Cause of death dependencies: impact of their hypothetical disruptions, evolution by age and effect on length of life

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Paris, 4. 4. 2024

The research was supported by the SCOR Foundation for Science through the funding for the "SCOR Chair in Mortality Research

Multiple causes of death

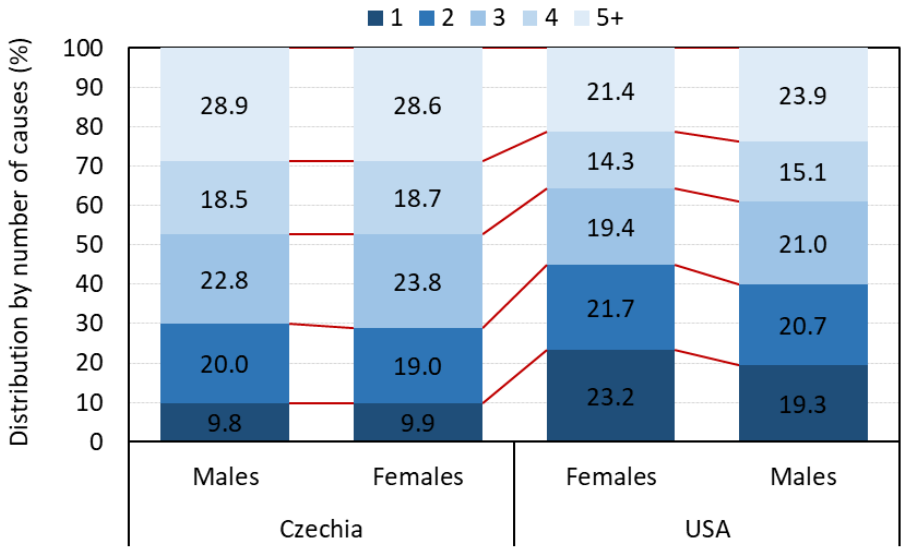
- 80% of deaths result from more than a single cause

Figure: Example of death certificate

27. PART I. Enter the diseases, injuries, or complications that caused the death. Do not enter the mode of dying, such as cardiac or respiratory arrest, shock, or heart failure. List only one cause on each line.		Approximate Interval Between Onset and Death
IMMEDIATE CAUSE (final disease or condition resulting in death)	a. **I46** *Cardiac Arrest*	*Mins.*
Sequentially list conditions, if any, leading to immediate cause. Enter **UNDERLYING CAUSE** (Disease or injury that initiated events resulting in death) **LAST**	Due to (or as a consequence of): b. **I21** *Acute myocardial infarction*	*6 days*
	Due to (or as a consequence of): c. **I25** *Chronic Ischemic Heart disease*	*5 years*
	Due to (or as a consequence of): d.	
PART II. Other significant conditions contributing to death but not resulting in the underlying cause given in Part I.		**28a.** AUTOPSY?
Diabetes, Chronic obstructive pulmonary disease, smoking **E11, J44, F17**		(*Yes or no*)

Chain of morbid events leading to death: I25 → I21 → I46
Contributory causes of death: E11, J44, F17
Underlying cause: initiates the chain of morbid events leading to death

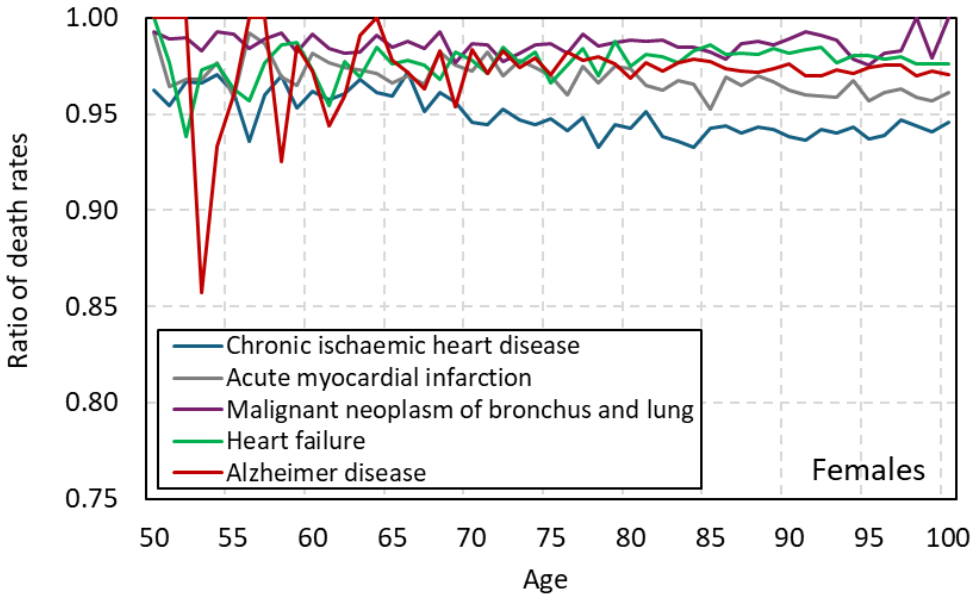
Multiple causes of death

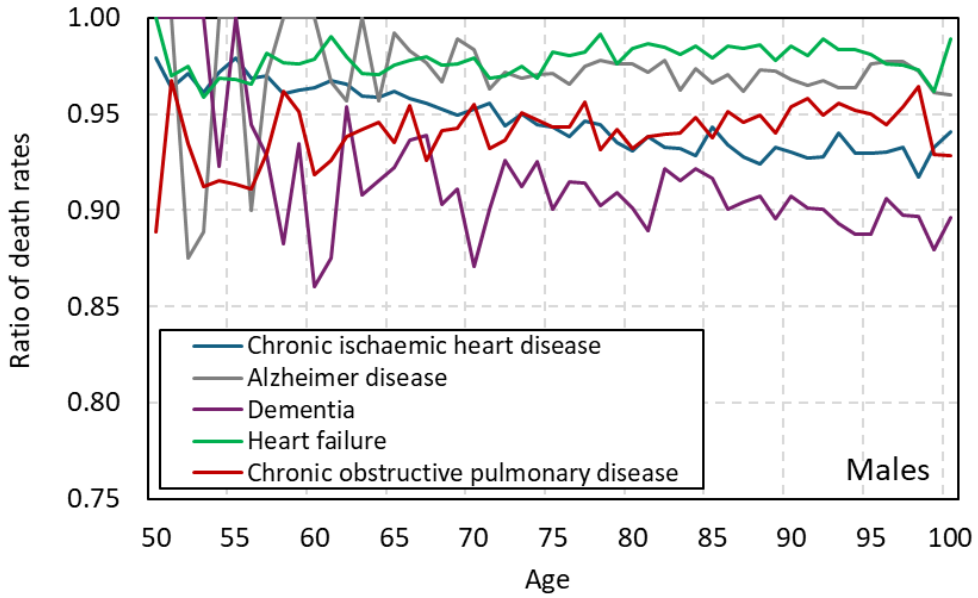


Figures:
← Distribution of deaths by number of causes listed on the death certificate by sex, USA and Czechia, 2018

↓ Ratio of age-specific mortality rates by leading causes of death (i) recorded by physician as underlying condition and (ii) oficially selected by ACME software as underlying cause of death, by sex, USA, 2019

Note: <1 implies, that ACME software selects the disease more often as underlying, than physician does





Research questions

How would the structure of cause of death dependencies change if leading causes of death were independent?

How does the strength of associations between causes of death change with age?

At what ages and for which cause of death groups is considering the dependency between causes of death most important?

- We **measure associations** between counts of death by cause with odds ratios (OR).
- We introduce **disruptions** to establish independence within cause of death pairs and measrue how this affects the dependence among all other disease pairs.
- We measure how cause of death **dependencies evolve with age**.
- We use age-specific probabilities of death to calculate multiple-decrement life tables and pattern-of-failure life tables and use them to measure the **effect of disease dependency on length of life**.

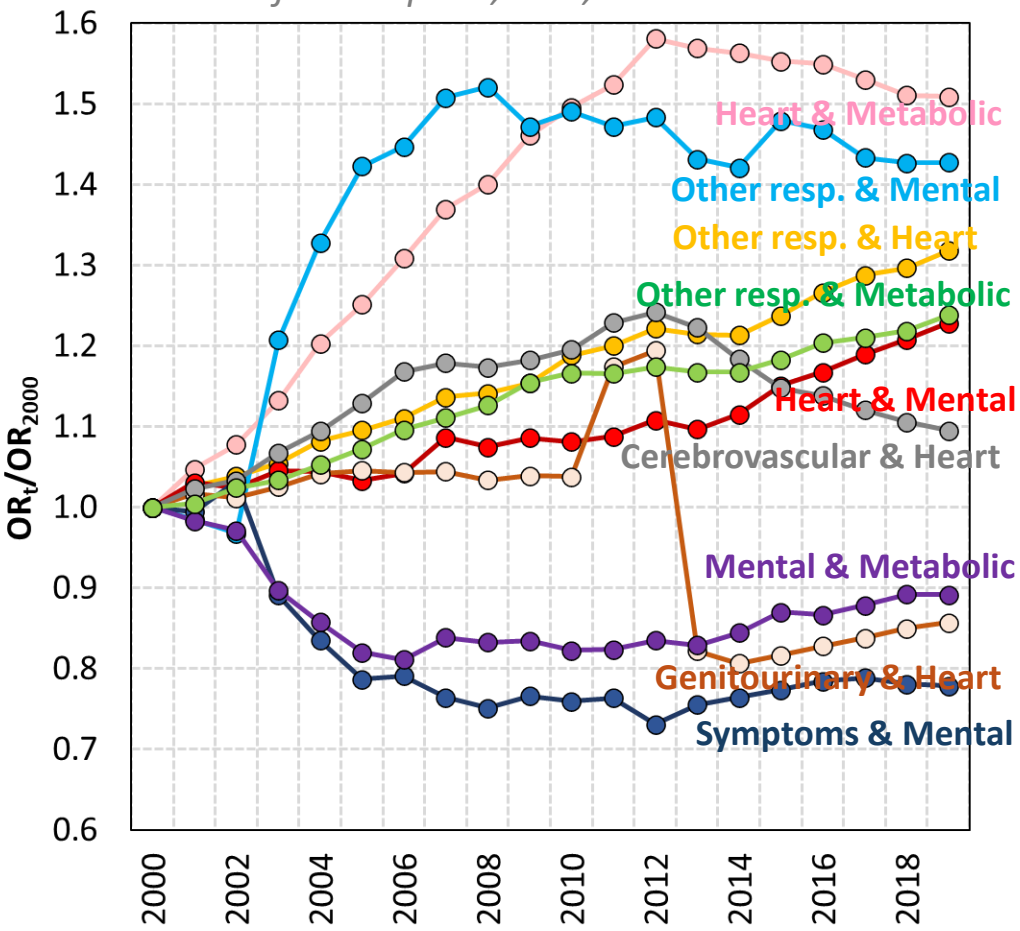
Cause of death dependencies

Figure: Odds ratios (OR) between major groups of causes of death, USA, 2019

	Infectious	Neoplasms	Diseases of blood	Metabolic	Mental	Nervous	Heart	Cerebrovascular	Other circulatory	Acute resp.	Other resp.	Digestive	Diseases of skin	Genitourinary	Perinatal	Symptoms
Symptoms	1.1	0.4	1.6	1.0	1.2	1.0	0.6	0.8	1.1	1.0	1.0	1.2	1.6	1.1	0.7	
Perinatal	0.7	0.1	1.1	0.4	0.2	0.6	0.3	0.4	1.1	0.8	0.5	0.7	0.7	0.7		0.7
Genitourinary	4.8	0.6	3.2	1.4	0.8	0.9	1.3	0.7	1.8	2.1	1.5	2.3	2.1		0.7	1.1
Diseases of skin	3.8	0.6	2.9	2.7	1.3	1.7	1.5	1.0	2.7	1.3	1.4	1.5		2.1	0.7	1.6
Digestive	4.1	0.8	4.0	1.4	0.8	0.5	0.7	0.5	1.9	0.9	1.1		1.5	2.3	0.7	1.2
Other resp.	1.9	0.7	1.6	1.2	2.0	0.9	1.2	0.8	1.0	2.5		1.1	1.4	1.5	0.5	1.0
Acute resp.	6.4	0.7	1.8	1.0	0.8	0.9	0.8	0.7	0.7		2.5	0.9	1.3	2.1	0.8	1.0
Other circulatory	1.4	0.6	2.5	1.8	1.3	0.8	2.2	1.5		0.7	1.0	1.9	2.7	1.8	1.1	1.1
Cerebrovascular	0.6	0.3	1.1	1.3	1.0	1.1	1.3		1.5	0.7	0.8	0.5	1.0	0.7	0.4	0.8
Heart	0.7	0.3	1.4	3.8	1.1	0.7		1.3	2.2	0.8	1.2	0.7	1.5	1.3	0.3	0.6
Nervous	0.7	0.2	0.9	1.2	0.7		0.7	1.1	0.8	0.9	0.9	0.5	1.7	0.9	0.6	1.0
Mental	0.7	0.8	1.0	1.4		0.7	1.1	1.0	1.3	0.8	2.0	0.8	1.3	0.8	0.2	1.2
Metabolic	1.3	0.6	2.4		1.4	1.2	3.8	1.3	1.8	1.0	1.2	1.4	2.7	1.4	0.4	1.0
Diseases of blood	2.8	1.8		2.4	1.0	0.9	1.4	1.1	2.5	1.8	1.6	4.0	2.9	3.2	1.1	1.6
Neoplasms	0.7		1.8	0.6	0.8	0.2	0.3	0.3	0.6	0.7	0.7	0.8	0.6	0.6	0.1	0.4
Infectious		0.7	2.8	1.3	0.7	0.7	0.7	0.6	1.4	6.4	1.9	4.1	3.8	4.8	0.7	1.1

$$OR = \frac{\frac{D_{i,j}}{D_{\neg i,j}}}{\frac{D_{i,\neg j}}{D_{\neg i,\neg j}}}$$

Figure: Index of odds ratios (base = 2000), leading cause of death pairs, USA, 2000–2019



Note: 70% of deaths are due to 9 leading cause of death pairs

Disruptions of cause of death dependencies

- We disrupted the connections between diseases within leading cause of death pairs by optimizing marginal totals within the contingency table.

Figure: One solution for finding independence between diseases i and j

Disease i: Heart disease, disease j: Endocrine, nutritional and metabolic diseases

		Disease j YES	NO	
Disease i	YES	376 200	1 052 256	1 428 456
	NO	123 205	1 309 862	1 433 067
		499 405	2 362 118	2 861 523

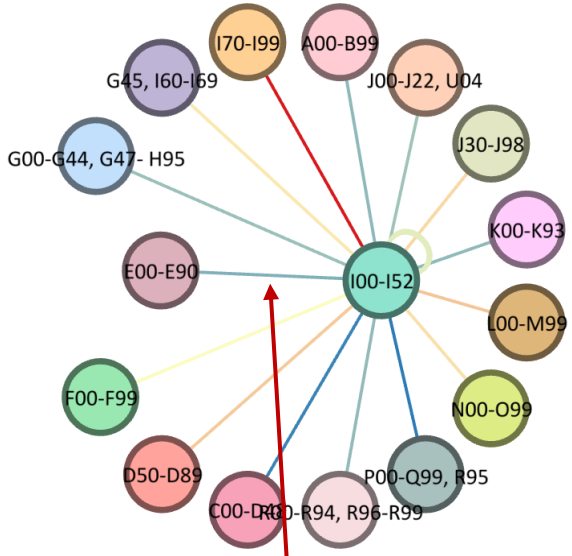
	Observed	Adjusted
Odds ratio	3.8010	1.0063

Former X^2 test:

	$D_{\neg i\neg j}$	$D_{\neg ij}$	$D_{i\neg j}$	D_{ij}	To be optimized: $D_{\neg i}$	D_i	$D_{\neg j}$	D_j	Constrain: Total	Total
Observed	1 309 862	123 205	1 052 256	376 200	**1 433 067**	**1 428 456**	**2 362 118**	**499 405**	2 861 523	2 861 523
Expected	1 182 962	250 105	1 179 156	249 300	1 433 067	1 428 456	1 433 067	1 428 456	2 861 523	2 861 523
X2	13 613	64 387	13 657	64 595						
SumX2	**156 252** Target value									
P-value	<0.000									

X^2 test adjusted for independence:

	$D_{\neg i\neg j}$	$D_{\neg ij}$	$D_{i\neg j}$	D_{ij}	To be optimized: $D\neg i$	Di	$D\neg j$	Dj	Constrain: Total	Total
Observed	936 213	279 305	1 269 805	376 200	**1 215 385**	**1 646 005**	**2 206 018**	**655 505**	2 861 523	2 861 523
Expected	936 970	278 415	1 268 945	377 060	1 215 385	1 646 005	1 215 385	1 646 005	2 861 390	2 861 390
X2	0.612	2.845	0.582	1.960						
SumX2	**6** Target value									
P-value	0.1117									

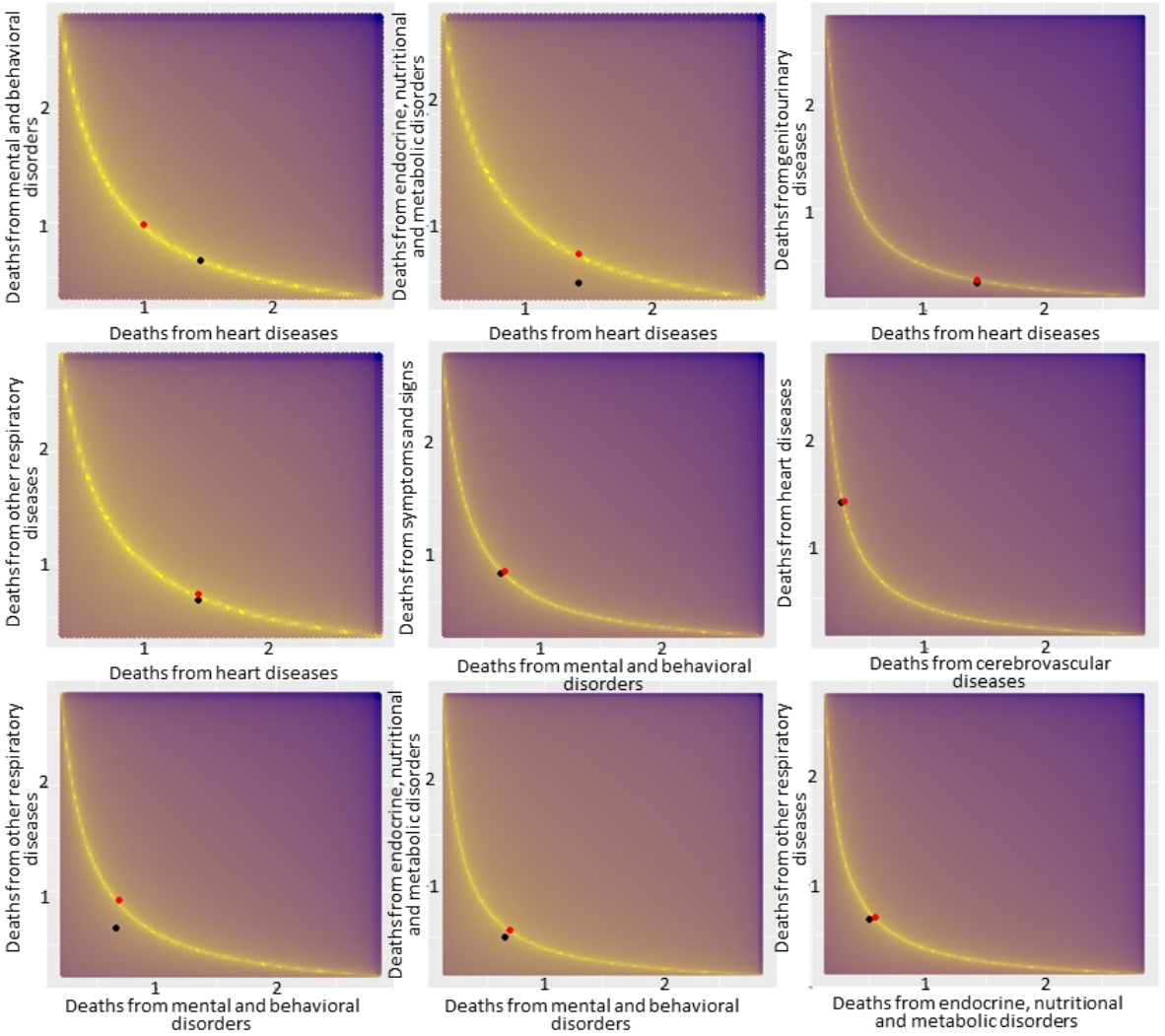


Making independent (*i* and *j*)

What is the effect of disruptions between *i* and *j* on association between *i* and *k*?

Disruptions of cause of death dependencies

Figure: Scenarios of independence between causes i and j (yellow curves)



Black dot: original combination of number of deaths from disease i and number of death from disease j

Red dot: „Minimum relocation scenario“ (independence scenario applied here)

Death counts on both axes are in 10^6.

Disruptions of cause of death dependencies

Table: Effect of disruption between i and j on associations on i (ratio of original OR and adjusted OR)

		Cause of death pair (i_j) being dissolved (minimum relocation scenario)								
		Endocrine, nutritional and metabolic diseases + Other respiratory diseases	Mental and behavioral disorders + Other respiratory diseases	Mental and behavioral disorders + Symptoms and signs	Mental and behavioral disorders + Endocrine, nutritional and metabolic diseases	Heart diseases + Other respiratory diseases	Heart diseases + Diseases of the genitourinary system and complications of pregnancy, childbirth and puerperium	Heart diseases + Endocrine, nutritional and metabolic diseases	Heart diseases + Mental and behavioral disorders	Cerebrovascular diseases + Heart diseases
Neighbouring disease of i	Infectious	1.15 (0.88)	0.67 (0.96)	0.64 (0.92)	0.64 (0.92)	0.70 (1.00)	0.70 (0.99)	0.70 (1.00)	1.42 (2.03)	0.51 (0.88)
	Neoplasms	0.50 (0.87)	0.78 (0.95)	0.74 (0.91)	0.74 (0.91)	0.30 (1.00)	0.30 (0.99)	0.30 (1.00)	0.69 (2.30)	0.26 (0.88)
	Diseases of blood	2.08 (0.88)	0.91 (0.96)	0.88 (0.92)	0.88 (0.92)	1.45 (1.00)	1.44 (0.99)	1.45 (1.00)	2.82 (1.95)	0.93 (0.88)
	Metabolic	()	1.31 (0.95)	1.25 (0.91)	()	3.80 (1.00)	3.78 (0.99)	()	8.81 (2.32)	1.12 (0.86)
	Mental	1.18 (0.85)	()	()	()	1.09 (1.00)	1.08 (0.99)	1.09 (1.00)	()	0.90 (0.86)
	Nervous	1.05 (0.87)	0.65 (0.95)	0.63 (0.92)	0.63 (0.92)	0.74 (1.00)	0.74 (0.99)	0.74 (1.00)	1.55 (2.09)	0.96 (0.87)
	Heart	2.60 (0.68)	1.00 (0.92)	0.93 (0.86)	0.93 (0.86)	()	()	()	()	()
	Cerebrovascular	1.15 (0.88)	1.00 (0.95)	0.96 (0.92)	0.96 (0.92)	1.29 (1.00)	1.28 (0.99)	1.29 (1.00)	2.64 (2.05)	()
	Other circulatory	1.58 (0.88)	1.23 (0.96)	1.19 (0.92)	1.19 (0.92)	2.18 (1.00)	2.17 (0.99)	2.18 (1.00)	4.30 (1.97)	1.31 (0.88)
	Acute resp.	0.87 (0.88)	0.8 (0.96)	0.78 (0.92)	0.78 (0.92)	0.79 (1.00)	0.79 (0.99)	0.79 (1.00)	1.56 (1.97)	0.62 (0.88)
	Other resp.	()	()	1.79 (0.90)	1.79 (0.90)	()	1.23 (0.99)	1.24 (1.00)	2.96 (2.38)	0.68 (0.86)
	Digestive	1.22 (0.88)	0.72 (0.96)	0.70 (0.92)	0.70 (0.92)	0.71 (1.00)	0.71 (0.99)	0.71 (1.00)	1.44 (2.02)	0.42 (0.88)
	Diseases of skin	2.37 (0.88)	1.27 (0.96)	1.22 (0.92)	1.22 (0.92)	1.47 (1.00)	1.47 (0.99)	1.47 (1.00)	2.87 (1.94)	0.91 (0.88)
	Genitourinary	1.27 (0.88)	0.74 (0.95)	0.72 (0.92)	0.72 (0.92)	1.32 (1.00)	()	1.32 (1.00)	2.72 (2.06)	0.63 (0.88)
	Perinatal	0.36 (0.89)	0.20 (0.96)	0.19 (0.93)	0.19 (0.93)	0.27 (1.00)	0.27 (0.99)	0.27 (1.00)	0.52 (1.91)	0.38 (0.89)
	Symptoms	0.82 (0.85)	1.10 (0.94)	()	1.05 (0.90)	0.64 (1.00)	0.64 (0.99)	0.64 (1.00)	1.57 (2.43)	0.66 (0.86)

Disruptions of cause of death dependencies

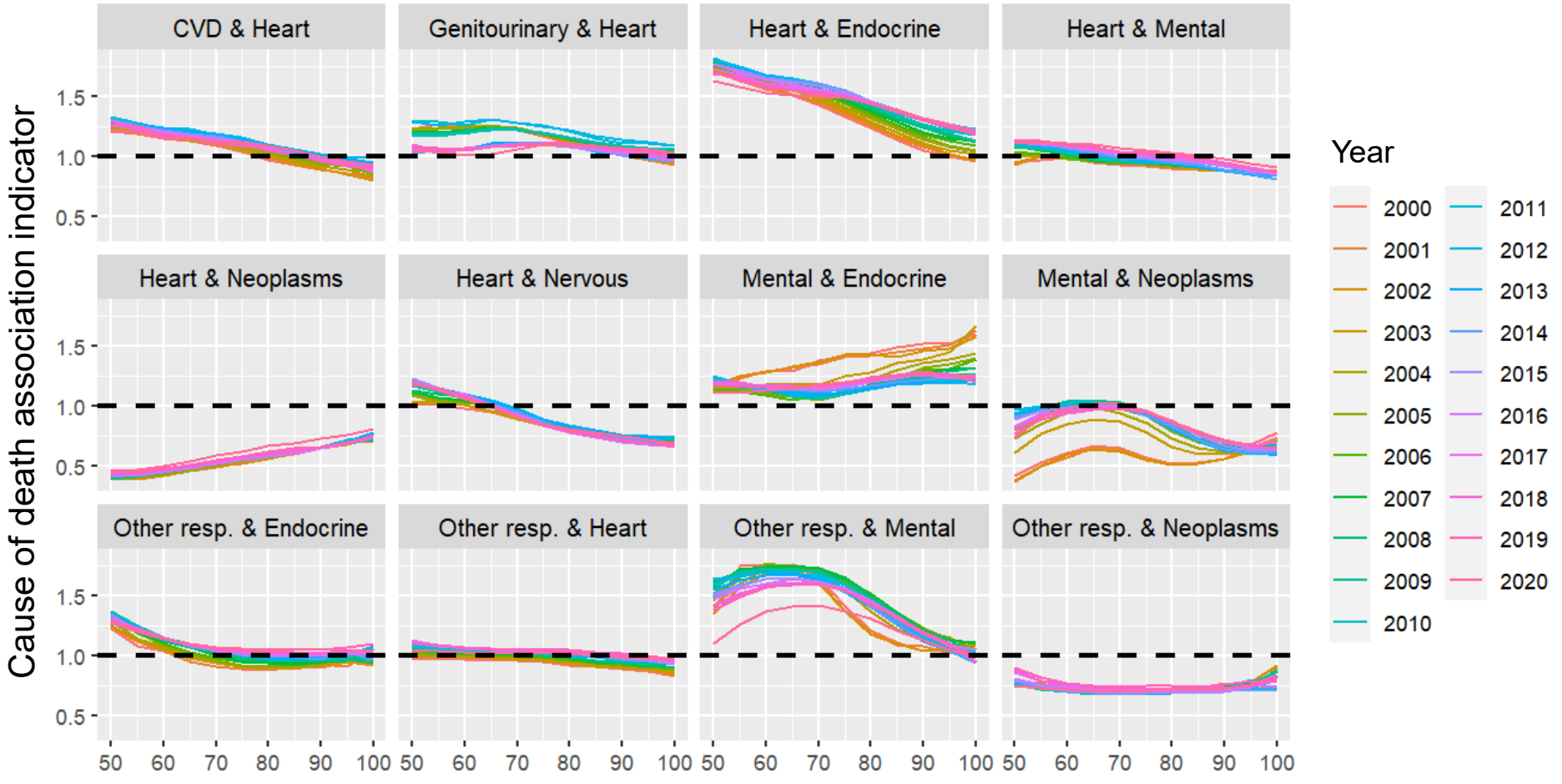
Table: Effect of disruption between i and j on associations on j (ratio of original OR and adjusted OR)

		Cause of death pair (i_j) being dissolved (minimum relocation scenario)								
		Endocrine, nutritional and metabolic diseases + Other respiratory diseases	Mental and behavioral disorders + Other respiratory diseases	Mental and behavioral disorders + Symptoms and signs	Mental and behavioral disorders + Endocrine, nutritional and metabolic diseases	Heart diseases + Other respiratory diseases	Heart diseases + Diseases of the genitourinary system and complications of pregnancy, childbirth and puerperium	Heart diseases + Endocrine, nutritional and metabolic diseases	Heart diseases + Mental and behavioral disorders	Cerebrovascular diseases + Heart diseases
Neighbouring disease of j	Infectious	1.78 (0.96)	1.11 (0.96)	1.11 (0.96)	1.08 (0.96)	1.65 (0.96)	4.04 (0.96)	0.73 (0.96)	0.38 (0.96)	0.70 (0.96)
	Neoplasms	0.69 (0.95)	0.41 (0.56)	0.36 (0.96)	0.47 (0.82)	0.64 (0.88)	0.53 (0.86)	0.31 (0.53)	0.40 (0.49)	0.30 (0.99)
	Diseases of blood	1.50 (0.96)	0.97 (0.62)	1.55 (0.97)	1.98 (0.84)	1.41 (0.90)	2.82 (0.87)	1.36 (0.58)	0.54 (0.56)	1.44 (0.99)
	Metabolic	()	0.70 (0.57)	0.92 (0.96)	()	1.08 (0.88)	1.23 (0.85)	()	0.70 (0.51)	3.77 (0.99)
	Mental	1.89 (0.95)	()	()	()	1.73 (0.86)	0.66 (0.85)	0.70 (0.51)	()	1.08 (0.99)
	Nervous	0.84 (0.96)	0.52 (0.60)	0.92 (0.96)	0.99 (0.82)	0.78 (0.89)	0.76 (0.87)	0.66 (0.55)	0.37 (0.54)	0.74 (0.99)
	Heart	1.15 (0.92)	0.51 (0.41)	0.61 (0.94)	2.26 (0.59)	()	()	()	()	()
	Cerebrovascular	0.76 (0.96)	0.48 (0.61)	0.74 (0.96)	1.08 (0.83)	0.71 (0.89)	0.63 (0.87)	0.73 (0.56)	0.57 (0.54)	()
	Other circulatory	0.99 (0.96)	0.64 (0.62)	1.07 (0.97)	1.50 (0.84)	0.93 (0.90)	1.54 (0.87)	1.03 (0.58)	0.72 (0.56)	2.17 (0.99)
	Acute resp.	2.37 (0.96)	1.51 (0.61)	0.96 (0.97)	0.82 (0.84)	2.21 (0.89)	1.86 (0.87)	0.57 (0.58)	0.47 (0.56)	0.79 (0.99)
	Other resp.	()	()	0.94 (0.96)	0.98 (0.80)	()	1.29 (0.84)	0.63 (0.51)	0.93 (0.47)	1.23 (0.99)
	Digestive	1.02 (0.96)	0.65 (0.61)	1.14 (0.96)	1.15 (0.83)	0.95 (0.89)	2.03 (0.86)	0.78 (0.56)	0.42 (0.55)	0.71 (0.99)
	Diseases of skin	1.30 (0.96)	0.84 (0.62)	1.54 (0.97)	2.25 (0.84)	1.22 (0.90)	1.88 (0.87)	1.55 (0.58)	0.74 (0.56)	1.47 (0.99)
	Genitourinary	1.48 (0.96)	0.92 (0.60)	1.09 (0.96)	1.20 (0.83)	1.37 (0.89)	()	0.81 (0.56)	0.42 (0.54)	1.31 (0.99)
	Perinatal	0.49 (0.96)	0.32 (0.63)	0.66 (0.97)	0.35 (0.85)	0.46 (0.90)	0.60 (0.88)	0.24 (0.59)	0.12 (0.57)	0.27 (0.99)
	Symptoms	0.93 (0.95)	0.53 (0.54)	()	0.77 (0.80)	0.85 (0.87)	0.95 (0.84)	0.49 (0.50)	0.55 (0.47)	0.64 (0.99)

Dependencies by age

- The strength of associations between causes of death varies by age and shows a specific shape for each pair of leading causes of death.

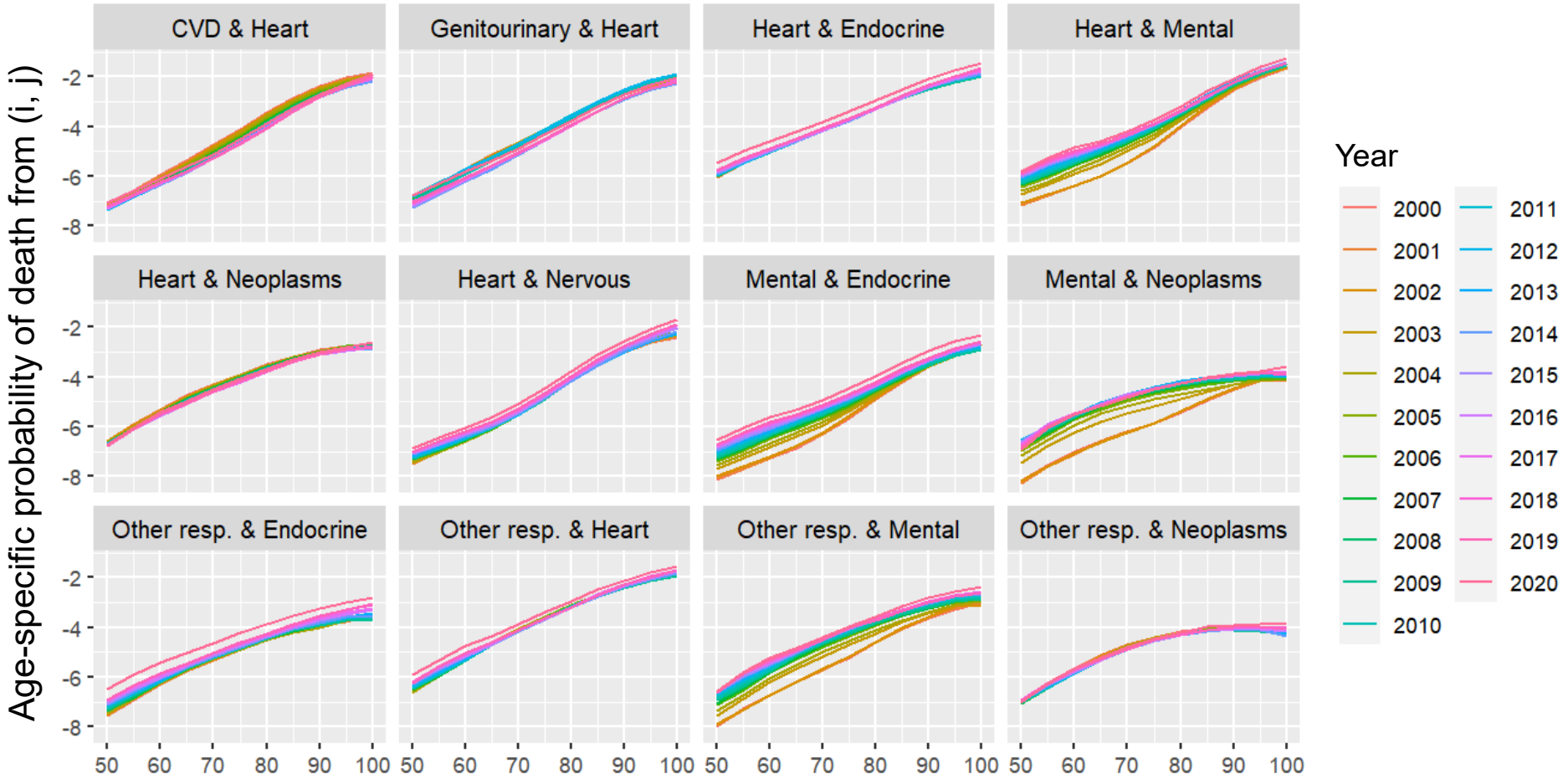
Figure: Cause of death associations by age, leading cause of death pairs, USA, 2000–2020



Dependencies by age

- Death from *i* is independent on death from *j* if following is true: $P(i \cap j) = P(i) \times P(j)$.
- Ratio → 1 suggests independence of events.

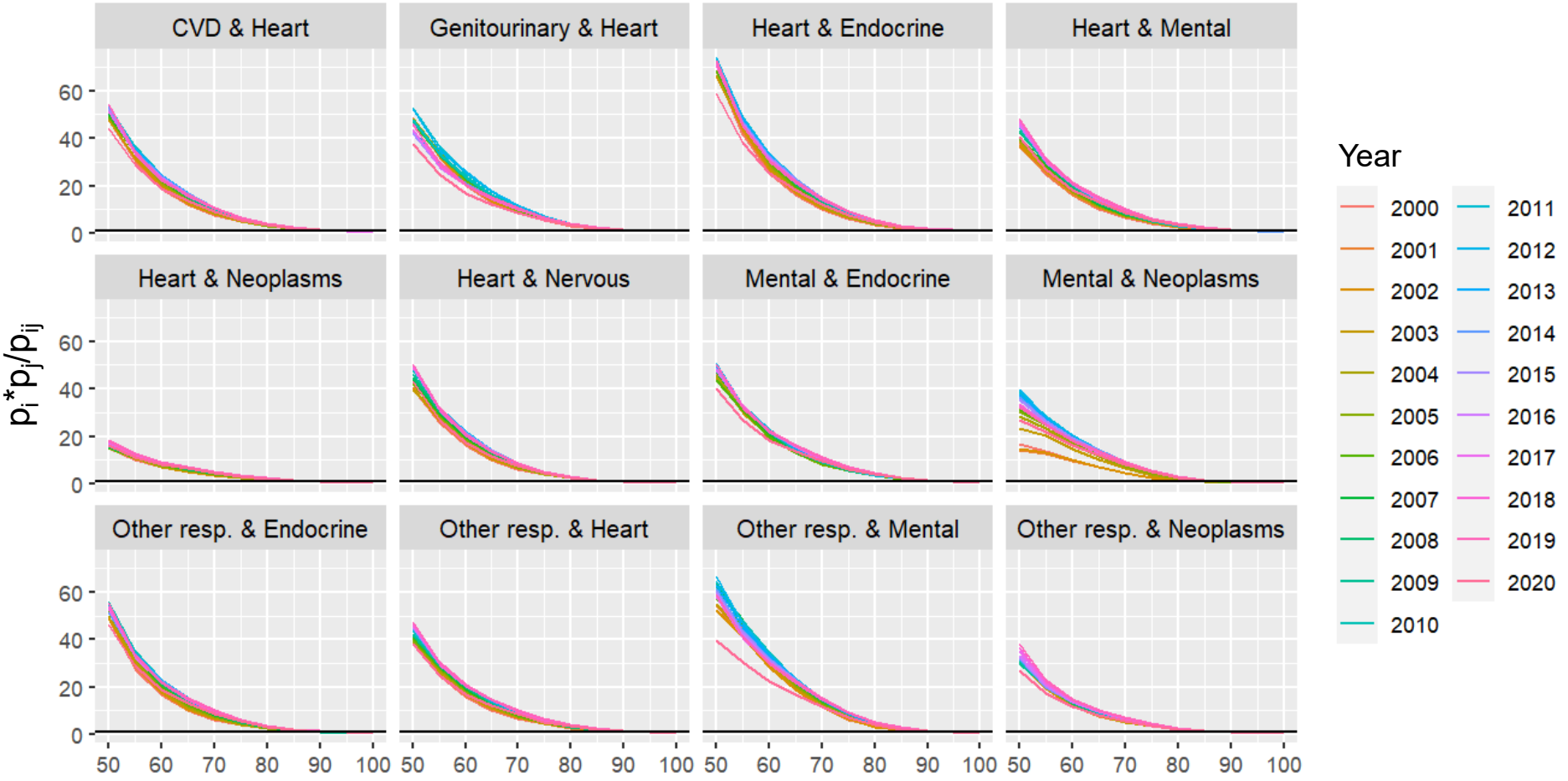
Figure: Age-specific probability of death from disease pair (i, j), leading cause of death pairs, USA, 2000–2020



Dependencies by age

- Death from *i* is independent on death from *j* if following is true: $P(i \cap j) = P(i) \times P(j)$.
- Ratio → 1 suggests independence of events.

Figure: Ratio of age-specific probabilities of death from i and from j to age-specific probabilities of death from (i, j)



Effect of dependencies on length of life

- Death from *i* is not independent from death from *j*. Standard life tables are based on the assumption of independence between decrements. Multiple cause of death life tables that allow a violation of this assumpion have been proposed previousely: **pattern-of-failure life tables**.
- For 2 causes of death 7 patterns of death can be identified:

Age	D_x^A	D_x^B	D_x^C	D_x^{AB}	D_x^{AC}	D_x^{BC}	D_x^{ABC}
0							
1							

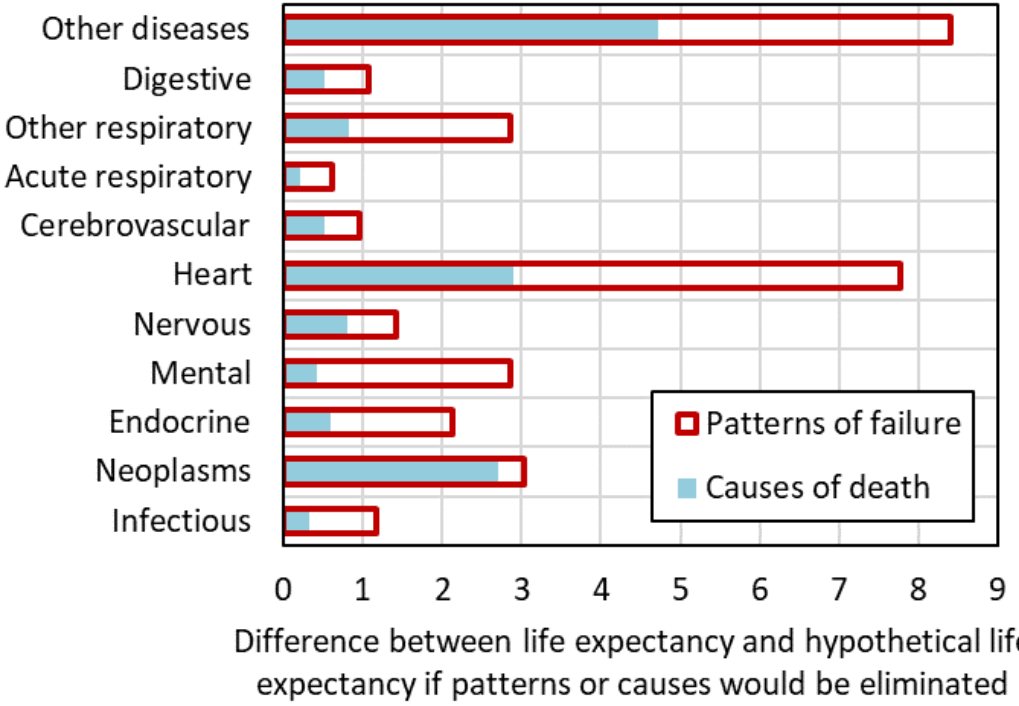
- Manton et al. (1976) suggest estimating the burden of non-underlying conditions by hypothetical **eliminations of patterns-of-failure**. According to Manton et al. (1976), the age-specific probability of death if pattern B were eliminated is equal to:

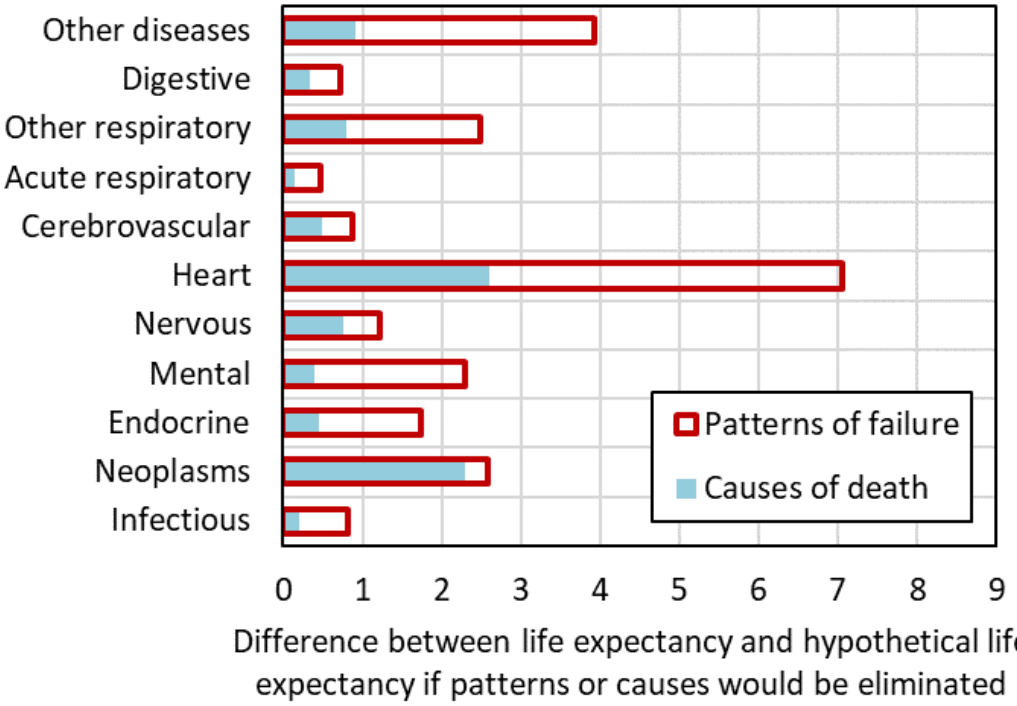
$$Q_{ij\cdot B} = \frac{Q_{ij}}{q_i - \sum_{\varphi \in B} Q_{i\varphi}} \times \left(1 - p_i^{\left[\frac{q_i - \sum_{\varphi \in B} Q_{i\varphi}}{q_i}\right]}\right)$$

Effect of dependencies on length of life

- Elimination of patterns would naturally lead to greater gains in life expectancy than elimination of causes.

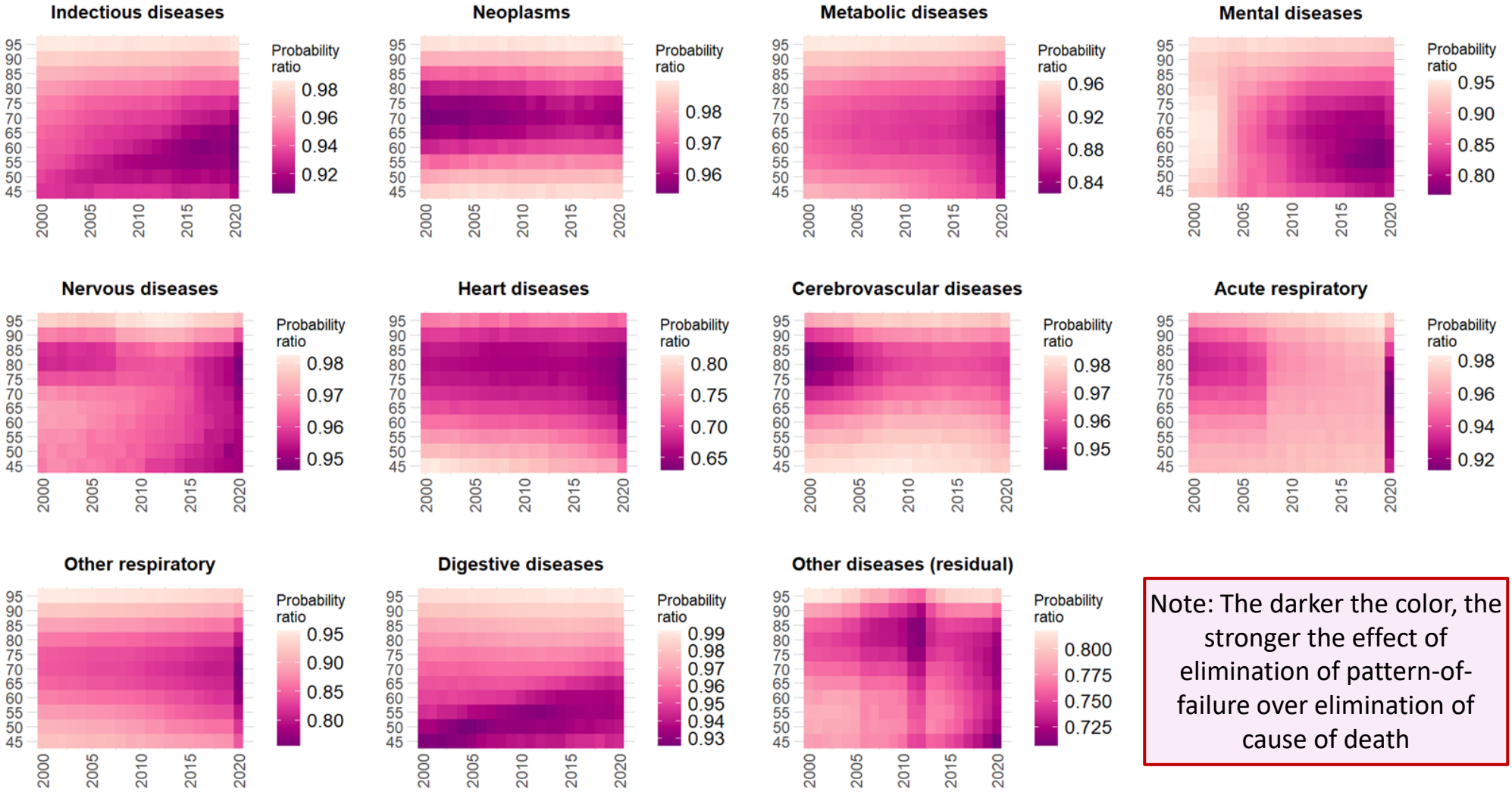
Figure: Gains in life expectancy if patterns of death or causes of death would hypothetically be eliminated, USA, 2019, age 0 (left) and age 65 (right)





Effect of dependencies on length of life

Figure: Ratio of probability of death in pattern-of-failure elimination life tables and probability of death in cause elimination life tables

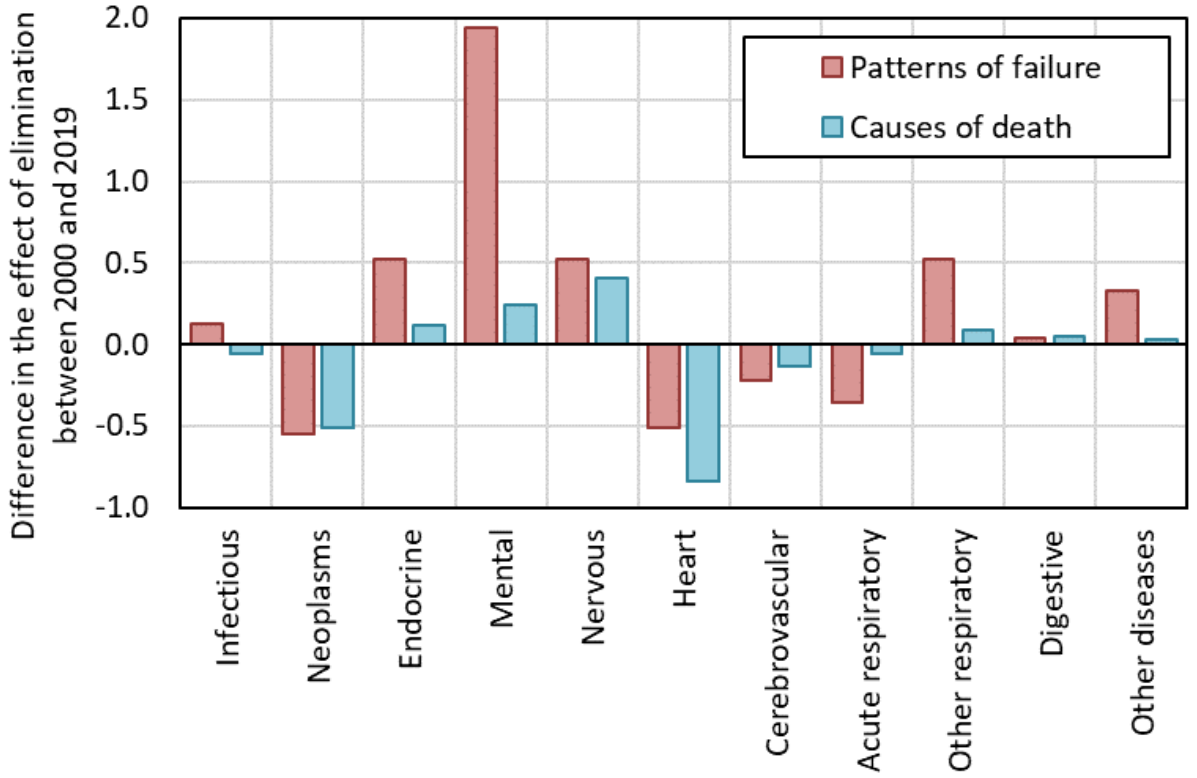


Note: The darker the color, the stronger the effect of elimination of pattern-of-failure over elimination of cause of death

Effect of dependencies on length of life

- Since 2000, there has been a shift in the impact of elimination. The increase in life expectancy resulting from the elimination of patterns involving mental diseases has risen by approximately 2 years between 2000 and 2020. Conversely, the increase in life expectancy if heart diseases were eliminated decreased by almost a year. These trends are evident only in pattern life tables.

Figure: Difference between gains in 2000 and in 2019 if causes or patterns were eliminated, USA, 2000–2019



Summary

How would the structure of cause of death dependencies change if leading causes of death were independent?

Disrupting the associations would have a broader impact on the dependencies between other diseases that are being disrupted, especially for metabolic and mental diseases.

How does the strength of associations between causes of death change with age?

As age increases, the death from *i* begins to become independent of death from *j.* Mental and metabolic diseases strenghten their association with age.

At what ages and for which cause of death groups is considering the dependency between causes of death most important?

Each disease group is characterized by specific ages in which the disease risk is the most underestimated because we assume, that only a single underlying cause of death could cause the death. The pattern-of-failure effect is greatest for mental, endocrine and respiratory diseases. Since 2000, the burden of heart diseases decreased, the opposite is true for mental diseases, nervous and endocrine.