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Research Article

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Abstract

In this paper we revisit the mortality profiles of France and Italy in 2003 using the multiple-cause-of-death approach. The method leads to a substantial upward reassessment of the role played by certain conditions – e.g. diseases of the blood and diseases of the skin - in overall mortality. Regarding the associations of causes, we distinguish three patterns of pairwise joint occurrence of causes that are common to both countries. The numerous similarities that emerge from the comparison of the two countries are a positive signal of the reliability of the multiple-cause-of-death data.

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1. Introduction

Although the monitoring of mortality trends is mostly based on the underlying cause of death – that is “the disease or injury which initiated the train of morbid events leading directly to death, or the circumstances of the accident or violence which produced the fatal injury” (WHO 1949), a growing number of studies use the entire set of causes listed on the death certificate, hereafter referred to as the multiple causes of death (MCOD), to portray the mortality profile of a country (Chamblee and Evans 1982; Manton and Stallard 1982; Manton 1986; Manton and Myers 1987; White, Selvin, and Merrill 1989; Mackenbach et al. 1995; Stallard 2002; Désesquelles and Meslé 2004; Redelings, Sorvillo, and Simon 2006; Redeling, Wise, and Sorvillo 2007; Frova et al. 2009) or to re-evaluate the contribution of a specific cause (Wing and Manton 1981; Israel, Rosenberg, and Curtin 1986; Nizard and Munoz-Pérez 1993; Coste and Jouglu 1994; Mannino et al. 1998; Wise and Sorvillo 2005; Fuhrman et al. 2006; Romon et al. 2008). As the first advocates of the MCOD approach (Janssen 1940; Dorn and Moriyama 1964) have stressed, the underlying-cause-of-death approach misdirects attention away from conditions that tend to be reported as contributory causes. As a consequence their contribution to overall mortality is underestimated. The MCOD approach should be especially useful for describing the medical circumstances surrounding the death of older people. At old ages, death is indeed often the final stage of a long morbid process involving several conditions. Clearly the MCOD approach is a potentially valuable tool for demographers, who are necessarily concerned with portraying the mortality profiles of aging populations as accurately as possible.

Notwithstanding these developments, studies that use multiple causes of death in order to compare a set of countries are still very scarce. This situation may be partly due to the quite widely shared scepticism about the quality, and consequently the comparability, of the multiple-cause-of-death data. To our mind, apart from certification issues, recent technological innovations in the coding systems represent a major advance towards improved quality of cause-of-death data. In a growing number of countries the recording of information on death certificates and the coding of causes have been automated (optical recognition and automatic coding system). Human intervention is limited to problematic cases that cannot be processed automatically and, at least in theory, the World Health Organization coding rules can be applied systematically and uniformly, irrespective of the coding agent or the country. Another consequence of these automated systems is that the number of coded causes is no longer limited. Researchers often have access to all medical information reported on the certificate instead of a limited selection of causes.

In this paper we use the MCOD approach in order to revisit the mortality profiles of France and Italy in 2003. Our goals are both substantive and methodological. First

we re-evaluate the cause-specific mortality profiles of the two countries, taking into account all the conditions reported on the death certificates. We then measure the pairwise joint occurrence of any underlying and any contributory cause (i.e. any multiple cause other than the underlying cause) in order to identify unexpectedly frequent associations. Researchers using the MCODE data face the problem of handling the enormous amount of information at their disposal. We propose a graphical tool that facilitates the reading and interpretation of results. In the discussion section we put special emphasis on examining the specific contribution of cross-country comparison, both in terms of data quality assessment and in terms of expanding our knowledge of the morbid train of events leading to death.

2. Data and method

2.1 Data

Data are from the Italian National Vital Statistics Death Registry on causes of death managed by the Italian National Institute of Statistics (Istat), and from the statistics of the medical causes of death managed by the French National Institute for Health and Medical Research (Inserm). They are based on the information reported on death certificates, which, in both countries, are designed according to WHO recommendations. The certificate comprises two parts. Part I is for the diseases or conditions that led directly to death. The condition recorded in the last completed line of Part I is usually the underlying cause of death, but the WHO procedures include several exceptions to that rule. Part II is for any other significant condition that unfavourably influenced the course of the morbid process but is not related to the condition directly causing death. The instructions provided to fill in this part of the certificate are not identical in the two countries, which may lead to a somewhat different distribution of the information reported in parts I and II of the certificate in France and Italy. Since we use all the causes mentioned on the certificate this slight difference is not problematic for our study. More importantly, it is worth noting that up to 13 causes can be reported on the Italian death certificate as compared to a maximum of 6 in France. The order of reporting is also different in the two countries. Under the WHO guidelines the certifying physician should report the morbid process in reverse chronological order, from the immediate cause of the death down to the initial condition that started the sequence. While the French certificate follows this guideline, the order of reporting is reversed in Italy (ISTAT 2004a).

France adopted the 10th revision of the International Classification of Diseases (ICD-10) (WHO 2005) in 2000. This change coincided with the introduction of an

automated coding system (STYX) that is derived from the American system (ACME - Automated Classification of Medical Entities) (Israel et al. 1972; Pavillon et al. 2005). Since then all the conditions listed on the certificate have been coded. Two-thirds of the certificates are coded by STYX without any human intervention. For the remaining cases the coding problem is often due to faulty optical recognition. Only 8% of the certificates require the intervention of a trained nosologist to select the underlying cause. Even in these cases all the causes mentioned on the certificate are coded.

Italy adopted the ICD-10 in 2003 but an automated coding system (CODSAN II) was introduced as early as 1995. CODSAN II is an adaptation of both ACME (ISTAT 2004b) and the American MICAR system (Mortality Medical Indexing, Classification, and Retrieval). About 80% of death certificates are entirely coded by CODSAN II. The automated coding system assigns a specific code (“U00”) to every rejected term and returns the rejected records.⁸ These records are then manually coded by trained nosologists. Whenever possible the temporary “U00” code is replaced by a real ICD-10 code, and the record is re-submitted to the automated system in order to select the underlying cause of death (Pace and Grippo 2007). Otherwise the medical expert determines only the underlying cause and leaves the rest of the information as it is. At the end of the coding process about 4% of all deaths still have at least one “U00” code as a contributory cause; among these 87% have only one “U00” code.

In Italy information on the contributory causes is not available for deaths assigned to an external cause and for infant deaths. All these cases (2,134 infant deaths and 25,684 deaths from external causes for Italy, 3,054 infant deaths and 41,577 deaths from external causes for France) were therefore excluded from the analysis. In addition we excluded 8,267 natural deaths over the age of one that occurred in the Italian provinces of Trento and Bolzano: the corresponding death certificates are coded locally and for the underlying cause only. Finally, our analysis is conducted on a total number of 507,704 deaths for France and 550,835 deaths for Italy.

2.2 List of causes of death

The list of causes used in the present analysis is very similar to the European short-list recommended by Eurostat for European comparisons (Eurostat 1998). Our list comprises 15 large groups that generally correspond to the ICD-10 chapters, and 66 sub-groups that give more details on causes of death that are of particular interest to us because they are likely to be frequently mentioned as a contributory cause of death (see appendix). As an example, the group of the “Endocrine, nutritional and metabolic diseases” has been divided into several subgroups: “Diabetes mellitus”, “Malnutrition

⁸ Even for rejected records, all the causes that match with a medical term are coded.

and other nutritional deficiency”, “Obesity” and “Disorders of the thyroid gland”. “Hypertensive diseases” and “Renal failure” have been isolated too. As population aging leads to an increased prevalence of various neurodegenerative disorders, we decided to use more detailed subcategories of the “Mental and behavioural disorders” and the “Diseases of the nervous system”. “Alzheimer's disease”, “Dementias excluding Alzheimer's disease” and “Parkinson's disease” have thus been isolated. Some conditions classified under ICD-10 with diseases of the nervous system (codes G31.0, G31.2, G31.8, G31.9), have been classified with dementias in the “Mental and behavioural disorders”. The group of “Symptoms, signs, abnormal findings and ill-defined causes” has been divided into three subgroups: “Senility”, “Mechanisms of death” (codes I46, I49.0, R09.2, R40.2, R57 that describe the mode of dying, e.g. heart failure, respiratory failure), and a residual group (“Other symptoms, signs, abnormal findings and ill-defined causes”).

Finally, two adjustments have been made to achieve full comparability between the French and the Italian datasets: 1) all “Z” codes (“Factors influencing health status and contact with health services”), used in France only, have been removed from the French database; 2) all “U00” codes, used in Italy only, have been included in the group of “Other symptoms, signs, abnormal findings and ill-defined causes”.

2.3 Indicators

We first calculated age- and sex-standardized mortality rates for 1) a given cause reported as the underlying cause of death, 2) the same cause reported as a multiple (underlying or contributory) cause of death. The standard population is the WHO 2003 European population by sex and five-year age groups. The Standardized Ratio of Multiple to Underlying cause (SRMU) is defined as the ratio of the second to the first of these two rates. It measures the underestimation of the role played by a given condition in the overall mortality when the analysis is performed using the underlying cause only: the SRMU is low for conditions that are usually selected as the underlying cause and high for conditions that are rarely the underlying cause.

We developed an indicator of the frequency of the combinations of causes that can be used to compare various underlying causes within a country, or various countries for a given underlying cause. For each country separately, we first calculated the proportions by five-year age groups 1) of a given contributory cause among all deaths assigned to a specific underlying cause, 2) of the same contributory cause among all deaths of the country. We then applied these proportions to the same death counts (the average number of deaths in France and Italy in 2003 by five-year age groups) in order to remove the effect of the varying age structure of deaths by underlying cause. The

Cause-of-Death Association Indicator (CDAI) is defined as the ratio between these two quantities. It is thus given by the following formula:

$$CDAI_{u,c} = \frac{\sum_x \left(\frac{{}_u d_{c,x}}{{}_u d_x} \cdot \bar{d}_x \right)}{\sum_x \bar{d}_x} \Bigg/ \frac{\sum_x \left(\frac{d_{c,x}}{d_x} \cdot \bar{d}_x \right)}{\sum_x \bar{d}_x} * 100 = \frac{\sum_x \frac{{}_u d_{c,x}}{{}_u d_x} \cdot \bar{d}_x}{\sum_x \frac{d_{c,x}}{d_x} \cdot \bar{d}_x} * 100$$

${}_u d_{c,x}$ = number of deaths observed at age x with underlying cause u and contributory cause c ;

${}_u d_x$ = number of deaths observed at age x with cause u as underlying cause;

$d_{c,x}$ = total number of deaths observed at age x with cause c as contributory cause (regardless of underlying cause);

d_x = total number of deaths observed at age x (regardless of underlying cause);

\bar{d}_x = average number of deaths at age x in France and Italy in 2003

The CDAI measures the deviation from the mean – represented by the denominator of the above formula – of the frequency of occurrence of a specific association of causes. If the CDAI is significantly over 100, then the corresponding association is more frequent than expected. Assuming independence of causes, the CDAIs should not be significantly different from 100.

3. Results

Considering the underlying cause of death only, the mortality profiles of the two countries look very similar. The total standardized mortality rate (excluding infant deaths and deaths from external causes) is only slightly lower in France (551 per 100,000) than in Italy (562 per 100,000) (Table 1). The cause-specific standardized mortality rates of the two countries are generally very similar too. However mortality rates for ill-defined causes and mechanisms of death, as well as for mental and behavioural disorders, are higher in France. Conversely, the rate of mortality assigned to diseases of the circulatory system is higher in Italy (216.9 per 100,000) than in

France (151.1 per 100,000). When ill-defined causes of death are excluded from the rankings, the top four underlying causes of death are the same in the two countries (neoplasms, diseases of the circulatory system, diseases of the respiratory system and diseases of the digestive system) but neoplasms and diseases of the circulatory system are first and second respectively in France while the situation is the reverse in Italy⁹.

3.1 A varying number of causes per certificate

The number of causes reported on the death certificate varies with age (Figure 1). In both countries it increases from age 20 up to age 80. When death occurs at an older age the number of listed causes is slightly lower. Figure 1 also shows that, on average, more causes are listed in Italy (4.0) than in France (3.1). When controlling for the different age and sex structure of the decedents in the two countries,¹⁰ the average number of causes per certificate remains unchanged. Some of the reported contributory conditions may be ill-defined causes or mechanisms of death that do not shed light on the mortality process. When excluding them from the computation (Table 2) we find that the difference between the two countries narrows (2.4 in France vs. 3.0 in Italy), suggesting that ill-defined causes of death are more frequently reported as contributory causes in Italy. For the remainder of the paper all the ill-defined contributory causes of death are excluded from the analysis, so the distribution of death certificates by the number of listed causes remains different in the two countries. The proportion of deaths with only one defined cause is 33% in France vs. 15% in Italy. Conversely, 58% of the Italian certificates vs. 39% of the French certificates include at least three defined causes.

⁹ For a detailed description of the mortality profiles based on the underlying cause of death, see Meslé (2006) for France and Ongaro and Salvini (2009) for Italy.

¹⁰ The standardization was performed using the average number of deaths in France and Italy as the standard population.

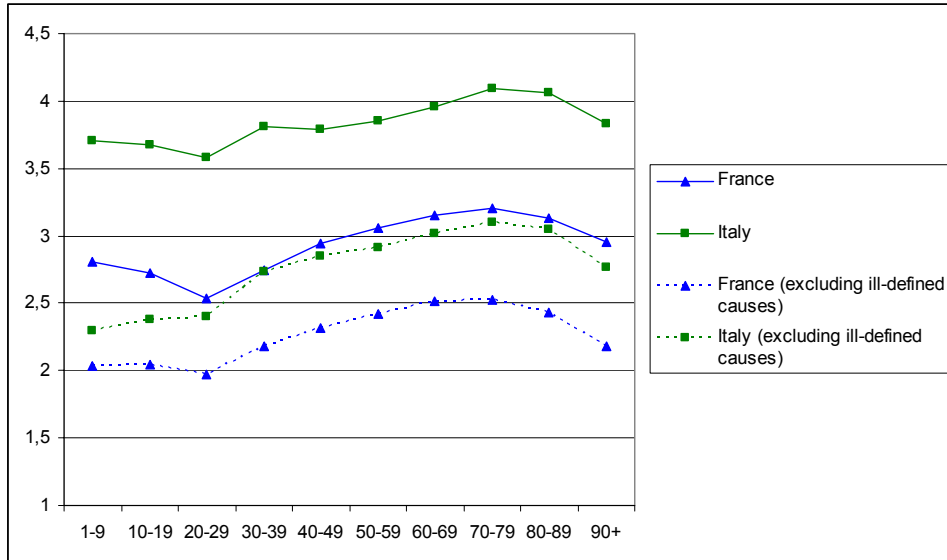
Table 1: Standardized mortality rates (per 100,000) for each cause reported as underlying cause (1) or multiple cause (2) and Standardized Ratio of Multiple to Underlying cause (2/1). Deaths over the age of one, excluding deaths from external causes, France and Italy, 2003

CAUSE OF DEATH	Italy			France		
	Underlying cause (1)	Multiple cause (2)	SRMU (2/1)	Underlying cause (1)	Multiple cause (2)	SRMU (2/1)
Infectious and parasitic diseases	9	34	4	12	48	4
Neoplasms	192	335	2	196	316	2
Diseases of the blood(-forming organs), Immunol.disorders	2	23	10	2	14	6
Endocrine, nutritional and metabolic diseases	23	86	4	22	78	4
Mental and behavioural disorders	9	30	3	20	58	3
Diseases of the nervous system	18	50	3	24	52	2
Diseases of the circulatory system	217	476	2	151	308	2
Diseases of the respiratory system	39	156	4	35	105	3
Diseases of the digestive system	25	89	4	29	77	3
Diseases of the skin and subcutaneous tissue	1	8	11	2	10	6
Diseases of the musculoskeletal system/connective tissue	3	11	4	4	9	3
Diseases of the genitourinary system	9	68	8	8	38	5
Other diseases	2	5	2	2	4	2
Symptoms, signs, abnormal findings, ill-defined causes and mechanisms of death	14	n.i.	-	45	n.i.	-
External causes	n.i.	n.i.	-	n.i.	n.i.	-
Total	562	1370	2	551	1119	2

n.i. : not included

Data: France: Inserm CépiDc mortality database / Italy: ISTAT mortality database

Figure 1: Average number of reported causes on the death certificate by age. Deaths over the age of one, excluding deaths from external causes, France and Italy, 2003



Data: France: Inserm mortality database / Italy: ISTAT mortality database

Table 2: Number of reported causes on the death certificate. Deaths over the age of one, excluding deaths from external causes, France and Italy, 2003

	(% III-defined causes and mechanisms of death)						Average number
	INCLUDED						
	1	2	3	4	5	6+	
France	15	26	25	17	9	8	3.1
Italy	1	10	34	25	15	15	4.0
	(% III-defined causes and mechanisms of death)						Average number
	EXCLUDED						
	1	2	3	4	5	6+	
France	33	29	20	11	5	4	2.4
Italy	15	28	27	16	8	7	3.0

Data: France: Inserm C epiDc mortality database / Italy: ISTAT mortality database

Table 3: Average number of reported causes on the death certificate by underlying cause of death (ill-defined causes reported as contributory causes of death are excluded). Deaths over the age of one, excluding deaths from external causes, France and Italy, 2003

UNDERLYING CAUSE OF DEATH	Italy	France
Infectious and parasitic diseases	3.5	2.7
Neoplasms	3.1	2.5
Diseases of the blood(-forming organs), immunol.disorders	3.0	2.8
Endocrine, nutritional and metabolic diseases	3.5	2.9
Mental and behavioural disorders	2.5	2.3
Diseases of the nervous system	2.6	2.3
Diseases of the circulatory system	3.0	2.5
Diseases of the respiratory system	2.9	2.4
Diseases of the digestive system	3.3	2.9
Diseases of the skin and subcutaneous tissue	2.8	2.5
Diseases of the musculoskeletal system/connective tissue	3.3	3.1
Diseases of the genitourinary system	3.0	2.8
Other diseases	3.1	2.9
Symptoms, signs, abnormal findings, ill-defined causes and mechanisms of death	1.0	1.0
External causes	n.i.	n.i.
Total	3.0	2.4
<i>Average number standardized for the structure by underlying cause of death</i>	2.9	2.5

n.i.: not included. The standardization was performed using the average of number of deaths in France and Italy as the standard population.

Data: France: Inserm CépiDc mortality database / Italy: ISTAT mortality database

The number of reported causes also depends on the underlying cause (Table 3).¹¹ The two groups with the lowest numbers of reported causes (“mental and behavioural disorders” and “diseases of the nervous system”) are common to both countries. In Italy the highest values are obtained for infectious diseases, for endocrine, nutritional and metabolic diseases, for diseases of the digestive system, and for diseases of the musculoskeletal system. In France, with the exception of infectious diseases that fall into a lower ranking, the same groups of causes also head the list. After controlling for the different underlying-cause-of-death structures of the two countries, the gap in terms of number of reported causes narrows further but does not disappear (2.5 reported causes in France vs. 2.9 in Italy).

¹¹ The same table is provided for the more detailed list of causes in the appendix (table A1).

3.2 Stability of the leading causes of death

Table 1 also displays the standardized ratios of multiple to underlying cause (SRMU). The smallest value is for neoplasms (1.6 in France and 1.7 in Italy). For all other groups of causes the SRMU is over two. Thus, in more than half of the cases where these causes are mentioned, they are recorded as a contributory cause. The multiple-cause-of-death approach only moderately reinforces the role played by diseases of the circulatory system: the SRMU is equal to 2.0 in France and 2.2 in Italy. The loss of information resulting from the single-cause-of-death approach is larger for respiratory diseases (SRMU equal to 3.0 in France and 4.0 in Italy). The highest values of the SRMU are for diseases of the blood (6.1 in France and 9.9 in Italy), for diseases of the skin and the subcutaneous tissues (5.9 in France and 11.4 in Italy), for diseases of the genitourinary system (4.6 in France and 7.6 in Italy), for infectious diseases (4.0 in both countries), and for endocrine, nutritional and metabolic diseases (3.6 in France and 3.7 in Italy). At a more detailed level of classification (see Table A.1 in the appendix), we find especially high values for septicaemia (6.2 in France and 7.9 in Italy), renal failure (respectively 5.6 and 8.1), malnutrition and other nutritional deficiencies (respectively 5.0 and 7.7), hypertensive diseases (respectively 5.5 and 4.2), as well as, more markedly for Italy, disorders of the thyroid gland (respectively 4.5 and 8.3) and hyperplasia of the prostate (respectively 3.2 and 8.7).

When comparing two broad age groups (over and under eighty - see Table A2 in the appendix) we find that, with very few exceptions, the SRMU is lower in the older age group. This result is in line with our previous observation that the average number of reported causes decreases at very old ages. The SRMU is also generally higher in Italy. As a consequence the multiple-cause-of-death approach results in a larger upward revision of the mortality rates in Italy than in France. However it does not dramatically alter the ranking of the causes of death. In Italy the top five causes of death are exactly the same – and with the same ranking – as when the underlying cause only is considered. In France the MCOD approach strongly reinforces the contribution to mortality of the endocrine, nutritional and metabolic diseases, which “jump” from the seventh to the fourth place of the ranking, just above diseases of the digestive system.

All in all the top five causes of death resulting from the MCOD are the same in the two countries but the order is slightly different: in France, neoplasms head the list, just above diseases of the circulatory system (the situation is the reverse in Italy) and diseases of the respiratory system. When comparing Italy and France, endocrine, nutritional and metabolic diseases, and diseases of the digestive system exchange rankings.

3.3 Three broad patterns of combination of causes

Figure 2.1 and 2.2 display graphically the cause-of-death association indicator (CDAI) for France and Italy.¹² The cells of the table that result from the cross-matching of every underlying and every contributory cause of death have been coloured according to the value of the corresponding CDAI. After computing the standard deviation (σ) of this indicator¹³, we created the five following classes: $[0;100[$, $[100;100+\sigma/4[$, $[100+\sigma/4;100+\sigma/2[$, $[100+\sigma/2;100+3\sigma/4[$ and $[100+3\sigma/4;\infty[$. The first class is white (weak association) while all other classes are progressively darker shades of pink.

60% of the cells of the two figures have exactly the same colour. In both countries most cells on the diagonal are dark pink: diseases that are classified in the same group as the underlying cause of death are more likely to be involved in the etiological sequence ending in death than other diseases. Not surprisingly, if the death is assigned to an ill-defined cause there is rarely another well-defined cause mentioned on the death certificate: in both France and Italy all corresponding cells (last horizontal line) are white.

Careful examination of the strength of the associations indicates that, depending on the underlying cause, three broad patterns of association can be distinguished. The combinations involving one of the three leading causes of death (neoplasms, diseases of the circulatory system, and respiratory diseases) are generally characterized by weak associations, whatever the “role” (underlying or contributory cause) these conditions play in the morbid process. Specifically to France, we find that a respiratory disease often contributes to the deaths assigned to a disease of the nervous system or to a mental or behavioural disorder.

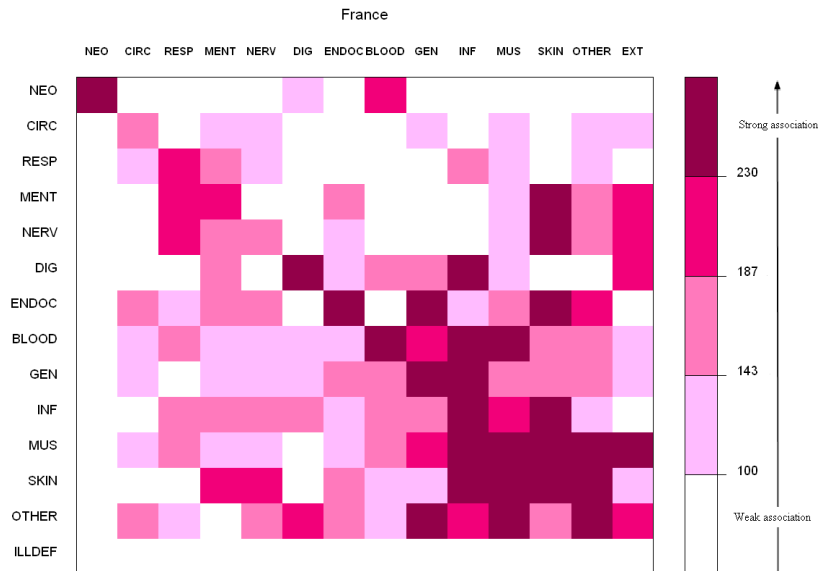
Three groups of causes display a completely opposite pattern in the two countries: “diseases of the skin and the subcutaneous tissue”, “diseases of the musculoskeletal system and the connective tissue” and the heterogeneous group of “other diseases”. Associations involving these causes, both as underlying and contributory causes of death, are more frequent than expected. These unexpectedly frequent associations are often symmetrical. As an example, the combination between the first (mainly: decubitus ulcer) and the second group (mainly: arthropathies and osteopathies) is visible in the two possible orders. Similarly, these two groups are very frequently and symmetrically associated with an infectious disease (mainly: septicaemia). We find that the deaths assigned to a mental or behavioural disorder (mainly: dementia), a disease of the nervous system (mainly: Parkinson’s and Alzheimer’s diseases) or to an endocrine, nutritional and metabolic disease (mainly: diabetes, volume depletion and malnutrition)

¹² These figures (see Figures A1 and A2 in the Appendix) were made for two separate age groups too (deaths over the age of one and under the age of 80, and death at age 80 or over).

¹³ The standard deviation was calculated taking into account all the values of the CDAI in the two countries.

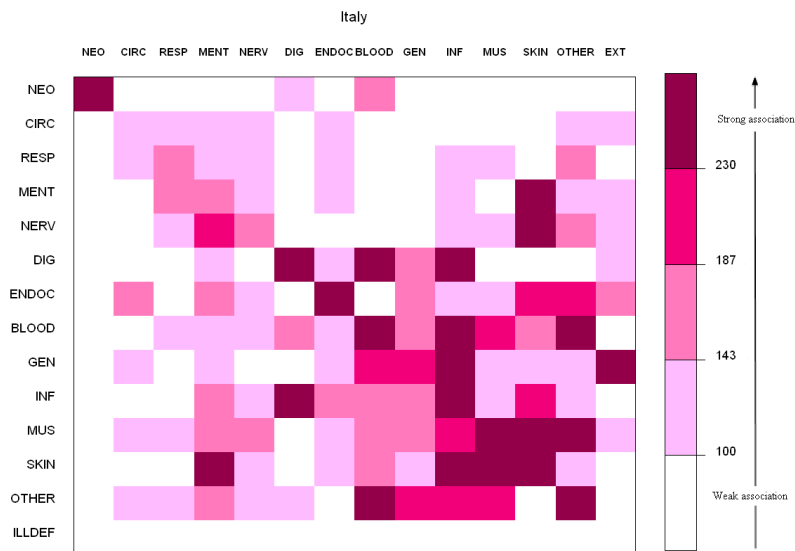
frequently involve a disease of the skin (mainly: decubitus ulcer or ulcer of lower limb). For diseases of the musculoskeletal system and the connective tissue (mainly: arthropathies and systemic connective tissue disorders), a frequent association with diseases of the blood and the genitourinary diseases (mainly: renal failure) is observed. Specifically to France, external causes (mainly: S and T codes “injury, poisoning and certain other consequences of external causes”) strongly contribute to the deaths assigned to musculoskeletal diseases (mainly: bone disorder). This French specificity is likely to be due to the fact that in Italy, if the automatic procedure fails to code external causes, the underlying cause is often the only coded cause.

Figure 2a): CDAIs –Deaths over the age of one, excluding deaths from external causes, France, 2003



Horizontal axis: contributory cause. Vertical axis: underlying cause
 Data: Inserm CépiDc mortality database

Figure 2b): CDAs –Deaths over the age of one, excluding deaths from external causes, Italy, 2003



Horizontal axis: contributory cause. Vertical axis: underlying cause
 Data: ISTAT mortality database

The infectious diseases display a pattern similar to the previous one, but they emerge more specifically as a very frequent contributory cause for several underlying causes. Their contribution is especially frequent when the underlying cause is a disease of the blood, of the digestive system, of the skin, of the musculoskeletal system and the connective tissue, or a disease of the genitourinary system. In many cases septicaemia is the reported condition. More specifically to Italy, digestive diseases (mainly: cirrhosis of the liver and hepatic failure) very frequently contribute to the deaths assigned to an infectious disease (mainly: chronic viral hepatitis).

Most cells involving the six remaining groups (“diseases of the blood and blood-forming organs” and “diseases of the genitourinary system”, “endocrine, nutritional and metabolic diseases”, “diseases of the digestive system”, “mental and behavioural disorders” and “diseases of the nervous system”) are in lighter shades of pink or in white. However several very frequent associations can be highlighted. In both countries, a condition belonging to the group “other diseases” (mainly: diseases of the eye and congenital malformations) is frequently mentioned as a contributory cause for an

endocrine, nutritional or metabolic disease. In France, the deaths assigned to that cause frequently involve a genitourinary disease (mainly: renal failure). Specifically to France too, we find that an external cause is frequently reported if the death is assigned to a mental and behavioural disorder (mainly: dementia and disorder assigned to alcohol use) or a disease of the nervous system (mainly: Parkinson's disease, Alzheimer's disease and epilepsy). In a large number of cases, these deaths are due to asphyxia caused by a foreign body in the respiratory tract, which, in practical terms, suggests that the death has been caused by regurgitation related to bed confinement.

4. Discussion

4.1 Impact of the MCODE approach

The multiple-cause-of-death approach does not substantially alter the ranking of the causes of death of either France or Italy. In the literature there are very few studies like ours that present an in-depth analysis of the impact of the MCODE approach for all causes of death. With a different list of causes, Stallard (Stallard 2002) found that the MCODE approach does not modify the hierarchy of the five leading causes of death in the US for the years 1990 and 1998. Likewise for the years 1968 and 1977 in the US, Manton and Stallard (1982) found no change in the five major causes of death except that hypertensive diseases and influenza/pneumonia exchange rankings.¹⁴ Not surprisingly the leading causes of death have the lowest values of the SRMU: given the severity of these diseases, which is reflected in their high ranking as underlying causes of death, it is unlikely that they play a contributory role only in the morbid process. However there is no simple negative correlation between the SRMU and the standardized mortality rate computed on the basis of the underlying cause of death. As an example, infectious and parasitic diseases on the one hand, and endocrine, nutritional and metabolic diseases on the other, have the same SRMU (4 in both France and Italy) but a very different ranking in the hierarchy of causes of death.

Though not modifying the ranking of the leading causes of death, our findings clearly indicate that omitting the contributory causes leads to a substantial underestimation of the role played by certain conditions in the process leading to death. These conditions can be broadly categorized in two groups. The first group consists of diseases that are not lethal in themselves but that play a role as "background factors for other causes" (Manton and Stallard 1982: 543): when combined with another serious disease, the risk of dying increases, reflecting either "synergistic" or "additive" morbid

¹⁴ Respectively number 4 and 5 with the single-cause-of-death approach and number 5 and 4 with the multiple-cause-of-death approach.

processes (Speizer, Trey, and Parker 1977: 336). Hypertension, identified by several other authors (Dorn and Moriyama 1964; Wing and Manton 1981; Manton and Stallard 1982; Stallard 2002) as a frequent contributory cause of the death, is a good example of a background factor. The second group consists of complications of the initiating disease or of the medical treatment. It is best exemplified by diseases of the blood. In line with the literature (Dorn and Moriyama 1964; Guralnick 1966; Chamblee and Evans 1982; Steenland et al. 1992), we find that the underlying cause approach overlooks the contribution to mortality of anaemia and coagulation defects. Blood disorders can be both the consequence of other diseases (e.g. diseases of the liver) or secondary effects of therapies (e.g. cancer therapies). Renal failure, septicaemia and diseases of the skin (mainly bedsores) also belong to that group. Bedsores, which generally result from bed-confinement, contribute to the process leading to death in so far as they participate in the overall weakening of the body. Renal failure is known to be a potential complication of diabetes. Regarding septicaemia and, more generally, infectious diseases, our results indicate that they continue to be an important factor of mortality, not as underlying cause – as was the case before the epidemiological transition (Omran 1971) – but as contributory cause. Moreover, the grouping of causes we used probably leads to an underestimation of the actual contribution of infectious diseases to mortality since many of them (e.g. influenza, pneumonia, acute bronchitis) are classified in other ICD chapters (e.g. with diseases of the respiratory system). According to Manton (Manton and Stallard 1982: 539), population aging could result in a fresh upsurge in infectious diseases, since chronic degenerative diseases “often progress to a point where the vitality of the organism as a whole is impaired, at which time the organism is susceptible to a lethal infectious complication – usually of the lungs or the blood”. Nam suggested “that the present notion of the stages of the epidemiological transition may be oversimplified, based as it is on the primary cause-of-death model” (Crews 1990: 202). In line with these comments, our results confirm the need to use the MCODE approach to monitor, both retrospectively and prospectively, the trends in mortality involving infectious diseases.

4.2 Combination of causes

Our results confirm that the assumption of independent occurrence of diseases is generally not valid. Many associations are indeed more frequent than would be predicted by a random occurrence of the diseases. We distinguish three broad patterns of associations that are common to both countries. They form a gradient from the three leading causes of death that often have no contributory cause, to far less lethal conditions – such as diseases of the skin or diseases of the musculoskeletal system – for

which several combinations appear to be much more frequent than expected. At this point we should draw attention to a side effect of how we calculate the cause-of-death association indicator. As pointed out earlier, the CDAI measures the deviation from the mean of the frequency of occurrence of a specific association of causes. Neoplasms and diseases of the circulatory system, whose weight in overall mortality is overwhelming, contribute much more to the average than the other causes of death. As a consequence all CDAIs computed for the combinations involving these diseases are less likely to be significantly different from 100.

Another striking result concerns the diagonal cells and, more generally, the symmetrical associations. In both countries about two-thirds of the strong associations (dark/very dark pink cells) are symmetrical. This result inevitably raises the question of the extent to which the order of reporting matters. In other words, “should a report of diabetes mellitus as the underlying cause with diseases of heart as contributory or contributory cause be considered the same disease process as the case where the heart disease is the underlying cause and diabetes the contributory condition?” (Guralnick 1966:985-986). Regarding the diagonal cells, we must acknowledge that the result depends on the level of aggregation used to group the causes of death: with a more detailed classification, cases where two reported causes belong to the same group would have been less frequent. But it clearly indicates that complications as well as background factors of the initiating cause are likely to belong to the same ICD chapter as the underlying cause. For the other symmetrical combinations, an analysis at a lower level of classification would provide identical results. Some of these associations (e.g. symmetrical association between a musculoskeletal disease and a disease of the skin) probably reflect the fact that the exact role of certain conditions in the etiological sequence leading to death is often questionable (Coste and Jouglu 1994). As suggested by Percy (Percy, Stanek, and Gloeckler 1981), symmetrical associations could also be a consequence of insufficient training of the certifying physicians who may not be fully aware that the order of entry of the terms on the death certificate ultimately determines the selection of the underlying cause by the coders.

4.3 Limitations

We will now return to the main limitation of our study on the quality of the multiple-cause-of-death data. The variation with age in the number of reported causes per certificate (Figure 1) illustrates this point clearly. The increase in the number of reported causes up to age 80 is consistent with the increased frequency of co-morbidity with age. We cannot rule out that the subsequent decline results from a selection effect: people with fewer diseases are likely to live longer. But we suspect that it is rather an

artifact resulting from a less thorough description of the morbid process when death occurs at very old ages (Mackenbach et al. 1995). The need to provide an extensive explanation is certainly less obvious when age seems to be the cause of the death.

There is an abundant literature on the accuracy of information reported by certifying physicians on death certificates (D'Amico et al. 1999; Mant et al. 2006; Speizer, Trey, and Parker 1977; Stallard 2002; Wall et al. 2005). Inconsistencies between death certificates and autopsy reports have been documented. As noted before, erroneous temporal sequencing of causes and incomplete reporting is often attributed to inadequate training of physicians. But even with proper training the certifying physicians may not be fully informed about the morbid process that led to death, and the accuracy of their reporting is likely to be dependent on how – i.e. where, when and why – the death occurred. As an example, reporting is probably less complete in cases of sudden death than in cases where the decedent was suffering from a long-term illness. Moreover, the content of the death certificate also reflects the state of the art of medical knowledge: if the biological plausibility of a combination is high – or is already well-established – then the physicians will be more likely to report this combination of causes (Redelings, Wise, and Sorvillo 2007). Finally, the fact that the death certificate is designed to select the underlying cause, implies that the certifying physician is forced to make a decision “as to the one etiological sequence ending in death”. As a consequence, “he may be prevented from describing the clinical course of death completely” (Guralnick 1966: 979). This is obviously not without consequences for the reporting of multiple causes.

All in all, these various sources of mis/underreporting may result in an inaccurate selection of the underlying cause of the death – which is problematic when the underlying cause only is taken into account – or in heterogeneous reporting of the contributory causes on the certificates. They may thus affect the results both in terms of the revised cause-specific mortality rates and the associations of causes. The next question concerns the extent to which the comparison of the two countries is distorted. The fact that the number of reported causes per certificate - as well as the SRMU - is higher in Italy than in France supports the idea that reporting practices are not alike in France and Italy. Most studies in other countries (White, Selvin, and Merrill 1989; Steenland et al. 1992; Redelings, Sorvillo, and Simon 2006; Australian Bureau of Statistics 2008) show an average number of causes per death certificate that is much lower than that of Italy and close to that of France, but these studies are not fully comparable with ours.¹⁵ Neither the different structure of deaths - by age, sex and underlying cause - of the two countries, nor the more extensive use of ill-defined causes as contributory cause in Italy than in France, suffice to explain the gap. Interestingly, most of the difference results from a higher proportion of deaths with no contributory

¹⁵ E.g., different reference period, inclusion of the deaths due to an external cause and/or under the age of one.

cause in France than in Italy. According to White (White, Selvin, and Merrill 1989), a higher number of causes per certificate signals better diagnosis and more complete recording and, as a consequence, better quality of the data. And indeed in a recent classification of the WHO member states based on the quality of cause-of-death statistics (Mahapatra et al. 2007), Italy is assessed as having medium-high quality data while France is assessed as having medium-low quality data. However, as mentioned earlier, the French and the Italian death certificates differ in two important ways. The fact that the Italian certificate comprises more lines than the French one and, second, the reverse ordering of the causal pathway on the Italian certificate (from the initial to the final cause) could result in an inflation of the number of causes listed by Italian physicians.

In addition to reporting practices, coding procedures also have a major impact on the cause-of-death statistics. In the case of Italy, where ICD-10 has only been in use since 2003, coding procedures are probably not yet stable, but it is not possible to predict how far this distorts the comparison. Regarding the automated coding systems, both countries use ACME to select the underlying cause of death. While STYX directly produces ICD-10 codes, CODSAN II relies on the USA-ERN (Entity Reference Number) system that translates each medical term into a number. A transition table is then used to convert the ERN into an ICD-10 code. So the two systems may produce different outputs at the level of the fourth digit of the ICD classification only. As a consequence we do not expect any impact on the results presented in this paper.

4.4 Why compare countries?

As we have seen, French and Italian cause-of-death data are neither flawless nor fully comparable. While this situation appears to preclude cross-country comparisons, we believe, on the contrary, that it argues in favour of this line of research. Both the similarities and dissimilarities that emerge from the comparison of a set of countries must be interpreted with caution, but they are a potentially fruitful source of information. Unless a clear bias can be identified mutually similar findings usually reinforce each other's credibility. Dissimilarities may reflect real differences in the morbid processes prevailing in the countries. They may correspond to country-specific certifying and coding practices too. So cross-country comparison helps to identify failures of the coding and/or certification practices as well as other drawbacks of the data gathering tools. It is thus likely to expand our knowledge of the reliability of the multiple-cause-of-death data, which in turn could result in an improvement of their quality. There are several ways to address these failures: adequate training of physicians (including emphasis on the utility of the cause-of-death statistics in terms of public

health), increased access of certifying physicians to the decedents' medical records, changes in the coding procedures or in the death certificate. Last but not least, we believe that international recommendations on the reporting of multiple causes, as has been done for the selection of the underlying cause, would greatly contribute to improving multiple-cause-of-death statistics. From that perspective particular attention should be paid to deaths that occur at old ages. In 2005 about half of the people who died in both France and Italy were aged 80 and over, and by 2050 the percentage could reach about 80%. In this context access to high quality multiple-cause-of-death data will become an increasingly compelling need.

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Appendix

Group #	Groups and subgroups	ICD-10 code
1	Infectious and parasitic diseases	
	Tuberculosis	A15-A19, B90
	AIDS (HIV-disease)	B20-B24
	Viral hepatitis	B15-B19, B94.2
	Septicaemia	A40-A41
	Intestinal infectious diseases	A00-A09
	Other Infectious and parasitic diseases	(A00-B99) excluding Supra codes
2	Neoplasms	
	Malignant neoplasm of lip, oral cavity, pharynx	C00-C14
	Malignant neoplasm of oesophagus	C15
	Malignant neoplasm of stomach	C16
	Malignant neoplasm of colon, rectum, and anus	C18,C19, C20, C21
	Malignant neoplasm of liver and intrahepatic bile ducts	C22
	Malignant neoplasm of pancreas	C25
	Malignant neoplasm of larynx and trachea/bronchus/lung	C32-C34
	Malignant melanoma of skin	C43
	Malignant neoplasm of skin	C44
	Malignant neoplasm of breast	C50
	Malignant neoplasm of cervix uteri and other parts of uterus	C53, C54, C55
	Malignant neoplasm of ovary	C56
	Malignant neoplasm of prostate	C61
	Malignant neoplasm of kidney	C64
	Malignant neoplasm of bladder	C67

	Malignant neoplasm of lymph, haematopoietic tissue	C81-C96
	Other malignant neoplasms	(C00-C99) excluding Supra codes
	Benign neoplasms, in situ neoplasms and neoplasms of uncertain or unknown behaviour	D00-D09, D10-D36, D37-D48
3	Diseases of the blood(-forming organs), immunol. disorders	D50-D89
4	Endocrine, nutritional and metabolic diseases	
	Diabetes mellitus	E10-E14
	Malnutrition and other nutritional deficiencies	E40-E64
	Obesity	E65-E68
	Disorders of thyroid gland	E00-E07
	Other endocrine, nutritional and metabolic diseases	(E00-E90) excluding Supra codes
5	Mental and behavioural disorders	
	Alcoholic psychosis/chronic alcohol abuse	F10, G31.2
	Drug dependence, toxicomania	F11-F16, F18-F19
	Dementias (excluding Alzheimer's)	F01, F03, G31.0, G31.8, G31.9
	Other mental and behavioural disorders	(F00-F99) excluding Supra F codes
6	Diseases of the nervous system	
	Epilepsy	G40-G41
	Alzheimer's disease	G30
	Parkinson's disease	G20, G21
	Other diseases of the nervous system	(G00-G98) excluding (G31.0, G31.2, G31.8, G31.9) and Supra codes

7	Diseases of the circulatory system	
	Ischaemic heart diseases	I20-I25
	Other heart diseases	I30-I33, I39-I45, I47-I48, I49.1-I52, I00-
	Cerebrovascular diseases	I60-I69
	Hypertensive diseases	I10-I15
	Other Diseases of the circulatory system	(I00-I99) excluding (I46, I49.0, I95.9, I99) and Supra codes
8	Diseases of the respiratory system	
	Influenza	J10-J11
	Pneumonia	J12-J18
	Other acute lower respiratory diseases	J00-J09, J19-J22
	Asthma	J45-J46
	Other chronic lower respiratory diseases	J40-J44
	Lung diseases due to external agents	J60-J70
	Other diseases of the respiratory system	(J00-J99) (J96.0, J96.9) excluding Supra codes
9	Diseases of the digestive system	
	Ulcer of stomach, duodenum and jejunum	K25-K28
	Chronic liver disease	K70, K73-K74
	Other diseases of the digestive system	(K00-K93) excluding Supra codes
10	Diseases of the skin and subcutaneous tissue	L00-L99
11	Diseases of the musculoskeletal system/connective tissue	
	Rheumatoid arthritis and arthrosis	M05-M06, M15-M19
	Other diseases of the musculoskeletal system/connective tissue	(M00-M99) excluding Supra codes

12	Diseases of the genitourinary system	
	Renal failure	N17-N19
	Other diseases of kidney and ureter	N00-N16
	Hyperplasia of prostate	N40
	Other diseases of the genitourinary system	(N00-N99) excluding Supra codes
13	Other diseases	
	Complications of pregnancy, childbirth and puerperium	O00-O99
	Certain conditions originating in the perinatal period	(P00-P96) excluding P28.5
	Congenital malformations and chromosomal abnormalities	Q00-Q99
	Diseases of the eye and adnexia	H00- H59
	Diseases of the ear and mastoid process	H60- H95
	SIDS	R95
14	Symptoms, signs, abnormal findings and ill- defined causes	
	Senility	R54
	Mechanisms of death °	I46, I49.0, R09.2, R40.2, R57
	Other symptoms, signs, abnormal findings and ill-defined causes °°	(R00-R94), (R96-R99), I95.9, I99, J96.0, J96.9, P.28.5, U00 excluding Supra R codes
15	External causes	S, T, V, W, X Y codes

°) Cardiac arrest (I46.0), Ventricular fibrillation (I49.0), Respiratory arrest (R09.2), Coma (R40.2), Shock (R57)

°°) Hypotension (I95.9), Other unspecified disorders of circulatory system (I99), Acute respiratory failure (J96.0), Respiratory failure unspecified (J96.9), Respiratory failure of newborn P(.28.5)

Abbreviations used for figures 2a, 2b, A1 and A2

#	Multiple cause group	Abbreviation
1	Infectious and parasitic diseases	INF
2	Neoplasms	NEO
3	Diseases of the blood(-forming organs), immunol.disorders	BLOOD
4	Endocrine, nutritional and metabolic diseases	ENDOC
5	Mental and behavioural disorders	MENT
6	Diseases of the nervous system	NERV
7	Diseases of the circulatory system	CIRC
8	Diseases of the respiratory system	RESP
9	Diseases of the digestive system	DIG
10	Diseases of the skin and subcutaneous tissue	SKIN
11	Diseases of the musculoskeletal system/connective tissue	MUS
12	Diseases of the genitourinary system	GEN
13	Other diseases	OTHER
14	Symptoms, signs, abnormal findings, ill-defined causes	ILLDEF
15	External cause	EXT

Table A-1: Standardized mortality rates (per 100,000) for each cause reported as underlying cause (UC) or multiple cause (MC) and Standardized Ratio of Multiple to Underlying cause (SRMU) – Deaths over the age of one, excluding deaths from external causes, France and Italy, 2003

Cause of death	France			Italy		
	UC	MC	SRMU	UC	MC	SRMU
Tuberculosis	1	2	2	1	1	3
AIDS (HIV-disease)	2	3	2	2	4	2
Viral hepatitis	1	3	4	3	8	3
Septicaemia	5	29	6	2	19	8
Intestinal infectious diseases	1	1	1	0	0	2
Other infectious and parasitic diseases	3	12	4	1	3	4
Malignant neoplasm of lip, oral cavity, pharynx	7	8	1	4	4	1
Malignant neoplasm of oesophagus	6	7	1	2	3	1
Malignant neoplasm of stomach	6	7	1	12	13	1
Malignant neoplasm of colon, rectum and anus	19	22	1	19	22	1
Malignant neoplasm of the liver and the intrahepatic bile ducts	9	11	1	11	12	1
Malignant neoplasm of pancreas	9	10	1	10	10	1
Malignant neoplasm of larynx and trachea/bronchus/lung	40	44	1	42	46	1
Malignant melanoma of skin	2	2	1	2	2	1
Malignant neoplasm of skin	1	1	1	0	1	2
Malignant neoplasm of breast	13	15	1	12	15	1
Malignant neoplasm of cervix uteri and other parts of uterus	3	4	1	3	3	1
Malignant neoplasm of ovary	4	4	1	3	4	1
Malignant neoplasm of prostate	12	17	1	9	13	1
Malignant neoplasm of kidney	4	5	1	3	4	1

Table A-1: (Continued)

Cause of death	France			Italy		
	UC	MC	SRMU	UC	MC	SRMU
Malignant neoplasm of bladder	6	7	1	6	7	1
Malignant neoplasm of lymph.haematopoietic tissue	15	19	1	15	19	1
Other malignant neoplasms	33	135	4	28	151	5
Benign neoplasms, in situ neoplasms and neoplasms of uncertain or unknown behaviour	7	12	2	9	16	2
Diseases of the blood(-forming organs), immunol.disorders	2	14	6	2	23	10
Diabetes mellitus	12	41	3	19	64	3
Malnutritionand other nutritional deficiencies	2	11	5	0	3	8
Obesity	1	5	4	1	4	4
Disorders of thyroid gland	1	3	4	0	3	8
Other endocrine, nutritional and metabolic diseases	6	25	4	3	16	6
Alcoholic psychosis/chronic alcohol abuse	5	18	4	0	2	5
Drug dependence, toxicomania	0	1	2	1	1	1
Dementia (excluding Alzheimers)	11	21	2	7	21	3
Other mental and behavioural disorders	3	23	7	1	6	6
Epilepsia	2	6	3	1	3	5
Alzheimers disease	10	16	2	6	10	2
Parkinsons disease	4	8	2	3	8	3
Other diseases of the nervous system	8	24	3	8	29	4
Ischaemic heart diseases	46	74	2	79	135	2
Other heart diseases	39	117	3	8	19	2
Cerebrovascular diseases	35	64	2	61	120	2
Hypertensive diseases	8	42	6	19	81	4
Other diseases of the circulatory system	23	61	3	50	206	4

Table A-1: (Continued)

Cause of death	France			Italy		
	UC	MC	SRMU	UC	MC	SRMU
Influenza	0	1	1	1	1	2
Pneumonia	11	38	3	7	38	5
Other acute lower respiratory diseases	3	9	3	1	3	4
Asthma	1	3	2	1	2	3
Other chronic lower respiratory diseases	9	19	2	23	57	3
Lung diseases due to external agents	3	10	4	1	5	4
Other diseases of the respiratory system	7	32	5	6	63	11
Ulcer of stomach, duodenum and jejunum	1	3	3	1	4	4
Chronic liver disease	13	23	2	12	25	2
Other diseases of the digestive system	15	56	4	12	67	5
Diseases of the skin and subcutaneous tissue	2	10	6	1	8	11
Rheumatoid arthritis and arthrosis	1	2	3	1	4	5
Other diseases of the musculoskeletal system/connective tissue	3	7	3	2	7	3
Renal Failure	5	30	6	7	59	8
Other diseases of kidney and ureter	1	2	3	0	2	5
Hyperplasia of prostate	0	1	3	0	2	9
Other diseases of the genitourinary system	2	6	3	1	7	7
Other Diseases	2	4	2	2	5	2
Senility	4	-	-	4	-	-
Mechanisms of death	19	-	-	7	-	-
Other Symptoms, signs, abnormal findings, ill-defined causes	22	-	-	3	-	-

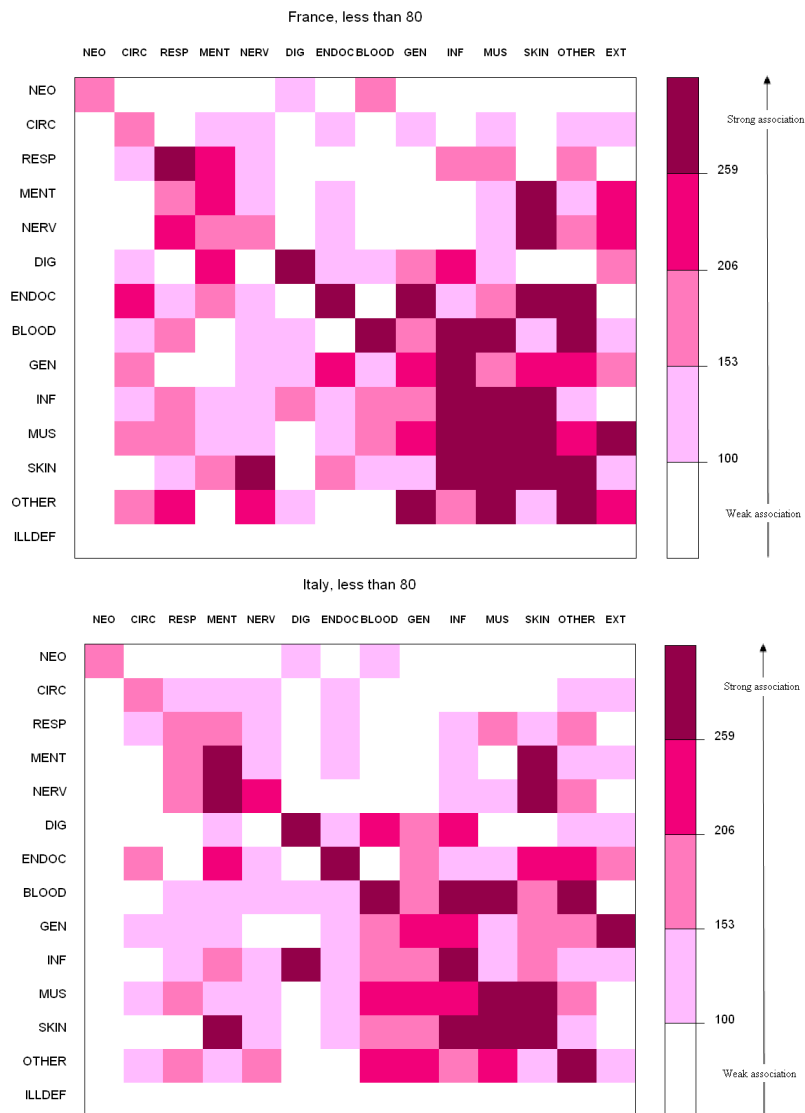
Data: France: Inserm CépiDc mortality database / Italy: ISTAT mortality database

Table A-2: Standardized ratio of multiple to underlying cause by age group and underlying cause of the death – Deaths over the age of one, excluding deaths from external causes, France and Italy, 2003

CAUSE OF DEATH	France		Italy	
	Under 80	80 or more	Under 80	80 or more
Infectious and parasitic diseases	4.2	3.6	3.8	4.8
Neoplasms	1.6	1.6	1.7	1.8
Diseases of the blood(-forming organs), immunol.disorders	7.1	4.6	11.0	8.7
Endocrine, nutritional and metabolic diseases	3.8	3.3	3.8	3.6
Mental and behavioural disorders	3.6	2.2	3.6	3.1
Diseases of the nervous system	2.4	1.9	2.7	2.9
Diseases of the circulatory system	2.1	2.0	2.3	2.1
Diseases of the respiratory system	3.6	2.6	4.6	3.5
Diseases of the digestive system	2.7	2.4	3.7	3.2
Diseases of the skin and subcutaneous tissue	8.5	4.9	13.3	10.4
Diseases of the musculoskeletal system/connective tissue	2.7	2.5	3.3	4.4
Diseases of the genitourinary system	5.6	3.8	8.4	6.9
Other diseases	2.1	10.3	2.1	5.5

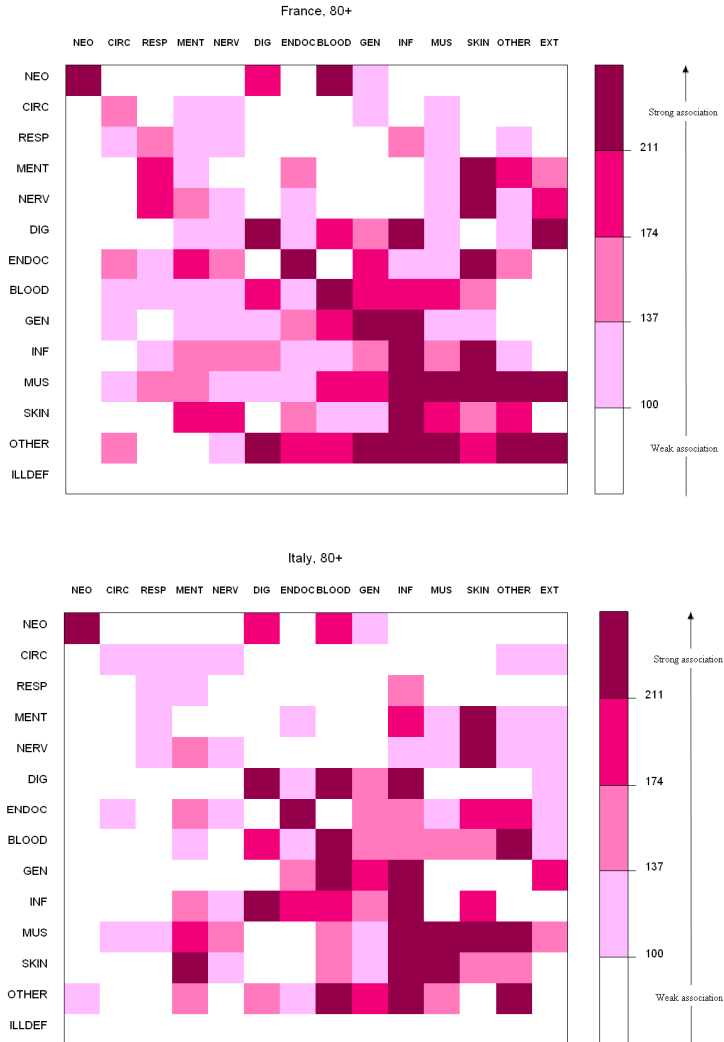
Data: France: Inserm CépiDc mortality database / Italy: ISTAT mortality database

Figure A1: CDAs – Deaths over the age of one and under the age of 80, excluding deaths from external causes, France and Italy, 2003.



Horizontal axis: contributory cause. Vertical axis: underlying cause
 Data: France: Inserm CépiDc mortality database / Italy: ISTAT mortality database

Figure A2: CDAIs – Deaths at the age of 80 or more, excluding deaths from external causes, France and Italy, 2003.



Horizontal axis: contributory cause. Vertical axis: underlying cause
 Data: France: Inserm CépiDc mortality database / Italy: ISTAT mortality database

