures differed in trans women compared with control men, with relatively more hip, spine, forearm, and humerus fractures. Fracture risk was not increased in trans men using long-term HT. In trans women, older age and lower T-score of the LS were associated with an increased fracture risk, while this was not found in trans men.

In trans women <50 years, fracture risk tended to be increased compared with control women but not compared with control men. Earlier studies found that trans women, also at younger ages, had a high prevalence of osteoporosis or low BMD even before hormonal treatment.[5,21] Although earlier short-term and long-term studies did not show a detrimental effect of HT on BMD [7,20], higher fracture risk in young trans women compared with control women may be explained by lower initial BMD even before start of HT. In the general population, men have a higher fracture incidence than women at younger ages and these fractures usually occur as a result of an accident.[26,27] It can be speculated that, although BMD in trans women is lower than in control men, fracture risk is not increased because trans women often tend to have a less active life style than control men and are therefore less likely to suffer an accident which leads to a fracture.

In trans women ≥50 years, fracture risk was increased compared with control men but similar to control women. At older ages, control women have a higher fracture risk than control men, mainly due to a decreased BMD in control women because of the loss of estrogens after menopause.[26] The similar risk in trans women compared with control women at older ages can be thought to be the result of decreased estrogen concentrations, possibly because of decreasing or discontinuation of estradiol supplementation in older trans women. However, this is not part of our clinical protocol and we did not find a difference in mean estradiol concentrations in trans women <50 years and ≥50 years. Control women usually have normal BMD before menopause, but it decreases during menopause because the loss of estrogen. Trans women, however, have low BMD but, in our center, do not stop or lower estrogen therapy at the age of 50 years and therefore do not experience a decrease in BMD because of the loss of estrogen. This might explain why the fracture risk becomes similar in trans women compared with control women after the age of 50 years, but higher than control men.

It was also found that the type of fractures differed in trans women compared with control men, with relatively more hip, spine, forearm, and humerus fractures, while it was similar to control women. This might be explained by the fact that hip, spine, forearm, and humerus fractures usually occur because of low BMD, while other fractures mostly occur because of accidents. As trans women have lower BMD than control men, the risk of getting a hip, spine, forearm, or humerus fractures is higher, but because of a less active life style, the risk for other fractures is lower.

Trans men had a similar fracture risk compared with control women, but a lower risk than control men. Earlier studies found no increased fracture risk [4,9,22], a normal BMD at baseline [9], and no detrimental effects of HT on BMD.[9,14,20] Therefore, it was not expected that fracture risk would be increased in trans men. The finding that trans men had a lower fracture risk than control men but similar to control women might be explained that trans men are more careful or participate less in (sporting) activities than the control men, leading to less fractures.

This study is the first study investigating the fracture risk in a large population of adult trans women and trans men using long-term HT. This population was linked to a random sample of 10 age-matched control men and women per person, which makes the control population more accurate. The occurrence of fractures was retrieved from the database from Statistics Netherlands, which stores all diagnoses of the visits to the emergency rooms nationwide. As in the Netherlands, everybody with a (suspicion of a) fracture visits the emergency room, this is a reliable source for fracture data. However, there are also some limitations. Firstly, the time frame for fracture occurrence was only three years. Although it is long enough for a point prevalence of fractures, most ideally transgender people would be followed from the moment they start with HT. Secondly, we did not have any clinical data of the control population. Therefore, no other factors with effects on bone health and fractures, for example smoking habits and physical

activity, could be analyzed in the control groups. However, in studies from our neighbor country Belgium, no differences (except smoking in trans men) were found in weight, smoking, and physical activity between the transgender population and control groups.[9,21] Thirdly, this study used data that were collected during clinical care. Therefore, not all data were available from the entire population, such as BMD and laboratory measurements. However, as they were known of the majority of the included population, these data were still analyzed, but should be interpreted cautiously. Fourthly, as this study was performed in collaboration with Statistics Netherlands, it was only allowed to show data if more than 10 individuals per group were present to protect the anonymity of the data. Therefore, only the overall fracture risk could be shown in trans men. Lastly, although the transgender population used HT for a long term, the population was still young of age. As most fractures occur at higher age, only the fracture risk at younger ages was assessed in this study. The effects of HT on fracture risk at old age therefore remains a topic for further research.

In conclusion, fracture risk was higher in older trans women using long-term HT compared with control men but similar to control women. In young trans women, fracture risk tended to be increased compared with control women but not compared with control men. Fracture risk was not increased in trans men using long-term HT. However, as type of fractures differed in trans women and the transgender population was still young, bone health remains an important health topic, particularly in trans women, and longer follow-up studies are needed.

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