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Cause-specific mortality analysis: Is the underlying cause of death sufficient?

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Résumé
L'analyse de la mortalité par cause repose principalement sur l'étude de la cause principale du décès. Notre point de vue est que cette approche n'est pas suffisante. Dans un nombre croissant de pays, toutes les causes reportées par les médecins sur les certificats de décès (ou «causes multiples») sont enregistrées et codées. Ces données peuvent être utilisées de deux façons principales : pour réévaluer le poids d'une cause particulière dans la mortalité ou pour examiner comment les causes sont associées les unes avec les autres. Dans cet article, nous nous appuyons sur une analyse des causes multiples de décès développée dans le cadre d'un projet comparatif franco-italien pour évaluer la qualité de ces données et pour montrer, tout particulièrement dans le contexte du vieillissement démographique, la pertinence de cette approche pour les politiques de santé publique.

Mots-clés
Mortalité, causes de décès, causes multiples, comparaisons transversales internationales, méthodes.

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Summary

Cause-specific mortality analysis is based predominantly on examination of the underlying cause of death. Our view is that this single-cause approach is not sufficient. With increasing data availability and technical developments in favor of better data quality, the time has come to consider all items of information reported by certifying physicians on death certificates (i. e. the multiple causes). These data can be used in two main ways: either to reassess the role played by a given cause in mortality, or to examine how causes combine with one another. In this paper, we rely on our experience of multiple cause-of-death (MCOD) analysis in the framework of a French-Italian comparative project to provide information on data quality, and to show that, especially in the context of population aging, MCOD analysis is a very relevant tool for public health policy.

Keywords

Mortality, causes of death, multiple causes, cross-country comparison, methods.

In 1940 Theodore Janssen, the then Chief of the Nosology Section at the Division of Vital Statistics of the US Bureau of the Census wrote: *«statistics showing combinations of causes come nearer the truth than do those based on the single cause principle because the majority of deaths actually result from a combination of causes»* (Janssen, 1940). So statisticians have long been aware of the idea that death often results from the conjunction of several diseases, conditions or risk factors, but their main efforts have focused on producing tables that assign one single cause to each death and on ensuring quality and cross-country comparability for this underlying cause of death (UC). As we enter the 21st century, cause-specific mortality analysis is still primarily conducted on the basis of the UC, but this does not mean that the multiple[4] cause-of-death (MCOD) data have been entirely ignored.

Firstly, the US, where MCOD data have been produced in electronic format since 1968, pioneered methodological research in this field. Following Janssen's recommendation, statisticians of the US National Center for Health Statistics (Guralnick, 1966) have proposed a number of methods for tabulating and analysing multiple causes of death. Since then, a variety of indicators have been developed to describe the frequency of multiple-cause of death certificate entries and to investigate relations between contributing and underlying causes of death (for a review of these methods see Désesquelles *et al.*, 2012). Secondly, a growing number of countries produce MCOD databases.

4. Multiple causes include both underlying and contributing causes.

These developments encouraged us to engage in a comparative study using the French and Italian MCOD data. The French National Institute for Health and Medical Research (INSERM) has provided access to the complete information reported on the death certificates since 2000, simultaneously with the adoption of the 10th revision of the International Classification of Diseases (ICD-10) and the implementation of an automatic coding system. In Italy, codes for all reported conditions have been available in databases since 1995, with the introduction of the automated coding system (Istat, 2004), but the first official release of MCOD data is for 2003, when the ICD-10 was adopted. Apart from data availability issues, one of the reasons why MCOD data has not been analysed as extensively as it could be is the widely shared scepticism about data quality. For this reason, much of our attention has been devoted to evaluating the quality of our data. In addition to that, we have improved existing indicators, specifically so that they can be used for cross-country comparisons. We first used this tool kit to produce results for France and Italy at quite aggregated levels of the ICD-10 (Désesquelles *et al*., 2010), before focusing our attention on specific groups of causes (e. g. cancers, Alzheimer's disease and Parkinson's disease, and infectious diseases).

This paper is the result of a critical and reflective exercise on our experience so far. We discuss the relative strengths and weaknesses of the MCOD approach on the basis of previous research findings. The paper has two main parts. We begin with an in-depth investigation of the data quality. We then address the question raised in the title of the paper: is the underlying cause of death sufficient? We give several reasons why we think that the multiple cause-of-death approach should be used alongside the underlying cause-of-death approach to analyse mortality. In the last part of the paper, we report on the main challenges that would confront the research community if this approach were to be adopted.

What do we know about MCOD data quality?

A two-step process

The production of cause-of-death statistics relies on two steps that are both crucial for quality. First, the certifying physician reports on the certificate the chain of events leading to death. Second, this information

is coded. A growing number of countries now use an automatic coding system. To our mind, this innovation represents a major advance towards improved data quality. Human intervention is limited to problematic cases that cannot be processed automatically and, at least in theory, the WHO coding rules can be applied systematically and uniformly, irrespective of the coding agent or the country.

Regarding certification problems, several questions need to be raised. Do the certifying physicians always report all the causes that directly led to death (part I of the international form recommended by the WHO[5]) as well as every «*other significant conditions contributing to the death but not relating to the disease or condition causing it*» (part II of the form)? Do they only report causes that actually contributed to the lethal process? Do they always report the causes in the correct order and on the right part of the certificate? Is the same contributing cause equally reported whatever the underlying cause? The answer to these questions is probably negative but the extent and direction of potential bias due to cases of misreporting is difficult to assess.

The average number of entries on the death certificate: A quality indicator?

It is sometimes suggested that the average number of entries on the death certificates is an indicator of the data quality (White *et al*., 1989). And indeed, some of our results support this line of interpretation. In a recently published paper (Désesquelles *et al*., 2012) we show that the average number of entries is higher when the death occurs in hospital[6]. Information available to the certifying physician is likely to be more complete when the death occurs in a medical facility. The fact that the average number of entries increases up to age 80 reflects the growing complexity of the clinical picture with age, but its decline at older ages may result from a less thorough description of the morbid process when death occurs at very old ages. So the average number of entries on the death certificates is obviously affected by data quality, but its variations may also reflect real differences in the morbid process (e. g. depending on the UC), so it would be hazardous to interpret this number as a pure unique indicator of quality.

5. See copy in appendix 1.

6. This result is obtained after controlling for the decedent's age group and underlying cause of death.

Lessons from the cross-country comparison

In the studies we have conducted so far (Désesquelles *et al*., 2010, 2012), we compare France and Italy. The French and Italian cause-of-death data are not fully comparable, but the data collection methods and the health and mortality profiles of the two countries are similar enough to ensure that their comparison is meaningful. The similarity of results for the two countries is striking. Figure 1 illustrates this point in a condensed way. It presents a broad comparison of the values[7] of the Cause-of-Death Association Indicator (CDAI) in France and in Italy. The CDAI (Désesquelles *et al*., 2010) is designed to identify the most frequent cause-of-death associations involving a specific (group of) diseases(s)[8]. It is computed as the ratio between:

- the age-standardized prevalence at death of a combination between a contributing cause and an underlying cause among all deaths assigned to that underlying cause;
- the age-standardized prevalence at death of the same contributing cause among all deaths.

The Cause-of-Death Association Indicator is given by the following formula:

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

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

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

$\bar{d}_x$ = standard number of deaths at age x.

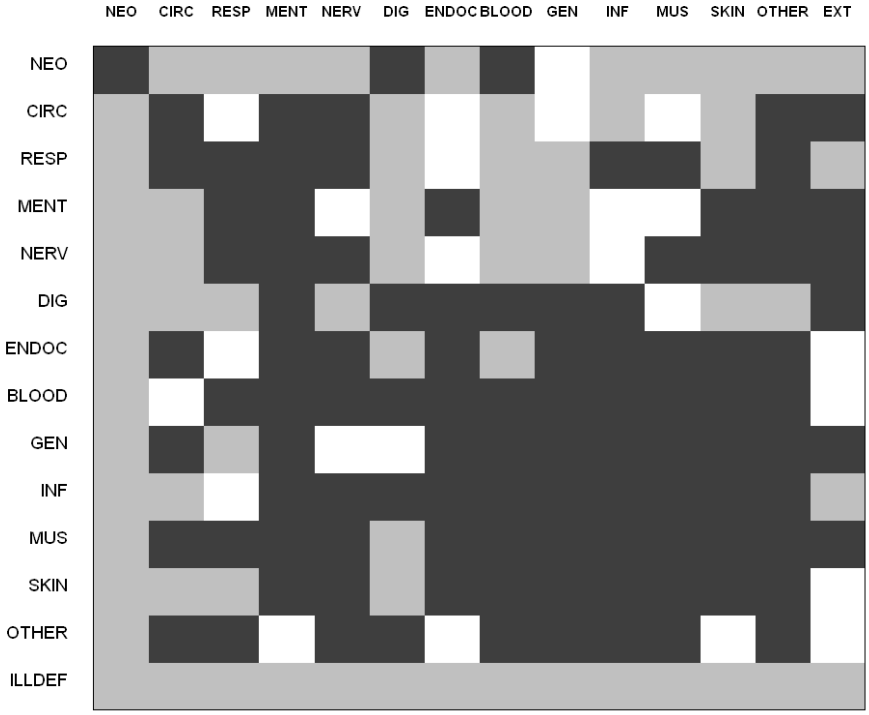
Standardization makes it possible to compare various UCs within a country, as well as a given UC across various countries. The results shown in Figure 1 were computed using standard death counts obtained

7. Data are for year 2003.

8. For a comprehensive and critical presentation of the indicators that can be used to measure the frequency of combinations of causes, see Désesquelles *et al*., 2012.

by averaging the number of deaths in France and in Italy in 2003 by five-year age groups.

FIGURE 1 Comparison of the CDAIs of France and Italy. Deaths over the age of one, excluding deaths from external causes, France and Italy, 2003



Horizontal axis: contributing cause. Vertical axis: underlying cause. See abbreviations in the appendix. Cells corresponding to CDAIs under (respectively over) 100 in both countries are light (respectively dark) grey. Cells corresponding to CDAI over 100 in France or Italy only are white. Data: France: Inserm mortality database / Italy: ISTAT mortality database.

Assuming independence of causes, the numerator and the denominator of the CDAI should be equal. If a CDAI is significantly over 100, then the corresponding association is more frequent than expected. On Figure 1 the cells of the table that results from the cross-matching of every underlying and every contributing cause of death have been coloured according to the values of the corresponding CDAIs in France and Italy. When the CDAI is under (respectively over) 100 in both countries, the corresponding cell on the graph is light (respectively dark) grey. When it is over 100 in France (respectively in Italy) only, it is white. Clearly,

grey (light and dark) is the dominant colour. We are inclined to interpret this similarity as a positive signal for data quality. Unless a clear bias can be identified, similar findings reinforce each other's credibility. But caution is obviously required, and we cannot rule out that similar bias in the two countries leads to similar results.

Consistency with medical knowledge

A third line of discussion with respect to MCOD data quality concerns consistency with medical knowledge. The paper we mentioned before (Désesquelles *et al*., 2012) includes an application of the MCOD approach to cancer-related mortality in France and Italy. On the basis of our detailed analysis of the causes that frequently contribute to cancer mortality we were able to classify them into five patterns of associations:

- The UC results from the degeneration of the contributing cause (e. g. chronic liver disease as contributing cause of a liver cancer). Since the contributing cause preceded the cancer, one might expect it to be selected as the UC. But in some cases, the WHO rules preclude this option.
- The contributing cause is a *risk factor* for the UC (e. g., specifically to France, alcohol and tobacco consumption as contributing causes of several cancers: lung, larynx, upper aero-digestive system, oesophagus, and liver).
- The contributing cause and the UC have a *common cause*. As an example, tobacco use is likely to be the hidden element behind the frequent association we find between bladder cancer and lung cancer. The link between cigarette smoking and bladder cancer is indeed well established (Sasco *et al*., 2004).
- The contributing cause is a *consequence or a complication* of the UC. Not surprisingly, this is the most frequent situation. As an example, we suspect that bone metastases are involved in the frequent association we find between diseases of the musculoskeletal system/connective tissue (mainly: pathological fractures) and several malignant cancers (breast, prostate, as well as lymphoid, haematopoietic and related tissue). Though it is difficult to distinguish between the two, it should be noted that the contributing cause may be a consequence of the UC or of its therapy. The strong association between diseases of the blood and several anatomic cancer sites potentially illustrates the latter case.

– The contributing cause is a *symptom* of the UC (e. g. brain cancer combined with epilepsy). This category may be considered a particular case of the previous one.

A sixth category can also be defined. Contributing causes may play a role as «*background factors for other causes*» (Manton, Stallard, 1982): when combined with another serious disease, the risk of dying increases, reflecting either «*synergistic*» or «*additive*» morbid processes (Speizer *et al.,* 1977). Typically, this is the case for hypertension that has been identified by several authors as a frequent contributing cause of death (Dorn, Moriyama, 1964; Wing, Manton, 1981; Manton, Stallard, 1982; Stallard, 2002).

Our ability to classify a given association in at least one of these categories – note that some associations may well belong to several – depends on the state-of-the-art of medical knowledge. In our opinion, the fact that, at least with regard to cancer mortality, most associations fit in with at least one category – and are therefore in line with medical knowledge – speaks in favour of good data quality. We must also acknowledge that some associations cannot be categorized in any of the proposed groups. In some cases we were able to find elements in the ongoing medical research literature that helped to classify the association. As an example, the associations we find between breast cancer and Alzheimer's disease in France and breast cancer and arthrosis in Italy echo recent research on potential shared mechanisms between breast cancer tumorigenesis on the one hand, and neurodegenerative processes, oxidative stress and inflammation on the other (Staropoli, 2008; Pavlides *et al*., 2010; Hedskog *et al*., 2011). The fact that certifying physicians report associations that are not validated by medical knowledge could be interpreted as a sign of inappropriate certification. However, since part II of the death certificate is for any condition that may have contributed to the death, we think that the reporting of these causes complies with WHO instructions.

Finally, in all our studies, only very few associations cannot be classified into any of our six categories. Do the corresponding certificates reflect «over-reporting» practices? Or do they (even involuntarily) reveal real interactions – whatever the category they belong to – between the reported causes? No doubt further investigation is needed before deciding to reject this second hypothesis.

Why analyse MCOD data?

Besides enhanced data availability and quality – with scope for further improvement – there are several reasons for considering that cause-specific mortality analysis should not be restricted to reporting the underlying cause of death only, but should also consider all contributing causes. The hierarchical organization of causes of death (underlying cause/contributing causes) conveys the idea that:

- one cause can be unambiguously selected as the UC among all the other causes reported on the death certificate, and that
- it is the cause that should receive most attention in public health policies designed to achieve further progress in mortality reduction.

The underlying cause of death is not always certain

It is important to bear in mind that the selection of the underlying cause is a complex decision-making process. In his editorial for the *American Journal of Public Health*, Glasser (Glasser, 1981) wrote:

> «the underlying cause takes on a seemingly sacrosanct monolithic posture. This appearance of certainty is deceiving, of course. The rules for cause of death coding are responsive to the complex chain of events. Here, too, arbitrary decisions are required».

Huge efforts have been made to ensure the quality of the reporting and coding of the UC. These efforts suggest that the task is not an easy one. As mentioned before, the complexity of the pathological profiles of very old persons makes the choice of the underlying cause by the certifying physicians even trickier. So with increasing longevity, the reliability of the UC is likely to decrease.

A handful of studies have tried to assess the reliability of UC selection. For a sample of 372 death certificates reporting ill-defined causes as UC or with at least one contributing cause, D'Amico (D'Amico *et al*., 1999) compared the assigned UC on the death certificate with the cause reattributed after interviewing the certifying physician or examining clinical records. The initially assigned code differed from the modified code for 54% of the ill-defined underlying causes and 55% of the certificates with multiple causes. In a study of 400 cardiac deaths (Mant *et al*., 2006), pairs of clinicians were asked to assign the underlying cause of death independently of each other. They agreed on the cause of death in 54% of cases only. The consensus decision of reviewers agreed with the death certificate diagnosis in 61.5% of the cases. In another study,

Tsung-Hsueh Lu (Tsung-Hsueh Lu *et al*., 2010) developed an algorithm to identify incorrect causal sequences on death certificates where diabetes was reported in Part I. The frequency of incorrect statements increased from 22% in 1985 to 35% in 2005.

MCOD is a useful tool for prevention policies

Regarding the idea that public health policies should focus on underlying causes of death, we believe that interventions targeted at causes other than the UC could also reduce mortality. Our categorization of the associations of causes provides a useful framework to support this view. Risk factors for the UC as well as diseases/conditions that caused both the UC and a contributing cause can be the target of primary and secondary prevention. Contributing causes that are consequences/complications of the UC (or its therapy) are typically the focus of tertiary prevention. As an example, in our study on Parkinson's disease, Alzheimer's disease and other dementias, we found that lung diseases due to external agents (mainly: pneumonitis due to food and vomit), malnutrition and other nutritional deficiencies (mainly: unspecified protein-energy malnutrition), diseases of the skin and subcutaneous tissue (mainly: decubitus ulcer), «other diseases of the genitourinary system» (mainly: urinary tract infection) as well as pneumonia, frequently contribute to deaths from these diseases. All these causes reflect circumstances such as bed confinement, loss of autonomy, and frailty that often characterize the end of life of people affected by these diseases. Better care provision might eliminate some of these contributory factors, while at the same time improving patients' quality of life.

Reassessing the role of certain causes in mortality

Finally, whatever their role in the process leading to death, there is a need to measure and monitor the weight of these contributing causes in overall mortality. For that purpose we compute the so-called «standardized ratio of multiple to underlying cause» (SRMU) which is defined as the ratio between[9]:

9. For a comprehensive and critical presentation of the indicators that can be used to measure the frequency of multiple-cause death certificate entries, see Désesquelles *et al*., 2012.

– the age- and sex-standardized mortality rates for a given disease reported as either underlying or contributing cause of death.
– the age- and sex-standardized mortality rates for the same disease reported as UC.

The SRMU measures the extent to which the role played by a disease in overall mortality is underestimated when the analysis is performed using the underlying cause only. It is low for diseases that are usually selected as the UC and high for diseases that are rarely the UC. Table 1 displays the results for deaths in France and Italy at ages 65 and over. The highest values are for diseases of the skin and the subcutaneous tissues (7 in France and 15 in Italy), diseases of the blood (6 in France and 11 in Italy), diseases of the genitourinary system (5 in France and 9 in Italy), infectious and parasitic diseases (4 in France and 5 in Italy), and for endocrine, nutritional and metabolic diseases (4 in France and 4 in Italy). SRMU also has a value of 4 in Italy for «diseases of the musculoskeletal system/connective tissue» and for «diseases of the respiratory system». So the role played by these groups of diseases in overall mortality is significantly underestimated. By contrast, most entries of a neoplasm are selected as the UC (SRMU in both countries is only slightly over 1). In our detailed analysis of cancer-related mortality (Désesquelles *et al.,* 2012), we show that most site-specific values of the SRMU are close to one. The most notable exception is for prostate cancer (1.4 in both countries). It may reflect the fact that prostate cancer is often diagnosed at advanced ages when people may have already developed other diseases. It may also indicate better survival chances for this cancer:

> «Better therapies for some diseases (ex: neoplasm) may result in death from another cause with the treated disease listed as contributing rather than underlying the death» (White, 1989).

And indeed – and this is another example of the aforementioned «background factor» category –, though not directly causing the death, prostate cancer may have contributed to it, either because the combinations of the cancer with another disease increased the patient's vulnerability or because treatments were not compatible.

Again, the results given in table 1 show that the causes whose weight in mortality is most severely underestimated when the UC only is considered, are common to both countries. However, it is also worth noting that the values of the SRMUs are almost always higher in Italy than in France. This result is obviously related to the fact that, on average, more causes are reported on the death certificates in Italy than in France (after excluding ill-defined mentions, 3.2 vs 2.5 for 2008). But it may also be that the propensity to select certain conditions as the underlying

cause differs in the two countries. Typically, this may occur for degenerative diseases, which often result in complex morbid processes. In that case, cross-country comparison based on the underlying cause only will lead to erroneous conclusions. This strongly supports the argument for examining cross-country similarities and dissimilarities in the underlying cause-of-death mortality rates in the light of results of MCOD analysis.

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 at ages 65 and over, France and Italy, 2008

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	46	232	5	62	263	4
Neoplasms	1'084	1'239	1	987	1'107	1
Diseases pf the blood (forming organs), immunological disorders	15	175	11	13	81	6
Endocrine, nutritional and metabolic diseases	155	606	4	121	437	4
Mental and behavioral disorders	94	242	3	101	298	3
Diseases of the nervous system	119	338	3	173	346	2
Diseases of the circulatory system	1'409	2'303	2	900	1'472	2
Diseases of the respiratory system	261	1'007	4	215	612	3
Diseases of the digestive system	141	440	3	130	309	2
Diseases of the skin and subcutaneous tissue	5	70	15	10	65	7
Diseases of the musculoskeletal system/connective tissue	21	89	4	23	61	3
Diseases of the genitourinary system	65	561	9	62	283	5
Other diseases	2	18	7	2	12	6
Symptoms, signs, abdominal findings, ill-defined causes and mechanisms of death	79	-	-	236	-	-
External causes	105	155	1	155	278	2
Total	3'601	-	-	3'035	-	-

Data: France: Inserm CépiDc mortality database; Italy: ISTAT mortality database.

The multiple cause-of-death approach: challenges for the research community

This last point supports our introductory statement that the single-cause and the multiple-cause approach should not be considered as competing but rather as complementary. The single-cause approach has proven to be a powerful tool for analysis of mortality trends and for cross-country comparisons. The MCOD approach unquestionably provides a more detailed picture of how people die. As such, it is a useful tool for

understanding morbid processes leading to death and for implementing appropriate public health policies. But the method is still in its infancy. As mentioned above, efforts to improve data quality are needed, such as harmonization of death certificates, or better training of physicians in the specific problems of multiple-cause reporting. We are convinced that the growing use of the MCOD data by the research community will give the impetus for data collection improvements. In turn, the availability of comparable indicators for a number of countries will provide new insights into data quality issues.

In that perspective, methodological choices regarding the use of the MCOD data must be discussed widely within the scientific community. As an example, the way we compute the denominators of the CDAIs is not neutral: the leading causes of death contribute more to the value of the denominator than other causes of death. As a consequence, associations involving causes that frequently contribute to deaths due to a cancer or a disease of the circulatory system are less likely to emerge as strong associations. Other solutions should be explored[10]. A methodological choice must also be made about how to count entries that belong to the same subgroups of the – more or less detailed – aggregated list of causes. In our previous studies, these causes are counted only once to calculate the SRMUs. Similarly, for CDAIs, only one mention of a given group as contributing cause is considered in the computation[11]. Distinct ICD-10 codes that are considered «redundant» with an aggregated classification could of course be considered as different if a more detailed categorization were chosen. This implies that values of the indicators computed at different levels of the classification cannot be compared. One option is to compute all indicators at the lowest level of the ICD-10. Yet, while this solution looks nice on paper, it is largely impracticable for the production of readable tables and graphs. This said, we think there is a need to develop new visual tools and statistical methods. The analysis we have conducted so far includes the computation of pairwise joint prevalences of every combination of underlying and contributing cause. This could be extended further to account for all the information report-

10. One possible alternative consists in replacing the $\frac{d_{c,x}}{d_x}$ terms in the denominator by the average value, for the various UCs, of the $\frac{{}_u d_{c,x}}{{}_u d_x}$ terms. In fact, both formulas lead to very similar results (see Désesquelles *et al*., 2012).

11. In cases where the underlying cause and the contributing cause belong to the same group, this association is counted once too.

ed on death certificates[12]. To achieve the objective that underpins our research – that of understanding more fully how people die – the huge amount of information we already process will inevitably increase.

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Appendix 1.
WHO recommended death certificate

INTERNATIONAL FORM OF MEDICAL CERTIFICATE OF CAUSE OF DEATH

Cause of death		Approximate interval between onset and death
I		
Disease or condition directly leading to death*	(a)	.....
	due to (or as a consequence of)	
Antecedent causes Morbid conditions, if any, giving rise to the above cause, stating the underlying condition last	(b)	.....
	due to (or as a consequence of)	
	(c)	.....
	due to (or as a consequence of)	
	(d)	.....
II		
Other significant conditions contributing to the death, but not related to the disease or condition causing it	.....	.....
	.....	.....

**This does not mean the mode of dying, e.g. heart failure, respiratory failure. It means the disease, injury, or complication that caused death.*

Appendix 2.
Abbreviations used for figure 1

Multiple cause group	Abbreviation
Infectious and parasitic diseases	INF
Neoplasms	NEO
Diseases of the blood(-forming organs), immunol. disorders	BLOOD
Endocrine, nutritional and metabolic diseases	ENDOC
Mental and behavioural disorders	MENT
Diseases of the nervous system	NERV
Diseases of the circulatory system	CIRC
Diseases of the respiratory system	RESP
Diseases of the digestive system	DIG
Diseases of the skin and subcutaneous tissue	SKIN
Diseases of the musculoskeletal system/connective tissue	MUS
Diseases of the genitourinary system	GEN
Other diseases	OTHER
Symptoms, signs, abnormal findings, ill-defined causes	ILLDEF
External causes	EXT