

SUPPLEMENTAL MATERIAL

Table S1. Association of sex (women vs men [reference]) with sex hormones and SHBG among participants of KORA F4.

Variable	β (95 % CI) Model 1	β (95 % CI) Model 2
SHBG	0.45 (0.41, 0.49)	0.45 (0.40, 0.49)
Sex hormones		
TT (nmol/L)	-14.82 (-15.22, -14.42)	-14.87 (-15.30, -14.44)
DHT (nmol/L)	-1.15 (-1.22, -1.08)	-1.16 (-1.23, -1.09)
DHEA (nmol/L)	-0.22 (-0.89, 0.45)	-0.35 (-1.08, 0.36)
DHEA-S (nmol/L)	-1368.06 (-1539.69, -1196.42)	-1326.52 (-1509.85, -1143.20)

Model 1: Age.

Model 2: Model 1 + smoking + alcohol consumption + physical activity.

SHBG is log-transformed.

Abbreviations: SHBG, sex hormone-binding globulin; TT, total testosterone; DHT, dihydrotestosterone; DHEA, dehydroepiandrosterone; DHEA-S, dehydroepiandrosterone-sulfate.

Table S2. Associations of sex hormones and SHBG (per 1 unit increase) with risk of stroke among male and female participants KORA F4 and FF4.

Variable	HR (95% CI) model 1	HR (95% CI) model 2
Male adults		
SHBG (nmol/L)	0.82 (0.41, 1.65)	0.83 (0.41, 1.68)
Sex hormones		
TT (nmol/L)	0.93 (0.88, 0.98)	0.94 (0.88, 0.99)
DHT (nmol/L)	0.40 (0.23, 0.69)	0.39 (0.22, 0.68)
DHEA (nmol/L)	0.96 (0.89, 1.04)	0.96 (0.89, 1.04)
DHEA-S (nmol/L)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
Female adults		
SHBG (nmol/L)	1.21 (0.52, 2.82)	1.25 (0.55, 2.93)
Sex hormones		
Testosterone (nmol/L)	1.17 (0.71, 1.92)	1.11 (0.65, 1.88)
DHT (nmol/L)	0.26 (0.01, 4.31)	0.32 (0.02, 5.02)
DHEA (nmol/L)	0.93 (0.84, 1.03)	0.93 (0.84, 1.03)
DHEA-S (nmol/L)	1.00 (1.00, 1.00)	0.95 (0.89, 1.01)

Model 1: Age.

Model 2: Model 1 + smoking + alcohol consumption + physical activity.

SHBG is log-transformed.

Abbreviations: HR, hazard ratio; SHBG, sex hormone-binding globulin; TT, total testosterone; DHT, dihydrotestosterone; DHEA, dehydroepiandrosterone; DHEA-S, dehydroepiandrosterone-sulfate.

Table S3. Association of sex (women vs men [reference]) with risk of stroke between KORA F4 and FF4.

Variable	HR (95% CI) model 1	HR (95% CI) model 2
Sex (women vs men [reference])	0.76 (0.47, 1.25)	1.01 (0.58, 1.76)

Model 1: Age.

Model 2: Model 1+ smoking+ alcohol consumption+ physical activity.

Abbreviations: HR, hazard ratio.

Table S4. Associations of sex hormones and SHBG (per 1 unit increase) with risk of MI among male and female participants KORA F4 and FF4.

Variable	HR (95% CI) model 1	HR (95% CI) model 2
Male adults		
SHBG (nmol/L)	0.91 (0.48, 1.73)	0.83 (0.43, 1.60)
Sex hormones		
TT (nmol/L)	0.99 (0.95, 1.04)	0.99 (0.95, 1.04)
DHT (nmol/L)	0.97 (0.72, 1.31)	0.98 (0.72, 1.35)
DHEA (nmol/L)	0.97 (0.92, 1.03)	0.97 (0.92, 1.03)
DHEA-S (nmol/L)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
Female adults		
SHBG (nmol/L)	0.33 (0.09, 1.20)	0.31 (0.08, 1.21)
Sex hormones		
Testosterone (nmol/L)	0.47 (0.08, 2.59)	0.52 (0.09, 3.02)
DHT (nmol/L)	1.35 (0.04, 38.3)	1.40 (0.06, 32.4)
DHEA (nmol/L)	1.00 (0.87, 1.15)	1.00 (0.87, 1.15)
DHEA-S (nmol/L)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)

Model 1: Age.

Model 2: Model 1 + smoking + alcohol consumption + physical activity.

SHBG is log-transformed.

Abbreviations: MI, myocardial infarction; HR, hazard ratio; SHBG, sex hormone-binding globulin; TT, total testosterone; DHT, dihydrotestosterone; DHEA, dehydroepiandrosterone; DHEA-S, dehydroepiandrosterone-sulfate.

Table S5. Association of sex (women vs men [reference]) with risk of MI between KORA F4 and FF4.

Variable	HR (95% CI) model 1	HR (95% CI) model 2
Sex (women vs men [reference])	0.24 (0.12, 0.50)	0.22 (0.10, 0.46)

Model 1: Age.

Model 2: Model 1+ smoking+ alcohol consumption+ physical activity.

Abbreviations: HR, hazard ratio.

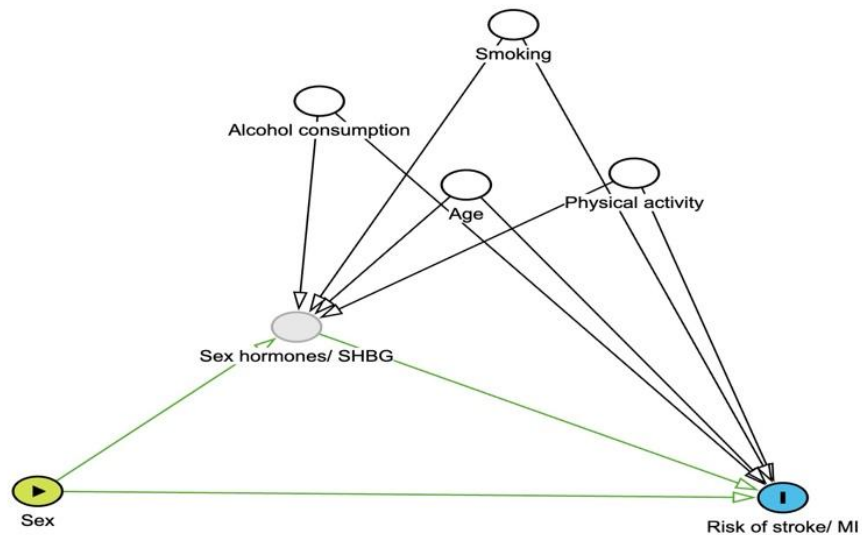
Table S6. Mediation analysis of total testosterone and dihydrotestosterone on the association between (women vs men [reference]) and risk of stroke between KORA F4 and FF4 (model 3).

Effects	HR (95% CI) model 3	p-value
TT		
DE	0.59 (0.22, 1.37)	0.19
IE	2.02 (1.03, 5.23)	0.04
TE	1.19 (0.63, 2.19)	0.59
PM	-	-
DHT		
DE	0.51 (0.22, 1.06)	0.07
IE	2.50 (1.38, 5.99)	0.001
TE	1.28 (0.68, 2.35)	0.44
PM	-	-

Model 3: Model 2+ waist circumference + SBP + antihypertensive medications + lipid lowering medications + total cholesterol + CRP + TSH and baseline diabetes.

Abbreviations: HR, hazard ratio; SBP, systolic blood pressure; CRP, C-reactive protein; TSH, thyroid stimulating hormone; TT, total testosterone; DHT, dihydrotestosterone; DE, direct effect; IE, indirect effect; TE, total effect; PM, proportion mediated.

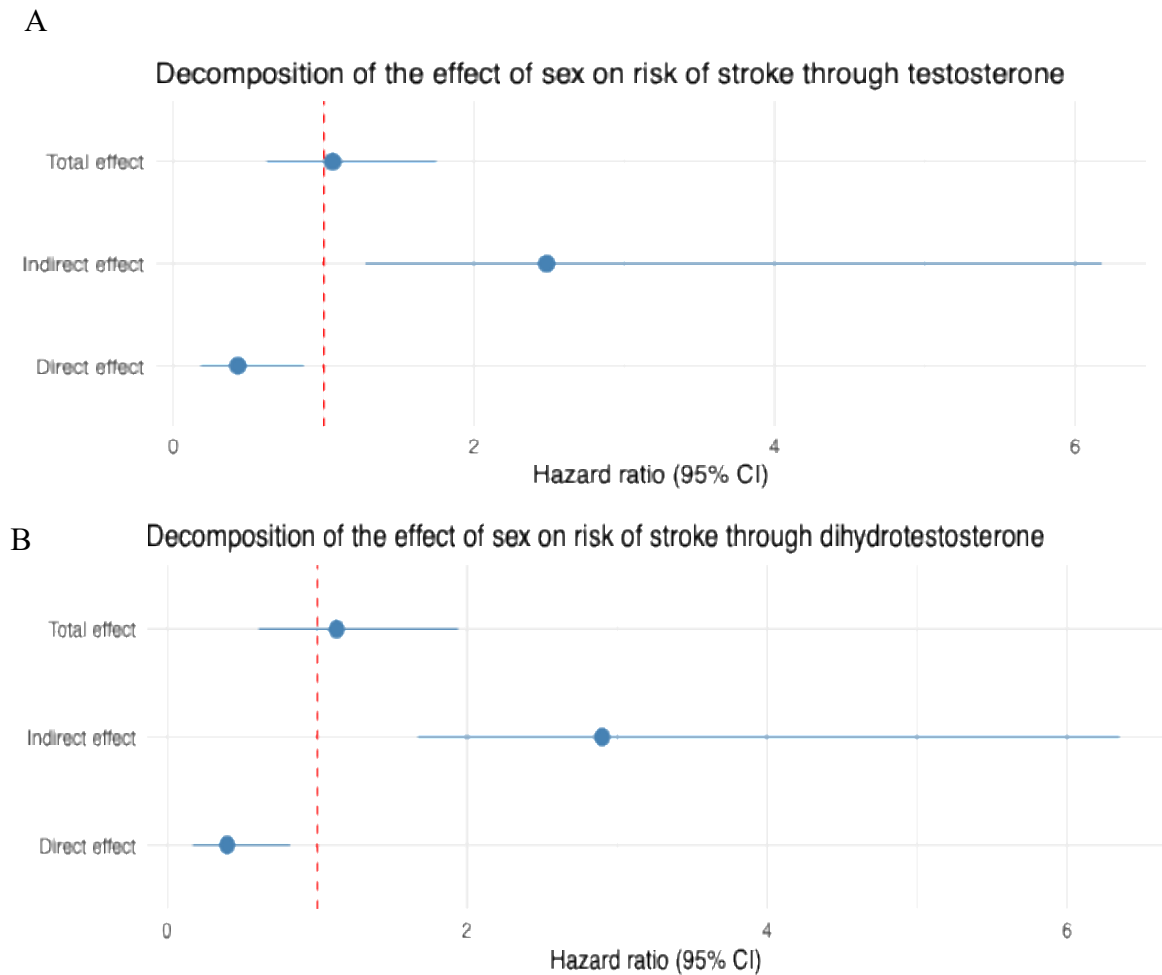
Figure S1. Directed acyclic graph (DAG) for the association of sex through, sex hormones (total testosterone, dihydrotestosterone, dehydroepiandrosterone, dehydroepiandrosterone-sulfate) or SHBG on risk of stroke/ myocardial infarction.



Study DAG for model 2, exposure = sex, mediator = sex hormones/ SHBG, outcome = stroke/ myocardial infarction, adjustment variables = age + alcohol consumption + smoking + physical activity.

Abbreviations: SHBG, sex hormone-binding globulin.

Figure S2. Forest plot showing the decomposition of the effect of sex on the risk of stroke into total, direct, and indirect effects.



Total Effect: Overall effect of sex on stroke risk, including both direct and mediator-driven pathways.

Direct Effect: Effect of sex on stroke risk not explained by the mediators.

Indirect Effect: Effect of sex on stroke risk that is mediated through sex hormones.

Panel A: total testosterone (TT).

Panel B: dihydrotestosterone (DHT).

Model adjustments: age+ smoking+ alcohol consumption+ physical activity. Effect estimates are shown as hazard ratio with 95% confidence intervals.