Mortality trends over five decades in adult transgender people receiving hormone treatment: a report from the Amsterdam cohort of gender dysphoria

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Summary

Background Increased mortality in transgender people has been described in earlier studies. Whether this increased mortality is still present over the past decades is unknown. Therefore, we aimed to investigate trends in mortality over five decades in a large cohort of adult transgender people in addition to cause-specific mortality.

Methods We did a retrospective cohort study of adult transgender people who visited the gender identity clinic of Amsterdam University Medical Centre in the Netherlands. Data of transgender people who received hormone treatment between 1972 and 2018 were linked to Statistics Netherlands. People were excluded if they used alternating testosterone and oestradiol treatment, if they started treatment younger than age 17 years, or if they had ever used puberty-blockers before gender-affirming hormone treatment. Standardised mortality ratios (SMRs) were calculated using general population mortality rates stratified by age, calendar period, and sex. Cause-specific mortality was also calculated.

Findings Between 1972 and 2018, 8831 people visited the gender identity clinic. 4263 were excluded from the study for a variety of reasons, and 2927 transgender women and 1641 transgender men were included in the study, with a total follow-up time of 40 232 person-years for transgender women and 17 285 person-years for transgender men. During follow-up, 317 (10·8%) transgender women died, which was higher than expected compared with general population men (SMR 1·8, 95% CI 1·6–2·0) and general population women (SMR 2·8, 2·5–3·1). Cause-specific mortality in transgender women was high for cardiovascular disease, lung cancer, HIV-related disease, and suicide. In transgender men, 44 people (2·7%) died, which was higher than expected compared with general population women (SMR 1·8, 95% CI 1·3–2·4) but not general population men (SMR 1·2, 95% CI 0·9–1·6). Cause-specific death in transgender men was high for non-natural causes of death. No decreasing trend in mortality risk was observed over the five decades studied.

Interpretation This observational study showed an increased mortality risk in transgender people using hormone treatment, regardless of treatment type. This increased mortality risk did not decrease over time. The cause-specific mortality risk because of lung cancer, cardiovascular disease, HIV-related disease, and suicide gives no indication to a specific effect of hormone treatment, but indicates that monitoring, optimising, and, if necessary, treating medical morbidities and lifestyle factors remain important in transgender health care.

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Introduction

Transgender people experience an incongruence between their sex assigned at birth and their gender identity. In 2015, it was estimated that 1:2800 birth-assigned males and 1:5200 birth-assigned females received medical treatment for gender dysphoria in the Netherlands. Over the past years, a substantial increase has been observed in the number of referrals for transgender health care, for either psychological, endocrine, or surgical treatment.[1,2]

Transgender people can be treated with gender-affirming hormones to induce desired physical changes.[3] Transgender women (male sex assigned at birth, female gender identity) are usually treated with antiandrogens and oestrogens to induce feminisation. To induce masculinisation, transgender men (female sex assigned at birth, male gender identity) are usually treated with testosterone. After 1 year of hormone treatment, transgender people can choose gender-affirming surgery as part of their transition. In transgender women, this can include orchiectomy with or without vaginoplasty, breast augmentation, and facial feminisation surgery. In transgender men, this can include mastectomy, removal of uterus with or without ovaries, and metaidoioplasty or phalloplasty. After orchiectomy in transgender women, antiandrogen treatment is ceased.

Hormone treatment in transgender people is generally considered to be safe.[4] However, data about long-term

Research in context

Evidence before this study

Transgender people, characterised by an incongruence between sex assigned at birth and gender identity, can receive gender-affirming hormone treatment (sex steroids) to reduce distress and induce desired physical changes. This gender-affirming hormone treatment potentially has side effects, such as cardiovascular disease and cancer, which might lead to increased mortality. Currently, there is limited information about mortality risk in transgender people receiving hormone treatment. We searched PubMed for available literature on Jan 9, 2021, using the following search terms: "transgender persons"[MeSH Terms] OR ("transgender"[All Fields] AND "persons"[All Fields]) OR "transgender persons"[All Fields] OR "transgender"[All Fields] OR "transgendered"[All Fields] OR "transgenders"[All Fields] combined with "mortality"[MeSH Terms] OR "mortality"[All Fields] OR "mortalities"[All Fields] OR "mortality"[MeSH Subheading].

Added value of this study

In this large study, we investigated trends in mortality risk in transgender people. Because about 90% of all transgender people in the Netherlands are treated in our centre, we were able to make reliable estimations of mortality risk. Moreover, we linked our cohort to Statistics Netherlands, which holds record of all dates and causes of death of residents of the Netherlands, which substantially improved data quality. Overall, mortality risk in transgender people was increased compared with people in the general population, with most causes of death considered not to be associated with hormone use. Increased mortality in transgender women was largely explained by an increased risk of death due to cardiovascular disease including myocardial infarction, HIV-related disease, lung cancer, and suicide. In transgender men, the slightly increased mortality risk was explained by a higher risk of non-natural causes of death than general population women.

Implications of all the available evidence

Although an increased mortality risk was observed in transgender people, this increase was largely explained by causes of death that were not associated with hormone treatment. Monitoring, optimising, and, if necessary, treating comorbidities, such as cardiovascular disease, tobacco use, and HIV, remain important in transgender health care.

effects on safety of hormone treatments are scarce, leading to insufficient evidence to determine long-term safety, especially regarding cancer and hormone-sensitive cancers specifically, as well as cardiovascular disease. Previous studies have showed an increased risk of strokes,[5,6] myocardial infarctions,[5] and venous thromboembolisms[5,6] among transgender women who received hormone treatment. In transgender men who received testosterone treatment, an increased risk of myocardial infarctions was described.[5] Furthermore, transgender women using long-term, high dose cyproterone acetate (a progestogenic antiandrogen) might have a higher risk of meningioma than do general population women and general population men.[7] Whether hormone treatment increases the risk of cancer in general and hormone-sensitive cancer specifically has not yet been fully established.[8] A strongly increased breast cancer risk in transgender women compared with general population men has been observed.[9] Nevertheless, the observed risk was still lower than the breast cancer risk in general population women.

The risk of certain diseases might be increased in transgender people who receive hormone treatment.[10] Although a decreasing trend over time was observed, the risk of death by suicide was increased in transgender people compared with cisgender people.[11] However, whether hormone treatment in transgender people influences overall mortality risk, cancer-associated mortality, or cardiovascular-associated mortality remains unclear. Several studies have addressed this topic in the past;[12–16] however, the information was limited because of short follow-up time, a high amount of missing data, and heterogeneity in study cohorts and control populations. We aimed to study the trends in mortality risk over five decades of transgender people receiving hormone treatment by use of general Dutch mortality rates stratified by age, calendar period, and sex as reference.

Methods

Study design and participants

In this retrospective cohort study, all adult transgender people who visited the gender identity clinic of the Amsterdam University Medical Centres, the Netherlands, were identified. People were included if they had started hormone treatment between 1972 and 2018, and were excluded if they used alternating testosterone and oestradiol treatment, if they started treatment younger than age 17 years, if they ever used puberty-blockers (ie, gonadotropin hormone-releasing hormone analogues) before gender-affirming hormone treatment, or if they were lost to follow-up. Additionally, people were excluded if there were no data available from at least one visit after the start of hormone treatment. The study protocol was assessed by the Ethical Review Board of the Amsterdam University Medical Centre (VU University Medical Centre, Amsterdam). The Medical Research Involving Human Subjects Act does not apply to this study, and necessity for informed consent was waived.

Procedures

Following formation of the study cohort, data about age at start of hormone treatment, type of hormone treatment, smoking habits (current or former smoker *vs* never smoker), medical history, and the last date of follow-up were retrieved from medical files. Subsequently, the data were linked to Statistics Netherlands (CBS), a Dutch governmental institution that gathers statistical information about the Netherlands and its inhabitants. Data about cause of death were retrieved from CBS and were available since 1996. Cause of death was determined from the death certificates, which were filled out by the medical doctor at the time of death. If the cause of death was not known, it was registered on these forms as unknown. Each deceased person is registered with a single death cause (primary cause of death).

Most transgender women were treated with either cyproterone acetate (between 10 mg and 100 mg daily, based on common clinical practice at the time) or spironolactone (between 100 mg and 200 mg daily) as an antiandrogen, which was often ceased after orchiectomy. In addition to antiandrogens, oestrogen was prescribed in the form of ethinyl oestradiol (between 25 mcg and 100 mcg daily), conjugated oestrogens (between 0·625 mg and 1·25 mg daily), oestradiol patches (between 50 mcg per day and 150 mcg per day twice weekly), implants (20 mg every 3–6 months), injections (between 10 mg and 100 mg every 2–4 weeks), valerate (between 2 mg and 6 mg daily), or gel (between 0·75 mg and 3 mg daily). From 2001 onwards, oestradiol valerate, patches, or gel were mainly used. Transgender men were treated with either testosterone gel (between 20 mg and 100 mg daily), intramuscular testosterone esters (between 125 mg and 250 mg every 2–3 weeks), or testosterone undecanoate (either oral [between 40 mg and 160 mg daily] or intramuscular [1000 mg every 10–14 weeks]). Some transgender men who experienced persistent menstrual blood loss during testosterone therapy were treated with additional progestogens such as lynestrenol (between 5 and 10 mg daily).

The primary outcome of this study was trends in overall mortality over five decades in transgender women and transgender men, compared with general population men and women. The secondary outcomes were cause-specific mortalities in transgender women and transgender men, compared with general population men and women.

Statistical analysis

The data of transgender women and transgender men were analysed separately. Standardised mortality ratios (SMRs) were calculated using an actuarial life table approach as described by Dickman and colleagues.[17,18] In order to calculate the SMRs, we first calculated age-specific and sex-specific mortality incidence rates in the adult Dutch population. Thereafter, the number of expected death cases in the cohort was calculated by multiplying the age-specific and sex-specific incidence rates of the general population by the number of individuals within a specific age and sex group. The number of expected cases was calculated twice in transgender women and transgender men; once using the reference numbers of birth-assigned males and once using reference numbers of birth-assigned females. Finally, SMRs were calculated by dividing the number of observed cases by the expected cases. Data are presented as percentages, mean (SD), median (IQR), or SMR (95% CI). Absolute numbers of people who died because of a certain cause are only presented if the number exceeds ten cases to guarantee anonymity of the people in the CBS database.

For analyses, the date of start of hormone treatment at our centre was used. Person-time was defined as the number of years from the start date of hormone treatment to the first terminating event. Terminating events were either date of death, end of study period (Dec 31, 2018), or last visit at our clinic for the people who could not be linked to CBS (eg, if a person was no longer a resident of the Netherlands). When possible, the mortality risk was further divided into categories of diseases including cardiovascular disease, infection, cancer, and non-natural causes of death (only for deaths between 1996 and 2018). We repeated the overall analysis for a subgroup of transgender women who ever used ethinyl oestradiol, because this synthetic hormone was used in the first decades and has been linked to a higher risk for venous thromboembolism.

For expediency, the control populations are referred to as general population men and general population women, although we were unable to verify that none of these people were transgender.

All analyses were done with STATA Statistical Software, version 14.1.

Role of the funding source

There was no funding source for this study.

Results

Between 1972 and 2018, 8831 people visited our gender identity clinic, of which 5350 were birth-assigned males and 3481 were birth-assigned females. 4263 people were excluded from the study for a variety of reasons including not using hormone treatment or using hormone treatment younger than age 17 years. 4568 transgender people were included in the study, 2927 transgender women and 1641 transgender men (figure 1).

The median age at the start of hormone treatment was 30 years (IQR 24–42) in transgender women and 23 years (20–32) in transgender men. The median follow-up time was 11 years (IQR 4–22) in transgender women and 5 years (2–17) in transgender men, leading to a total follow-up time of 40 232 person-years in transgender women and 17 285 person-years in transgender men. The characteristics of the study

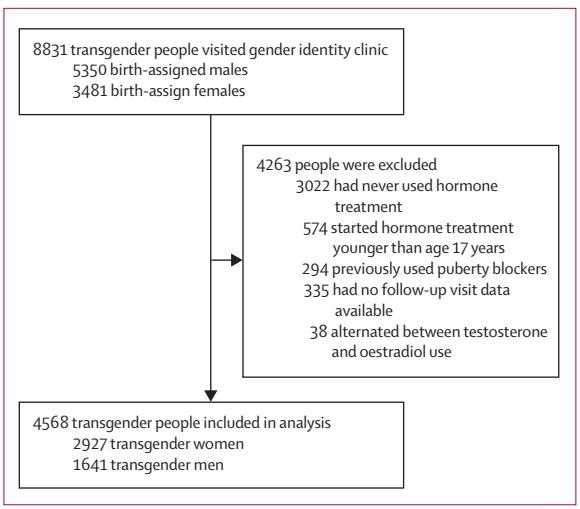

Figure 1: **Study flowchart**

	Transgender women (n=2927)	Transgender men (n=1641)
Age at start of hormone therapy, years	30 (24–42)	23 (20–32)
White ethnicity	1967/2171 (90·6%)	1307/1411 (92·6%)
Ever-smokers	815/1861 (43·8%)	503/1138 (44·2%)
Body-mass index, kg/m²	23·6* (4·3)	25·4† (5·7)
Previous gonadectomy	1891 (64·6%)	1006 (61·3%)
Median oestradiol levels during hormone therapy, pmol/L	215‡ (126–345)	119§ (81–177)
Median testosterone levels during hormone therapy, nmol/L	0·9¶ (0·6–1·3)	21·0‖ (14·0–32·0)
Median person-time, years	11 (4–22)	5 (2–17)
Total person-time, years	40 232	17 285

Data are mean (SD), median (IQR), n (%), n/N (%), or number of years. *Data available for 1858 people. †Data available for 1209 people. ‡Data available for 2253 people. §Data available for 1435 people. ¶Data available for 1802 people. ‖Data available for 1427 people.

Table 1: **Characteristics of the study cohort**

population are presented in table 1. During follow-up, 317 (10·8%) of 2927 transgender women and 44 (2·7%) of 1641 transgender men died, resulting in an overall mortality of 628 deaths per 100 000 person-years.

The overall mortality risk in transgender women was increased compared with general population men (SMR 1·8, 95% CI 1·6–2·0) and general population women (SMR 2·8, 2·5–3·1). As shown in table 2, mortality risk did not decrease over the studied decades. Trangender women who died during follow-up received hormone treatment for a median of 16 years (IQR 7–25). Cumulative mortality shows impaired survival in transgender women compared with general population men and women (figure 2). Mortality risk in transgender women was further divided in causes of death (table 3). Compared with general population men, transgender women died more frequently because of either cardiovascular disease (SMR 1·4, 95% CI 1·0–1·8), lung cancer (SMR 2·0, 1·4–2·8), infection (SMR 5·4, 2·9–8·7), or non-natural causes of death (SMR 2·7, 1·8–3·7). In the infection causes of death category, SMR was high for deaths related to Human Immunodeficiency Virus (HIV)-related disease (SMR 14·7, 95% CI 1·8–40·9). In the non-natural causes of death category, SMR was highest for suicide deaths (SMR 3·1, 95% CI 1·8–4·7). Compared with general population women, transgender women died more frequently because of either cardiovascular disease (SMR 2·6, 95% CI 1·9–3·4), lung cancer (SMR 3·1, 2·1–4·2), infection (SMR 8·7, 4·7–14·1), or non-natural causes of death (SMR 6·1, 4·2–8·4). In the cardiovascular disease category, risk of death because of myocardial infarction (SMR 3·0, 95% CI 1·7–4·5) showed the largest SMR. HIV-related disease (SMR 47·6, 95% CI 5·8–132·6) resulted in the largest SMR in the infection category and suicide (SMR 6·8, 4·1–10·3) showed the largest SMR in the non-natural causes category. Similar results regarding overall mortality were found when analyses were restricted to only transgender women who used ethinyl oestradiol (n=717; SMR 1·8, 95% CI 1·5–2·1 *vs* general population men; SMR 2·8, 2·4–3·2 *vs* general population women).

In transgender men, the overall mortality risk was comparable with general population men (SMR 1·2, 95% CI 0·9–1·6) and increased compared with general population women (SMR 1·8, 1·3–2·4). The increased overall mortality risk compared with general population women was mainly because of increased mortality risk in people who started hormone treatment between 1990 and 2000 (table 2). Transgender men who died during follow-up received hormone treatment for a median 13 years (IQR 7–24). Figure 2 shows impaired overall survival in transgender men compared with general population men and women. The cause-specific mortality risk for transgender men compared with general population men and general population women is shown in table 3. Transgender men had a higher risk of death from non-natural causes (SMR 3·3, 95% CI 1·2–6·4) compared with general population women. No increased risk compared with general population men was observed.

No analyses could be done on different types of hormone treatment in both transgender women and transgender men, because treatment was often changed over the follow-up period, or little variation in treatment regimen was present, which was specifically the case for antiandrogen treatment.

Discussion

This study showed an approximate two-fold increase in mortality risk in transgender people compared with people from the general population. This risk did not decrease over the five decades studied. Increased mortality in transgender women showed high risks of death because of

	Transgender women			Transgender men		
	Number of patients who died (n)	SMR compared with general population men	SMR compared with general population women	Number of patients who died (n)	SMR compared with general population women	SMR compared with general population men
Overall	317	1·8 (1·6–2·0)	2·8 (2·5–3·1)	44	1·8 (1·3–2·4)	1·2 (0·9–1·6)
<1980	51	1·7 (1·3–2·2)	2·7 (2·0–3·5)	<10	2·3 (0·9–4·3)	1·5 (0·6–2·9)
1980–90	125	1·8 (1·5–2·1)	2·8 (2·3–3·3)	10	1·0 (0·5–1·7)	0·7 (0·3–1·1)
1990–2000	74	1·7 (1·3–2·1)	2·5 (2·0–3·1)	15	2·6 (1·5–4·1)	1·8 (1·0–2·9)
2000–10	41	1·8 (1·3–2·4)	2·6 (1·8–3·4)	<10	2·1 (0·9–2·8)	1·5 (0·7–2·8)
2010–18	26	3·7 (2·4–5·2)	5·2 (3·4–7·4)	<10	2·4 (0·7–5·3)	1·6 (0·4–3·4)

Data are absolute values or standardised mortality ratio (95% CI). N indicates the number of patients who started hormone therapy in each decade who died. Absolute numbers of people who died are only presented if the number exceeds ten cases to guarantee patient anonymity. SMR=standardised mortality ratio.

Table 2: **SMRs in transgender women and transgender men over 10-year periods based on year of hormone treatment initiation**

cardiovascular disease, HIV-related disease, lung cancer, and suicide. In transgender men, the observed increased mortality compared with general population women was mainly attributed to non-natural causes of death.

The overall mortality in transgender people in the current study was 628 deaths per 100 000 person-years, which is slightly increased[12,14] or decreased[15] compared with earlier studies in the transgender population. In accordance with previous studies, we observed an increased mortality due to HIV-related disease and suicide in transgender women.[12–15,19] Notably, most of the deaths from HIV-related disease in this study occurred in the first decades studied, indicating an effect of improved HIV treatment over recent years. Moreover, we observed that most suicide cases occurred in the first decades studied. This might be due to increased awareness among health-care providers regarding suicide risk in transgender people and improved suicide prevention strategies. Furthermore, a reduction of psychological distress among transgender individuals because of improvement of social acceptance might have contributed to the decreased number of suicides over the past years as well as the increased availability and accessibility of medical treatment.

In accordance with earlier studies done,[12] an increased risk of cardiovascular-associated death in transgender women was observed in this study. This increased risk was particularly observed compared with general population women. This observed increased risk might be associated with metabolic changes such as a change in serum lipids, blood pressure, glucose or insulin metabolism, and changes in body composition as previously described.[20,21] Another explanation might be lifestyle factors and increased psychological distress because of minority stress and the marginalised position they sometimes have in society.[22,23] Although social acceptance of transgender people in society has improved over the past years, acceptance was impaired when the people in the first cohorts of this study started their treatment, which could have contributed to the observed increased risk. Furthermore, the lack of acceptance of transgender people in society during that time might have led a life more withdrawn from society with increased risk of substances use (such as nicotine), and obesity. Additionally, in that time, transgender people might not have felt confident to visit a doctor when they experienced health problems,[24] which could have led to delayed diagnosis and impaired cardiovascular risk management. This reluctance to visit a doctor not only might have contributed to the increased cardiovascular mortality risk, but also to the increased mortality from lung cancer. Previous studies have suggested a higher incidence of smoking among transgender people than in cisgender people;[25] although some studies have shown a contrasting result.[26,27] In the present study, we were able to distinguish former smokers from never smokers. About 44% of transgender women and transgender men were former smokers, a statistic that was not increased compared with the general Dutch population (56% of

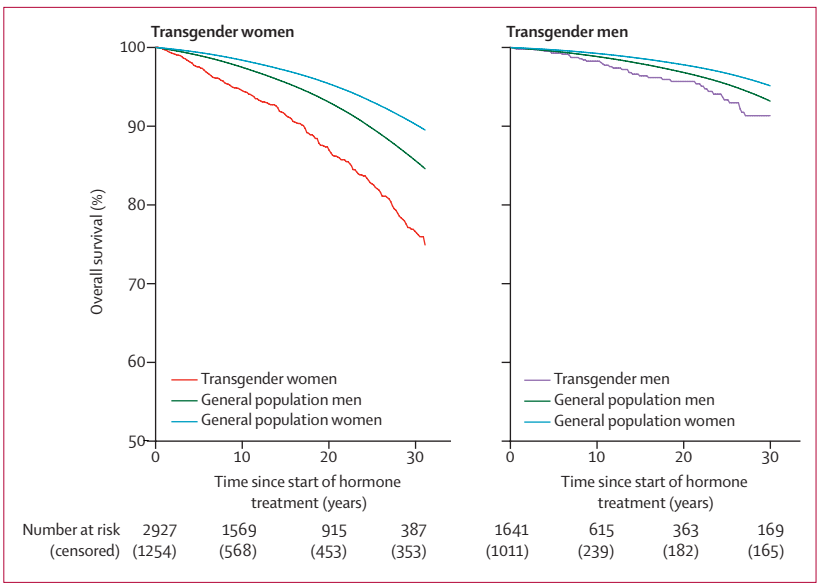

Figure 2: **Cumulative survival in transgender women and transgender men during follow-up**

	Transgender women			Transgender men		
	Number who died (n)	SMR compared with general population men	SMR compared with general population women	Number who died (n)	SMR compared with general population women	SMR compared with general population men
Overall*	241	1·6 (1·4–1·9)	2·4 (2·1–2·7)	34	1·6 (1·1–2·1)	1·1 (0·8–1·5)
Cardiovascular disease	50	1·4 (1·0–1·8)	2·6 (1·9–3·4)	<10	1·6 (0·5–3·2)	0·8 (0·3–1·6)
Myocardial infarction	17	1·1 (0·7–1·7)	3·0 (1·7–4·5)	<10	1·0 (0·0–3·7)	0·4 (0·0–1·4)
Thromboembolism	NA	NA	NA	NA	NA	NA
Other	33	1·5 (1·1–2·1)	2·5 (1·7–3·4)	<10	1·8 (0·5–4·0)	1·1 (0·3–2·3)
Cancer	76	1·3 (1·0– 1·6)	1·6 (1·3–2·0)	<10	0·8 (0·4–1·4)	0·8 (0·4–1·4)
Lung cancer	34	2·0 (1·4–2·8)	3·1 (2·1–4·2)	<10	1·1 (0·2–2·7)	1·0 (0·2–2·3)
Cancer of digestive tract	17	1·0 (0·6–1·5)	1·5 (0·9–2·4)	<10	0·4 (0·0–1·6)	0·3 (0·0–1·0)
Other	25	1·1 (0·7–1·6)	1·0 (0·6–1·4)	<10	0·8 (0·3–1·6)	1·1 (0·4–2·2)
Infection	13	5·4 (2·9–8·7)	8·7 (4·7–14·1)	NA	NA	NA
HIV	<10	14·7 (1·8–40·9)	47·6 (5·8–132·6)	NA	NA	NA
Other	<10	4·8 (2·4–8·0)	7·6 (3·8–12·7)	NA	NA	NA
Non-natural cause	32	2·7 (1·8–3·7)	6·1 (4·2–8·4)	<10	3·3 (1·2–6·4)	1·3 (0·5–2·5)
Suicide	18	3·1 (1·8–4·7)	6·8 (4·1–10·3)	<10	2·8 (0·6–6·8)	1·2 (0·3–3·0)
Other	<14	2·3 (1·2–3·6)	5·2 (2·9–8·4)	<10	4·0 (0·8–9·7)	1·3 (0·3–3·2)
Other	70	1·9 (1·5–2·3)	2·7 (2·1–3·4)	14	2·8 (1·6–4·5)	1·9 (1·0–3·0)

Data are absolute values or standardised mortality ratio (95% CI). N indicates the number of patients who started hormone therapy who died. Absolute numbers of people who died are only presented if the number exceeds ten cases to guarantee patient anonymity. SMR=standardised mortality ratio. NA=not applicable (no deaths in the population). HIV=human immunodeficiency virus. *Overall mortality risk for the period that cause-specific death data were available (1996–2018).

Table 3: **Cause-specific standardised mortality ratios in transgender women and transgender men compared with general population men and general population women**

general population men and 48% of general population women were former smokers).[28] Furthermore, the transgender population is a very diverse group, not only regarding type of hormone treatment but also regarding non-hormone-related risk factors such as smoking and alcohol use and the use of co-medication.[4,29,30] Because we were not able to study these differences in the present study, future studies should examine and compare mortality risk in subgroups of transgender people to be able to formulate specific prevention recommendations.

Notably, an even higher mortality risk was observed in transgender women than in general population men and women, particularly in the last decade compared with earlier decades. This difference in mortality risk between different decades might be because of differences in comorbidity and lifestyle factors between people who started treatment in earlier years (1970–90) and more recently (2000–18). In the past, health-care providers at our centre were reluctant to provide medical treatment to people with, for example, a known history of cardiovascular disease or hormone-sensitive cancer. Nowadays, comorbidities rarely result in a complete denial or withdrawal of hormone treatment. Because of the change in clinical practice over time, the people in this cohort who started hormone treatment in the early years probably had a better overall health and less comorbidities than did the people who started hormone treatment more recently. This could be an explanation for the higher SMR in people who started treatment in the more recent decades. Although mortality risk was increased in this cohort, this risk does not seem to be caused by hormone treatment itself because increased mortality showed highest risks for non-hormone related causes of death (such as suicide, lung cancer, and HIV-related disease). However, monitoring, optimising, and, if necessary, treating comorbidities, such as cardiovascular disease, tobacco use, and HIV, remain important in health care for the transgender population.

This large, nationwide cohort study consisting of people in a wide age range and with a long follow-up time, provides new insight into the trends in mortality risk in transgender people, which is useful for clinical practice. However, this study has several limitations. First, this is a retrospective study, and although the occurrence and causes of death were well documented, information about treatment regimen, comorbidities, lifestyle, and other risk factors were retrieved from medical files and are therefore incomplete. These lifestyle and other factors might contribute to an increased morbidity and mortality risk in general. We also cannot rule out an effect of other parts of gender-affirming treatment, such as psychological help and surgery. Second, due to the method used to study mortality in this cohort, no information about morbidity was available. Although this was not the aim of this study, knowledge regarding morbidity in transgender people receiving hormone treatment would be interesting because it would provide information on the benefits of hormone

treatment in this population. Third, in transgender men, the number of observed deaths was relatively small. Therefore, doing subgroup analyses on cause-specific deaths was difficult. Fourth, although the included people in this cohort had a wide age range, the population was overall relatively young. Fifth, we were not able to analyse data on transgender youth in this study as the transgender youth population in our cohort is a very diverse group in which people started treatment at different ages and stages of puberty. Moreover, transgender youth included in this cohort were exposed to different durations of puberty blockers before the start of gender-affirming hormone treatment, resulting in the emergence of very small sub-groups. Because of a lot of missing data, we were not able to analyse data from transgender youth in this study. Finally, the results of this study might not be generalisable to people in other global regions, because only people who received treatment in the Netherlands were included. Differences in access to health care but also in other factors (eg, body-mass index ranges) might differ globally, and therefore these data should be interpreted with caution in other regions.

In conclusion, a two-fold increased mortality risk in transgender people was observed. This increased mortality risk did not decrease over time. Increased mortality in this cohort showed highest cause-specific risks for death because of cardiovascular disease (including myocardial infarction), HIV-related disease, lung cancer, and non-natural causes of death (including suicide), most of which were not considered to be related to hormone use. In the coming years, improving the knowledge of health-care providers about the hormone treatment of transgender people is important. Moreover, increasing social acceptance and treatment of cardiovascular risk factors might also contribute to decrease the mortality risk in transgender people.

Contributors

CJMdeB, CMW, DMvanV, ASS, NMN, LJGG, BPCK, and MdenH designed the study. CJMdeB, CMW, DMvanV, ASS, NMN, and MdenH collected and analysed data. CJMdeB, CMW, DMvanV, ASS, NMN, LJGG, BPCK, and MdenH interpreted the data. CJMdeB drafted the manuscript. CJMdeB, CMW, DMvanV, ASS, NMN, LJGG, BPCK, and MdenH revised the content of the manuscript and approved the final version. CJMdeB, CMW, DMvanV, and MdenH verified the underlying data. All authors had full access to all the data in the study and accept responsibility to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

Data will not be shared, because CBS prohibit data sharing at an individual level to guarantee the anonymity of the people in their databases.

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