

Supplementary Materials

This appendix has been provided by the authors to give readers additional information about the following paper:

Interaction between mental disorders and social disconnectedness on mortality: a population-based cohort study

Authors: Lisbeth Mølgaard Laustsen, Linda Ejlskov, Danni Chen, Mathias Lasgaard, Jaimie L. Gradus, Søren Dinesen Østergaard, Marie Stjerne Grønkjær, Oleguer Plana-Ripoll

Contents

Supplementary Appendices	2
Supplementary Appendix 1 (SA1): Definition of covariates.....	2
Supplementary Appendix 2 (SA2): Multiple imputation	4
Supplementary Appendix 3 (SA3): Statistical analysis	9
Supplementary Figures	10
Supplementary Figure 1 (SF1). Flowchart for the cohort.....	10
Supplementary Figure 2 (SF2): Venn diagrams of the distribution of loneliness, social isolation, and low social support	11
Supplementary Figure 3 (SF3). Subgroup analyses of the independent and joint association of mental disorders and social connections with mortality.....	12
Supplementary Figure 4 (SF4). Applying alternative operationalizations of mental disorders in the estimation of the independent and joint association of mental disorders and social connections with mortality	14
Supplementary Figure 5 (SF5): Association with mortality for specific scores/responses on social connections	15
Supplementary Figure 6 (SF6): Applying alternative modelling assumptions in estimation of the independent and joint association of mental disorders and social connections with mortality	16
Supplementary Tables	17
Supplementary Table 1 (ST1): Overview of prior studies on mental disorders, social disconnectedness and mortality	17
Supplementary Table 2 (ST2): Independent and joint associations of mental disorders and social connections with mortality among women and men	18
Supplementary References	19

Supplementary Appendices

Supplementary Appendix 1 (SA1): Definition of covariates

Cause of death

The cause of death was categorized, as done previously¹, into external causes including suicides (ICD-10 codes: X60-X84, Y87.0), homicides (ICD-10 codes: X85-Y09, Y87.1) and accidents (ICD-10 codes: V01X59, Y10-Y86, Y87.2, Y88-Y89) and natural causes (all other ICD-10 codes).

Classification of the initial diagnosis

The diagnosis obtained in the earliest contact with psychiatric hospital services was classified in the broad diagnostic categories shown in SA1 Table 1, following the procedure of previous studies.¹⁻⁴ If two diagnoses were recorded with the earliest contact, both were included as initial diagnoses.

SA1 Table 1. Diagnostic classification of mental disorders according to the International Classification of Diseases, 10th revision (ICD-10)

Mental disorders	ICD-10
Substance use disorders	F10 – F19
Schizophrenia and related disorders	F20 – F29
Mood disorders	F30 – F39
Anxiety or neurotic disorders	F40 – F48
Eating disorders	F50
Specific personality disorders	F60
Pervasive developmental disorders	F84
Behavioural and emotional disorders	F90 – F98

Alternative operationalizations of mental disorders

Since the Danish Psychiatric Central Research Register only comprises hospital-diagnosed mental disorders, we also applied the following alternative operationalizations of mental disorders in a sensitivity analysis:

- i) self-reported information on any preceding or current mental disorder from the Danish National Health Survey
- ii) at least one redeemed prescription for psychopharmacological treatment in 18 years preceding survey participation recorded in the Danish National Prescription Registry; based on a prior study,⁵ we included antipsychotics (N05A except N05AN), antidepressants (N06A), lithium (N05AN), anxiolytics (N05B except N05BA01), medication for ADHD (C02AC02, N06BA02, N06BA04, N06BA09, and N06BA12), and medication for alcohol and opioid dependence (N07BB-N07BB04)
- iii) at least one consultation with a private practicing psychiatrist in 18 years preceding survey participation recorded in the Danish National Health Service Register

Pseudo-index dates

We chose to replicate the distribution of index dates among individuals with a mental disorder stratified by sex and age group at survey participation (16-25, >25-35, >35-45, >45-55 >55-65, and >65 years). For each sex- and age-specific group, we estimated the cumulative distribution of time since the first diagnosis of a mental disorder (i.e., the index date) among individuals with a mental disorder. For individuals without a mental disorder, we drew random numbers from a uniform distribution (0;1) and found the equivalent time since index date from the estimated cumulative distribution to assign pseudo-index dates. We additionally drew new random numbers for 38 individuals (0.02%) who were given a pseudo-index date at a lower age than the lowest age at diagnosis among individuals with a mental disorder. This procedure ensured that the cumulative distribution of index and pseudo-index dates was similar within the sex- and age-specific groups. However, the distribution in the entire sample could differ between the two groups due to different age- and sex-distributions.

Somatic morbidity

Information on somatic morbidity was included using the Nordic Multimorbidity Index⁶ for each individual using data preceding the index or pseudo-index date. The Nordic Multimorbidity Index consists of 50 predictors identified through hospital diagnoses recorded in the Danish National Patient Register and redeemed prescriptions recorded in the Danish National Prescription Registry. We excluded six predictors that are related to mental disorders (diagnosis codes F10 and F17 and prescription codes N05A, N05BA, N05CD, N05CF, N06A, and N07BC). The Danish National Patient Register contains information on admissions to inpatient facilities since 1977 and visits to outpatient and emergency departments since 1995, whereas the Danish National Prescription Registry contains information on prescriptions redeemed at community pharmacies in Denmark since 1995. This registry data allowed calculation based on complete data for the majority of the study population (i.e., those with an index or pseudo-index date in or after year 2000).

Educational level

Information on the highest level of completed education was obtained in the calendar year before the index or pseudo-index date. Applying the International Standard Classification of Education (ISCED),⁷ we classified the highest educational level as a bachelor's degree or higher (ISCED levels 6–8); the middle educational level as upper secondary school, vocational education, or short-cycle tertiary education (ISCED levels 3–5); and the lowest educational level as up to secondary school (ISCED levels 0–2).

Income and wealth

Information on annual disposable equivalised household income and equivalised household wealth was likewise obtained in the calendar year before the index or pseudo-index date. Both were based on household values and equivalised using OECD's modified equivalence scale⁸ to obtain individual-level values. To account for inflation, values were standardized to those in 2016 using the new gross domestic product deflator from the World Bank (worldbank.org). Disposable income included any registered work income, capital income, and transfers of public benefits after deduction of tax and, to allow for comparison between homeowners and tenants, the estimated rental value of housing for homeowners after exclusion of their interest expenses.⁹ Wealth included all assets and debts in properties, financial institutions, investment deposits, and credit unions, but did not include pension assets, debt owed to private individuals, investments outside deposits, cash holdings, and other assets such as cars or yachts.¹⁰

Supplementary Appendix 2 (SA2): Multiple imputation

As shown in SA2 Table 2, a complete case analysis would exclude 25,698 individuals (15.8% of the cohort) due to missing survey and/or register data. We observed that partly missing survey data were associated with mortality after adjustment for covariates (SA2 Table 3); thus, a complete case analysis could provide biased estimates.^{11,12} Individuals with missing survey data were more likely to be older, live alone, and be out of employment, whereas individuals with missing register data were more likely to be younger and born abroad (SA2 Table 4). To handle the potential bias, we applied multiple imputation by chained equations (MICE). We estimated missing values using predictive mean matching (PMM) with a donor pool of 10 observations, as recommended.¹³ We applied two imputation models: one for imputation of survey data and one for imputation of register data, each performing 15 imputations with a burn-in of 10.

Survey data were imputed for specific scores/responses on loneliness, social isolation, and social support and for the binary item on a self-reported mental disorder. We included an interaction term between hospital-diagnosed mental disorders and death during follow-up to reflect the investigated interaction.¹⁴ Register data were imputed for educational level, income, wealth, and country of birth, stratified by aged below 30 years at the index or pseudo-index date, reflecting that parental values were used as a proxy for individuals below 30 years. We included the Nelson-Aalen estimate of the cumulative hazard function of mortality,¹⁵ the censoring variable,¹⁵ and population weights¹⁶ as covariates, as recommended. We employed additional auxiliary variables from the Danish National Health Survey and the Income Statistics Register as shown in SA2 Table 5 and 6. The distribution of complete and imputed data are shown in SA2 Table 7.

SA2 Table 1: Overview of missing data in the analytical sample

	All individuals: N = 162,497	Individuals with a mental disorder: N = 10,347 (6.4%)	Individuals without a mental disorder: N = 152,150 (93.6%)
Overall			
Missing on any variable, N (%)	25,698 (15.8)	1,651 (16.0)	24,047 (15.8)
Missing on survey data, N (%)	20,530 (12.6)	1,451 (14.0)	19,079 (12.5)
Missing on register data, N (%)	6,435 (4.0)	254 (2.5)	6,181 (4.1)
Survey data			
Missing on loneliness, N (%)	9,485 (5.8)	793 (7.7)	8,692 (5.7)
Missing on social isolation, N (%)	13,078 (8.0)	1,036 (10.0)	12,042 (7.9)
Missing on social support, N (%)	7,153 (4.4)	632 (6.1)	6,521 (4.3)
Missing on self-reported mental disorder, N (%)	11,684 (7.2)	773 (7.5)	10,911 (7.2)
Missing on all survey variables above, N (%)	4,282 (2.6)	378 (3.7)	3,904 (2.6)
Register data			
Missing on educational level, N (%)	6,433 (4.0)	254 (2.5)	6,179 (4.1)
Missing on annual disposable equivalised household income, N (%)	5,019 (3.1)	152 (1.5)	4,867 (3.2)
Missing on equivalised household wealth, N (%)	5,019 (3.1)	152 (1.5)	4,867 (3.2)
Missing on all register variables above, N (%)	5,017 (3.1)	152 (1.5)	4,865 (3.2)

Absolute numbers and proportions are unweighted.

SA2 Table 2: Quantitative bias analysis

	Deaths/person-years at risk	Mortality rate ratio (95% CI)
All individuals with register linkage (N = 162,497)		
Included in CCA	6,109/748,221	1 (ref.)
Missing survey data	2,728/112,953	1.25 (1.19–1.33)*
Missing register data	342/31,883	0.94 (0.83–1.08)
All individuals with complete survey data (N = 141,967)		
Included in CCA	6,109/748,221	1 (ref.)
Missing register data	227/26,652	0.96 (0.82–1.14)**
All individuals with complete register data (N = 156,062)		
Included in CCA	6,109/748,221	1 (ref.)
Missing survey data	2,613/107,722	1.14 (0.70–1.85)***

CCA: Complete case analysis. Deaths and person-years at risk are unweighted, whereas the mortality estimates are weighted based on register data to represent the population of the included regions in 2013 and 2017.

* Adjusted for age, sex, year of survey participation, somatic morbidity, and mental disorders.

** Adjusted for age, sex, year of survey participation, somatic morbidity, mental disorders, loneliness, social isolation, and low social support

*** Adjusted for age, sex, year of survey participation, somatic morbidity, mental disorders, country of birth, educational level, income, and wealth

SA2 Table 3: Characteristics of individuals with missing data

	Included in CCA (N = 136,799)	Missing survey data (N = 20,530)	Missing register data (N = 6,435)
Key characteristics			
Survey participation in 2013 as opposed to 2017, N (%)	26,687 (21.3)	5,724 (26.2)	1,127 (16.4)
Women, N (%)	73,374 (50.1)	11,418 (52.6)	3,522 (52.8)
Born abroad, N (%)	6,771 (7.0)	1,848 (14.9)	4,334 (78.9)
At survey participation			
Age, mean (SD)	47.8 (18.5)	54.7 (21.8)	40.5 (17.3)
The Nordic Multimorbidity Index, mean (SD)	1.4 (4.4)	2.8 (6.7)	1.3 (4.1)
Hospital-diagnosed mental disorder, N (%)	8,696 (7.9)	1,451 (8.5)	254 (3.9)
Psychopharmacological treatment, N (%)	36,027 (25.9)	7,029 (33.2)	1,161 (15.2)
Consultation with a private practising psychiatrist, N (%)	7,429 (6.0)	1,049 (5.6)	221 (3.2)
Living with a partner (self-reported), N (%)	90,176 (60.0)	7,590 (51.2)	3,876 (61.6)
Mental wellbeing score (item 6-7 in SF-12), mean (SD)	8.6 (2.0)	7.9 (2.4)	8.2 (2.2)
Sum of the Perceived Stress Scale, mean (SD)	19.2 (4.1)	18.7 (5.4)	19.4 (4.9)
Enrolled in education cf. register data, N (%)	11,028 (11.4)	1,317 (8.6)	570 (12.0)
In employment cf. register data, N (%)	77,653 (56.5)	7,322 (36.9)	3,334 (53.1)
Cohabitation cf. register data, N (%)	104,926 (71.3)	13,388 (60.0)	4,498 (65.7)
Years since index or pseudo-index date, mean (SD)	8.9 (5.4)	9.1 (5.5)	9.3 (5.2)
At index or pseudo-index date			
Age, mean (SD)	39.0 (18.0)	45.5 (21.3)	31.1 (17.0)
The Nordic Multimorbidity Index, mean (SD)	0.7 (2.5)	1.2 (3.7)	0.4 (2.2)

CCA: Complete case analysis; SF-12: 12-Item Short Form Survey. Absolute numbers are unweighted, whereas means, SDs, and proportions are weighted based on register data to represent the population of the included regions in 2013 and 2017.

SA2 Table 4: Variables applied in imputation of survey data

	N (%) missing	Range	Mean (SD)
Imputed variables			
Three-Item Loneliness Scale, item 1	8,471 (5.2)	1 to 3	1.3 (0.5)
Three-Item Loneliness Scale, item 2	8,497 (5.2)	1 to 3	1.4 (0.6)
Three-Item Loneliness Scale, item 3	8,911 (5.5)	1 to 3	1.3 (0.5)
Social isolation, living alone	8,386 (5.2)	0 to 1	0.2 (0.4)
Social isolation, out of employment and not enrolled in education	9,269 (5.7)	0 to 1	0.4 (0.5)
Social isolation, less than monthly contact with friends	8,383 (5.2)	0 to 1	0.1 (0.3)
Social isolation, less than monthly contact with family	7,399 (4.6)	0 to 1	0.1 (0.3)
The social support item	7,153 (4.4)	1 to 4	1.6 (0.8)
Self-reported mental disorder	11,684 (7.2)	0 to 1	0.1 (0.4)
Analysis model variables			
Population weights*	0 (0)	1 to 226	29.2 (19.6)
Age**	0 (0)	16 to 103	52.2 (18.4)
Female	0 (0)	0 to 1	0.5 (0.5)
Born abroad	≤5 (NA)	0 to 1	0.1 (0.3)
Year of survey	0 (0)	2,013 to 2,017	2,016.2 (1.6)
Hospital-diagnosed mental disorder	0 (0)	0 to 1	0.1 (0.2)
The Nordic Multimorbidity Index at survey participation*	0 (0)	-5 to 78	1.7 (5.0)
Death during follow-up	0 (0)	0 to 1	0.1 (0.2)
Emigration during follow-up	0 (0)	0 to 1	0.02 (0.1)
The Nelson-Aalen estimate of cumulative hazard function*	0 (0)	0.00002 to 0.1	0.1 (0.02)
Auxiliary variables at survey participation			
Psychopharmacological redemption	0 (0)	0 to 1	0.3 (0.4)
Consultation with a private practising psychiatrist	0 (0)	0 to 1	0.1 (0.2)
Enrolled in education cf. register data	1,409 (0.9)	0 to 1	0.1 (0.3)
In employment cf. register data	1,409 (0.9)	0 to 1	0.5 (0.5)
Cohabitation cf. register data	1,409 (0.9)	0 to 1	0.8 (0.4)
Living with a partner, self-reported	10,890 (6.7)	0 to 1	0.7 (0.5)
Long-term disease, self-reported	7,691 (4.7)	0 to 1	0.4 (0.5)
The sum of the Perceived Stress Scale*	10,717 (6.6)	0 to 40	19.0 (4.3)
Score on getting enough sleep to feel rested	6,469 (4.0)	1 to 3	1.5 (0.7)
Spending time unwanted alone*	7,293 (4.5)	1 to 4	3.2 (0.9)
Evaluation of own health (item 1 in SF-12)*	1,081 (0.7)	1 to 5	2.6 (0.9)
Mental wellbeing score (item 6 in SF-12)*	5,074 (3.1)	2 to 10	8.6 (2.0)
Activities limited due to physical or mental health (item 9-11 in SF-12)*	6,132 (3.8)	3 to 15	9.3 (1.6)
Social contact limited due to physical or mental health (item 12 in SF-12)*	3,188 (2.0)	1 to 5	4.5 (0.9)

NA: Not applicable; SF-12: 12-Item Short Form Survey. Absolute numbers, percentages, means, and SDs are unweighted. The range is shown using means of the 5 lowest and highest values.

* Included in the imputation model as a linear term

** Included in the imputation model as a natural cubic spline with 3 knots

SA2 Table 5: Variables applied in imputation of register data

	Aged <30 years at index or pseudo-index date (N = 43,184): Imputation of parental educational level, income, and wealth			Aged ≥30 years at index or pseudo-index date (N = 119,313): Imputation of own educational level, income, and wealth		
	N (%) missing	Range	Mean (SD)	N (%) missing	Range	Mean (SD)
Imputed variables						
Parental/own educational level	3,450 (8.0)	1 to 3	2.2 (0.7)	2,983 (2.5)	1 to 3	2.0 (0.7)
Parental/own annual disposable equivalised household income (1,000 DKK)	3,313 (7.7)	-4,417 to 17,028	266.4 (295.5)	1,706 (1.4)	-3,690 to 19,480	263.9 (216.3)
Parental/own equivalised household wealth (1,000 DKK)	3,313 (7.7)	-63,079 to 109,924	425.1 (2,015.1)	1,706 (1.4)	-31,187 to 141,447	579.2 (2,024.8)
Born abroad	≤5 (NA)	0 to 1	0.1 (0.3)	≤5 (NA)	0 to 1	0.1 (0.2)
Analysis model variables						
Population weights*	0 (0)	2 to 226	39.5 (23.6)	0 (0)	1 to 203	25.5 (16.4)
Mean of parental/own age at index or pseudo-index date**	3,299 (7.6)	23 to 81	49.4 (7.2)	0 (0)	30 to 99	51.3 (12.9)
Female	NA	NA	NA	0 (0)	0 to 1	0.5 (0.5)
Hospital-diagnosed mental disorder	0 (0)	0 to 1	0.1 (0.3)	0 (0)	0 to 1	0.1 (0.2)
The Nordic Multimorbidity Index*	0 (0)	-3 to 28	0.3 (1.2)	0 (0)	-5 to 63	0.9 (3.1)
Death during follow-up	0 (0)	0 to 1	0.002 (0.05)	0 (0)	0 to 1	0.1 (0.3)
Emigration during follow-up	0 (0)	0 to 1	0.05 (0.2)	0 (0)	0 to 1	0.01 (0.1)
The Nelson-Aalen estimate of cumulative hazard function*	0 (0)	0.00008 to 0.1	0.1 (0.02)	0 (0)	0.00002 to 0.1	0.1 (0.02)
Auxiliary variables at index or pseudo-index date						
Year of the index or pseudo-index date*	0 (0)	1,995 to 2,017	2,006.9 (5.5)	0 (0)	1,995 to 2,017	2,006.5 (5.7)
Mother's age at childbirth**	4,154 (9.6)	14 to 47	28.4 (4.9)	NA	NA	NA
Number of children in own/parents' household(s) the year prior*	3,312 (7.7)	0 to 8	0.7 (1.0)	1,705 (1.4)	0 to 7	0.6 (0.9)
Number of adults in own/parents' household(s) the year prior*	3,312 (7.7)	1 to 7	2.4 (0.9)	1,705 (1.4)	1 to 6	2.0 (0.7)
Parental/own educational level 5 years prior	3,534 (8.2)	1 to 3	2.2 (0.7)	3,772 (3.2)	1 to 3	2.0 (0.7)
Parental/own annual disposable equivalised household income 5 years prior (1,000 DKK)*	3,419 (7.9)	-3,597 to 8,074	236.3 (166.7)	2,597 (2.2)	-5,125 to 10,469	244.9 (165.3)
Parental/own equivalised household wealth 5 years prior (1,000 DKK)*	3,419 (7.9)	-65,908 to 96,464	260.7 (1,999.8)	2,597 (2.2)	-29,296 to 105,270	408.0 (1,564.5)
Offspring's annual disposable equivalised household income the year prior (1,000 DKK)*	2,730 (6.3)	-2,350 to 4,623	205.6 (126.7)	NA	NA	NA
Offspring's equivalised household wealth the year prior (1,000 DKK)*	2,825 (6.5)	-24,994 to 72,034	167.2 (1,266.2)	NA	NA	NA

NA: Not applicable. Absolute numbers, percentages, means, and SDs are unweighted. The range is shown using means of the 5 lowest and highest values.

* Included in the imputation model as a linear term

** Included in the imputation model as a natural cubic spline with 3 knots

SA2 Table 6: Distribution of variables in complete and imputed data

	In complete data	In imputed data
Survey data		
Lonely, N (%)	8,937 (7.3)	892 (11.4)
Socially isolated, N (%)	3,963 (3.2)	757 (6.5)
Low social support, N (%)	20,264 (14.7)	1,105 (17.2)
Self-reported mental disorder, N (%)	22,391 (16.3)	2,008 (18.3)
Register data		
Educational level		
Lowest, N (%)	43,327 (31.0)	2,096 (34.0)
Middle, N (%)	75,977 (47.5)	2,956 (45.9)
Highest, N (%)	36,760 (21.6)	1,381 (20.1)
Annual disposable equivalised household income (1,000 DKK), mean (SD)	255 (228)	216 (382)
Equivalised household wealth (1,000 DKK), mean (SD)	476 (2,038)	267 (3,031)

Absolute numbers are unweighted, whereas means, SDs, and proportions are weighted based on register data to represent the population of the included regions in 2013 and 2017.

Supplementary Appendix 3 (SA3): Statistical analysis

Adjustment procedures

Age was included as a time-varying covariate in 1-year incremental age groups and modelled as a natural cubic spline with 5 knots. For analyses in subgroups based on age group (16-55, 55-75, and >75 years), we remodelled age using a natural cubic spline with 4 knots fitted for the specific age group. Income and wealth were also included using a natural cubic spline with 5 knots.

Interaction contrast

The interaction contrast (IC) is derived from the absolute risk for the doubly exposed group (p_{11}), the absolute risk for each of the singly exposed groups (p_{01} and p_{10}), and the absolute risk for the reference group (p_{00}). The IC is then calculated as the difference between the absolute risk difference in the doubly exposed group ($p_{11}-p_{00}$) and the sum of the absolute risk difference in the singly exposed groups ($p_{01}-p_{00}$ and $p_{10}-p_{00}$):¹⁷

$$IC = (p_{11} - p_{00}) - ((p_{01} - p_{00}) + (p_{10} - p_{00}))$$

Attributable proportion of joint effects

The attributable proportion of joint effects has been estimated less commonly than the attributable proportion of doubly exposed risk, however, it has several attractive properties such as invariance to reversing the coding of the outcome and reaching 100% when the total of the association can be attributed to interaction.¹⁸ The attributable proportion of joint effects can be derived from the relative excess risk due to interaction (RERI), which is calculated as the relative risk for each of the singly exposed groups (RR_{01} and RR_{10}) subtracted from the relative risk for the doubly exposed group (RR_{11}) and added with 1 to only subtract the reference risk once:¹⁷

$$RERI = RR_{11} - RR_{01} - RR_{10} + 1$$

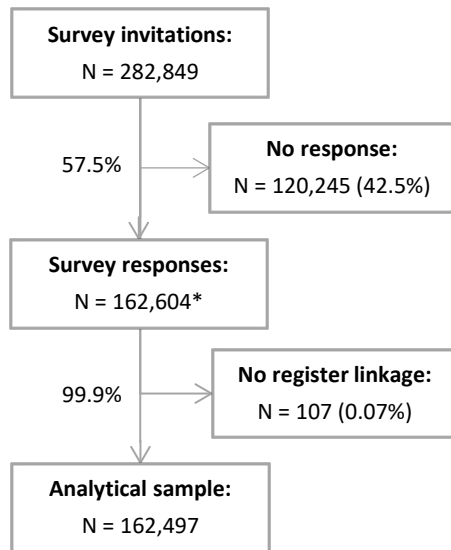
The attributable proportion of joint effects (AP) is then derived as the RERI divided by the relative risk for the doubly exposed group (RR_{11}) minus 1 to exclude the reference risk:¹⁷

$$AP = \frac{RERI}{RR_{11} - 1}$$

However, as this study cannot assert causal inference, we did not estimate the joint effect, but rather the joint association with the outcome.

Supplementary Figures

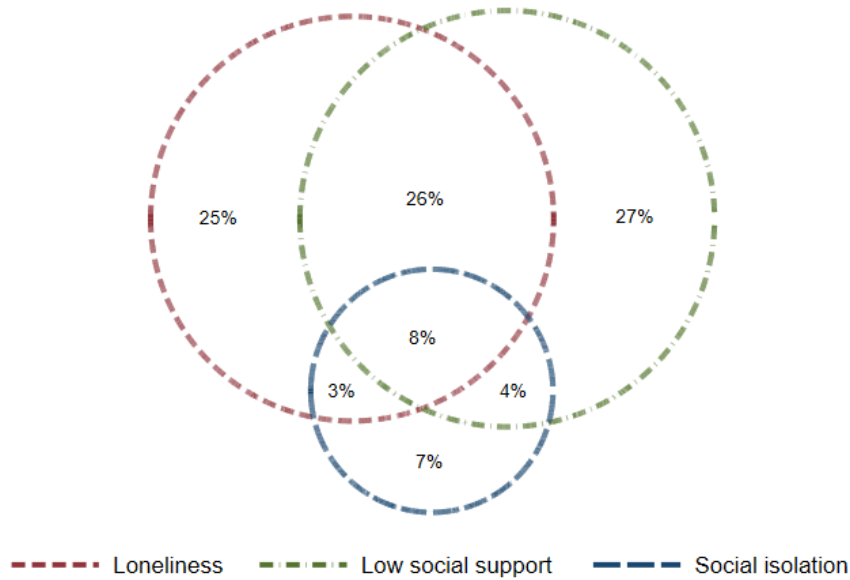
Supplementary Figure 1 (SF1). Flowchart for the cohort



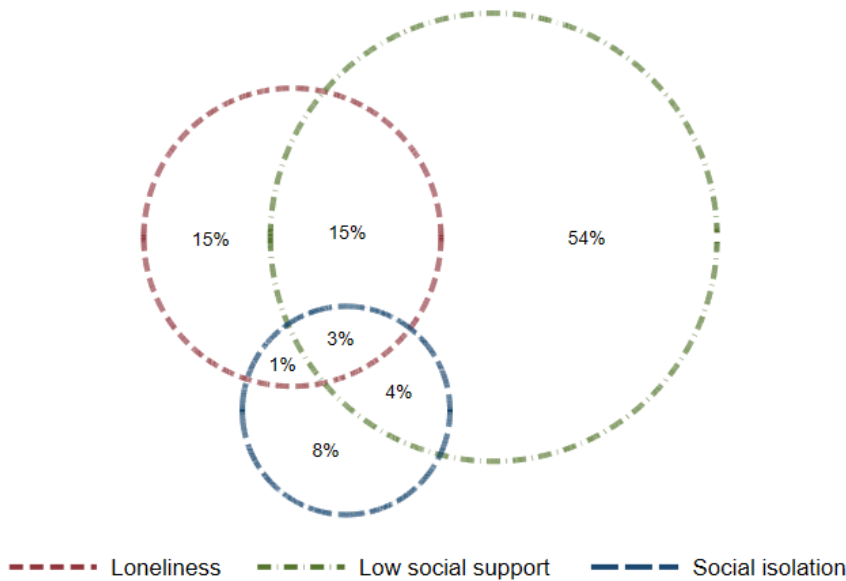
* For a small number (N = 23) of survey participants in 2013, the specific date of survey participation was missing and replaced with the median date.

Supplementary Figure 2 (SF2): Venn diagrams of the distribution of loneliness, social isolation, and low social support

A. Individuals with diminished social connections and a mental disorder (N = 3,869)

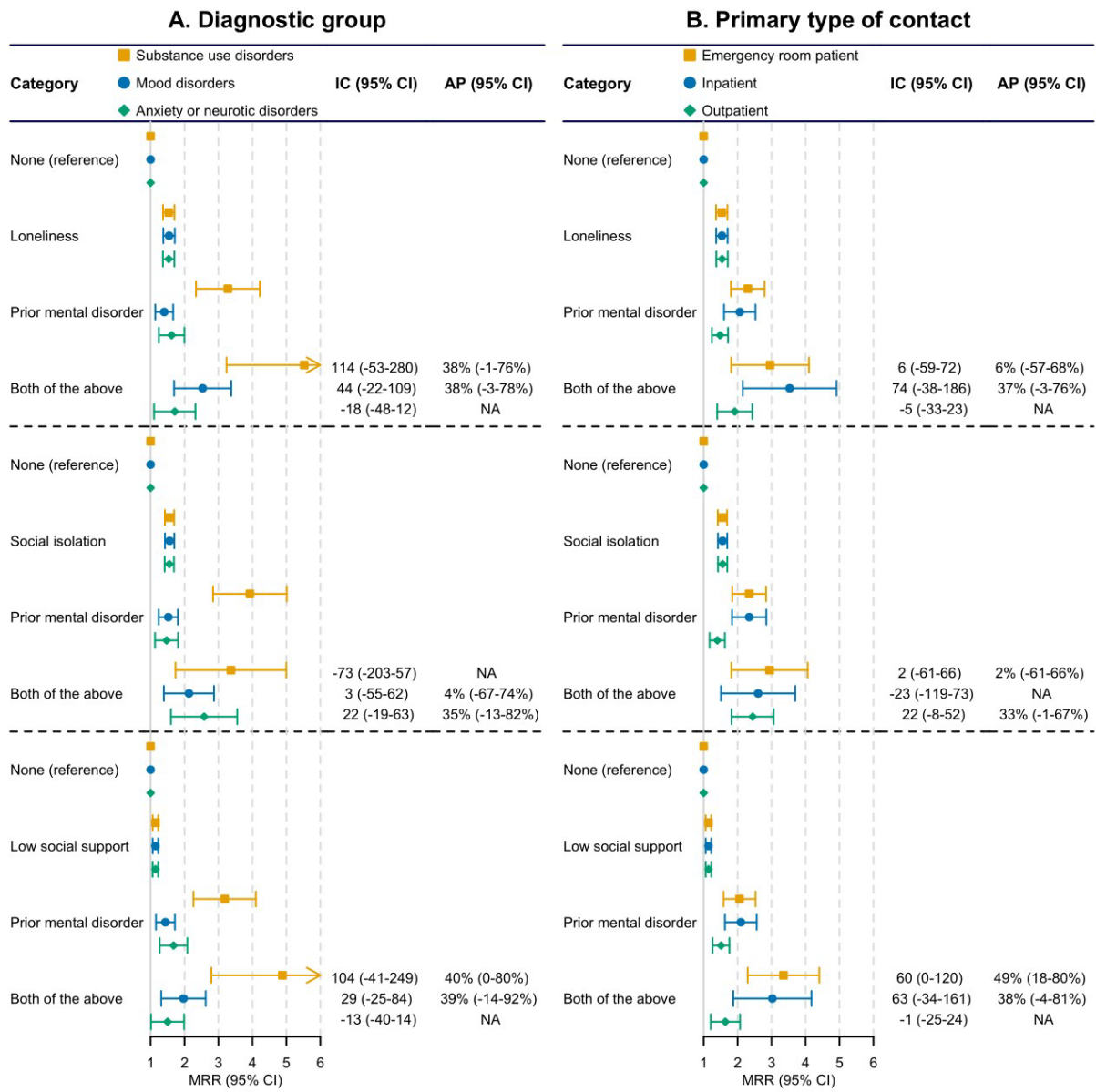


B. Individuals with diminished social connections and without a mental disorder (N = 24,414)

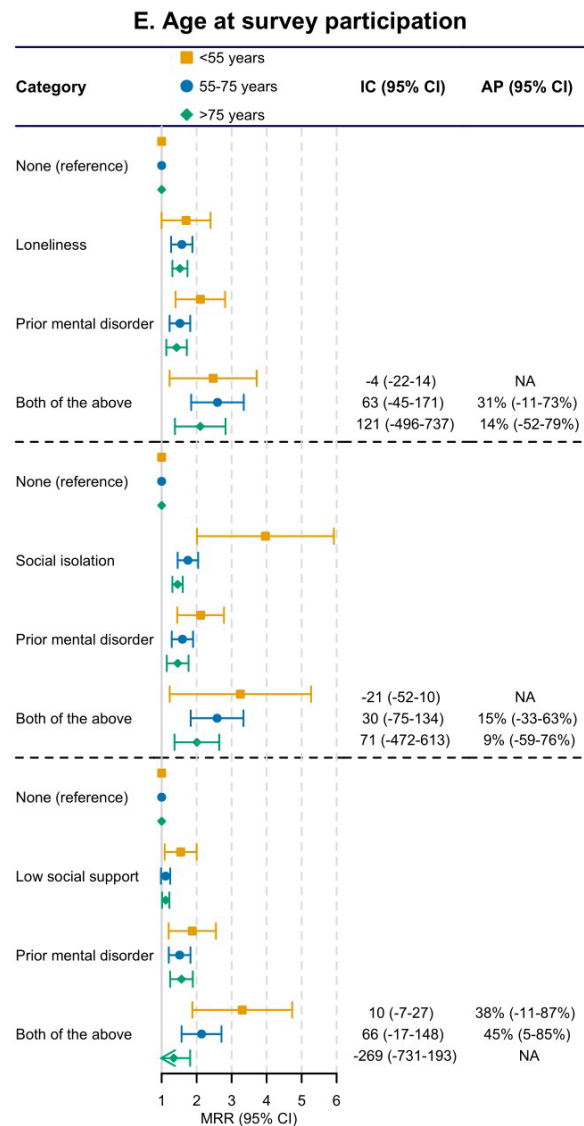
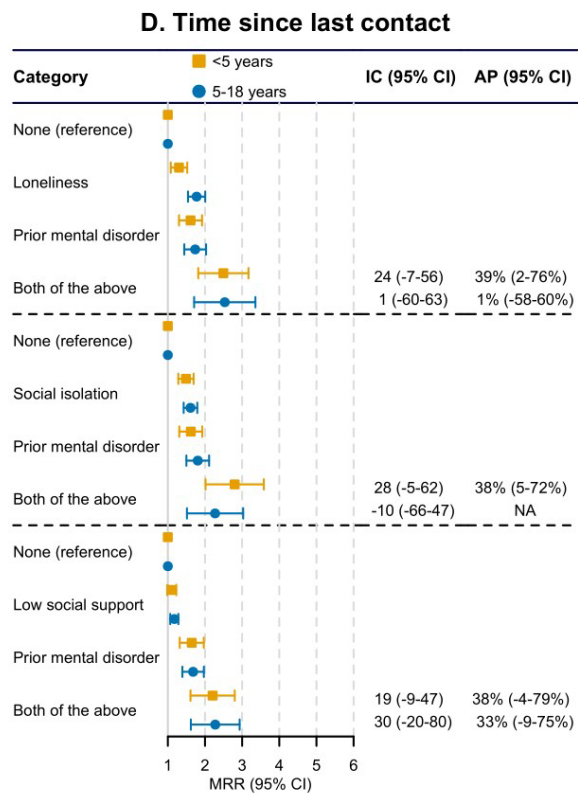
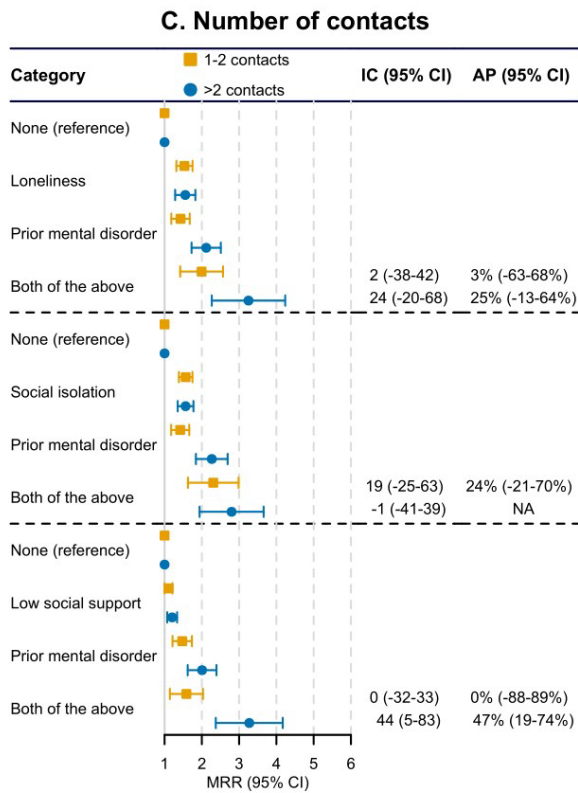


Missing data were imputed using multiple imputation by chained equations. Proportions are shown for individuals with at least one of the indicators of diminished social connections and weighted based on register data to represent the population of the included regions in 2013 and 2017.

Supplementary Figure 3 (SF3). Subgroup analyses of the independent and joint association of mental disorders and social connections with mortality

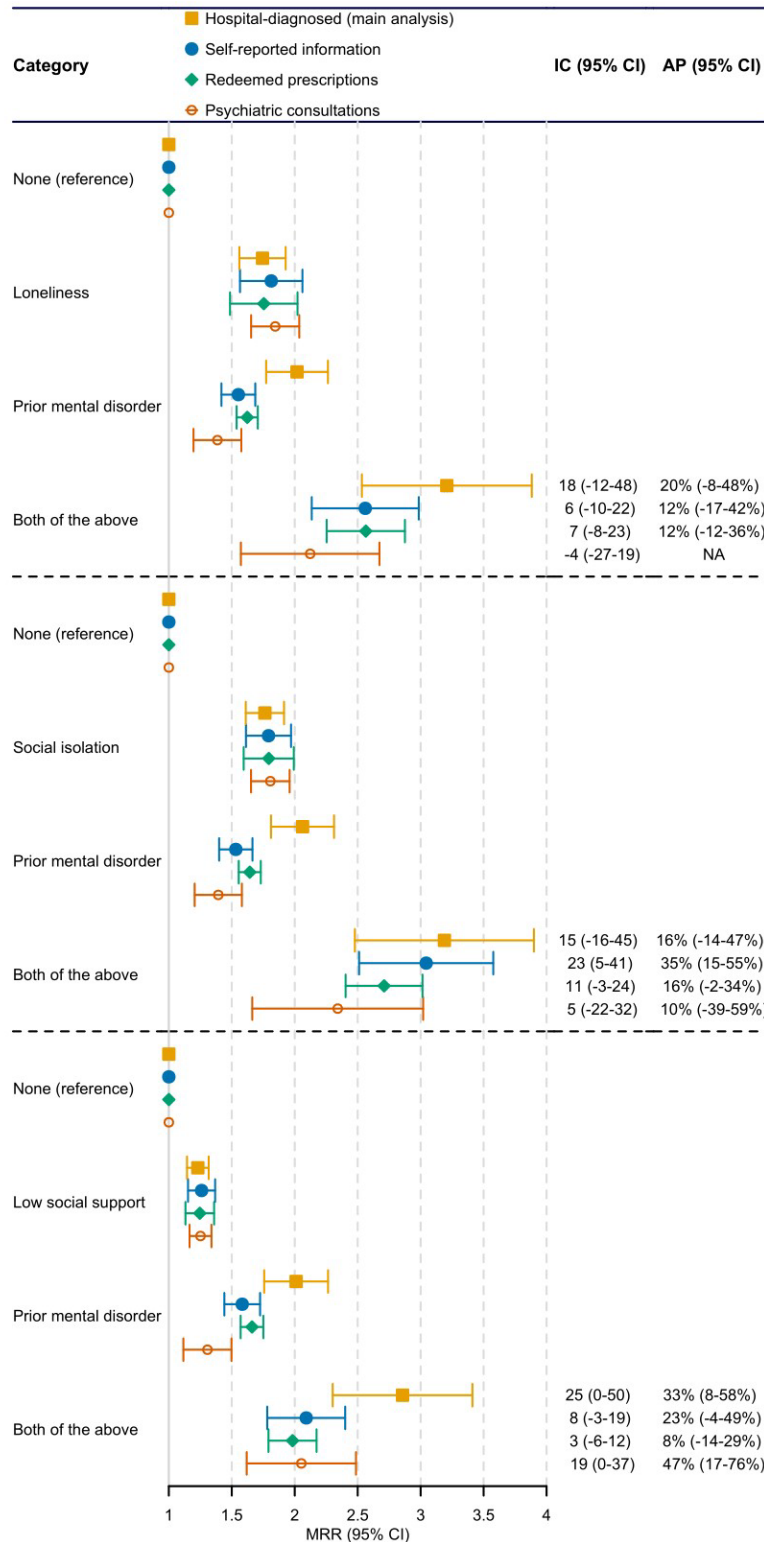


(continued)



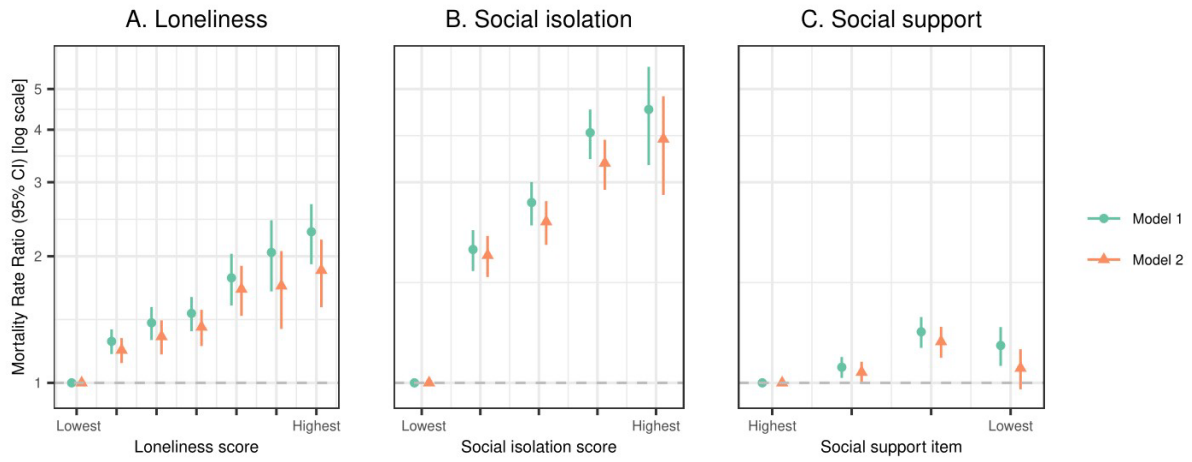
AP: Attributable proportion; IC: Interaction contrast per 10,000 person-years; MRR: Mortality rate ratio; NA: Not applicable. Missing data were imputed using multiple imputation by chained equations, and the results are weighted based on register data to represent the population of the included regions in 2013 and 2017. The attributable proportion was calculated if a synergistic interaction was found. Interaction contrasts are calculated using marginal standardization to individuals with at least one of loneliness, social isolation, and low social support. The models are adjusted for age, sex, year of survey participation, country of birth, somatic morbidity, educational level, income, and wealth.

Supplementary Figure 4 (SF4). Applying alternative operationalizations of mental disorders in the estimation of the independent and joint association of mental disorders and social connections with mortality



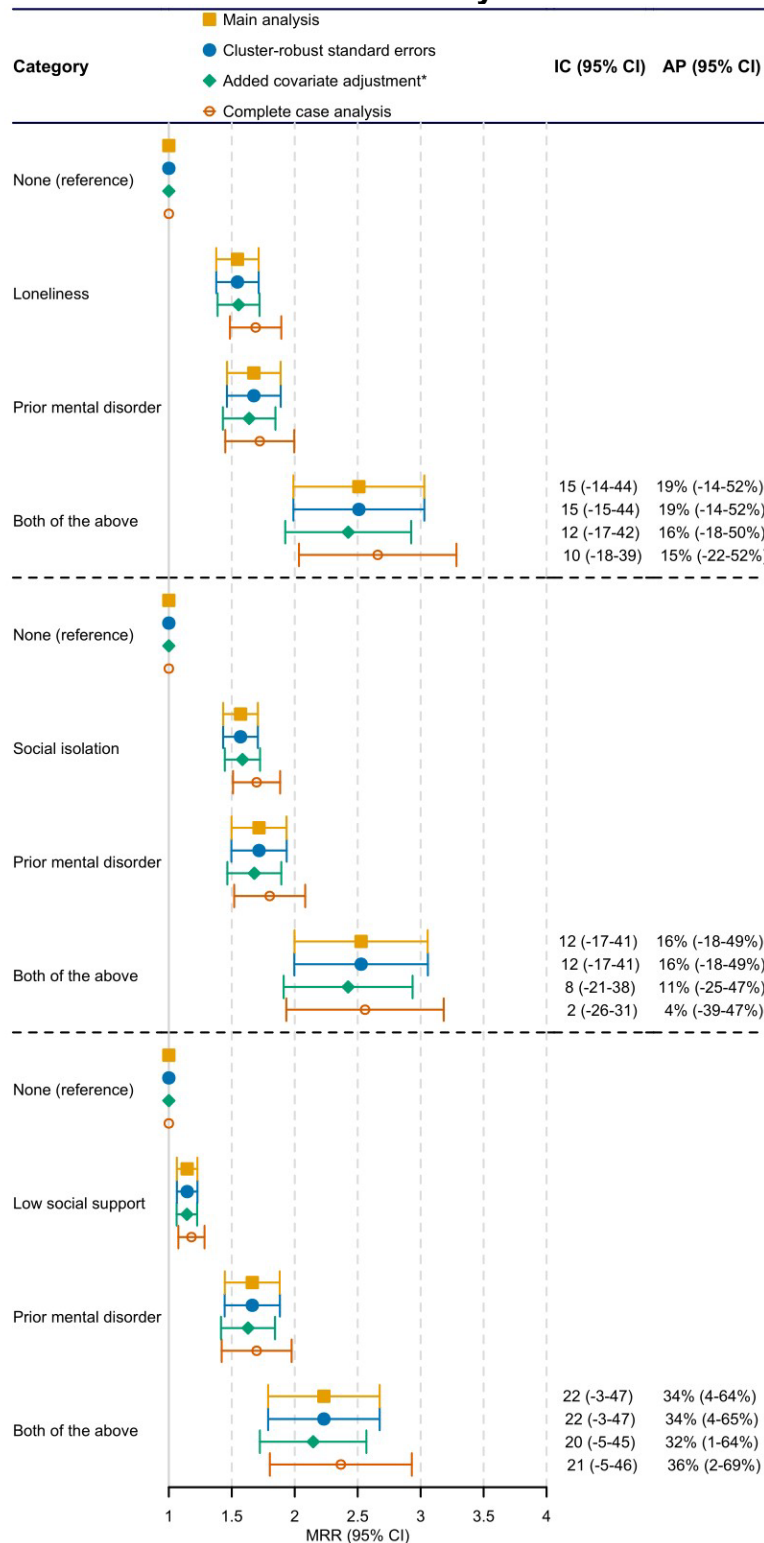
AP: Attributable proportion; IC: Interaction contrast per 10,000 person-years; MRR: Mortality rate ratio; NA: Not applicable. Missing data were imputed using multiple imputation by chained equations, and the results are weighted based on register data to represent the population of the included regions in 2013 and 2017. The attributable proportion was calculated if a synergistic interaction was found. Interaction contrasts are calculated using marginal standardization to individuals with at least one of loneliness, social isolation, and low social support. The models are adjusted for age, sex, and year of survey participation.

Supplementary Figure 5 (SF5): Association with mortality for specific scores/responses on social connections



Missing data were imputed using multiple imputation by chained equations, and the results are weighted based on register data to represent the population of the included regions in 2013 and 2017. In model 1, we adjusted for age, sex, and year of survey participation, and in model 2, we further adjusted for country of birth, somatic morbidity, educational level, income, and wealth.

Supplementary Figure 6 (SF6): Applying alternative modelling assumptions in estimation of the independent and joint association of mental disorders and social connections with mortality



AP: Attributable proportion; IC: Interaction contrast per 10,000 person-years; MRR: Mortality rate ratio. Missing data were imputed using multiple imputation by chained equations, and the results are weighted based on register data to represent the population of the included regions in 2013 and 2017. Interaction contrasts are calculated using marginal standardization to individuals with at least one of loneliness, social isolation, and low social support. The models are adjusted for age, sex, year of survey participation, country of birth, somatic morbidity, educational level, income, and wealth.

*Adjustment for median income in the five years preceding survey participation and added adjustment for interaction between education and birth cohort, between income and age, and between wealth and age.

Supplementary Tables

Supplementary Table 1 (ST1): Overview of prior studies on mental disorders, social disconnectedness and mortality

Author, publication year, country	Study design (period, follow-up)	Study population and response rate	Measure of mental disorders	Measure of diminished social connections	Measure of mortality	Results
Otsuka et al., 2022, Japan (1)	Cohort study (2006–2017, ≤11 years)	43,015 individuals from the general population aged ≥40 years. Response rate: 64%.	Mood or anxiety disorders assessed with the Kessler six-item Distress Scale	Social support assessed with five items on perceived emotional and instrumental support	Suicidal deaths based on residential registries	Greater social support was associated with a lower risk of suicidal death only among participants with moderate or severe psychological distress.
Parmar et al., 2022, UK (2)	Cohort study (2007–2018, mean of 7.2 years)	26,745 mental health patients with a mean age of 47.2 years. Response rate not relevant.	All mental disorders based on active referral to mental healthcare	Loneliness assessed in medical records with a natural language processing algorithm	All-cause mortality based on register data	Loneliness did not predict mortality (hazard ratio: 0.98 [95% CI: 0.92, 1.05]).
Holwerda et al., 2016, Netherlands (3)	Cohort study (1992–2011, ≤19 years)	2,878 individuals from the general population with a mean age of 70 years. Response rate: 53% (combined based on first 62%, then 85%).	Depression assessed with the Centre for Epidemiologic Studies Depression Scale	Loneliness assessed with De Jong-Gierveld loneliness scale	All-cause mortality based on register data	Severe depression was associated with excess mortality in men, but not women, who were lonely.
Finlay et al., 2014, USA (4)	Matched cohort study (not reported, ≤30 years)	848 patients and 848 matched controls with a mean age of 39.7 years. Response rate: 76–96% (varied between waves).	Depression assessed with the DSM-IV criteria for depression	Social isolation assessed by organizational memberships, number of visits by friends and family, social activities, and number of close relationships	All-cause mortality based on register data	Different indicators of social participation provided different results, e.g., organizational membership predicted higher mortality, but number of social activities and visits by friends or family predicted lower mortality.
Stek et al., 2005, Netherlands (5)	Cohort study (1997–2002, ≤5 years)	476 individuals from the general population enrolled at their 85-year birthday. Response rate: 87%.	Depression assessed with the Geriatric Depression Scale	Loneliness assessed with De Jong-Gierveld Loneliness Scale	All-cause mortality based on register data	Loneliness predicted mortality in the depressed sample, but not in the general one.
Christensen et al., 1999, USA (6)	Cohort study (1934 until all patients were deceased, mean of 58.2 years)	133 patients with a mean age of 28.7 years. Response rate not relevant.	Schizophrenia assessed with the DSM-IV criteria for schizophrenia	Social isolation assessed by two independent evaluators as the quantity of social resources available	All-cause mortality based on register data	No significant interaction between schizophrenia and social isolation was found (results not provided).
Fuhrer et al., 1999, France (7)	Cohort study (1988–1995, ≤5 years)	3,421 individuals from the general population aged >65 years. Response rate: 69%.	Depression assessed with the Center for Epidemiologic Studies-Depression scale	Social isolation assessed with an adaptation of the Berkman-Syme Social Network Index	All-cause mortality based on participants' general practitioner and/or register data	Greater quantity of social interactions predicted higher survival (hazard ratio: 0.75 for 1-point increase in the measure social interactions with a SD of 0.80).

Supplementary Table 2 (ST2): Independent and joint associations of mental disorders and social connections with mortality among women and men

Mental disorder	Social connections	Deaths/ person-years at risk	Model 1			Model 2		
			Mortality rate ratio (95% CI)	Interaction contrast per 10,000 person-years (95% CI)	Attributable proportion (95% CI)	Mortality rate ratio (95% CI)	Interaction contrast per 10,000 person-years (95% CI)	Attributable proportion (95% CI)
Women								
<i>Mental disorder & loneliness</i>								
No	No	3,379/422,942	1 (ref.)	–	–	1 (ref.)	–	–
No	Yes	346/22,218	1.68 (1.43–1.94)	–	–	1.54 (1.34–1.75)	–	–
Yes	No	213/26,783	1.98 (1.65–2.31)	–	–	1.70 (1.41–1.98)	–	–
Yes	Yes	55/7,455	2.48 (1.72–3.25)	-7 (-40–26)	NA	1.95 (1.36–2.53)	-14 (-47–18)	NA
<i>Mental disorder & social isolation</i>								
No	No	3,245/436,399	1 (ref.)	–	–	1 (ref.)	–	–
No	Yes	480/8,760	1.71 (1.49–1.93)	–	–	1.54 (1.34–1.75)	–	–
Yes	No	218/32,398	1.97 (1.65–2.29)	–	–	1.70 (1.41–1.98)	–	–
Yes	Yes	50/1,840	2.81 (1.79–3.82)	5 (-36–45)	7% (-50–64%)	2.27 (1.52–3.02)	1 (-36–39)	2% (-62–66%)
<i>Mental disorder & low social support</i>								
No	No	3,178/396,688	1 (ref.)	–	–	1 (ref.)	–	–
No	Yes	547/48,471	1.27 (1.13–1.41)	–	–	1.19 (1.06–1.33)	–	–
Yes	No	204/26,526	2.03 (1.68–2.37)	–	–	1.75 (1.45–2.06)	–	–
Yes	Yes	64/7,711	2.19 (1.53–2.85)	-4 (-33–25)	NA	1.74 (1.22–2.26)	-10 (-39–20)	NA
Men								
<i>Mental disorder & loneliness</i>								
No	No	4,505/371,426	1 (ref.)	–	–	1 (ref.)	–	–
No	Yes	296/15,601	1.83 (1.56–2.10)	–	–	1.57 (1.33–1.80)	–	–
Yes	No	183/15,862	2.06 (1.69–2.42)	–	–	1.62 (1.32–1.93)	–	–
Yes	Yes	70/4,327	4.17 (3.01–5.33)	56 (2–110)	40% (14–66%)	3.26 (2.36–4.17)	61 (6–115)	47% (21–74%)
<i>Mental disorder & social isolation</i>								
No	No	4,263/376,866	1 (ref.)	–	–	1 (ref.)	–	–
No	Yes	538/10,162	1.82 (1.61–2.02)	–	–	1.59 (1.40–1.77)	–	–
Yes	No	187/17,996	2.17 (1.78–2.56)	–	–	1.73 (1.40–2.07)	–	–
Yes	Yes	66/2,193	3.54 (2.58–4.50)	24 (-21–69)	22% (-13–56%)	2.75 (2.00–3.49)	24 (-22–69)	24% (-15–63%)
<i>Mental disorder & low social support</i>								
No	No	4,030/333,773	1 (ref.)	–	–	1 (ref.)	–	–
No	Yes	771/53,254	1.21 (1.10–1.32)	–	–	1.11 (1.01–1.21)	–	–
Yes	No	164/14,664	1.99 (1.62–2.37)	–	–	1.56 (1.25–1.87)	–	–
Yes	Yes	89/5,525	3.51 (2.64–4.37)	57 (16–98)	52% (29–75%)	2.69 (2.00–3.38)	59 (16–101)	61% (35–86%)

NA: Not applicable. Missing data were imputed using multiple imputation by chained equations, and the results are weighted based on register data to represent the population of the included regions in 2013 and 2017. The attributable proportion was calculated if a synergistic interaction was found. Interaction contrasts are calculated using marginal standardization to individuals with at least one of loneliness, social isolation, and low social support. Model 1 is adjusted for age, sex, and year of survey participation, and model 2 is further adjusted for country of birth, somatic morbidity, educational level, income, and wealth.

Supplementary References

1. Plana-Ripoll O, Pedersen CB, Agerbo E, et al. A comprehensive analysis of mortality-related health metrics associated with mental disorders: a nationwide, register-based cohort study. *Lancet*. 2019;394(10211):1827-1835. doi:10.1016/S0140-6736(19)32316-5
2. Plana-Ripoll O, Pedersen CB, Holtz Y, et al. Exploring comorbidity within mental disorders among a Danish national population. *JAMA Psychiatry*. 2019;76(3):259-270. doi:10.1001/jamapsychiatry.2018.3658
3. Momen NC, Plana-Ripoll O, Agerbo E, et al. Association between mental disorders and subsequent medical conditions. *N Engl J Med*. 2020;382(18):1721-1731. doi:10.1056/NEJMoa1915784
4. Pedersen CB, Mors O, Bertelsen A, et al. A comprehensive nationwide study of the incidence rate and lifetime risk for treated mental disorders. *JAMA Psychiatry*. 2014;71(5):573-581. doi:10.1001/jamapsychiatry.2014.16
5. Kessing LV, Ziersen SC, Caspi A, Moffitt TE, Andersen PK. Lifetime incidence of treated mental health disorders and psychotropic drug prescriptions and associated socioeconomic functioning. *JAMA Psychiatry*. Published online July 12, 2023. doi:10.1001/jamapsychiatry.2023.2206
6. Kristensen KB, Lund LC, Jensen PB, et al. Development and validation of a Nordic multimorbidity index based on hospital diagnoses and filled prescriptions. *Clin Epidemiol*. 2022;14:567-579. doi:10.2147/CLEP.S353398
7. OECD/Eurostat/UNESCO Institute for Statistics. *ISCED 2011 Operational Manual: Guidelines for Classifying National Education Programmes and Related Qualifications*. OECD Publishing; 2015. https://www.oecd-ilibrary.org/education/isced-2011-operational-manual_9789264228368-en
8. OECD. Framework for integrated analysis. In: *OECD Framework for Statistics on the Distribution of Household Income, Consumption and Wealth*. OECD Publishing; 2013:171-192. doi:10.1787/9789264194830-11-en
9. Statistics Denmark. TIMES variabel - FAMDISPONIBEL_13. Accessed June 30, 2023. <https://www.dst.dk/da/Statistik/dokumentation/Times/familieindkomst/famdisponibel-13>
10. Statistics Denmark. TIMES variabel - FAMFORMREST_NY05. Accessed June 30, 2023. <https://www.dst.dk/da/Statistik/dokumentation/Times/familieindkomst/famformrest-ny05>
11. Bartlett JW, Harel O, Carpenter JR. Asymptotically unbiased estimation of exposure odds ratios in complete records logistic regression. *Am J Epidemiol*. 2015;182(8):730-736. doi:10.1093/aje/kwv114
12. Hughes RA, Heron J, Sterne JAC, Tilling K. Accounting for missing data in statistical analyses: multiple imputation is not always the answer. *Int J Epidemiol*. 2019;48(4):1294-1304. doi:10.1093/ije/dyz032
13. Morris TP, White IR, Royston P. Tuning multiple imputation by predictive mean matching and local residual draws. *BMC Med Res Methodol*. 2014;14:75. doi:10.1186/1471-2288-14-75
14. Tilling K, Williamson EJ, Spratt M, Sterne JAC, Carpenter JR. Appropriate inclusion of interactions was needed to avoid bias in multiple imputation. *Clin Epidemiol*. 2016;80:107-115. doi:10.1016/j.jclinepi.2016.07.004
15. White IR, Royston P, Wood AM. Multiple imputation using chained equations: issues and guidance for practice. *Stat Med*. 2011;30(4):377-399. doi:10.1002/sim.4067
16. Wulff JN, Ejlskov L. Multiple imputation by chained equations in praxis: guidelines and review. *Electron J Bus*. 2017;15(1).

Supplementary appendix to *Interaction between mental disorders and diminished social connections in the association with mortality: a Danish population-based cohort study*

17. Lash TL, VanderWeele TJ, Haneuse S, Rothman KJ. *Modern Epidemiology*. Fourth edition. Wolters Kluwer; 2021.
18. VanderWeele TJ. Reconsidering the denominator of the attributable proportion for interaction. *Eur J Epidemiol*. 2013;28(10):10.1007/s10654-013-9843-9846. doi:10.1007/s10654-013-9843-6