

Supplementary Table 1 International Classification of Diseases (ICD) codes for exposure, outcome and covariate identification

Major category	Subgroup	ICD-10 codes	ICD-9 codes (Swedish version)
<u>Stress related disorder</u>			
Posttraumatic stress disorder		F43	308, 309
Acute stress reaction		F43.1	309B
Adjustment disorder		F43.0	308, 309A
		F43.2	309X
		F43.8	309X
Other stress reactions	Other specified reactions to severe stress, including exhaustion disorder		
	Reactions to severe stress, unspecified	F43.9	309X
<u>Other psychiatric disorders</u>			
Any other psychiatric disorder		F00-F99 (excl. F43)	209-315 (excl. 308, 309)
Depression		F32, F33	296B
Anxiety		F40, F41	300A, 300C
Substance use disorders		F10-F19	291, 303, 304, 305A, 305X
<u>Major life-threatening infections</u>			
Sepsis		A02.1, A04.0–A04.3, A39 (excl. A39.0, A39.1, A39.81, A39.9), A40–A41, A42.7, A48, A90–A99, B37.7, B38.7, B39.3, B40.7, B41.7, B42.7, B44.7, B45.7, B46.4, B95–B99	036C–036E, 038, 084, 112F, 117D
Endocarditis		I33, I38, I39	421, 424X
Meningitis		A17, A39.0, A39.9, G00–G03	013, 036A, 036X, 320–322
Other central nervous system infections		A06.6, A39.81, A80–A89, B00.3, B00.4, B01.0, B01.1, B02.0, B02.1, B05.0, B05.1, B06.0, B22.0, B26.1, B26.2, B37.5, B38.4, B43.1, B50.0, B58.2, B60.2, G04–G08	006F, 036B, 045–049, 052B, 053A, 053B, 054D, 054H, 055A, 056A, 062–064, 072B, 072C, 094, 136C, 323–325
<u>Infection-related death (from the Cause of Death Register)</u>			
Death due to major life-threatening infections	(Sepsis/endocarditis/meningitis/other CNS infections)	See above	See above
Death due to other infections			
Infection of respiratory tract	Upper respiratory infections and infections of the ear	J00–J06, J32, J35.0, J37.0, J37.1, H60, H65–H67, H70	380–383, 460–465, 473, 474
	Lower respiratory infections	J09–J18, J20–J22, J40–J42	466, 480–487, 490, 491B
Sexually transmitted, reproductive, and urinary tract infections		A50–A60, A63.0, A63.8, A64, B20–B24(excl. B22.0), B37.3, B37.4, N10–12, N13.6, N15.1, N15.9, N30, N34.0, N39.0, N41.0–N41.3, N43.1, N45, N48.1, N48.2, N49, N61, N70–N76, N77.1	042–044, 054B, 078J, 090–093, 095–098 (excl. 098E), 099A, 099C, 099D, 099E, 112B, 112C, 131A, 590, 595, 599A, 601A–601D, 603B, 604A, 604X, 607B, 607C, 608A, 608E, 614–616

Infections of gastrointestinal tract	Intestinal infections	A00-A09 (excl. A02.1, A04.0–A04.3, A06.6)	001-009 (excl.006F)
	Hepatitis	B15-B19	070
	Gastritis and duodenitis	K29	535
	Appendicitis	K35-K37	540-542
Other infections	Skin	A46, L01-L08	035,680-686
	Eye infections	A54.3, B30, H00.0, H01.0, H04.0, H04.3, H05.0, H05.1, H10, H16, H32	077, 098E, 360A, 360B, 370, 372A-372D, 373, 375A, 376A, 376B
	Infections of the circulatory system (excl. endocarditis)	I30.0, I30.1, I40.0	420, 422
	Infections of the musculoskeletal system and connective tissue	M00, M01, M46, M60.0, M65, M71.0, M71.1, M86	711, 727A, 728A, 729E, 730
	Other bacterial infections	A15-A19, A20-A28, A30-A38, A39 (excl.A39.0, A39.81, A39.9), A42 (excl. A42.7), A43-A45, A47, A49, A65-A69, A70-A79	010-012, 014-018, 020-027,030-034, 035, 036 (excl. 036A,036B, 036X), 037,039-041(excl.040W), 080-083, 100-104
	Other viral infections	B00-B09 (excl. B00.3, B00.4, B01.0, B01.1, B02.0, B02.1, B05.0, B05.1, B06.0), B25, B26 (excl. B26.1, B26.2), B27-B29,B31-B34	050-059 (excl. 052B, 053A, 053B, 054D, 054H, 055A, 056A), 060, 061, 065, 066, 071-076 (excl. 072B, 072C), 078, 079
	Other infectious and parasitic diseases	B35, B36, B37(excl. B37.3-B37.5, B37.7), B38 (excl. B38.4, B38.7), B39-B89 (excl. B43.1, B44.7, B45.7, B46.4, B50.0, B58.2, B60.2)	084-088, 110-111,112A,112D,112E,112X, 113-118(excl. 117D), 120-139 (excl.131A, 136C)

Covariates: severe somatic conditions

Myocardial infarction	I21, I22, I25.2	410,412
Congestive heart failure	I50	428
Cerebrovascular disease	G45, G46, I60-I69	430-438
Chronic pulmonary disease	J40-J47	490-496
Connective tissue disease	M05, M06, M32-M34, M35.1, M35.3	710A, 710B, 710E, 714A, 714B, 714C, 714W,714X, 725
Diabetes	E10-E14	250
Renal diseases	N01, N03, N05.2-N05.7	582,583
Liver diseases	K70.2-K70.4, K71.7, K72.1, K72.9, K73, K74, K76.6, K76.7	571C, 571E,571F, 571G, 572C, 572D, 572E, 572W, 456A, 456B, 456C
Ulcer diseases	K25-K28	531-534
HIV infection/AIDS	B20-B24 (excl. B22.0)	042-044
<u>Covariates: any infectious diseases (from National Patient Register)</u>	A00- B99, G00–G08, H10, K29, K35-K37, L01-L08, M00, M01, M46, M60.0, M65, N10-12, N30, N41, N45, J00-J06, J09-J18, J20-J22, J32, J40-J42, I30, I33, I38-I40	001-139, 320–325, 372, 535, 540-542, 680-686, 711, 590, 595, 601, 604, 460-466, 472-474, 480-487, 490, 420-422, 424X

Covariates: for sensitivity analyses

Injury and poisoning		S00-T98 F10, G31.2, G62.1, I42.6, K29.2, K70, K85.2	800-995 291,303,305A, 357F, 425F, 535D, 571A-D
	Alcohol use disorder and somatic diseases explicitly linked to alcohol misuse		
Substance use or sleep-related diagnoses	Tobacco use disorder and somatic diseases highly relevant to tobacco use	F17, J41-J44	305B, 491,492
	Drug use disorder	F11-F16, F18, F19	304
	Sleep disorder	G47, F51, F90	780F,307E
Congenital heart diseases		Q20-Q28, Q33.2, I15.8, I15.9	745-747, 748F, 405
Congenital diseases of nervous system		Q00-Q07	740-742

Supplementary Table 2 Crude incidence rate (IR) and hazard ratios (HRs) with 95% confidence intervals (CIs) for life-threatening infections among individuals with different types of stress-related disorders, *compared to matched unexposed individuals*, by different characteristics

	Posttraumatic stress disorder		Acute stress reaction		Adjustment disorder and other stress reactions	
	Number of cases (IR, per 1 000 person-years), exposed/unexposed	HR (95% CI)*	Number of cases (IR, per 1 000 person-years), exposed/unexposed	HR (95% CI)*	Number of cases (IR, per 1 000 person-years), exposed/unexposed	HR (95% CI)*
By gender						
Men	94(3.73)/405(1.54)	2.12 (1.65 to 2.73)	729(3.27)/3537(1.50)	1.55 (1.42 to 1.69)	621(3.25)/3092(1.54)	1.54 (1.40 to 1.70)
Women	150(2.72)/636(1.13)	1.87 (1.53 to 2.29)	841(2.69)/3964(1.24)	1.58 (1.45 to 1.71)	857(2.62)/4050(1.22)	1.56 (1.44 to 1.70)
By time since index date						
< 1 year	25(2.31)/104(0.96)	1.86 (1.12 to 3.10)	213(3.37)/677(1.06)	2.26 (1.91 to 2.68)	172(2.71)/657(1.03)	1.84 (1.53 to 2.22)
1-4 years	71(2.27)/313(1.00)	1.59 (1.19 to 2.13)	479(2.44)/2290(1.15)	1.45 (1.30 to 1.62)	495(2.44)/2450(1.19)	1.45 (1.30 to 1.61)
5-9 years	61(3.08)/206(1.02)	2.42 (1.74 to 3.37)	374(2.60)/1890(1.27)	1.46 (1.29 to 1.65)	376(2.62)/1845(1.25)	1.49 (1.32 to 1.69)
≥10 years	87(4.74)/418(2.11)	2.01 (1.56 to 2.60)	504(3.82)/2644(1.85)	1.57 (1.41 to 1.75)	435(4.07)/2190(1.89)	1.68 (1.49 to 1.88)
History of severe somatic diseases[†]						
Yes	77(6.15)/206(2.95)	1.45 (0.91 to 2.30)	496(6.18)/1642(3.46)	1.37 (1.14 to 1.64)	471(5.99)/1604(3.42)	1.39 (1.16 to 1.66)
No	167(2.46)/835(1.11)	1.86 (1.54 to 2.25)	1074(2.36)/5859(1.15)	1.65 (1.53 to 1.77)	1007(2.29)/5538(1.14)	1.63 (1.51 to 1.75)
By calendar year at index date						
1987-2000	116(3.36)/543(1.49)	2.03 (1.63 to 2.54)	804(3.07)/3819(1.38)	1.63 (1.50 to 1.78)	644(3.11)/3039(1.38)	1.67 (1.52 to 1.84)
2001-05	66(2.76)/252(1.05)	2.21 (1.62 to 3.00)	436(2.63)/2285(1.36)	1.38 (1.23 to 1.54)	533(2.75)/2646(1.35)	1.46 (1.31 to 1.61)
2006-13	62(2.83)/246(1.12)	1.60 (1.16 to 2.21)	330(3.06)/1397(1.28)	1.69 (1.48 to 1.94)	301(2.58)/1457(1.24)	1.55 (1.35 to 1.78)
By history of other psychiatric disorders[‡]						
Yes	105(3.57)/125(2.58)	2.29 (1.47 to 3.56)	729(4.73)/1091(3.50)	1.24 (1.05 to 1.46)	631(4.07)/1092(3.53)	1.17 (0.98 to 1.39)
No	139(2.73)/916(1.18)	2.14 (1.76 to 2.59)	841(2.20)/6410(1.22)	1.70 (1.57 to 1.83)	847(2.34)/6050(1.21)	1.84 (1.70 to 1.98)
By family history of major life-threatening infections						
Yes	20(3.35)/83(1.63)	2.86 (0.88 to 9.31)	144(3.64)/611(1.77)	1.59 (1.06 to 2.38)	136(3.24)/565(1.53)	1.96 (1.33 to 2.89)
No	224(3.01)/958(1.24)	1.93 (1.64 to 2.28)	1426(2.87)/6890(1.32)	1.59 (1.49 to 1.69)	1342(2.82)/6577(1.33)	1.57 (1.47 to 1.68)

**By history of inpatient visit
for infectious diseases**

Yes	106(4.34)/256(1.73)	2.08 (1.47 to 2.96)	707(4.33)/2026(2.04)	1.69 (1.48 to 1.93)	592(3.90)/2039(2.09)	1.31 (1.14 to 1.50)
No	138(2.47)/785(1.16)	1.81 (1.48 to 2.22)	863(2.32)/5475(1.20)	1.61 (1.49 to 1.74)	886(2.42)/5103(1.17)	1.76 (1.63 to 1.91)

* Cox models were stratified by matching identifiers (sex, birth year, and county of birth), and adjusted for education level, family income, marital status, history of severe somatic diseases, history of other psychiatric disorder, history of inpatient visit for infectious diseases, and family history of major life-threatening infections.

† Involved somatic diseases included myocardial infarction, congestive heart failure, cerebrovascular disease, chronic pulmonary disease, connective tissue disease, dementia, 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 3 months prior to the index date

Supplementary Table 3 Relative risks of life-threatening infections among individuals with stress-related disorders, sub- grouped by the type of medical care received at diagnosis, *compared to full siblings or matched unexposed individuals*

	Type of medical care received at diagnosis	Sibling-based analysis		Population-based analysis	
		Number of cases (incidence rate, per 1 000 person-years), exposed/siblings	Hazard ratios (95% confidence intervals)*	Number of cases (incidence rate, per 1 000 person-years), exposed/unexposed	Hazard ratios (95% confidence intervals)†
Any stress-related disorder	Inpatient	1351(2.92)/1648(1.71)	1.52 (1.39 to 1.67)	2065(3.20)/9422(1.39)	1.66 (1.57 to 1.75)
	Outpatient	846(2.41)/998(1.65)	1.39 (1.25 to 1.56)	1227(2.52)/6262(1.28)	1.48 (1.38 to 1.58)
Posttraumatic stress disorder	Inpatient	94(3.20)/109(1.81)	1.81 (1.27 to 2.57)	136(3.36)/591(1.39)	2.15 (1.74 to 2.65)
	Outpatient	76(2.67)/66(1.33)	2.29 (1.44 to 3.65)	108(2.71)/450(1.13)	1.71 (1.35 to 2.18)
Acute stress reaction	Inpatient	682(2.79)/875(1.71)	1.44 (1.27 to 1.64)	1077(3.15)/4970(1.38)	1.60 (1.48 to 1.72)
	Outpatient	331(2.40)/395(1.66)	1.41 (1.18 to 1.69)	493(2.55)/2531(1.30)	1.49 (1.35 to 1.66)
Adjustment disorder and other stress reactions	Inpatient	575(3.04)/664(1.70)	1.57 (1.37 to 1.81)	852(3.23)/3861(1.39)	1.67 (1.53 to 1.82)
	Outpatient	439(2.38)/537(1.69)	1.34 (1.15 to 1.56)	626(2.47)/3281(1.29)	1.44 (1.31 to 1.58)

* Cox models were stratified by family identifiers, and adjusted for sex, birth year, education level, family income, marital status, history of severe somatic diseases, history of other psychiatric disorder, and history of inpatient visit for infectious diseases.

† Cox models were stratified by matching identifiers (sex, birth year, and county of birth), and adjusted for education level, family income, marital status, history of severe somatic diseases, history of other psychiatric disorder, history of inpatient visit for infectious diseases, and family history of major life-threatening infections.

Supplementary Table 4 Relative risks for life-threatening infections among individuals with stress-related disorders* *with difference status of serotonin selective reuptake inhibitors (SSRI) use*

Information on SSRI use during the first year after a stress-related disorder diagnosis	Number of cases (incidence rate, per 1 000 person-years) among exposed patients	Hazard ratios (95% confidence intervals) [†]
SSRI user[€]		
No	582(2.72)	Reference
Yes	133(2.63)	0.81 (0.66 to 0.98)
<i>P</i> for difference		0.032
Average dosage level of SSRI (by median)		
Not user	582(2.72)	Reference
≤ 1.2 DDD	62(2.32)	0.77 (0.63 to 0.93)
> 1.2 DDD	71(2.98)	0.86 (0.69 to 1.07)
<i>P</i> for trend [‡]		0.090
Duration of SSRI (by tertiles)		
Not user	582(2.72)	Reference
≤179 days	29(3.10)	0.96 (0.66 to 1.40)
180-319 days	54(2.74)	0.85 (0.64 to 1.13)
≥320 days	50(2.33)	0.70 (0.52 to 0.94)
<i>P</i> for trend [‡]		0.014

DDD, Defined Daily Dose

* Restricted to patients diagnosed after July 2005, and with more than one year of follow-up (n=74,691).

[†] Cox models were adjusted for age at index date, sex, county of birth, education level, family income, marital status, history of severe somatic diseases, history of other psychiatric disorder, history of inpatient visit for infectious diseases, family history of major life-threatening infections, and combination use of other psychiatric drugs (yes/no). The first year after the study entry was excluded.

[€] We defined SSRI users as individuals with two or more dispensations of SSRIs within the first year after a stress-related disorder diagnosis.

[‡] *P* for trend was calculated using Wald test.

Supplementary Table 5 Crude incidence rate (IR) and hazard ratios (HRs) with 95% confidence intervals (CIs) for life-threatening infections among individuals with stress-related disorders, ***compared to full siblings or matched unexposed individuals***, restricting to participants without any diagnosis of severe somatic diseases/injury/infectious diseases within 1 year prior to the index date*

	Sibling-based analysis		Population-based analysis	
	Number of cases (IR, per 1 000 person- years), exposed/siblings	HR (95% CI) [†]	Number of cases (IR, per 1 000 person- years), exposed/unexposed	HR (95% CI) [€]
Any stress-related disorder	1425(2.28)/1617(1.45)	1.52 (1.39 to 1.65)	2146(2.46)/10034(1.19)	1.62 (1.54 to 1.71)
Posttraumatic stress disorder	113(2.64)/106(1.38)	2.10 (1.49 to 2.97)	160(2.67)/666(1.15)	1.91 (1.57 to 2.31)
Acute stress reaction	647(2.24)/755(1.44)	1.46 (1.28 to 1.66)	1016(2.51)/4742(1.20)	1.63 (1.51 to 1.76)
Adjustment disorder and other stress reactions	665(2.27)/756(1.47)	1.52 (1.34 to 1.72)	970(2.39)/4626(1.18)	1.58 (1.47 to 1.71)

* Sample size for analysis in the sibling cohort: 77,746 in exposed group and 126,379 in sibling group; in the population-matched cohort: 110,125 in exposed group and 1,019,447 in unexposed group.

[†] Cox models were stratified by family identifiers, and adjusted for sex, birth year, education level, family income, marital status, history of severe somatic diseases, history of other psychiatric disorder, and history of inpatient visit for infectious diseases.

[€] Cox models were stratified by matching identifiers (sex, birth year, and county of birth), and adjusted for education level, family income, marital status, history of severe somatic diseases, history of other psychiatric disorder, history of inpatient visit for infectious diseases, and family history of major life-threatening infections.

Supplementary Table 6 Crude incidence rate (IR) and hazard ratios (HRs) with 95% confidence intervals (CIs) for life-threatening infections among individuals with stress-related disorders, ***compared to full siblings or matched unexposed individuals***, restricting to participants without any congenital malformations of heart and nerves system*

	Sibling-based analysis		Population-based analysis	
	Number of cases (IR, per 1 000 person- years), exposed/siblings	HR (95% CI) [†]	Number of cases (IR, per 1 000 person- years), exposed/unexposed	HR (95% CI) [€]
Any stress-related disorder	2116(2.65)/2492(1.64)	1.49 (1.39 to 1.60)	3168(2.85)/14866(1.31)	1.58 (1.51 to 1.65)
Posttraumatic stress disorder	975(2.60)/1204(1.66)	1.95 (1.48 to 2.59)	1510(2.87)/7091(1.32)	1.93 (1.64 to 2.26)
Acute stress reaction	980(2.67)/1125(1.64)	1.44 (1.30 to 1.60)	1423(2.80)/6781(1.31)	1.56 (1.47 to 1.66)
Adjustment disorder and other stress reactions	161(2.83)/163(1.52)	1.50 (1.35 to 1.67)	235(2.98)/994(1.24)	1.56 (1.46 to 1.66)

* Sample size for analysis in the sibling cohort: 101,314 in exposed group and 179,031 in sibling group; in the population-matched cohort: 142,378 in exposed group and 1,405,627 in unexposed group.

[†] Cox models were stratified by family identifiers, and adjusted for sex, birth year, education level, family income, marital status, history of severe somatic diseases, history of other psychiatric disorder, and history of inpatient visit for infectious diseases.

[€] Cox models were stratified by matching identifiers (sex, birth year, and county of birth), and adjusted for education level, family income, marital status, history of severe somatic diseases, history of other psychiatric disorder, history of inpatient visit for infectious diseases, and family history of major life-threatening infections.

Supplementary Table 7 Association of stress-related disorders with life-threatening infection, additionally adjusted for the presence of severe somatic diseases (as a time-varying variable) or substance use/sleep-related diagnoses (as a binary variable) during follow-up — analyses restricted to individuals without a history of severe somatic diseases*

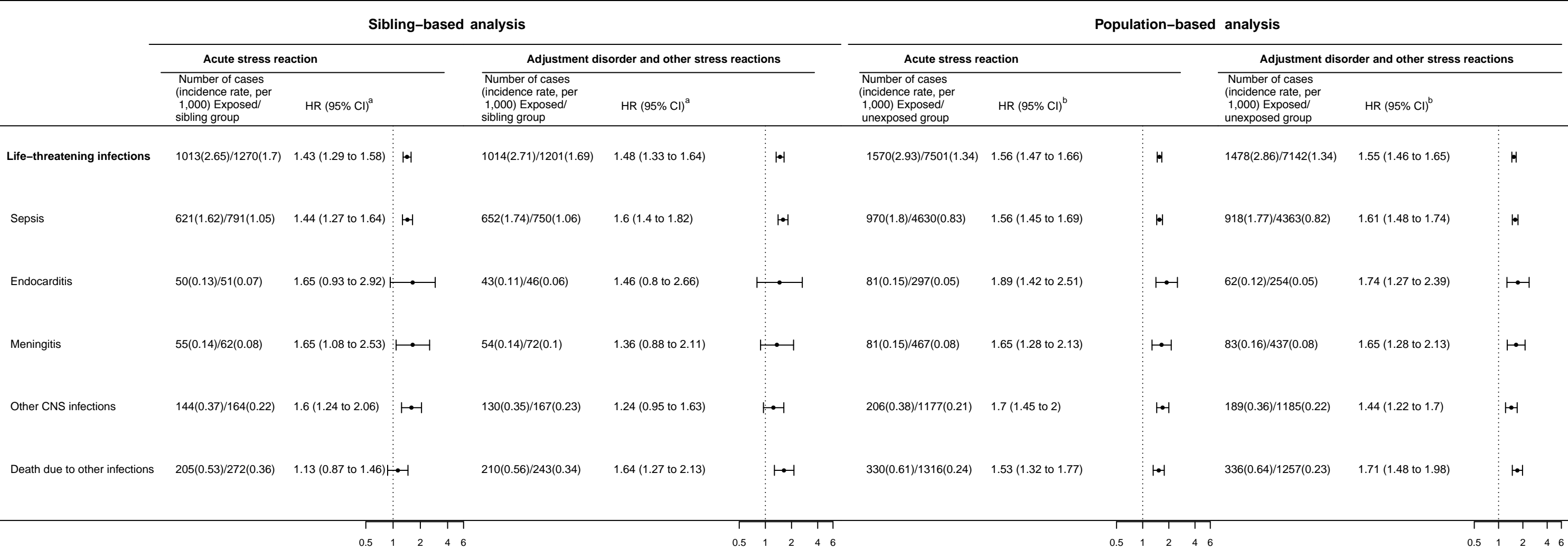
	Sibling-based analysis				Population-based analysis			
	Number of cases (incidence rate, per 1 000 person-years), exposed/siblings	HR (95% CI) [†]	HR (95% CI) [†] , additionally adjusted for severe somatic diseases	HR (95% CI) [†] , additionally adjusted for substance use/sleep-related diagnoses	Number of cases (incidence rate, per 1 000 person-years), exposed/unexposed	HR (95% CI) ^ε	HR (95% CI) ^ε , additionally adjusted for severe somatic diseases	HR (95% CI) ^ε , additionally adjusted for substance use/sleep related diagnoses
Any stress-related disorder	1521(2.19)/1613(1.35)	1.49 (1.37 to 1.62)	1.43 (1.30 to 1.56)	1.42 (1.30 to 1.55)	2248(2.34)/9930(1.10)	1.65 (1.57 to 1.73)	1.57 (1.49 to 1.66)	1.50 (1.43 to 1.58)
Posttraumatic stress disorder	115(2.35)/115(1.37)	1.95 (1.40 to 2.73)	1.90 (1.35 to 2.67)	1.83 (1.29 to 2.58)	167(2.46)/682(1.08)	1.86 (1.54 to 2.25)	1.72 (1.42 to 2.09)	1.70 (1.40 to 2.06)
Acute stress reaction	716(2.19)/754(1.32)	1.49 (1.31 to 1.69)	1.41 (1.23 to 1.60)	1.40 (1.23 to 1.60)	1074(2.36)/4741(1.10)	1.65 (1.53 to 1.77)	1.57 (1.45 to 1.69)	1.49 (1.38 to 1.60)
Adjustment disorder and other stress reactions	690(2.17)/744(1.38)	1.45 (1.28 to 1.64)	1.40 (1.23 to 1.59)	1.40 (1.23 to 1.59)	1007(2.29)/4507(1.10)	1.63 (1.51 to 1.75)	1.56 (1.44 to 1.68)	1.49 (1.38 to 1.61)

CI, confidence intervals; HR, Hazard ratios.

* Sample size for analysis in the sibling cohort: 86,052 in exposed group and 136,047 in sibling group; in the population-matched cohort: 120,915 in exposed group and 1,093,047 in unexposed group.

[†] Cox models were stratified by family identifiers, and adjusted for sex, birth year, education level, family income, marital status, history of severe somatic diseases, history of other psychiatric disorder, and history of inpatient visit for infectious diseases.

^ε Cox models were stratified by matching identifiers (sex, birth year, and county of birth), and adjusted for education level, family income, marital status, history of severe somatic diseases, history of other psychiatric disorder, history of inpatient visit for infectious diseases, and family history of major life-threatening infections.



Psychological comorbidity*

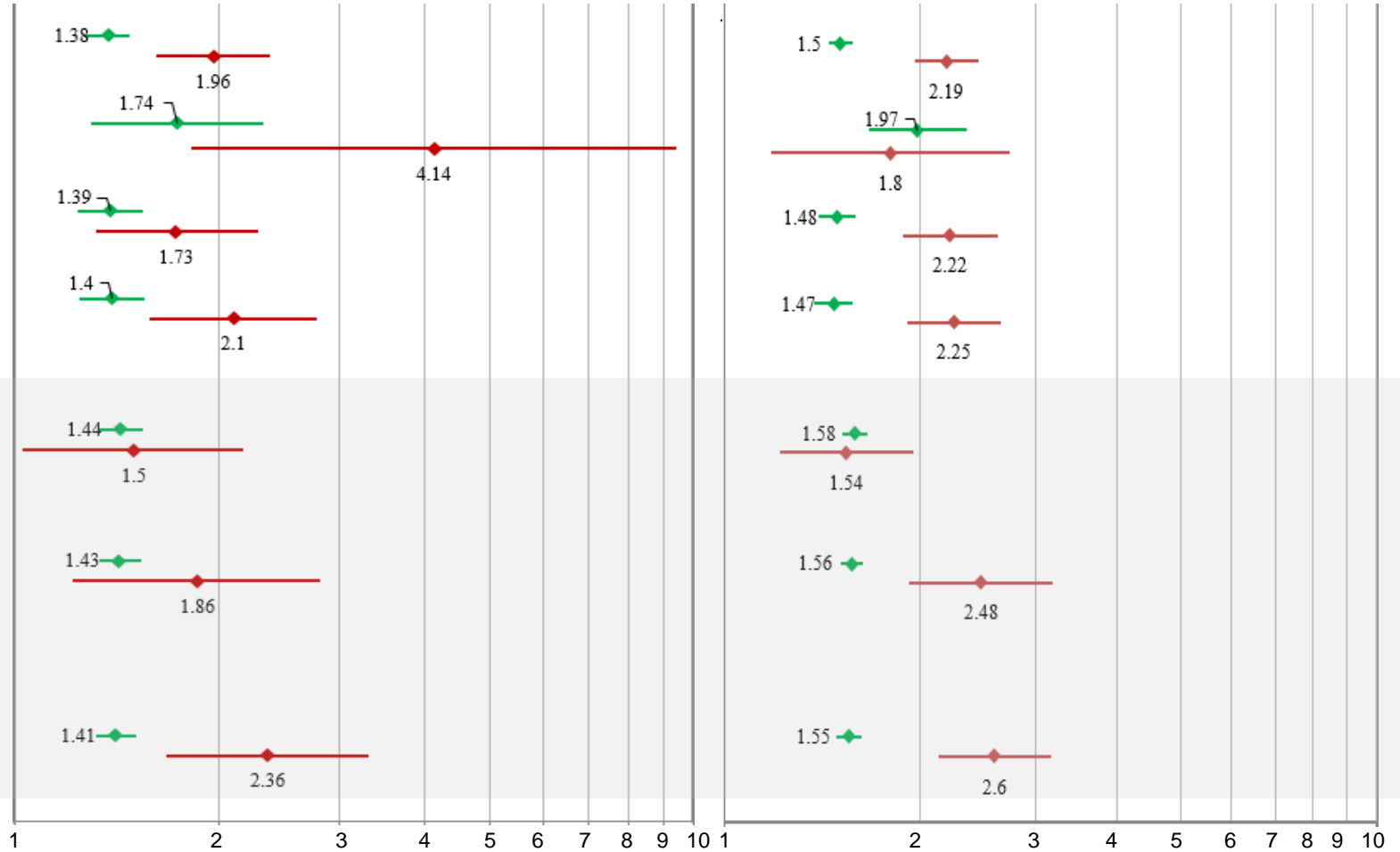
Hazard ratio (95% confidence interval)

Sibling-based analysis†

Population-based analysis€

Any psychiatric comorbidity

Any stress-related disorder No
Yes
Posttraumatic stress disorder No
Yes
Acute stress reaction No
Yes
Adjustment disorder and other stress reactions No
Yes



Supplementary Figure 2 Relative risks of life-threatening infections among individuals with stress-related disorders, sub- grouped by the occurrence of psychiatric comorbidity, *compared to full siblings or matched unexposed individuals*

* Psychiatric comorbidity was defined as a new-onset psychiatric disorder, any (excluding stress-related disorder) or specific type (depression, anxiety, and substance use disorders), diagnosed from 3 months before to 1 year after the diagnosis of a stress-related disorder.

† Cox models were stratified by family identifiers, and adjusted for sex, birth year, education level, family income, marital status, history of severe somatic diseases, history of other psychiatric disorder, and history of inpatient visit for infectious diseases.

€ Cox models were stratified by matching identifiers (sex, birth year, and county of birth), and adjusted for education level, family income, marital status, history of severe somatic diseases, history of other psychiatric disorder, history of inpatient visit for infectious diseases, and family history of major life-threatening infections.