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Incident Diabetes Risk Is Not Increased in Transgender Individuals Using Hormone Therapy

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Abstract

Context: In trans women receiving hormone therapy, body fat and insulin resistance increases, with opposite effects in trans men. These metabolic alterations may affect the risk of developing type 2 diabetes in trans women and trans men.

Context: We aimed to compare the incidence of type 2 diabetes of adult trans women and trans men during hormone therapy with rates from their birth-assigned sex in the general population.

Methods: Retrospective data from the Amsterdam Cohort of Gender Dysphoria with transgender individuals on hormone therapy between 1972 and 2018 were linked to a nationwide health data registry. Because no central registry of diabetes is available, the occurrence of diabetes was inferred from the first dispense of a glucose-lowering agent. Standardized incidence ratios (SIR) were computed for trans women and trans men in comparison with the same birth sex from the general population.

Results: Compared with their birth-assigned sex in the general population, no difference in the incidence of type 2 diabetes mellitus was observed in trans women (N = 2585, 90 cases; SIR 0.94; 95% CI, 0.76-1.14) or trans men (N = 1514, 32 cases; SIR 1.40; 95% CI, 0.96-1.92).

Conclusion: Despite studies reporting an increase in insulin resistance in feminizing hormone therapy and a decrease in insulin resistance in masculinizing hormone therapy, the incidence of diabetes in transgender individuals after initiation of hormone therapy was not different compared with the general population.

Key Words: diabetes mellitus, transgender endocrine care, hormone therapy

Abbreviations: ACOG, Amsterdam Cohort of Gender Dysphoria; BMI, body mass index; CPA, cyproterone acetate; HOMA-IR, homeostasis model assessment of insulin resistance; HR, hazard ratio; SIR, standardized incidence ratio.

Transgender individuals often receive gender-affirming hormone therapy to induce physical characteristics matching the experienced gender. Trans women (male sex assigned at birth, female gender identity) often receive estrogen with or without anti-androgen therapy to induce feminization, whereas trans men (female sex assigned at birth, male gender identity) often receive testosterone to induce masculinization (1).

Aside from the changes in physical characteristics, such as breast development or hair growth (2, 3), hormone therapy also affects body composition and metabolism. Klaver et al reported an increase in total body fat of 28% in trans women during the first year of hormone therapy, while total body fat decreased by 10% in trans men (4), which is in line with data from a meta-analysis on body composition change in transgender individuals (5). Another study showed changes in insulin sensitivity in transgender individuals during hormone therapy, measured by hyperinsulinemic clamp. A decrease in insulin sensitivity in trans women but no effect in trans men was observed (6). Two larger and more recent studies confirmed the development of insulin resistance in trans women, estimated by homeostatic model assessment of insulin resistance (HOMA-IR), and noted an increase in insulin sensitivity in trans men (7, 8).

Changes in body weight and insulin sensitivity are strongly associated with risk of type 2 diabetes (9, 10). However, whether type 2 diabetes is indeed more frequently present in transgender individuals using hormone therapy compared to adults in the general population is still unknown. Based on the studies above, it may be hypothesized that trans women have a higher risk of type 2 diabetes compared with men in the general population, and that the risk is lower in trans men compared with women in the general population. This would be in line with the currently unexplained increased incidence of cardiovascular disease (11) and cardiovascular related mortality in trans women (12). Given the association of insulin resistance with type 2 diabetes, early recognition and prevention is paramount. If the incidence of type 2 diabetes is indeed increased in trans women, prevention may be especially important in this group, as hormone therapy is generally life-long and started at a young age.

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Therefore, the aim of the current study is to investigate the incidence of type 2 diabetes in a large cohort of adult trans women and trans men during hormone therapy and to compare with the incidence rates of men and women in the general population.

Methods

Study Design and Population

The current study is part of the Amsterdam Cohort of Gender Dysphoria (ACOG), which currently includes all individuals who have visited the gender identity clinic of the Amsterdam University Medical Centre in the Netherlands between 1972 and 2018. The study design and the initially included study population of this cohort have been described in more detail in a previous report (13).

In the present study, we included only adult participants from the ACOG who had started with hormone therapy at 17 years of age or older and had not been using puberty blockers prior to the start of hormone therapy. Only participants with at least one follow-up visit after initiation of hormone therapy were included. Participants were excluded if the starting date of hormone therapy was unknown or if they had been alternating the use of testosterone and estradiol. The study was approved by the Medical Ethics Committee of the Amsterdam University Medical Centre, location VUmc. It was determined that the Medical Research Involving Human Subjects Act (WMO) does not apply to this study, and necessity for informed consent was waived.

As hormone therapy options for transgender individuals have changed over time, the cohort contains several options of treatment modalities. In trans women, hormone therapy consisted of anti-androgens in combination with estrogens. The most commonly prescribed estrogens were estradiol patches (50-150 µg/24 hours twice a week), oral estradiol valerate (2-4 mg daily), or estradiol gel (0.75-1.5 mg daily). In the past (until 2001, 2005, and 2014 respectively), ethinyl estradiol (50-150 µg daily), conjugated estrogens (0.625-2.5 mg daily), and 17-beta estradiol implants (20-40 mg per 3 months), were mostly used. Cyproterone acetate (25-100 mg daily) was most often prescribed as anti-androgen, which was usually ceased after orchiectomy.

In trans men, hormone therapy consisted only of testosterone, administered in the form of either testosterone gel (20-60 mg daily), intramuscular or oral testosterone undecanoate (1000 mg per 12-14 weeks, or 40-240 mg daily, respectively), or intramuscular testosterone esters (250 mg or 125 mg every 2-3 weeks). When over 18 years of age and after at least one year of hormone therapy, transgender individuals were eligible for gender-affirming surgery which includes vaginoplasty with orchiectomy in trans women and hysterectomy with oophorectomy in trans men (hereinafter referred to as gonadectomy).

Nationwide Data Registry

Data from the ACOG was linked to a nationwide data registry (Statistics Netherlands, The Hague, the Netherlands). Using data from the National Civil Record Registry, age-, sex-, and calendar year–specific incidence rates of type 2 diabetes were calculated for both the study cohort and the general Dutch population.

Definition of Type 2 Diabetes

In the Netherlands, data registries recording certain diseases based on international classification of disease-codes are only available for healthcare received in hospital. As type 2 diabetes is generally diagnosed and treated by the general practitioner, no such data registry could be used to identify incident cases of type 2 diabetes. As an alternative, the dispense of medical products was used to identify type 2 diabetes cases. In the Netherlands, the dispense of a medical product by a pharmacy is recorded for all civilians in the National Civil Record Registry. The presence of diabetes was defined as the dispense of all glucose-lowering agents, which were identified by codes A10A and A10B using the Anatomical Therapeutic Chemical (ATC) classification.

A clear distinction between type 2, type 1 diabetes, and gestational diabetes could not be made based on these data. To account for type 1 diabetes in men, all individuals below 35 years of age who had solely received insulin-like products were considered type 1 patients. To account for type 1 diabetes mellitus and gestational diabetes in women, individuals below 50 years of age who had received solely insulin-like products were considered type 1 or cases of gestational diabetes. As the incidences of type 1 diabetes and gestational diabetes above these age thresholds are very low (14), the current definition approximates the incidence of type 2 diabetes in the general population. For a sensitivity analysis, incident cases were identified as the first use of any glucose-lowering product, thus also encompassing type 1 diabetes mellitus and gestational diabetes. *The same criteria were used for both transgender individuals and men and women from the general population throughout this study.*

Data Availability

The registration of medication dispense by Statistics Netherlands was started in 2006. Thus, for the current study data on dispense of medication were available from 2006 to 2018 for the current study. To calculate incidence rates, the exact year of diagnosis had to be known. We defined diabetes as the *first* dispense of a glucose-lowering agent. Data of the year 2006 could not be used, as we were unable to determine if this specific year was the first in which glucose-lowering products were prescribed. Therefore, the observation period in which incidence rates of diabetes could be calculated in both the study and reference population ranges from 2007 to 2018. As the current study could thus only include individuals who were at risk of diabetes during the observation period, individuals who developed diabetes prior to this observation period were excluded.

Data Collection

For the transgender population, information on body mass index (BMI) at the start of hormone therapy, whether gonadectomy had been performed, smoking habits (yes or no), alcohol consumption (units consumed per week), comorbidity, and comedication were retrospectively gathered from medical files. Data on prescribed comedication throughout follow-up were also available from the medication dispensation data provided by Statistics Netherlands. Censoring occurred in case of death or after reaching the end of the study period (end of 2018). Duration of hormone therapy was defined as the time between the starting date of hormone therapy and the development of type 2 diabetes or censoring.

For the general population, only data on a population level, but not individual participant data on the above-mentioned covariates were available. To circumvent this and allow for a comparison of characteristics between the cohort and the general population, age-standardized means of characteristics (smoking, alcohol use, BMI) of the general population were calculated and compared to the age-standardized means from the study cohort (standardized to the Dutch age structure of 2015). Data for the general population were derived from nationwide health surveys in the Netherlands (15, 16).

Statistical Analysis

Calculation of standardized incidence ratios

Using an actuarial life table approach (17), standardized incidence ratios (SIRs) were used to compare the incidence of type 2 diabetes of trans women and trans men with men and women from the general population, respectively. First, age- and sex-specific incidence rates for type 2 diabetes in the adult Dutch population were calculated using the previously defined definition of type 2 diabetes. This was performed by dividing the total number of individuals with incident type 2 diabetes by the total number of individuals at risk at the start of each calendar year (2007 to 2018). The total number of individuals at risk was defined as all individuals alive on January 1 for that current year, minus the number of prevalent type 2 diabetes cases.

Second, the number of expected type 2 diabetes cases in the cohort was calculated by multiplying the age-, sex- and calendar year–specific incidence rates of the general population by the number of individuals within a specific age and sex and calendar year group. Finally, SIRs were calculated by dividing the number of observed cases by the expected cases. The corresponding graph was curtailed at 10% of total remaining observations to avoid interpretation of inconsequential data based on high uncertainty, as suggested by Pocock et al (18).

Transgender individuals were considered at risk from the start of hormone therapy. However, incidence rates could only be determined from 2007 to 2018. Therefore, risk could not be evaluated for individuals who started hormone therapy at an earlier time until their follow-up reached the observation period (2007 to 2018). A period analysis was therefore performed, specifying delayed study entry from 2007 to account only for the years in which an individual was effectively at risk. Through the use of this method, a person who, for example, started hormone therapy in the year 2000, only adds information to the years 7 to 18 in a cumulative probability curve. Each individual thus only contributes information to the years in which the outcome could be observed, avoiding bias that would be introduced if left-truncated data was included in the cumulative probability curve.

The incidence of type 2 diabetes generally rises with increasing age. Analyses were thus repeated in different age categories at start of hormone therapy and calendar years in which hormone therapy was started, to study age and cohort-effects. A sensitivity analysis was performed using the alternate definition of type 2 diabetes, defined as the use of any glucose-lowering product.

Determinants of type 2 diabetes risk in transgender individuals

Characteristics of the transgender population are presented as mean with SD, median with interquartile range (IQR), or percentages. Within the cohort, Cox regression analyses were used to study determinants of type 2 diabetes risk in transgender individuals. Possible determinants of type 2 diabetes risk include effects of age at start of hormone therapy, BMI at start of hormone therapy, smoking, and alcohol consumption. These determinants were analyzed separately for trans women and trans men. Age and BMI at start of hormone therapy were added as covariates, if possible, as they were considered important confounding variables with regard to type 2 diabetes risk. Finally, among individuals with type 2 diabetes, comorbidity, and use of medication at baseline were evaluated. If a certain disease or medication was present in more than 5% of type 2 diabetes cases, the frequency was compared to individuals without type 2 diabetes.

Missing data in the clinical characteristics of the study group (smoking, alcohol use, BMI at start of hormone therapy) were imputed using multiple imputation with predictive mean matching or logistic regression with 50 iterations and 50 imputations.

Statistical analyses were performed using STATA Statistical Software (StataCorp, College Station, TX, USA), version 16, utilizing the *stsres* relative survival add-on package to estimate SIRs (17). For expediency, the control populations are referred to as general population men and general population women. We were unable to verify that none of these people were transgender.

Results

Study Population

The total study population consisted of 8831 individuals. Of the total study population, 3022 transgender individuals were excluded as they did not (yet) start hormone therapy. 574 started hormone therapy below 17 years of age and an additional 294 people were excluded after previously being treated with puberty blockers. Follow-up data were unavailable in 335 individuals and 38 people were excluded for alternately using testosterone and estradiol. Individual data could not be matched with the civil data registry in 261 people. Finally, 208 transgender individuals had either passed away or had been diagnosed with type 2 diabetes prior to the start of the observation period. The final study population consisted of 2585 trans women and 1514 trans men. Figure 1 presents a detailed overview of the final study population selection.

The median age at start of hormone therapy for trans women was 30 (23-41) years and 23 (20-31) years for trans men. The median follow-up period in years from start of hormone therapy until censoring was 11.3 (3.6-22.4) in trans women and 5.2 (2.2-16.4) in trans men. The effective median time under observation (from 2007 until censoring) in years was 9.0 (3.3-12.0) in trans women and 4.9 (2.2-12.0) in trans men. The total number of effective person-years under observation (after 2007) was 20 129 in trans women and 9492 in trans men. During the observation period, 90 trans women and 32 trans men developed type 2 diabetes. The mean age of individuals who developed type 2 diabetes was 55 ± 11 years in trans women and 50 ± 13 years in trans men. Additional characteristics of the study population are shown in Table 1.

Risk of Type 2 Diabetes Compared With the General Population

The cumulative incidence of type 2 diabetes during the observation period (2007 to 2018) in trans women was 4.5

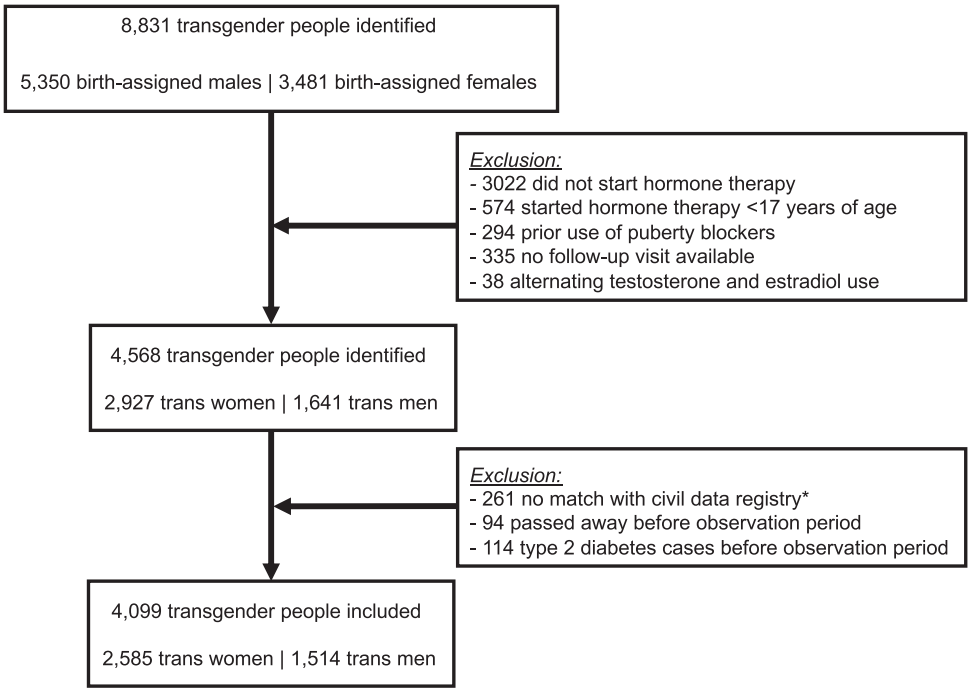

Figure 1. Flow chart of eligible study population. *Not currently living in the Netherlands, erroneous data on personal information needed to link with data registry or migration prior to recording of civil data.

Table 1. Cohort characteristics and estimates from the general population

	Men in the general population	Trans women	Women in the general population	Trans men
Age-standardized characteristics				
Body mass index (kg/m^2)	25.6	24.4	25.0	26.7
Smoking (% yes)	32.2	35.8	24.7	38.9
Median number of cigarettes smoked daily	10	10	9	10
Alcohol use (% yes)	86.4	83.3	76.1	73.3
Median units of alcohol consumed weekly	8	3	4	3
Cohort-specific characteristics		**Trans women** *N = 2585*		**Trans men** *N = 1514*
Age at start hormone therapy (years)		30 (23–41)		23 (20–31)
Age at end of study period (years)		48 (33–58)		32 (24–49)
Median follow-up from 2007 (years)		9.0 (3.2–12.0)		4.9 (2.1–12.0)
Effective person-years at risk from 2007 (years)		20 129		9492
Number of cases (N)		90		32
Gonadectomy (% yes)		63.4		61.4

Data are presented as mean ± SD or median (interquartile range) in case of parametric or nonparametric distributed data, respectively.
Age-standardized characteristics are standardized to the age structure of the Dutch population of 2015.
Characteristics from the general population were derived from a nationwide health survey performed in 2015 by Statistics Netherlands.

per 1000 person-years. This corresponded to a SIR of 0.94 (95% CI, 0.76-1.14). In trans men, the cumulative incidence of type 2 diabetes was 3.4 per 1000 person-years with a SIR of 1.40 (95% CI, 0.96-1.92). The cumulative probability of developing type 2 diabetes during follow-up is displayed in Fig. 2.

Analyses were repeated in different age categories at start of hormone therapy and calendar years in which hormone therapy was initiated, to study age- and cohort-specific effects, but no differences between groups were observed. An overview is presented in Table 2.

Similar overall effects were found using the alternative definition of diabetes mellitus (the use of any glucose-lowering product) in a sensitivity analysis (SIR 0.92 [95% CI, 0.74-1.13] for trans women and SIR 1.38 [95% CI, 0.93-1.91] for trans men).

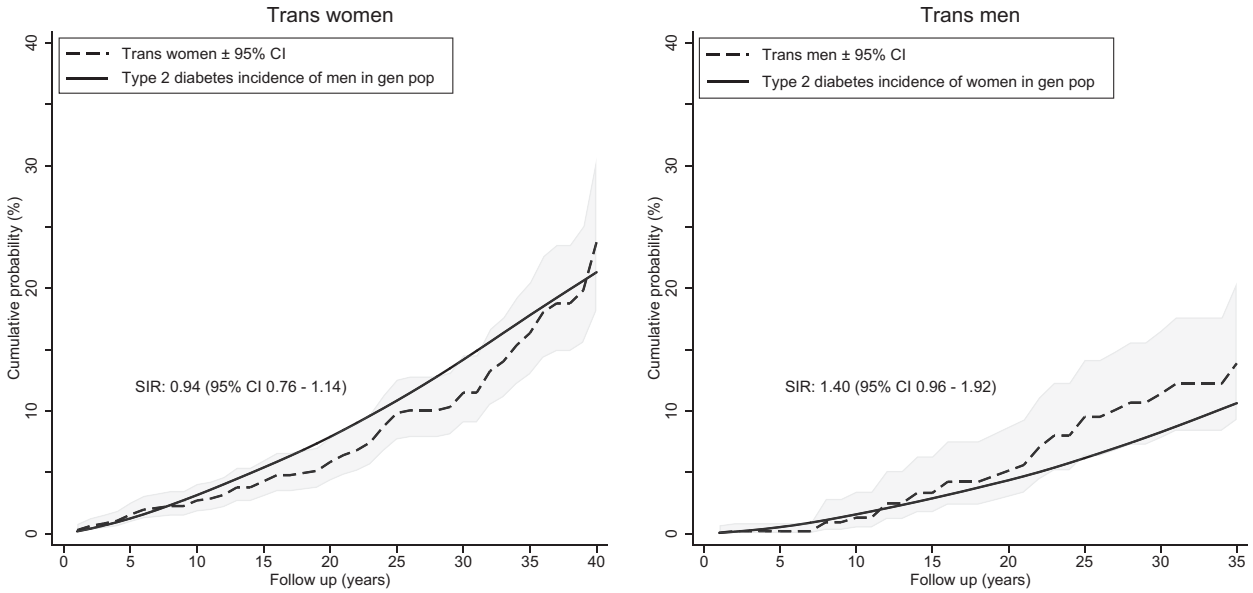

Figure 2. Cumulative probability of type 2 diabetes. For each year of follow-up, the observed cumulative probability was set out against the expected cumulative probability in the general population derived from reference rates of age- sex- and calendar year–matched men or women from the general population.

Table 2. Standardized incidence ratios: age- and cohort-specific effects

	Trans women N = 2585		Trans men N = 1514	
	N cases	SIR ± 95% CI	N cases	SIR ± 95% CI
Overall	90	0.94 (0.76–1.14)	32	1.40 (0.96–1.92)
Age categories at start of HT				
18-30 years old	[a]	1.12 (0.75–1.56)	20	2.00 (1.22–2.96)
30-50 years old	53	1.00 (0.75–1.28)	[a]	0.98 (0.49–1.64)
50 + years old	[a]	0.48 (0.21–0.86)	[a]	0.60 (0.02–2.21)
Decade of start HT				
< 1980	14	1.65 (0.90–2.62)	[a]	3.05 (0.83–6.68)
1980-1990	23	0.90 (0.57–1.30)	11	1.68 (0.84–2.81)
1990-2000	26	0.96 (0.63–1.36)	[a]	1.46 (0.67–2.56)
2000-2010	15	0.59 (0.33–0.93)	[a]	1.03 (0.38–2.00)
2010-2018	12	1.30 (0.67–2.13)	[a]	0.65 (0.08–1.82)

Abbreviations: HT, hormone therapy; SIR, standardized incidence ratio.
[a]Censored to avoid disclosure of cells with < 10 cases; the national data registry prohibits the display of cells with less than 10 observations to avoid disclosure of identity.

Risk Factors for Type 2 Diabetes in the Transgender Population

BMI at start of hormone therapy was an important risk factor for type 2 diabetes in both trans women (hazard ratio [HR] 1.12 [95% CI, 1.06-1.19]), for a 1-point increase in BMI, and trans men (1.09 [95% CI, 1.01-1.18]). The HR associated with a 5-year increase in age was (HR 1.11 [95% CI, 1.01-1.23]) in trans men and (HR 1.10 [95% CI, 0.89-1.36] in trans women). No increased risk was observed for smoking or use of alcohol. Among individuals with type 2 diabetes, there was no frequently prescribed comedication or relevant comorbidity associated with increased diabetes risk present at start of hormone therapy.

Discussion

Due to the decrease in insulin sensitivity in feminizing hormone therapy and an increase in insulin sensitivity in masculinizing hormone therapy, we hypothesized an increase in incident type 2 diabetes in trans women and a decrease in trans men. However, in the present uniquely large cohort study including 4099 transgender individuals, we found no clear differences in the incidence of type 2 diabetes in trans women and trans men after initiation of hormone therapy.

When comparing transgender individuals to men from the general population, type 2 diabetes incidence was not increased in trans women. These reassuring results refute the concerns of increased type 2 diabetes risk in trans women

raised in previous reports. In trans men, the risk of type 2 diabetes tended to be higher (although no statistical difference was observed) compared with women in the general population, which is in contrast to the hypothesized decreased risk due to increases in peripheral insulin sensitivity. This seemingly higher relative risk compared with women was however partly explained by a higher bodyweight at start of hormone therapy in trans men as explained further on.

As incidence rates of type 2 diabetes in transgender individuals did not differ much from rates in the general population, we thus do not recommend routine additional screening for type 2 diabetes mellitus in transgender individuals. With regard to cardiometabolic risk, the current Endocrine Society guideline for transgender care only recommends routine evaluation of cholesterol (1). To add to this, it may still be beneficial to evaluate fasting glucose in older, obese transgender individuals for whom primary care is not readily available. Otherwise, the general focus should remain on counseling overweight patients on the importance of lifestyle management during clinic visits.

Individual participant data from the general population was unavailable in the current study; therefore, our results may be subject to residual confounding. For example, trans women had a lower BMI at the start of hormone therapy compared with men from the general population, while the opposite was true for trans men. Accordingly, this would respectively decrease and increase the risk of type 2 diabetes in trans women and trans men compared to their same birth sex peers from the general population.

Using data from a large meta-analysis (19) and similar point estimates for a 1-point difference in BMI observed in the current study, the magnitude of the effect of BMI differences between transgender individuals and the general population on incident diabetes risk can be estimated. In the current study, a 1-point difference in BMI in trans women was associated with a HR of 1.12 on diabetes risk. Compared to the general population, trans women on average had a 1.2 kg/m^2 lower BMI than men in the general population. This means that if we accounted for differences in BMI between transgender women and men in the general population, we would expect a SIR of 0.90 (e.g., $1.09^{-1.2}$) for trans women. This estimate remains within the 95% CI of the SIR reported for trans women in this study (SIR 0.94; 95% CI, 0.76-1.14) and thus strengthens our belief that hormone therapy does not increase incident diabetes risk in trans women. Using the same method, we would expect a SIR of 1.15 in trans men, based on a 1.7 kg/m^2 difference in BMI between trans men and women in the general population and a HR of 1.09 for a 1-point difference in BMI. This finding also supports our belief that hormone therapy does not affect diabetes risk in trans men (SIR 1.40; 95% CI, 0.96-1.92).

There is evidence that socioeconomic factors, such as lower income and less education, have negative health impact on transgender individuals compared with the general population and that these factors are comparable between trans women and trans men (20). If these factors were significant confounding variables in this current study, we would have expected higher incidence rates of type 2 diabetes in both trans women and trans men. As incidence rates in trans women and men were not different from the general population, we feel that, despite the inability to account for these factors, we can safely conclude that hormone therapy does not increase diabetes risk.

The results of the current study are different from what might be expected based on the studies reporting on large changes in insulin sensitivity in transgender individuals. Although the specific effects of hormone therapy on type 2 diabetes risk could not be fully distinguished in the current study, there are several mechanistic possibilities—aside from the methodological differences between these studies—that may explain the paradoxical finding that feminizing hormone therapy induces insulin resistance but does not increase the risk of type 2 diabetes. First, while HOMA-IR has a good correlation to insulin resistance measured by the gold standard clamp technique (21), it is less informative with regard to β-cell function (which is better estimated by HOMA-B). B-cell dysfunction is a prerequisite for the development of type 2 diabetes, which is illustrated by the fact that most obese individuals do not develop the disease. Treatment with 17β-estradiol in rodents prolongs β-cell survival and activation of the 3 estrogen receptors (ERα, ERβ, and GPER) each have beneficial effects on β-cell function and survival by increasing glucose-stimulated insulin biosynthesis and secretion and by mitigating proapoptotic stimuli (22). These beneficial effects of estrogen may outweigh the decrease in peripheral insulin sensitivity.

Second, there are other factors associated with the development of type 2 diabetes aside from insulin resistance. Metabolic syndrome, for example, is strongly associated with incident diabetes, independent of insulin resistance (23-25). Masculinizing hormone therapy has shown to negatively affect components of the metabolic syndrome, while effects in the opposite direction are reported in feminizing hormone therapy (4, 26). It is possible that these metabolic alterations also affect the long-term type 2 diabetes risk, opposite the direction of—and possibly outweighing—the risk encumbered with the changes in insulin sensitivity after 12 months of hormone therapy.

Finally, and possibly the most likely explanation, is that prior reports on the effects of hormone therapy on insulin sensitivity in transgender individuals have all been performed within the first year of hormone therapy. These studies were performed before gonadectomy and thus trans women were treated with an anti-androgen agent (6, 7). Cyproterone acetate (CPA), a steroid with progestogenic effects, was the anti-androgen agent prescribed in the cited studies. Previous studies have thus been unable to specifically attribute the observed effects on insulin sensitivity to either estrogen or CPA. However, a recent prospective observational study compared metabolic alterations after 5 years of hormone therapy with either CPA or the gonadotropin-releasing hormone (GnRH) analogue leuprolide and found that HOMA-IR increased only in the CPA group (27). While this study was small and there was a baseline difference in HOMA-IR between the CPA and leuprolide group, it is possible that the decrease in insulin sensitivity could be attributed to CPA, rather than estrogen. Although uncertain, a possible mechanism could be through mild activation of the glucocorticoid receptor at higher doses of CPA (28). As most individuals underwent gonadectomy in the current study, the subsequent discontinuation of CPA may be the most likely explanation for the contrasting results between the current study and previous reports on insulin resistance in trans women.

Strengths and Limitations

The main strength of the current study is the large study population and long follow-up duration. As incident cases could only be determined from 2007 to 2018, the analysis was limited to this observation period and individuals with diabetes before this period were excluded. While this did artificially lower the prevalence of diabetes in our cohort, it did not affect the validity of the calculated SIRs, as incident rates were also specifically standardized by calendar year of diagnosis.

This study however is also subject to some limitations. First, the lack of individual patient data from the control group (general population), made it difficult to control for potential confounding variables and separate hormonal effects from differences in lifestyle factors between transgender individuals and men and women from the general population. Another limitation of the study is the definition of type 2 diabetes through the use of glucose-lowering medication. As the first step in management of impaired fasting glucose or early disease is lifestyle management, a portion of individuals with type 2 diabetes in this study were undetected. We are thus unable to compare differences in incidence of mild cases of type 2 diabetes. However, we feel that the grounds to initiate glucose-lowering medication are equal for transgender individuals and the general population and the direct comparison in our study should therefore be unbiased. However, especially younger transgender individuals make hospital visits more frequently than their peers in the general population, possibly leading to an earlier detection of metabolic changes (although glucose levels are not routinely checked in our hospital). Whether this would lead to earlier healthy lifestyle advice or earlier initiation of medical therapy—and how it would affect the study results—is uncertain. Another limitation was the relatively young age of transgender individuals (especially trans men) in the cohort. This led to a lower number of cases, as diabetes generally develops at an older age. Our study results are thus limited to transgender individuals below 70 years of age.

Finally, over 90% of the study population was of white ethnic background and therefore the results are not necessarily applicable to other geographical regions (13).

Conclusion

Despite earlier studies reporting a strong increase in insulin resistance in feminizing hormone therapy and an increase in insulin sensitivity in masculinizing hormone therapy, the incidence of type 2 diabetes in transgender individuals after initiation of hormone therapy was not different compared to the general population. These results are reassuring and suggest that there is no specific reason to increase the frequency of screening of type 2 diabetes in transgender individuals above that of the general population. Earlier studies on the effect of cross-sex hormones on insulin sensitivity might have revealed specific effects of cyproterone acetate rather than effects of estradiol.

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Conflict of Interest

All authors state they have no conflicts of interest.

Disclosures

All authors state they have nothing to disclose.

Data Availability

The data that support the findings of this study are available from the corresponding author and Statistics Netherlands, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Most data are however available from the authors upon reasonable request and with permission of Statistics Netherlands.

References

1. Hembree WC, Cohen-Kettenis PT, Gooren L, *et al*. Endocrine treatment of gender-dysphoric/gender-incongruent persons: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2017;102(11):3869-3903.
2. de Blok CJM, Klaver M, Wiepjes CM, *et al*. Breast development in transwomen after 1 year of cross-sex hormone therapy: results of a prospective multicenter study. *J Clin Endocrinol Metab*. 2018;103(2):532-538.
3. Wierckx K, Van Caenegem E, Schreiner T, *et al*. Cross-sex hormone therapy in trans persons is safe and effective at short-time follow-up: results from the European network for the investigation of gender incongruence. *J Sex Med*. 2014;11(8):1999-2011.
4. Klaver M, de Blok CJM, Wiepjes CM, *et al*. Changes in regional body fat, lean body mass and body shape in trans persons using cross-sex hormonal therapy: results from a multicenter prospective study. *Eur J Endocrinol*. 2018;178(2):165-173.
5. Klaver M, Dekker M, de Mutsert R, Twisk JWR, den Heijer M. Cross-sex hormone therapy in transgender persons affects total body weight, body fat and lean body mass: a meta-analysis. *Andrologia*. 2017;49(5):10.1111/and.12660. doi:10.1111/and.12660
6. Elbers JM, Giltay EJ, Teerlink T, *et al*. Effects of sex steroids on components of the insulin resistance syndrome in transsexual subjects. *Clin Endocrinol*. 2003;58(5):562-571.
7. Shadid S, Abosi-Appeadu K, De Maertelaere AS, *et al*. Effects of gender-affirming hormone therapy on insulin sensitivity and incretin responses in transgender people. *Diabetes Care*. 2020;43(2):411-417.
8. Klaver M, van Velzen D, de Blok C, *et al*. Change in visceral fat and total body fat and the effect on cardiometabolic risk factors during transgender hormone therapy. *J Clin Endocrinol Metab*. 2022;107(1):e153-e164.
9. DeFronzo RA, Ferrannini E, Groop L, *et al*. Type 2 diabetes mellitus. *Nat Rev Dis Primers*. 2015;1:15019. doi:10.1038/nrdp.2015.19
10. Lebovitz HE, Banerji MA. Point: visceral adiposity is causally related to insulin resistance. *Diabetes Care*. 2005;28(9):2322-2325.
11. Nota NM, Wiepjes CM, de Blok CJM, Gooren LJG, Kreukels BPC, den Heijer M. Occurrence of acute cardiovascular events in transgender individuals receiving hormone therapy. *Circulation*. 2019;139(11):1461-1462.

12. de Blok CJM, Wiepjes CM, van Velzen DM, *et al*. Mortality trends over five decades in adult transgender people receiving hormone treatment: results from the Amsterdam cohort of gender dysphoria. *Lancet Diabetes Endocrinol*. 2021;**9**(10):663-670.
13. Wiepjes CM, Nota NM, de Blok CJM, *et al*. The Amsterdam Cohort of gender dysphoria study (1972-2015): trends in prevalence, treatment, and regrets. *J Sex Med*. 2018;15(4):582-590.
14. Thomas NJ, Jones SE, Weedon MN, Shields BM, Oram RA, Hattersley AT. Frequency and phenotype of type 1 diabetes in the first six decades of life: a cross-sectional, genetically stratified survival analysis from UK Biobank. *Lancet Diabetes Endocrinol*. 2018;6(2):122-129.
15. StatisticsNetherlands. *Health Survey as of 2014*. The Hague, 2014, Statistics Netherlands. https://opendata.cbs.nl/statline/#/CBS/nl/dataset/81628NED/table?ts=1641809217540. Updated December 22, 2021. Accessed November 1, 2021.
16. Environment NIoPHa. *NL de Maat Genomen*. Bilthoven, 2012. www.rivm.nl/nldemaat. Updated January 1 2012. Accessed November 1, 2021.
17. Dickman PW, Coviello E. Estimating and modeling relative survival. *Stata J*. 2015;15(1):186-215.
18. Pocock SJ, Clayton TC, Altman DG. Survival plots of time-to-event outcomes in clinical trials: good practice and pitfalls. *Lancet*. 2002;359(9318):1686-1689.
19. Kodama S, Horikawa C, Fujihara K, *et al*. Comparisons of the strength of associations with future type 2 diabetes risk among anthropometric obesity indicators, including waist-to-height ratio: a meta-analysis. *Am J Epidemiol*. 2012;176(11):959-969.
20. Crissman HP, Berger MB, Graham LF, Dalton VK. Transgender demographics: a household probability sample of US Adults, 2014. *Am J Public Health*. 2017;107(2):213-215.
21. Bonora E, Targher G, Alberiche M, *et al*. Homeostasis model assessment closely mirrors the glucose clamp technique in the assessment of insulin sensitivity: studies in subjects with various degrees of glucose tolerance and insulin sensitivity. *Diabetes Care*. 2000;23(1):57-63.
22. Tiano JP, Mauvais-Jarvis F. Importance of oestrogen receptors to preserve functional beta-cell mass in diabetes. *Nat Rev Endocrinol*. 2012;8(6):342-351.
23. Meigs JB, Rutter MK, Sullivan LM, Fox CS, D'Agostino RB Sr. Wilson PW. Impact of insulin resistance on risk of type 2 diabetes and cardiovascular disease in people with metabolic syndrome. *Diabetes Care*. 2007;30(5):1219-1225.
24. Sattar N, McConnachie A, Shaper AG, *et al*. Can metabolic syndrome usefully predict cardiovascular disease and diabetes? Outcome data from two prospective studies. *Lancet*. 2008;371(9628):1927-1935.
25. Ford ES, Li C, Sattar N. Metabolic syndrome and incident diabetes: current state of the evidence. *Diabetes Care*. 2008;31(9):1898-1904.
26. van Velzen DM, Paldino A, Klaver M, *et al*. Cardiometabolic effects of testosterone in transmen and estrogen plus cyproterone acetate in transwomen. *J Clin Endocrinol Metab*. 2019;104(6):1937-1947.
27. Gava G, Mancini I, Alvisi S, Seracchioli R, Meriggiola MC. A comparison of 5-year administration of cyproterone acetate or leuprolide acetate in combination with estradiol in transwomen. *Eur J Endocrinol*. 2020;183(6):561-569.
28. Kuhl H. Pharmacology of estrogens and progestogens: influence of different routes of administration. *Climacteric*. 2005;8(Suppl 1):3-63.