Supplementary Material*

Getahun D, Nash R, Flanders WD, Baird TC, Becerra-Culqui TA, Cromwell L, et al. Cross-Sex Hormones and Acute Cardiovascular Events in Transgender Persons. A Cohort Study. Ann Intern Med. doi:10.7326/M17-2785

Supplement. **Technical Appendix**

from Kaiser Permanente in northern California (KPNC), southern California (KPSC), and Georgia (KPGA) (2006-2016).

Appendix Figure 3. **Kaplan-Meier plots comparing unweighted cumulative incidence of VTE (panel A) and IS (panel B) among TF cohort members who initiated estrogen therapy after the index date compared with matched reference cohorts, from KPNC, KPSC, and KPGA (2006-2016).**

Appendix Figure 4. **Log minus log plots for the analysis of venous thromboembolism (panel A) and ischemic stroke (panel B) in the TF estrogen initiation subcohort.**

Appendix Figure 5. **Adjusted cumulative incidence curves comparing rates of acute cardiovascular events among all transmasculine cohort members compared with matched reference males (top three panels A-C) and reference females (bottom three panels D-F) from Kaiser Permanente in Northern California (KPNC), Southern California (KPSC), and Georgia (KPGA) (2006-2016).**

* This supplementary material was provided by the authors to give readers further details on their article. The material was reviewed but not copyedited.

TECHNICAL APPENDIX

Transgender cohort ascertainment

As summarized in the Appendix Figure 1, cohort selection involves a three-step algorithm that included initial EMR search to identify cohort candidates (Step 1); validation of transgender status (Step 2); and determination of TM/TF status (Step 3).

In Step 1, EMR data pertaining to all KPGA, KPNC, and KPSC members of all ages enrolled between January 1, 2006 and December 31, 2014 were used to identify two types of evidence supporting transgender status: 1) relevant International Classification of Diseases, Ninth Edition (ICD-9) codes; and 2) presence of relevant specific keywords in free-text notes. The list of diagnostic codes and keywords is included in Appendix Table 1.

In Step 2 (validation) a separate computer program extracted short strings of text that included 100 characters before and 50 characters after the keyword of interest. Eligibility status was independently verified by two trained reviewers with disagreement adjudicated by a committee that included the project manager (RN) and two investigators (MG and VT). Members who had no keywords in their records, but had two or more ICD-9 codes of interest, were considered transgender. The validity of this approach was confirmed using unstructured chart review during pilot testing of the study protocol, as described previously (1).

For the determination of TM/TF status (Step 3), we used all keyword text strings and ICD-9 codes extracted for Step 1 to identify additional words such as "male-to-female," "female-to-male," and gender affirmation codes as described in detail elsewhere (2). During the validation of transgender status, the reviewers were also instructed to categorize each eligible person as "natal male," "natal female," or "unclear." For persons with ICD-9 codes only or for whom

TM/TF status could not be determined after the initial review, a second free-text program was developed to search for keywords reflecting natal sex anatomy (e.g., testes or ovaries), history of specific procedures (e.g., orchiectomy or hysterectomy) or evidence of hormonal therapy (e.g., estrogen or testosterone). The keywords used for assigning TM/TF status are included in the Appendix Table 2. Text strings containing TM- and TF-specific keywords were reviewed and adjudicated as discussed above.

Ten male and ten female cisgender KP enrollees were matched to each member of the final validated transgender cohort on race/ethnicity (non-Hispanic white, non-Hispanic black, Asian/Pacific Islander, Hispanic, and other), year of birth (within a 5-year interval), study site, and calendar year of membership based on the index date. Index date was defined as the first recorded evidence of transgender status.

In situations when a cisgender referent was matched to more than one transgender cohort member that cisgender person was randomly assigned to one of the potential matches. As a result, 16% of transgender cohort members were matched to fewer than ten cisgender males or females; however, no transgender participant had fewer than seven referents of either sex. Members of the reference cohorts had no ICD-9 codes or keywords reflecting transgender status. For expediency, we will refer to these as cisgender, but we recognize that we were unable to verify that each of these members was not transgender.

Variable characterization

All study participants were characterized with respect to their KP enrollment history and cigarette smoking, body mass index (BMI, kg/m^2), blood pressure, and total blood cholesterol at baseline. Smoking status was categorized as current smoker or not because it is current smoking that may be considered a risk factor for vascular events such as VTE (3). BMI was categorized

as normal or low weight (< 25.0 kg/m^2), overweight (25.0-29.9 kg/m^2), obese (≥30.0 kg/m^2), or unknown. Blood pressure and total blood cholesterol were determined from laboratory data within 2 years of the index date and categorized using the published clinical cutoffs (4). Blood pressure (systolic, diastolic) was categorized as normal (≤120 and ≤80), borderline (121–139 or 81–89), elevated (≥140 or ≥90), or unknown and total blood cholesterol (mg/dL) was categorized as normal (<200 mg/dL), borderline (200–239 mg/dL), high (≥240 mg/dL), not done (unknown for persons younger than 40 years), or unknown.

Missing covariate values for BMI, blood pressure, and total cholesterol were assigned based on multiple imputation methods (5 imputations) using the proc mi procedure in SAS. In addition to BMI, blood pressure, and total cholesterol, the imputation models included age at index, natal sex, race, and cigarette smoking status. Cox regression models were run for each imputation separately and the overall effect was estimated using proc mianalyze in SAS.

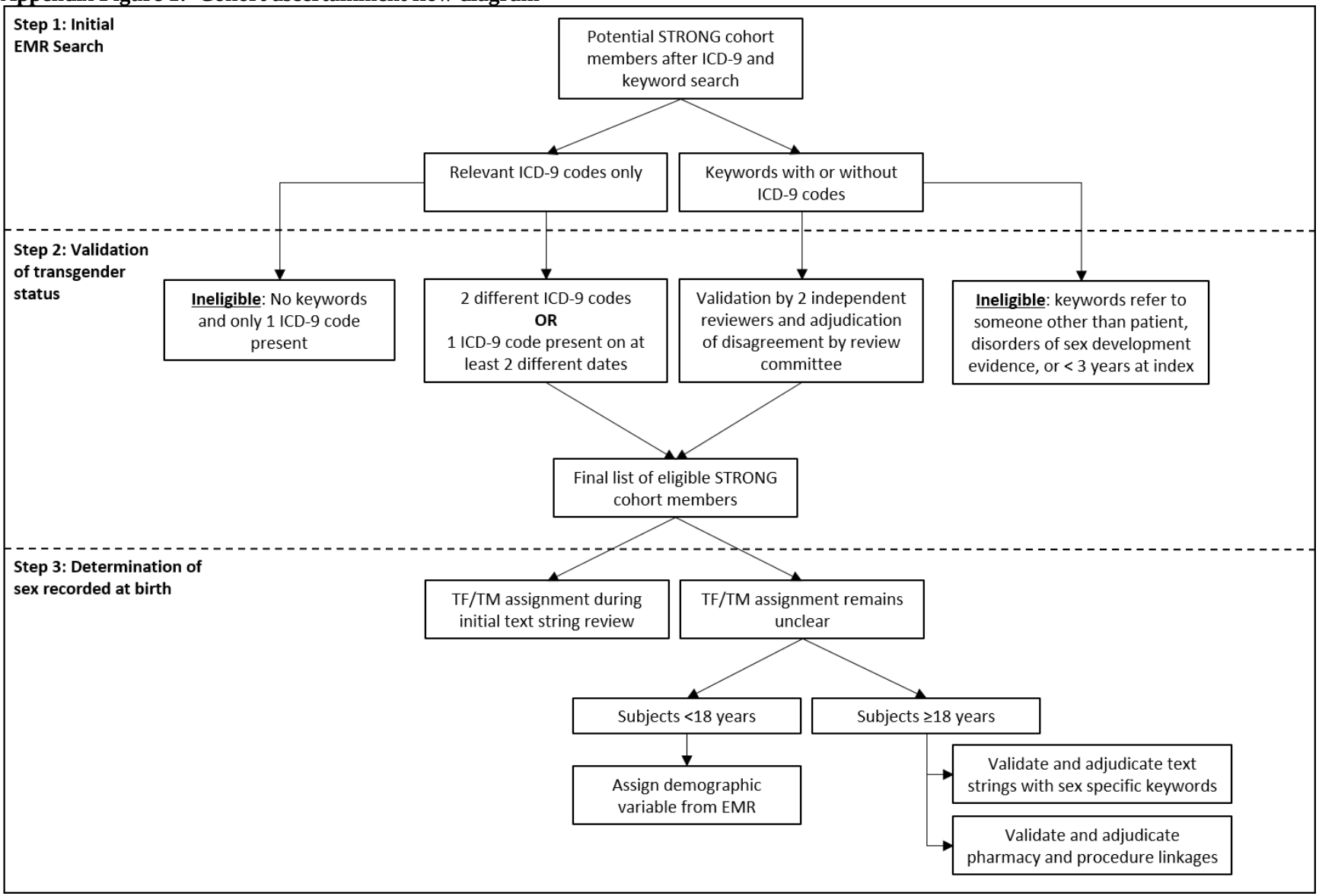
Sensitivity analyses

To assess impact of disease severity, we first restricted the case definition by limiting ACVE to those associated with inpatient or emergency department encounters. To assess whether the increase in risk may be attributable to surgical procedures during the follow-up, we excluded all persons in the estrogen initiation sub-cohort who had any gender affirmation surgery following estrogen initiation. To account for the high recurrence risk, we calculated adjusted HR (95% CI) estimates after restricting the cohort to persons without history of any ACVE before the follow up initiation.

To investigate effects of unaccounted confounding we calculated a range of e-values for the main results observed in Cox regression models. The e-value is defined as the minimum strength of association of unmeasured confounders with both the exposure and the outcome of interest

that would be needed to fully explain away the observed exposure–outcome associations (5). Separate e-values were calculated for point estimates and lower limits of the 95% CI.

Appendix Figure 1: Cohort ascertainment flow diagram



Appendix Table 1: ICD-9 codes and keywords used to identify potentially eligible persons among KPNC, KPSC, and KPGA members

ICD-9 diagnostic codes[a]	ICD-9 V-codes[b] + internal KP codes	Keywords
302.5 – Trans-sexualism 302.50 – Transsexualism with unspecified sexual history (a.k.a. "transsexualism not otherwise specified") 302.51 – Transsexualism with asexual history 302.52 – Transsexualism with homosexual history; 302.53 – Transsexualism with heterosexual history 302.85 – Gender identity disorder in adolescents or adults 302.6 – Gender identity disorder in children 302.3 – Transvestic fetishism	V49.89 + 121141596 – Other conditions influencing health: transgender. V45.77 +121141596 – Acquired absence of genital organs: history of sex reassignment surgery V07.8 + 12124952 – Other specified prophylactic measure: male-to-female hormone supplementation V07.8 + 12124310 – Other specified prophylactic measure: female-to-male hormone supplementation	Transgender Transsexual Transvestite Gender identity Gender dysphoria Gender reassignment

[a]Only ICD-9 codes were used because cohort ascertainment ended at the end of 2014, before ICD-10 codes became available.

[b]ICD-9 V codes are used for supplementary classification of factors influencing health status.(6, 7) As V codes may cover several conditions they have to be used in conjunction with internal KP codes to ensure specificity

Appendix Table 2: Keywords used for determination of sex recorded at birth

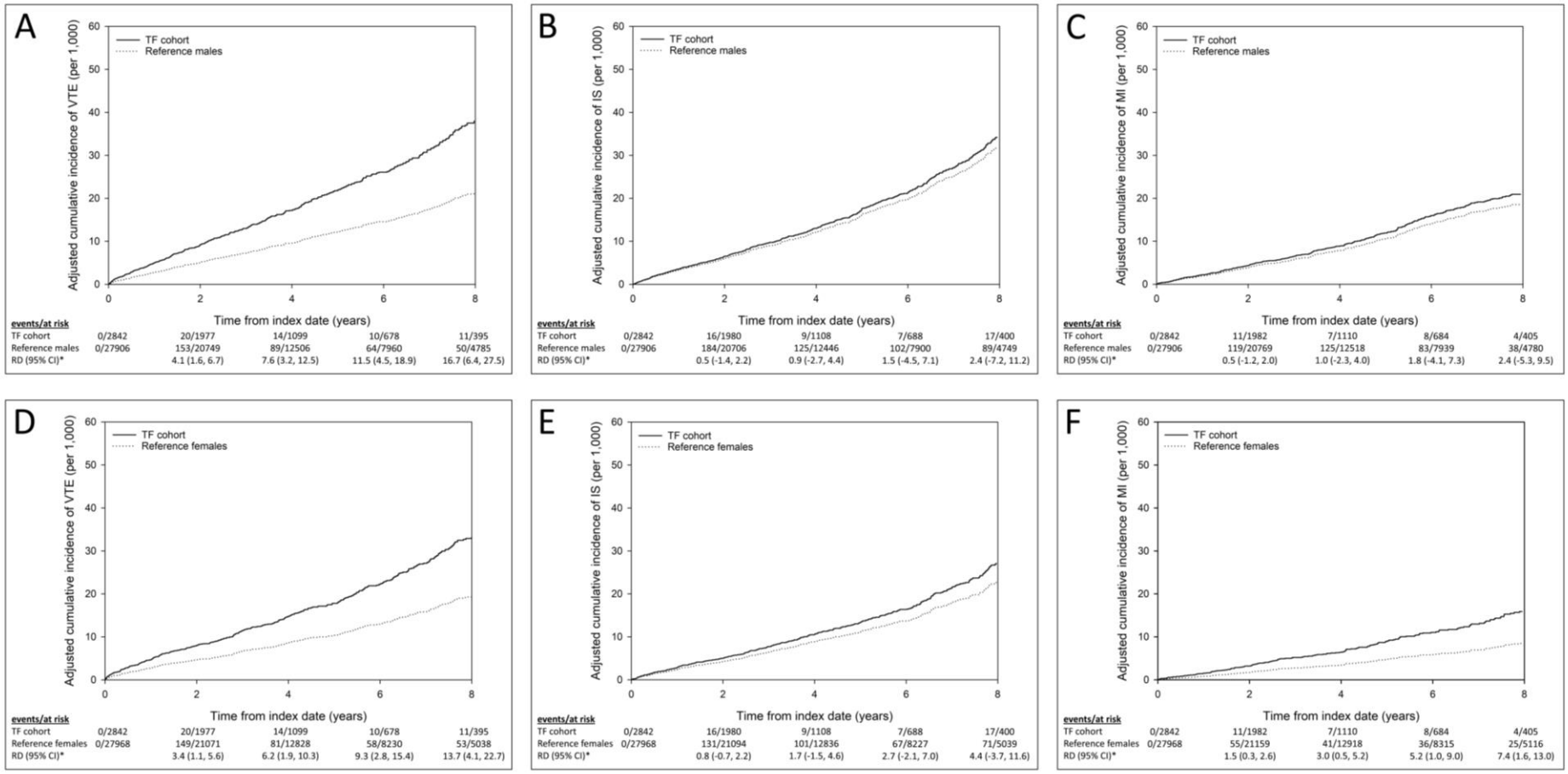
Trans-feminine	**Sex recorded at birth keywords**	testes, testicular, penis, penile, prostate, prostatic, PSA, scrotum, neovagina, neo-vagina, neo vagina, sperm, erection
	Hormonal therapy keywords	estrogen, anti-androgen, progesterone, aldactone, avodart, cenestin, climara, cyprostat, cyproterone, delestrogen, depo-estradiol, divigel, dutasteride, elestrin, enjuvia, estrace, estradiol, estroderm, estrogel, estrosorb, flutamide, finasteride, lupron, medroxyprogesterone, premarin, premphase, prempro, propecia, proscar, prometrium, provera, spironolactone,
	Procedure keywords	castration, orchiectomy, penectomy, vaginoplasty, breast augmentation, breast enlargement, laryngeal shave, feminization, electrolysis, hair transplant, collagen, silicone, voice therapy
Trans-masculine	**Sex recorded at birth keywords**	ovary, ovaries, ovarian, cervix, uterus, uterine, vagina, PAP smear, menstrual bleeding, menses
	Hormonal therapy keywords	android, androderm, androgel, axiron, delatestryl, depo-testosterone, striant, testim
	Procedure keywords	vaginectomy, phalloplasty, metoidioplasty, mastectomy, hysterectomy, oophorectomy

Appendix Table 3: ICD-9 and ICD-10 codes used to identify acute cardiovascular events among KPNC, KPSC, and KPGA members

Diagnostic code description	ICD-9 codes	ICD-10 codes	Participants with code*
Pulmonary embolism	415.1	I26.0, I26.9	340
Phlebitis and deep vein thromboembolism	451.1, 451.2, 451.8, 451.9	I80.x	311
Other venous embolism and thrombosis	452.x, 453.x	I81.x, I82.x	821
Occlusion and stenosis of precerebral arteries	433.x	I65.x	790
Occlusion of cerebral arteries	434.x	I66.x	709
Cerebral infarction		I63.x	152
Acute myocardial infarction	410.x	I21.x	1165

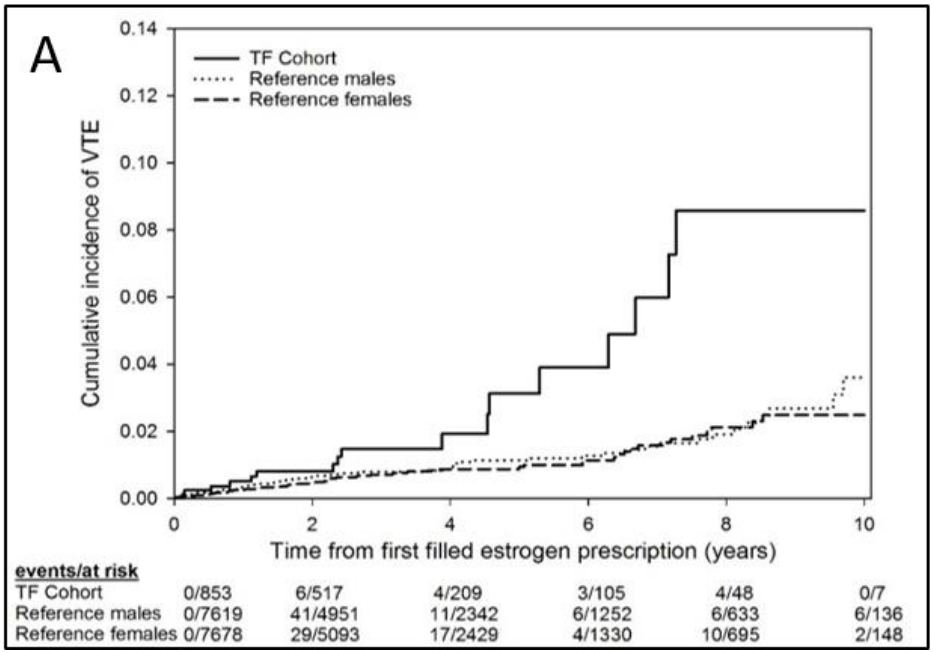
*Does not represent unique subjects as subjects could have more than one code on the same day or more than one event in the follow-up period
'x' denotes any digit

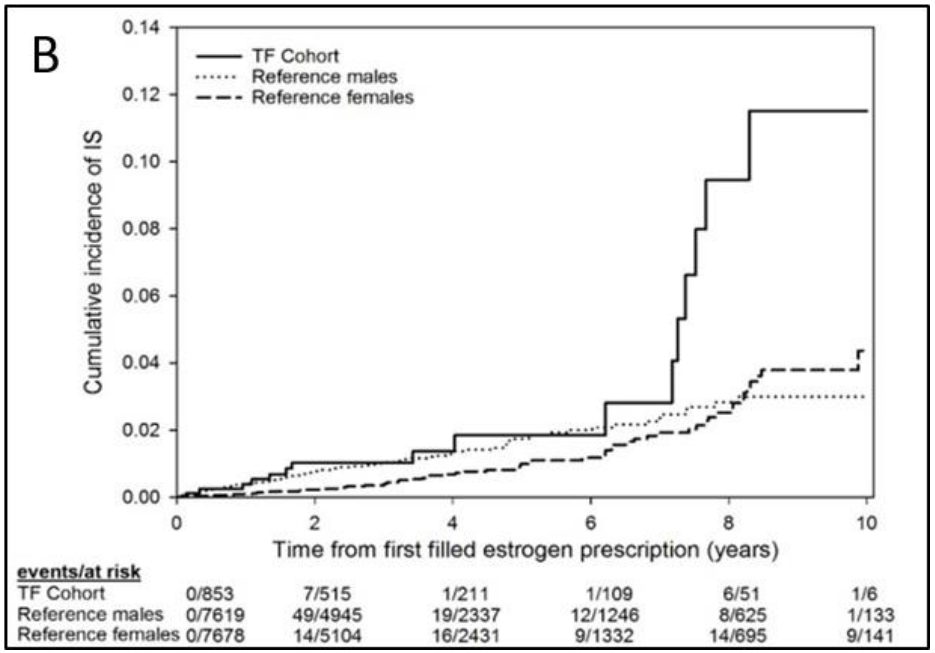
Appendix Figure 2: Adjusted cumulative incidence curves comparing rates of acute cardiovascular events (ACVE) among all transfeminine cohort members with matched reference males (top three panels A-C) and reference females (bottom panels D-F) from Kaiser Permanente in Northern California (KPNC), Southern California (KPSC), and Georgia (KPGA) (2006 - 2016). Panels A and D present data for venous thromboembolism (VTE), panels B and E present data for ischemic stroke (IS), and panels C and F present data for myocardial infarction (MI). Adjustment for covariates was made at the population mean values.



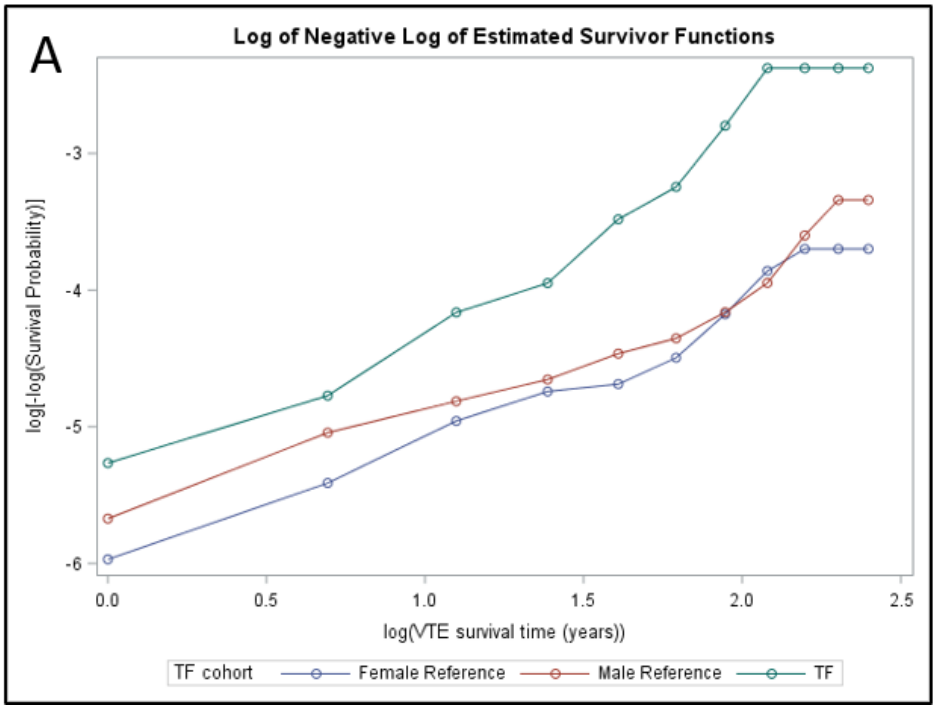
*Risk difference (95% CI) per 1,000 persons

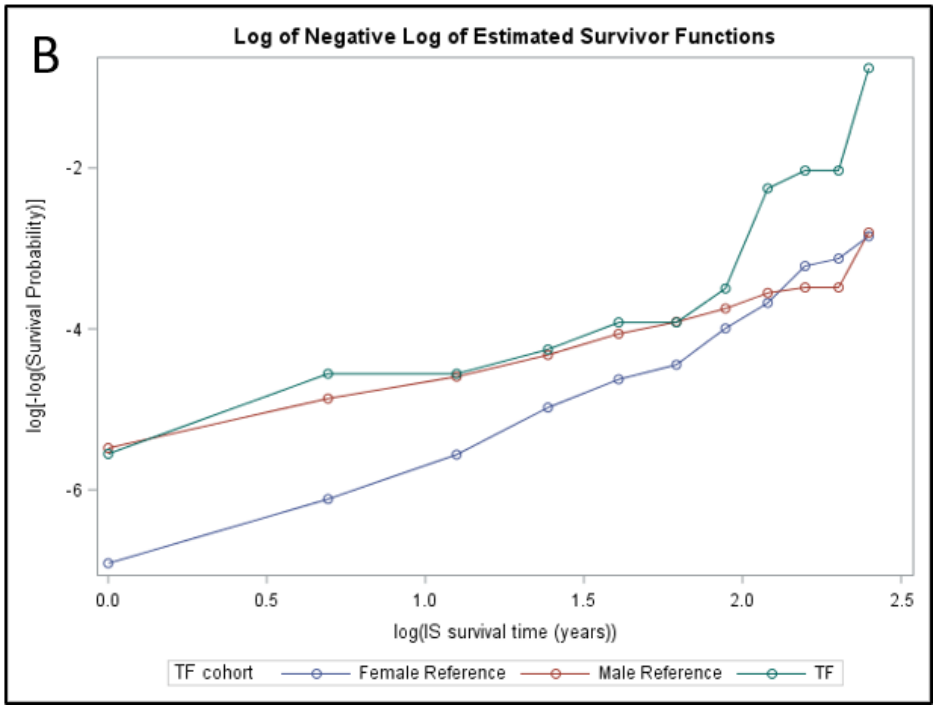
Appendix Figure 3: Kaplan-Meier plots comparing unweighted cumulative incidence of VTE (panel A) and IS (panel B) among TF cohort members who initiated estrogen therapy after the index date compared with matched reference cohorts, from KPNC, KPSC, and KPGA (2006-2016).





Appendix Figure 4: Log minus log plots for the analysis of venous thromboembolism (panel A) and ischemic stroke (panel B) in the TF estrogen initiation subcohort.





Appendix Table 4: Incidence rates and adjusted hazard ratios for acute cardiovascular events (ACVE) among transfeminine cohort members compared to matched reference cohorts from KPNC, KPSC, and KPGA (2006-2014) without controlling for matching.

	Transfeminine cohort		Adjusted HR (95% CI)†	
Cohort and event of interest	Number of ACVE	Incidence rate (95% CI)*	vs. reference men	vs. reference women
Transfeminine overall cohort (N=2842)				
Venous thromboembolism in the overall cohort	61	5.5 (4.3, 7.0)	1.7 (1.3, 2.2)	1.7 (1.3, 2.2)
Ischemic stroke in the overall cohort	54	4.8 (3.7, 6.3)	1.0 (0.7, 1.3)	1.2 (0.9, 1.5)
Myocardial infarction in the overall cohort	33	2.9 (2.1, 4.1)	1.0 (0.7, 1.5)	1.8 (1.2, 2.6)
Transfeminine estrogen cohort (N=853)				
Venous thromboembolism in the estrogen initiation cohort	17	6.6 (4.1, 10.6)	2.7 (1.5, 4.6)	2.7 (1.6, 4.7)
Estrogen initiation cohort 0-2 years of follow-up‡	6	4.3 (1.9, 9.6)	1.5 (0.6, 3.5)	1.8 (0.7, 4.3)
Estrogen initiation cohort 2+ years of follow-up‡	11	9.3 (5.2, 16.8)	4.8 (2.3, 9.8)	3.8 (1.9, 7.6)
Ischemic stroke in the estrogen initiation cohort	17	6.6 (4.1, 10.6)	1.7 (1.0, 2.9)	2.3 (1.3, 4.0)
Estrogen initiation cohort 0-6 years of follow-up‡	9	3.8 (2.0, 7.3)	1.0 (0.5, 2.0)	1.7 (0.8, 3.5)
Estrogen initiation cohort 6+ years of follow-up‡	8	36.2 (18.1, 72.4)	7.0 (2.8, 17.8)	3.7 (1.6, 8.5)
Myocardial infarction in the estrogen initiation cohort	4	1.5 (0.6, 4.1)	0.7 (0.3, 2.0)	1.4 (0.5, 3.9)

HR = hazard ratio; 95% CI = 95% confidence interval; ACVE = acute cardiovascular events

*Calculated as number of cases per 1,000 person-years

† Stratified by history of any ACVE; BMI (normal, overweight, obese), smoking status (current vs not), blood pressure (elevated, borderline, normal), and total blood cholesterol (normal, not done [for persons <40 years of age], borderline, high) are included in the model as covariates (for details of variable characterization see Technical Appendix)

‡ Extended models due to violation of proportional hazards assumptions

Appendix Table 5: Incidence rates and adjusted hazard ratios for acute cardiovascular events (ACVE) among transmasculine cohort members compared to matched reference cohorts from KPNC, KPSC, and KPGA (2006-2014) without controlling for matching.

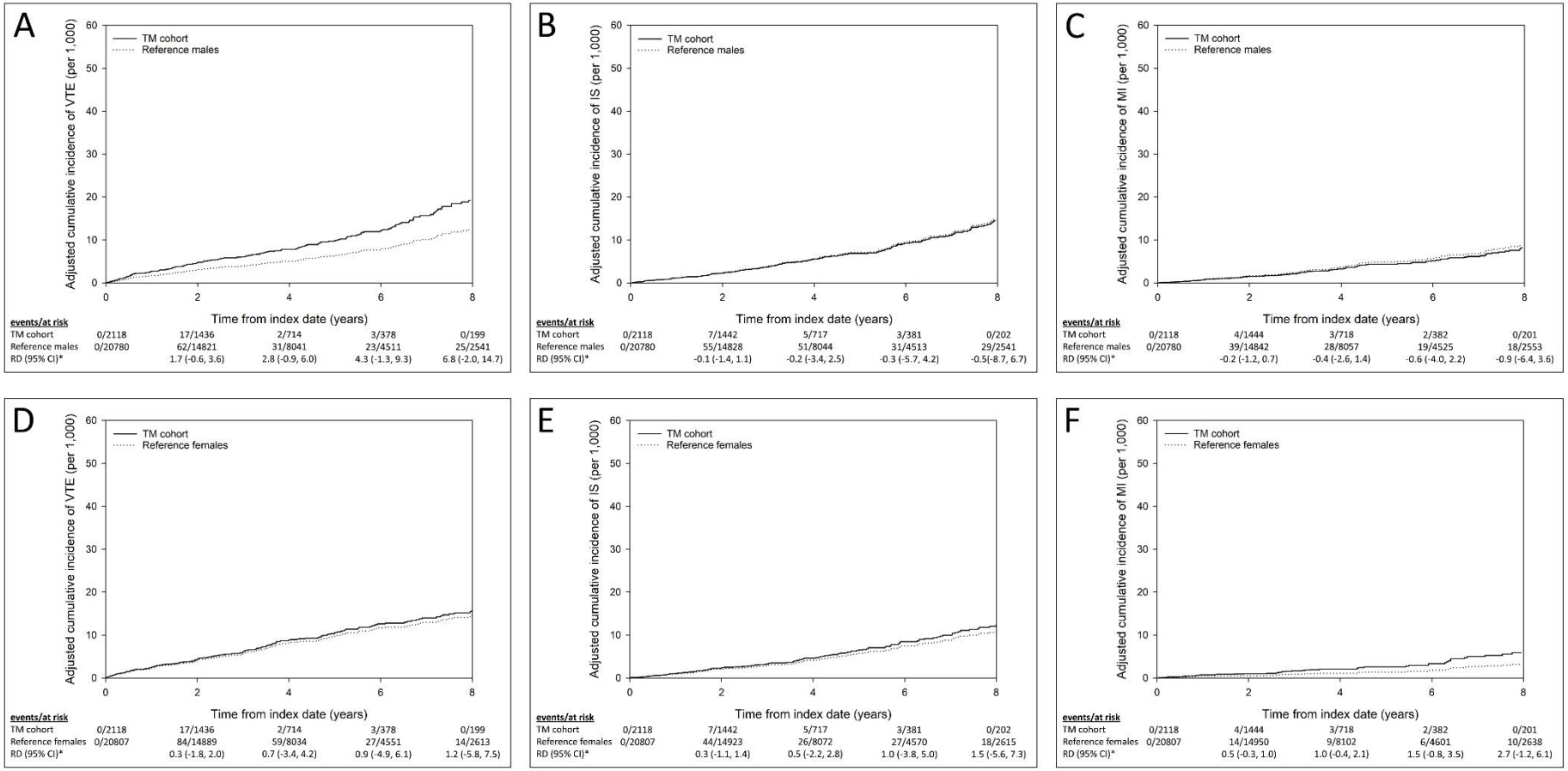
	Transmasculine cohort		Adjusted HR (95% CI)†	
Cohort and event of interest	Number of ACVE	Incidence rate (95% CI)*	vs. reference men	vs. reference women
Transmasculine overall cohort (N=2118)				
Venous thromboembolism in the overall cohort	23	3.1 (2.0, 4.6)	1.4 (0.9, 2.2)	1.0 (0.6, 1.5)
Ischemic stroke in the overall cohort	16	2.1 (1.3, 3.5)	0.8 (0.5, 1.3)	1.0 (0.6, 1.6)
Myocardial infarction in the overall cohort	9	1.2 (0.6, 2.3)	0.7 (0.3, 1.3)	1.5 (0.7, 3.2)
Transmasculine testosterone cohort (N=585)				
Venous thromboembolism in the testosterone initiation cohort	4	3.3 (1.3, 8.9)	1.6 (0.5, 4.8)	1.0 (0.3, 2.9)
Ischemic stroke in the testosterone initiation cohort	2	1.7 (0.4, 6.7)	NC	NC
Myocardial infarction in the testosterone initiation cohort	0			

HR = hazard ratio; 95% CI = 95% confidence interval; ACVE = acute cardiovascular events; NC = not calculated due to small numbers

*Calculated as number of cases per 1,000 person-years

† Stratified by history of any ACVE; BMI (normal, overweight, obese), smoking status (current vs not), blood pressure (elevated, borderline, normal), and total blood cholesterol (normal, not done [for persons <40 years of age], borderline, high) are included in the model as covariates (for details of variable characterization see Technical Appendix)

Appendix Figure 5: Adjusted cumulative incidence curves comparing rates of acute cardiovascular events among all transmasculine cohort members compared with matched reference males (top three panels A-C) and reference females (bottom three panels D-F) from Kaiser Permanente in Northern California (KPNC), Southern California (KPSC), and Georgia (KPGA) (2006-2016). Panels A and D present data for venous thromboembolism (VTE), panels B and E present data for ischemic stroke (IS), and panels C and F present data for myocardial infarction (MI). Adjustment for covariates was made at the population mean values.



*Risk difference (95% CI) per 1,000 persons

Appendix Table 6: Secondary and sensitivity analyses using multivariable Cox proportional hazards models comparing rates of ACVE among transfeminine cohort members to matched reference cohorts from KPNC, KPSC, and KPGA (2006 - 2016)

Cohort and event of interest	Transfeminine cohort		Adjusted HR (95% CI)†	
	Number of ACVE	Incidence rate (95 % CI)*	vs. reference men	vs. reference women
Transfeminine overall cohort (N=2842)				
Venous thromboembolism				
Overall cohort, excluding persons with history of any ACVE	53	4.9 (3.7, 6.4)	1.9 (1.4, 2.7)	2.1 (1.5, 2.9)
Overall cohort, only inpatient or emergency department encounters	38	3.4 (2.5, 4.7)	1.9 (1.3, 2.8)	2.8 (1.8, 4.2)
Overall cohort with no recorded evidence of hormone therapy in the EMR	15	4.8 (2.9, 8.0)	2.3 (1.2, 4.5)	2.4 (1.2, 4.7)
Overall cohort with any recorded evidence of hormone therapy in the EMR	46	5.7 (4.3, 7.6)	1.8 (1.3, 2.7)	1.9 (1.3, 2.7)
Ischemic stroke				
Overall cohort, excluding persons with history of any ACVE	48	4.4 (3.3, 5.8)	1.3 (0.9, 1.8)	1.8 (1.3, 2.6)
Overall cohort, only inpatient or emergency department encounters	29	2.6 (1.8, 3.7)	0.9 (0.6, 1.4)	1.7 (1.1, 2.5)
Overall cohort with no recorded evidence of hormone therapy in the EMR	15	4.8 (2.9, 8.0)	1.2 (0.6, 2.4)	1.6 (0.8, 3.1)
Overall cohort with any recorded evidence of hormone therapy in the EMR	39	4.8 (3.5, 6.6)	1.3 (0.9, 1.8)	1.9 (1.3, 2.8)
Myocardial infarction				
Overall cohort, excluding persons with history of any ACVE	24	2.2 (1.5, 3.3)	1.0 (0.6, 1.6)	1.8 (1.1, 2.9)
Overall cohort, only inpatient or emergency department encounters	31	2.8 (1.9, 3.9)	1.0 (0.7, 1.7)	1.9 (1.1, 3.1)
Overall cohort with no recorded evidence of hormone therapy in the EMR	13	4.2 (2.4, 7.2)	1.9 (0.9, 4.2)	4.7 (2.0, 11.3)
Overall cohort with any recorded evidence of hormone therapy in the EMR	20	2.5 (1.6, 3.8)	0.7 (0.4, 1.2)	1.3 (0.7, 2.4)
Transfeminine estrogen cohort (N=853)				
Venous thromboembolism				
Estrogen initiation cohort excluding any surgery after estrogen initiation	12	5.6 (3.2, 9.8)	2.0 (0.9, 4.6)	2.1 (0.8, 5.0)
Estradiol initiation cohort 0-2 years of follow-up excluding surgery‡	5	4.2 (1.8, 10.3)	1.8 (0.7, 4.4)	2.1 (0.8, 5.4)
Estradiol initiation cohort 2+ years of follow-up excluding surgery‡	7	7.1 (3.4, 14.9)	3.7 (0.5, 25.5)	2.0 (0.2, 20.7)
Estrogen initiation cohort with no oral estrogen	4	6.0 (2.3, 16.1)	1.6 (0.3, 7.7)	2.9 (0.6, 14.3)
Estrogen initiation cohort with only non-estradiol or non-estradiol first	2	6.4 (1.6, 25.7)	NC	NC
Estrogen initiation cohort with only estradiol or estradiol first	15	7.4 (4.5, 12.3)	4.1 (1.9, 9.2)	2.8 (1.3, 5.8)
Estradiol initiation cohort 0-2 years of follow-up‡	5	4.3 (1.8, 10.4)	1.5 (0.4, 6.1)	1.6 (0.4, 6.1)
Estradiol initiation cohort 2+ years of follow-up‡	10	11.5 (6.2, 21.3)	8.2 (2.8, 23.4)	3.7 (1.5, 9.3)
Ischemic stroke				
Estrogen initiation cohort excluding any surgery after estrogen initiation	15	6.9 (4.2, 11.5)	2.5 (1.3, 5.0)	3.8 (1.8, 7.8)

Estradiol initiation cohort 0-6 years of follow-up excluding surgery‡	7	3.5 (1.7, 7.4)	1.3 (0.5, 3.2)	2.3 (0.9, 6.1)
Estradiol initiation cohort 6+ years of follow-up excluding surgery‡	8	43.1 (21.5, 86.1)	12.4 (3.3, 46.1)	8.9 (2.5, 31.7)
Estrogen initiation cohort with no oral estrogen	7	10.7 (5.1, 22.4)	2.0 (0.7, 5.5)	2.0 (0.6, 6.0)
Estrogen initiation cohort with only non-estradiol or non-estradiol use first	4	12.8 (4.8, 34.1)	1.8 (0.4, 8.8)	25.4 (0.7, 898.5)
Estrogen initiation cohort with only estradiol or estradiol first	13	6.3 (3.7, 10.9)	2.7 (1.3, 5.4)	2.8 (1.4, 5.6)
Estradiol initiation sub-cohort 0-6 years of follow-up‡	6	3.2 (1.4, 7.1)	1.3 (0.5, 3.2)	2.1 (0.8, 5.4)
Estradiol initiation sub-cohort 6+ years of follow-up‡	7	44.1 (21.0, 92.6)	20.3 (4.1, 101.5)	4.1 (1.5, 11.4)
Transfeminine oral estrogen cohort (N=622)^				
Venous thromboembolism in oral estrogen cohort	14	7.6 (4.5, 12.8)	4.8 (2.1, 10.9)	2.7 (1.2, 6.1)
Oral estrogen initiation sub-cohort 0-2 years of follow-up‡	4	4.0 (1.5, 10.6)	2.9 (0.7, 11.9)	1.5 (0.4, 6.2)
Oral estrogen initiation sub-cohort 2+ years of follow-up‡	10	11.9 (6.4, 22.1)	6.3 (2.3, 17.6)	3.8 (1.4, 10.6)
Ischemic stroke in oral estrogen cohort	10	5.3 (2.9, 9.9)	2.5 (1.1, 5.8)	4.4 (1.8, 10.7)
Oral estrogen initiation sub-cohort 0-6 years of follow-up‡	6	3.5 (1.6, 7.8)	1.8 (0.7, 4.9)	3.7 (1.3, 10.5)
Oral estrogen initiation sub-cohort 6+ years of follow-up‡	4	23.8 (8.9, 63.5)	7.4 (1.4, 39.4)	7.0 (1.3, 36.3)

HR = hazard ratio; 95% CI = 95% confidence interval; ACVE = acute cardiovascular events; EMR = electronic medical records at Kaiser Permanente; NC = not calculated due to small numbers

*Calculated as number of cases per 1,000 person-years

† Stratified by cluster ID and history of any ACVE; BMI (normal, overweight, obese), smoking status (current vs not), blood pressure (elevated, borderline, normal), and total blood cholesterol (normal, not done [for persons <40 years of age], borderline, high) are included in the model as covariates (for details of variable characterization see Technical Appendix)

‡ Extended models due to violation of proportional hazards assumptions

^Follow-up in the oral estrogen subcohort extends from first filled oral estrogen prescription to event of interest, death, disenrollment, or end of study. Subjects in this cohort may or may not have other routes of estrogen

Appendix Table 7: Secondary and sensitivity analyses using multivariable Cox proportional hazards models comparing rates of ACVE among transmasculine cohort members to matched reference cohorts from KPNC, KPSC, and KPGA (2006 - 2016)

	Transmasculine cohort		Adjusted HR (95% CI)†	
	Number of ACVE	Incidence rate (95% CI)*	vs. reference men	vs. reference women
Transmasculine overall cohort (N=2118)				
Venous thromboembolism				
Overall cohort, excluding persons with history of any ACVE	17	2.3 (1.4, 3.7)	1.7 (1.0, 3.1)	1.2 (0.7, 2.2)
Overall cohort, only inpatient or emergency department encounters	16	2.1 (1.3, 3.5)	1.1 (0.5, 2.5)	1.2 (0.5, 2.6)
Overall cohort with no recorded evidence of hormone therapy in the EMR	10	4.0 (2.2, 7.5)	0.9 (0.3, 2.8)	0.8 (0.3, 2.4)
Overall cohort with any recorded evidence of hormone therapy in the EMR	13	2.6 (1.5, 4.5)	2.0 (1.0, 4.1)	1.4 (0.7, 2.8)
Ischemic stroke				
Overall cohort, excluding persons with history of any ACVE	14	1.9 (1.1, 3.2)	1.0 (0.5, 2.0)	1.4 (0.7, 2.8)
Overall cohort, only inpatient or emergency department encounters	8	1.1 (0.5, 2.1)	1.0 (0.4, 2.3)	1.2 (0.5, 2.7)
Overall cohort with no recorded evidence of hormone therapy in the EMR	7	2.8 (1.3, 5.9)	1.3 (0.5, 3.5)	1.3 (0.5, 3.6)
Overall cohort with any recorded evidence of hormone therapy in the EMR	9	1.8 (0.9, 3.4)	1.1 (0.5, 2.4)	1.3 (0.6, 3.1)
Myocardial infarction				
Overall cohort, excluding persons with history of any ACVE	5	0.6 (0.3, 1.6)	0.7 (0.3, 1.9)	1.4 (0.4, 4.4)
Overall cohort, only inpatient or emergency department encounters	9	1.2 (0.6, 2.3)	0.7 (0.3, 1.9)	1.5 (0.5, 4.6)
Overall cohort with no recorded evidence of hormone therapy in the EMR	1	0.4 (0.1, 2.8)	NC	NC
Overall cohort with any recorded evidence of hormone therapy in the EMR	8	1.6 (0.8, 3.2)	1.4 (0.5, 3.7)	2.9 (0.8, 10.2)

HR = hazard ratio; 95% CI = 95% confidence interval; ACVE = acute cardiovascular events; EMR = electronic medical records at Kaiser Permanente; NC = not calculated due to small numbers

*Calculated as number of cases per 1,000 person-years

† Stratified by cluster ID and history of any ACVE; BMI (normal, overweight, obese), smoking status (current vs not), blood pressure (elevated, borderline, normal), and total blood cholesterol (normal, not done [for persons <40 years of age], borderline, high) are included in the model as covariates (for details of variable characterization see Technical Appendix)

Appendix Table 8: Sensitivity analyses presenting possible effects of unaccounted confounding expressed as e-values for the main results observed in Cox regression models.*

Analysis Type	Point estimate		Lower 95% CI limit	
	Observed value	e-value	Observed value	e-value
VTE in overall TF cohort vs. reference men	1.9	3.2	1.4	2.2
VTE in overall TF cohort vs. reference women	2.0	3.4	1.4	2.2
IS in overall TF cohort vs. reference men	1.2	1.7	0.9	N/A
IS in overall TF cohort vs. reference women	1.9	3.2	1.3	1.9
VTE in estrogen cohort vs. reference men full follow up	3.2	5.9	1.5	2.4
VTE in estrogen cohort vs. reference women full follow up	2.5	4.4	1.2	1.7
VTE in estrogen cohort vs. reference men (2+ years of follow up)	5.1	9.7	2.1	3.6
VTE in estrogen cohort vs. reference women (2+ years of follow up)	3.2	5.9	1.3	1.9
IS in estrogen cohort vs. reference men full follow up	2.3	4.0	1.2	1.7
IS in estrogen cohort vs. reference women full follow up	2.9	5.3	1.5	2.4
IS in estrogen cohort vs. reference men (6+ years of follow up)	9.9	19.3	3.0	5.5
IS in estrogen cohort vs. reference women (6+ years of follow up)	4.1	7.7	1.5	2.4

VTE = venous thromboembolism; IS = ischemic stroke; TF = transfeminine; CI = confidence interval; RR = risk ratio

*E-value is defined as the minimum strength of association of an unmeasured confounder with both the exposure and the outcome of interest to fully explain the observed risk or rate ratio (RR); values obtained using E-value calculator https://evalue.hmdc.harvard.edu/app/ for hazard ratios with outcome prevalence <15%

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