Cureus
Part of SPRINGER NATURE

Open Access Original Article

Hidden in the Hills: Cardiovascular Risk in Transgender Populations in Rural Appalachia

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Review began 07/02/2026
Review ended 11/08/2026
Published 11/11/2026

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DOI: 10.7759/cureus.119487

Abstract

Background: Transgender adults have a higher burden of several cardiovascular risk factors in national surveys. Electronic health record data from rural Central Appalachia, a region with high background cardiometabolic risk, are lacking.

Objective: This study aims to compare the prevalence of cardiovascular risk factors between transgender and cisgender adults receiving care at the same rural Appalachian clinic and to describe patterns by gender identity and by gender-affirming hormone therapy (GAHT).

Materials and methods: We conducted a retrospective cross-sectional study of electronic health record data from an academic outpatient clinic in southern West Virginia. We compared 74 transgender adults with documented gender identity and 69 randomly selected cisgender adults from the same clinic. Outcomes were current tobacco use, current alcohol use, obesity, hypertension, diabetes, prediabetes or diabetes, low-density lipoprotein cholesterol (LDL-C) ⩾100 mg/dL, statin use, and aspirin use. Firth penalized logistic regression was used to estimate adjusted odds ratios (aORs) for age and sex assigned at birth. Sensitivity analyses varied the covariates, age range, and outcome definitions and used multiple imputation for missing data.

Results: Mean age was 30.4 years among transgender adults and 29.9 years among cisgender adults. Current tobacco use was more common among transgender adults (33.8% vs 11.6%, aOR 3.64 (95% CI 1.55-9.28)), and this finding was consistent across all sensitivity analyses. Prediabetes or diabetes was also more common (17.6% vs 4.3%, aOR 3.94 (95% CI 1.20-16.43)), although the estimate was imprecise and did not remain significant after correction for multiple comparisons. Obesity (54.1% vs 53.6%), hypertension, and elevated LDL-C did not differ between the groups. Among transgender adults, obesity was more common in transgender men than in transgender women (68.1% vs 29.6%). In analyses restricted to transgender adults, GAHT was not associated with tobacco, alcohol, or statin use.

Conclusions: In this rural Appalachian clinic, the prevalence of current tobacco use among transgender adults was nearly three times that among cisgender adults, and prediabetes or diabetes was more common, against a high shared prevalence of obesity. These hypothesis-generating findings support guideline-based tobacco cessation treatment and glycemic screening in gender-affirming and primary care.

Categories: Cardiology, Preventive Medicine, Epidemiology/Public Health
Keywords: appalachia, cardiovascular, cisgender, smoking, transgender

Introduction

Cardiovascular disease remains a leading cause of death worldwide, and prevention depends on identifying risk factors early in populations in which they may be missed in routine care [1]. The American Heart Association has called for more systematic cardiovascular risk assessment in transgender and gender-diverse people. It notes that the evidence base is limited and that prevention should address both traditional risk factors and the social conditions that shape access to care [2]. The term "transgender" describes a person whose gender identity differs from the sex assigned at birth. Current psychological, clinical, and endocrine guidance emphasizes respectful care, individualized assessment, and medically indicated gender-affirming treatment [3-5].

An estimated 2.8 million people aged 13 years or older in the United States identify as transgender, including about 2.1 million adults [6]. Population-based surveys have reported a higher prevalence of tobacco use, cardiometabolic disease, and self-reported cardiovascular disease among transgender adults than among

cisgender adults [7-10]. Large clinical cohorts have also raised concern about higher rates of selected cardiovascular events in some transgender subgroups receiving hormone therapy, with risk varying by sex assigned at birth, hormone regimen, duration of exposure, and baseline risk factors [11,12].

Most of the evidence that informs prevention for transgender patients comes from two kinds of studies, and each has important limits. National surveys rely on self-reported diagnoses without laboratory confirmation and cannot describe care within a particular health system [7-10]. Clinic-based studies, such as a large cohort of patients presenting for gender-affirming care at an urban academic center, provide chart-verified data, but they have compared transgender patients with expected or historical risk estimates rather than with a concurrent cisgender comparison group from the same practice [13]. Neither design addresses the question that matters most to a rural clinician: whether transgender patients carry additional, modifiable risks compared with other patients who share the same practice, region, and high background risk.

Rural Central Appalachia makes this question both important and scientifically distinctive. The region has excess heart disease mortality, high rates of smoking and diabetes, and substantial socioeconomic disadvantage compared with the rest of the United States [14], and modifiable risk factors frequently cluster among asymptomatic patients in Central Appalachia [15]. Transgender people in rural areas face further structural barriers, including few knowledgeable clinicians, long travel distances, limited specialty access, concerns about confidentiality in small communities, and prior negative experiences with health systems [16]. Social determinants of health are increasingly recognized as drivers of cardiovascular risk and outcomes [17], and recent cohort work has shown that multidimensional social adversity, assessed in a structured way, is independently associated with mortality in medically complex populations [18]. Minority stress theory also describes how stigma, discrimination, expectation of rejection, and concealment can shape coping behaviors such as smoking and alcohol use, as well as avoidance of preventive care [19-21]. Rural Appalachia therefore combines regional disadvantage, rural barriers to access, and gender-related minority stress. This setting is one in which excess risk among transgender patients may be particularly consequential, and it is a setting where this risk has not been measured.

The objective of this study was to compare the prevalence of cardiovascular risk factors between transgender and cisgender adults receiving care in the same rural Appalachian clinic, using chart-verified diagnoses, medications, and laboratory values. Secondary objectives were to compare transgender men with transgender women and, among transgender adults, to compare those with and without documented GAHT.

This article was previously presented as a meeting abstract at the American Heart Association Scientific Sessions 2023, held November 11-13, 2023, in Philadelphia, Pennsylvania, titled "Cardiovascular Risks Among the Transgender Population in Rural United States: Spotlight on the Appalachian Region." The estimates reported here supersede those in the abstract, which were based on a preliminary analytic sample and outcome definitions.

Materials And Methods

Study design and setting

This retrospective cross-sectional study used electronic health record data from an academic teaching-hospital outpatient clinic in southern West Virginia that provides primary care and gender-affirming care to a predominantly rural Central Appalachian population. Participants were sampled according to gender identity (transgender or cisgender) rather than according to any cardiovascular outcome, and the analysis therefore compares the prevalence of cardiovascular risk factors between groups. The study was approved by the Institutional Review Board of Marshall University (approval number: 1977160-2) and is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline [22].

Study population

All 90 patients on the clinic's list of patients seen for gender-related care were screened. Patients were eligible if the medical record documented a gender identity different from the sex assigned at birth, or a diagnosis of gender dysphoria or gender incongruence, and if they were 18 years of age or older at the time of data abstraction. Records with no documentation of transgender identity or gender incongruence (n = 11) were excluded, as were one duplicate record and four patients younger than 18 years. The comparison group comprised 69 cisgender adults randomly selected from the list of patients who attended the same clinic, without individual matching. The final analytic sample consisted of 74 transgender and 69 cisgender adults.

Data collection

Data were abstracted between November and December 2022 by trained abstractors using a standardized worksheet with written variable definitions, and the same worksheet and definitions were applied to both groups. Because the study had no single index date, each variable represents the most recent status documented in the record at the time of abstraction. For laboratory measures, the most recent value recorded between 2017 and 2022 was abstracted. Information was collected on demographic characteristics, family history of coronary artery disease (CAD), prevalent atherosclerotic cardiovascular disease (ASCVD,

comprising angina, acute coronary syndrome, peripheral artery disease, stroke, or transient ischemic attack), venous thromboembolism, tobacco and alcohol use, body mass index (BMI), blood pressure, diagnoses, current medications, the lipid panel, and glycated hemoglobin (HbA1c). For transgender participants, documented gender-affirming hormone therapy (GAHT), including type, route, and age at initiation, and any gender-affirming surgery were also recorded. The hormone dose was not consistently documented and was not abstracted.

Exposure

The primary exposure was transgender status, defined as a documented gender identity that differed from the sex assigned at birth or a documented diagnosis of gender dysphoria or gender incongruence. Cisgender participants formed the reference group. Two secondary exposures were examined among transgender participants only. The first was gender identity (transgender men compared with transgender women), and the second was documented GAHT, defined as any recorded use of testosterone- or estradiol-based therapy, compared with no recorded use. GAHT duration was calculated as the difference between age at abstraction and age at initiation.

Outcomes

Nine cardiovascular risk factors were examined as binary outcomes. Tobacco use and alcohol use were each recorded as current, former, or never, and current use was analyzed for both. The quantity of use (e.g., packs per day or drinks per day) was not recorded. Because the option to record former tobacco use was available on the abstraction worksheet for transgender participants but not for comparison participants, ever use (current or former) was analyzed only in a sensitivity analysis. Obesity was defined as a BMI greater than 30 kg/m^2 [23]. Hypertension was defined as a blood pressure above 140/90 mm Hg or the use of antihypertensive medication, a threshold more conservative than the 2017 American College of Cardiology/American Heart Association definition of stage 1 hypertension [24]. Diabetes was defined as an HbA1c of 6.5% or higher or the use of glucose-lowering medication [25]. A composite outcome of prediabetes or diabetes was defined as diabetes or an HbA1c ⩾5.7% [25], and participants without an HbA1c measurement were classified based on diabetes status alone. HbA1c was additionally categorized as below 5.7%, 5.7% to 6.4%, or 6.5% or higher among participants with a measurement. A low-density lipoprotein cholesterol (LDL-C) ⩾100 mg/dL was classified as above optimal [26]. Statin and aspirin use were ascertained from the medication list, and statin use was analyzed separately from LDL-C because treatment lowers measured LDL-C.

Covariates

Age was calculated in years at the time of abstraction and was modeled as a continuous linear term. Sex assigned at birth (female or male) and current gender identity (man or woman) were obtained from the demographic and clinical documentation, and no participant had a nonbinary identity recorded. Race was obtained from the demographic field and categorized as White, Black, or not recorded. Family history of CAD was obtained from the family history section and coded as present or absent.

Confounders were selected on substantive grounds using a causal framework, as factors plausibly associated with both transgender status and the outcomes that are not consequences of transgender status. Models comparing transgender with cisgender participants were adjusted for age and sex assigned at birth, both of which are determinants of the outcomes and differed in distribution between the groups. Current gender identity was not included because it is defined in part by the exposure. Gender-affirming treatment, other cardiovascular risk factors, and behaviors that may be shaped by minority stress were not included because they may lie on the causal pathway between transgender status and the outcomes, and adjustment for them would yield an estimate of a direct rather than a total association. Family history of CAD predicts several outcomes but cannot plausibly influence gender identity, so it was examined only in a sensitivity analysis. Race was not included because 72 of the 74 transgender participants were White, and race was not recorded for 32 comparison participants. Within the transgender group, sex assigned at birth is determined by gender identity, so the comparison of transgender men with transgender women was adjusted for age only, and the comparison by GAHT status was adjusted for age and sex assigned at birth.

Statistical analysis

Continuous variables were summarized as means with standard deviations (SDs) or medians with interquartile ranges (IQRs) for skewed distributions, and categorical variables as counts and percentages of participants with nonmissing data. Between-group differences in proportions were expressed as prevalence differences (%) with Newcombe hybrid score 95% confidence intervals (CIs). Categorical variables were compared using the Pearson chi-square test or Fisher's exact test when any expected cell count was below 5. Continuous variables were compared using the Welch t-test, which does not assume equal variances, or the Wilcoxon rank-sum test for skewed variables.

Each outcome was modeled in a separate logistic regression. Because several outcomes had few events, models were estimated using Firth penalized likelihood, which reduces small-sample bias in maximum likelihood estimates and yields finite estimates under sparse data or separation [27,28]. Odds ratios (ORs) are

reported with 95% CIs based on the profile penalized likelihood, and p-values were obtained from penalized likelihood ratio tests. ORs were interpreted as the ratio of the odds of each risk factor in the exposed group to the odds in the reference group. Because the OR overstates the prevalence ratio when an outcome is common, crude prevalence ratios and prevalence differences are also reported. Adjusted models were fitted only when the less frequent outcome category contained at least 10 participants; unadjusted estimates alone are reported when it contained five to nine participants, and outcomes with fewer than five events were described without modeling.

The primary analysis was restricted to participants with complete data for the variables in each model. The extent of missing data was described for each variable, and logistic regression was used to examine whether the absence of LDL-C or HbA1c measurements was associated with group, age, sex assigned at birth, obesity, hypertension, or tobacco use. Multiple imputation by chained equations (50 imputations) was then performed for LDL-C, HbA1c category among participants without diabetes, and family history of CAD, using imputation models that included group, age, sex assigned at birth, obesity, hypertension, tobacco use, diabetes, and statin use. Estimates were combined using Rubin's rules [29].

Further sensitivity analyses of the transgender versus cisgender comparison added family history of CAD to the adjusted models, used conventional maximum likelihood logistic regression, included the four adolescents with documented transgender identity, restricted both groups to the shared age range of 18 to 40 years, analyzed ever tobacco use in place of current use, and restricted the prediabetes or diabetes outcome to participants with a measured HbA1c. Because multiple outcomes were examined, Holm-adjusted p-values are reported for the seven adjusted transgender versus cisgender comparisons in addition to unadjusted p-values. Two-sided p-values below 0.05 were considered statistically significant. Analyses were performed in R version 4.4.2 (R Core Team, Vienna, Austria).

Results

Participant characteristics

Of the 90 patients screened, 16 were excluded, and the analytic sample comprised 74 transgender and 69 cisgender adults (Figure *1*). Characteristics of the two groups are presented in Table *1*. Mean age was 30.4 years (SD 11.5) among transgender participants and 29.9 years (SD 6.7) among cisgender participants (p = 0.73), with ranges of 18-66 and 18-40 years, respectively. Ten transgender participants were older than 40 years. The proportion assigned female at birth was 63.5% among transgender participants and 73.9% among cisgender participants (p = 0.18). Of the transgender participants, 47 (63.5%) identified as men and 27 (36.5%) as women. Family history of CAD was recorded for 15.3% of transgender and 29.7% of cisgender participants (p = 0.04), and no participant in either group had prevalent ASCVD.

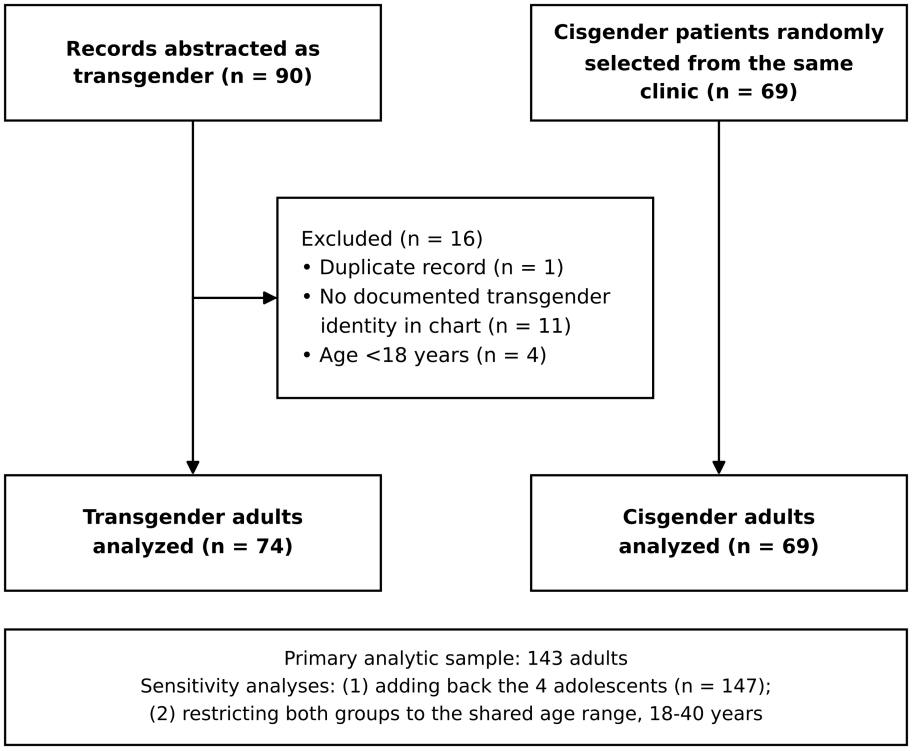


FIGURE 1: Percent prevalence of cardiovascular risk factors among transgender and cisgender participants

Bars represent percentages, and labels show n/N (%) for each group. Denominators vary because of missing values and are listed in Table 1. The figure is descriptive; corresponding bivariate tests are shown in Table 1. A two-sided $p < 0.05$ was considered statistically significant for inferential comparisons.

Variable		Transgender	Cisgender	Test statistic	p-value
Age, years, mean (SD) (n = 158)		29.19 (11.83)	29.86 (6.74)	-0.42	0.6776
LDL-C, mg/dL, mean (SD) (n = 109)		105.8 (37.48)	108.2 (31.32)	-0.36	0.7223
Sex assigned at birth (n = 158)	Female	56 (62.9%)	51 (73.9%)	2.15	0.1427
	Male	33 (37.1%)	18 (26.1%)		
Gender identity (n = 158)	Woman	33 (37.1%)	51 (73.9%)	21.18	<0.0001
	Man	56 (62.9%)	18 (26.1%)		
Hypertension (n = 147)	No	65 (83.3%)	58 (84.1%)	0.01	0.9056
	Yes	13 (16.7%)	11 (15.9%)		
Current tobacco use (n = 147)	No	46 (59.0%)	61 (88.4%)	13.83	0.0002
	Yes	32 (41.0%)	8 (11.6%)		
Current alcohol use (n = 147)	No	70 (89.7%)	68 (98.6%)	3.08	0.0793
	Yes	8 (10.3%)	1 (1.5%)		
Obesity (n = 147)	No	37 (47.4%)	32 (46.4%)	0.02	0.898
	Yes	41 (52.6%)	37 (53.6%)		
Prediabetes/diabetes composite (n = 148)	No diabetes/normal HbA1c	66 (83.5%)	66 (95.7%)	4.65	0.031
	Diabetes diagnosis, diabetes medication use, or HbA1c ≥5.7%	13 (16.5%)	3 (4.4%)		
Statin use (n = 145)	No	64 (84.2%)	65 (94.2%)	3.68	0.0551
	Yes	12 (15.8%)	4 (5.8%)		
Aspirin use (n = 146)	No	75 (97.4%)	67 (97.1%)	0.01	0.9114
	Yes	2 (2.6%)	2 (2.9%)		
LDL-C status (n = 109)	High (≥100 mg/dL)	32 (55.2%)	34 (66.7%)	1.5	0.2205
	Normal	26 (44.8%)	17 (33.3%)		
Family history of CAD (n = 140)	No	64 (84.2%)	45 (70.3%)	3.88	0.049
	Yes	12 (15.8%)	19 (29.7%)		

TABLE 1: Baseline characteristics of transgender and cisgender participants

Data are presented as n (%) unless otherwise indicated. Continuous variables are reported as mean (SD). Percentages use the available nonmissing denominator within each group. The test statistic column reports the t-statistic for continuous variables and the chi-square statistic for categorical variables. P-values were calculated using two-sample t-tests for continuous variables and chi-square tests for categorical variables. Two-sided $p < 0.05$ was considered statistically significant.

LDL-C: low-density lipoprotein cholesterol, HbA1c: glycated hemoglobin, CAD: coronary artery disease, SD: standard deviation

GAHT was documented for 58 of the 72 transgender participants with known treatment status (80.6%), and treatment status was unknown for two. All 36 transgender men receiving GAHT used testosterone, and all 21 transgender women receiving GAHT used estradiol-based regimens. The route of administration was intramuscular for 32 participants, oral for 12, subcutaneous for eight, and topical for four. Among the 48 participants with a recorded age at initiation, the median duration of GAHT was four years (IQR 2-6). Ten transgender participants (13.5%) had undergone gender-affirming surgery, nine of whom also had documented GAHT.

Missing data

Race was not recorded for 32 cisgender participants. Other demographic, behavioral, diagnostic, and medication variables had no more than five missing values each (Table *1*). LDL-C was unavailable for 17 transgender and 18 cisgender participants (24% overall), and HbA1c for 41 and 35 participants, respectively (53% overall). The proportion with a measured value did not differ between groups for LDL-C (p = 0.67) or HbA1c (p = 0.58). In multivariable models, the absence of an LDL-C measurement was not associated with group, age, sex assigned at birth, obesity, hypertension, or tobacco use. Participants with obesity had higher odds of having an HbA1c measurement; this association was of borderline statistical significance (OR 2.08 (95% CI 1.00-4.32), p = 0.050).

Transgender compared with cisgender adults

The prevalence of current tobacco use was 33.8% among transgender adults and 11.6% among cisgender adults, a prevalence difference of 22.2% (95% CI 8.5% to 34.8%) and a crude prevalence ratio of 2.91 (Table *1*, Figure *2*). After adjustment for age and sex assigned at birth, the odds of current tobacco use were higher among transgender adults (aOR 3.64 (95% CI 1.55-9.28), p = 0.003), and the association remained statistically significant after Holm correction (p = 0.02, Table *2*).

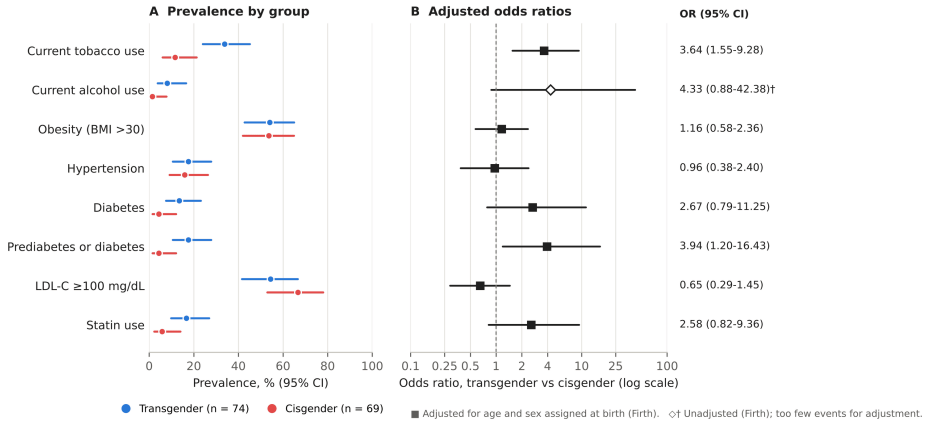


FIGURE 2: Prevalence by groups

OR: odds ratio, CI: confidence interval

Cardiovascular risk factor	Unadjusted OR	Unadjusted 95% CI	Unadjusted test statistic	Unadjusted p-value	Adjusted OR	Adjusted 95% CI	Adjusted test statistic	Adjusted p-value
Current tobacco use	5.3	2.24-12.58	13.83	0.0002	6.64	2.59-17.01	13.83	0.0002
Hypertension	1.06	0.40-2.54	0.01	0.91	0.95	0.38-2.39	0.01	0.92
Current alcohol use	7.77	0.95-63.80	3.65	0.056	7.07	0.84-59.22	3.28	0.07
Obesity	0.96	0.50-1.83	0.02	0.9	1.02	0.52-2.01	0	0.95
Diabetes diagnosis	3.24	0.85-12.28	2.87	0.09	2.9	0.74-11.37	2.29	0.13
Diabetes diagnosis, diabetes medication use, or HbA1c ≥5.7%	4.33	1.18-15.92	4.71	0.03	3.98	1.05-15.15	4.1	0.043
LDL-C ≥100 mg/dL	0.62	0.28-1.34	1.5	0.22	0.61	0.28-1.33	1.57	0.21
Aspirin use	0.89	0.12-6.52	0.01	0.91	0.02	0.01-9.84	0.02	0.88
Statin use	3.05	0.93-9.95	3.28	0.07	2.64	0.76-9.10	2.42	0.12

TABLE 2: Logistic regression models comparing transgender and cisgender participants

Each row represents a separate logistic regression model with the listed cardiovascular risk factor as the dependent variable and transgender status (transgender vs cisgender) as the predictor. The test statistic columns report Wald chi-square statistics. Adjusted models included age and family history of ASCVD. Two-sided p < 0.05 was considered statistically significant.

OR: odds ratio, CI: confidence interval, HbA1c: glycated hemoglobin, LDL-C: low-density lipoprotein cholesterol, ASCVD: atherosclerotic cardiovascular disease

The prevalence of prediabetes or diabetes was 17.6% among transgender adults and 4.3% among cisgender adults, a prevalence difference of 13.2% (95% CI 2.8% to 23.8%). The adjusted odds were higher among transgender adults (aOR 3.94 (95% CI 1.20-16.43), p = 0.02), but the association was not statistically significant after Holm correction (p = 0.14). Among participants with a measured HbA1c, values below 5.7%, between 5.7% and 6.4%, and at least 6.5% were observed in 20, 4, and 9 of 33 transgender participants and in 31, 0, and 3 of 34 cisgender participants. Of the 10 transgender adults with diabetes, eight met the HbA1c criterion, and two were classified based on glucose-lowering medication, with HbA1c values between 5.7% and 6.4%. One additional transgender participant had an HbA1c of 6.5% or higher without a documented diagnosis or treatment. All three cisgender adults with diabetes met the HbA1c criterion. The prevalence of diabetes alone was 13.5% and 4.3%, respectively, and the adjusted odds did not differ significantly (aOR 2.67 (95% CI 0.79-11.25)).

The prevalence of obesity was 54.1% among transgender adults and 53.6% among cisgender adults (aOR 1.16 (95% CI 0.58-2.36)). No statistically significant differences were observed for hypertension (17.6% and 15.9%, aOR 0.96 (95% CI 0.38-2.40)) or LDL-C of 100 mg/dL or higher (54.4% and 66.7%, aOR 0.65 (95% CI 0.29-1.45)). Mean HDL cholesterol was 46.8 mg/dL among transgender adults and 53.0 mg/dL among cisgender adults (p = 0.04). Statin use was more prevalent among transgender adults (16.7% vs 5.8%, p = 0.04), but the adjusted association was not statistically significant (aOR 2.58 (95% CI 0.82-9.36)). Current alcohol use was reported by 8.1% of transgender and 1.4% of cisgender adults (Fisher exact p = 0.12, unadjusted OR 4.33 (95% CI 0.88-42.38)). Aspirin use was recorded for two participants in each group and was not modeled.

Transgender men compared with transgender women

Within the transgender group, the prevalence of obesity was 68.1% among transgender men and 29.6% among transgender women, a prevalence difference of 38.5% and a crude prevalence ratio of 2.30. After adjustment for age, the odds of obesity were higher among transgender men (aOR 11.28 (95% CI 3.29-49.81), p < 0.001, Table 3). An LDL-C of 100 mg/dL or higher was observed in 63.9% of transgender men with a measurement and 38.1% of transgender women (crude prevalence ratio 1.68, aOR 3.17 (95% CI 1.01-10.85), p = 0.048). No statistically significant differences between transgender men and transgender women were observed for current tobacco use, hypertension, diabetes, prediabetes or diabetes, or statin use.

Cardiovascular risk factor	Unadjusted OR	Unadjusted 95% CI	Unadjusted test statistic	Unadjusted p-value	Adjusted OR	Adjusted 95% CI	Adjusted test statistic	Adjusted p-value
Current tobacco use	0.45	0.17-1.15	2.87	0.09	0.78	0.26-2.27	0.22	0.64
Hypertension	0.6	0.18-1.99	0.71	0.4	0.91	0.24-3.52	0.02	0.89
Current alcohol use	0.52	0.12-2.27	0.74	0.39	0.84	0.16-4.43	0.04	0.84
Obesity	4.85	1.77-13.29	9.55	0.002	13.39	3.30-54.30	6.97	0.0083
Diabetes diagnosis	0.51	0.13-1.95	0.95	0.33	0.84	0.19-3.77	0.06	0.81
Diabetes diagnosis, diabetes medication use, or HbA1c ≥5.7%	0.88	0.26-2.99	0.05	0.83	2.16	0.46-10.20	0.95	0.33
LDL-C ≥100 mg/dL	3	1.00-9.01	3.78	0.052	3.46	1.03-11.59	4.02	0.045
Statin use	0.73	0.21-2.58	0.23	0.63	2.11	0.41-10.81	0.8	0.37

TABLE 3: Logistic regression models among transgender participants: transgender men compared with transgender women

Each row represents a separate logistic regression model among transgender participants, with transgender man versus transgender woman as the predictor. The test statistic columns report Wald chi-square statistics. Adjusted models included age and family history of ASCVD. Two-sided $p < 0.05$ was considered statistically significant.

OR: odds ratio, CI: confidence interval, HbA1c: glycated hemoglobin, LDL-C: low-density lipoprotein cholesterol, ASCVD: atherosclerotic cardiovascular disease

Gender-affirming hormone therapy

Among the 72 transgender adults with known treatment status, 58 had documented GAHT, and 14 (nine men and five women) did not (Table *4*). Current tobacco use was recorded for 39.7% of participants receiving GAHT and 14.3% of those not receiving GAHT, and the adjusted association was not statistically significant (aOR 2.39 (95% CI 0.61-13.33)). Current alcohol use (10.3% and 0.0%) and statin use (21.1% and 0.0%, aOR 4.79 (95% CI 0.51-638.16)) did not differ significantly by GAHT status. Obesity was present in 36 of 58 (62.1%) participants receiving GAHT and three of 14 (21.4%) participants not receiving GAHT (crude prevalence ratio 2.90, aOR 5.21 (95% CI 1.33-25.37)). Gender-affirming surgery was recorded for 10 participants, and outcome prevalences by surgery status are reported in the footnote to Table *4*.

Cardiovascular risk factor	Unadjusted OR	Unadjusted 95% CI	Unadjusted test statistic	Unadjusted p-value	Adjusted OR	Adjusted 95% CI	Adjusted test statistic	Adjusted p-value
Current tobacco use	6.77	3.00-15.24	21.28	<0.0001	6.69	2.80-15.98	18.3	<0.0001
Hypertension	1.08	0.44-2.62	0.03	0.87	0.78	0.30-2.06	0.25	0.62
Current alcohol use	13.65	1.66-112.27	5.92	0.015	11.31	1.34-95.53	4.71	0.03
Obesity	1.93	0.98-3.78	3.54	0.06	1.75	0.87-3.52	2.42	0.12
Diabetes diagnosis, diabetes medication use, or HbA1c ≥5.7%	1.84	0.59-5.78	1.07	0.3	1.3	0.38-4.50	0.18	0.67
HbA1c ≥5.7%	2.79	0.96-8.15	3.74	0.053	2	0.63-6.30	1.38	0.24
LDL-C ≥100 mg/dL	0.53	0.24-1.16	2.55	0.11	0.51	0.23-1.12	2.87	0.09
Aspirin use	1.54	0.21-11.22	0.18	0.67	0.1	0.001-6.37	1.22	0.27
Statin use	5.41	1.65-17.75	7.88	0.005	3.97	1.14-13.81	4.71	0.03

TABLE 4: Logistic regression models comparing participants with and without documented gender-affirming surgery and/or hormone treatment

Each row represents a separate logistic regression model with documented gender-affirming surgery and/or hormone treatment versus no such documentation as the predictor. The test statistic columns report Wald chi-square statistics. Adjusted models included age and family history of ASCVD. Two-sided $p < 0.05$ was considered statistically significant.

OR: odds ratio, CI: confidence interval, HbA1c: glycated hemoglobin, LDL-C: low-density lipoprotein cholesterol, ASCVD: atherosclerotic cardiovascular disease

Sensitivity analyses

Across the sensitivity analyses, aORs for current tobacco use ranged from 3.47 to 3.90, and all 95% CIs excluded one. The aOR for prediabetes or diabetes was 6.22 (95% CI 1.64-30.32) when the analysis was restricted to participants with a measured HbA1c (39.4% and 8.8%), 5.93 (95% CI 1.05-33.47) after multiple imputation of missing HbA1c values, and 8.60 (95% CI 2.12-44.71) when both groups were restricted to ages 18 to 40 years (64 transgender and 69 cisgender participants). In the age-restricted sample, the adjusted odds of diabetes (aOR 6.68 (95% CI 1.65-33.87)) and statin use (aOR 5.58 (95% CI 1.43-25.95)) were also higher among transgender adults. The aOR for ever tobacco use was 5.80 (95% CI 2.44-15.17). Associations for obesity, hypertension, and LDL-C were not statistically significant in any sensitivity analysis.

Discussion

In this rural Appalachian clinic, the prevalence of current tobacco use among transgender adults was nearly three times that among cisgender adults from the same practice, and the association was robust to every analytic approach we examined. Transgender adults were also more likely to have prediabetes or diabetes. That estimate was imprecise and did not survive correction for multiple comparisons, but its direction was consistent across all sensitivity analyses. In contrast, obesity affected more than half of both groups, and hypertension and elevated LDL-C did not differ. Taken together, these findings suggest that transgender patients in this setting carry excess risk in specific and modifiable areas, namely tobacco use and glycemia, on top of a high cardiometabolic burden that they share with their cisgender neighbors.

This study adds to the literature in three ways. To our knowledge, it is the first clinic-based comparison from rural Central Appalachia, a region with high background cardiovascular risk and structural barriers to care [14-16]. Its comparison group came from the same clinic over the same calendar period, so the contrast is not confounded by differences in health system, geography, or era, and it asks whether transgender status adds risk beyond the regional baseline. Previous clinic-based work compared transgender patients with expected or historical risk [13], and national surveys rely on self-report [7-10]. Finally, outcomes in this study were based on chart-verified diagnoses, medication lists, and laboratory values, and the analysis used methods suited to sparse data, along with a broad set of sensitivity analyses.

The tobacco findings agree with national data. Analyses of the Population Assessment of Tobacco and Health Study and the Behavioral Risk Factor Surveillance System have shown that transgender and gender diverse adults are more likely than cisgender adults to use nicotine and tobacco [30,31]. The prevalence difference in our sample was large, at 22%. Tobacco cessation is among the most effective cardiovascular prevention measures available in primary care, and the regular visits that accompany gender-affirming care

offer repeated opportunities to provide it. Higher tobacco use among transgender people is consistent with minority stress models, which link stigma and discrimination to substance use as a coping mechanism [19-21]. It is also consistent with the broader social determinants that shape cardiovascular risk [17,18]. Our data did not include measures of stigma, mental health, income, insurance, or other forms of social adversity, so we could not examine these pathways. Future studies in Appalachia should measure social determinants with structured instruments rather than inferring them from clinical notes.

Current alcohol use was more frequent among transgender adults (8.1% compared with 1.4%), but it was too uncommon to allow a precise or adjusted estimate. Larger studies have found a higher prevalence of alcohol use disorder diagnoses and alcohol-related problems among transgender adults [32,33]. A systematic review has noted that alcohol use is measured inconsistently in this population [34], and the simple yes or no measure available in our records shares that limitation.

The higher prevalence of prediabetes or diabetes among transgender adults is clinically relevant because six of the 13 affected transgender adults were younger than 35 years, the age at which the US Preventive Services Task Force (USPSTF) begins to recommend routine screening for adults with overweight or obesity [35]. The estimate was imprecise, and HbA1c had been measured in fewer than half of the participants. However, the association became stronger rather than weaker when we restricted the analysis to participants with a measured HbA1c and when we imputed missing values. This suggests that incomplete testing is more likely to have hidden a difference than to have created one. Reviews of sex steroid exposure describe mixed effects on insulin sensitivity and body composition [36-38], and we found no association between GAHT and dysglycemia among transgender adults. Shared behavioral and social risk factors are at least as plausible an explanation as hormone exposure.

Within the transgender group, transgender men had a higher prevalence of obesity and of elevated LDL-C than transgender women. These patterns are consistent with prospective studies showing that testosterone- and estradiol-based regimens lead to different changes in body composition, fat distribution, and lipid levels [39,40], and with the higher prevalence of obesity among GAHT users in our sample. However, gender identity, sex assigned at birth, and hormone type cannot be separated in these data. The OR for obesity is large mainly because obesity was common and the subgroups were small, and the prevalence ratio of 2.30 gives a more realistic sense of the difference. Differences in body composition between transgender and cisgender youth suggest that some of these patterns may be present before GAHT is started [41].

The findings on GAHT should be interpreted narrowly. When the analysis was restricted to transgender adults, GAHT was not associated with tobacco, alcohol, or statin use. Such associations appear only when cisgender participants are included in the untreated group, because treatment status then largely reflects transgender status. The association between GAHT and obesity rests on 14 untreated participants, only three of whom had obesity. It may reflect reverse causation, longer engagement in care, more frequent measurement of weight, or confounding by unmeasured factors rather than an effect of hormones. None of the associations reported here should be interpreted as evidence that gender-affirming care causes cardiovascular risk. These data also cannot address cardiovascular events, which require long-term cohort studies that account for regimen, dose, and duration [11,12].

Clinical implications

These findings support consistent use of existing, guideline-based prevention in gender-affirming and primary care. They do not support withholding or delaying gender-affirming treatment [2,4,5]. Clinicians should ask every adult about tobacco use at each visit, advise those who use tobacco to quit, and offer behavioral support combined with pharmacotherapy approved by the US Food and Drug Administration, which is a grade A recommendation of the USPSTF [42]. Blood pressure should be measured in all adults, and the diagnosis of hypertension should be confirmed with readings taken outside the clinic [43]. Diabetes testing is recommended for adults of any age with overweight or obesity who have at least one additional risk factor, and for all adults aged 35 years or older, with repeat testing at least every three years when results are normal and every year for people with prediabetes [25]. The USPSTF recommends screening adults aged 35 to 70 years who have overweight or obesity [35]. For adults aged 20 to 39 years, traditional risk factors, including a lipid profile, should be assessed every four to six years. Beginning at age 40 years, the 10-year ASCVD risk should be estimated to guide decisions about statin therapy [26,44,45]. Adults should also be screened for unhealthy alcohol use and offered brief counseling when indicated [46]. In rural Appalachian clinics, delivering these services may require standardized prevention checklists within gender-affirming visits, telehealth support for tobacco cessation, and careful attention to confidentiality and trust [16].

Strengths and limitations

The strengths of this study include a comparison group drawn from the same clinic over the same period, chart-verified outcomes, transparent reporting of missing data, statistical methods suited to sparse data, and consistent results across sensitivity analyses. The study also has important limitations. The sample was small and came from a single center, so the estimates are imprecise, particularly for subgroup analyses and rare outcomes, and some outcomes could not be adjusted or modeled at all. The findings should therefore be

considered hypothesis-generating. Both groups were drawn from patients who reached care, and transgender people who cannot access gender-affirming care may differ from those studied. The random selection of comparison participants was not documented beyond the use of the clinic patient list. Records excluded for lacking documentation of transgender identity may have included transgender patients whose identity was not recorded.

Residual confounding by socioeconomic status, insurance, rurality, mental health, and minority stress is likely, because these factors were not recorded. Tobacco and alcohol use were recorded without quantity, so we could not assess pack-years or drinking intensity, and former use was recorded differently for the two groups. Current use was therefore the primary outcome, and the estimate for ever use is likely biased away from the null. Laboratory values were missing for 24% of participants for LDL-C and 53% for HbA1c, and HbA1c was more often measured in participants with obesity, which suggests that testing followed clinical indication. Because the composite outcome treats an unmeasured HbA1c as normal, it probably underestimates the prevalence of prediabetes or diabetes in both groups. Comparison participants were aged 18 to 40 years, whereas some transgender participants were older, which is why we performed an age-restricted sensitivity analysis. GAHT dose and adherence were not recorded, and because the study had no single index date, the order in which GAHT, laboratory testing, and risk factors occurred could not be established. Race was missing for nearly half of the comparison participants, and the sample consisted predominantly of White participants, which limits generalizability. Finally, we examined several outcomes without a single prespecified primary hypothesis, so isolated nominally significant results should be interpreted with caution.

Conclusions

Among adults receiving care at the same rural Appalachian clinic, the prevalence of current tobacco use among transgender patients was nearly three times that among cisgender patients, and prediabetes or diabetes was more common, while obesity was common in both groups. Within the transgender group, transgender men had more obesity and elevated LDL-C than transgender women. GAHT was not associated with tobacco, alcohol, or statin use once the analysis was restricted to transgender adults. These findings support integrating guideline-based tobacco cessation treatment, glycemic screening, and ASCVD risk assessment into gender-affirming and primary care in rural settings. Larger prospective multicenter studies that measure social determinants of health are needed.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. Institutional Review Board of Marshall University issued approval 1977160-2.
Animal subjects: All authors have confirmed that this study did not involve animal subjects or tissue.
Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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