Innovations in medical care and mortality trends from four circulatory diseases between 1970 and 2005

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Background: Governments have identified innovation in pharmaceuticals and medical technology as a priority for health policy. Although the contribution of medical care to health has been studied extensively in clinical settings, much less is known about its contribution to population health. We examine how innovations in the management of four circulatory disorders have influenced trends in cause-specific mortality at the population level. Methods: Based on literature reviews, we selected six medical innovations with proven effectiveness against hypertension, ischaemic heart disease, heart failure and cerebrovascular disease. We combined data on the timing of these innovations and cause-specific mortality trends (1970–2005) from seven European countries. We sought to identify associations between the introduction of innovations and favourable changes in mortality, using Joinpoint-models based on linear spline regression. Results: For both ischaemic heart disease and cerebrovascular disease, the timing of medical innovations was associated with improved mortality in four out of five countries and five out of seven countries, respectively, depending on the innovation. This suggests that innovation has impacted positively on mortality at the population level. For hypertension and heart failure, such associations could not be identified. Conclusion: Although improvements in cause-specific mortality coincide with the introduction of some innovations, this is not invariably true. This is likely to reflect the incremental effects of many interventions, the time taken for them to be adopted fully and the presence of contemporaneous changes in disease incidence. Research on the impact of medical innovations on population health is limited by unreliable data on their introduction.

Introduction

It is now widely accepted that improvements in health care are among the factors that have contributed to the reductions in mortality observed in all industrialized countries over recent decades. However, while this view can draw on a wealth of research showing that specific interventions improve the outcomes of various diseases, with at least some of the studies measuring reduction in mortality, it has been rather more difficult to attribute the decline in deaths from particular conditions to specific interventions. A few studies have found associations between the timing of certain interventions and reductions in mortality at the level of populations, but such analyses are few.1–3 Yet, the extent to which innovations in health care have actually contributed to population health gain is a non-trivial but important question that is still not answered adequately.1–3 Several studies have tried to quantify the impact of health care on the decline in cardiovascular mortality after 1970 assuming that there are factors attributable to medical care (cholesterol, hypertension, other treatments) and external factors (smoking, alcohol and nutrition). Yet, while there is considerable disagreement on the magnitude of the impact, varying between 25,4 40,5–9 7110 and 75%,11 there is a consensus that the contribution of medical care is far from trivial.

This article presents a new methodology to assess empirically the effect of selected medical innovations on four cardiovascular causes of death, which are among the most common in the European Union.

Hypertension

Although this condition is often considered as a risk factor for other circulatory diseases, it is also an important cause of death in its own right. In the last few decades, several treatments have been introduced, such as beta-blockers, angiotensin converting enzyme (ACE) inhibitors, diuretics and calcium antagonists.12 However, while all have been shown to be effective in lowering blood pressure in clinical trials, there is a lack of direct evidence linking their use to a decrease in mortality from hypertension at a
population level, probably because such an effect has previously been assumed and it would be impossible to differentiate the effect of any particular class of drug given the considerable overlap in their introduction. Therefore, we chose as key intervention the progressive expansion of those eligible for treatment with anti-hypertensive drugs (expansion to older patients and those with lower initial blood pressure).

**Ischaemic heart disease**

Major innovations have included thrombolytics, \(^{13,14}\) beta-blockers \(^{15,16}\) and coronary care units. \(^{17,18}\) We chose the latter two because reliable data on the introduction of thrombolytics was unavailable.

**Heart failure**

As intervention, we selected ACE inhibitors \(^{19,20}\) although diuretics also reduce mortality \(^{21}\) but, as they have been in widespread use for many years it would have been more difficult to obtain data on the timing of their introduction.

**Cerebrovascular disease**

The most important intervention was the prevention by treatment of hypertension, which is the most important risk factor for stroke. \(^{22–24}\) In principle, this refers to the interventions against hypertension listed above. Partly their effect on stroke has been recognized only after their introduction against hypertension. A second important innovation against cerebrovascular disease (CVD) is the intensive management of acute stroke, with brain imaging followed by thrombolytic therapy and surgical intervention where appropriate. \(^{25,26}\)

In the present study, we analyze whether the introduction of the chosen medical innovations coincided with declines in cause-specific mortality in seven European countries between 1970 and 2005.

**Methods**

**Mortality data**

We studied Estonia, France, Germany-West, The Netherlands, Spain, Sweden and the UK, which represent different European regions and health systems. For these countries, cause-specific mortality data covering the whole population and describing the period from 1970 to the latest available year (2005, 2006 or 2007) by 5-year age categories and gender were provided by the national statistical offices. Data on mortality from heart failure could not be obtained in Estonia because the Soviet coding system was used in the early part of the period. An overview of the number of deaths and the exact ICD coding is given in table 1.

**Selection of relevant medical innovations**

Country-specific information was obtained on the year of introduction and the process of diffusion for six health care innovations related to the four causes of death. To define a distinct clinical innovation of proven effectiveness introduced between 1970 and 2005, a series of systematic literature reviews was undertaken, which sought two types of evidence on the effectiveness of the innovation on mortality. First, evidence from well-conducted observational studies documenting a decline in mortality that could plausibly be attributed to the intervention and, second, randomized controlled trials showing a decline in mortality in those studied of \(\geq 30\%\). This was more difficult than expected as surprisingly few trials used mortality as an end point and many of those were on highly selected populations. Applying these criteria yielded six interventions related to the chosen conditions (table 2).

**Timing of introduction of medical innovations in seven European countries**

We developed a questionnaire in which national experts were asked to identify sources of information about the introduction of innovations and to provide information from a wide range of data sources, such as national guidelines, committee reports, scientific publications, expert interviews and data on registration and on introduction and sales of pharmaceuticals. National formularies were hand searched for evidence that a drug was included in a national benefits package. Documentation of the main source of information for each innovation in each country is provided as online material. The information was carefully checked for consistency and plausibility identifying both early signs of the introduction and indications of continued diffusion. This was integrated within a theoretical framework of ‘diffusion of innovation’ \(^{27}\) further developed by Rogers \(^{28,29}\) to determine when a favourable change in mortality at a population level in each country could be expected. Based on the timing of introduction, we derived periods of 4–9 years where a decline in cause-specific mortality could be expected, taking into account two time lags, one for a sufficient diffusion of a medical innovation, and one for the impact on mortality on the patient level. Within the project we made sure that the periods were defined without taking the mortality trends into account.

**Description of mortality trends**

To identify significant changes in mortality that might be associated with health care, we used jointpoint models based on linear spline regression (using the software R) to identify ‘knots’ in the national gender-specific mortality trend that mark the years in which the mortality trend changes significantly. \(^{30,31}\) We restricted the model to three knots, i.e. three changes in the mortality trend between 1970 and 2005, as visual inspection of all graphs showed that this reflects all actual mortality trend accurately. Besides the timing of the knots, this analysis also produced the Percent Annual Change for each of the periods between the knots.

Within the period between 1970 and 2005, several ICD-coding systems were in use. We developed a method to calculate correction factors to adjust for the influence of changes in ICD coding on the

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**Table 1** Number of deaths by cause (ICD-9 and ICD-10), country and gender

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
<td>Men</td>
<td>Women</td>
</tr>
<tr>
<td>France (1970–2005)</td>
<td>89 244</td>
<td>149 286</td>
<td>954 608</td>
<td>760 620</td>
</tr>
<tr>
<td>Netherlands (1970–2007)</td>
<td>12 750</td>
<td>20 253</td>
<td>487 888</td>
<td>330 232</td>
</tr>
<tr>
<td>Spain (1970–2007)</td>
<td>47 484</td>
<td>88 261</td>
<td>725 146</td>
<td>517 370</td>
</tr>
<tr>
<td>Sweden (1970–2006)</td>
<td>87 84</td>
<td>12 668</td>
<td>560 258</td>
<td>417 955</td>
</tr>
<tr>
<td>UK (1970–2006)</td>
<td>80 833</td>
<td>102 404</td>
<td>2 871 221</td>
<td>2 238 964</td>
</tr>
</tbody>
</table>
mortality trends based on the Polydec method. To take into account of any possible cohort effect on mortality trends an age-period-cohort analysis was performed. As these analyses did not identify cohort effects, we retained the original analyses. Based on the spline regression, we produced figures with the mortality trend age-standardized with the European standard population. In a first set of analyses, no age limit was used. Then we repeated the analysis for the age range 0–74 years.

**Association between mortality trends and innovations in health care**

We established whether a favourable change in mortality ('knot') occurred during the period of expected mortality decline. If a knot falls within this period, this was defined as a 'match', suggesting that the innovation had a positive impact on mortality. To conclude that a certain number of matches is sufficient evidence for an association, we followed two approaches:

a) Likelihood test: For each cause of death, we calculated the likelihood to find the actual number of matches under the assumption that the knots are randomly distributed in time. From this theoretical probability, we derived the expected number of matches and compared this with the actual number of matches. The observed probability of a match is then compared with the theoretical probability and we report the statistical significance of this difference. Finding reliable data on the introduction of innovation in each country was a difficult task and we had to use different datasets with varying reliability. Because of these problems, we performed a sensitivity analysis that grouped the data on innovation into better groups of more and less reliability and repeated the statistical sensitivity analysis that divided the innovation data into two periods of varying reliability. Because of these problems, we performed a sensitivity analysis that divided the innovation data into two periods of varying reliability. Because of these problems, we performed a sensitivity analysis that divided the innovation data into two periods of varying reliability. Because of these problems, we performed a sensitivity analysis that divided the innovation data into two periods of varying reliability. Because of these problems, we performed a sensitivity analysis that divided the innovation data into two periods of varying reliability. Because of these problems, we performed a sensitivity analysis that divided the innovation data into two periods of varying reliability. Because of these problems, we performed a sensitivity analysis that divided the innovation data into two periods of varying reliability. Because of these problems, we performed a sensitivity analysis that divided the innovation data into two periods of varying reliability. Because of these problems, we performed a sensitivity analysis that divided the innovation data into two periods of varying reliability.

b) Count of matches by condition on the level of countries: To reveal which of the four causes of death were responsive to predefined innovations in health care, we counted the countries that show a match for a condition, weighting countries where only one sex showed the association by 0.5. If more than half of all countries with available data show the association, we interpreted this as evidence consistent with an impact of the innovation on mortality. A detailed description of our study design has been published elsewhere.

**Results**

Table 2 gives an overview of the periods of expected mortality decline for each innovation. If a favourable change in mortality ('knot') falls within this period, we present the year of this match in the line below the period.

Figure 1a–d shows the mortality trends of the four causes of death for all countries for men. The straight horizontal lines below the mortality graphs indicate the period of mortality decline that can be expected as a consequence of the specific innovation in health care. Mortality from hypertension (figure 1a) decreased in the 1970s in almost all countries, and in some countries it increased again in the 1990s, resulting in a U-shaped trend in mortality. In France, mortality from hypertension has increased, followed by a decrease after 1976. In Estonia, a limited decline of mortality was observed followed by a sharp increase after 1995. Mortality from ischaemic heart disease (IHD) (figure 1b) has declined since the 1970s in many European countries, but with variations in the speed of mortality decline. This decline was preceded by an increase in some countries. Mortality from heart failure (figure 1c) decreased steeply in the 1970s in most countries, but the decline slowed down in later decades, and in some countries, periods of decreasing mortality alternate with periods of increasing mortality. Mortality from CVD (figure 1d) has strongly decreased in all countries throughout the study period from 1970 to 2005 with several fluctuations. The only exception is Estonia, where mortality was almost stable and even increasing for men until 1993, followed by a steep decline. Across causes of death, international mortality differences tend to converge during the study period, which may partly be due to a floor-effect, but also to the exchange and spread of health care practice across Europe leading to similar mortality levels (corresponding figures for women and for the two remaining medical innovation are available as online-only content Supplementary figures 1–8).

The upper part of table 3 shows the results of the likelihood test for the randomness of the occurrence of matches. The assumption of a random distribution can be rejected only for CVD because for this cause of death, the number of matches found in our analysis is significantly higher than would be the case by pure chance. It should be mentioned that the statistical power of this test by cause of death is low and so is the chance of a significant difference. A sensitivity analysis that grouped the data on innovation into better
Figure 1 (a) Estimated standardized all-age mortality trend from hypertension for men and expected period of mortality decline based on timing of an increased number of patients. (b) Estimated standardized all-age mortality trend from IHD for men and expected period of mortality decline based on timing of introduction of beta-blockers. (c) Estimated standardized all-age mortality trend from heart failure for men and expected period of mortality decline based on timing of introduction of ACE inhibitors. Note: after discussion of the Estonian mortality data with national experts and data providers and literature reviews, we decided to exclude Estonia from the study of heart failure because the data on mortality from hypertension was unreliable. (d) Estimated standardized all-age mortality trend from CVD for men and expected period of mortality decline based on introduction of prevention by treatment of hypertension.

Table 3 Test for the likelihood of the number of matches found and counts of countries with a match

<table>
<thead>
<tr>
<th>Likelihood test for each CAUSE OF DEATH</th>
<th>Hypertension</th>
<th>IHD</th>
<th>Heart failure</th>
<th>CVD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of favourable knots, M + F for all countries</td>
<td>11</td>
<td>68</td>
<td>12</td>
<td>51</td>
</tr>
<tr>
<td>Theoretical probability of a match</td>
<td>0.20</td>
<td>0.20</td>
<td>0.20</td>
<td>0.20</td>
</tr>
<tr>
<td>Expected number of matches</td>
<td>2</td>
<td>14</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>Actual number of matches</td>
<td>4</td>
<td>15</td>
<td>1</td>
<td>17</td>
</tr>
<tr>
<td>Observed probability of a match</td>
<td>0.36</td>
<td>0.22</td>
<td>0.08</td>
<td>0.33</td>
</tr>
<tr>
<td>P-value for the difference between theoretical and observed probability (one-sided $\chi^2$ test)</td>
<td>0.142</td>
<td>0.369</td>
<td>0.074</td>
<td>0.027</td>
</tr>
</tbody>
</table>

Counts of matches for each INTERVENTION

<table>
<thead>
<tr>
<th>Counts of matches for each INTERVENTION</th>
<th>Increased number of patients</th>
<th>Coronary care units</th>
<th>Beta-blockers</th>
<th>ACE inhibitors</th>
<th>Intensive management</th>
<th>Treatment of hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Two sexes match</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>0</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>One sex matches</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>No match</td>
<td>4</td>
<td>1</td>
<td>2</td>
<td>5</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>No data</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Association</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

For some conditions, data on mortality could not be used or data on innovations were unavailable; therefore, the total number of countries that could be taken into account is sometimes less than seven.
and poorer quality found that where the data were of higher quality there were statistically significant differences for all conditions, whereas the lower quality data show no significant differences (results not shown).

Our main criterion for identifying evidence of an effect of health care is the count of countries showing an association between health care and mortality (table 3, lower part). We counted the number of countries where we found (i) a match for both sexes, (ii) a match for only one sex and (iii) no match. The results suggest that mortality from IHD and CVD has been responsive to main relevant innovations because for them we find a match in more than half of the countries. To explore the age sensitivity of our results according to the common assumption that the amenability of mortality is higher below a certain age limit, we repeated the analysis also to mortality from 0 to 74. This did not result in a closer correlation between innovation dates and changes in mortality (results not shown). More results from this study can be found in the final project report at http://amiiehs.lshtm.ac.uk.

Discussion

This study sought to determine whether the introduction of important medical innovations coincided with a favourable change in the trend of mortality from four circulatory causes of death in seven European countries. We found such a correlation for IHD and CVD, while for hypertension and heart failure we did not. In addition to these new findings on the effect of medical innovations on population health, our study demonstrates a rigorous approach to linking changes in population health to the timing of medical innovations. Some limitations must be mentioned: First, when defining the conditions and the main interventions for this study, we were faced with the considerable problem that some treatments are used for several related health conditions and that these indications may vary over time. The use of anti-hypertensives increased before they were shown to prevent CVD. Consequently, their use may have influenced mortality from CVD earlier than was indicated in guidance for prevention of CVD. A similar, albeit smaller, problem may occur for ACE-inhibitors and heart failure, as they were used for treatment of hypertension before they were used for heart failure. However, patients with heart failure may have had also hypertension and may have received the drug for their hypertension. Second, we focus on medical innovations. Yet improvements in population health owing to health care reflect three factors: innovations, improvement in the quality of care and mortality differences among countries and regions, which are in-}

Estonia, average systolic blood pressure has decreased between 1980 and 2008.36 Our study relates to two strands of epidemiologic literature: the first explores the general impact of health care on cardiovascular diseases, and the second tries to more specifically look at certain conditions as indicators of amenable mortality, based on the obvious requirement that to be a useful indicator for the quality of health care, mortality from a chosen cause of death needs to be responsive to major innovations in health care. With regard to the first, the literature on this topic that we presented above found a significant effect of health care on cardiovascular mortality. Most of these studies are focussed on single countries and they use different approaches to their estimates: from reasonable assumptions based on background data to advanced statistical models. Our international comparative approach confirms the effect of innovations on mortality from two cardiovascular diseases and offers the opportunity to assess the effect of health care on a larger geographical scale. On the other hand, it also requires the availability and reliability of national data describing the timing of innovations in health care, including the timing of their widespread adoption. Our test of likelihood combining all expected periods of mortality decline for all countries for one cause of death showed that the overall correlation between our predictions and changes in mortality is weak. Our second approach, counting the number of countries in which an association between innovations and mortality could be found seems more appropriate than looking only at formal statistical significance, first, because of the small number of countries, second, because the statistical test is mainly meant to illustrate the risk of spurious associations and, third, because the statistical test is based on average numbers of expected/actual matches across all countries and not on countries as cases that either show an association or not. The threshold of 50% of all countries is arbitrary but our results and conclusions are not sensitive to the exact threshold because there is such a clear difference in terms of the share of countries showing an association between the four innovations we confirmed and the two we did not confirm. We want to stress that results from both approaches suggest that it is difficult to prove effectiveness of specific medical innovations against circulatory diseases on the population level given the available data.

The more specific issue of validating amenable mortality as an outcome of health care has been addressed in literature by two means; first, time series analyses show considerable declines in mortality from most of the conditions identified as amenable in recent decades.3,4,37 This has been used to support the argument that at least part of the overall mortality decline is due to improvements in health care, but a clear correlation between therapeutic innovation and mortality on the population level has never been established. Second, two studies of geographical variation also find mortality differences among countries and regions,38 which are interpreted as being partly due to differences in health care, but no clear association between predictors in health care and mortality could be found. The fact that our study confirms two out of four potential indicators of amenable mortality among circulatory diseases, led us to the conclusion that such indicators have to be interpreted with caution when being used as indicators of health care performance in a specific country.39 Rates are likely to reflect the influence of health care, but also of many other factors such as life style, incidence and prevalence, which together reflect that different countries may be in different stages of a larger process, e.g. differences in the IHD epidemic between Estonia and Western countries. Our results confirm the effect of health care on population health but also identify the need for further analysis that takes into account these factors and use better data on the timing of medical innovations. Currently, the lack of such data is a barrier for monitoring the contribution of health care to population health, even though it undeniably exists.
Supplementary Data

Supplementary data are available at EURPUB online.

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Conflicts of interest: None declared.

Key points

- Several clinical studies have shown the effect of medical innovation on cardiovascular diseases, but much less is known on their contribution to declines in cardiovascular mortality on the population level.
- We examine how innovations in the management of four circulatory disorders have impacted on trends in cause-specific mortality at the population level in seven European countries between 1970 and 2005.
- Changes in population level mortality reflect many factors within and outside health care. Research on the effect of medical innovations on population health is limited by a lack of reliable data on their introduction.

References