

Multiple cause of death approach to analyze mortality patterns

Luisa Frova¹, Michele Antonio Salvatore², Marilena Pappagallo³, Viviana Egidi⁴

Introduction

Nowadays, chronic-degenerative diseases have a key role in mortality. Because the age of death has risen, most deaths are registered at older ages, characterised by complex pathological contexts. The death often results from the association of different diseases and conditions, therefore it is difficult to identify the single cause. As indicated by the World Health Organization, the single cause, indicated as the “underlying” cause, must be the one that “initiated the train of morbid events leading directly to death”(WHO, 1977). The pathological frame of a person who dies at a very old age often shows a group of diseases that are not individually lethal but, when considered as a whole and when interacting, lead to death. In such situations, it could be more informative to include all the diseases and conditions indicated by the certifier on the death certificate: either diseases linked with the underlying cause by causal contiguity and diseases that cannot be deemed as a direct consequence of the underlying cause.

In Italy, the health section of the death certificate provides four questions in which the doctor who is in charge of completing the form can describe the disease process from its beginning to the death; the doctor may also indicate any other relevant disease or condition.

This study aims at analysing the association between the underlying cause of death (U.C.) and the other diseases and/or conditions reported on the death certificate by the medical doctor. In particular an overview on multiple causes is given for all deaths and an in-depth analysis of the associations is carried out on circulatory diseases.

Any disease or condition that is not selected as the underlying cause of death is referred to as an associated cause of death (A.C.), while any disease or condition entered on the death certificate (as underlying or associated cause) is referred to as a multiple cause (M.C.).

Data

The data refer to year 2001 and come from the Italian National Vital Statistics Death Registry on causes of death, managed by Istat. Data on multiple causes of death, coded following the ICD9 revision, refer to the subset of certificates submitted to automated coding for which the process of identification and coding has yielded good results. Data from the Italian provinces of Trento and Bolzano are excluded from the analysis, being the deaths certificates locally coded, as well as for the external deaths and deaths under 1 year of age, whose underlying cause is manually coded.

Therefore, data on multiple causes are available for 413,167 records out of the 556,892 deaths occurred in Italy in 2001. To verify the representativeness of the group made up of all the certificates automatically coded, the only ones for which the data on multiple causes are available, an in-depth comparative analysis was carried out on the characteristics of the two populations according to gender, age, average number of certified pathologies and underlying cause of death. The results showed a strong similarity between the two groups whose profiles tended to overlap on numerous aspects. These differences, were evaluated by means of a Chi-square test applied to a sample of 3% of the deaths, obtained by means of a simple random sampling without duplication. The results showed that the total population of the deaths and the one made up of the successfully codified records are not significantly different in relation to the

¹ Italian National Institute of Statistics, Istat, Servizio Sanità e Assistenza, frova@istat.it

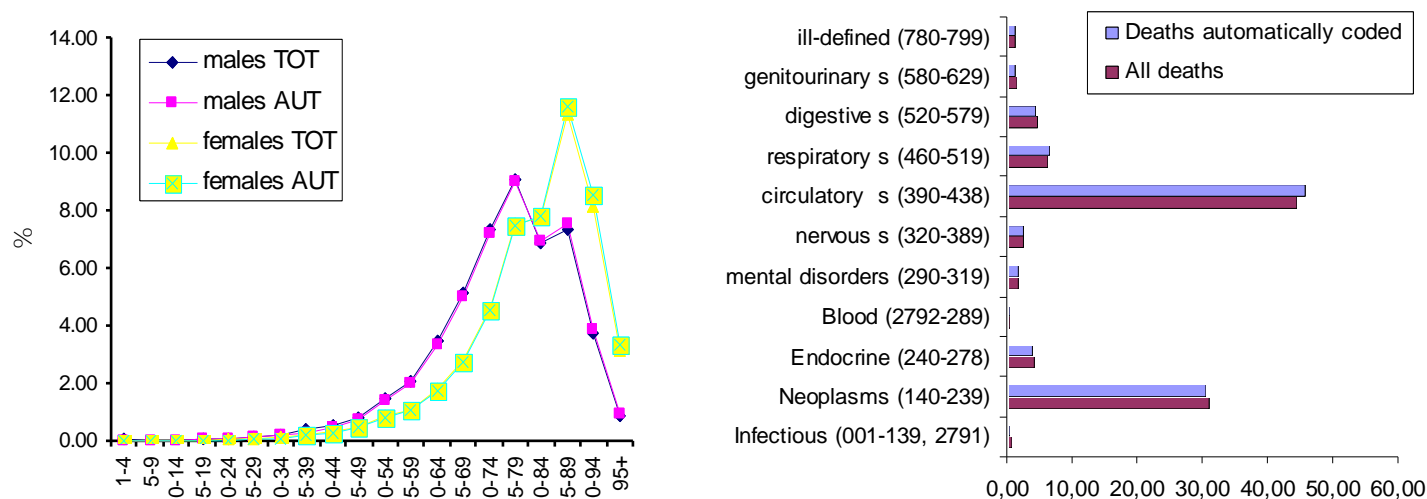
² Department of Demographic Sciences, University of Rome “La Sapienza”, antonio.salvatore@uniroma1.it

³ Italian National Institute of Statistics, Istat, Servizio Sanità e Assistenza, pappagal@istat.it

⁴ Department of Demographic Sciences, University of Rome “La Sapienza”, viviana.egidi@uniroma1.it

variables: gender, age and causes of death, but differ as far the variable “number of certified pathologies” is concerned. Such result was, nevertheless, expected as the performance of the automated coding proved to be poorer in records that presented a higher number of diseases. Nonetheless, as the analysis of the rejected medical terms revealed that the rejects presented casual and not systematic errors, the nature of such differences could be considered as the result of a mere quantitative effect (higher the number of causes, higher the probability of having at least one cause not automatically coded).

Figure 1 – Percentage distribution of deaths by age and gender and by underlying cause in overall deaths and in deaths automatically coded (Italy, 2001)



Legend: TOT=All deaths; AUT=Deaths automatically coded.

This study focuses on the 325,229 deaths of persons aged 70 and over. Fifteen different groups of causes of death were selected in order to analyse the multiple cause data file. The groups and the corresponding ICD9 codes are shown in Table 1.

Methods

To analyse the data, a descriptive analysis was first adopted, based on indicators widely used in literature, such as the average number of associated causes and the ratio between the frequency of a disease as underlying cause and the number of times the same disease occurs on death certificates (ABS 2003).

Afterwards, a cluster analysis was performed to provide a synthesis able to identify the most relevant relations between underlying and associated causes.

Finally, a study was conducted to analyse the associations between the underlying cause of death and the other diseases on the death certificate: focusing on some underlying causes that the cluster analysis highlighted as strongly discriminating in identifying the groups, multiple logistic regression models were performed to estimate adjusted and interaction odds ratios for ischaemic heart diseases, cerebrovascular diseases and other diseases of the circulatory system by age (70-79 years; 80 years and over), gender and the associated causes identified, for each underlying cause, by the cluster analysis.

Direct causes of death (e.g. cardiac arrest, respiratory arrest or coma, etc), symptoms, signs and ill-defined conditions were excluded from the multivariate analysis, as they do not provide any relevant information for studying the association among causes.

Results

Descriptive analysis

For the 325,229 death certificates related to individuals aged 70 years and over automatically coded, 1,063,994 medical terms were codified (duplications of subcategories excluded), representing 3.3 pathologies per death record on average (including the U.C). The number of diseases or conditions associated to the U.C. was usually 2 (42.5% of the death certificates) or 3 (23.6%). The average number of M.C. in a death certificate varied between 3.2 for cerebrovascular diseases and 3.7 for infectious diseases and endocrine disorders (Table 1). The only exception is represented by the deaths in which a “direct” cause or an “ill defined” cause was selected as underlying cause of death, whose average number of associated causes is particularly low (2.3 and 1.7 M.C., respectively). This is due to the high proportion of certificates without associated causes (25.3% and 41.4%, respectively) or with only one associated cause (38.3% and 53.5%, respectively).

Table 1 - Percentage distribution of all deaths over 70 years of age by number of associated causes and underlying cause of death and average number of multiple causes on death certificate

| Underlying cause | Icd 9 | Number of deaths | Number of associated causes (A.C.) (percentage) | | | | | | | Average number of M.C. |
|--------------------|-----------------------------------|------------------|--|------|------|------|------|-----|-----|------------------------|
| | | | 0 | 1 | 2 | 3 | 4 | 5 | 6+ | |
| Infectious | 001-139, 2791 | 1,487 | 0.3 | 11.6 | 38.5 | 29.0 | 13.7 | 5.2 | 1.8 | 3.7 |
| Neoplasms | 140-239 | 80,616 | 0.4 | 17.2 | 49.3 | 22.8 | 7.5 | 2.2 | 0.6 | 3.3 |
| Endocrine | 240-278 | 12,528 | 0.1 | 8.5 | 39.9 | 29.7 | 14.5 | 5.3 | 2.0 | 3.7 |
| Blood | 2792-289 | 1,508 | 0.4 | 14.8 | 38.9 | 28.0 | 12.3 | 3.5 | 2.1 | 3.6 |
| Mental | 290-319 | 6,903 | 0.4 | 18.1 | 46.3 | 23.5 | 8.6 | 2.4 | 0.7 | 3.3 |
| Nervous | 320-389 | 8,712 | 0.3 | 20.0 | 44.8 | 23.7 | 8.2 | 2.5 | 0.5 | 3.3 |
| Cerebrovascular | 430-438 | 47,958 | 1.6 | 24.6 | 41.2 | 21.8 | 7.8 | 2.2 | 0.7 | 3.2 |
| Ischaemic diseases | 410-414 | 48,526 | 1.2 | 17.4 | 41.7 | 26.4 | 9.7 | 2.9 | 0.7 | 3.4 |
| Other circulatory | 390-459 minus 430-438, 410-414 | 54,365 | 0.9 | 17.8 | 43.0 | 26.1 | 9.0 | 2.6 | 0.7 | 3.4 |
| Respiratory | 460-519 | 24,747 | 0.6 | 21.5 | 40.5 | 24.6 | 9.1 | 3.0 | 0.8 | 3.3 |
| Digestive | 520-579 | 12,992 | 0.6 | 15.5 | 39.2 | 27.1 | 12.0 | 4.1 | 1.5 | 3.5 |
| Genitourinary | 580-629 | 5,215 | 0.5 | 18.1 | 44.4 | 25.2 | 8.5 | 2.6 | 0.7 | 3.3 |
| Ill-defined | 780-799 | 3,164 | 41.4 | 53.5 | 4.2 | 0.4 | 0.2 | 0.1 | 0.1 | 1.7 |
| Direct causes | 4275, 7855, 7991, 7800 | 14,831 | 25.3 | 38.3 | 23.5 | 9.2 | 2.9 | 0.6 | 0.1 | 2.3 |
| Other causes | residuals | 1,677 | 0.1 | 12.4 | 43.6 | 27.3 | 11.9 | 3.5 | 1.3 | 3.5 |
| All causes | | 325,229 | 2.3 | 19.7 | 42.5 | 23.6 | 8.6 | 2.6 | 0.7 | 3.3 |

Legend: Label / ICD9 group: Infectious / Infectious and parasitic disease; Neoplasms / Neoplasms; Endocrine / Endocrine, nutritional and metabolic diseases, immunol. disorders; Blood / Diseases of the blood (-forming organs); Mental / Mental and behavioural disorders; Nervous / Diseases of the nervous system and the sense organs; Respiratory / Diseases of the respiratory system; Digestive / Diseases of the digestive system; Genitourinary / Diseases of the genitourinary system; Ill-defined / Symptoms, signs, abnormal findings, ill-defined causes; Direct causes / 4275=Cardiac arrest; 7855=Shock, without mention of trauma; 7991=Respiratory collapse; 7800=Coma and stupor; Cerebrovascular / Cerebrovascular diseases; Ischaemic / Ischaemic heart diseases; Other circulatory / Other diseases of the circulatory system; Other causes / Other causes.

Table 2 shows that for several causes of death mortality data per underlying cause don't always highlight the mortality burden evaluable by considering all the mentions. It also shows the ratio between the frequency of a cause as underlying and its frequency as multiple cause, an indicator that can be defined as the “degree of agreement between U.C. and M.C.”. Such indicator shows a good agreement as for the ischaemic heart diseases, the malignant tumours and the cerebrovascular diseases: when they are certified by the doctor they are selected as U.C. in 65%, 58% and 55% of the cases, respectively. However, for other groups of causes the ratio is

very low and U.C. data capture only a fraction of deaths including these conditions. Excluding the “direct” and “ill defined” causes, which are correctly low represented among the U.C., approximately 2 out of three mentions do not appear in U.C. mortality statistics for mental disorders or diseases of the nervous system or diseases of the digestive system or diseases of the respiratory system or other diseases of the circulatory system or endocrine disorders. Some other diseases that are rarely selected as U.C. are frequently mentioned in M.C: this is for the case of the infectious diseases (20%), the diseases of the genitourinary system (16%) and the diseases of the blood (15%).

Direct causes and symptoms and ill-defined conditions are very often mentioned in death certificates (274,607 out of 325,229 deaths), but they are selected as U.C. only if they are the sole causes listed.

Table 2 – Frequency of the leading causes of death over 70 years of age in Italy in 2001, using underlying cause of death and multiple causes of death statistics.

| Causes | U.C. Underlying cause of death data | M.C. Number of times the cause occurs on death certificate | U.C. as a percentage of M.C. |
|---|---|---|------------------------------------|
| Neoplasms | 80,616 | 138,329 | 58 |
| Other diseases of the circulatory system | 54,365 | 180,183 | 30 |
| Ischaemic heart diseases | 48,526 | 74,559 | 65 |
| Cerebrovascular diseases | 47,958 | 86,915 | 55 |
| Diseases of the respiratory system | 24,747 | 83,313 | 30 |
| Direct causes (cardiac arrest, shock, respiratory collapse) | 14,831 | 264,323 | 6 |
| Diseases of the digestive system | 12,992 | 38,309 | 34 |
| Endocrine, nutritional and metabolic diseases | 12,528 | 43,598 | 29 |
| Diseases of the nervous system and the sense organs | 8,712 | 24,302 | 36 |
| Mental and behavioural disorders | 6,903 | 17,780 | 39 |
| Diseases of the genitourinary system | 5,215 | 32,700 | 16 |
| Symptoms, signs, abnormal findings, ill-defined causes | 3,164 | 52,594 | 6 |
| Other causes of death | 1,677 | 10,078 | 17 |
| Diseases of the blood | 1,508 | 9,752 | 15 |
| Infectious and parasitic disease | 1,487 | 7,259 | 20 |
| All causes | 325,229 | 1,063,994 | 31 |

Analysis of the groups

Table 3 illustrates the main results of the explorative analysis carried out on the multiple causes of death of persons aged over 70.

The cluster analysis carried out on the first 10 factors⁵ drawn from the Multiple Correspondence Analysis, led to the identification of 8 groups that presented particular profiles regarding both the causes of death (underlying and associated) and the demographic characteristics. The first cluster is the most numerous one as it gathers 21.4% of all deaths. It presents a profile strongly characterised by neoplasms: 4 times the average as underlying causes, and 3.8 times the average as associated causes; 85.4% of all deaths attributed to neoplasms (82% of those mentioning neoplasms as associated causes) belong to this cluster. A higher proportion of associated causes of blood and blood-forming organs diseases are also associated to this

⁵ Those factors are identified following criterion proposed by Benzecri, that is to consider as non-insignificant all factors whose self-value is above the average self-value $1/k$, k being the number of active variables. In this application $k=23$.

profile. As regards the demographic variables, this cluster has a generally younger age structure than the average and a higher proportion of men (25% more). The second cluster (15.2% of the deaths) is even more selective as it gathers 99.2% of all deaths attributed to cerebrovascular diseases, with a percentage that is 6.5 times the average. The diseases of the nervous system, the cerebrovascular diseases, the mental disorders and, to a lesser extent, the direct causes are frequently associated to this cause. The age profile of this group is clearly older than the previous one while the female component is more present than the average. The third group (14.9%) regards the cluster of ischaemic heart diseases (95.7% of all deaths attributed to this cause belong to this cluster), which are indicated both as underlying and as associated cause, in addition to the endocrine disorders, the other diseases of the circulatory system, the respiratory and the cerebrovascular diseases. The cluster's age and gender profile is very close to the average one. The fourth cluster, the second per dimension (17.2% of deaths), has a profile characterised by a higher proportion of deaths attributable to other diseases of the circulatory system (97.6% of deaths due to these causes belong to the cluster). The associated causes include diseases belonging to the same group, the one of the respiratory and of the genitourinary systems, as well as mental disorders. The age profile is rather older and the proportion of women is relatively higher. The profile of the fifth cluster (7.6% of deaths) is clearly characterised by the diseases of the respiratory system, which are selected as underlying cause 13 times the average (99.8% of the deaths attributed to this cause are included in this group). In this case, prevail as associated causes mental disorders, diseases of the respiratory system and ischaemic heart diseases. While the age profile is older, the gender profile is characterised by a higher-than-average presence of men. The sixth group is the cluster (6.7%) of the diseases of the digestive system (100% of the deaths attributed to this cause are classified in this group), which is associated to pathologies belonging to the same chapter, to blood and blood-forming organs diseases, to diseases of the genitourinary system and to endocrine disorders. The age profile is relatively younger while the gender profile is very similar to the average one. The seventh one (13.1% of the deaths) is a cluster that gathers, both as underlying and as associated cause, all the causes that are symptoms of possible problems in the quality of the death certificate, eventually due to poor information available to the certifier. It includes the direct causes, the diseases of the nervous system, the mental disorders, selected as underlying cause of death, and the ill-defined conditions as associated causes (2.9 times the average). The cluster's age structure is older and the proportion of women is higher. The eighth group is a smaller cluster characterised by a higher proportion of deaths attributed to endocrine disorders (3.9% of the deaths and 99.9% of the deaths attributed to these causes). The associated causes are rather varied and represents, just like in the third cluster, the association between the endocrine disorders and the ischaemic heart diseases. The age profile is relatively younger, while the proportion of women is higher than the average.

Table 3: Cluster's profiles of the death certificates and ratio between the proportion of certificates with a specific characteristic in the cluster and in the overall population over 70 years of age.

| Cluster1 | Ratio | Cluster2 | Ratio | Cluster3 | Ratio | Cluster4 | Ratio |
|---------------------|-------|--------------------|-------|---------------------|-------|---------------------|-------|
| UC Neoplasms | 4.00 | UC Cerebro vascul | 6.51 | UC Ischaemic | 6.44 | UC Other circulat | 5.68 |
| AC Neoplasms | 3.84 | AC Nervous syst | 2.76 | AC Ischaemic | 2.52 | AC Respiratory syst | 1.46 |
| AC Blood | 1.81 | AC Cerebrovascular | 1.72 | AC Other circulat | 1.56 | AC Other circulat | 1.45 |
| 70-74 years | 1.77 | UC Other causes | 1.28 | AC Endocrine | 1.38 | AC Genitourinary s | 1.32 |
| 75-79 years | 1.39 | AC Mental disord | 1.27 | AC Respiratory syst | 1.35 | AC Cerebrovascular | 1.23 |
| Male | 1.25 | AC Direct causes | 1.07 | AC Cerebro vascul | 1.17 | AC Mental disord | 1.20 |
| | | 85-89 years | 1.21 | | | AC Direct causes | 1.05 |
| | | 90-94 years | 1.22 | | | 85-89 years | 1.15 |
| | | 95 + years | 1.11 | | | 90-94 years | 1.35 |
| | | Female | 1.14 | | | 95 + years | 1.56 |
| | | | | | | Female | 1.13 |
| Cluster5 | Ratio | Cluster6 | Ratio | Cluster7 | Ratio | Cluster8 | Ratio |
| UC Respiratory syst | 13.09 | UC Digestive syst | 14.95 | UC Direct causes | 7.58 | UC Endocrine | 25.55 |
| AC Mental disord | 1.89 | AC Digestive syst | 8.47 | UC Nervous syst | 7.49 | AC Ischaemic | 2.98 |
| AC Respiratory syst | 1.32 | AC Blood | 2.91 | UC Mental disord | 7.23 | AC Cerebrovascular | 2.32 |
| AC Ischaemic | 1.29 | AC Genitourinary s | 1.52 | AC Ill-defined | 2.87 | AC Endocrine | 2.32 |
| AC Direct causes | 1.17 | AC Endocrine | 1.12 | UC Other causes | 1.78 | AC Genitourinary s | 1.86 |
| AC Nervous syst | 1.10 | UC Neoplasms | 1.06 | AC Mental disord | 1.14 | AC Mental disord | 1.54 |
| 85-89 years | 1.77 | AC Direct causes | 1.05 | 85-89 years | 1.05 | UC Other causes | 1.36 |
| 90-94 years | 1.15 | 70-74 years | 1.37 | 90-94 years | 1.29 | AC Other circulat | 1.31 |
| 95 + years | 1.20 | 75-79 years | 1.19 | 95 + years | 1.65 | AC Nervous syst | 1.18 |
| Male | 1.27 | | | Female | 1.12 | 70-74 years | 1.06 |
| | | | | | | 75-79 years | 1.09 |
| | | | | | | 80-84 years | 1.10 |
| | | | | | | Female | 1.20 |

Analysis of the associations

In order to fully benefit the analytical potential of the multiple cause approach, it has been studied the mortality associated with the diseases of the circulatory system (ischaemic heart diseases, cerebrovascular diseases and “other diseases of the circulatory system”), when they are underlying causes of death. This selection has been done because these diseases represent the main causes of death in the traditional U.C.- based analysis (about 46% of all deaths of persons aged 70 and over), and they are also often indicated as associated cause (Table 3). Hence, they contribute to the risk of death even within those morbid processes whose underlying cause is a different one (Table 2).

Deaths due to ischaemic heart diseases amounted to 48,526, with 163,866 M.C. and an average of 3.4 causes per record. Excluding the ill-defined symptoms and the direct causes, the multiple causes, within this group, amounted to 122,971, with an average number of M.C. per death equal to 2.5. The cerebrovascular diseases accounted for 47,958 deaths (dropping from 153,165 to 106,618 M.C. and from an average of 3.2 to 2.2 causes per record, once the direct and the ill defined causes are removed). Besides, 182,206 M. C. were registered for the 54,365 deaths attributable to “other diseases of the circulatory system”, a figure that drops to 130,521 when considering only the “relevant” multiple causes (with an average number of causes that decreases from 3.4 to 2.4).

Three distinct logistic regression models were estimated to study the associations between the A.C. found in clusters 2, 3 and 4 and their respective underlying causes (cerebrovascular diseases, ischaemic heart diseases and “other diseases of the circulatory system”). The adjusted odds ratios (OR), as well as the most significant interactions, are shown in Table 4.

In general, the risk of identifying a specific underlying cause in the death certificate is usually higher when A.C. belong to the same group. Thus, the morbid context is in most cases homogeneous, as the diseases indicated generally belong to the same chapter of the ICD9. Therefore, by correctly applying the certification guidelines, the certifiers first describe the disease process that led to death. Nevertheless, the analysis also shows other important associations, such as the one between ischaemic heart diseases and diseases of the respiratory

system and/or diabetes, or the one between diseases of the nervous system and cerebrovascular diseases.

The probability of having an ischaemic heart disease as underlying cause of death is, in the presence of other ischaemic diseases, six times that observed when the latter are not present (OR=6.56). The odds ratio equals 3.69 for "other diseases of the circulatory system"; 2.00 for the diseases of the respiratory system; 1.98 for cerebrovascular diseases and 1.10 for endocrine disorders. As regard to the interaction effects, when among the A.C. "other ischaemic diseases" or "other diseases of the circulatory system" are included, the risk for the underlying cause to be an ischaemic disease increases: for example, it doubles when in A.C. is added an ischaemic heart disease (other than the one indicated as underlying) or one of the "other diseases of the circulatory system" to a disease of the respiratory system or to a cerebrovascular disease. Besides the circulatory group, an other important association is the one between endocrine disorders and diseases of the respiratory system. More precisely, the probability of having an ischaemic heart disease as U.C. doubles every time that in A.C. a disease of the respiratory system is added to an endocrine disorder (OR=2.22).

With regard to the deaths due to a cerebrovascular disease, the OR equals 4.44 for diseases of the nervous system, 2.66 for "other cerebrovascular diseases" and 1.69 for mental disorders. Hence, for this group, risks are higher not for the A.C. belonging to the same group as that of the U.C., but when the diseases of the nervous system are present. The latter significantly interact with both cerebrovascular diseases and with mental disorders. The risk of having a cerebrovascular disease as U.C. is 1.58 when a disease of the nervous system is added to a cerebrovascular disease other than the one indicated as underlying. The OR of having a cerebrovascular disease as U.C. is 2.77 when a disease of the nervous system is added to a mental disorders.

As observed for the ischaemic heart diseases, the OR of having as U.C. a disease classified as "other diseases of the circulatory system" is higher when the A.C. belong to the same group (2.90). It remains high when A.C. are cerebrovascular diseases (equal to 2.26), but also when belong to other chapters, such as diseases of the respiratory system (1.98), diseases of the genitourinary system (1.58) and mental disorders (1.54).

Unlike the previous two groups, the context that results from the analysis on the double interactions is much varied as it presents significant combinations of different A.C. The ORs show a strong increase every time the A.C. include "other diseases of the circulatory system" or cerebrovascular diseases. The highest odds ratios are obtained when an "other disease of the circulatory system" is added to a mental disease or to a disease of the respiratory system (OR equal to 2.22 and 2.06, respectively), or when a cerebrovascular disease is added to a disease of the genitourinary system (OR=1.97). The risk also increases when a disease of the respiratory system is added to a disease of the genitourinary system or to a mental disorder (OR=1.73 and OR=1.69, respectively).

Age and gender are significantly associated both in the cluster of "other diseases of the circulatory system" and in the one of cerebrovascular diseases. The probability of having as underlying cause "other diseases of the circulatory system" in persons aged 80 and over is almost double that in persons aged 70-79 years (OR=1.96); women, moreover, are greatly disadvantaged compared with men (OR=1.36). As regards the cerebrovascular diseases, the probability for persons aged 80 and over is clearly higher than that for persons aged 70-79 years (OR=1.79); women are even more disadvantaged (OR=1.41).

Table 4 – Logistic regression – Estimated odds ratios (OR)

| | OR | Confidence interval 95% | |
|---|------|----------------------------|------|
| Model 1 | | | |
| Response variable: UC Ischaemic heart diseases (<i>Yes/No</i>) | | | |
| Simple effects | | | |
| Gender (<i>Female vs Male</i>) | 0.95 | 0.91 | 0.98 |
| Endocrine diseases (<i>Presence/Absence</i>) | 1.10 | 1.04 | 1.16 |
| Cerebrovascular (<i>Presence/Absence</i>) | 1.98 | 1.90 | 2.08 |
| Ischaemic residual (<i>Presence/Absence</i>) | 6.56 | 6.23 | 6.92 |
| Other circulatory (<i>Presence/Absence</i>) | 3.69 | 3.55 | 3.83 |
| Respiratory (<i>Presence/Absence</i>) | 2.00 | 1.90 | 2.11 |
| Selected interaction effects: | | | |
| (Ischaemic res.+ Cerebrovascular) vs Cerebrovascular | 2.01 | 1.78 | 2.27 |
| (Other circulatory + Cerebrovascular) vs Cerebrov. | 2.16 | 2.03 | 2.30 |
| (Ischaemic res. + Respiratory) vs Respiratory | 2.02 | 1.84 | 2.22 |
| (Other circulatory + Respiratory) vs Respiratory | 2.01 | 1.89 | 2.13 |
| (Respiratory + Endocrine) vs Endocrine | 2.22 | 2.04 | 2.42 |
| (Cerebrovascular + Endocrine) vs Endocrine | 1.79 | 1.64 | 1.95 |
| Model 2 | | | |
| Response variable: UC Cerebrovascular (<i>Yes/No</i>) | | | |
| Simple effects | | | |
| Age (<i>80 years and over vs 70-79 years of age</i>) | 1.79 | 1.73 | 1.86 |
| Gender (<i>Female vs Male</i>) | 1.41 | 1.36 | 1.47 |
| Nervous (<i>Presence/Absence</i>) | 4.44 | 4.06 | 4.86 |
| Cerebrovascular residual (<i>Presence/Absence</i>) | 2.66 | 2.51 | 2.81 |
| Mental (<i>Presence/Absence</i>) | 1.69 | 1.52 | 1.88 |
| Selected interaction effects: | | | |
| (Nervous + Cerebrovascular res.) vs Cerebrovascular res. | 1.58 | 1.41 | 1.78 |
| (Nervous + Mental) vs Mental | 2.77 | 2.32 | 3.32 |
| Model 3 | | | |
| Dependent variable: UC Other diseases of the circulatory system (<i>Yes/No</i>) | | | |
| Simple effects | | | |
| Age (<i>80 years and over vs 70-79 years of age</i>) | 1.96 | 1.89 | 2.04 |
| Gender (<i>Female vs Male</i>) | 1.36 | 1.32 | 1.40 |
| Respiratory (<i>Presence/Absence</i>) | 1.98 | 1.87 | 2.09 |
| Other circulatory residual (<i>Presence/Absence</i>) | 2.90 | 2.77 | 3.03 |
| Genitourinary (<i>Presence/Absence</i>) | 1.58 | 1.48 | 1.69 |
| Cerebrovascular (<i>Presence/Absence</i>) | 2.26 | 2.09 | 2.44 |
| Mental (<i>Presence/Absence</i>) | 1.55 | 1.36 | 1.75 |
| Selected interaction effects: | | | |
| (Other circulatory res. + Mental) vs Mental | 2.22 | 1.99 | 2.48 |
| (Other circulatory res. + Respiratory) vs Respiratory | 2.06 | 1.93 | 2.20 |
| (Cerebrovascular + Genitourinary) vs Genitourinary | 1.97 | 1.75 | 2.22 |
| (Respiratory + Genitourinary) vs Genitourinary | 1.73 | 1.59 | 1.89 |
| (Respiratory + Mental) vs Mental | 1.69 | 1.50 | 1.91 |

Conclusion

The multiple cause approach offers new and valuable possibilities to study more in-depth the mortality. By reconstructing the complete pathological picture at the time of death, it is possible to highlight diseases or conditions that, though having contributed in the risk of death, are rarely indicated as the underlying cause of death. This is the case of relevant diseases or chronic

conditions certified as complications but which are often not fatal: the multiple cause data represent the only statistical source to evaluate how diseases contributed to death. Actually this study has shown a very low “degree of agreement” between underlying cause and multiple causes for some diseases such as disease of the blood (15%), diseases of the genitourinary system (16%), infectious diseases (20%), but also for respiratory system (30%), diseases of the nervous system (36%) and mental disorders (39%).

Moreover, the multiple cause approach enables to study the relevance of some associations among causes that could alter the risk of death, increasing the probability of dying for a specific disease. An example is the association found between cerebrovascular diseases (as underlying cause) and diseases of the nervous system (as associated cause).

Nevertheless, some critical elements still persist, especially regarding the accuracy and exhaustiveness of the data reported in the death certificates by medical doctors⁶. Although the quality indicators generally adopted reveal a progressive improvement (for example, the ratio of deaths whose underlying cause is due to “symptoms, signs or other ill-defined disease conditions” has decreased in Italy more than in other countries), the multiple cause approach offers a different and less reassuring perspective. Certifiers who under-evaluate the importance of the certification activity, provide data full of gaps or poorly informative. Through the analysis of the multiple-causes of death it is possible to verify that, still now, it is rather frequent to find death certificates that bear irrelevant data (e.g. “heart arrest”), describe symptoms or indicate ill-defined categories (such as senility), contain improbable disease sequence.

These aspects, that are consequences of badly filled certificates, could diminish the informative potential of the multiple cause, as well of the underlying cause. Despite the undeniable progresses made so far, much needs yet to be done to increase the sensitivity and preparation of physicians in this sector.

References

ABS - AUSTRALIAN BUREAU OF STATISTICS (2003), 3319.0.55.001 - Multiple Cause of Death Analysis, 1997-2001, Release, 22/07/2003, www.abs.gov.au.

CHAMBLEE R.F., EVANS M.C. (1982), “New dimensions in cause of death statistics”, *Am J Public Health* 72(11): 1265-1270.

COSTE J., BERNARDIN E., JOUGLA E. (2006), “Patterns of mortality and their changes in France (1968-1999): insights into the structures of diseases leading to death and epidemiological transition in an industrialised country”, *J.Epidemiol. Community Health* 60(1): 945-955.

DESEQUELLES A., MESLE F. (2004), “Intéret de l’analyse des causes multiples dans l’étude de la mortalité aux grands ages: l’exemple français”, *Cahiers québécois de démographie* 33(1): 83-116.

EGIDI V., FALLONE R., FROVA L., PAPPAGALLO M. (2006), “Multiple Cause of Death: Preliminary Results of the Analysis of the Italian Mortality in Older Ages”, *Atti della XLIII Riunione Scientifica della SIS*, Torino.

GOLDACRE M.J., ROBERTS S.E., GRIFFITH M. (2003), “Multiple cause coding of death from myocardial infarction: population-based study of trends in death certificate data”, *Journal of Public Health Medicine* 25: 69-71.

GOODMAN R.A., MANTON K.G., NOLAN JR T.F. *et al.* (1982), “Mortality data analysis. Using a multiple-cause approach”, *JAMA* 247(6): 793-96.

HANSELL A.L., WALK J.A., SORIANO J.B. (2003), “What do chronic obstructive pulmonary disease patients die from? A multiple cause coding analysis”, *Eur Respir J.* 22(5): 809-14.

⁶ Because such aspect was so much surveyed, Eurostat financed a project called “Preparation of a EU training package on certification of causes of death” to prepare general instruments that would improve the quality and comparability of the certification of causes of death in Europe.

- ISRAEL R.A., ROSENBERG H.M., CURTIN L.R.(1986), “Analytical Potential for Multiple Cause-of-Death Data”, *American Journal of Epidemiology* 124(2): 161-79.
- LINDAHL B.I.B., JOHANSSON L.A. (1994), “Multiple cause-of-death data as a tool for detecting artificial trends in the underlying cause statistics: a methodological study”, *Scandinavian Journal of Social Medicine* 22(2): 145-158.
- MACKENBACH J.P., KUNST A.E., LAUTENBACH H. *et al.* (1997), “Competing causes of death: A Death Certificate Study”, *Journal of Clinical Epidemiology* 50(10): 1069-1077.
- MACKENBACH J.P., KUNST A.E., LAUTENBACH H. *et al.* (1999), “Gains in life expectancy after elimination of major causes of death: revised estimates taking into account the effect of competing causes”, *Journal of Epidemiology and Community Health* 53(1): 32-37.
- MANNINO D.M., FORD E., GIOVINO G.A., THUN M. (1998), “Lung cancer deaths in the United States from 1979 to 1992”, *International Journal of Epidemiology* 27: 159-166.
- MANT J., WILSON S., PARRY J. *et al.* (2006), “Clinicians didn't reliably distinguish between different causes of cardiac death using case histories”, *Journal of Clinical Epidemiology* 59(8): 862-867.
- MANTON K.G., BAUM H.M. (1984), “CVD mortality, 1968-1978: observations and implications”, *Stroke* 15(3): 451-457.
- MC COY L., REDELINGS M., SORVILLO F., SIMON P. (2005), “A Multiple Cause-of Death Analysis of Asthma Mortality in the United States, 1990-2001”, *Journal of Asthma* 42: 757-763.
- MOSS M., MANNINO D.M. (2002), “Race and Gender Differences in Acute Respiratory Distress Syndrome Deaths in the United States: An Analysis of Multiple-Cause Mortality Data (1979-1996)”, *Critical Care Med*, 30(8): 1679-1685.
- NAM C.B. (1990), “Mortality Differentials from a Multiple Cause of death Perspective”, in VALLIN J., STAN D'SOUZA, PALLONI A. eds., “Measurement and Analysis of Mortality: new approaches”, London: Oxford Press, pp. 328-342.
- WHO, World Health Organization (1977), *International Classification of Diseases, Ninth Revision*, Geneva.
- REDELINGS M.D., SORVILLO F., SIMON P. (2006), “A comparison of underlying cause and multiple causes of death. US vital statistics, 2000-2001”. *Epidemiology* 17(1): 100-103.
- REDELINGS M.D., WISE M., SORVILLO F. (2007), “Using Multiple Cause-of-Death Data to Investigate Associations and Causality between Conditions Listed on the Death Certificate”, *American Journal of Epidemiology* 166(1): 104-108.
- ROMON I., JOUGLA E., BALKAU B., FAGOT-CAMPAGNA A. (2008), "The burden of diabetes-related mortality in France in 2002: an analysis using both underlying and multiple causes of death", *Eur J Epidemiol*, Apr 2 (Epub ahead of print).
- STALLARD E. (2002), “Underlying and multiple cause mortality at advanced ages: United States, 1980-1998”, *North American Actuarial Journal* 6(3): 64-87.
- STEELNAND K. *et al.* (1992), “Use of multiple-cause mortality data in epidemiologic analyses: US rate and proportion files developed by the National Institute for Occupational Safety and Health and the National Cancer Institute”, *American Journal of Epidemiology* 136(7): 855-862.
- TARDON A.G., ZAPLANA J., HERNANDEZ R., CUETO A. (1995), “Usefulness of the codification of multiple causes of death in mortality statistics”, *International Journal of Epidemiology*, 25(5): 1132-1137.
- WALL M.M., HUANG J., OSWALD J., MCCULLEN D. (2005), “Factors associated with reporting multiple causes of death”, *BMC Med Res Methodol.* 5(1):4.
- WHITE M.C., SELVIN S., MERRILL D.W. (1989), “A study of multiple causes of death in California: 1955 and 1980”, *Journal of Clinical Epidemiology* 42(4): 355-365.

WILKINS K., WYSOCKI M., MORIN C., WOOD P. (1997), "Multiple causes of death", *Health Reports* 9(2): 19-29.

WING S., MANTON G. (1981), "A multiple cause of death analysis of hypertension-related mortality in North Carolina, 1968-1977", *American Journal of Public Health* 71(8): 823-830.

YASHIN A.I., ULKRAINTSEVA S.V., AKUSHEVICH I.V. *et al.* (2008), "Trade-off between cancer and aging: what role do other diseases play? Evidence from experimental and human population studies", *Mech Ageing Dev.* Mar 25 (Epub ahead of print).