From trauma to disease

Variations in human health response to major life adversities

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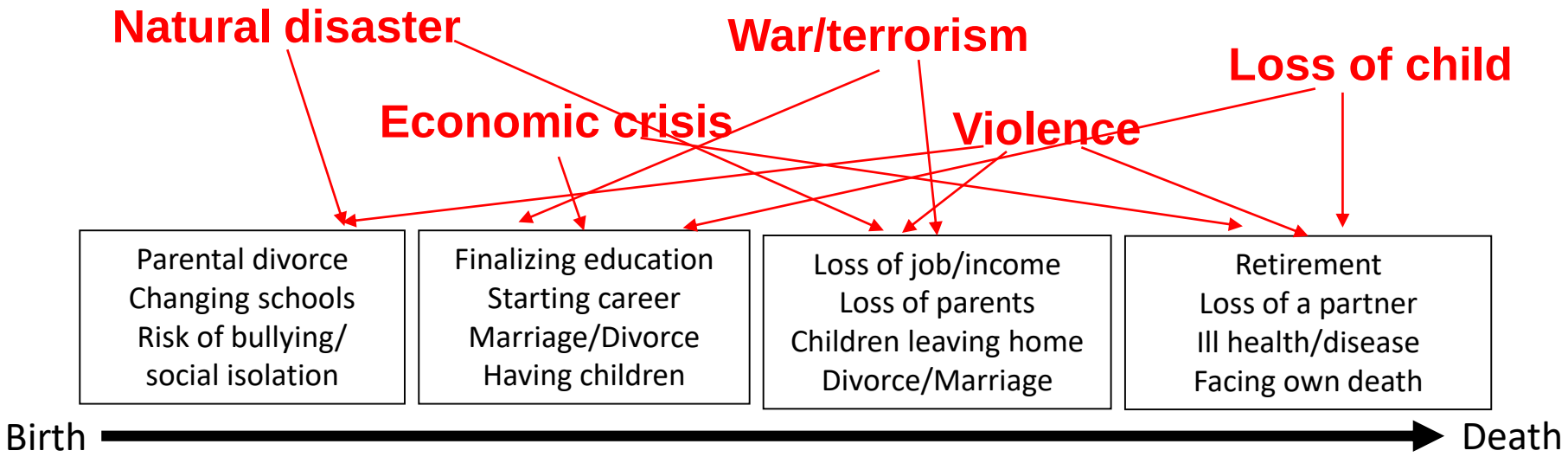
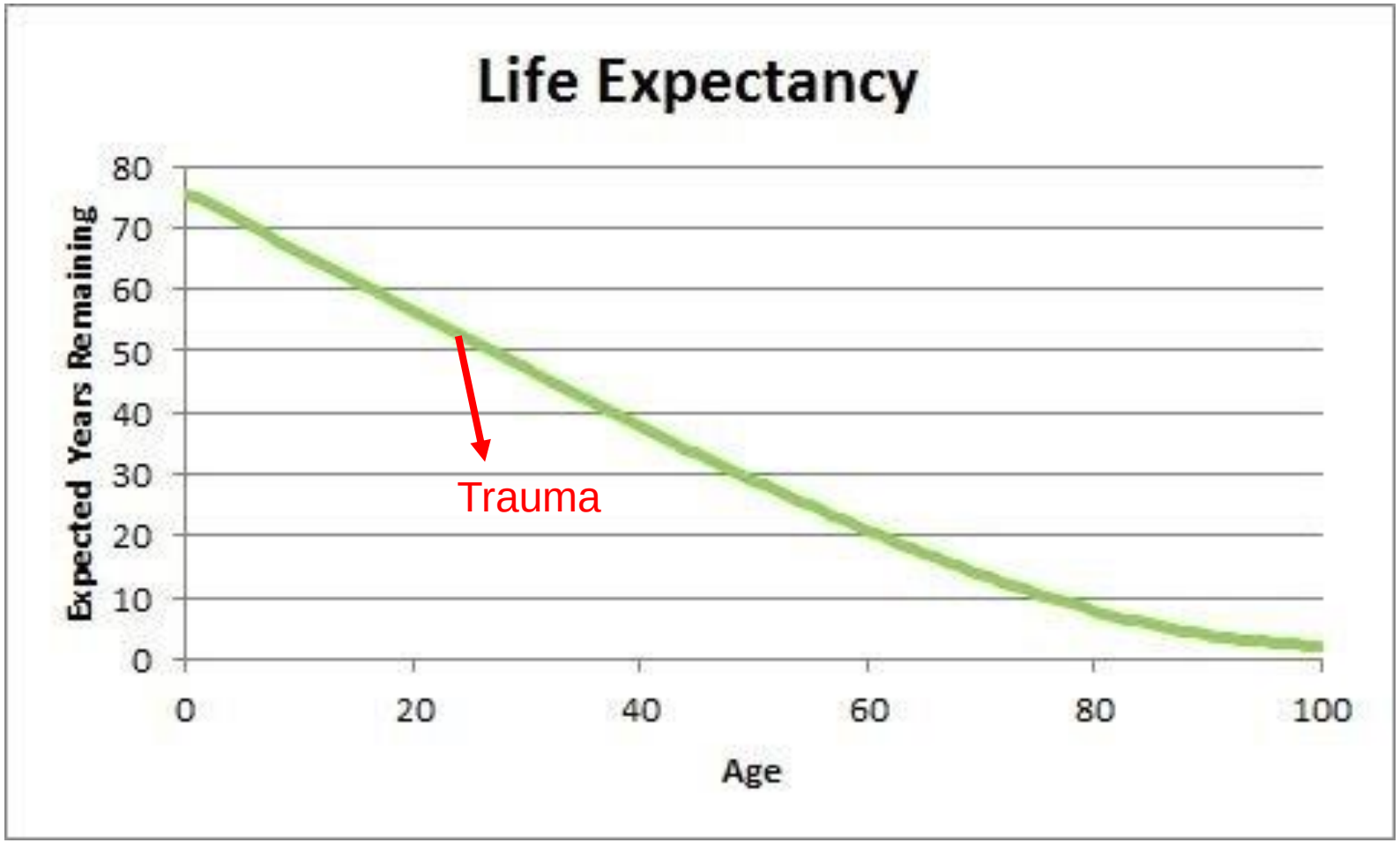
Adjunct Professor of Epidemiology, Department of Epidemiology, Harvard TH Chan School of Public Health

Life stressors… attack us throughout life!




Stressors
Psychological processes
Life events
Social isolation
Socioeconomic burden
Perceived stress
Depression
Poor coping
CRH/locus coeruleus
↓Oxytocin
↓Dopamine
Hypothalamic-pituitary-adrenal axis
ACTH
Adrenal gland
• Cortisol
Autonomic nervous system
• Norepinephrine
• Epinephrine
• Other neuropeptides



Turning points of health

Nordic Countries
– a cohort of 26 million individuals

- **Personal Identification Numbers**
  - Assigned at birth or immigration

- **Record Linkage between:**
  - Drug Prescription Registers
  - Causes of Death Registers
  - Medical Birth Registers
  - Inpatient Registers
  - Cancer Registers
  - Social, demographic, academic info
  - Multigenerational Registers

Today

- ✓ **Societal disasters**
  - ✓ Economic collapse
  - ✓ Natural disasters
  - ✓ War migration
- ✓ **Individual adversities**
  - ✓ Loss of family member
  - ✓ Cancer diagnosis
  - ✓ Violence
- ✓ **Stress-related disorders and disease**
  - ✓ Ongoing studies: ERC program

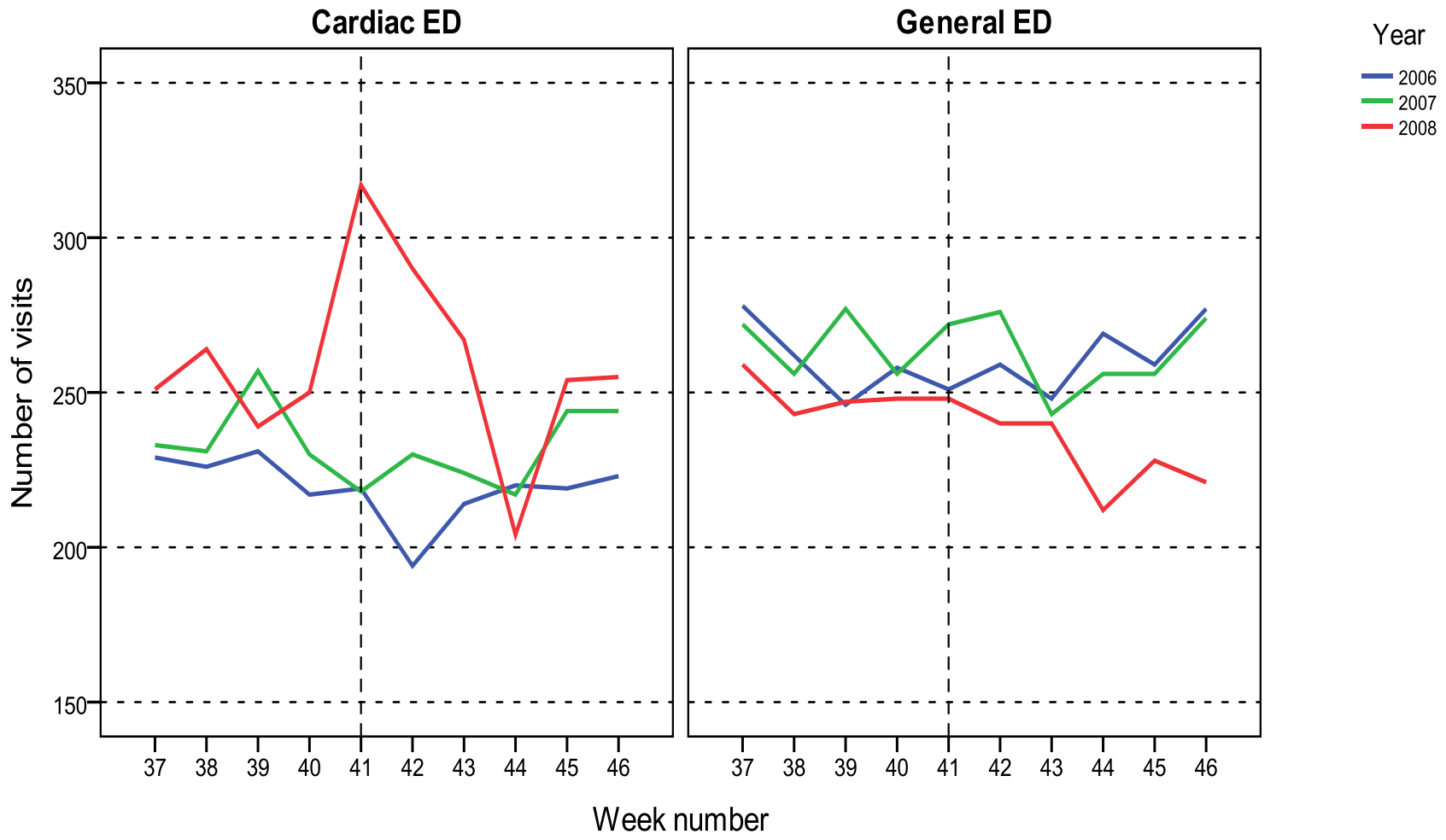
“GOD BLESS ICELAND”

Oct. 6, 2008 – In a direct TV broadcast

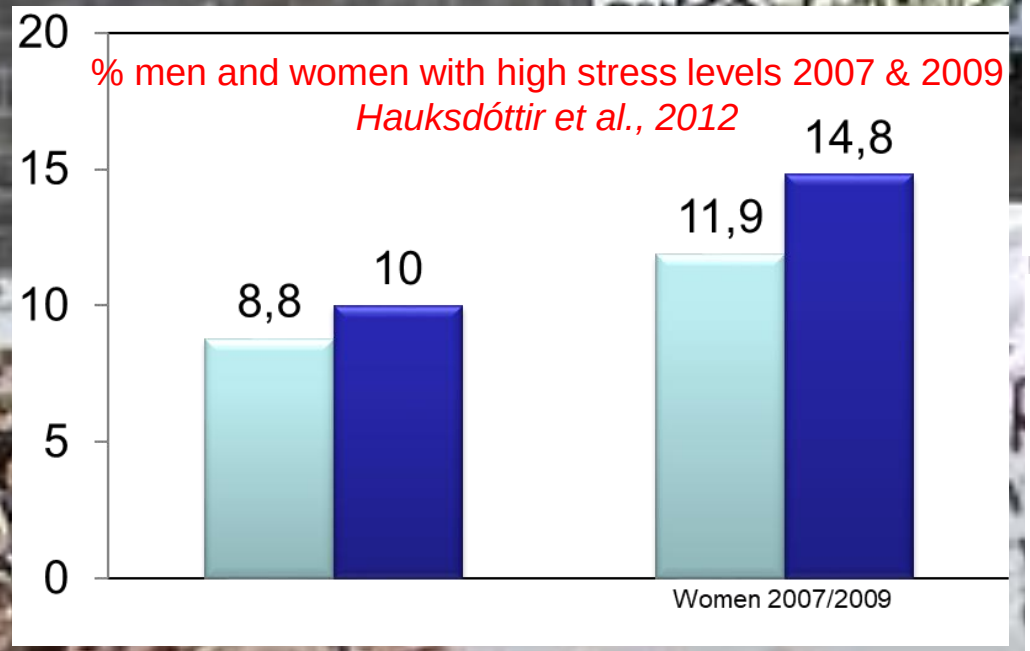
Prime Minister Geir Haarde announces that Iceland is at risk of national bankruptcy

*“**There is a very real danger,***
***fellow citizens**, that the Icelandic*
economy, in the worst case, could be
sucked with the banks into the whirlpool
*and **the result could be national bankruptcy…***
God bless Iceland!”

Number of weekly visits to emergency departments in Reykjavik from week 37 through week 46 in 2006, 2007 and 2008.



Gudjonsdottir et al., 2012



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PLOS ONE

Low Birth Weight, Small for Gestational Age and Preterm Births before and after the Economic Collapse in Iceland: A Population Based Cohort Study

Védís Helga Eiríksdóttir[1]*, Tinna Laufey Ásgeirsdóttir[2], Ragnheiður Ingibjörg Bjarnadóttir[3], Robert Kaestner[4], Sven Cnattingius[5], Unnur Anna Valdimarsdóttir[6,7]

1 Centre of Public Health Sciences, University of Iceland, Reykjavik, Iceland, 2 Department of Economics, University of Iceland, Reykjavik, Iceland, 3 Department of Obstetrics and Gynecology, Landspitali University Hospital, Reykjavik, Iceland, 4 Department of Economics and the Institute of Government and Public Affairs, University of Illinois, Chicago, Illinois, United States of America, 5 Unit of Clinical Epidemiology, Department of Medicine, Karolinska Institutet, Solna, Stockholm, Sweden, 6 Centre of Public Health Sciences, University of Iceland, Reykjavik, Iceland, 7 Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts, United States

PLOS ONE

RESEARCH ARTICLE

Pregnancy-Induced Hypertensive Disorders before and after a National Economic Collapse: A Population Based Cohort Study

Védís Helga Eiríksdóttir[1]*, Unnur Anna Valdimarsdóttir[1,2], Tinna Laufey Ásgeirsdóttir[3], Arna Hauksdóttir[1], Sigrún Helga Lund[1], Ragnheiður Ingibjörg Bjarnadóttir[4], Sven Cnattingius[5], Helga Zoëga[1]

2008 Economic Collapse:

-Increase in high stress levels among women

-Gestational hypertension

-Increase in low birth weight

Economic Collapse

Psychiatric disorders and suicide attempts in Swedish survivors of the 2004 southeast Asia tsunami: a 5 year matched cohort study

Filip K Arnberg, Ragnhildur Gudmundsdóttir, Agnieszka Butwicka, Fang Fang, Paul Lichtenstein, Christina M Hultman, Unnur A Valdimarsdóttir

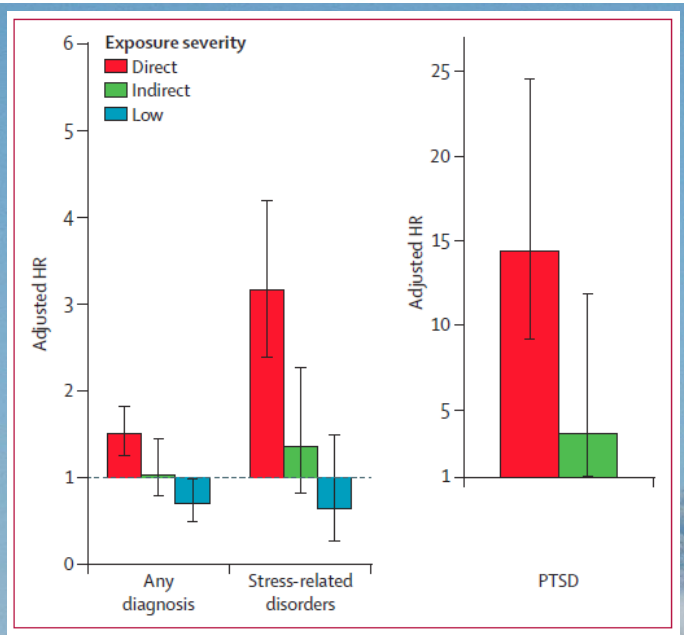


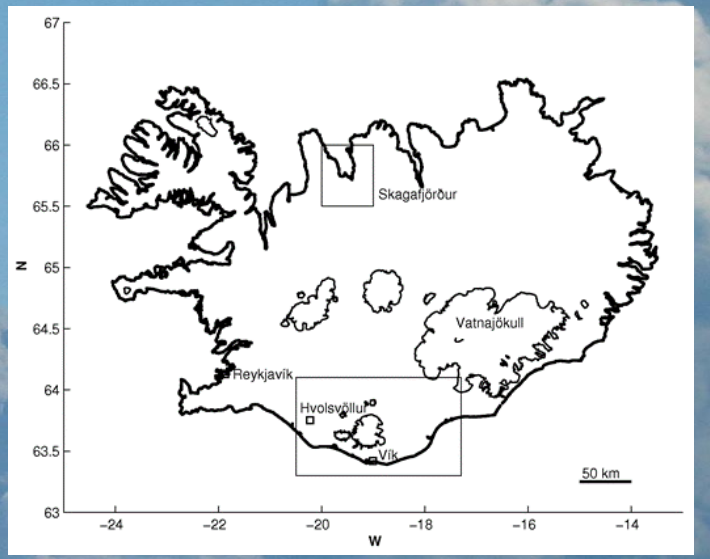
Figure 2: Risk of any psychiatric diagnosis, stress-related disorders, and PTSD in tsunami survivors

EUROPEAN JOURNAL OF PSYCHOTRAUMATOLOGY

BASIC RESEARCH ARTICLE

Sixteen-year follow-up of childhood avalanche survivors

Edda Bjork Thordardottir[1]*, Unnur Anna Valdimarsdottir[1,2,3], Ingunn Hansdottir[4], Arna Hauksdóttir[1], Atle Dyregrov[5,6], Jillian C. Shipherd[7,8], Ask Elklit[9,10], Heidi Resnick[11] and Berglind Gudmundsdottir[12,13]



Severe psychiatric and somatic outcomes after:

SA-Asian Tsunami (2004)

Vestfjords avalanche (1995)

Eyjafjallajökull eruption (2010)

Natural disasters and human health

5-year register-based follow-up of Swedish Tsunami survivors

	Total				Men			Women		
	Exposed (n=8762)	Unexposed (n=864 088)	Crude HR (95% CI)	Adjusted HR* (95% CI)	Exposed (n=4544)	Unexposed (n=448 057)	Adjusted HR* (95% CI)	Exposed (n=4218)	Unexposed (n=416 031)	Adjusted HR* (95% CI)
Any psychiatric disorder	547 (6·24%)	47734 (5·52%)	1·14 (1·04–1·24)	1·21 (1·11–1·32)	246 (5·41%)	21519 (4·80%)	1·17 (1·02–1·33)	301 (7·14%)	26215 (6·30%)	1·25 (1·11–1·40)
Suicide attempt, definite	38 (0·43%)	2752 (0·32%)	1·36 (0·99–1·87)	1·54 (1·11–2·13)	16 (0·35%)	1205 (0·27%)	1·41 (0·85–2·34)	22 (0·52%)	1547 (0·37%)	1·65 (1·08–2·53)
Suicide attempt, uncertain	43 (0·49%)	3438 (0·40%)	1·24 (0·92–1·68)	1·27 (0·94–1·71)	27 (0·59%)	2035 (0·45%)	1·32 (0·91–1·92)	16 (0·38%)	1403 (0·34%)	1·19 (0·73–1·94)
Unipolar depression	176 (2·01%)	18130 (2·10%)	0·96 (0·83–1·11)	1·03 (0·88–1·19)	56 (1·23%)	7208 (1·61%)	0·79 (0·61–1·04)	120 (2·84%)	10922 (2·63%)	1·19 (0·99–1·43)
Alcohol abuse or dependence	102 (1·16%)	8467 (0·98%)	1·17 (0·97–1·43)	1·27 (1·04–1·54)	72 (1·58%)	5775 (1·29%)	1·30 (1·03–1·64)	30 (0·71%)	2692 (0·65%)	1·20 (0·84–1·72)
Substance abuse or dependence	42 (0·48%)	4073 (0·47%)	1·01 (0·75–1·37)	1·11 (0·82–1·50)	29 (0·64%)	2392 (0·53%)	1·27 (0·88–1·83)	13 (0·31%)	1681 (0·40%)	0·87 (0·50–1·50)
Anxiety disorders	148 (1·69%)	16434 (1·90%)	0·89 (0·76–1·04)	0·95 (0·81–1·12)	62 (1·36%)	6386 (1·43%)	1·00 (0·78–1·29)	86 (2·04%)	10048 (2·42%)	0·92 (0·75–1·14)
Stress-related disorders	187 (2·13%)	8831 (1·02%)	2·10 (1·82–2·43)	2·27 (1·96–2·62)	71 (1·56%)	3211 (0·72%)	2·30 (1·81–2·90)	116 (2·75%)	5620 (1·35%)	2·25 (1·87–2·71)
Acute stress reaction	75 (0·86%)	3636 (0·42%)	2·03 (1·62–2·54)	2·16 (1·72–2·71)	29 (0·64%)	1492 (0·33%)	1·96 (1·36–2·83)	46 (1·09%)	2144 (0·52%)	2·30 (1·72–3·08)
Post-traumatic stress disorder	46 (0·52%)	692 (0·08%)	6·61 (4·95–8·83)	7·51 (5·47–10·32)	16 (0·35%)	168 (0·04%)	11·5 (6·77–19·47)	30 (0·71%)	524 (0·13%)	6·30 (4·25–9·34)
Reaction to severe stress NOS	46 (0·52%)	2000 (0·23%)	2·26 (1·69–3·01)	2·44 (1·82–3·27)	19 (0·42%)	718 (0·16%)	2·78 (1·78–4·34)	27 (0·64%)	1282 (0·31%)	2·26 (1·53–3·32)

Individuals matched for sex, year of birth, income, and marital, educational, and occupational status. HR=hazard ratio. NOS=not otherwise specified. *Adjusted for any psychiatric disorder before the tsunami.

Table 2: **Relative risks of psychiatric disorders and attempted suicide in adults during the 5 years after the tsunami**

Arnberg et al., Lancet Psychiatry, 2015

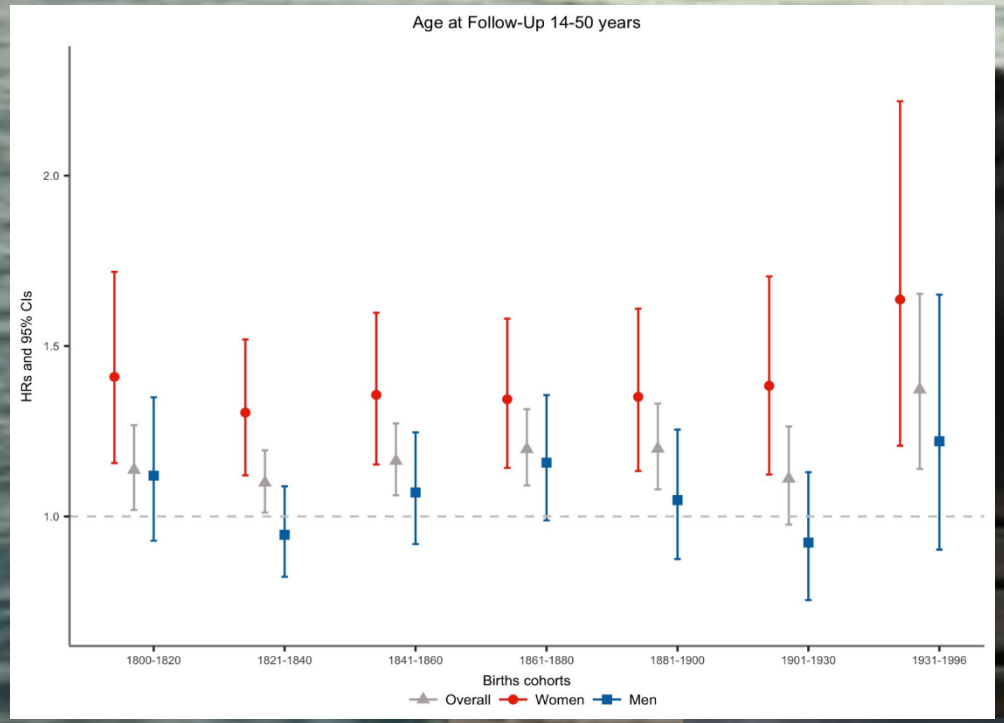
Health of War Migrants

A cohort study in Sweden

- 105.000 individuals immigrating to Sweden from Balkan 1991-2001
  - Population Register
  - Immigration from Bosnia-Herzegovina, Yugoslavia, Albania, Croatia, Macedonia, and Serbia
- 147.000 individuals immigrating from other European countries during the same period
  - Population Register
- Outcomes ascertained from Patient-, Cancer- and Causes of Death Register
- Models adjusted for age, sex, SES and country-level smoking prevalence

Conclusion

- Large scale societal disasters do not go unnoticed
- Extremely vulnerable populations
- Important to screen and intervene



Prevention and Epidemiology

Cancer Research

Bereavement Is Associated with an Increased Risk of HPV Infection and Cervical Cancer: An Epidemiological Study in Sweden

Donghao Lu[1], Karin Sundström[2], Pär Sparén[1], Katja Fall[3,4], Arvid Sjölander[1], Joakim Dillner[1,2], Nathalie Ylitalo Helm[5], Hans-Olov Adami[1,4], Unnur Valdimarsdóttir[1,4,6], and Fang Fang[1]

Parental cancer diagnosis and child mortality—A population-based cohort study in Sweden

Ruoqing Chen [a,*], Arvid Sjölander [a], Unnur Valdimarsdóttir [b], Catherine Varnum [c], Catarina Almqvist [a,d], Weimin Ye [a], Katja Fall [e], Kamila Czene [a], Fang Fang [a]

[a] Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden
[b] Center of Public Health Sciences, Faculty of Medicine, University of Iceland, Reykjavik, Iceland
[c] University of Maryland School of Medicine, Baltimore, MD, USA
[d] Lung and Allergy Unit, Astrid Lindgren Children's Hospital, Karolinska University Hospital, Stockholm, Sweden
[e] Clinical Epidemiology and Biostatistics Unit, School of Health and Medical Sciences, Örebro University and Örebro University Hospital, Örebro, Sweden

Prevention and Epidemiology

Cancer Research

Risk of Infection-Related Cancers after the Loss of a Child: A Follow-up Study in Sweden

Fang Fang[1], Katja Fall[1,2,3], Pär Sparén[1], Hans-Olov Adami[1,2], Heiddis B. Valdimarsdóttir[4,5], Mats Lambe[1,6], and Unnur Valdimarsdóttir[1,2,3]

Mortality

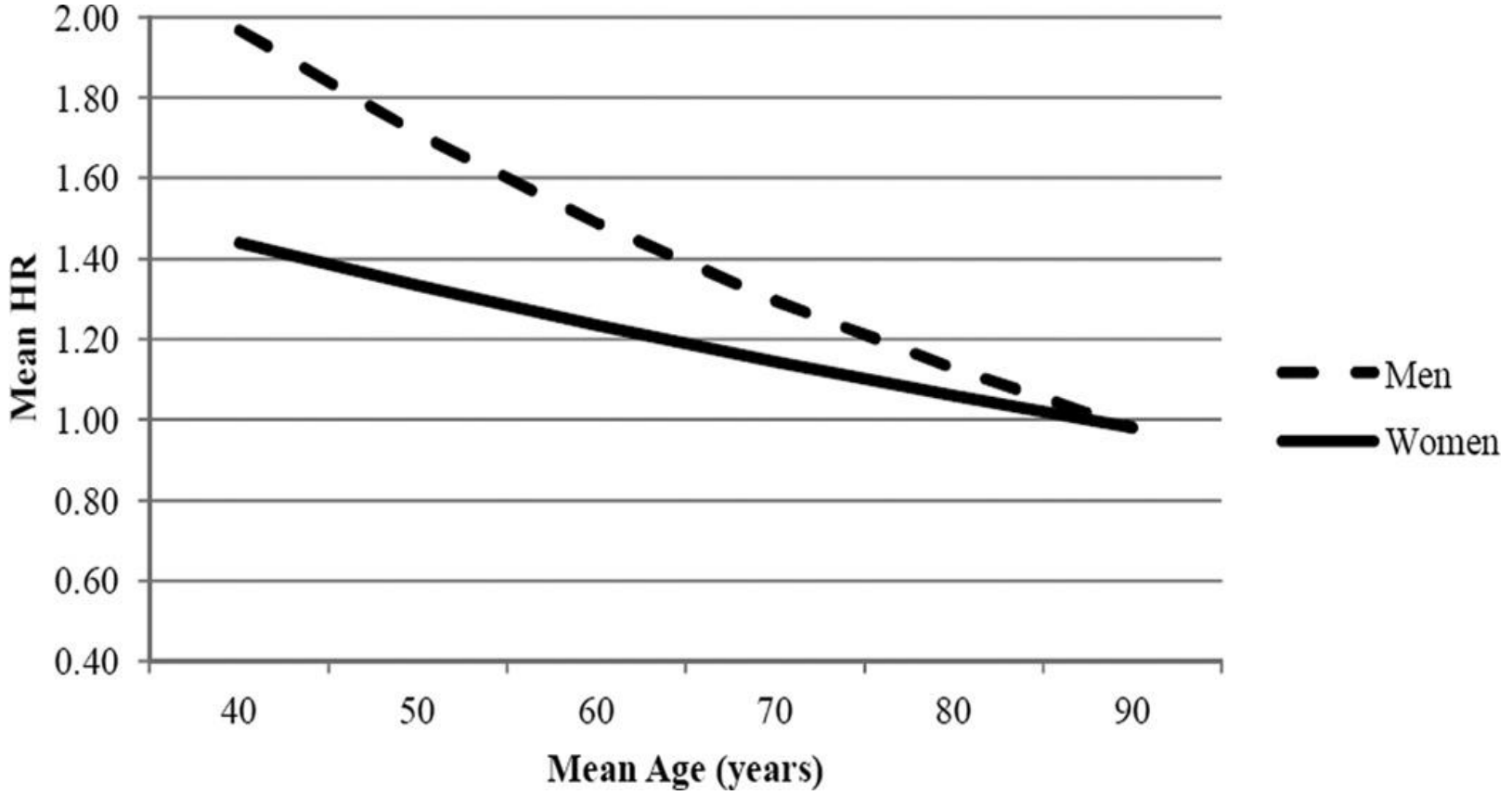
Psychiatric morbidity, self-harm

Infection-related cancers, pancreas cancer

Cardiovascular disease

Major illness or death of family member

Mortality after spousal loss



Shor et al., 2012

Parent mortality after child loss

Danish study of 21.000 parents who lost a child after 1980

	Parents			Fathers			Mothers		
	E/U	Hazard ratio (95% CI)*	p	E/U	Hazard ratio (95% CI)*	p	E/U	Hazard ratio (95% CI)*	p
All deaths	2·23/1·89	1·22 (1·12–1·35)	<0·0001	2·74/2·51	1·09 (0·95–1·23)	0·1947	1·90/1·35	1·43 (1·24–1·64)	<0·0001
Natural deaths	1·76/1·54	1·14 (1·04–1·28)	0·0110	2·12/1·99	1·07 (0·93–1·24)	0·3480	1·43/1·16	1·26 (1·07–1·47)	0·0047
Cancer	0·76/0·68	1·13 (0·93–1·30)	0·1191	0·76/0·74	1·02 (0·78–1·24)	0·8848	0·76/0·6	1·26 (1·01–1·55)	0·0406
Circulatory diseases	0·48/0·46	1·03 (0·85–1·30)	0·7272	0·72/0·72	0·99 (0·77–1·24)	0·9470	0·27/0·2	1·16 (0·83–1·72)	0·4344
Digestive diseases	0·12/0·10	1·30 (0·90–2·03)	0·1807	0·19/0·12	1·56 (0·98–2·71)	0·0562	0·07/0·0	0·93 (0·47–1·76)	0·8307
Other	0·40/0·31	1·28 (1·02–1·59)	0·0497	0·46/0·40	1·15 (0·85–1·55)	0·6437	0·34/0·2	1·47 (1·06–2·03)	0·0236
Unnatural deaths	0·53/0·35	1·53 (1·28–1·89)	<0·0001	0·61/0·52	1·15 (0·89–1·50)	0·3236	0·46/0·2	2·45 (1·84–3·26)	<0·0001
Motor vehicle accidents	0·11/0·06	1·83 (1·23–2·75)	0·0221	0·10/0·09	1·10 (0·58–1·97)	0·9646	0·12/0·04	3·38 (1·97–6·04)	0·0002
Suicide	0·25/0·17	1·44 (1·09–2·06)	0·0097	0·30/0·27	1·11 (0·82–1·70)	0·5698	0·21/0·09	2·34 (1·56–3·78)	0·0001
Other	0·17/0·11	1·51 (1·08–2·21)	0·0195	0·20/0·16	1·26 (0·79–1·87)	0·2876	0·14/0·07	2·04 (1·19–3·42)	0·0093

E/U=mortality rates (per 1000 person years) in the exposed cohort/mortality rates (per 1000 person years) in the unexposed cohort. *Adjusted for age, sex, school education, place of residence, number of children in the family, number of parents in the family.

Table 3: **Effect of the death of a child on parental mortality**

Li et al., Lancet, 2003

Developmental changes

	Infant mortality / 1000 births	
World-wide	Developing countries	Developed/western
	~100	<8
Iceland	1880-1885	2005-2010
	238	2.07

What do the bereaved die from?

Danish study of 21.000 parents who lost a child after 1980

	Parents			Fathers			Mothers		
	E/U	Hazard ratio (95% CI)*	p	E/U	Hazard ratio (95% CI)*	p	E/U	Hazard ratio (95% CI)*	p
All deaths	2·23/1·89	1·22 (1·12–1·35)	<0·0001	2·74/2·51	1·09 (0·95–1·23)	0·1947	1·90/1·35	1·43 (1·24–1·64)	<0·0001
Natural deaths	1·76/1·54	1·14 (1·04–1·28)	0·0110	2·12/1·99	1·07 (0·93–1·24)	0·3480	1·43/1·16	1·26 (1·07–1·47)	0·0047
Cancer	0·76/0·68	1·13 (0·93–1·30)	0·1191	0·76/0·74	1·02 (0·78–1·24)	0·8848	0·76/0·63	1·26 (1·01–1·55)	0·0406
Circulatory diseases	0·48/0·46	1·03 (0·85–1·30)	0·7272	0·72/0·72	0·99 (0·77–1·24)	0·9470	0·27/0·23	1·16 (0·83–1·72)	0·4344
Digestive diseases	0·12/0·10	1·30 (0·90–2·03)	0·1807	0·19/0·12	1·56 (0·98–2·71)	0·0562	0·07/0·08	0·93 (0·47–1·76)	0·8307
Other	0·40/0·31	1·28 (1·02–1·59)	0·0497	0·46/0·40	1·15 (0·85–1·55)	0·6437	0·34/0·20	1·47 (1·06–2·03)	0·0236
Unnatural deaths	0·53/0·35	1·53 (1·28–1·89)	<0·0001	0·61/0·52	1·15 (0·89–1·50)	0·3236	0·46/0·20	2·45 (1·84–3·26)	<0·0001
Motor vehicle accidents	0·11/0·06	1·83 (1·23–2·75)	0·0221	0·10/0·09	1·10 (0·58–1·97)	0·9646	0·12/0·0	3·38 (1·97–6·04)	0·0002
Suicide	0·25/0·17	1·44 (1·09–2·06)	0·0097	0·30/0·27	1·11 (0·82–1·70)	0·5698	0·21/0·0	2·34 (1·56–3·78)	0·0001
Other	0·17/0·11	1·51 (1·08–2·21)	0·0195	0·20/0·16	1·26 (0·79–1·87)	0·2876	0·14/0·0	2·04 (1·19–3·42)	0·0093

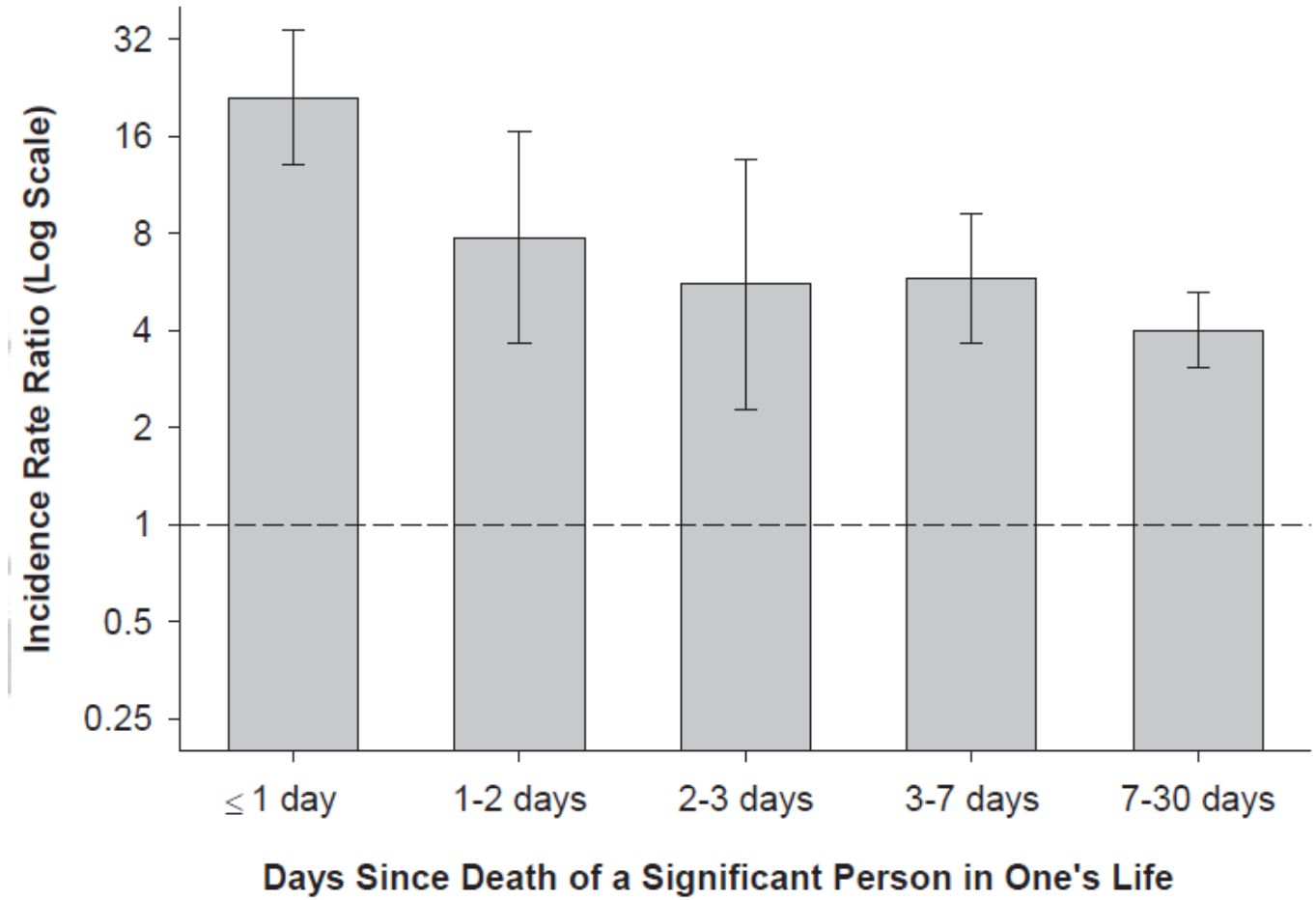
E/U=mortality rates (per 1000 person years) in the exposed cohort/mortality rates (per 1000 person years) in the unexposed cohort. *Adjusted for age, sex, school education, place of residence, number of children in the family, number of parents in the family.

Table 3: **Effect of the death of a child on parental mortality**

Li et al., Lancet, 2003

Risk of Acute Myocardial Infarction after Death of a Significant Person in One's Life: The Determinants of MI Onset Study

Elizabeth Mostofsky, Malcolm Maclure, Jane B. Sherwood, Geoffrey H. Tofler, James E. Muller and Murray A. Mittleman



Mostofsky et al., Circulation, 2012

Conclusion

- Child loss has at least for two centuries been associated with premature maternal mortality rate
- Spousal loss is associated with increased mortality rates of widows and widowers, particularly in early life
- Self-harm and CVD major contributors to increased mortality rates among the bereaved
- These populations are often in contact with health care

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Suicide and Cardiovascular Death after a Cancer Diagnosis

Fang Fang, M.D., Ph.D., Katja Fall, M.D., Ph.D., Murray A. Mittleman, M.D., Dr.P.H., Pär Sparén, Ph.D., Weimin Ye, M.D., Ph.D., Hans-Olov Adami, M.D., Ph.D., and Unnur Valdimarsdóttir, Ph.D.

ABSTRACT

BACKGROUND

Receiving a diagnosis of cancer is a traumatic experience that may trigger immediate adverse health consequences beyond the effects of the disease or treatment.

METHODS

Using Poisson and negative binomial regression models, we conducted a historical cohort study involving 6,073,240 Swedes to examine the associations between a cancer diagnosis and the immediate risk of suicide or death from cardiovascular causes from 1991 through 2006. To adjust for unmeasured confounders, we also performed a nested, self-matched case-crossover analysis among all patients with cancer who died from suicide or cardiovascular diseases in the cohort.

JAMA Oncology | Original Investigation

Clinical Diagnosis of Mental Disorders Immediately Before and After Cancer Diagnosis

A Nationwide Matched Cohort Study in Sweden

Donghao Lu, MD; Therese M. L. Andersson, PhD; Katja Fall, MD, PhD; Christina M. Hultman, MD, PhD; Kamila Czene, PhD; Unnur Valdimarsdóttir, PhD; Fang Fang, MD, PhD

Figure 1. Hazard Ratios and 95% CIs of Depression, Anxiety, Substance Abuse, Somatoform/Conversion Disorder, and Stress Reaction/Adjustment Disorder Before and After Cancer Diagnosis in a Matched Cohort Study in Sweden, 1999 to 2010

After cancer diagnosis - a dramatic rise in:

Psychiatric disorders and suicide

Accidents

Cardiovascular disease

Cancer Diagnosis – a major trauma

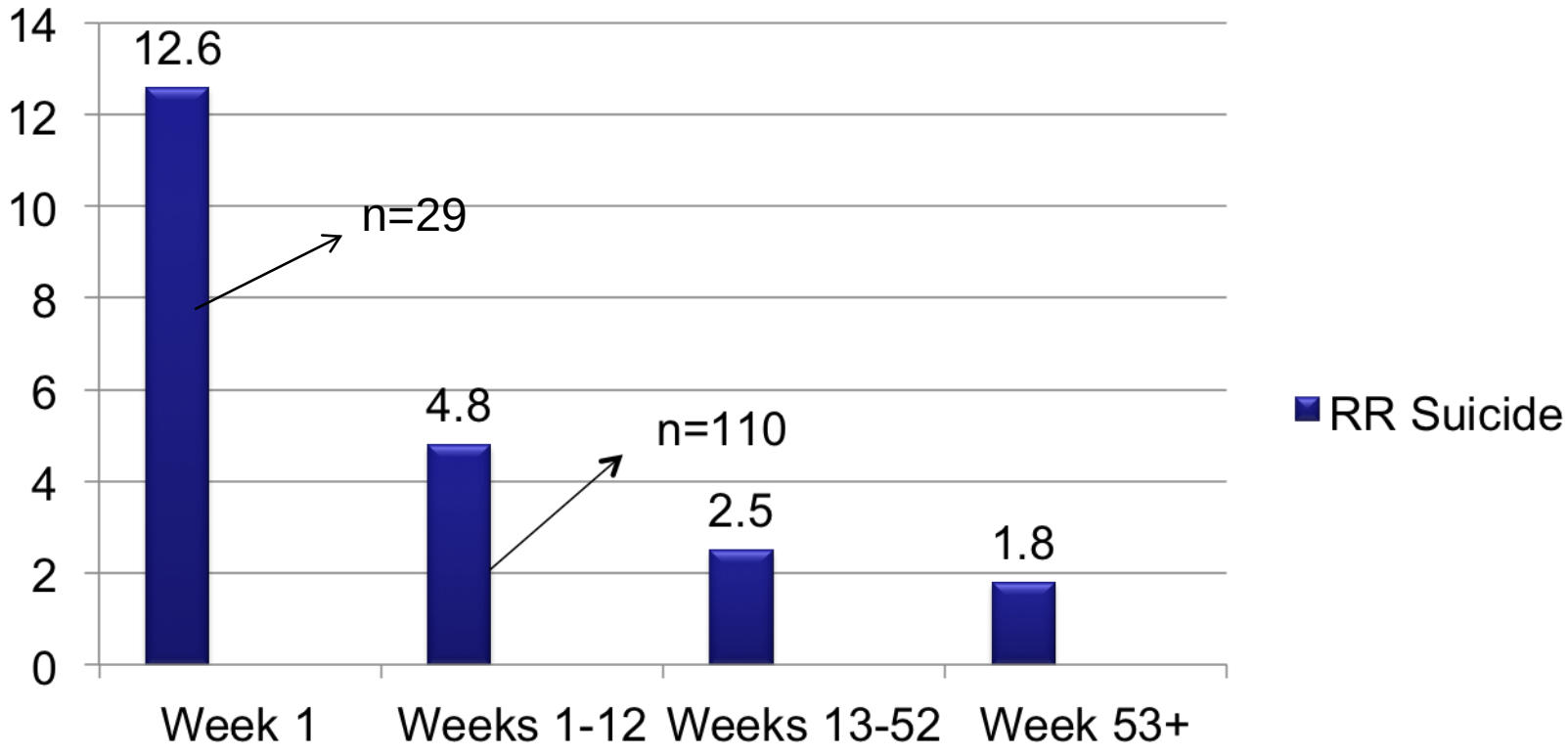
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Suicide and Cardiovascular Death after a Cancer Diagnosis

Fang Fang, M.D., Ph.D., Katja Fall, M.D., Ph.D., Murray A. Mittleman, M.D., Dr.P.H., Pär Sparén, Ph.D., Weimin Ye, M.D., Ph.D., Hans-Olov Adami, M.D., Ph.D., and Unnur Valdimarsdóttir, Ph.D.

Relative Risk of Suicide



Relative risk of Cardiovascular Death

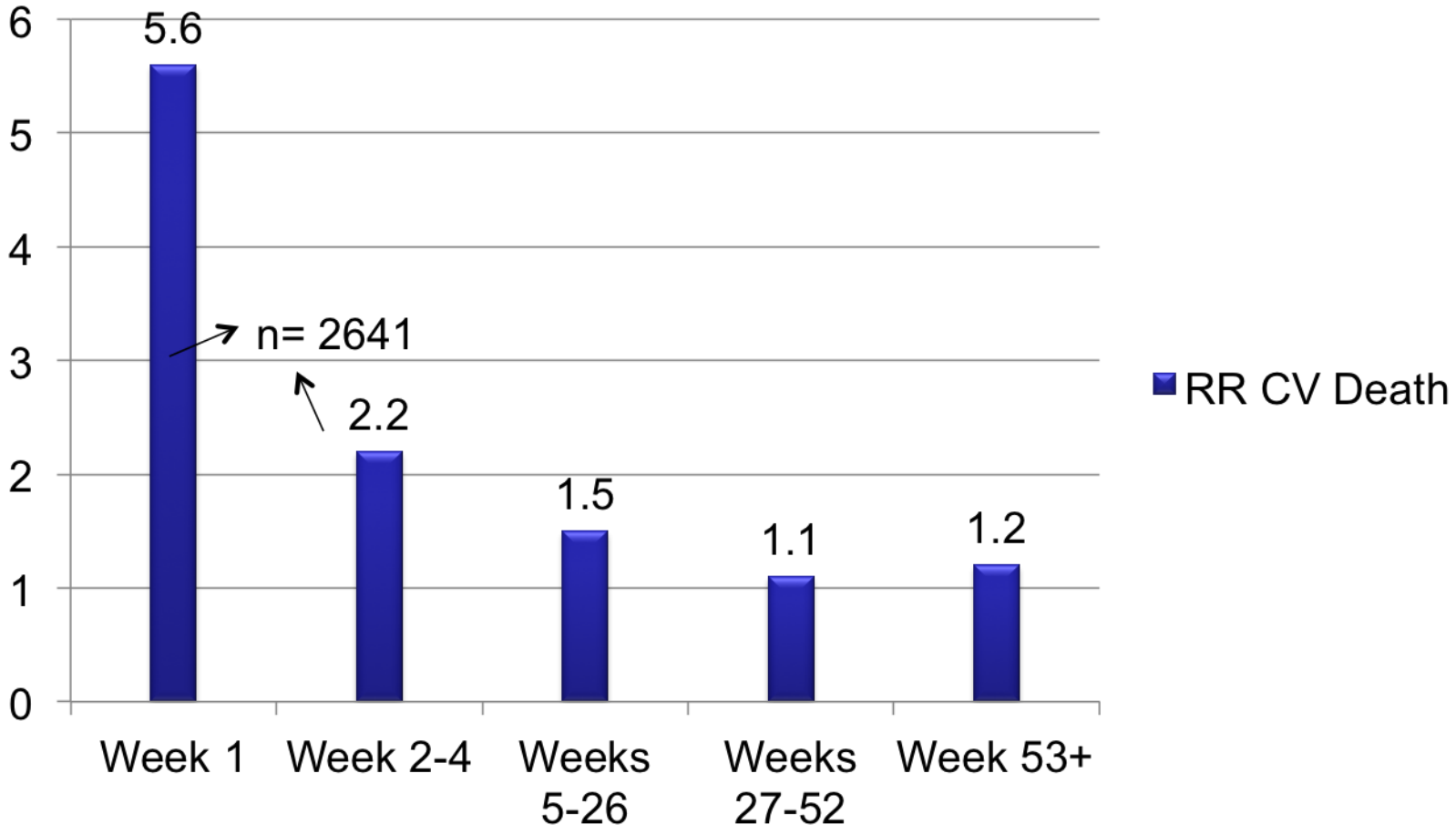


Table 1. Relative Risks of Suicide or Cardiovascular Death after a Cancer Diagnosis, According to Time Period.

Variable	Any Cancer (N=534,154)*	Prostate Cancer (N=95,786)	Breast Cancer (N=74,977)†	Colorectal Cancer (N=62,719)	Skin Cancer (N=47,169)	Lymphatic or Hematopoietic Cancer (N=36,648)	Lung Cancer (N=34,743)	CNS Tumors (N=13,447)‡	Esophageal, Liver, or Pancreatic Cancer (N=26,335)
	multivariable relative risk (95% confidence interval)§								
Suicide									
Cancer-free	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
After cancer diagnosis									
Weeks 1 to 12	4.8 (4.0–5.8)	3.2 (2.0–4.9)	3.4 (1.3–6.9)	4.7 (2.6–7.8)	1.4 (0.3–3.6)	2.5 (0.8–5.9)	12.3 (7.4–18.9)	7.8 (2.4–18.1)	16.0 (9.2–25.5)
Weeks 13 to 52	2.5 (2.1–2.9)	2.0 (1.5–2.8)	0.7 (0.2–1.7)	2.1 (1.2–3.3)	0.9 (0.2–2.6)	1.7 (0.7–3.2)	6.1 (3.6–9.6)	2.3 (0.6–6.0)	5.2 (2.2–10.1)
Week 53 onward¶	1.8 (1.6–2.0)	1.9 (1.6–2.2)	1.6 (1.2–2.1)	1.6 (1.2–2.0)	1.4 (1.0–1.8)	1.3 (0.6–2.4)	3.3 (1.3–6.8)	2.3 (1.3–3.6)	4.5 (2.2–8.2)
Cardiovascular death									
Cancer-free	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
After cancer diagnosis									
Week 1	5.6 (5.2–5.9)	2.8 (2.3–3.2)	1.8 (1.2–2.4)	5.4 (4.6–6.2)	1.2 (0.8–1.6)	8.7 (7.3–10.2)	12.4 (10.5–14.5)	26.9 (19.9–35.4)	14.9 (12.8–17.3)
Weeks 2 to 4	2.2 (2.1–2.3)	1.4 (1.2–1.6)	1.4 (1.1–1.8)	2.1 (1.8–2.4)	0.8 (0.6–1.0)	3.5 (2.9–4.1)	4.8 (4.0–5.6)	5.3 (3.4–7.8)	5.0 (4.2–6.0)
Weeks 5 to 26	1.5 (1.4–1.5)	0.9 (0.9–1.0)	1.2 (1.0–1.3)	1.2 (1.1–1.3)	0.9 (0.8–1.0)	2.1 (2.0–2.3)	2.6 (2.3–2.9)	4.1 (3.3–5.0)	2.6 (2.3–3.0)
Weeks 27 to 52	1.1 (1.0–1.1)	0.9 (0.8–1.0)	1.0 (0.9–1.1)	0.8 (0.7–0.9)	1.0 (0.9–1.0)	1.3 (1.2–1.5)	2.2 (1.9–2.5)	1.4 (0.9–2.0)	1.8 (1.5–2.2)
Week 53 onward ¶	1.2 (1.1–1.2)	1.0 (1.0–1.1)	1.0 (1.0–1.0)	0.9 (0.9–1.0)	1.0 (1.0–1.1)	1.2 (1.1–1.3)	1.6 (1.4–1.7)	1.1 (1.0–1.2)	1.3 (1.1–1.4)

* To preclude potential misdiagnosis between tumors of the central nervous system (CNS) and stroke, CNS tumors were excluded from "any cancer" in the analysis of cardiovascular death. Other cancers that are not listed were diagnosed in 142,330 patients.

† The analysis for breast cancer was conducted only among women.

‡ To preclude potential misdiagnosis between CNS tumors and stroke, stroke was excluded from "cardiovascular death" in the analysis of CNS tumors.

§ Relative risks were adjusted for age at follow-up (≤49 years, 5-year groups for 50 to 74 years, or ≥75 years for suicide; and ≤44 years, 5-year groups for 45 to 94 years, or ≥95 years for cardiovascular death), sex, calendar period at follow-up (5-year groups for suicide and 1-year groups for cardiovascular death), civil status (cohabitation or noncohabitation), socioeconomic status (blue-collar, white-collar, self-employed, or unclassified), and educational level (≥9 years, <9 years, or missing).

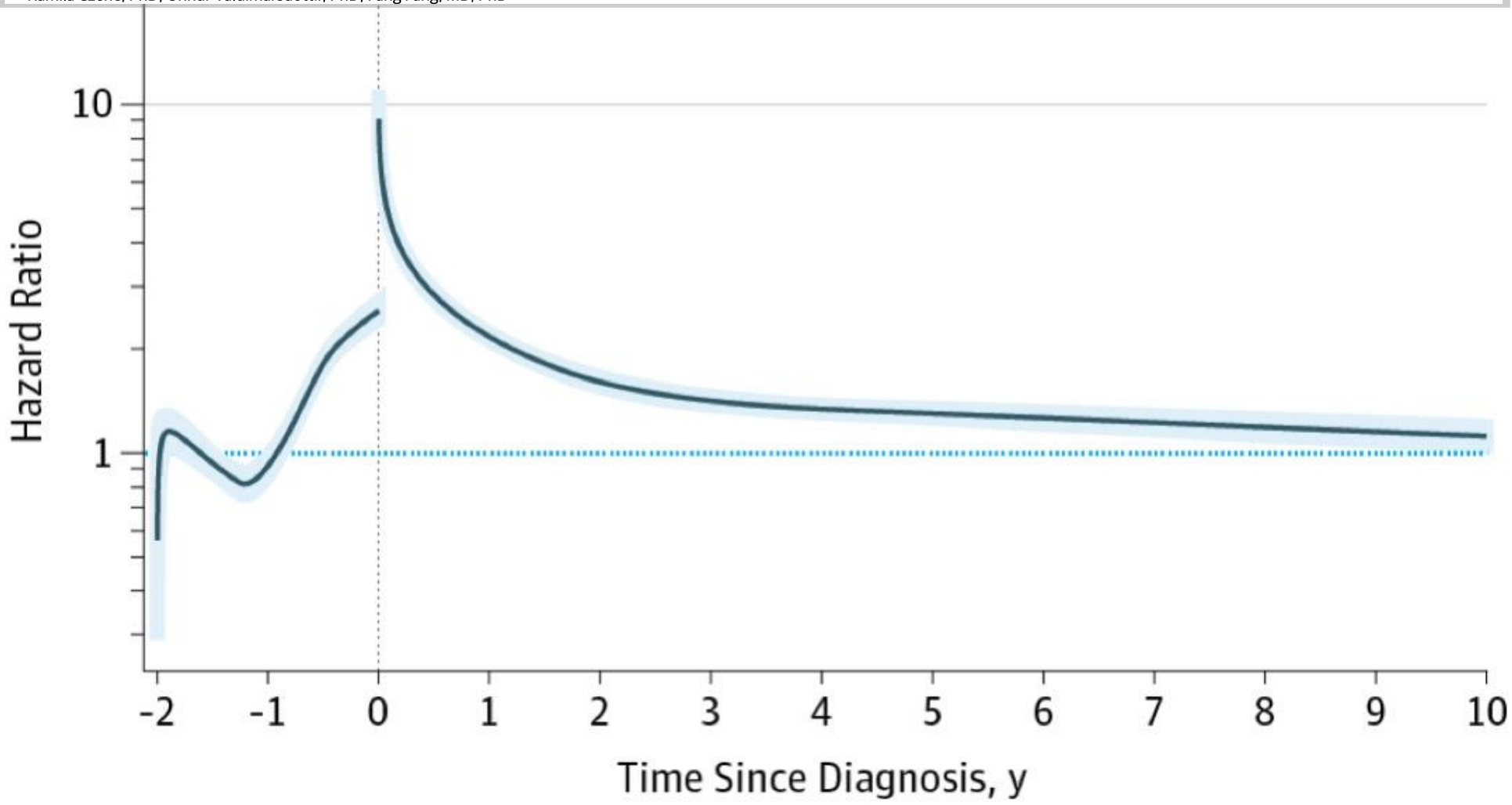
¶ The mean follow-up of patients in whom cancer was diagnosed was 4.07 years (median, 2.65; range, 0 to 15.99).

JAMA Oncology | Original Investigation

Clinical Diagnosis of Mental Disorders Immediately Before and After Cancer Diagnosis

A Nationwide Matched Cohort Study in Sweden

Donghao Lu, MD; Therese M. L. Andersson, PhD; Katja Fall, MD, PhD; Christina M. Hultman, MD, PhD; Kamila Czene, PhD; Unnur Valdimarsdóttir, PhD; Fang Fang, MD, PhD



First-onset mental disorders after cancer diagnosis and cancer-specific mortality: a nationwide cohort study

J. Zhu[1*], F. Fang[1], A. Sjölander[1], K. Fall[1,2], H. O. Adami[1,3,4] & U. Valdimarsdóttir[1,3,5]

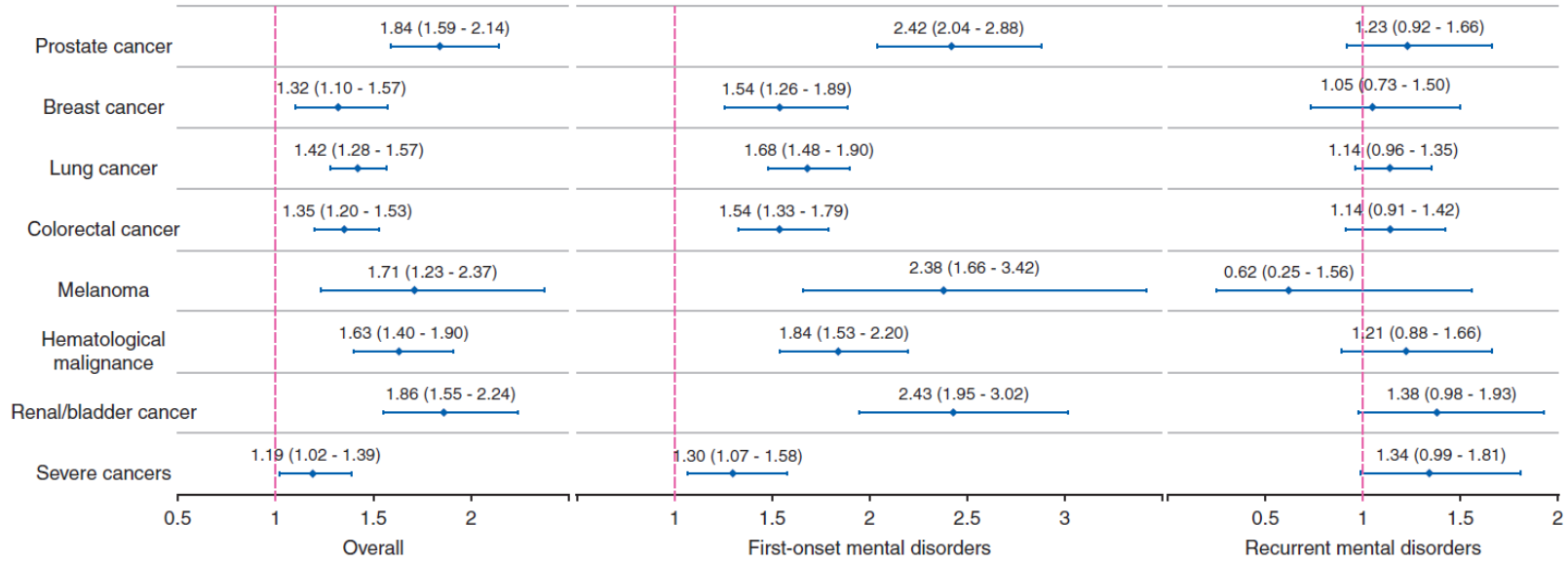
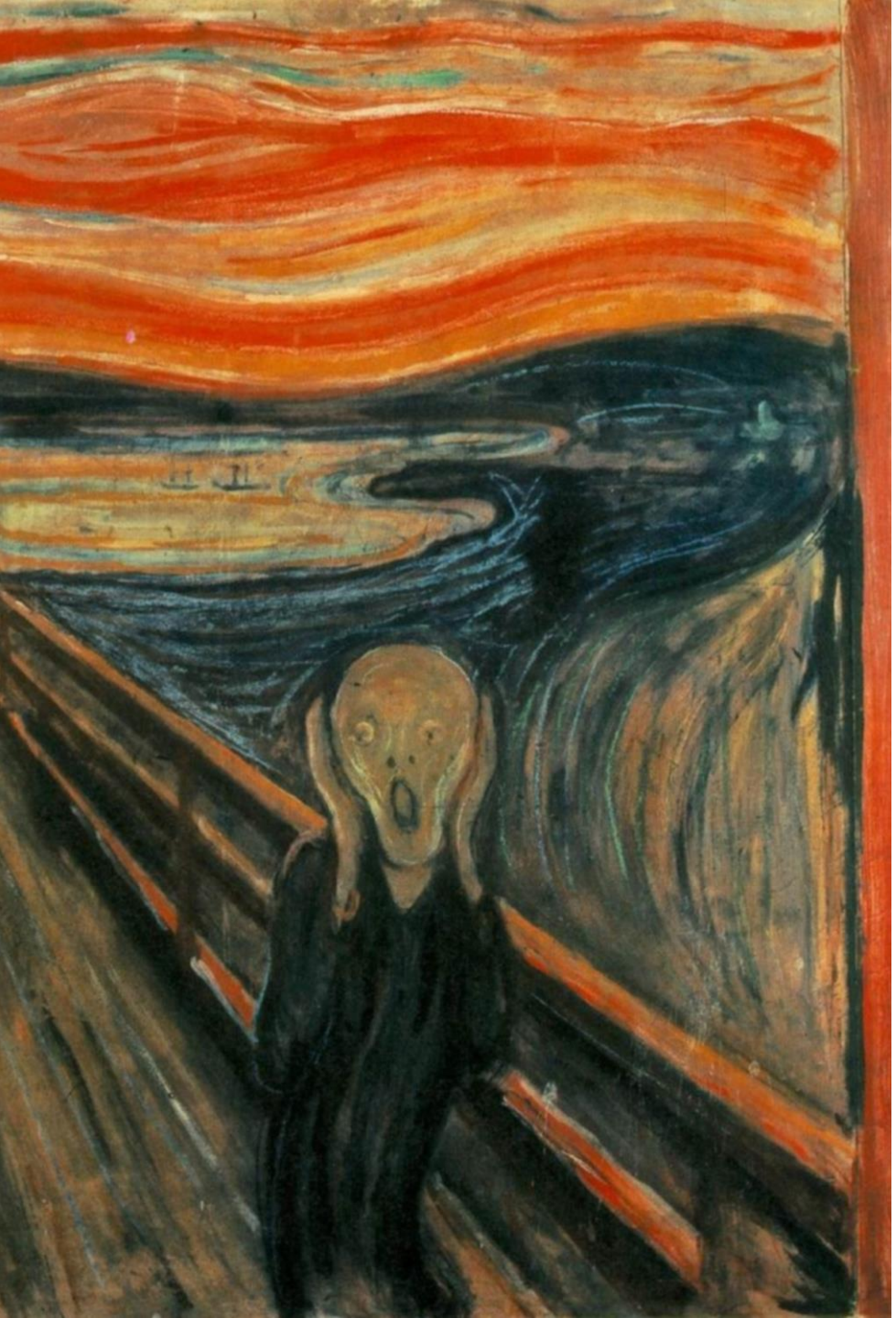


Figure 1. Hazard ratios of cancer-specific mortality among patients with studied mental disorders after cancer diagnosis when compared with patients without any mental disorders after cancer diagnosis, further stratified with respect to previous mental disorders (ICD10: F00–F99).

Psychiatric disorders among cancer patients associated with:

Increased cancer-specific mortality (all cancers)

Mental health matters for cancer survival



Conclusion

- A cancer diagnosis is associated with a rapid rise in rates of psychiatric disorders, suicide and CVD deaths
- Psychiatric disorders after cancer diagnosis associated with reduced cancer-specific survival
- The first days and weeks after cancer diagnosis represent a critical time window for screening and intervention

A THIRD OF ALL WOMEN WORLDWIDE EXPOSED TO VIOLENCE (WHO, 2013)

Violence against women - lifetime %

- **33% sexual and/or physical violence**

Women 15 years and older in high income areas – WHO, 2013

- **43-50% sexual and/or physical violence**

Denmark, Sweden, Finnland; UN Women, 2011

- **36% Iceland; 34% Denmark; 37% Norway; 30% Sweden lifetime abuse among 7174 pregnant women**

Lucasse et al., AOGS 2014

- **30% sexual and/or physical violence <u>in relationships</u>**

Starrs et al., Lancet 2018

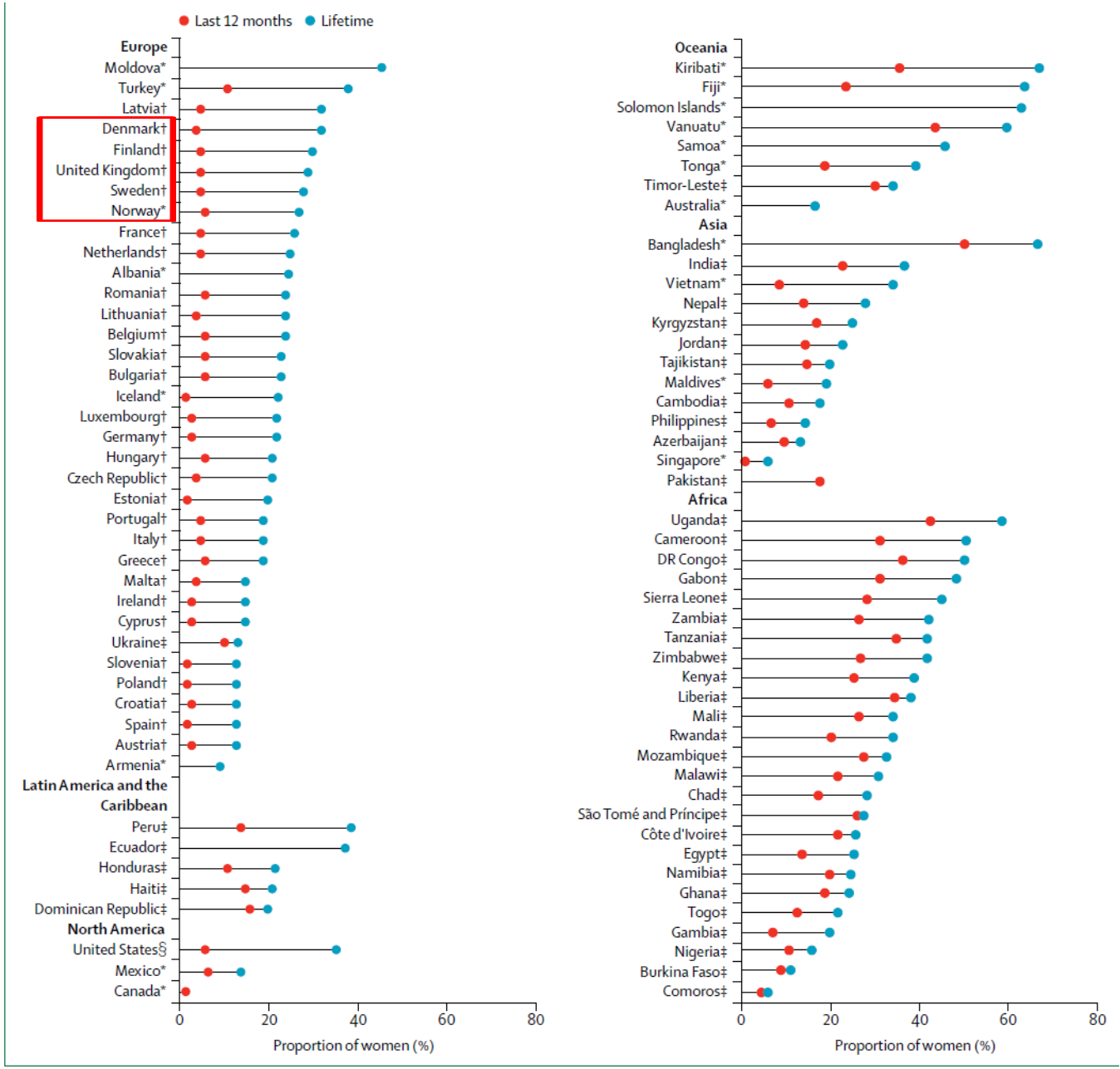


Figure 4: **Proportion of women who have experienced partner violence (physical or sexual) during their lifetime and in the past 12 months, 2000–15**
Not all countries have data available on both indicators, the proportion experiencing partner violence in the past 12 months and lifetime. *Data from age groups covered differ across countries from 2000–13, from UN Department of Economic and Social Affairs, 2015.[78] §Data from ever-partnered women aged 17–74 years, from European Union Agency for Fundamental Rights, 2014[79] ‡Data from Demographic Health Surveys Programme, 2016.[80] ¥Data from women aged 18 years and older about their experiences of rape, physical violence or stalking (or both) from Black MC et al., 2011.[81]

Overarching aim:
Genetics of posttraumatic stress disorder

Other knowledge gained

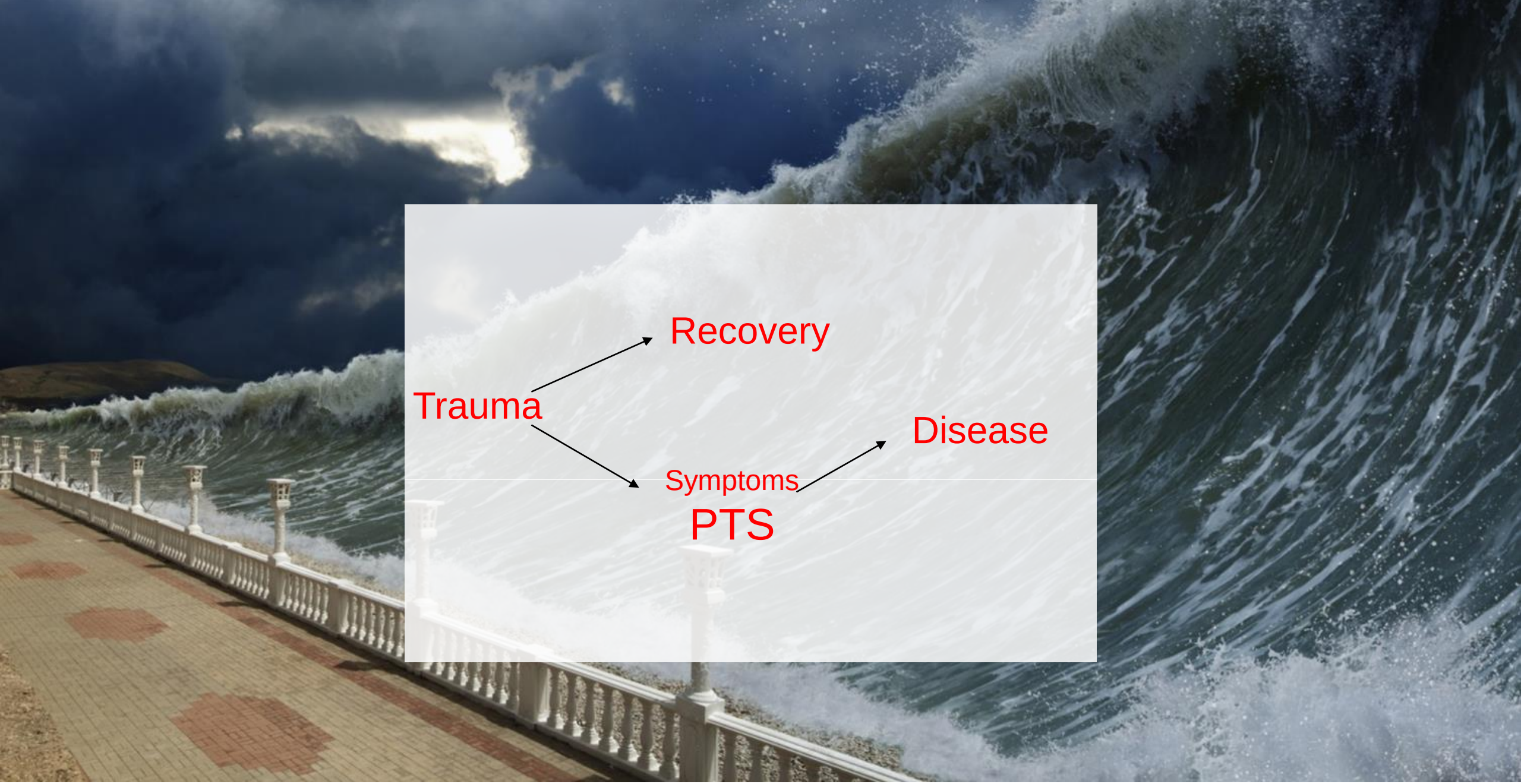
- Prevalence of trauma among females?
- Association between trauma and health?
- Risk and protective factors for adverse outcomes?

Invited*:*
Women in Iceland 18-69 years

Participants:
32.000 women

The SAGA COHORT

Different health trajectories after trauma



Risk modified by posttraumatic stress (PTS)

Cohort studies in Sweden

- 106.000 individuals with stress-related disorders 1981-2013
  - National Patient Register
  - Diagnoses: F43 – PTSD, ASR, adjustment disorders, other reactions to severe stress

- 1.060.000 individuals (1:10; matched on age and sex) without such disorders
  - Population Register

- 126.000 siblings of individuals with stress-related disorders
  - Multigenerational Register

- Cox models adjusted for: education level, family income, marital status, comorbidity index, family history index disease, and previous history of psychiatric disorder

JAMA | Original Investigation

Association of Stress-Related Disorders With Subsequent Autoimmune Disease

Huan Song, MD, PhD; Fang Fang, MD, PhD; Gunnar Tomasson, MD, PhD; Filip K. Arnberg, PhD; David Mataix-Cols, PhD; Lorena Fernández de la Cruz, PhD; Catarina Almqvist, MD, PhD; Katja Fall, MD, PhD; Unnur A. Valdimarsdóttir, PhD

IMPORTANCE Psychiatric reactions to life stressors are common in the general population and may result in immune dysfunction. Whether such reactions contribute to the risk of autoimmune disease remains unclear.

OBJECTIVE To determine whether there is an association between stress-related disorders and subsequent autoimmune disease.

DESIGN, SETTING, AND PARTICIPANTS Population- and sibling-matched retrospective cohort study conducted in Sweden from January 1, 1981, to December 31, 2013. The cohort included 106 464 exposed patients with stress-related disorders, with 1 064 640 matched unexposed persons and 126 652 full siblings of these patients.

Supplemental content

Results

	No of autoimmune disease cases/ 1000 person-years (incidence rate, per 1 000 person-years)		Absolute rate difference, per 1 000 person-years (95% confidence interval)	Hazard ratio (95% confidence interval)[a]
	Exposed patients	Matched unexposed Individuals		
All	**8284/911.7(9.1)**	**57711/9675.7(6.0)**	**3.12 (2.99-3.25)**	**1.36 (1.33-1.40)**
Post-traumatic stress disorder	532/50.3(10.6)	3412/533.1(6.4)	4.18 (4.14-4.21)	1.46 (1.32-1.61)
Acute stress reaction	3449/376.6(9.2)	24103/3990.0(6.0)	3.12 (2.80-3.43)	1.35 (1.30-1.40)
Adjustment disorder and other stress reactions	4303/484.8(8.9)	30196/5152.6(5.9)	3.02 (2.74-3.29)	1.37 (1.32-1.41)

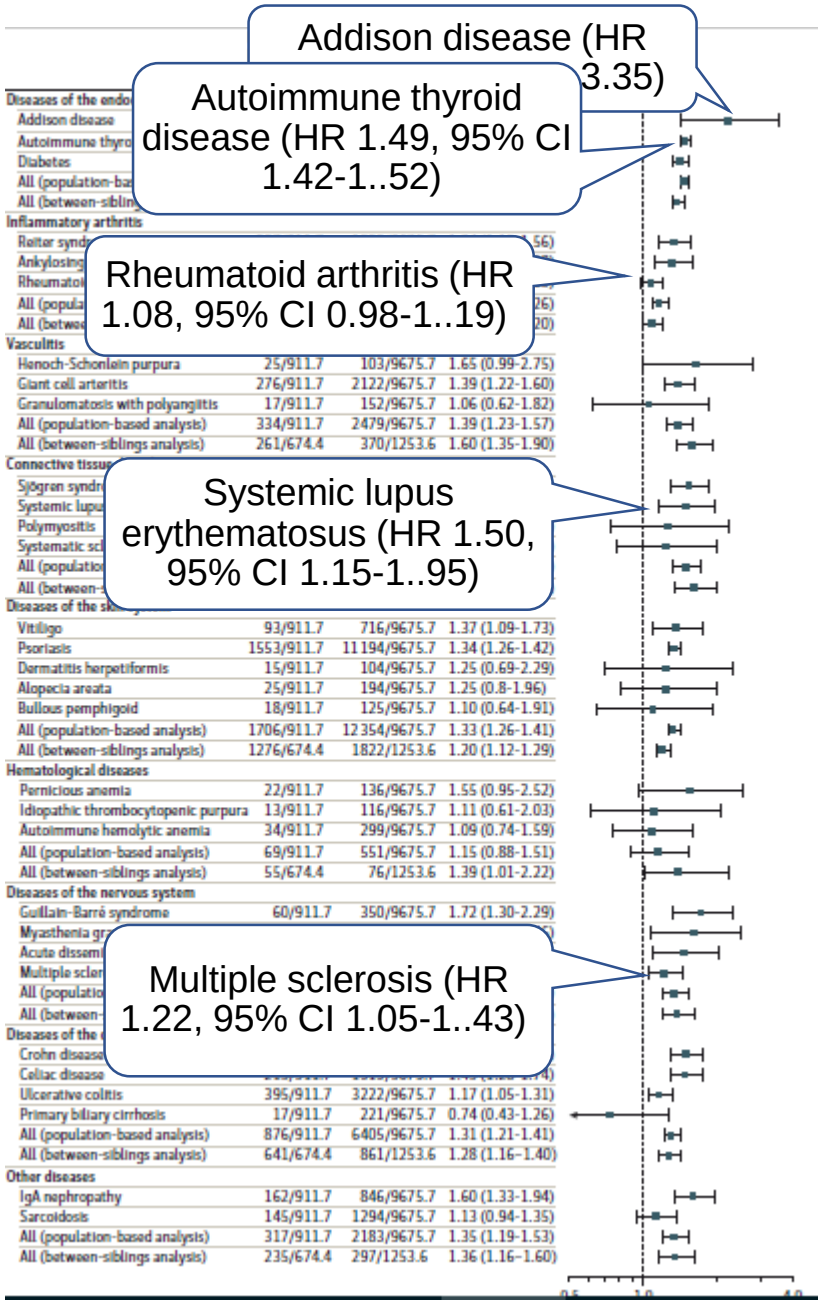
[a] Cox models were stratified by matching identifiers (birth year and sex), and adjusted for education level, family income, marital status, Charlson comorbidity index score, family history of autoimmune disease, and history of other psychiatric disorders.

The first year of follow-up was excluded for all analyses.

Results

41 distinct autoimmune diseases

- Significant associations were noted for 18 individual autoimmune diseases
- The relative risk levels varied considerably



Modification by SSRI use?

Table 3. Risk of Autoimmune Disease Among Patients With Any Stress-Related Disorder or Posttraumatic Stress Disorder by Psychiatric Care Indicators Compared With Matched Unexposed Individuals (continued)

Psychiatric Care Indicators	Patients With Any Stress-Related Disorder					Patients With Posttraumatic Stress Disorder				
	No. of Autoimmune Disease Cases/No. of Accumulated Person-Years × 1000 (Incidence Rate/1000 Person-Years)		Absolute Rate Difference/1000 Person-Years (95% CI)	Hazard Ratio (95% CI)[a]	*P* Value[b]	No. of Autoimmune Disease Cases/No. of Accumulated Person-Years × 1000 (Incidence Rate/1000 Person-Years)		Absolute Rate Difference/1000 Person-Years (95% CI)	Hazard Ratio (95% CI)[a]	*P* Value[b]
	Exposed Patients	Matched Unexposed Individuals				Exposed Patients	Matched Unexposed Individuals			
Use of selective serotonin reuptake inhibitors within the first year after diagnosis[e]										
Dose level										
No medication	1185/116.5 (10.2)	8309/1195.5 (7.0)	3.22 (2.62-3.82)	1.31 (1.22-1.39)		83/7.3 (11.4)	546/75.1(7.2)	4.09 (1.57-6.61)	1.25 (0.96-1.62)	
Low dose (≤1.0 DDD/d)										
≤179	25/3.1 (8.1)	229/30.970 (7.4)	0.74 (-2.6-4.07)	1.08 (0.71-1.64)		6/0.2 (32.0)	16/2.0 (8.0)	24.0 (-1.9-49.9)	4.21 (1.40-12.6)	
180-319	104/7.4 (14.0)	510/76.170 (6.7)	7.27 (4.53-10.0)	1.98 (1.57-2.51)		12/0.6 (21.8)	29/5.7 (5.1)	16.6 (4.19-29.1)	3.64 (1.46-9.08)	
≥320	111/7.9 (14.1)	587/80.740 (7.3)	6.83 (4.14-9.52)	1.78 (1.43-2.22)		8/0.7 (11.4)	49/7.0 (7.0)	4.42 (-3.7-12.6)	1.19 (0.49-2.89)	
High dose (>1.0 DDD/d)					.73[f]					.03[f]
≤179	93/6.3 (14.7)	473/66.440 (7.1)	7.56 (4.51-10.6)	1.68 (1.31-2.16)		11/0.5 (23.9)	37/4.9 (7.5)	16.4 (2.05-30.7)	3.10 (1.28-7.50)	
180-319	168/13.5 (12.5)	960/137.3 (7.0)	5.50 (3.56-7.44)	1.48 (1.23-1.78)		18/1.2 (15.0)	80/12.4 (6.5)	8.56 (1.47-15.6)	2.38 (1.24-4.57)	
≥320	155/12.0 (12.9)	879/122.6 (7.2)	5.73 (3.65-7.82)	1.74 (1.46-2.07)		16/1.0 (16.7)	79/9.8 (8.1)	8.65 (0.28-17.0)	1.99 (1.14-3.50)	

Stress related disorders and risk of cardiovascular disease: population based, sibling controlled cohort study

Huan Song,[1,2] Fang Fang,[2] Filip K Arnberg,[3,4] David Mataix-Cols,[5,6] Lorena Fernández de la Cruz,[5,6] Catarina Almqvist,[2,7] Katja Fall,[2,8] Paul Lichtenstein,[2] Gudmundur Thorgeirsson,[1] Unnur A Valdimarsdóttir[1,2,9]

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Accepted: 12 March 2019

ABSTRACT

OBJECTIVE

To assess the association between stress related disorders and subsequent risk of cardiovascular disease.

DESIGN

Population based, sibling controlled cohort study.

SETTING

Population of Sweden.

PARTICIPANTS

136 637 patients in the Swedish National Patient Register with stress related disorders, including post-traumatic stress disorder (PTSD), acute stress reaction, adjustment disorder, and other stress reactions, from 1987 to 2013; 171 314 unaffected full siblings of these patients; and 1 366 370 matched unexposed people from the general population.

MAIN OUTCOME MEASURES

Primary diagnosis of incident cardiovascular disease—any or specific subtypes (ischaemic heart disease, cerebrovascular disease, emboli/thrombosis, hypertensive diseases, heart failure, arrhythmia/conduction disorder, and

their unaffected full siblings, and the matched unexposed individuals, respectively. In sibling based comparisons, the hazard ratio for any cardiovascular disease was 1.64 (95% confidence interval 1.45 to 1.84), with the highest subtype specific hazard ratio observed for heart failure (6.95, 1.88 to 25.68), during the first year after the diagnosis of any stress related disorder. Beyond one year, the hazard ratios became lower (overall 1.29, 1.24 to 1.34), ranging from 1.12 (1.04 to 1.21) for arrhythmia to 2.02 (1.45 to 2.82) for artery thrombosis/embolus. Stress related disorders were more strongly associated with early onset cardiovascular diseases (hazard ratio 1.40 (1.32 to 1.49) for attained age ‹50) than later onset ones (1.24 (1.18 to 1.30) for attained age ≥50; P for difference=0.002). Except for fatal cardiovascular diseases, these associations were not modified by the presence of psychiatric comorbidity. Analyses within the population matched cohort yielded similar results (hazard ratio 1.71 (1.59 to 1.83) for any cardiovascular disease during the first year of follow-up and 1.36 (1.33 to 1.39) thereafter).

CONCLUSION

Stress related disorders are robustly associated

Table 2 | Crude incidence rates and hazard ratios with 95% confidence intervals for cardiovascular diseases among patients with any stress related disorder, compared with their full siblings or matched unexposed individuals, by time of follow-up (<1 or ≥1 year)

	Sibling cohort		Population matched cohort	
Model information	No of cases (incidence*) in patients/siblings	Hazard ratio (95% CI)†	No of cases (incidence*) in patients/unexposed individuals	Hazard ratio (95% CI)†
<1 year of follow-up				
Controlled for sex, birth year, educational level, family income, and marital status	811 (8.06)/806 (4.92)	1.77 (1.58 to 1.98)	1094 (8.45)/5624 (4.32)	1.92 (1.80 to 2.05)
As above + history of other psychiatric disorder		1.65 (1.47 to 1.86)		1.74 (1.62 to 1.86)
As above + history of severe somatic diseases		1.64 (1.45 to 1.84)		1.72 (1.60 to 1.84)
As above + family history of cardiovascular disease		-		1.71 (1.59 to 1.83)
≥1 year of follow-up				
Controlled for sex, birth year, educational level, family income, and marital status	7246 (10.30)/11 276 (8.87)	1.39 (1.34 to 1.44)	9827 (10.81)/69 483 (7.26)	1.52 (1.49 to 1.56)
As above + history of other psychiatric disorder		1.30 (1.25 to 1.34)		1.39 (1.36 to 1.42)
As above + history of severe somatic diseases		1.29 (1.24 to 1.34)		1.37 (1.33 to 1.40)
As above + family history of cardiovascular disease		-		1.36 (1.33 to 1.39)

*Per 1000 person years.
†Derived from Cox regression models, stratified by family identifier (for sibling based comparison) or matching identifier (birth year and sex, for population based comparison) and adjusted for covariates listed in model information column. Time since index date was used as underlying time scale.

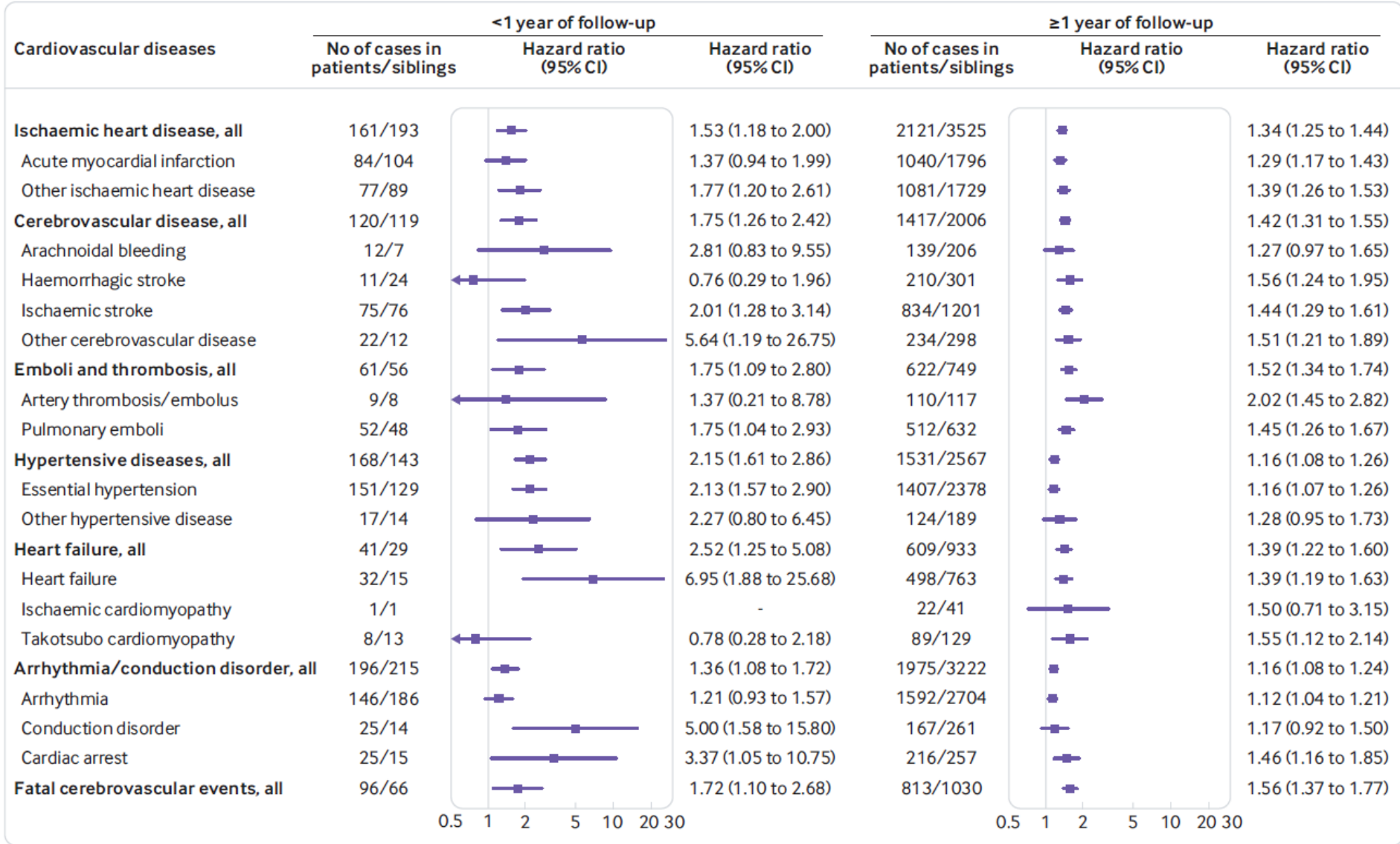

Fig 2 | Relative risks of developing different types of cardiovascular disease among patients with any stress related disorder, compared with their fu siblings, by time of follow-up (‹1 or ≥1 year). All Cox models were stratified by family identifiers and adjusted for age at index date, sex, educational 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

Stress related disorders and subsequent risk of life threatening infections: population based sibling controlled cohort study

Huan Song,[1,2,3] Katja Fall,[2,4] Fang Fang,[2] Helga Erlendsdóttir,[5,6] Donghao Lu,[2] David Mataix-Cols,[7,8] Lorena Fernández de la Cruz,[7,8] Brian M D'Onofrio,[2,9] Paul Lichtenstein,[2] Magnús Gottfreðsson,[5,10] Catarina Almqvist,[2,11] Unnur A Valdimarsdóttir[1,2,12]

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Additional material is published online only. To view please visit the journal online.

Cite this as: *BMJ* 2019;367:l5784 http://dx.doi.org/10.1136/bmj.l5784

ABSTRACT

OBJECTIVE

To assess whether severe psychiatric reactions to trauma and other adversities are associated with subsequent risk of life threatening infections.

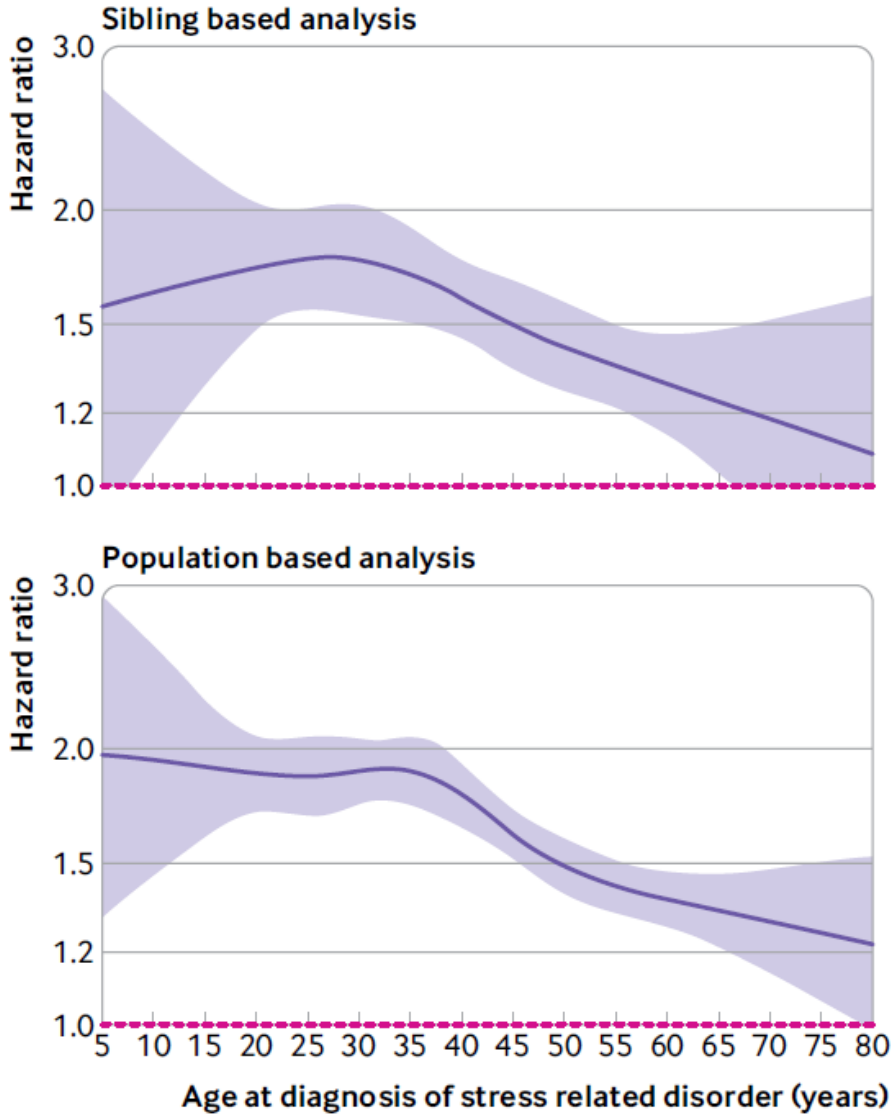
DESIGN

Population and sibling matched cohort study.

SETTING

Swedish population.

threatening infections per 1000 person years was 2.9 in individuals with a stress related disorder, 1.7 in siblings without a diagnosis, and 1.3 in matched individuals without a diagnosis. Compared with full siblings without a diagnosis of a stress related disorder, individuals with such a diagnosis were at increased risk of life threatening infections (hazard ratio for any stress related disorder was 1.47 (95% confidence intervals1.37 to 1.58) and for PTSD was



	No of cases (incidence rate per 1000 person years)	Hazard ratio (95% CI)
Sibling based analysis	**Exposed/sibling group**	
Any stress related disorder		
Life threatening infections	2197(2.7)/2646(1.69)	1.47 (1.37 to 1.58)
Sepsis	1384(1.7)/1651(1.05)	1.52 (1.39 to 1.66)
Endocarditis	103(0.12)/105(0.07)	1.57 (1.08 to 2.30)
Meningitis	120(0.15)/142(0.09)	1.63 (1.23 to 2.16)
Other CNS infections	296(0.36)/358(0.23)	1.45 (1.21 to 1.73)
Death due to other infections	445(0.54)/551(0.35)	1.39 (1.16 to 1.65)
Post-traumatic stress disorder		
Life threatening infections	170(2.94)/175(1.59)	1.92 (1.46 to 2.52)
Sepsis	111(1.91)/110(1)	1.84 (1.30 to 2.61)
Endocarditis	10(0.17)/8(0.07)	5.38 (0.46 to 62.9)
Meningitis	11(0.14)/8(0.07)	3.03 (0.63 to 14.6)
Other CNS infections	22(0.37)/27(0.24)	1.90 (0.85 to 4.24)
Death due to other infections	30(0.51)/36(0.33)	1.85 (0.89 to 3.83)
Population based analysis	**Exposed/unexposed group**	
Any stress related disorder		
Life threatening infections	3292(2.9)/15 684(1.34)	1.58 (1.51 to 1.65)
Sepsis	2044(1.8)/96 24(0.82)	1.61 (1.52 to 1.70)
Endocarditis	158(0.14)/591(0.05)	1.89 (1.55 to 2.32)
Meningitis	181(0.16)/962(0.08)	1.70 (1.43 to 2.02)
Other CNS infections	429(0.38)/2531(0.22)	1.58 (1.41 to 1.76)
Death due to other infections	711(0.62)/2769(0.24)	1.64 (1.48 to 1.81)
Post-traumatic stress disorder		
Life threatening infections	244(3.04)/1041(1.26)	1.95 (1.66 to 2.28)
Sepsis	156(1.94)/631(0.76)	2.01 (1.65 to 2.45)
Endocarditis	15(0.19)/40(0.05)	2.90 (1.46 to 5.76)
Meningitis	17(0.21)/58(0.07)	2.80 (1.49 to 5.26)
Other CNS infections	34(0.42)/169(0.2)	1.88 (1.23 to 2.87)
Death due to other infections	45(0.55)/196(0.24)	1.99 (1.37 to 2.90)

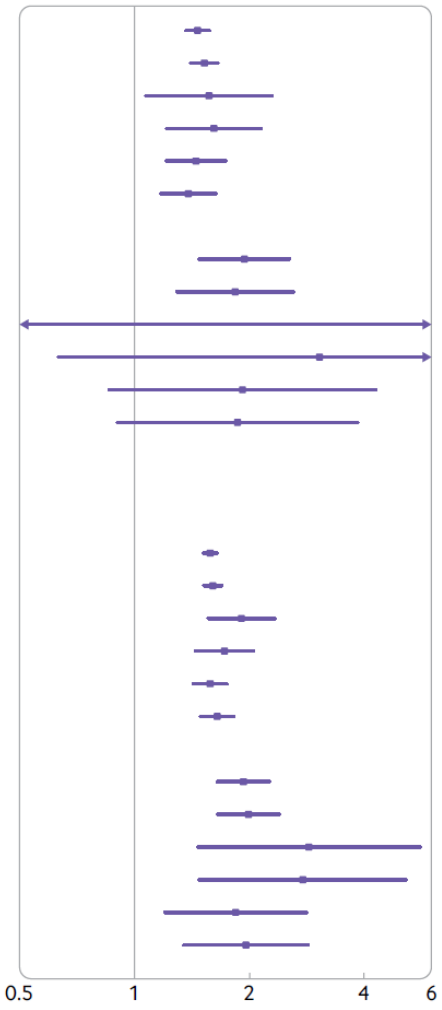


Fig 3 | Association between stress related disorders and life threatening infections

incidence and hazard ratios (95% confidence intervals) for life threatening infections among individuals with any stress related

The effect of multiple adverse childhood experiences on health: a systematic review and meta-analysis

Karen Hughes, Mark A Bellis, Katherine A Hardcastle, Dinesh Sethi, Alexander Butchart, Christopher Mikton, Lisa Jones, Michael P Dunne

2017 Lancet - meta-analysis & systematic review of studies assessing the asssociation of ACEs and health outcomes in adulthood

37 studies; n= 253 719 participants

MAIN RESULTS:
Experiencing ≥ 4 adverse childhood experiences was associated with an increased risk of **all** health outcomes

Physical health outcomes

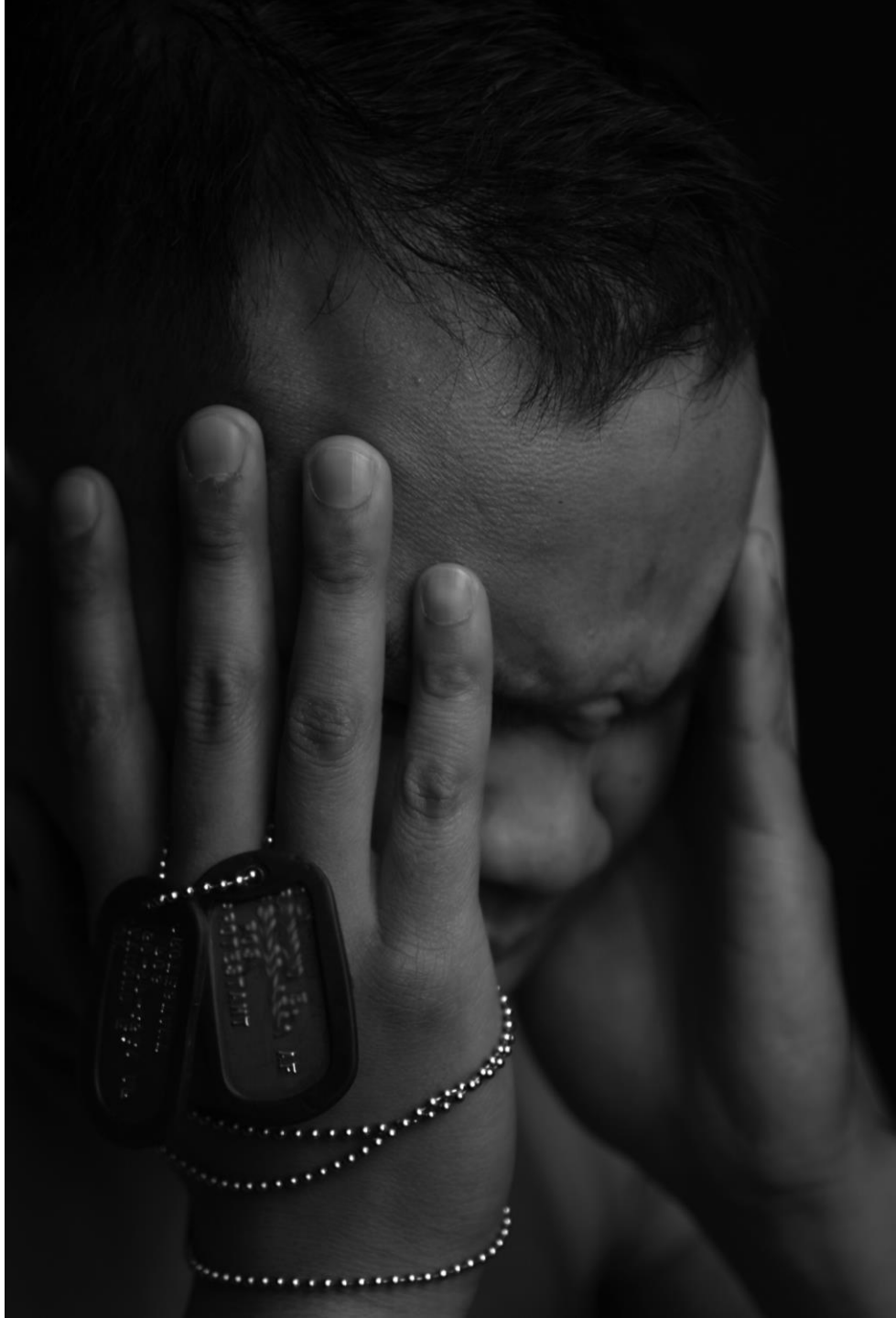
	OR	Heterogeneity (I^2)
Physical inactivity	1·25 (1·03–1·52)	65·2% (23·6–79·7)
Excluding outliers	1·12 (0·97–1·29)	35·7% (0–68·2)
Overweight or obesity	1·39 (1·13–1·71)	75·1% (39·6–86·0)
Diabetes	1·52 (1·23–1·89)	48·3% (0–75·2)
Excluding outliers	1·38 (1·20–1·60)	0% (0–58·5)
Cardiovascular disease	2·07 (1·66–2·59)	23·7% (0–65·9)
Heavy alcohol use	2·20 (1·74–2·78)	75·0% (43·5–85·6)
Excluding outliers	2·00 (1·69–2·37)	46·4% (0–73·5)
Cancer	2·31 (1·82–2·95)	0% (0–67·9)
Liver or digestive disease	2·76 (2·25–3·38)	0% (0–61·0)
Smoking	2·82 (2·38–3·34)	87·1% (82·1–90·2)
Excluding outliers	2·70 (2·34–3·11)	71·9% (51·4–81·4)
Respiratory disease	3·05 (2·47–3·77)	0% (0–56·3)

Conclusion

- Psychiatric reactions to severe stress increase subsequent risk of:
  - Autoimmune disease
  - Cardiovascular disease
  - Severe infections

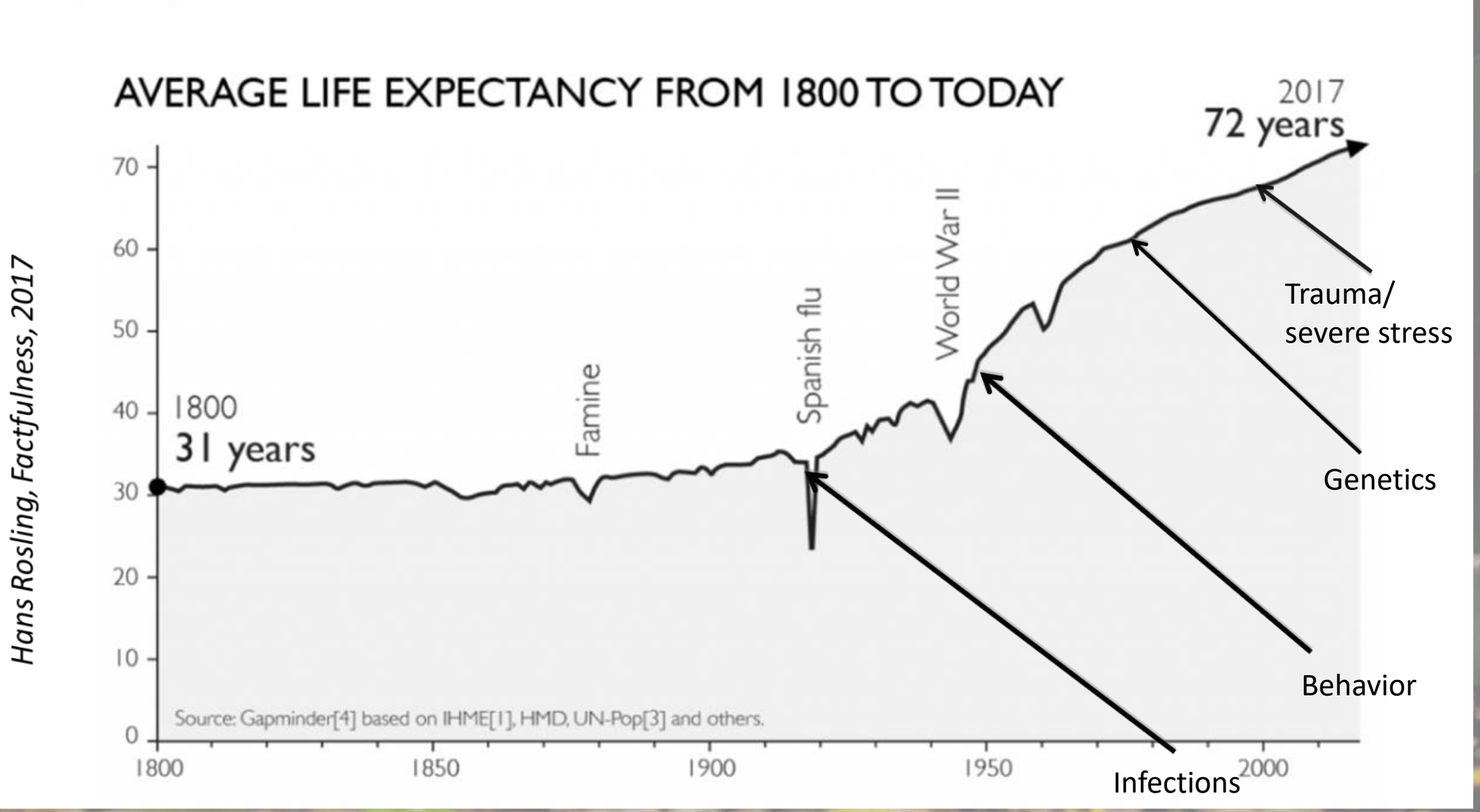
- Young age at exposure and severe disorders (PTSD) associated with even higher risk elevations

- Early interventions – medication or CBT – need to be tested
  - Persistent use of SSRIs after PTSD diagnosis may reduce the risk of adverse outcomes



- Individuals experiencing trauma or adversities are often in contact with health care, e.g.:
  - Oncology
  - Emergency Medicine
  - Obstetrics-Gynecology
- Psychiatry has the tools for intervention
- Requires co-operation across disciplines

THE OPPORTUNITY TO INTERVENE



Looking back and ahead..

2017 – ERC Consolidator Grant:

The genetics of morbidity and survival in response to significant life stressors

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