

Multiple causes of death

Marie-Pier Bergeron Boucher Associate professor, CPop, University of Southern Denmark (SDU) 21/05/2025

Presented in collaboration with Cosmo Strozza and Elizaveta Ukolova from CPop, SDU



















1. Introduction

Why and from what do we die?

Relates to how long we can live

Help finding ways to save lives

Inform on the burden of specific diseases in a population



Historical perspective

Causes of death, European Region (WHO), 1980

The estimated annual number of deaths from each cause. Estimates come with wide uncertainties, especially for countries with poor vital registration¹.



Causes of death, European Region (WHO), 2021

Our World in Data Our World in Data

The estimated annual number of deaths from each cause. Estimates come with wide uncertainties, especially for countries with poor vital registration¹.

on	Cardiovascular diseases				3.92 million
	Cancers			2.20 million	
	COVID-19		1.63 million		
	Dementia	494,000			
	Digestive diseases	442,000			
	Chronic respiratory diseases	390,000			
	Lower respiratory infections	220,000			
	Kidney diseases	206,000			
	Diabetes	205,000			
	Suicide	121,000			
	Parkinson's disease	90,700			
	Road injuries	70,700			
	Alcohol use disorders	55,500			
	Neonatal disorders	31,600			
	HIV/AIDS	31,500			
	Homicide	30,200			
	Drug use disorders	21,900			
	Diarrheal diseases	19,000			
	Tuberculosis	18,000			
	Drowning	17,600			
	Heat (hot and cold exposure)	14,100			
	Fire	13,100			
	Nutritional deficiencies	11,700			
	Poisonings	8,290			
	Meningitis	4,700			
	Maternal disorders	1,120			
	Conflict and terrorism	769			
	Acute hepatitis	736			
	Natural disasters	420			
	Measles	23.6			
	Malaria	0.00			
3Y	Data source: IHME, Global Burde	en of Disease (2024)		OurWorldinData.org/causes-of-de	eath CC BY

1. Civil Registration and Vital Statistics system A Civil Registration and Vital Statistics system (CRVS) is an administrative system in a country that manages information on births, marriages, deaths and divorces. It generates and stores 'vital records' and legal documents such as birth certificates and death certificates.

📄 You can read more about how deaths are registered around the world in our article: How are causes of death registered around the world?

1. Civil Registration and Vital Statistics system A Civil Registration and Vital Statistics system (CRVS) is an administrative system in a country that manages information on births, marriages, deaths and divorces. It generates and stores 'vital records' and legal documents such as birth certificates and death certificates.

📄 You can read more about how deaths are registered around the world in our article: <u>How are causes of death registered around the world?</u>



We die once, but from how many causes?

Causes of death statistics often only show the underlying cause of death. But...

- Multiple causes can contribute to one death
- Only looking at one cause can downplay the roles of other diseases in the mortality process
- Can hide the mortality burden of specific diseases in a population.



Medical Certificate of Cause of Death

Time interval between onset and death

PART I

Disease or condition directly leading to death

Antecedent causes

The conditions, if any, giving rise to the above cause, with the underlying condition stated last

a.	immediate (or direct) cause of death	due to (or as a consequence of) the next listed condition	
b. c.	- intermediate causes	due to (or as a consequence of) the next listed condition	
d.] e.	underlying cause of death	the cause listed last	

PART II

Other significant conditions contributing to the death, but not related to the disease or condition causing it

other contributory causes

FIGURE 1. Layout of a standard international form of Medical Certificate of Cause of Death.



How many causes?



Source: https://mcod.web.ined.fr/wiki/Accueil



8 | Multiple causes of death



How many causes? Example for the U.S.



Source: https://www.nber.org/research/data/mortality-datavital-statistics-nchs-multiple-cause-death-data



Mortality underestimation with underlying approach



Source: Fedeli, U., Zoppini, G., Goldoni, C. A., Avossa, F., Mastrangelo, G., & Saugo, M. (2015). Multiple causes of death analysis of chronic diseases: the example of diabetes. Population health metrics, 13, 1-10.

Mortality underestimation with underlying approach Alzheimer and dementia

Figure 2

Crude mortality rate from Alzheimer's disease as underlying and contributing



400

Source: Multiple-Cause-of-Death file, 2004 to 2011.

Source: Park, J. (2016). Mortality from Alzheimer's disease in Canada: A multiple-cause-of-death analysis, 2004 to 2011. Statistics Canada. Adair, T., Temple, J., Anstey, K. J., & Lopez, A. D. (2022). Is the rise in reported dementia mortality real? Analysis of multiple-cause-of-death data for Australia and the United States. American Journal of Epidemiology, 191(7), 1270-1279. 1 | Multiple causes of death

11



Mortality underestimation with underlying approach Sepsis



Source: McPherson, D., Griffiths, C., Williams, M., Baker, A., Klodawski, E., Jacobson, B., & Donaldson, L. (2013). Sepsis-associated mortality in England: an analysis of multiple cause of death data from 2001 to 2010. BMJ open, 3(8), e002586.;

Fedeli, U., Piccinni, P., Schievano, E., Saugo, M., & Pellizzer, G. (2016). Growing burden of sepsis-related mortality in northeastern Italy: a multiple causes of death analysis. *BMC infectious diseases*, *16*, 1-6.



Fig. 1 Deaths from sepsis as the underlying cause (UCOD), and mentioned anywhere on the death certificate (multiple causes, MCOD): trends in age-standardized rates per 100,000 population (standard = regional population in 2008) among male and female residents of the Veneto Region (Italy), 2008 to 2013

Mortality underestimation with underlying approach

Cardiovascular diseases

Figure 1 Age-standardised mortality rates for acute myocardial infarction (AMI), other ischaemic heart disease and heart failure from 1995 to 2010 for the population aged 35 years and over.

Source: Rahimi, K., Duncan, M., Pitcher, A., Emdin, C. A., & Goldacre, M. J. (2015). Mortality from heart failure, acute myocardial infarction and other ischaemic heart disease in England and Oxford: a trend study of multiple-cause-coded death certification. J Epidemiol Community Health, 69(10), 1000-1005.



Association between causes



Source: Egidi V., Salvatore M. A., Rivellini G., & D'Angelo S. (2018). A network approach to studying cause-of-death interrelations. *Demographic Research*, 38, 373-400

14 | Multiple causes of death



Take home message

The underlying causes of death only represent the tip of the iceberg!

Multiple causes of death analysis can better capture the role of specific diseases in the process leading to death!



2. Accuracy of multiple causes of death

Research questions

Are the MCoD data representative of end of life health conditions?

• NO!

- Do they better represent the chain of events leading to death?
 - MAYBE!



Data: Danish registers

Cause of death register

- Including all information on leading cause of death, contributing causes, and co-causes
- Register of chronic diseases
 - Including individuals diagnosed with: COPD, dementia, and diabetes



Data: Study population

Danish population diagnosed with a chronic condition from 2010 who are at least 50 years old:

Sex

Birth date

- Date (and age) at diagnosis
- Date (and age) at death
- Cause of death (1.a-1.d, 2.1-2.4)



Methods: Descriptive analysis

- Exploratory analysis to investigate:
 - Number of times (%) each chronic disease appears on the death certificate (in any position), both for the whole study population and only for those with 1 year elapsed between diagnosis and death
 - Location of the chronic disease on the death certificate (%), for those who have the chronic disease on the death certificate
 - Number of deaths (%) by causes of death, for those who have the chronic disease on the death certificate



Methods: Descriptive analysis

Multiple decrement life tables computed by:

Sex

- Period: 2010-11 to 2018-19
- Chronic disease: COPD, dementia, and diabetes
- Cause of death: Human Cause of Death Database (HCD), 17 categories



Descriptive results dementia - I

Total st	udy populatio	n	Subsample of t from	hose died with m diagnosis	nin a year
Has dementia	n	%	Has dementia	n	%
FALSE	20054	44,8	FALSE	7590	59,3
TRUE	24665	55,2	TRUE	5207	40,7
Placement on death certificate	n	%	Placement on death certificate	n	%
1.a	5323	21,6	1.a	759	14,6
1.b	2694	10,9	1.b	482	9,3
1.c	779	3,2	1.c	166	3,2
1.d	3776	15,3	1.d	615	11,8
2.1	8752	35,5	2.1	2152	41,3
2.2	2300	9,3	2.2	696	13,4
2.3	745	3,0	2.3	238	4,6
2.4	271	1,1	2.4	92	1,8



Proportion of deaths among those with dementia by three leading causes of death, sex, year





Descriptive results dementia - II

Among those with dementia somewhere in the death certificate						
CoD group	CoD name	n	%			
1	Infectious diseases	263	28,6			
2	Neoplasm	1598	34,8			
3	Diseases of blood	51	31,7			
4	Endocrine diseases	446	34,9			
5	Mental disorders	10480	98,3			
6	Nervous system diseases	5944	84,0			
7	Hearth diseases	2111	39,6			
8	Cerebrovascular diseases	1387	39,4			
9	Other circulatory diseases	175	35,9			
10	Acute respiratory diseases	95	5,2			
11	Other respiratory diseases	883	34,0			
12	Digestive system diseases	435	34,0			
13	Skin and musculoskeletal diseases	85	32,7			
14	Genitourinary and precnancy diseases	146	18,9			
15	Perinatal and congenital	48	50,0			
16	External causes	514	48,2			
17	Ill-defined causes	4	0,1			



Descriptive results diabetes - I

Total st	udy populatio	on	Subsample of t fro	hose died wit m diagnosis	hin a year
Has diabetes	n	%	Has diabetes	n	%
FALSE	17381	85,9	FALSE	3340	86,8
TRUE	2855	14,1	TRUE	507	13,2
Placement			Placement		
on death certificate	n	%	on death certificate	n	%
1.a	6	0,2	1.a	15	3,0
1.b	62	2,2	1.b	13	2,6
1.c	72	2,5	1.c	16	3,2
1.d	111	3,9	1.d	243	47,9
2.1	1287	45,1	2.1	146	28,8
2.2	866	30,4	2.2	60	11,8
2.3	359	12,6	2.3	14	2,8
2.4	90	3,2	2.4		

25

Proportion of deaths among those with diabetes by three leading causes of death, sex, year





Descriptive results diabetes - II

Among those with diabetes somewhere in the death certificate					
CoD group	CoD name	n	%		
1	Infectious diseases	51	11,1		
2	Neoplasm	679	9,5		
3	Diseases of blood	16	18,2		
4	Endocrine diseases	498	36,7		
5	Mental disorders	102	12,8		
6	Nervous system diseases	81	13,3		
7	Hearth diseases	544	17,0		
8	Cerebrovascular diseases	179	15,6		
9	Other circulatory diseases	49	15,2		
10	Acute respiratory diseases	70	11,7		
11	Other respiratory diseases	321	16,6		
12	Digestive system diseases	154	16,3		
13	Skin and musculoskeletal diseases	15	12,3		
14	Genitourinary and precnancy diseases	46	15,3		
15	Perinatal and congenital	4	20,0		
16	External causes	46	12,9		
17	Ill-defined causes	•	<u> </u>		



Preliminary take home message

MCoD data cannot be used as proxy of individual's health conditions at the end of life

At most half of the times (dementia) the chronic disease appears somewhere in the death certificate

MCoD seem to be suitable for better understanding the chain of events leading to death

- Looking at specific causes of death, associated with the chronic disease, it seems that the appearance rate is much higher
- This is however not the case for diabetes





- Investigate empirically whether age at diagnosis, age at death, time between diagnosis and death, cause of death (...) influence whether the chronic disease appears on the death certificate and where
- Look deeper into the MDLT results: compute confidence intervals to highlight differences between causes and over time
- Analyze cancer data and hospitalizations caused by health shocks (e.g., strokes)



3. Cause diversification

Diversification in causes of death

- Shift from a few major causes of death towards more diverse ("smaller") causes of death
- Causes of death profile is becoming increasingly complex
- Lead to lower predictability of causes of death
- Lead to more fragmented effort to reduce mortality
- But, cause diversity are often analysed based on the underlying cause only

How to estimate MCoD diversity

- Number of causes
- Relative abundance of causes
 - Diversity measures (e.g., Simpson index and Shannon entropy)
 - Are causes equally contributing to diversity or should the UCD be more important?

We came up with a framework to estimate MCoD diversity accounting for all aspects of diversity. All indicators proposed can be decomposed into constituent parts, so we can better understand differences.

Number of causes



Number of causes – Decomposition, 2006 - 2019

	C			
	changes in age distribution	changes in UCD distribution	Increase in number of causes across ages and UCD	Total
Denmark	0.002	-0.024	0.240	0.217
France	-0.001	-0.031	0.127	0.095
United States	-0.004	0.023	0.088	0.107



Relative abundance – All causes contributes to diversity





Relative abundance – All causes contributes to diversity - Decomposition





Relative abundance – UCD-centric





Relative abundance – UCD-centric – Decomposition 2006-2019

	Contribu		
	changes in UCD distribution	Changes in MCoD diversity for each UCD	Total
Denmark	0.010	0.011	0.021
France	0.004	0.004	0.008
United States	0.010	0.004	0.014



Take home message

Causes of death profile is becoming increasingly complex across countries due to both

- Increase in the number of causes
- Increase in the complexity of the relative abundance of causes
- Harder to keep improving life expectancy?
- Harder to predict cause-specific mortality?

4. Competing causes

Competing risk

Throughout life, individuals are exposed to multiple risks, where the occurrence of one can prevent the others.

This is known as competing risks.



Competing causes of death

What is the probability to die from one cause (UCD) before another?

We do pairwise comparison across 10 causes!



UCD analysis only – Diseases of the circulatory system first





MCoD analysis – Diseases of the circulatory system first





MCoD analysis – Diseases of the nervous system first





More to come...

- Cross-countries comparison
- Comparing results with diseases history



5. Cause association

Cause of death association indicator, 2010







Observed number of deaths with both diseases is more than 1.5 times higher than expected, if both diseases were independent Otherwise





Cause of death association indicator, 2010



Aim: go beyond interactions → model mechanism of interplay Focus on contributory causes of death recorded in Part 2 of the death certificate RQ: Are contributory causes of death recorded in Part 2 of the death certificate mediators of chains of morbid events leading to death?



Aim: go beyond interactions \rightarrow model mechanism of interplay Focus on contributory causes of death recorded in Part 2 of the death certificate RQ: Are contributory causes of death recorded in Part 2 of the death certificate mediators of chains of morbid events leading to death?



Aim: go beyond interactions \rightarrow model mechanism of interplay Focus on contributory causes of death recorded in Part 2 of the death certificate RQ: Are contributory causes of death recorded in Part 2 of the death certificate mediators of chains of morbid events leading to death?

Attribution process



Result: Best models for leading triads of diseases

53

UCD CC non-U		non-UCD	Model	Pathway	AF	Diff. 1	Diff. 2
Females, age 60-79	·						
COPD	Hypertension	Respiratory failure	6	6	0.67	-0.50	-0.38
COPD	Congestive heart failure	Respiratory failure	3	4	0.57	-0.35	-0.33
Acute myocardial infarction	Hypertension	Ischemic heart disease	2	5	0.64	-0.33	-0.33
Ischemic heart disease	Hypertension	Cardiac arrest	3	4	0.51	-0.18	-0.15
Ischemic heart disease	Diabetes mellitus	Hypertensive heart disease	5	2	0.56	-0.33	-0.18
Ischemic heart disease	COPD	Congestive heart failure	3	4	0.53	-0.40	-0.19
Ischemic heart disease	Hypertension	Congestive heart failure	3	4	0.59	-0.42	-0.33
Ischemic heart disease	Chronic kidney disease	Congestive heart failure	1	4	0.57	-0.43	-0.31
Ischemic heart disease	Diabetes mellitus	Congestive heart failure	3	4	0.41	-0.15	-0.09
Acute myocardial infarction	Diabetes mellitus	Ischemic heart disease	3	4	0.71	-0.57	-0.41
Males, age 60-79							
Acute myocardial infarction	Hypertension	Ischemic heart disease	2	5	0.60	-0.34	-0.29
Ischemic heart disease	Diabetes mellitus	Hypertensive heart disease	5	2	0.52	-0.05	-0.20
Ischemic heart disease	Hypertension	Cardiac arrest	1	6	0.63	-0.28	-0.03
Ischemic heart disease	Chronic kidney disease	Congestive heart failure	1	4	0.59	-0.46	-0.32
Ischemic heart disease	Hypertension	Congestive heart failure	2	5	0.59	-0.33	-0.02
Ischemic heart disease	COPD	Congestive heart failure	1	4	0.56	-0.42	-0.19
Acute myocardial infarction	Diabetes mellitus	Ischemic heart disease	4	5	0.96	-0.92	-0.60
Ischemic heart disease	Diabetes mellitus	Congestive heart failure	5	5	0.70	-0.43	-0.37
Ischemic heart disease	Diabetes mellitus	Cardiac arrest	5	5	0.70	-0.41	-0.40
Ischemic heart disease	Atrial fibrillation and flutter	Congestive heart failure	1	4	0.69	-0.54	-0.42

Result: Best models for leading triads of diseases

54

UCD	CC	non-UCD	Model	Pathway	AF	Diff. 1	Diff. 2
Females, age 80 and older							
Ischemic heart disease	Hypertension	Congestive heart failure	3	4	0.61	-0.43	-0.34
Ischemic heart disease	Atrial fibrillation and flutter	Congestive heart failure	1	4	0.60	-0.45	-0.32
Ischemic heart disease	Chronic kidney disease	Congestive heart failure	1	4	0.57	-0.40	-0.32
Ischemic heart disease	Hypertension	Cardiac arrest	2	5	0.64	-0.33	-0.04
Acute myocardial infarction	Hypertension	Ischemic heart disease	2	5	0.70	-0.41	-0.35
lschemic heart disease	COPD	Congestive heart failure	1	4	0.51	-0.38	-0.22
Atrial fibrillation and flutter	Hypertension	Congestive heart failure	3	4	0.75	-0.60	-0.39
Ischemic heart disease	Dementia	Cardiac arrest	6	6	0.59	-0.21	-0.22
Ischemic heart disease	Dementia	Congestive heart failure	2	5	0.74	-0.54	-0.42
COPD	Congestive heart failure	Respiratory failure	3	4	0.55	-0.37	-0.30
Males, age 80 and older							
Ischemic heart disease	Atrial fibrillation and flutter	Congestive heart failure	1	4	0.54	-0.40	-0.19
Ischemic heart disease	Chronic kidney disease	Congestive heart failure	1	4	0.49	-0.34	-0.22
Ischemic heart disease	Hypertension	Congestive heart failure	2	5	0.63	-0.39	-0.06
Ischemic heart disease	COPD	Congestive heart failure	1	4	0.47	-0.29	-0.10
Ischemic heart disease	Hypertension	Cardiac arrest	2	5	0.57	-0.26	-0.09
Acute myocardial infarction	Hypertension	Ischemic heart disease	2	5	0.65	-0.32	-0.31
Ischemic heart disease	Diabetes mellitus	Congestive heart failure	2	5	0.66	-0.51	-0.35
Ischemic heart disease	Atrial fibrillation and flutter	Cardiac arrest	2	5	0.62	-0.28	-0.19
Ischemic heart disease	Dementia	Congestive heart failure	2	5	0.84	-0.69	-0.53
COPD	Congestive heart failure	Respiratory failure	3	4	0.57	-0.39	-0.31

Take home message

Results suggested that CC in Part 2 are integral components of the trains of morbid events leading to death. **Three broader categories** of roles that CCs in Part 2 can play in the lethal process can be distinguished: 1. Some act as mediators in the chain of morbid events leading to death (atrial fibrillation and flutter, heart failure, COPD, chronic kidney disease).

2. Others do not exhibit any interaction with the conditions listed in Part 1 (dementia).

3. Additionally, as demonstrated by several models involving contributory diabetes, they can even play a role in the development of UCDs.

Furthermore, for certain diseases—particularly hypertension and diabetes—the interplay between diseases might be age-dependent, with older age groups showing lower levels of synergy within triads.



6. Effect on mortality risks

Mortality by multimorbidity

How does risk of death by age vary by multimorbidity patterns? How this developed in the latest decade?

Data: Czech health registry data, 2014-2024

Context: Czechia has, in EU, one of the highest prevalences of self-reported multimorbidity. Czechia is one of the first countries in Eastern Europe having registry data. Czechia experienced one of the highest mortality increases during the COVID-19 pandemic.



Age-specific mortality rates by age, leading combinations of chronic diseases, Czechia, 2022-2023



Changes between 2014 and 2023 in age-specific mortality rates by age, leading combinations of chronic diseases, Czechia



Results of decomposition analysis

	Cerebrovas. dis.	COPD	Diabetes	Neoplasm
CDR 2014-2015 (‰)	95.041	36.703	41.108	85.862
CDR 2022-2023 (‰)	89.238	33.465	40.143	78.935
Difference	-5.803	-3.237	-0.965	-6.927
Rate effect	2.772	0.681	3.502	-2.820
Multimorbidity effect	-8.775	-5.548	-7.021	-8.614
Age effect	0.199	1.630	2.553	4.507
Total	-5.803	-3.237	-0.965	-6.927

Table quantifies the importance of the factors of change in mortality in subgroups living with leading chronic conditions, between 2014 and 2023.

Mortality mostly decreased. This was due to reduction in multimorbid populations after COVID-19 pandemic. The pure rate effect shows upward trend in mortality.

Take home message

Upward trend in disease prevalence during 2014-2023, but lower burden of extremely complex multimorbidity patterns (4+ diseases).

Divergent trends in mortality were observed across morbidity groups, as well as within multimorbidity groups. Generally, adding additional diagnoses was associated with increased mortality.

Between 2014 and 2023, the mortality rate declined in subpopulations with leading morbidities, most notably in those with neoplasms. However, these declines were primarily attributed to changes in multimorbidity composition, which refer to a significant decline in the proportion of individuals with complex multimorbidity. In contrast, the rate effect was positive, implying rising intensity of mortality in chronically ill people in Czechia.



Conclusion

- Pathway to death is (increasingly) complex
- But multiple causes data still undercount the number of conditions present at the end of life
- The causes can compete to be the UCD, but they also interact
- Having multiple conditions increase mortality risks
- Multiple causes of death are more informative of pathway to death, BUT...
- Looking at multi-morbidities would capture even better the burden of diseases





Thank You

Marie-Pier Bergeron Boucher, Associate professor Cosmo Strozza, Assistant professor Elizaveta Ukolova, PhD student 21/05/2025







How many causes? (US example)



Fig. 1 Proportional mortality by gender and age class from diabetes selected as the underlyir position of the death certificate: Veneto region, 2008–2010

Figure 4. Deaths with any mention of major diseases on death certificate and as underlying and associated causes among decedents aged 65 years and over, United States, 2004



*Ratio of the number of deaths with any mention of a particular condition on the death certificate to the number of deaths for which that same condition was identified as the underlying cause. SOURCE: National Vital Statistics System

Standardized ratio of multiple to underlying cause for major disease groups, 2010



68

Stan. ratio of multiple to underlying