

**Fourth meeting of the MultiCause network**

**INED, Salle Sauvy, 16&17 May, 2019**

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**Programme and abstracts**





## 4th Meeting of the MultiCause Network

**Thursday 16th May**

**9:30 - 10:00 Welcome**

**10:00 - 10:45 Session 1: Country-reports**

Chair: Aline Désesquelles (INED)

Multiple Cause of Death in the Swiss Causes of Death statistics  
*AbdulKarim Abawi, Christoph Junker*

Investigating the possibility of MCODE analysis in Russia  
*Sergey Timonin, Elena Papanova*

**10:45 - 11:00 Guidelines for R programmes for the computation of the  
Standard MCODE indicators** (*Arnaud Bringé, INED*)

**11:00 - 11:15 Coffee break**

**11:15 - 12:45 Session 2 : From the 10th to the 11th ICD**

Chair: France Meslé (INED)

Multiple causes of death and the Eleventh Revision of the International Classification of  
Diseases (ICD-11)  
*Robert N. Anderson*

Explorative multiple cause analysis in view of Iris Decision Tables transition to ICD-11  
*Daniele De Rocchi, Vincenzo Della Mea, Francesco Grippo, Simone Navarra, Chiara Orsi, Stefanie  
Weber*

Impact of the implementation of ICD-10 version 2016 and Iris software: a bridge coding  
study on multiple causes statistics  
*Chiara Orsi, Simone Navarra*

Changing the history of anaphylaxis mortality statistics through the international classification of diseases ICD-11

*Luciana Kase Tanno, Pascal Demoly*

12:45 – 14:00 **Lunch**

14:00 - 14:45 **Session 3 : Country-reports**

Chair: Luisa Frova (ISTAT)

The Canadian Multiple Causes of Death Database: Overview and Potential Uses

*Baudelaire Augustin, Robert Bourbeau*

Multiple cause of death data in Japan

*Reiko Hayashi, Futoshi Ishii, Motomi Beppu, Yu Korekawa and Emiko Shinohara*

14:45-15:00 **Coffee break**

15:00 – 16:30 **Session 4: Certain diseases/conditions**

Chair: Carlo-Giovanni Camarda (INED)

Drug and Pregnancy Related Deaths: Levels, trends, and geographic differentials During the Recent Drug Epidemic. A multiple cause-of-death approach.

*Hayley Pierce, Magali Barbieri*

Use of multiple causes of death to estimate excess mortality related to liver diseases among Italian people with AIDS

*Martina Taborelli, Barbara Suligoj, Federica Toffolutti, Luisa Frova, Enrico Grande, Francesco Grippo, Marilena Pappagallo, Lucia Pugliese, Vincenza Regine, Diego Serraino and Antonella Zucchetto*

Comorbidity in alcohol-related deaths

*Markéta Pechholdová*

Alcohol-Induced Conditions as Underlying and Contributory Cause of Death: Policy Impact on the Level of the Alcohol-Related Mortality in Estonia

*Gleb Denissov, Luule Sakkeus and Liili Abuladze*

**Friday 17th May**

**09:30-11:00 Session 5 : Certain diseases/conditions**

Chair: Magali Barbieri (INED/ University of Berkeley)

What women with breast cancer die from? - A multiple cause-of-death analysis based on French death certificates

*Salomé Quetier-Parent, Aline Désesquelles*

Mortality and morbidity in hospitalized diabetics from cause of death data

*Nehama Goldberger, Ethel-Sherry Gordon, Ziona Haklai*

The cardiovascular revolution in a cohort perspective: The case of France

*Marília R. Nepomucen, Nicolas Brouard*

Demographic and clinical factors associated with having ischemic heart disease as a multiple contributing cause of death among diabetes deaths in the United States

*Maaya Kita Sugai, Shuhei Nomura, Stuart Gilmour, Gretchen A. Stevens*

**11:00 - 11:15 Coffee break**

**11:15 - 12:45 Session 6 : Certain diseases/conditions**

Chair: Viviana Egidi (Sapienza University of Rome)

Collider and Reporting Biases Involved in Analyses of Causes of Death Associations in Death Certificates: an Illustration with Cancer and Suicide

*Moussa Laanani, Vivian Viallon, Joël Coste, Grégoire Rey*

Use of multiple cause-of-death analysis for improving statistics on AIDS mortality

*Luisa Frova, Enrico Grande, Francesco Grippo, Marilena Pappagallo, Lucia Pugliese, Vincenza Regine, Diego Serraino, Barbara Suligoi, Martina Taborrelli, Saverio Virdone, Antonella Zucchetto*

Estimating global sepsis-related mortality using a multiple cause of death analysis

*Sarah C. Johnson, Katya Shackelford, Mohsen Naghav*

Prioritization of causes of death as an indicator of the perception of a disease: The case of schizophrenia from 1968 to 2015

*Raphael Petit, Nicolas Brouard, Armelle Andro*

12:45-14:00 **Lunch**

**14:00 - 15:00 Session 7 : Country-reports**

Chair: Marilena Pappagallo (ISTAT)

The MCoD analysis for Poland: how garbage codes impact the results

*Agnieszka Fihel, Karolina Madej, France Meslé*

Reassessment of the epidemiological potential of multiple-cause-of-death use in Brazil, 2015?

*Augusto Hasiak Santo, Celso Escobar Pinheiro*

Dementia related death – a study into multiple cause coding

*Peter Harteloh, Eva Krpelanova*

15:00-15:15 **Coffee break**

**15:15 – 16:45 Session 8: Multimorbidity at death**

Chair: Marketa Pechholdova (University of Economics, Prague)

Deprivation and chronic disease mortality: first analysis of multiple cause of death statistics in England, 2001-2015

*Madhavi Bajekal, Annie Campbell, Rosie Amery*

How to better visualise the frequency of multimorbidity expected at the end of life in a “standard” French GP surgery? A multiple cause-of-death analysis of end of life trajectories in mortality database.

*Sébastien Moine, Aline Désesquelles, Scott Murray*

Multi-morbidity and frailty at death: a new classification of death records for an aging world

*Francesco Grippo, Marilena Pappagallo, Luisa Frova, Antonio Salvatore, France Meslé, Viviana Egidi, Aline Désesquelles*

**16:45 - 17:15: Concluding remarks : Michel Guillot (INED)**

## ABSTRACTS

### **Multiple Cause of Death in the Swiss Causes of Death statistics**

*AbdulKarim Abawi, Christoph Junker (Swiss Federal Statistical Office FSO - Section of Population Health)*

Background: Multiple causes are registered in the Swiss Causes of Death (CoD) statistics since 1969. From 1969 to 1994, up to 3 diagnoses and since 1995 up to 5 diagnoses are coded. In 2016, 9.9% of deaths had one diagnosis, 22% two, 27% three and 38% four. In 3.3% of deaths, the diagnosis were unknown. The number of diagnoses increases with age. Currently, there is a sparse use of these codes, e.g. to look up notifiable infectious diseases, reported to the Federal Office for Public Health.

Methods: Methods to analyze multiple causes of death must first be developed. We will begin with very simple analysis, counting of diagnoses.

Results: We will present for each chapter of ICD-10, the number of final CoD and of secondary CoD. We will also investigate if the reporting of multiple CoD changes over time.

Discussion: It seems to us important to have a closer look at multiple cause coding. Which causes are independent from each other and which are closely correlated and therefore cannot be counted as two different diagnoses?

### **Investigating the possibility of MCODE analysis in Russia**

*Sergey Timonin, Elena Papanova (Higher School of Economics, Russia, Moscow)*

In Russia, unlike many European countries, there is no centralized automated system for cause-of-death coding including selection of the underlying cause of death (UCD) in accordance with the ICD guidelines. Medical death certificates are issued by physicians (doctors, pathologists, forensic experts or feldshers) who are obliged themselves to put the codes and to choose the UCD. Russian Ministry of Healthcare does not provide a direct rule whether it is necessary to code all the indicated conditions or only the underlying cause of death that leads to different practices across hospitals and regions of Russia. Medical death certificates are collected by the regional civil registration offices, and then the information is transferred to the state statistical bureau (Rosstat) with no changes.

Rosstat tabulates only underlying causes of death and publishes official statistics in accordance with the Russian Abridged Classification. However, the microdata provided by Rosstat should contain the cause-of-death codes for all conditions indicated in the medical death certificate and originally coded by the physicians (some conditions are not coded and thus not included in the Rosstat database).

Regions of Russia have separately started to implement various electronic systems for data collection and management. Some of them are aimed only to fill in the death certificates, while the others have the automated coding modules. Physicians in about half of the regions still fill in the death certificates manually. The lack of centralized automated coding systems obviously affects the quality of cause-of-death statistics and its comparability at the subnational and cross-country levels.

The aim of our study is to investigate the possibilities for conducting MCODE analysis in Russia using the Rosstat microdata (2000-2017) and several regional datasets for Moscow,

Arkhangelsk and Samara Oblasts obtained directly from the civil registration offices and/or hospitals.

### **Multiple causes of death and the Eleventh Revision of the International Classification of Diseases (ICD-11)**

*Robert N. Anderson (US National Center for Health Statistics)*

The Eleventh Revision of the International Classification of Diseases (ICD-11) was released to the public in June 2018 and will be submitted to the World Health Assembly for approval in May 2019. Substantial advancements in medicine and the science of disease have occurred over the past 30 years since the introduction of ICD-10 making a revision necessary. Substantial structural changes were needed to some chapters that could not be handled under the normal ICD-10 updating mechanism. There is also an increasing need to operate in an electronic environment and to capture more information, especially for morbidity use cases. In addition to new content and some structural changes, new features of ICD-11 include electronic authoring and maintenance, compatibility with electronic tools, web services and electronic health records, an electronic index (coding tool) and a more flexible coding structure. The new coding structure, i.e., reliance on extension codes and cluster coding to represent important detail and disease relationships, has important implications for multiple cause analysis, although the impact will depend on the extent to which these features are implemented at the national level. Because extension codes and cluster coding is not mandatory for reporting to WHO, variability in implementation at the national level may also have some effect on international comparability.

### **Explorative multiple cause analysis in view of Iris Decision Tables transition to ICD11**

*Daniele De Rocchi<sup>1</sup>, Vincenzo Della Mea<sup>1</sup>, Francesco Grippo<sup>2</sup>, Simone Navarra<sup>2</sup>, Chiara Orsi<sup>2</sup>, Stefanie Weber<sup>3</sup>*

*1 University of Udine*

*2 Italian National Institute of Statistics (ISTAT)*

*3 German Institute of Medical Documentation and Information (DIMDI)*

*as part of team of the Iris Institute evaluation project for integration of ICD11 into Iris*

In June 2018, WHO released the first version of ICD11 for preparation of implementation. For mortality, it will be necessary to adapt the software Iris, a widely used software for automated coding. The translation of decision tables, the core part of Iris describing the relationships between pairs of codes, is the main step toward the adoption of the ICD11 in mortality. With the aim to estimate time and resources to complete the translation, the Iris Institute launched a project including a preliminary multiple cause analysis to assess the most frequent and significant relationships between pairs of codes reported on death certificates. The comparison of the reported relationship with those included in decision tables and with ICD provisions will be informative for defining a priority scale of parts of the tables to be revised.

Multiple causes of deaths of about 600.000 certificates registered in Italy (2016) were analyzed, taking into account the position of each code in the sequence leading to death as reported by certifying physicians. The Chi-Square test was adopted to assess the association between pairs of codes and if those codes are reported in a causal relationship.

First step of the analysis allowed to identify the association between all pairs of codes independently from their position on the certificate. The analysis of the position allows to distinguish: 1. unidirectional causal relationship between pairs, 2. bidirectional causal relationship, 3 pairs without causal relationship. The comparison with decision tables allows to focus on most critical relationships, i.e. statistical significant relationships in certificates that are not reported in decision tables.

Further steps will include the extension of the methodology to data from other countries and the evaluation of graphic and statistical strategies for summarizing results

### **Impact of the implementation of Icd10 version 2016 and Iris software: a bridge coding study on multiple causes statistics**

*Chiara Orsi, Simone Navarra on behalf of the cause-of-death mortality group (Italian National Institute of Statistics)*

From the reference year 2016, for cause-of-death coding, the Italian National Institute of Statistics adopted the 2016 version of ICD10 and the automated coding software Iris. Until 2015, the 2009 version of ICD10 and the Mortality Medical Data System software were used. In order to document the impact of the new coding framework a bridge coding study was carried out: 63,525 deaths occurred in 2015 were re-coded with the new system.

Overall, 79% of deaths had the same underlying cause in the two systems and this agreement reached 89% at three-digit level of the ICD codes. Changes in the multiple causes statistics were also documented and interesting analogies and differences were found in comparison with the underlying cause results.

In multiple causes, a decrease of 19% of certificates mentioning infectious and parasitic diseases was observed with the new system, mostly due to the update of ICD10 which classifies septic shock among symptoms and signs (code R57.2). Consequently, the number of certificates with sepsis decreased (-31%) and those mentioning symptoms and signs increased (+7%). A 28% increase of certificates with external causes was also found, while an increase of 3% was seen in underlying cause, mostly justified by updates of indexing of cerebral injury terms. A small decrease (-3%) of diseases of the skin and a corresponding increase (+2%) of diseases of the musculoskeletal system were also observed, due to the new subcategory R26.3 (immobility) for coding many terms that were previously coded M62.3.

The changes in multiple causes are mainly due to updates of the ICD10. Some differences are attributable to changes of automated coding system. The results are useful in order to evaluate the potential impact of changing classification on multiple causes coding, as well as to explain part of the differences observed among countries using different classification systems.

### **Changing the history of anaphylaxis mortality statistics through the international classification of diseases (ICD-11)**

*Luciana Kase Tanno<sup>1,2</sup>, Pascal Demoly<sup>1,2</sup>*

*1 University Hospital of Montpellier, Montpellier, and Sorbonne Universités, UPMC Paris 06, UMR-S 1136, IPLESP, Equipe EPAR, 75013, Paris, France*

*2 WHO Collaborating Centre on Scientific Classification Support*

Rationale: In 2012, an analysis of the Brazilian mortality database (SIM) demonstrated under-notification of anaphylaxis deaths due to difficult coding under the International Classification of Diseases (ICD)-10. This work triggered academic strategic international actions supported by the Joint Allergy Academies and the ICD WHO representatives to update the classifications of allergic disorders in the ICD-11 revision, which resulted in the construction of the new “Allergic and hypersensitivity conditions” section. We proposed to analyze the capacity of the new ICD-11 framework to capture anaphylaxis deaths.

Methods: We re-estimated the anaphylaxis deaths that occurred in Brazil during the period 2008 to 2010, utilizing this new framework and the SIM that had been extracted in May 2011.

Results: We identified 639 anaphylaxis deaths, of which 95% were classified as “definitive anaphylaxis deaths”. In contrast to the 2012 publication, we found higher number of cases; moreover, all 606 definitive anaphylaxis deaths would be considered as underlying causes of death utilizing the ICD-11 revision.

Conclusion: Clearer was the effect on the accuracy reaching 95% for definite anaphylaxis when ICD11 was used. This is the first example of how the new “Allergic and hypersensitivity conditions” section of the ICD-11 can improve the quality of official vital statistics. A systematic review confirmed that other countries have been facing similar issues regarding anaphylaxis mortality recording. Data was provided to the WHO Mortality Reference Group and resulted in changes of coding rules by the addition of allergies as underlying cause of deaths in official mortality records. Immediate consequences are expected with the new classification and the logic of the ICD-11: (i) although currently anaphylaxis fatalities are perceived as rare, the reported number may increase and (ii) cases will be included in official mortality statistics, providing a global standard for comparability and, therefore, for decision-making and prevention.

### **The Canadian Multiple Causes of Death Database: Overview and Potential Uses**

*Baudelaire Augustin (Statistics Canada, Vital Statistics), Robert Bourbeau (Département de démographie, Université de Montréal)*

In Canada, in accordance with international standards, deaths are classified and tabulated by a single underlying cause. In most cases, several conditions or diseases are reported on the medical certificate of death as having caused the death. However, most research has relied on single cause mortality data to analyze disease prevalence, understand disease etiology, and examine patterns over time.

Focussing on a single underlying cause is useful for diseases and conditions that are isolated in nature, such as acute and infectious diseases. However, chronic conditions are now among the major causes of death, many of which are difficult to classify by a single cause and generally represent a number of coexisting conditions. These other conditions or diseases comprise the multiple causes of death and provide details regarding the death.

Except for specific research projects, multiple cause data have only recently become available in Canada. Since the year 2000, the Statistics Canada’s multiple cause of death dataset electronically captures underlying and additional causes reported on death certificates. The presentation will provide an overview of the collection, processing, coverage, and potential uses of multiple cause data. The co-morbidity assessment of the five

leading causes of deaths in Canada will be used as an example of how multiple cause of deaths may help to better analyze specific diseases and conditions.

### **Multiple cause of death data in Japan**

*Reiko Hayashi<sup>1</sup>, Futoshi Ishii<sup>1</sup>, Motomi Beppu<sup>1</sup>, Yu Korekawa<sup>1</sup> and Emiko Shinohara<sup>2</sup>*

*1 National Institute of Population and Social Security Research (IPSS), Japan*

*2 The University of Tokyo*

Although the cause of death statistics are available since 1899 in Japan, the original death certificate which doctors state the causes of death was only used to identify the underlying cause of death and discarded thereafter until 2003 when the online registration has started. The 5(4+1) causes of death and the time interval from onset to death information in accordance with WHO form of medical certificate of cause of death are now hand-written by doctors, digitalized at the health centers and collected at the national level. These data were requested by authors and provided in accordance with the Statistics Act and basic analysis was conducted.

As the coverage of online registration expanded gradually, the proportion of data available was 8.6% of total deaths in 2003, then increased gradually to 96.4% in 2016. Throughout the period from 2003 to 2016, almost all (at least 98.4% in 2011) death causes were written with time interval information.

We computed the standard indicators, SRMU and CDAI, for Japan following the guidelines by the MultiCause Network. We compared the indicators for 2009 with those of other countries, such as France, Italy, etc. We also analyzed the time series trends of them for Japan. Using these estimated indicators, we will exhibit the characteristics of multiple cause of death in Japan.

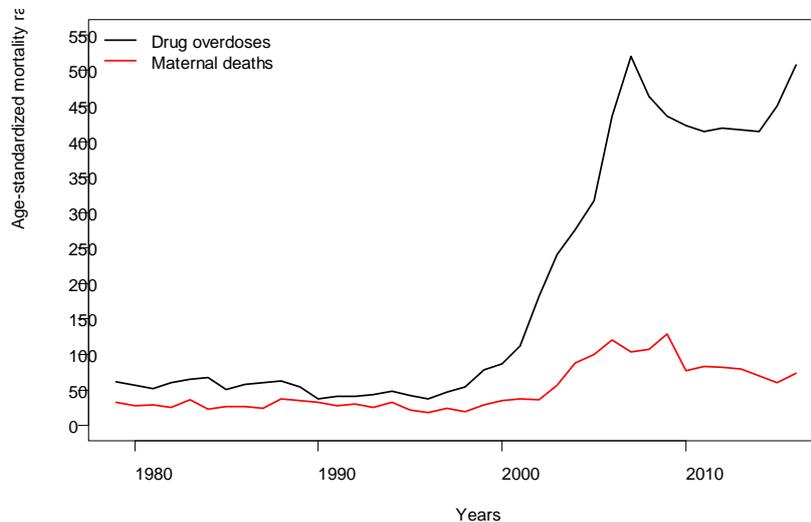
### **Drug and Pregnancy Related Deaths: Levels, trends, and geographic differentials During the Recent Drug Epidemic. A multiple cause-of-death approach**

*Hayley Pierce (Brigham Young University, USA), Magali Barbieri (Institut national d'études démographiques, Paris)*

The drug and opioid epidemic in the US is affecting women of reproductive age in a pattern very similar to adult men. The timing of the epidemic coincides with an increase in maternal mortality (Figure 1). We analyze multiple cause-of-death data with mentions of both maternal mortality and drug use (prescription and illegal) by state to assess the relationship between maternal mortality and substance abuse in the US at the regional level, thus filling a gap in knowledge. We map where maternal deaths with a mention of drug poisoning have been occurring, at what rate, and how this has changed over time using a combination of mortality data from the US National Center for Health Statistics and life tables from the United States Human Mortality DataBase ([www.usa.mortality.org](http://www.usa.mortality.org)). The series we build start in 1999, when the 10th Revision of the ICD was first implemented in the US, and 2016, the last year for which multiple cause-of-death data are available. Understanding the relationship between maternal mortality and drug abuse will contribute to a better understanding of the factors driving increasing maternal mortality in the context of the drug epidemic. The results of our study could help better target

interventions aimed at reducing the growing number of deaths of reproductive-age women in the US.

**Figure 1. Female age-standardized death rates per 1,000 women from maternal mortality and drug overdoses, United States, 1979-2016**



**Source:** Mortality Multiple Cause Files, National Center for Health Statistics, 1979-2016 (available at [https://www.cdc.gov/nchs/data\\_access/vitalstatsonline.htm](https://www.cdc.gov/nchs/data_access/vitalstatsonline.htm) and accessed September 13, 2018)

**Note:** Deaths classified under the 9<sup>th</sup> Revision of the International Classification of Diseases (i.e., ICD-9, implemented in years 1979-1998) have been allocated to ICD-10 codes using the 1996 US bridge-coding study. The ICD-10 codes identifying maternal deaths are all those in Chapter XV (O00-O99). The ICD-10 codes identifying drug overdoses are included in Chapter XX (X40-X44, X85, Y10-Y14, Y45, Y47, Y49).

### Use of multiple causes of death to estimate excess mortality related to liver diseases among Italian people with AIDS

Martina Taborelli<sup>1</sup>, Barbara Suligoi<sup>2</sup>, Federica Toffolutti<sup>1</sup>, Luisa Frova<sup>3</sup>, Enrico Grande<sup>3</sup>, Francesco Grippo<sup>3</sup>, Marilena Pappagallo<sup>3</sup>, Lucia Pugliese<sup>2</sup>, Vincenza Regine<sup>2</sup>, Diego Serraino<sup>1</sup> and Antonella Zucchetto<sup>1</sup>

<sup>1</sup> Unit of Cancer Epidemiology, Centro di Riferimento Oncologico di Aviano (CRO) IRCCS, Aviano PN, Italy

<sup>2</sup> Centro Operativo AIDS, Istituto Superiore di Sanità, Rome, Italy

<sup>3</sup> Servizio Sanità, Salute ed Assistenza, Istituto Nazionale di Statistica, Rome, Italy.

**Background.** Liver diseases, especially viral hepatitis, fibrosis and cirrhosis, and hepatic failure, have been shown to be main causes of death among people with HIV/AIDS in Italy. This study aimed to quantify the excess risk of death related to these diseases among Italian people with AIDS (PWA), as compared to non-AIDS general population (non-PWA), using a multiple causes of death (MCoD) approach.

**Methods.** We conducted a nationwide, population-based, retrospective cohort study including 7912 Italian PWA, aged 15–74 years, diagnosed between 2006 and 2015. Date of death and MCoD data (ICD-10 codes) were retrieved up to December 2015. Excess mortality,

as compared to non-PWA, was estimated using sex- and age-standardized mortality ratios (SMRs) and corresponding 95% confidence intervals (CIs).

Results. Among 2076 deceased PWA, 583 (28.1%) death certificates mentioned at least one liver disease, including 382 (18.4%) reporting viral hepatitis (ICD-10 codes: B16-B18), 370 (17.8%) non-viral liver diseases (K70-K76), and 41 (2.0%) liver cancer (C22). As compared to non-PWA, particularly higher mortality emerged for viral hepatitis (SMR=132.4; 95% CI: 119.5-146.4). Excess mortality emerged also for non-viral liver diseases (SMR=29.9; 95% CI: 27.0-33.1), including fibrosis and cirrhosis (n=266, SMR=41.8, 95% CI: 36.9-47.1), and hepatic failure (n=131; SMR=25.1, 95% CI: 21.0-29.8). The SMR for liver cancer was 11.2 (95% CI: 8.1-15.3). Finally, the SMRs were particularly elevated among younger PWA and those infected through injecting drug use.

Conclusions. The use of MCoD data allowed to evidence the extremely higher mortality related to several liver diseases among Italian PWA, as compared to non-PWA, suggesting a key role played by co-infection of HIV and hepatitis viruses B and C in this population. Study results claim for the implementation of preventive strategies for liver related diseases, starting at young age among HIV/AIDS patients and focusing on drug users.

### **Comorbidity in alcohol-related deaths**

*Markéta Pechholdová (University of Economics, Prague)*

Alcohol is largely under-estimated as a co-factor in pathological course when only underlying causes of death are taken into account. As a side effect, low death counts make it difficult to assess the substance of alcohol-related trends and differentials. The present study aims at measuring the extent of this underestimation and its possible mechanisms. We are using individual-level death records for the population of the Czech Republic since 1998. By looking at both underlying and multiple mentions, we quantify the burden the alcohol-related mortality and compare it to indirect (survey-based) methods. We also look at qualitative aspects of alcohol-related comorbidity and their relation to current epidemiological knowledge.

### **Alcohol-Induced Conditions as Underlying and Contributory Cause of Death: Policy Impact on the Level of the Alcohol-Related Mortality in Estonia**

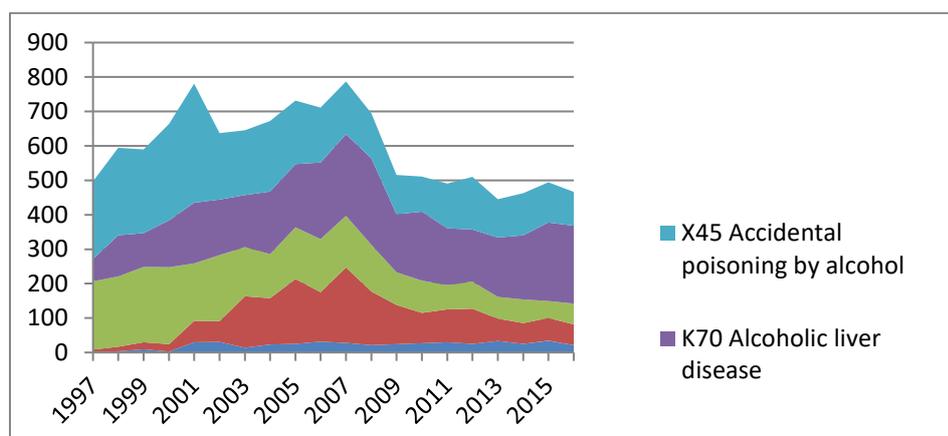
*Gleb Denissov<sup>1</sup>, Luule Sakkeus<sup>2</sup> and Lilli Abuladze<sup>2</sup>*

*1 Estonian Causes of Death Registry, National Institute for Health Development*

*2 Estonian Institute for Population Studies, Tallinn University*

The purpose of this study is to estimate burden of alcohol-induced conditions reported as contributory cause of death with Estonian medical death certificates in 1997-2018 and link variations in alcohol-related mortality to policies pursued during this period. We have estimated that the under-reporting might not be a big issue in Estonia. We use multilevel analysis to understand different policy impacts to the drop in alcohol-related mortality levels over time. We try to understand which contextual factors have affected most the levels of alcohol-related mortality: economic crisis, excise duties, bans on accessibility. Recently the excise duties have been significantly increased in Estonia, bringing about tourism for alcohol to Latvia. Although the time lag is too short we try to see whether that has increased the mortality to these causes again.

### Alcohol-related mortality in Estonia in 1997-2016 as underlying cause of death, absolute numbers.



### What women with breast cancer die from? - A multiple cause-of-death analysis based on French death certificates

Salomé Quetier-Parent (IDUP, Université Paris1), Aline Désesquelles (Institut national d'études démographiques, Paris)

In France like in most western countries, breast cancer is the most frequent cancer among women. Despite improved survival, breast cancer still ranks first among females' death due to cancer. In France, average age at diagnosis is 63 years but death often occurs many years after diagnosis. Considering this, a relevant question is: what women with breast cancer die from? We investigate this point examining the death certificates mentioning a breast cancer in France at two points in time. The decline in mortality involving breast cancer – either as underlying or contributing cause – between 2000 and 2014, and the increase in the average age at death is not associated with major changes in the content of the death certificates. Deaths with breast cancer as a contributing cause occur at older ages (82.5 years) than deaths with breast cancer as underlying cause (72.4 years). In 2014, the standardized ratio of multiple to underlying mortality rate (SRMU) was 1.19 – as compared to 1.08 for all cancers – reaching 1.40 for deaths over the age of 80. At older ages, breast cancer is thus frequently not selected as the underlying cause, which often is a disease of the circulatory system, another cancer (mainly: cancer of the respiratory and digestive organs as well as cancer of lymphoid or hematopoietic tissue) or dementia (Alzheimer's disease and other dementias). In the majority of the cases, breast cancer is the underlying cause. Four in five of these death certificates mention secondary malignant neoplasms (mainly: secondary malignant neoplasm of respiratory and digestive organs and of the lymph nodes). Other frequently mentioned complications of the breast cancer or its treatment are hepatic failure, sepsis, pulmonary embolism, pneumonia and pleural effusion.

### Mortality and morbidity in hospitalized diabetics from cause of death data

Nehama Goldberger, Ethel-Sherry Gordon, Ziona Haklai (Ministry of Health, Israel)

BACKGROUND: The mortality rate in Israel from diabetes as an underlying cause is amongst the highest in the Western world. Multiple cause of death data for a nationwide group of persons hospitalized with a diabetes diagnosis compared to the rest of the population can be

used to examine the assignment and coding of their underlying cause of death, and provide indications of trends in their mortality and morbidity.

**METHODS:** The national hospitalization database, which records hospitalizations since 1995, was checked to identify patients hospitalized until 2016 with diabetes listed as a diagnosis ("diabetic" group). These people were followed up at ages 45 and above to find deaths between 2007 and 2016, for which multiple causes of death are available.

The proportion of deaths with diabetes as underlying cause (UC) or mentioned among multiple cause (MC) was calculated for the diabetic group for the total period, by year and by cause. Standard mortality ratios (SMRs) and age adjusted mortality rates were calculated to compare the diabetic group with the rest of the population ("controls ") for underlying and multiple causes of death, and the ratio of multiple to underlying standardized rates (SRMU) were compared between groups. We checked for trends in rates and SMR's by cause over the period.

**RESULTS:** In 2016 there were approximately 300,000 people in the diabetic group aged 45 and over, 12% of the total population of that age group, increasing from 10% in 2007. Between 2007 and 2016, total deaths of the diabetic group (145,350) comprised 37% of all deaths aged 45+. Diabetes as an underlying cause was reported in 14% of the diabetic group deaths and as a multiple cause in 39% of their deaths.

Among deaths in the diabetic group, UC with frequent mention of diabetes were Alzheimer (49%), Parkinson (46%) and chronic lower respiratory diseases (41%), while least frequent mentions were with suicide (7%), septicemia (12%) pneumonitis due to solids/liquids (13%), flu/pneumonia and kidney disease (19% each).

The SMR for total deaths of the diabetic group compared to controls was 2.2 and was significantly high for most leading UCs and MCs, especially for liver disease (4.4 UC and 4.4 MC) followed by kidney disease (2.9 and 3.2, respectively) and septicemia (2.6 and 2.7). The SRMU's of leading causes of death for the diabetic group were similar but slightly higher than the control group, with the exception of hypertension, which was 22.8 for diabetics compared to 8.7 for non-diabetics.

We found a decrease in diabetes both as UC and MC in the diabetic group between 2007 and 2016, from 17% to 12% of deaths as UC and from 47% to 32% as MC. The SMRs for diabetes decreased correspondingly. However since the total SMR remained the same over the period (2.2), there was an increase in SMRs of most other UCs, in particular liver disease (from 3.3 to 4.9), cerebrovascular disease (1.8 to 2.2), Alzheimer and hypertension. SMRs for MCs increased only slightly with the exception of liver disease (71% increase).

**CONCLUSIONS:** People hospitalized with a diagnosis of diabetes were found to have a greater than two-fold risk of death compared to the rest of the population, and similarly higher risk of death from most leading causes, in particular liver disease, kidney disease, and septicemia. Rates of comorbid diseases mentioned among multiple causes were also higher, in particular hypertension.

Despite the high rate of diabetes as UC in Israel, it was the UC in a relatively small proportion of deaths of a diabetic group, and mentioned as MC in less than half of their deaths. It is not clear whether the decreasing occurrence of diabetes as UC and mention as MC over the

study period is due to changes in coding practice of physicians filling out the death certificate, or as one would hope, better treatment of diabetics leading to less diabetes related deaths.

### **The cardiovascular revolution in a cohort perspective: The case of France**

*Marília R. Nepomuceno (Max Planck Institute for Demographic Research), Nicolas Brouard (Institut national d'études démographiques, Paris)*

The cardiovascular revolution is a period marked by reductions in mortality by cardiovascular diseases. In France, deaths by cardiovascular diseases (CVD) has been declining since the 1960s, resulting in important gains in life expectancy. Between 1965 and 2005, French life expectancy increased 7.9 years, and more than 40% of this gain was due to reductions in adult mortality by cardiovascular diseases. Over this period, advances in medical technology had driven important reductions in mortality by cardiovascular disease. However, although we currently monitor gains in life expectancy due to declines in CVD mortality rates between time periods, little is still known about mortality declines by cardiovascular diseases in a cohort perspective in France. In order to investigate this, we do a longitudinal analysis by causes of death using CEPI/DC data from 1968 to 2015. Although we use a shorter historical time series than previous studies to monitor trends in mortality in France, we are adding a new approach by investigating how mortality by cardiovascular diseases has been changing across birth cohorts. We also hope to shed some light on how birth cohorts faced some period of mortality improvements by cardiovascular diseases (period shocks), and if cohort mortality by cardiovascular diseases differs between sexes. After bringing an overall picture of the cardiovascular revolution in a cohort perspective in France, we will look at how the underlying causes of main chapters interact with contributing causes in specific birth cohorts from 1968 onward, trying to calculate the Cause-of-Death Association Indicator (CDAI) in a cohort perspective. This analysis is possible because from 1968, the CépiDc technical service of the French Institute for Medical Research (INSERM) took over the treatment of causes of death treated until then by the Statistics Institute (INSEE) and coded the handwritten records of a death certificate into four causes, the underlying cause, the immediate cause, and two other causes, which contributed to the death. It is important to mention here that the codification corresponded to ICD-8 until 1978 and to ICD-9 from 1979 to 1999, and since 2000, all mentioned causes have been coded according to ICD-10. We believe that the main contribution of this study is the longitudinal analysis of cardiovascular diseases, by adding both the cohort-specific mortality pattern of CVD and the relationship between contributing causes of death to CVD “controlled” by the evolution of the CDAI index over the years.

### **Demographic and clinical factors associated with having ischemic heart disease as a multiple contributing cause of death among diabetes deaths in the United States**

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Introduction: Understanding multiple contributing causes of death (MCD) is a global public health challenge, especially for deaths with diabetes as one of MCD, which is likely to be assigned to cardiovascular disease (CVD) including ischemic heart disease (IHD) as

underlying cause of death (UCD). To help improve validity and comparability of cause-of-death statistics of diabetes, this study aimed to determine the factors for having IHD as an MCD among deaths with diabetes as the UCD (DM-UCD).

Methods: We used death records in the United States in 2012-2015, provided by World Health Organization and Centers for Disease Control and Prevention. A multivariate logistic regression analysis was conducted to identify demographic and clinical factors associated with having IHD as an MCD among DM-UCD.

Results: A total of 305,885 DM-UCD deaths were identified in the study periods, of which 116,125 (38.0%) deaths had IHD as one of MCDs. Marital status, age, race, place of death, smoking, high cholesterol, and existence of autopsy were significantly associated to having IHD as an MCD for both sexes ( $p < 0.05$ ). Obesity for men and hypertension for women were also significantly associated with having IHD as an MCD ( $p < 0.01$ ).

Conclusion: There is a need to improve the comparability of diabetes cause-of-death assignment, especially in relation to IHD. Better information on risk factors for having IHD as an MCD would allow medical officers or physicians for a more robust assessment of cause of diabetes death.

## **Collider and Reporting Biases Involved in Analyses of Causes of Death Associations in Death Certificates: an Illustration with Cancer and Suicide**

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National causes-of-death data are widely used to describe the health of populations. These data are exhaustive and collected in a standardized way across countries, allowing international comparisons. Data from death certificates include several diagnoses (causes) that could have led, according to the certifying physician, to death. These data have thus long been studied to explore causal associations between diseases. However, using data from death certificates to estimate such associations in the general population is subject to two main types of biases, which can lead to spurious findings: collider and reporting biases. Collider bias is a selection bias which is here due to restricting the study sample to dead individuals, while death is a common effect of all diseases under study. Reporting bias is an information bias due to the definition of “causes of death” –which have to potentially contribute to the death to be mentioned on the certificate–, and to the possibly incomplete filling of death certificates.

This paper aims to assess to what extent associations of causes of death estimated from individual mortality data can be extrapolated to the general population, given the aforementioned biases. First, we describe the construction of multiple causes-of-death data and the framework for the assessment of associations between causes of death and of the biases involved in such studies. We then present an illustrative application example assessing the cancer/suicide association in death certificates, and the amplitude of the biases. We conclude by discussing how to improve the use of multiple causes-of-death data.

### **Use of multiple cause-of-death analysis for improving statistics on AIDS mortality**

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The introduction of highly-active-antiretroviral-therapy (HAART) resulted in increased survival and proportion of deaths due to non-AIDS related causes among HIV-infected people. Monitoring figures on AIDS deaths is crucial for appropriate health interventions, nevertheless, estimates of AIDS mortality based on surveillance systems and cause-of-death registers significantly differ.

To investigate the reasons of these differences, we analyzed data derived from a record-linkage between the Italian cause-of-death register (RCOD) and the national AIDS surveillance register (RAIDS), using multiple cause-of-death (MCoD) information. Deaths in the RCOD were initially classified according to: i) presence/absence in the RAIDS; ii) presence/absence of ICD10 codes of HIV/AIDS (B20-B24, R75) among MCoD. In 2006-2012, 4,530 deaths in RCOD were linked to RAIDS: 80.5% (3,646) had also a mention of HIV/AIDS in the death certificate. Conversely, 3,796 deaths in RCOD were not linked to RAIDS but reported a mention of HIV/AIDS.

Successively, all deaths were re-classified as AIDS and non-AIDS according to surveillance criteria: presence of AIDS-defining conditions/indication of HIV infection. Using those criteria, among 3,796 non-linked deaths, the MCoD analysis allowed to identify 1,484 (39.1%) deaths of people with AIDS who had been not notified to RAIDS. Finally, 6,014 (4,530+1,484) AIDS deaths were identified.

Results indicate that most of the differences in figures are due to different criteria adopted in the two data sources. Cause-of-death registries tend to overestimate the total number of AIDS deaths, since in ICD10 AIDS deaths can be hardly discriminated from HIV without AIDS. Nevertheless there have been significant improvements in ICD rules in recent years not adopted in Italian RCOD until 2016. On the other side, statistics based on AIDS surveillance only, tend to underestimate the AIDS mortality. The study showed how the integration between surveillance and mortality registers, together with the use of MCoD, could help to provide more accurate estimates of AIDS mortality.

### **Estimating global sepsis-related mortality using a multiple cause of death analysis**

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Introduction: Sepsis, a life-threatening acute organ dysfunction due to dysregulated host response to infection is a critical public health problem. Though accurate quantification of sepsis mortality is critical for public health leaders, little population-based data are available on mortality due to sepsis. Additionally, sepsis is a contributing cause of death most often caused by other diseases, and analyses based on underlying causes of death underestimate the true burden.

Objectives: Given the need to more accurately quantify the sepsis burden, we estimated the global, regional, national, and, for selected locations, subnational mortality of sepsis across 195 countries and territories, and 282 underlying causes from 1990 to 2017. Methods: We identified sepsis-related deaths from ICD codes reported on the death certificates in Mexico, Brazil, USA, and Taiwan spanning 1980-2017 using a multiple cause of death analysis. Sepsis fractions were modeled using a mixed effects binomial logistic regression with health access and quality index (HAQI) as the primary continuous explanatory variable. Underlying causes of death were grouped into 17 mutually exclusive categories according to physiological relatedness in order to use a nested random effect by category and underlying cause to predict sepsis fractions for underlying causes not present in the MCoD data.

$$\text{[logit(sepsis fraction)]}_{(age, sex, location, year, cause)} = \beta_{\text{HAQI}} + \beta_{\text{sex}} + \pi_{\text{age}} + \pi_{(\text{category}, \text{underlying cause})} + \varepsilon$$

Predictions and uncertainty intervals were generated for the fraction of sepsis-related deaths by drawing 1000 times from the normal distribution of the fixed and random coefficients (separately) for each standard GBD location, age, sex, cause from 1990-2017. The number of sepsis-related deaths were estimated by multiplying sepsis fractions by deaths as estimated in GBD 2017.

Results: Over 9 million sepsis deaths were identified in the MCOD data. Globally, we estimate 11.0 million (95% UI 10.1 – 12.0) individuals died of sepsis-related deaths in 2017. The global age standardized mortality rate of sepsis related deaths has decreased from 308 per 100,000 (287-384) in 1990 to 145 (134-158) per 100,000 in 2017.

Conclusions: Analysis of MCOD data and subsequent predictions of modeled results suggest an overall decrease in sepsis-related mortality worldwide from 1990 to 2017. MCOD data is a useful tool to estimate the burden and time trends of sepsis-related deaths.

### **Prioritization of causes of death as an indicator of the perception of a disease: The case of schizophrenia from 1968 to 2015**

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When a doctor completes a death certificate, he has to choose which cause of death is the underlying from the one observed, meaning the cause of the death that is at the origin of the death process, and those that are secondary. For the passing of someone suffering from schizophrenia, the place of the cause of death schizophrenia gives us an information on the representation of the disease by the doctor. We want to question the subjectivity by analyzing the causes of death from 1968 to 2015 (Veenhoven 2007). In this case the choice made to place schizophrenia in the underlying cause or an associated cause. Therefore a direct influence of the disease on the death process or an indirect influence.

Method: The population studied is all the people that died with schizophrenia among their causes of death between 1968 and 2015. From 1968, the CEPI/DC as a new technical service of INSERM, takes over the treatment of causes of death treated until then by the INSEE and codes (according to the CIM 8 until 1978 and to the ICD 9 from 1979 to 1999), the physician's written records into four causes, the underlying cause, the immediate cause, and two other causes, which contributed to the death. Since 2000, all mentions (sometimes up to 6 or more) are coded almost automatically according to ICD 10.(Pavillon 2003, 2007). By creating two categories based on the place of the schizophrenia among the causes of death, we determine different dynamics, in terms of age at death, sex ratio or causes of death associated. Therefore we try to discuss in which measures this two categories describe a different perception of schizophrenia in the death process.

Results:

-The number of people dying with schizophrenia mentioned among their causes of death has triple from 1968 to 2015.

-The sex ratio has gone from 1:1 in 1968, for 1 women for 2 men in 2015. The distinction we decided show us differences between the two categories:

- Age at death is superior for people with schizophrenia in underlying cause of death
- This age of death has diminished since 2000 for underlying cause, while it has increased for the rest of people who died with schizophrenia among their causes of death.
- Violent death happened later for people with schizophrenia as underlying cause of death.

Conclusion: On one hand, we see a continuity by using a Multiple correspondences analysis on sex, age at death, marital status and immediate causes of death compared to the decade of death. On the other hand, the proportion of death with schizophrenia as principal cause of death has doubled from 1968 to 2015. Therefore we observe a variation of the perception of the disease in the death process.

### **The MCoD analysis for Poland: how garbage codes impact the results**

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In Poland highly trained medical doctors (coders) are responsible for coding the underlying causes of death on the basis of death certificates issued by medical doctors stating the death. The number of mentions of intermediate and immediate causes remains unlimited. In this paper, we present preliminary results of the multiple causes of death (MCoD) analysis for Poland. The MCoD dataset includes 388 thousand deaths registered in 2013 and the average number of disease entities mentioned in death certificates amounts to 3.1, varying relevantly between the age groups. More advanced analysis of MCoD in Poland encounters a serious methodological problem caused by a low quality of certification procedures. Since the introduction of the 10th revision of WHO ICD in 1997, the percentage of deaths assigned to the WHO's extended list of so-called garbage codes oscillates between 25 and 30% and displays an important and persistent territorial variation across 16 regions of Poland. In our dataset, 26% of deaths were registered with garbage code mention (single or multiple), and this percentage varies from 17 to 44 between regions.

Our objective is to investigate whether relatively high frequency of garbage codes registration affects the results of MCoD analysis. First, we explore whether garbage codes are assigned in Poland independently of health and death conditions or, on the contrary, replace some specific well-defined causes of death. Second, we present and discuss possible ways of overcoming the problem of garbage codes, which in turn could lead to the standard MCoD analysis: by focusing on selected regions where the frequency of garbage codes is relatively low, or by redistributing the deaths assigned to garbage codes among well defined causes of death. We discuss the advantages and disadvantages of each solution and present preliminary results of MCoD analysis after allowing for garbage codes.

### **Reassessment of the epidemiological potential of multiple-cause-of-death use in Brazil, 2015**

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This study aims to reevaluate the potential use of multiple-cause-of-death methodology in Brazil, its Regions and Federal Units, comparing their current settings with the ones observed in the previous study.

Multiple-causes-of-death are considered all mentions of causes and other conditions listed on the International Form of Medical Certificate of Cause of Death and are qualified as underlying cause and associated (non-underlying) causes of death. A list of 120 classes displays the most important causes of death after being processed by the Multiple Cause Tabulator.

Important fact was the incorporation to the study deaths occurred in the states of Acre, Alagoas, Amazonas, Rondônia and Roraima. In Brazil, between 2003 and 2015, by each death certificate, the crude mean number of listed causes changed from 2.81 to 3.02 and the proportion of certificates with a mode of three causes increased from 26.99% to 28.53%, mode which currently includes the entire Northeast Region. As well, all over this period, the number of ill-defined deaths reduced 56,22% and their identification as an underlying cause diminished 46.22%, values that reflect the improvement of mortality data. The discussion of the methodology use of multiple-causes-of-death contains synopses of the main national epidemiological correlated studies. Stressed the need to standardize conventions and definitions about the use of multiple-causes-of-death. The inclusion of coding critical control lists for processing causes of death in the Mortality Information System was recommended.

#### **Dementia related death – a study into multiple cause coding.**

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Abstract not available.

#### **Deprivation and chronic disease mortality: first analysis of multiple cause of death statistics in England, 2001-2015.**

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We present first-ever analysis of multiple cause of death data for England. From our separate longitudinal analysis of life expectancy with and without multimorbidity (having two or more chronic diseases concurrently) we know that multimorbidity is the norm at ages over 65, with earlier age of onset and faster accumulation of diseases prior to death in deprived populations compared to advantaged groups. To some extent the increase in the number of chronic conditions diagnosed with advancing age is reflected in the increase in the average number of causes of death mentioned in the death certificate. But paradoxically, the distinct codes used to certify death fall within an increasingly narrower range of conditions with age. It is plausible that those who delay or escape age-associated diseases to later in life, either die from a smaller cluster of lethal conditions – eg acute infections, cardiovascular disease; or that some concurrent chronic conditions are (justifiably) not considered to contribute to death; or the morbid process is less well documented in death records in the presence of complex health conditions.

We aim to better understand the dynamic interplay between diseases diagnosed over the life time and cause of death statistics at the end of life. Hence, in the first stage of our

investigation, we describe the patterns of multiple cause of death (MCoD) by age (25y and older), gender, deprivation, place of death and place of residence at time of death for all deaths registered in England. Our analysis is focused on deaths from ‘natural’ causes (ie excluding external or ill-defined underlying CoD). We present age-standardised trends in selected leading causes of death using both UCoD and MCoD (2001-2015, England) as well as standardized rate ratios by ICD chapters,

With a firmer understanding of patterns and trends in the national-level MCoD statistics, we intend in the next stage to delve further to understand the relationship between diagnosed chronic diseases and multiple causes of death for a large representative cohort of patients with linked health and vital statistics records.

### **How to better visualise the frequency of multimorbidity expected at the end of life in a “standard” French GP surgery? A multiple cause-of-death analysis of end of life trajectories in mortality database.**

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Theory/ framework: Multimorbidity is increasingly frequent in primary care within ageing populations. A better understanding of this phenomenon is pivotal to develop accountable health policies, so that the specific needs of the people are met towards the end of life.

Methods: We use cause-of-death data for all deaths at ages 20-64, 65-79 and 80+. We allocate underlying causes of death to the three main illness trajectories (“Cancer”, “Organ failure”, “Frailty”). We examine what contributing causes are reported in each trajectory.

Results: Contributing causes of death related to “Organ failure” and “Frailty” (= secondary trajectories) are more frequently associated with each primary trajectory (sorted by underlying cause of death) after 65 years.

Conclusion: Data on multimorbidity at the end of life is crucial to tailor service provision to the needs of the persons. Evidence-based educational material on early palliative care and illness trajectories may help primary care professionals, patients and caregivers better identifying and coping with these specific needs.

### **Multi-morbidity and frailty at death: a new classification of death records for an aging world**

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We present a new classification of death records based on the multiple causes of death. Our aim is to summarize the information on the death certificates according to two main criteria: multi-morbidity and frailty. With increased life expectancy, an ever-growing share of the population is living with several diseases. Multimorbid patients represent a major challenge for caregivers. Interactions between diseases make clinical care more complex, while polypharmacy increases the risk for adverse drug events and non-adherence to treatments. Epidemiologic studies have demonstrated that these patients are at higher risk of dying. As a

consequence, mortality analysis needs to extend to the description and the monitoring of the importance of multi-morbidity at death.

Identifying multimorbidity at death is not a simple count of the cases where part 2 of the death certificate is not empty. In particular, the certifying physician may have reported more than one causal process on part 1. We developed decision rules that account for this situation. In addition to multimorbidity, our classification also takes into account the presence of frailty at death, which is another symptom of aging populations. We were able to automatize these rules in a SAS procedure that can be applied to all deaths of a given country. In this study data are for Italy and France in 2014. We present results for deaths at age 50 and over, and discuss the potential and the limitations of this new approach.