

## **Online supplement DS1**

### **Method**

#### *Study setting*

We conducted an epidemiological register-based cohort study on the Danish population. The main exposure variables were defined as a first psychiatric inpatient or outpatient contact for anxiety disorders. The outcome variable was defined as death by any natural cause (mortality from internal causes – diseases and medical conditions) or unnatural cause (mortality from external causes – suicide, accidents and homicide) within the follow-up period. Data was collected on the cohort of people born in Denmark between January 1, 1955, and November 31, 2006. The study cohort included 3270650 persons, who were alive and residing in Denmark at their first birthday. The follow-up-time started on their 1st birthday or January 1, 2002, whichever came later, in order to ensure complete information on cohort members. Follow-up ended at date of emigration from Denmark, date of death or December 31, 2011, whichever came first. This provided a maximum follow-up period of 10 years and a maximum age of 57 for the cohort members. We particularly focused on deaths among younger age groups of the population in order to reduce probable biases of selective survival in older age groups. The study was approved by the Danish Data Protection Agency. All personal information from the registers is anonymized when used for research purposes, and by Danish law, informed consent is not needed for register-based studies.

#### *Data sources*

Data on cohort members was collected through linkage of four Danish population registers described below. All residents of Denmark, including immigrants, have a unique personal

identification (CRS) number that is used in all national registers, which enables data to be linked across these registers.

The Danish Civil Registration System<sup>1</sup> was established in 1968 and contains information on all persons living in Denmark. For each person registered, the system includes a ten-digit personal identification number, the CRS, and information on sex, date and place of birth, vital status (continuously updated), and parents' personal identifiers. The Danish Psychiatric Central Register<sup>2</sup> includes data on all people admitted to any hospital for assessment, treatment or both in Denmark from 1969 onwards, or people who had appointments with psychiatric outpatient services from 1995 onwards<sup>2</sup>. The Danish National Patient Register<sup>3</sup> contains information on somatic as well as psychiatric inpatient and outpatient contacts to all hospitals in Denmark from 1977 and onwards. Diagnoses of these registers are based on the International Classification of Diseases, depending on the time of diagnosis in its eighth (ICD-8) or tenth revision (ICD-10). As in Denmark every individual has equal and free access to both somatic and mental health care, the registered admissions are highly representative. The Danish Register of Causes of Death<sup>4</sup> was computerized in 1970 and provides data on all causes of death among Danish residents dying in Denmark. This register enables to differentiate between natural and unnatural causes of death as well as individual specific causes of death.

### *Exposure variables*

The main exposure variables were defined as treatment for anxiety disorders. Using the Danish Psychiatric Central Register and the Danish National Patient Register we identified all patients diagnosed with anxiety disorders (ICD-10: F40.00-F40.20, F41.00-F41.10, F42.00-F43.10); covering acute stress reaction, agoraphobia, generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, post-traumatic stress disorder, specific phobia, and social phobia. Date of onset was defined as the day of the first contact (inpatient, outpatient or emergency

department) with the diagnosis in question. Initially our analyses of anxiety disorders also included ICD-8 codes (300.09, 300.19, 300.29). As however only the ICD-10 allows a finer sub-classification of specific anxiety disorders and sensitivity analyses revealed no differences in the mortality risk of anxiety disorders based on ICD-8 and ICD-10; we restricted our analyses to ICD-10 codes.

### *Outcome variables*

The outcome of interest was time to death. The date and cause of death were identified from the Danish Register of Causes of Death. All-cause mortality was defined as ICD-10 codes A00-Y98 and categorized into the following groups: deaths from diseases and medical conditions (natural death) ICD 10: A00-R99, and deaths from external causes (unnatural death) ICD-10: V01-Y98. Unnatural causes of death comprised suicides (ICD-10: X60–X84, Y10-Y34), homicides (ICD-10: X85–Y09, Y87.1), and accidents (ICD-10: V01–X59, Y10–Y86, Y87.2). Natural causes comprised death by cancer (ICD-10: C00–D48), cardiac diseases (ICD-10: I00-I99), respiratory diseases (ICD-10: J00–J99), digestive conditions (ICD-10: K00–K93), and a combined group of the remaining causes of death.

### *Covariates*

Information on age, sex, calendar period, maternal and paternal age at time of birth was obtained from the Danish Civil Registration System. Alike, we derived information on place of residence at time at birth to model the urbanization level during upbringing. Somatic comorbidities were assessed using the Charlson Comorbidity Index. The Charlson Index is an indicator of the somatic disease burden based on 19 severe chronic diseases, each assigned a weight from one to six corresponding to the severity of the disease<sup>5</sup>. Information on substance abuse (ICD8 codes 291.xx, 303.xx, 304.xx, 571.09, 571.1x and the ICD-10 code F10-F16, F18, F19, I85, K70) and depression (ICD-8 code: 296.x9, 298.09, 298.19, 300.49, 301.19; ICD-10 code: F32.00-F33.99,

F34.10-F34.90, F38.00-F39.99) was retrieved from the Danish National Hospital Register and the Danish Psychiatric Central Register.

### *Sibling control studies*

To account for possible familial confounding, we performed additional analyses that used unaffected full siblings of patients as controls. In this analysis, we identified as cases those individuals with anxiety disorders who also had full siblings without anxiety disorders, and these individuals were compared with their unaffected full siblings using matched conditional cox regression.

### *Data Analyses*

Mortality rate ratios (MRRs) were calculated for natural and unnatural causes of death as well as all causes. Time to mortality was the central outcome variable, which was censored at either the time of death, time of dropout or the end date of follow-up (December 31, 2011). We fitted three models of survival analysis to these outcomes, using the log-linear Poisson regression with the Genmod procedure in SAS, version 9.3 (SAS Institute, Cary, NC, USA). The first model included demographic characteristics such as calendar year, age, sex, and the interaction of age with sex. The second model added maternal and paternal age, sex, place of residence at time of birth (as described elsewhere<sup>6</sup>), and somatic comorbidity, which was defined as a Charlson score of 0, 1, 2, 3 or more. In the third model effects of anxiety disorders on mortality risk were adjusted for comorbid depression. Of special interest was to evaluate whether the MRRs varied between the three subgroups of diseases (anxiety disorders only, depression only, or both disorders) by testing for statistical interaction. As anxiety disorders and depression are also frequently comorbid with substance abuse<sup>7,8</sup>, we additionally adjusted results for comorbid substance abuse. Finally, we studied potential moderating effects of somatic comorbidity and substance abuse on mortality risk. In our sensitivity analyses, we assessed differences in the psychiatry-mortality associations

by sex, and time since diagnosis. P values and 95% confidence intervals (CIs) were based on likelihood ratio tests.

### **Additional references**

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8. Fenton MC, Keyes KM, Martins SS, Hasin DS. The role of a prescription in anxiety medication use, abuse, and dependence. *Am J Psychiatry*. 2010; **167**: 1247-1253.

**Table DS1: General Description of the Study Cohort**

Covariates		Double Diagnosis			Anxiety Disorders only		
		N Deaths	Person Years	Rate per 1000 PY	N Deaths	Person Years	Rate per 1000 PY
<b>Calendar Year</b>	2002-2006	96	13583.57	70.67	160	62050.20	25.79
	2006-2011	234	40615.00	57.61	392	130748.18	29.98
	2011	80	12965.00	61.70	104	33904.45	30.67
<b>Age</b>	1-30	34	18890.98	17.00	93	85582.92	10.87
	30-40	88	22508.40	39.10	160	72387.12	22.10
	40-50	215	21040.71	102.18	302	58443.18	51.67
	50-57	73	4723.47	154.55	101	10289.61	98.16
<b>Maternal Age</b>	<25	307	50721.53	60.5266	486	167804.60	28.9623
	25-30	61	11138.85	54.7633	110	40670.47	27.0467
	>30	42	5303.19	79.1977	60	18227.76	32.9168
<b>Paternal Age</b>	<30	331	54221.19	61.05	503	182907.84	27.50
	30-35	43	7817.28	55.01	92	24274.54	37.90
	>35	36	5125.09	70.24	61	19520.44	31.25
<b>Sex</b>	Female	183	44254.96	41.3513	259	140024.77	18.4967
	Male	227	22908.61	99.0894	397	86678.05	45.8017
<b>Place of Residence</b>	Capital	99	13490.51	73.38	162	49149.40	32.96
	Capital Suburb	35	7488.89	46.74	65	30704.04	21.17
	Provincial City	52	8889.01	58.50	82	25799.53	31.78
	Provincial Town	131	22796.46	57.47	221	73606.83	30.02
	Rural Area	93	14498.69	64.14	126	47443.03	26.56
<b>Somatic Comorbidity</b>	0	196	48883.38	40.10	263	176232.35	14.92
	1	81	10932.84	74.09	109	32051.16	34.01
	2	39	3655.46	106.69	70	10398.56	67.32
	3	27	1735.53	155.57	57	3954.15	144.15
	>=4	67	1956.35	342.47	157	4066.60	386.07
<b>Substance Abuse</b>	Yes	308	20314.65	151.62	404	36164.22	111.71
	No	102	46848.92	21.77	252	190538.61	13.23

**Table DS1: General Description of the Study Cohort (continued)**

Covariates		Depression only			General Population		
		N Deaths	Person Years	Rate per 1000 PY	N Deaths	Person Years	Rate per 1000 PY
<b>Calendar Year</b>	2002-2006	542	9887.06	54.81	8130	11847708.97	6.86
	2006-2011	1060	214397.44	49.44	13229	15608589.73	8.48
	2011	278	56974.72	48.79	2931	3092827.77	9.48
<b>Age</b>	1-30	175	108458.18	16.14	4139	16771054.91	2.47
	30-40	409	113713.94	35.97	4685	6526457.43	7.18
	40-50	932	119682.29	77.87	11097	6089839.17	18.22
	50-57	364	28404.81	128.15	4369	1161774.95	37.61
<b>Maternal Age</b>	<25	1375	276960.70	49.65	17835	20929786.21	8.52
	25-30	315	63193.44	49.85	4114	6743198.51	6.10
	>30	190	30105.08	63.11	2341	2876141.75	8.14
<b>Paternal Age</b>	<30	1441	296775.41	48.56	18779	23894176.68	7.86
	30-35	242	44775.68	54.05	740	318104.66	23.26
	>35	197	28708.13	68.62	4771	6336845.14	7.53
<b>Sex</b>	Female	716	231159.33	30.9743	7980	14753782.31	5.4088
	Male	1164	139099.90	83.6809	16310	15795344.66	10.3258
<b>Place of Residence</b>	Capital	413	64494.77	64.04	4610	4604711.10	10.01
	Capital Suburb	161	36295.09	44.36	2083	3369591.26	6.18
	Provincial City	253	46962.75	53.87	2981	3849760.98	7.74
	Provincial Town	630	129169.49	48.77	8008	9861725.70	8.12
	Rural Area	423	93337.12	45.32	6608	8863337.43	7.46
<b>Somatic Comorbidity</b>	0	839	278207.25	30.16	9116	26580091.90	3.43
	1	303	54609.15	55.49	3170	2733836.48	11.60
	2	209	19829.56	105.40	3320	768036.70	43.23
	3	130	8073.47	161.02	1694	232551.30	72.84
	>=4	399	9539.79	418.25	6990	234610.09	297.94
<b>Substance Abuse</b>	Yes	1112	86427.03	128.66	6923	804156.24	86.09
	No	768	283832.20	27.06	17367	29744970.23	5.84

**TABLE DS2. Mortality Rate Ratio of Persons with Anxiety Disorders Stratified by Time Since Diagnosis (2002-2011)**

Time Since Diagnosis	Anxiety Disorders	
	Mortality Rate Ratio	95% CI
< 1 year	2.42	2.05-2.84
1-2 years	1.85	1.52-2.21
3-4 years	1.63	1.40-1.79
5-9 years	1.49	1.34-1.65
≥ 10 years	1.59	1.40-1.79

Table DS2: *Mortality Rate Ratio of Persons with Anxiety Disorders Stratified by Time since Diagnosis (2002-2011)*. Mortality rate ratios were adjusted for calendar year, age, maternal and paternal age, sex, place of residence at time of birth, somatic comorbidity, depression, and the interaction of age with sex.



**TABLE DS3. Mortality Rate Ratio of Persons with Anxiety Disorders Stratified by Sex (2002-2011)**

Anxiety Disorders	All Causes		Unnatural Causes		Natural Causes	
	Mortality Rate Ratio	95% CI	Mortality Rate Ratio	95% CI	Mortality Rate Ratio	95% CI
Men	1.76	1.61-1.91	2.75	2.40-6.85	1.42	1.27-1.59
Women	1.47	1.33-1.63	2.21	1.82-2.66	1.34	1.18-1.51

Table DS3: *Mortality Rate Ratio of Persons with Anxiety Disorders Stratified by Sex (2002-2011)*. Mortality rate ratios were adjusted for calendar year, age, maternal and paternal age, sex, place of residence at time of birth, somatic comorbidity, depression, and the interaction of age with sex.

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**TABLE DS4. Mortality Rate Ratio of Persons with Anxiety Disorders Stratified by Somatic Comorbidity (2002-2011)**

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Anxiety Disorders	With Somatic Comorbidity		Without Somatic Comorbidity	
	Mortality Rate Ratio	95% CI	Mortality Rate Ratio	95% CI
All Causes	1•43	1•31-1•55	2•40	2•16-2•65
Unnatural Causes	2•35	1•94-2•81	2•48	2•17-2•83
Natural Causes	1•28	1•16-1•41	2•26	1•92-2•64

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Table DS4: *Mortality Rate Ratio of Persons with Anxiety Disorders Stratified by Somatic Comorbidity (2002-2011)*. Mortality rate ratios were adjusted for calendar year, age, maternal and paternal age, sex, place of residence at time of birth, depression, and the interaction of age with sex.

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**TABLE DS5. Mortality Rate Ratio of Persons with Anxiety Disorders Stratified by Substance Abuse (2002-2011)**

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Anxiety Disorders	With Substance Abuse		Without Substance Abuse	
	Mortality Rate Ratio	95% CI	Mortality Rate Ratio	95% CI
All Causes	1.21	1.11-1.31	1.32	1.19-1.47
Unnatural Causes	1.62	1.43-1.84	1.72	1.42-2.07
Natural Causes	1.03	0.93-1.14	1.18	1.03-1.35

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Table DS5: *Mortality Rate Ratio of Persons with Anxiety Disorders Stratified by Substance Abuse (2002-2011)*. Mortality rate ratios were adjusted for calendar year, age, maternal and paternal age, sex, place of residence at time of birth, somatic comorbidity, depression, and the interaction of age with sex.

**TABLE DS6. Mortality Rate Ratio of Persons with Single and Double Diagnoses Stratified by Somatic Comorbidity (2002-2011)**

Diagnosis	With Somatic Comorbidity		Without Somatic Comorbidity	
	Mortality Rate Ratio	95% CI	Mortality Rate Ratio	95% CI
<b>All Causes</b>				
Double Diagnosis	4.95	4.47-5.45	9.21	7.94-10.60
Depression	3.85	3.66-4.04	6.31	5.85-6.80
Anxiety Disorders	2.82	2.60-3.05	3.76	3.31-4.25
General Population	1.00	(Reference)	1.00	(Reference)
<b>Unnatural Causes</b>				
Double Diagnosis	8.40	6.50-10.67	13.67	11.39-16.26
Depression	5.51	4.74-6.37	9.31	8.46-10.23
Anxiety Disorders	3.64	2.85-4.57	4.46	3.77-5.25
General Population	1.00	(Reference)	1.00	(Reference)
<b>Natural Causes</b>				
Double Diagnosis	1.54	1.30-1.81	5.46	4.22-6.92
Depression	1.66	1.54-1.78	3.82	3.36-4.32
Anxiety Disorders	1.49	1.33-1.66	3.05	2.51-3.67
General Population	1.00	(Reference)	1.00	(Reference)

Table DS6: *Mortality Rate Ratio of Persons with Single and Double Diagnoses Stratified by Somatic Comorbidity (2002-2011)*. Mortality rate ratios were derived from multivariate analysis and adjusted for calendar year, age, maternal and paternal age, sex, place of residence at time of birth, and the interaction of age with sex.

**TABLE DS7. Mortality Rate Ratio of Persons with Single and Double Diagnoses Stratified by Substance Abuse (2002-2011)**

Diagnosis	With Substance Abuse		Without Substance Abuse	
	Mortality Rate Ratio	95% CI	Mortality Rate Ratio	95% CI
<b>All Causes</b>				
Double Diagnosis	1.46	1.30-1.64	2.07	1.69-2.50
Depression	1.19	1.12-1.27	2.46	2.28-2.65
Anxiety Disorders	1.20	1.08-1.32	1.65	1.45-1.86
General Population	1.00	(Reference)	1.00	(Reference)
<b>Unnatural Causes</b>				
Double Diagnosis	2.99	2.51-3.53	8.68	6.50-11.33
Depression	5.51	4.74-6.37	9.31	8.46-10.23
Anxiety Disorders	1.69	1.42-1.99	3.07	2.42-3.85
General Population	1.00	(Reference)	1.00	(Reference)
<b>Natural Causes</b>				
Double Diagnosis	0.99	0.84-1.16	1.13	0.84-1.47
Depression	0.96	0.88-1.03	1.50	1.36-1.66
Anxiety Disorders	1.02	0.90-1.16	1.37	1.17-1.58
General Population	1.00	(Reference)	1.00	(Reference)

Table DS7: *Mortality Rate Ratio of Persons with Single and Double Diagnoses Stratified by Substance Abuse (2002-2011)*. Mortality rate ratios were derived from multivariate analysis and adjusted for calendar year, age, maternal and paternal age, sex, place of residence at time of birth, somatic comorbidity, and the interaction of age with sex.