Supplementary Table A Summary of prospective cohort studies addressing the association between stress-related disorders and cardiovascular outcomes

Paper	Study design and database	Exposure	Outcomes	Sample size and follow-up	Main findings	Control for	
						Familial factor?	Other psychiatric comorbidities?
Kubzansky LD 2007[1]	Prospective cohort, community-dwelling men who served in the military	PTSD symptoms	CHD (angina pectoris, MI, and fatal CHD), self-reported with medical record checking	1996 men mean age 60 years; mean follow-up of 13.2 or 9.8 years	Top 10 percentile in combat-related PTSD score vs others: OR 1.12 (0.92 to 1.36) for all CHD	No	Controlled for self-reported depressive symptoms prevalent to PTSD
Kubzansky LD 2009[2]	Prospective cohort, civilian community-dwelling women	PTSD symptoms	CHD (angina pectoris, nonfatal MI, fatal MI, and other cardiac death), self-reported or tracked from National Death Index	1059 women mean age 44.4 years; up to 14-year follow-up	Top 4 percentile (five or more symptom) vs 89.1% of the sample reporting 0 symptoms: OR 3.46 (95% CI 1.35 to 8.90)	No	No
Jordan HT 2011[3]	Prospective cohort, adults exposed to the September 11, 2001 World Trade Center disaster	PTSD Checklist score ≥44	Self-reported physician-diagnosed angina, heart attack, and/or other heart diseases	39,324 participants (men 24222, women 15102; >18 years at exposure), 2.9 years follow-up	Participants with PTSD vs without PTSD at baseline: HR 1.68, 95% CI 1.33 to 2.12 in women, HR 1.62, 95% CI 1.34 to 1.96 in men	No	No
Jordan HT 2013[4]	Prospective cohort, adults exposed to the September 11, 2001 World Trade Center disaster	PTSD Checklist score ≥44	Cerebrovascular or heart disease hospitalization	46 346 participants (men 27667, women 18679; >18 years at exposure), mean follow-up 6.5 years	Participants with PTSD vs without PTSD at baseline: HR 1.32, 95% CI 1.01 to 1.71 in women but HR 1.16, 95% CI 0.97 to 1.40 in men	No	No
Vaccarino V 2013[5]	Prospective cohort, twins from the Vietnam Era Twin Registry (veteran sample)	PTSD diagnosis	CHD diagnosed during clinical visit, identified through clinical events or quantitative measures of myocardial perfusion	562 twins (281 pairs) mean age 42.6 years; median follow-up 13 years	Twins with PTSD vs Twins without: OR 2.1 (95% CI 1.1 to 3.9)	Yes, a twin study	Controlled for major depression, alcohol or drug abuse/dependence at baseline
Sumner JA 2015[6]	Prospective cohort, women in the Nurses' Health Study II	Trauma exposure and PTSD symptoms	CVD events (MI and stroke) confirmed by additional information or medical record review	49978 women mean age 35 at entry follow-up up to 20 years	Compared to individuals with no trauma exposure, ≥4 PTSD symptoms:HR,1.60 95% CI 1.20 to 2.13; 1 to 3 PTSD symptoms: 0.99 (0.71 to 1.38) ; trauma-exposed and no PTSD symptoms: 1.45 (1.15 to 1.83)	No	No
Roy SS 2015[7]	Prospective cohort, community-based sample of veterans	PTSD diagnosis	Incident heart failure	8242 veterans , mean age 63 years at entry,	Veterans with PTSD vs without PTSD: HR1.47(95% CI 1.13 to 1.92)	No	A sensitivity analysis was performed where comorbid illnesses (including depression,

[1] Kubzansky, L. D., et al. (2007). "Prospective study of posttraumatic stress disorder symptoms and coronary heart disease in the normative aging study." Archives of General Psychiatry 64(1): 109-116.
[2] Kubzansky, L. D., et al. (2009). "A prospective study of posttraumatic stress disorder symptoms and coronary heart disease in women." Health Psychol 28(1): 125-130.
[3] Jordan, H. T., et al. (2011). "Heart disease among adults exposed to the September 11, 2001 World Trade Center disaster: Results from the World Trade Center Health Registry." Preventive Medicine 53(6): 370-376.
[4] Jordan, H. T., et al. (2013). "Cardiovascular disease hospitalizations in relation to exposure to the September 11, 2001 World Trade Center Disaster and posttraumatic stress disorder." Journal of the American Heart Association 2(5).
[5] Vaccarino, V., et al. (2013). "Post-traumatic stress disorder and incidence of coronary heart disease: a twin study." Journal of the American College of Cardiology 62(11): 970-978.
[6] Sumner, J. A., et al. (2015). "Trauma exposure and posttraumatic stress disorder symptoms predict onset of cardiovascular events in women." Circulation 132(4): 251-259.
[7] Roy, S. S., et al. (2015). "Posttraumatic stress disorder and incident heart failure among a community-based sample of US veterans." American Journal of Public Health 105(4): 757-763.

				mean follow-up of 7.2 years			anxiety disorder, and adjustment disorder) , were added to the model (data not shown)
Gradus JL 2015[8]	Prospective cohort Danish national registry data	PTSD and adjustment disorder diagnoses	CVD events including MI, stroke, ischemic stroke and VTE	4724 PTSD, 64,855 adjustment disorder mean age 19 years mean follow-up 7.9 years	PTSD patients vs general population: SIR 1.5 (95% CI 1.1 to 1.9) for MI; 1.7(1.4 to 2.1) for stroke; 1.8 (1.4 to 2.4 for ischemic stroke; and 2.1 (95% CI 1.7 to 2.7) for VTE adjustment disorder patients vs general population: SIR 1.5 (95% CI 1.4 to 1.6) for MI; 1.8(1.7 to 1.9) for stroke; 1.7 (1.6 to 1.9) for ischemic stroke; and 1.9 (95% CI 1.8 to 2.0) for VTE	No	Adjusted for depression or alcohol abuse diagnoses at baseline
Sumner JA 2016[9]	Prospective cohort, Women in the Nurses' Health Study II	Trauma exposure and PTSD symptoms	Incident hypertension (physician-diagnosed), self-reported at baseline, and subsequent biennial questions	47 514 women mean age 35 at entry, follow-up up to 22 years	Compared to women with no trauma exposure, 6-7 PTSD symptoms: HR 1.20, 95% CI 1.12 to 1.30; 4-5 symptoms: HR 1.17, 95% CI 1.10 to 1.25; 1-3 symptoms: HR 1.12, 95% CI 1.06 to 1.18; no symptom HR 1.04, 95% CI 1.00 to 1.09	No	Adjusted for self-reported lifetime depression (≥2 weeks) in sensitivity analysis---HRs were attenuated to 1.10, 1.11, 1.05, 0.98
Sumner JA 2016[10]	Prospective cohort, Women in the Nurses' Health Study II	Trauma exposure and PTSD symptoms	Physician-diagnosed VTE, self-reported at baseline, and subsequent biennial questions	49296 women, mean age 35 at entry, follow-up up to 22 years	Compared to women with no trauma exposure, 6-7 PTSD symptoms: HR 2.42, 95% CI 1.83 to 3.20; 4-5 symptoms: HR 2.00, 95% CI 1.55 to 2.59; 1-3 symptoms: HR 1.44, 95% CI 1.12 to 1.84; no symptom HR 1.72, 95% CI 1.43 to 2.08	No	Adjusted for self-reported lifetime depression (≥2 weeks) in sensitivity analysis---HRs were attenuated to 2.06, 1.77, 1.34, 1.68
Burg MM 2017[11]	Prospective cohort, representative sample of veterans	PTSD diagnosis	Incident hypertension identified through:(1) a clinical diagnosis of hypertension (2) a prescription for antihypertensive medication (3) a clinic blood pressure test (≥140/90 mm Hg, systolic/diastolic)	194,319 veterans (85% were men), median age 27.9; median follow-up 2.4 years	Veterans with PTSD vs. without PTSD: HRs ranged from 1.12 (95% CI, 1.08 to 1.17) to 1.30 (95% CI, 1.26 to 1.34), depending on different approaches of hypertension case identification	No	Partly, adjusted for major depression at baseline

CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; MI, myocardial infarction; OR, odds ratio; PTSD, posttraumatic stress disorder; SIR, standardized incidence rate; VTE, venous thromboembolism.

[8] Gradus, J. L., et al. (2015). "Associations between stress disorders and cardiovascular disease events in the Danish population." Bmj Open 5(12).
[9] Sumner, J. A., et al. (2016). "Post-traumatic stress disorder symptoms and risk of hypertension over 22 years in a large cohort of younger and middle-aged women." Psychological Medicine 46(15): 3105-3116.
[10] Sumner, J. A., et al. (2016). "Associations of trauma exposure and posttraumatic stress symptoms with venous thromboembolism over 22 years in women." Journal of the American Heart Association 5(5).
[11] Burg, M. M., et al. (2017). "Risk for incident hypertension associated with posttraumatic stress disorder in military veterans and the effect of posttraumatic stress disorder treatment." Psychosomatic Medicine 79(2): 181-188.

Supplementary Table B International Classification of Diseases (ICD) codes for exposure and outcome identifications

		ICD-9	ICD-10
All stress-related disorders		309, 308	F43
Posttraumatic stress disorder		309B	F43.1
Acute stress reaction		309A, 308	F43.0
Adjustment disorder		309X	F43.2
Other stress reactions		309X	F43.8, F43.9
Any psychiatric disorder		290–315	F**
Any cardiovascular disease		390-438, 440,444,445	I00-I70, I730, I74-I75
Major category	*Individual diagnosis*		
Ischemic heart disease	Acute myocardial infarction	410, 411	I21, I23, I24
	Other ischemic heart disease (excluding ischemic cardiomyopathy)	412-414	I20, I22, I25 (excl. I25.5)
Cerebrovascular disease*	Arachnoidal bleeding	430	I60
	Hemorrhagic stroke	431, 432	I61-I62
	Ischemic stroke	433, 434	I63-I64
	Other cerebrovascular disease	436-438	I65-I69
Emboli and thrombosis	Artery thrombosis/embolus	444,445	I74,I75
	Pulmonary emboli	415	I26
Hypertensive diseases	Essential hypertension	401	I10
	Other hypertensive disease	402-405	I11- I16, I674
Heart failure	Heart failure	428	I50
	Ischemic cardiomyopathy	-	I25.5
	Takotsubo cardiomyopathy	-	I42.0, I42.8, I42.9
Arrhythmia/conduction disorder	Arrhythmia	427 (excl.427F)	I47-I49
	Conduction disorder	426	I44-I45
	Cardiac arrest	427F	I46
Covariates: history of severe somatic conditions			
Chronic pulmonary disease		490-496	J40-J47
Connective tissue disease		710A, 710B, 710E, 714A, 714B, 714C, 714W,714X, 725	M05, M06, M32-M34, M35.1, M35.3
Diabetes		250	E10-E14
Renal diseases		582,583	N01, N03, N05.2-N05.7
Liver diseases		571C, 571E,571F, 571G, 572C, 572D, 572E, 572W, 456A, 456B, 456C	K70.2-K70.4, K71.7, K72.1, K72.9, K73, K74, K76.6, K76.7
Ulcer diseases		531-534	K25-K28
HIV infection/AIDS		042-044	B20-B24

*We additionally defined acute cerebrovascular disease as a diagnosis of arachnoid bleeding, intracerebral haemorrhage, or cerebral infarction (ICD 9 430,431,434 and ICD 10 I60, I61, I63).

Supplementary Table C Crude incidence rates and hazard ratios with 95% confidence intervals for cardiovascular diseases (CVD) among patients with **posttraumatic stress disorder**, compared to *their full siblings or matched unexposed individuals*, **stratified by time of follow-up** (<1 or ≥1 year)

		Analyses of sibling cohort		Analyses of population-matched cohort	
		Number of cases (incidence rate*), patients/ siblings	Hazard ratio (95% confidence interval)†	Number of cases (incidence rate*), patients/unexposed individuals	Hazard ratio (95% confidence interval)†
	Model information	**<1 year of follow-up**			
Any CVD	i. Controlled for sex, birth year, education level, family income, and marital status	54(6.65)/63(4.73)	1.96 (1.25 to 3.06)	73(6.98)/354(3.37)	1.94 (1.50 to 2.52)
	ii. above + history of other psychiatric disorder		2.05 (1.20 to 3.49)		1.63 (1.22 to 2.17)
	iii. above + history of severe somatic diseases		2.03 (1.19 to 3.47)		1.55 (1.16 to 2.06)
	iv. above + family history of CVD		-		1.53 (1.14 to 2.04)
Subtypes of CVD‡					
Ischemic heart disease		6(0.74)/10(0.75)	2.25 (0.63 to 8.10)	8(0.76)/72(0.69)	0.89 (0.40 to 2.00)
Cerebrovascular disease		8(0.98)/10(0.75)	3.70 (0.78 to 17.6)	11(1.05)/45(0.43)	1.63 (0.71 to 3.72)
Emboli and thrombosis		3(0.37)/5(0.37)	1.11 (0.13 to 9.44)	7(0.67)/20(0.19)	3.22 (0.93 to 11.1)
Hypertensive disease		14(1.72)/14(1.05)	2.17 (0.80 to 5.90)	18(1.72)/63(0.60)	2.60 (1.39 to 4.86)
Heart failure		2(0.25)/0(0)	-	3(0.29)/15(0.14)	1.57 (0.23 to 10.7)
Arrhythmia/conduction disorder		11(1.35)/18(1.35)	0.98 (0.32 to 3.00)	15(1.43)/103(0.98)	0.97 (0.53 to 1.79)
Fatal CVD events€		5(0.61)/2(0.15)	0.28 (0.01 to 7.88)	5(0.48)/24(0.23)	1.24 (0.38 to 4.09)
	Model information	**≥1 year of follow-up**			
Any CVD	i. Controlled for sex, birth year, education level, family income, and marital status	507(10.10)/723(7.99)	1.59 (1.38 to 1.83)	676(10.51)/4575(6.83)	1.59 (1.46 to 1.73)
	ii. above + history of other psychiatric disorder		1.45 (1.24 to 1.69)		1.41 (1.29 to 1.54)
	iii. above + history of severe somatic diseases		1.44 (1.23 to 1.68)		1.38 (1.26 to 1.51)
	iv. above + family history of CVD		-		1.37 (1.25 to 1.50)
Subtypes of CVD‡					
Ischemic heart disease		144(2.74)/220(2.36)	1.46 (1.06 to 2.00)	191(2.85)/1264(1.84)	1.29 (1.09 to 1.53)
Cerebrovascular disease		126(2.39)/129(1.37)	2.15 (1.53 to 3.01)	158(2.35)/776(1.12)	1.91 (1.57 to 2.31)
Emboli and thrombosis		45(0.85)/41(0.43)	2.45 (1.28 to 4.68)	54(0.80)/319(0.46)	1.57 (1.14 to 2.16)
Hypertensive disease		111(2.10)/157(1.67)	1.58 (1.14 to 2.18)	146(2.17)/1155(1.67)	1.18 (0.97 to 1.42)
Heart failure		45(0.85)/64(0.68)	1.77 (1.03 to 3.04)	60(0.88)/360(0.52)	1.29 (0.95 to 1.75)
Arrhythmia/conduction disorder		128(2.43)/214(2.29)	1.09 (0.82 to 1.44)	183(2.73)/1398(2.03)	1.19 (1.00 to 1.41)
Fatal CVD events€		43(0.85)/55(0.61)	1.84 (0.97 to 3.52)	60(0.94)/344(0.51)	1.30 (0.95 to 1.79)

CVD, cardiovascular diseases

* per 1,000 person-years

† Hazard ratios and 95% confidence intervals were derived from Cox models, stratified by family identifier (for sibling-based comparison) or matching identifier (birth year and sex, for population-based comparison), and adjusted for factors listed in model information column. Time since the index date was used as underlying time scale.

‡ The calculation of hazard ratios and 95% confidence intervals for subtypes of CVD was based on fully adjusted COX models (model iii for sibling-based comparison, and model iv for population-based comparison)

€ A fatal CVD was defined as death within 30 days after a major incident CVD event. This group involved fatal CVD cases from all above subtypes.

Supplementary Table D Crude incidence rates and hazard ratios with 95% confidence intervals for cardiovascular diseases (CVD) among patients with **acute stress reaction**, compared to *their full siblings or matched unexposed individuals*, **stratified by time of follow-up** (<1 or ≥1 year)

		Analyses of sibling cohort		Analyses of population-matched cohort	
		Number of cases (incidence rate*), patients/ siblings	Hazard ratio (95% confidence interval)†	Number of cases (incidence rate*), patients/unexposed individuals	Hazard ratio (95% confidence interval)†
	Model information	**<1 year of follow-up**			
Any CVD	i. Controlled for sex, birth year, education level, family income, and marital status	380(8.23)/378(4.99)	1.74 (1.48 to 2.06)	517(8.67)/2558(4.26)	2.00 (1.82 to 2.20)
	ii. above + history of other psychiatric disorder		1.63 (1.37 to 1.94)		1.77 (1.60 to 1.96)
	iii. above + history of severe somatic diseases		1.62 (1.36 to 1.93)		1.75 (1.59 to 1.94)
	iv. above + family history of CVD		-		1.75 (1.58 to 1.93)
Subtypes of CVD‡					
Ischemic heart disease		95(2.05)/97(1.28)	1.69 (1.17 to 2.45)	517(8.67)/2558(4.26)	1.81 (1.48 to 2.23)
Cerebrovascular disease		55(1.19)/52(0.68)	1.81 (1.11 to 2.96)	131(2.19)/573(0.95)	2.08 (1.62 to 2.68)
Emboli and thrombosis		31(0.67)/26(0.34)	2.03 (1.00 to 4.10)	86(1.44)/353(0.59)	1.89 (1.28 to 2.81)
Hypertensive disease		71(1.53)/59(0.78)	2.28 (1.47 to 3.53)	38(0.63)/146(0.24)	1.89 (1.49 to 2.41)
Heart failure		19(0.41)/15(0.20)	4.37 (1.04 to 18.42)	92(1.54)/472(0.78)	2.02 (1.27 to 3.21)
Arrhythmia/conduction disorder		85(1.84)/105(1.38)	1.28 (0.89 to 1.83)	26(0.43)/106(0.18)	1.48 (1.20 to 1.82)
Fatal CVD events€		48(1.04)/31(0.41)	3.65 (1.55 to 8.59)	116(1.94)/730(1.21)	2.24 (1.64 to 3.05)
	Model information	**≥1 year of follow-up**			
Any CVD	i. Controlled for sex, birth year, education level, family income, and marital status	3461(10.34)/5439(8.87)	1.40 (1.33 to 1.48)	4713(10.82)/33227(7.27)	1.54 (1.49 to 1.59)
	ii. above + history of other psychiatric disorder		1.32 (1.25 to 1.39)		1.41 (1.36 to 1.46)
	iii. above + history of severe somatic diseases		1.31 (1.24 to 1.38)		1.39 (1.34 to 1.43)
	iv. above + family history of CVD		-		1.38 (1.34 to 1.43)
Subtypes of CVD‡					
Ischemic heart disease		1043(3.00)/1761(2.78)	1.39 (1.26 to 1.54)	1425(3.15)/9080(1.93)	1.44 (1.36 to 1.53)
Cerebrovascular disease		688(1.96)/984(1.54)	1.44 (1.27 to 1.62)	956(2.10)/5630(1.19)	1.55 (1.44 to 1.67)
Emboli and thrombosis		286(0.81)/356(0.56)	1.46 (1.20 to 1.78)	382(0.83)/2273(0.48)	1.49 (1.32 to 1.67)
Hypertensive disease		713(2.04)/1225(1.92)	1.15 (1.03 to 1.29)	975(2.14)/8170(1.74)	1.24 (1.15 to 1.33)
Heart failure		286(0.81)/455(0.71)	1.40 (1.14 to 1.71)	412(0.90)/2563(0.54)	1.31 (1.17 to 1.47)
Arrhythmia/conduction disorder		944(2.70)/1488(2.34)	1.21 (1.09 to 1.33)	1260(2.77)/10185(2.17)	1.24 (1.16 to 1.32)
Fatal CVD events€		393(1.17)/528(0.86)	1.43 (1.19 to 1.72)	581(1.34)/2640(0.58)	1.79 (1.61 to 1.98)

CVD, cardiovascular diseases

† Hazard ratios and 95% confidence intervals were derived from Cox models, stratified by family identifier (for sibling-based comparison) or matching identifier (birth year and sex, for population-based comparison), and adjusted for factors listed in model information column. Time since the index date was used as underlying time scale.

‡ The calculation of hazard ratios and 95% confidence intervals for subtypes of CVD was based on fully adjusted COX models (model iii for sibling-based comparison, and model iv for population-based comparison)

€ A fatal CVD was defined as death within 30 days after a major incident CVD event. This group involved fatal CVD cases from all above subtypes.

Supplementary Table E Crude incidence rates and hazard ratios with 95% confidence intervals for cardiovascular diseases (CVD) among patients with **adjustment disorder and other stress reactions**, compared to *their full siblings or matched unexposed individuals*, **stratified by time of follow-up** (<1 or ≥1 year)

		Analyses of sibling cohort		**Analyses of population-matched cohort**	
		Number of cases (incidence rate*), patients/ siblings	Hazard ratio (95% confidence interval)†	Number of cases (incidence rate*), patients/unexposed individuals	Hazard ratio (95% confidence interval)†
	Model information	**<1 year of follow-up**			
Any CVD	i. Controlled for sex, birth year, education level, family income, and marital status	377(8.13)/365(4.90)	1.77 (1.49 to 2.10)	504(8.48)/2712(4.54)	1.84 (1.68 to 2.03)
	ii. above + history of other psychiatric disorder		1.65 (1.39 to 1.98)		1.72 (1.56 to 1.91)
	iii. above + history of severe somatic diseases		1.64 (1.37 to 1.96)		1.70 (1.54 to 1.88)
	iv. above + family history of CVD		-		1.69 (1.53 to 1.88)
Subtypes of CVD‡					
Ischemic heart disease		60(1.29)/86(1.15)	1.33 (0.88 to 2.01)	87(1.46)/582(0.97)	1.40 (1.10 to 1.79)
Cerebrovascular disease		57(1.23)/57(0.76)	1.77 (1.08 to 2.89)	79(1.33)/331(0.55)	1.93 (1.48 to 2.52)
Emboli and thrombosis		27(0.58)/25(0.33)	2.29 (0.91 to 5.74)	39(0.65)/175(0.29)	1.94 (1.34 to 2.81)
Hypertensive disease		83(1.78)/70(0.94)	2.40 (1.52 to 3.78)	109(1.83)/537(0.90)	2.02 (1.62 to 2.51)
Heart failure		20(0.43)/14(0.19)	5.73 (1.07 to 30.6)	23(0.39)/96(0.16)	1.77 (1.08 to 2.93)
Arrhythmia/conduction disorder		100(2.15)/92(1.23)	1.52 (1.08 to 2.15)	132(2.22)/804(1.34)	1.54 (1.27 to 1.87)
Fatal CVD events€		43(0.92)/33(0.44)	1.36 (0.71 to 2.61)	59(0.99)/203(0.34)	2.04 (1.46 to 2.85)
	Model information	**≥1 year of follow-up**			
Any CVD	i. Controlled for sex, birth year, education level, family income, and marital status	3278(10.21)/5116(9.01)	1.34 (1.27 to 1.41)	4438(10.72)/31681(7.33)	1.50 (1.46 to 1.55)
	ii. above + history of other psychiatric disorder		1.25 (1.18 to 1.32)		1.36 (1.31 to 1.41)
	iii. above + history of severe somatic diseases		1.23 (1.17 to 1.31)		1.34 (1.30 to 1.39)
	iv. above + family history of CVD		-		1.34 (1.29 to 1.38)
Subtypes of CVD‡					
Ischemic heart disease		934(2.80)/1544(2.63)	1.28 (1.15 to 1.43)	1289(2.99)/8476(1.91)	1.39 (1.30 to 1.48)
Cerebrovascular disease		603(1.80)/893(1.51)	1.34 (1.18 to 1.53)	833(1.92)/5260(1.18)	1.43 (1.32 to 1.54)
Emboli and thrombosis		291(0.86)/352(0.59)	1.51 (1.25 to 1.83)	398(0.91)/2050(0.46)	1.79 (1.59 to 2.02)
Hypertensive disease		707(2.11)/1185(2.01)	1.13 (1.00 to 1.27)	947(2.19)/7973(1.79)	1.21 (1.12 to 1.30)
Heart failure		278(0.83)/414(0.70)	1.41 (1.15 to 1.73)	404(0.93)/2413(0.54)	1.39 (1.23 to 1.56)
Arrhythmia/conduction disorder		903(2.71)/1520(2.59)	1.09 (0.98 to 1.21)	1217(2.82)/9533(2.15)	1.25 (1.18 to 1.34)
Fatal CVD events€		377(1.17)/447(0.79)	1.64 (1.35 to 2.00)	541(1.30)/2432(0.56)	1.60 (1.44 to 1.79)

CVD, cardiovascular diseases

* per 1,000 person-years

† Hazard ratios and 95% confidence intervals were derived from Cox models, stratified by family identifier (for sibling-based comparison) or matching identifier (birth year and sex, for population-based comparison), and adjusted for factors listed in model information column. Time since the index date was used as underlying time scale.

‡ The calculation of hazard ratios and 95% confidence intervals for subtypes of CVD was based on fully adjusted COX models (model iii for sibling-based comparison, and model iv for population-based comparison)

€ A fatal CVD was defined as death within 30 days after a major incident CVD event. This group involved fatal CVD cases from all above subtypes.

Supplementary Table F Number of cases and crude incidence rates (per 1000 person-years) for cardiovascular diseases (CVD) among patients with stress-related disorders, compared to ***their full siblings or matched unexposed individuals***, by different characteristics

	Analyses of sibling cohort, patients/siblings				**Analyses of population-matched cohort,** patients/unexposed individuals			
	All stress-related disorders	Posttraumatic stress disorder	Acute stress reaction	Adjustment disorder and other stress reactions	All stress-related disorders	Posttraumatic stress disorder	Acute stress reaction	Adjustment disorder and other stress reactions
Overall	8057(9.98)/12082(8.42)	561(9.59)/786(7.57)	3841(10.10)/5815(8.44)	3655(9.94)/5481(8.53)	10921(10.46)/75107(6.91)	749(10.04)/4929(6.36)	5230(10.57)/35785(6.92)	4942(10.42)/34393(6.99)
By sex								
Male	3875(12.80)/7118(9.93)	243(14.01)/476(9.05)	1968(12.72)/3449(10.0)	1664(12.73)/3193(9.96)	5161(13.15)/37060(8.87)	312(13.84)/2145(9.07)	2634(13.14)/18669(8.70)	2215(13.07)/16246(9.04)
Female	4182(8.30)/4964(6.91)	318(7.74)/310(6.05)	1873(8.28)/2366(6.85)	1991(8.42)/2288(7.11)	5760(8.84)/38047(5.69)	437(8.39)/2784(5.17)	2596(8.82)/17116(5.65)	2727(8.94)/18147(5.81)
By age at index date (tertiles), years								
≤28	956(3.58)/988(2.23)	90(3.89)/88(2.32)	448(3.49)/485(2.28)	418(3.62)/415(2.15)	1246(3.54)/6451(1.82)	112(3.81)/488(1.64)	597(3.53)/3155(1.84)	537(3.51)/2808(1.82)
29-42	2375(7.89)/3186(6.18)	164(8.29)/199(5.70)	1198(8.22)/1605(6.29)	1013(7.47)/1382(6.13)	3044(8.03)/18892(4.79)	215(8.71)/1202(4.67)	1547(8.40)/9511(4.95)	1282(7.53)/8179(4.64)
≥43	4726(19.7)/7908(16.6)	307(19.7)/499(16.1)	2195(20.5)/3725(16.8)	2224(19.1)/3684(16.5)	6631(21.17)/49764(14.71)	422(20.55)/3239(14.65)	3086(21.81)/23119(15.01)	3123(20.66)/23406(14.44)
By attained age, i.e. age during follow-up, years								
<50	3116(5.38)/3429(3.57)	255(5.88)/238(3.29)	1474(5.35)/1645(3.56)	1387(5.33)/1546(3.63)	3985(5.35)/21934(2.90)	329(6.01)/1421(2.55)	1909(5.37)/10525(2.91)	1747(5.23)/9988(2.95)
≥50	4941(21.64)/8653(18.2)	306(20.30)/548(17.42)	2367(22.39)/4170(18.39)	2268(21.09)/3935(18.13)	6936(23.15)/53178(16.05)	420(21.16)/3508(16.03)	3321(23.80)/25261(16.26)	3195(22.78)/24409(15.84)
By calendar year at index date								
1987-1996	3156(11.3)/5465(9.47)	257(11.8)/416(9.45)	1635(11.3)/2879(9.54)	1264(11.3)/2170(9.39)	4382(11.98)/30951(7.84)	355(12.69)/2588(8.54)	2285(12.01)/15945(7.79)	1742(11.81)/12418(7.78)
1997-2006	3392(9.72)/4845(8.26)	182(8.90)/234(6.74)	1557(9.88)/2172(8.13)	1653(9.66)/2439(8.56)	4541(10.09)/31460(6.81)	234(9.08)/1492(5.68)	2088(10.21)/14305(6.78)	2219(10.10)/15663(6.97)
2007-2013	1509(8.41)/1772(6.52)	122(7.53)/136(5.41)	649(8.25)/764(6.37)	738(8.74)/872(6.88)	1998(8.75)/12696(5.51)	160(7.67)/849(4.06)	857(8.55)/5535(5.45)	981(9.15)/6312(5.85)
By history of severe somatic diseases*								
Yes	1870(13.95)/2145(11.68)	138(13.25)/153(11.27)	866(13.84)/1037(11.93)	866(14.18)/955(11.49)	2581(14.35)/12235(10.12)	183(13.37)/789(9.34)	1201(14.17)/5765(10.13)	1197(14.70)/5681(10.24)
No	6187(9.19)/9937(7.94)	423(8.80)/633(7.01)	2975(9.33)/4778(7.94)	2789(9.09)/4526(8.09)	8340(9.65)/62872(6.51)	566(9.29)/4140(5.99)	4029(9.82)/30020(6.52)	3745(9.53)/28712(6.57)

By previous history of psychiatric disorders[†]								
Yes	2947(12.8)/1573(11.9)	242(11.3)/98(9.55)	1352(13.0)/749(11.7)	1353(12.8)/726(12.4)	4022(13.21)/6243(10.58)	306(11.22)/419(9.61)	1852(13.34)/2927(10.59)	1864(13.48)/2897(10.72)
No	5110(8.86)/10509(8.07)	319(8.58)/688(7.34)	2489(8.98)/5066(8.11)	2302(8.78)/4755(8.14)	6899(9.33)/68864(6.70)	443(9.36)/4510(6.16)	3378(9.49)/32858(6.71)	3078(9.16)/31496(6.77)
By family history of CVD among first-degree relatives								
Yes	5100(14.4)/7904(12.2)	349(14.4)/496(11.1)	2387(14.5)/3738(12.1)	2364(14.3)/3670(12.4)	6566(14.99)/44756(10.47)	442(14.76)/2839(10.00)	3069(14.99)/20917(10.46)	3055(15.02)/21000(10.54)
No	2957(6.52)/4178(5.32)	212(6.20)/290(4.91)	1454(6.70)/2077(5.46)	1291(6.38)/1811(5.24)	4355(7.19)/30351(4.60)	307(6.87)/2090(4.25)	2161(7.45)/14868(4.69)	1887(6.96)/13393(4.57)

* Involved severe somatic diseases include chronic pulmonary disease, connective tissue disease, diabetes, renal diseases, liver diseases, ulcer diseases, and HIV infection/AIDS.
† The first diagnosis of a psychiatric disorder, other than stress-related disorders, occurred *more than* three months prior to the index date

Supplementary Table G Change of relative risk for acute cardiovascular events over follow-up time among patients with stress-related disorders, compared to ***their full siblings***

	Acute cerebrovascular disease		**Acute myocardial infarction**		**Cardiac arrest**	
	Number of cases (incidence rate*), patients/ siblings	Hazard ratio (95% confidence interval)†	Number of cases (incidence rate*), patients/ siblings	Hazard ratio (95% confidence interval)†	Number of cases (incidence rate*), patients/ siblings	Hazard ratio (95% confidence interval)†
< 1 months	28(1.08)/31(0.74)	1.85 (0.99 to 3.44)	25(0.97)/19(0.46)	2.81 (1.33 to 5.91)	3(0.35)/0(0)	-
1-5 months	17(0.68)/18(0.45)	1.84 (0.79 to 3.41)	18(0.72)/31(0.77)	0.92 (0.45 to 1.90)	12(0.29)/7(0.10)	3.71 (0.88 to 8.59)
6-11months	42(0.85)/40(0.49)	1.79 (1.06 to 3.03)	41(0.83)/54(0.67)	1.23 (0.75 to 2.02)	10(0.20)/8(0.10)	2.34 (0.63 to 8.78)
1-4 years	298(0.94)/349(0.66)	1.81 (1.50 to 2.17)	261(0.82)/450(0.85)	1.28 (1.07 to 1.55)	64(0.20)/58(0.11)	2.24 (1.48 to 3.39)
5-9 years	267(1.17)/428(1.06)	1.23 (1.03 to 1.47)	313(1.38)/492(1.23)	1.45 (1.22 to 1.74)	62(0.27)/73(0.18)	1.53 (1.03 to 2.28)
≥ 10 years	489(2.56)/744(1.92)	1.65 (1.44 to 1.90)	466(2.48)/854(2.24)	1.57 (1.37 to 1.81)	90(0.47)/126(0.33)	1.65 (1.19 to 2.28)

* per 1,000 person-years

† Cox models were stratified by family identifiers, and adjusted for age at index date, sex, education level, family income, marital status, history of severe somatic diseases, and history of other psychiatric disorders. Time since the index date was used as underlying time scale.

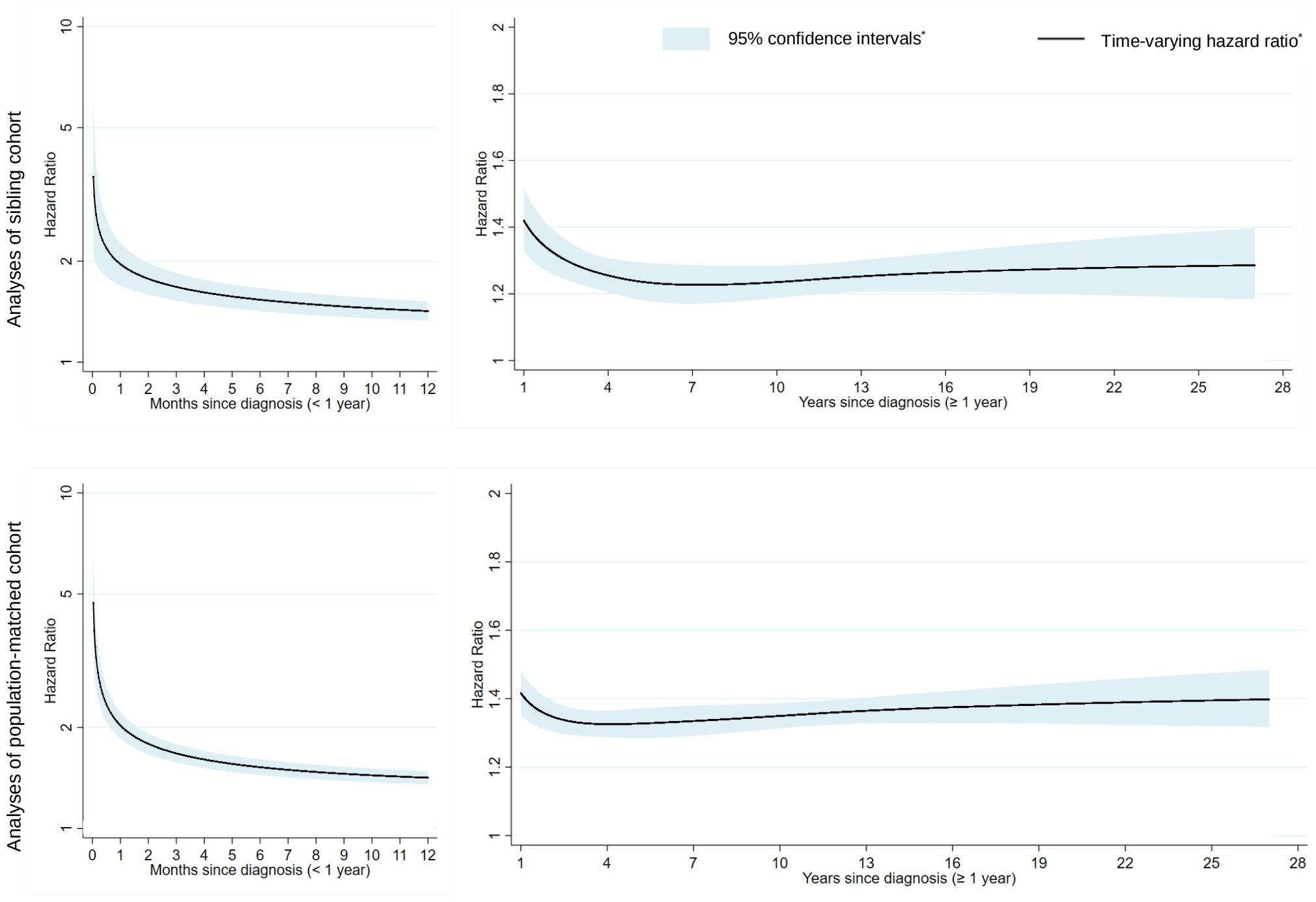
Supplementary Table H Hazard ratios with 95% confidence intervals for cardiovascular diseases (CVD) among patients with stress-related disorders, compared to ***their full siblings***, using altered definition for the history of other psychiatric disorders (as one covariate)

	All stress-related disorders	Posttraumatic stress disorder	Acute stress reaction	Adjustment disorder and other stress reactions
		<1 year of follow-up		
Any CVD	1.64 (1.45 to 1.85)	1.90 (1.13 to 3.20)	1.63 (1.37 to 1.93)	1.64 (1.37 to 1.96)
Ischemic heart disease	1.53 (1.17 to 1.99)	2.84 (0.57 to 14.2)	1.69 (1.17 to 2.45)	1.32 (0.88 to 2.00)
Cerebrovascular disease	1.73 (1.25 to 2.39)	5.36 (0.64 to 45.1)	1.81 (1.11 to 2.96)	1.77 (1.08 to 2.91)
Emboli and thrombosis	1.74 (1.08 to 2.78)	1.17(0.14 to 9.82)	1.98 (0.97 to 4.02)	2.29 (0.91 to 5.74)
Hypertensive disease	2.12 (1.60 to 2.81)	3.26 (0.75 to 14.1)	2.25 (1.46 to 3.47)	2.36 (1.51 to 3.70)
Heart failure	2.42 (1.22 to 4.82)	-	4.37 (1.04 to 18.4)	5.29 (1.02 to 27.4)
Arrhythmia/conduction disorder	1.38 (1.09 to 1.75)	0.69 (0.14 to 3.38)	1.29 (0.90 to 1.85)	1.54 (1.09 to 2.17)
Fatal CVD events[†]	1.77 (1.13 to 2.75)	0.28 (0.10 to 7.88)	3.65 (1.55 to 8.59)	1.42 (0.74 to 2.75)
		≥1 year of follow-up		
Any CVD	1.29 (1.25 to 1.34)	1.45 (1.25 to 1.70)	1.31 (1.24 to 1.39)	1.24 (1.17 to 1.31)
Ischemic heart disease	1.35 (1.26 to 1.45)	1.45 (1.06 to 1.98)	1.40 (1.27 to 1.55)	1.29 (1.16 to 1.43)
Cerebrovascular disease	1.43 (1.31 to 1.55)	2.13 (1.52 to 2.99)	1.43 (1.27 to 1.62)	1.35 (1.19 to 1.54)
Emboli and thrombosis	1.52 (1.33 to 1.73)	2.54 (1.34 to 4.84)	1.48 (1.21 to 1.79)	1.48 (1.22 to 1.79)
Hypertensive disease	1.17 (1.08 to 1.26)	1.58 (1.15 to 2.19)	1.16 (1.04 to 1.30)	1.14 (1.01 to 1.28)
Heart failure	1.40 (1.22 to 1.60)	1.73 (1.01 to 2.98)	1.40 (1.14 to 1.71)	1.41 (1.15 to 1.73)
Arrhythmia/conduction disorder	1.16 (1.08 to 1.24)	1.10 (0.84 to 1.46)	1.21 (1.09 to 1.34)	1.09 (0.99 to 1.21)
Fatal CVD events[†]	1.57 (1.38 to 1.78)	1.84 (0.97 to 3.49)	1.45 (1.21 to 1.74)	1.64 (1.35 to 2.00)

CVD, cardiovascular diseases

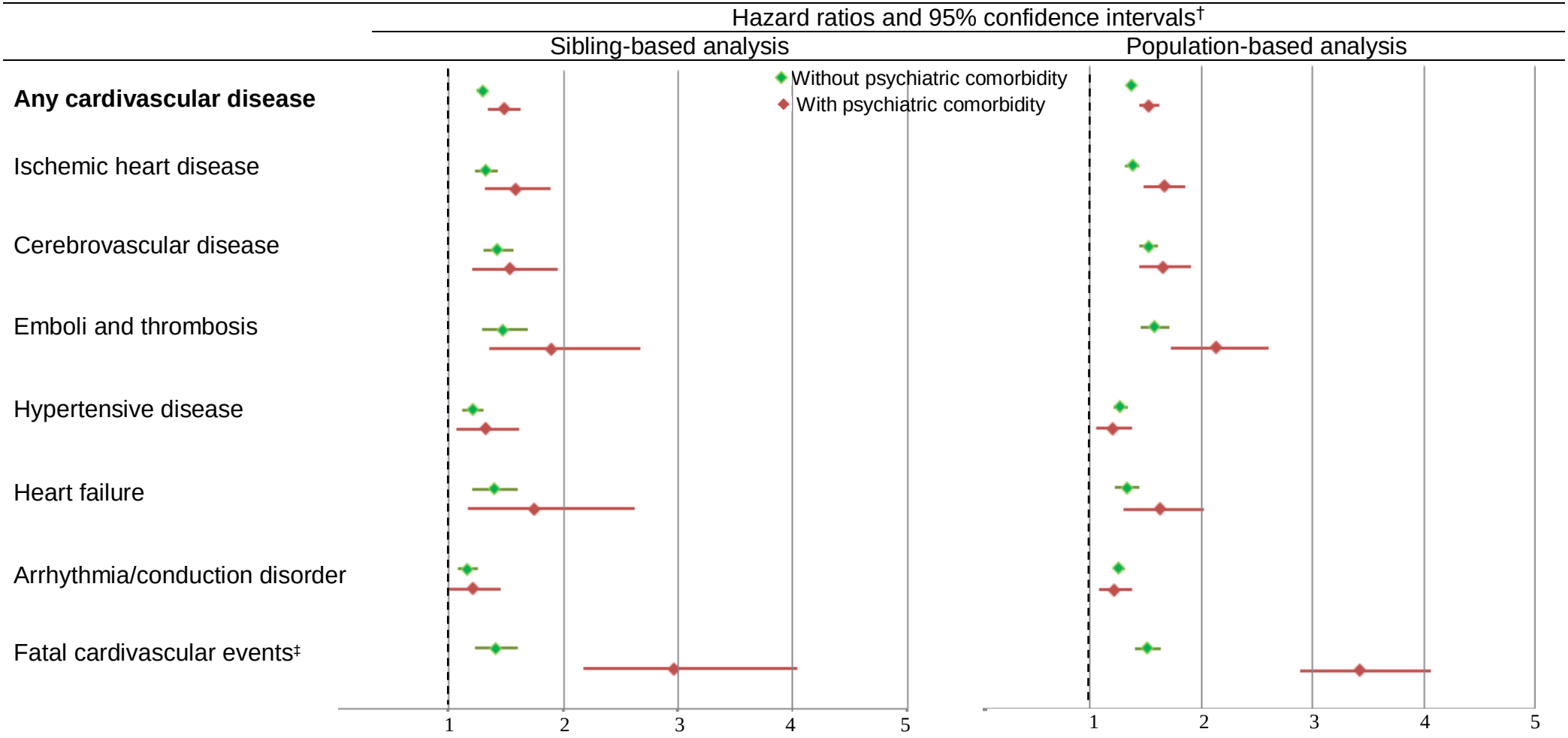
[*] Cox models were stratified by matching identifiers (birth year and sex), and adjusted for education level, family income, marital status, history of severe somatic diseases, and history of other psychiatric disorders (180 days prior to the diagnosis of stress-related disorder). Time since the index date was used as underlying time scale.

[†]A fatal CVD was defined as death within 30 days after a major incident CVD event. This group involved fatal CVD cases from all above subtypes.


Analyses of sibling cohort
Analyses of population-matched cohort
Hazard Ratio
Months since diagnosis (< 1 year)
Years since diagnosis (≥ 1 year)
95% confidence intervals*
Time-varying hazard ratio*

Supplementary Figure A Change of the relative risk for cardiovascular diseases over follow-up time among patients with any stress-related disorder, compared to their full siblings (analyses of sibling cohort) or matched unexposed individuals (analyses of population-matched cohort)

* Time-varying hazard ratios and 95% confidence intervals were derived from flexible parametric survival models, allowing the effect of stress-related disorders to vary over time. A spline with 5 df (4 intermediate knots and 2 knots at each boundary, placed at quintiles of distribution of events) was used for the baseline rate, while 3 df was used for the time-varying effect. All models were adjusted for age at index date, sex, education level, family income, marital status, history of severe somatic diseases, family history of CVD, and history of other psychiatric disorders.



Supplementary Figure B. Relative risks for cardiovascular diseases or specific cardiovascular events among stress-related disorder patients, sub-grouped by the occurrence of psychiatric comorbidity*, compared to ***their full siblings or matched unexposed individuals***

*Defined as new-onset psychiatric disorder (other than stress-related disorder) diagnosed from ***three months before*** to ***one year after*** the diagnosis of stress-related disorder.

† For sibling-based analysis, the Cox models were stratified by family identifiers, and adjusted for age, sex, education level, family income, marital status, history of severe somatic diseases, and history of other psychiatric disorders. For population-based analysis, the Cox models were stratified by matching identifiers (birth year and sex), and adjusted for education level, family income, marital status, history of severe somatic diseases, family history of CVD, and history of other psychiatric disorders. Time since the index date was used as underlying time scale. The occurrence of psychiatric comorbidity was considered as a time-varying variable.

‡ A fatal cardiovascular event was defined as death within 30 days after a major incident CVD event. This group involved fatal CVD cases from all above subtypes.