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Trends in in-hospital and out-of-hospital Coronary Heart Disease mortality in French registries during the period 2000 to 2016

Stefy Gbokou¹, Katia Biasch¹, Jean Dallongeville², Samantha Huo Yung Kai^{3,4}, Michèle Montaye², Philippe Amouyel², Aline Meirhaeghe², Jean Ferrières^{3,5}, Marie Moitry^{*1,6}

- 1- University of Strasbourg, Department of Epidemiology and Public Health, Strasbourg, France.
- 2- University of Lille, Inserm, University Hospital of Lille, Institute Pasteur of Lille, U1167 - RID-AGE - Risk factors and molecular determinants of age-related diseases, Lille, France.
- 3- University Paul Sabatier, Department of Epidemiology, Health Economics and Public Health, UMR Inserm 1295, Toulouse, France.
- 4- University Hospital of Toulouse, Department of Public Health, Toulouse, France.
- 5- Toulouse Rangueil University Hospital, Department of Cardiology, Toulouse, France.
- 6- University Hospital of Strasbourg, Department of Public Health, Strasbourg, France.

All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

***Corresponding author**

Marie Moitry, University of Strasbourg, 4, rue Kirschleger, 67085 Strasbourg CEDEX, France. Fax: +33 (0)3 68 85 31 89. Tel: +33 (0)3 68 85 31 95. E-mail: mmoitry@unistra.fr

ABSTRACT

Purpose: To estimate trends of in- and out-of-hospital Acute Coronary Events (ACEs) mortality rates from 2000 to 2016 and their respective contributions to total ACE mortality in France.

Methods: All fatal coronary events occurring between January 2000 and December 2016 were recorded for patients age 35 to 74 in the French MONICA registries. Trends in age-standardized and crude mortality rates were expressed as annual percentage change (APC).

Results: Between 2000 and 2016, 20,822 fatal events were recorded, of which 69.4% were out-of-hospital. Almost 90% of out-of-hospital deaths occurred at home. Decreases in ACE mortality were greater inside than outside the hospital (APC: -4.3% versus -2.9% in men; -5.0% versus -3.2% in women), resulting in a higher contribution of out-of-hospital mortality to overall ACE mortality, from 65.3% in 2000 to 71.4% in 2016. This trend was more pronounced for elderly than younger patients.

Conclusions: Between 2000 and 2016, ACE mortality declined in France. This trend was more pronounced for in- than for out-of-hospital. These results underline the importance of out-of-hospital mortality in driving ACE mortality rates and the need to further investigate ways to reduce it.

Word count: 185

Keywords

Acute coronary syndrome; coronary heart disease; in-hospital mortality; mortality rate; out-of-hospital mortality; registries

Abbreviations

CHD: Coronary Heart Disease

ACE: Acute Coronary Event

SMR: Standardized Mortality Rate

CMR: Crude Mortality Rate

APC: Average Percentage Change

MI: Myocardial Infarction

INTRODUCTION

In recent decades, a constant fall in Coronary Heart Disease (CHD) mortality rates has been observed, in particular across Western countries and Europe [1–4]. Many factors, including improvements in risk factor control in primary care, more sensitive biological diagnosis, progress in medical management and intensification of secondary prevention, have contributed to a regular decline of CHD rates and a decrease in mortality rates, with some variability across countries [5,6].

Death from CHD occurs either in a medical environment during hospitalization, or out of hospital during a severe ischemic event. Improvements in medical care in the acute phase of CHD events are likely to explain the decrease in in-hospital mortality. On the other hand, healthier lifestyle habits, control of risk factors and increased accessibility to pre-hospital life-saving procedures may contribute to the decrease in out-of-hospital CHD mortality. Addressing the issue of place of death from CHD is therefore crucial to understanding how prevention measures may contribute to further reduce CHD mortality [7].

Previous reports have shown a steeper decrease in in-hospital CHD mortality compared to out-of-hospital mortality in the 1990s and early 2000s [8–10], and thus an increase in the proportion of CHD deaths occurring outside the hospital [10,11]. Since then, the definition of Myocardial Infarction (MI) has substantially evolved. Whereas in the past, MI was characterized by elevated CPK and Q waves on the ECG, ACE are now defined by repolarization abnormalities and elevated troponin levels. These changes might have affected, at least partially, CHD epidemiological indicators [12,13] and particularly CHD mortality rates. Thus, precise and up-to-date information on both in- and out-of-hospital CHD mortality, based on the most recent standardized definition of fatal coronary events is necessary to adapt public health strategies and to reduce preventable CHD deaths.

Therefore, the objective of this study was to estimate trends in in- and out-of-hospital ACE mortality rates from 2000 to 2016 and their respective contributions to total CHD mortality. To this end, we mobilized data from the population-based CHD MONICA registries, which record in- and out-of-hospital fatal ACEs using a standardized and a reproducible protocol.

MATERIAL AND METHODS

Study population

Data were provided by the French Coronary Heart Disease population-based registries from three administrative regions: Bas-Rhin, Urban Community of Lille, and Haute-Garonne. All fatal Acute Coronary Events (ACE) occurring between January 1st, 2000 and December 31st, 2016 were recorded according to the WHO MONICA initial protocol, for subjects aged 35 to 74 years living in one of the three geographical areas covered by the registries. These registries cover approximately five hundred thousand inhabitants belonging to the 35-74 age group.

These registries constitute the national network of registries subordinate to the national epidemiological surveillance agency. Their methodology is validated and approved by the National Registry Committee and is used for official national statistics in France (Santé Publique France).

Data sources and classification of events

Diagnostic criteria and coding rules are based on the WHO MONICA Manual [14], extended and updated to comply with most recent definitions of acute coronary event. All deaths (either in- or out-of-hospital) among the 35–74 year population are identified and selected for validation from a list of diagnoses recorded on the death certificates, according to the International Classification of Diseases, ninth or tenth revision (ICD9-10). This list includes all fatal events with an ischemic cardiac cause (ICD9 codes 410–414, ICD10 codes I21; I22, I23, I24, I25) whether as underlying, immediate or associated cause. Also, other fatal events from cardiovascular cause such as ICD9 codes 415, 425–429, 430–438, 440–444, ICD10 codes I27, I44-52, I64, I70-79; or other fatal events with no precise cause of death such as ICD9 codes 798 and 999 or ICD10 codes R95-99, whether as underlying or immediate cause, are selected for further investigation. Details on circumstances of out-of-hospital deaths, including nature of symptoms (cardiac arrest, thoracic pain or other symptoms evocative of a coronary event) and time elapsed between first symptoms and death is then obtained with interviews with the physician who signed the death certificate and, if necessary and possible, with the patient's general practitioner or cardiologist. Emergency medical service records and autopsy reports are also checked when available. Existence of previous CHD is checked in the MONICA database and, GPs are specifically interviewed for further investigations when needed. In-hospital fatal events are thoroughly investigated by means of the hospital medical

records. These events may also be found with the continuous verification of all discharge diagnoses in the cardiology and emergency departments of the three geographical areas. Finally, hospital database systems on hospitalizations with an acute coronary event occurring in all hospitals regardless of the department are annually screened for event completion.

After thorough research, each death is classified in a diagnostic category:

- Myocardial Infarction (MI). The fatal event occurred during the 28 days following MI definitely diagnosed as such, whether clinically or at autopsy.
- Coronary death. Fatal event, whether sudden or not, for which there is no good evidence of another cause of death (clinically or at autopsy) and with typical or atypical symptoms, or with a history of chronic CHD, or with evidence of chronic coronary occlusion or stenosis or old MI at necropsy.
- Possible coronary death. Rapid death in less than 24 hours, with no history of typical or atypical symptoms, no history of chronic CHD, no necropsy and with no other diagnosis.
- Death with insufficient data. The cause of death remains unknown and/or the time until death could not be determined. As previously, it is a death with no history of typical or atypical symptoms, no history of chronic CHD, no necropsy and with no other diagnosis.
- Non-coronary death.

For this study, only events characterized in the MONICA protocol as fatal myocardial infarctions, coronary deaths or possible coronary deaths are included. Deaths with insufficient data or non-coronary death are excluded, such as deaths for which location cannot be clearly identified (N=45).

The definition of in- and out-of-hospital deaths is based on the place where the death occurred. Out-of-hospital deaths are deaths occurring at home (including non-medicalized departments such as retirement homes, psychiatric or rehabilitation institutions), in public places or in an ambulance. In-hospital deaths are deaths occurring in cardiology, intensive care or other medical units of a hospital center. Persons brought to the hospital with a cardiac arrest in whom resuscitation attempts were unsuccessful are defined as an out-of-hospital death. If a patient hospitalized with an ACE was discharged within 28 days after the episode and finally died outside the hospital in that time period, the death is considered as out-of-hospital (N=276).

Data quality insurance

According to the MONICA procedures, data on each death is double-checked and validated by the principal investigator of each center. In case of discrepancy, the case is discussed with other members of the team for case ascertainment. Data items are subjected to logic checks and a diagnostic algorithm in each center. The core data are sent to the coordination Data Centre in Strasbourg, where further checks are rerun, reinforcing local quality assurance procedures. Rigorous efforts are made to prevent and detect changes in coding over time and thereby to confirm that any apparent trends detected are genuine.

Statistical methods

Qualitative variables were described by percentages and compared using Chi square tests. Mortality rates were calculated using the number of deaths (in- or out-of-hospital) as the numerator, and the person-years at risk in the area covered by the registries provided by the National Institute of Statistics and Economic Studies (INSEE) as the denominator. Overall, in- and out-of-hospital age-standardized mortality rates (SMRs) were estimated using the corresponding 10-year age group in the standard world population [15]. Crude mortality rates (CMRs) were estimated by sex, 20-year age group and calendar year. The respective proportions of in- and out-of-hospital mortality rates in overall CHD mortality were calculated. Then, trends in overall in- and out-of-hospital mortality rates were estimated using the Joinpoint Regression Program using the zero joinpoint model (version 4.7.0.0, February 2019; Statistical Methodology and Applications Branch, Surveillance Research Program, National Cancer Institute, Bethesda, MA, USA) [16] and expressed as annual percentage changes (APC). We considered the mortality rate as the dependent variable and the calendar year as the independent variable. The 95% confidence intervals of APCs were calculated using the standard error. Finally, we used log-linear Poisson regression models to test interactions between year, sex, place of death and age. P values for trends and interaction significance were 2-tailed. Their significance threshold set was set at 0.05. Analyses were performed using SAS 9.4 and Joinpoint 4.7.0.0 software (National Cancer Institute, Statistical, applications Branch).

RESULTS

From 2000 to 2016, 20,822 fatal ACEs were recorded. Overall SMRs decreased over the period from 146.2 per 100,000 inhabitants to 83.2 per 100,000 in men and from 46.1 to 25.4 per 100,000 in women (supplementary material).

Out-of-hospital mortality (Table 1)

More than two-thirds of deaths were out-of-hospital deaths (69.4%, N=14,456), among which 89.3% occurred at home. Subjects who experienced out-of-hospital death were 4 years younger than those who were initially treated at hospital (median 67 years vs. 63, $p < 10^{-4}$), and were less often affected by pre-existing CHD (25.8% vs. 51.5%, $p < 10^{-4}$). A larger proportion of out-of-hospital deaths occurred within less than an hour after the first symptoms (54.1% vs. 17.1% for in-hospital deaths, $p < 10^{-4}$).

In- and out-of-hospital mortality (Table 2, Figures 1 and 2)

The contribution of out-of-hospital mortality to overall ACE mortality increased from 65.3% to 71.4% between 2000 in 2016 (supplementary material). In-hospital SMRs decreased more rapidly than out-of-hospital (-4.5% vs. -2.9%, p for interaction $< 10^{-4}$). The same trends were observed when analyses were performed by sex: in men, in-hospital SMRs annually decreased by -4.3%, while a -2.9% annual decrease was observed for out-of-hospital (p for interaction = 10^{-4}). In women, annual decreases were -5.0% and -3.2%, respectively (p for interaction = 0.002).

On the other hand, trends in in- and out-of-hospital mortality differed according to age. In the 55-74 age group, declines in in-hospital mortality were more pronounced than out-of-hospital in both men (APC -5.2%, vs. -3.6%, p for interaction $< 10^{-4}$) and women (APC -6.3% vs. -3.9%; p for interaction $< 10^{-4}$). In contrast, in the 35-54 age group, the in- and out-of-hospital CMRs trends were similar in men (APC -1.4% vs. -1.6%, p for interaction = 0.87) and women (APC -3.5% vs. -3.0%, p for interaction = 0.73).

DISCUSSION

In the French CHD population-based MONICA registries, between 2000 and 2016, almost 70% of fatal ACEs occurred outside the hospital, 90% of which occurred at home. In the meantime, ACE mortality declined. This trend was more pronounced for in-hospital than out-of-hospital deaths, especially in the 55-74-year age group, whereas the decline in in-hospital and out-of-hospital ACE mortality was similar in the 35-54 age group. These results underline the weight of out-of-hospital mortality in driving coronary mortality trends and the need to further investigate ways to prevent it, especially in young adults.

Out-of-hospital mortality

In this population-based study, a high proportion of deaths from ACE (70%) occurred outside the hospital. Similar observations have been reported by others in Europe [10,11] and the USA [8]. Out-of-hospital CHD deaths include a heterogeneous group of cases, mainly of people who died suddenly from their first-ever acute coronary event (incident event) or those who died from a recurrent event. In this study, three-quarter of out-of-hospital deaths occurred among subjects with no history of CHD, especially in the youngest age categories (86.2%). Contrary to most chronic diseases, out-of-hospital death is often the first manifestation of CHD in young adults [17], and thus calls for better detection of high risk subjects at a younger age. Younger people, who are at lower risk of CHD, are less likely to be appropriately screened and treated for possible cardiovascular risk factors or less aware of prodromic symptoms and therefore less likely to seek emergency care. As for patients with a past history of CHD, our results show that the vast majority (96%) died more than 28 days after their previous event, suggesting that their fatal ACE was not related to a recent exacerbation of their index event. For this population, rigorous secondary prevention, follow-up of compliance with treatment and promotion of a healthy lifestyle should be intensified.

Interestingly, more than 50% of out-of-hospital deaths occurred within one hour after onset of the first symptoms, and 90% occurred at home (i.e., very few at work, in public places or in the Medicare ambulance). In the presence of a witness, presence of automatic defibrillators in public places, such as stadiums, is undeniably useful [18], but remains insufficient for out-of-hospital cardiac arrests with an initial non-shockable rhythm, or for those occurring at home. Consequently, the ability of bystanders to administer proper cardiopulmonary resuscitation, in addition to the deployment of automatic defibrillators is crucial, as the survival and long-term functional outcomes of patients presenting with out-of-hospital cardiac arrest greatly depend on both [19]. This supports the importance of promoting life-saving techniques in the general population.

Trends in in- and out-of-hospital ACE mortality

The higher contribution of out-of-hospital mortality to CHD mortality trends is in line with the transition observed from in- to out-of-hospital mortality in previous cohorts [10]. In our study, between 2000 and 2016, in- and out-of-hospital ACE mortality rates decreased in both sexes, with in-hospital mortality decreasing more steeply. These trends are consistent with previous observations [4,8–10,20,21], and extend the conclusions of those observations to a more contemporary cohort, using the most recent diagnosis criteria for myocardial infarction. Analysis by age group, however, revealed that the steeper decrease in in-hospital mortality was primarily driven by trends in the oldest age group (55-74 age group), which seems to have largely benefitted from improvements in CHD diagnosis and management in the acute phase.

Methodological aspects

This study has several strengths. It provides recent, comprehensive data on CHD mortality over a seventeen-year period, with a total headcount of more than 20,000 fatal events recorded by three French MONICA registries from distinct geographical areas: North, East and South-West.

These registries, which have collected data on ACEs since the 1980s, have a high degree of case ascertainment and comprehensiveness, based on standardized data collection and multiple data sources: hospital charts, data from emergency departments, death certificates and interviews with practitioners. All subjects aged 35-74 and living in one of the three areas covered by the registries are included, regardless of where death occurred. Moreover, data collection is standardized, and criteria for the definition of fatal events remained unchanged over the period (regardless of changes in international classification codes in death certificates or evolutions in ACE definitions), thus it is unlikely that this may have affected mortality rates.

The major input of this study is its focus on the respective contributions of in- and out-of-hospital mortality to overall ACE mortality. Recent data on out-of-hospital mortality (including patients who had never been hospitalized for coronary events) are currently lacking. Population-based registries are run to record comprehensive data on all fatal events, wherever the death occurs. Hospital data, obtained from medico-administrative information systems or intensive care databases are basically focused on in-hospital events in France.

Limitations

One limitation of this study is that the analyses presented here were performed on French data only. Generalization to other countries, particularly those with different CHD risk factors may therefore be limited.

Another limit is that the registries included subjects aged 35-74 years old and no trends above this age could be assessed. Yet this age range is optimal for promoting CVD prevention measures early on to avoid CHD events at an older age. Although they are less affected by CHD, targeting young people might be important in terms of future quality of life, potential years of life lost, and consequences for families and the community [11].

As in most population investigations on CHD mortality, a misclassification of coronary death is possible, and the issue of sudden death etiology may be raised. However, CHD is known to be the most common cardiac disease underlying out-of-hospital cardiac arrests [22], with up to two-thirds of out-of-hospital sudden cardiac deaths being related to ischemic heart disease [23]. This proportion can even reach 70 to 75% among men age 35 and over [17], men being represented in the largest numbers in our population study. Only systematic autopsies, which are rarely performed in real life in France, could ultimately identify the cause of death. The issue of sudden death etiology remains debated, and our work cannot be an exception. Our methodology is however transparent, and remained unchanged over the study period. Deaths with non-cardiac cause were not included in this study. Furthermore, case ascertainment in the MONICA registries is made after in-depth investigation into the cause of death by trained staff, verified by the principal investigator. Consequently, even non-coronary etiologies of sudden deaths (cardiomyopathies, inherited arrhythmia syndromes, and valvular heart disease) cannot be excluded, and we are confident that our results are robust and reliable.

Despite the high number of events recorded, coronary deaths occurring in the youngest group remain rare, especially in women. For example, in 2016, only 42 deaths were recorded in women aged 35-54, of which 10 were out-of-hospital, resulting in some fluctuations in mortality rates. However, given the high level of completion of our registries, apart from a lack of precision, it is unlikely that this could affect or bias our results.

As the MONICA registry also includes patients who could not get to a hospital in time – thus for whom most of the clinical information is not available - data on the cardiovascular risk factors of these patients could not be collected. Consequently, we could not simultaneously assess the trends in CHD mortality and their risk factors.

However, in contrast to observational studies, or hospital series, data from population-based registries are exhaustive and thus unbiased with respect to case selection.

CONCLUSION

Over the 2000-2016 period, both in- and out-of-hospital CHD mortality decreased. The decrease was less pronounced for out-of-hospital mortality, especially among the youngest subjects. This highlights the need to improve the means for detecting high risk subjects and focusing attention on primary and secondary prevention. Furthermore, intensification of life-saving training programs for the entire population may further help to reduce CHD mortality.

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AUTHORS' CONTRIBUTIONS

SG, KB, JD, SHYK, MMon, PA, AM, JF and MMoi contributed to the conception or design of the work. SG, KB, JD, SHYK, MMon, PA, AM, JF and MMoi contributed to the acquisition, analysis, or interpretation of data for the work. SG, JD and MMoi drafted the manuscript. SG, KB, JD, SHYK, MMon, PA, AM, JF, and MMoi critically revised the manuscript for important intellectual content.

ETHICAL APPROVAL

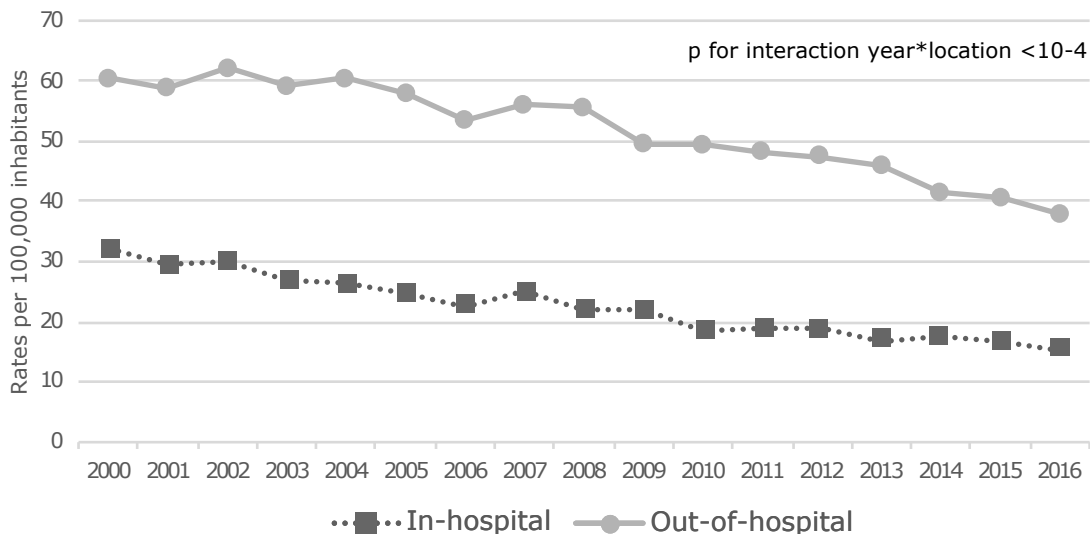
The study complies with the Declaration of Helsinki. It was approved by the advisory committee on data processing in health research (Comité Consultatif sur le Traitement de L'information en Matière de Recherche dans le domaine de la Santé; reference: 97.002.B), the French national data protection commission (Commission Nationale de l'Informatique et des Libertés; reference: 997139-v3) and the French national registry committee (reference: 2016/12/1).

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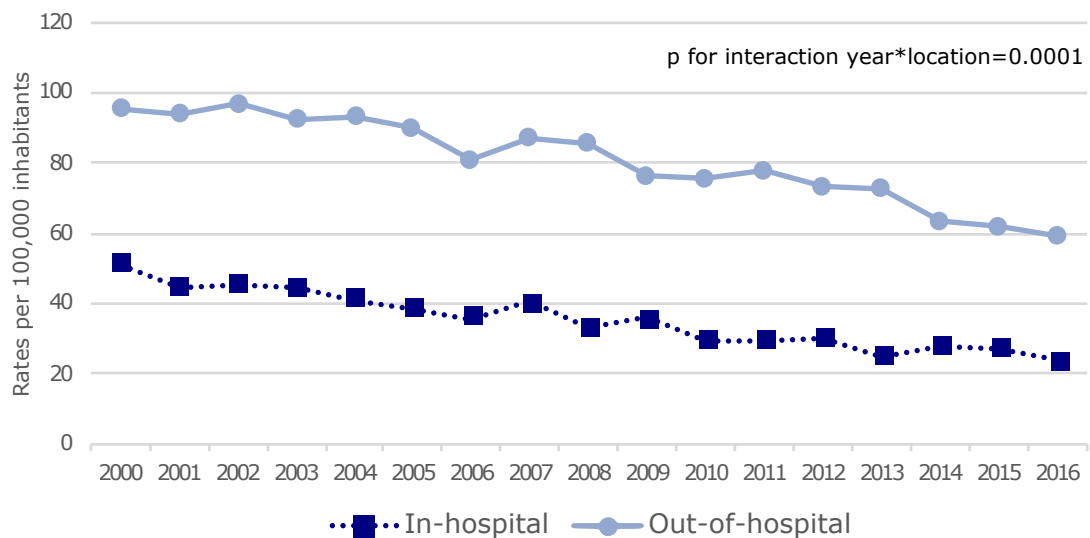
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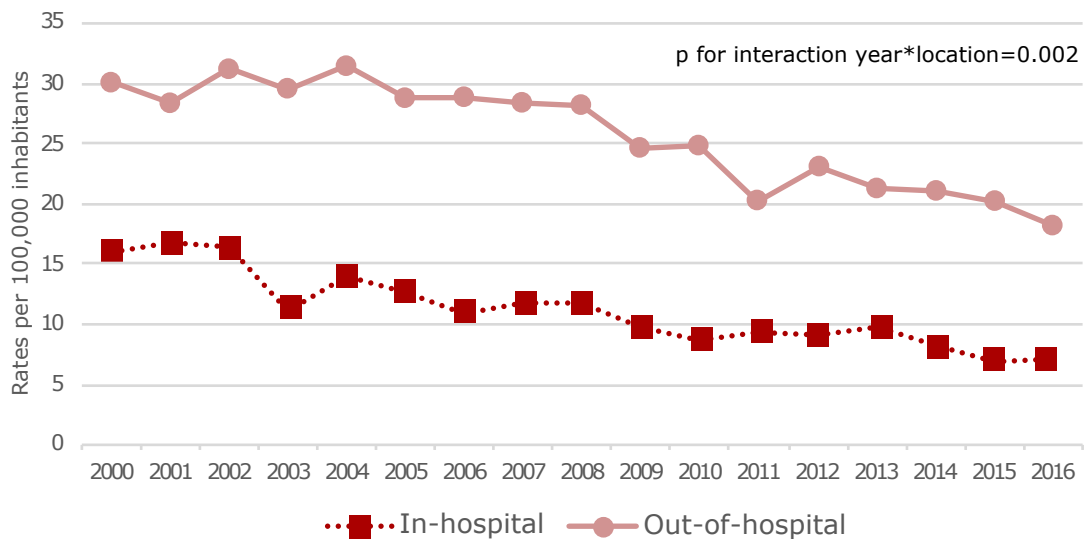
Trends in age-standardized CHD mortality rates



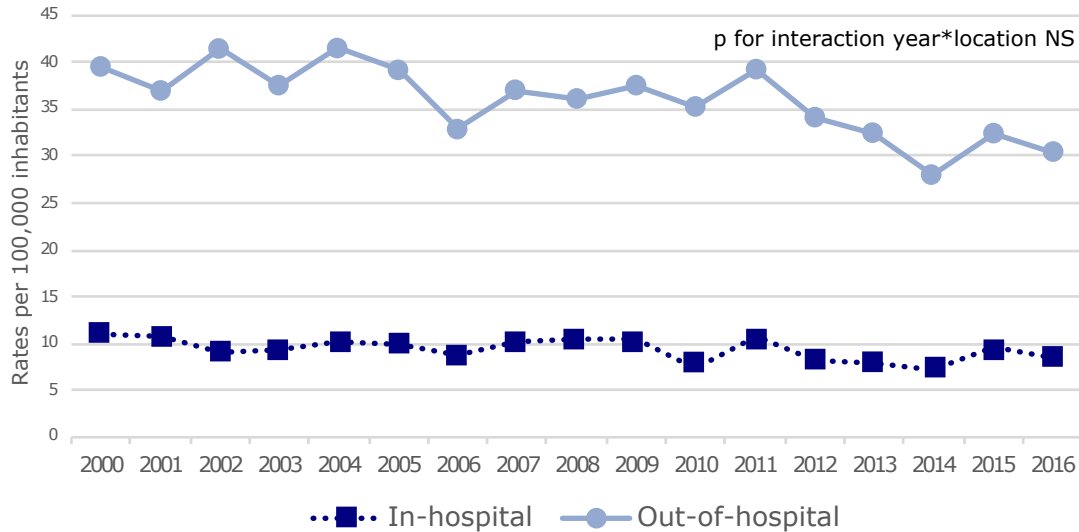
Men: trends in age-standardized CHD mortality rates



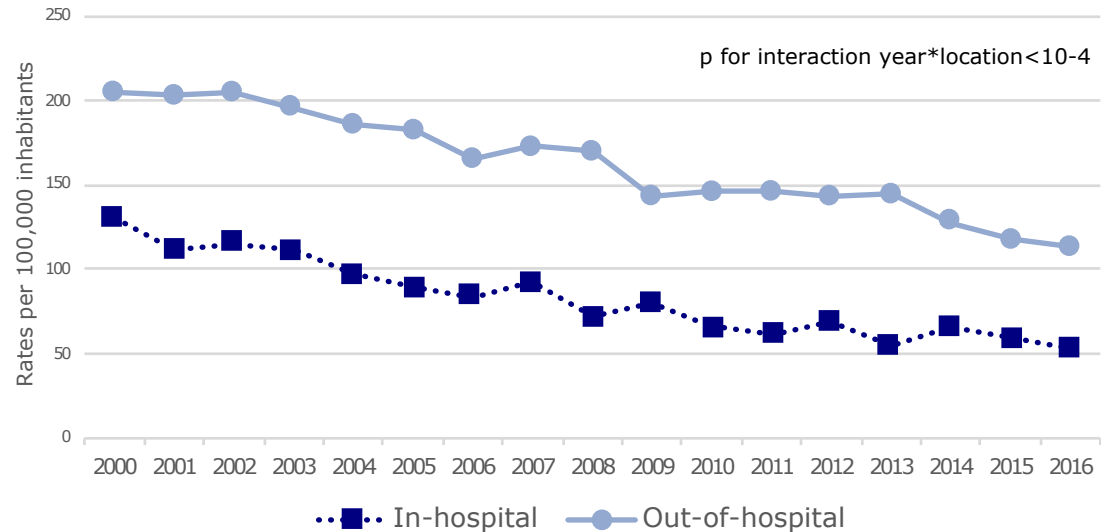
Women: trends in age-standardized CHD mortality rates



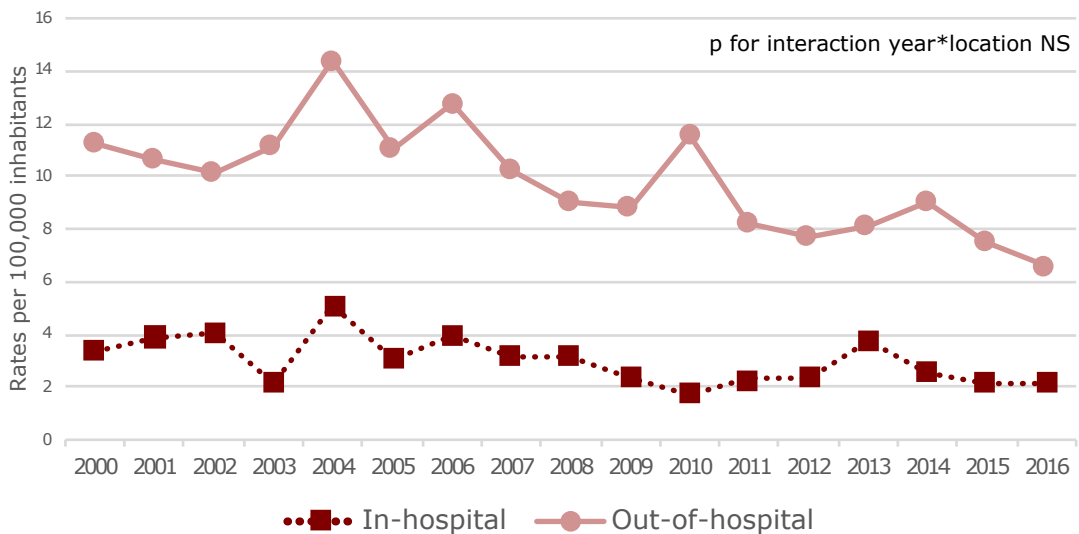
Men age 35-54 : trends in CHD crude mortality rates



Men age 55-74 : trends in CHD crude mortality rates



Women age 35-54 : trends in CHD crude mortality rates



Women age 55-74 : trends in CHD crude mortality rates

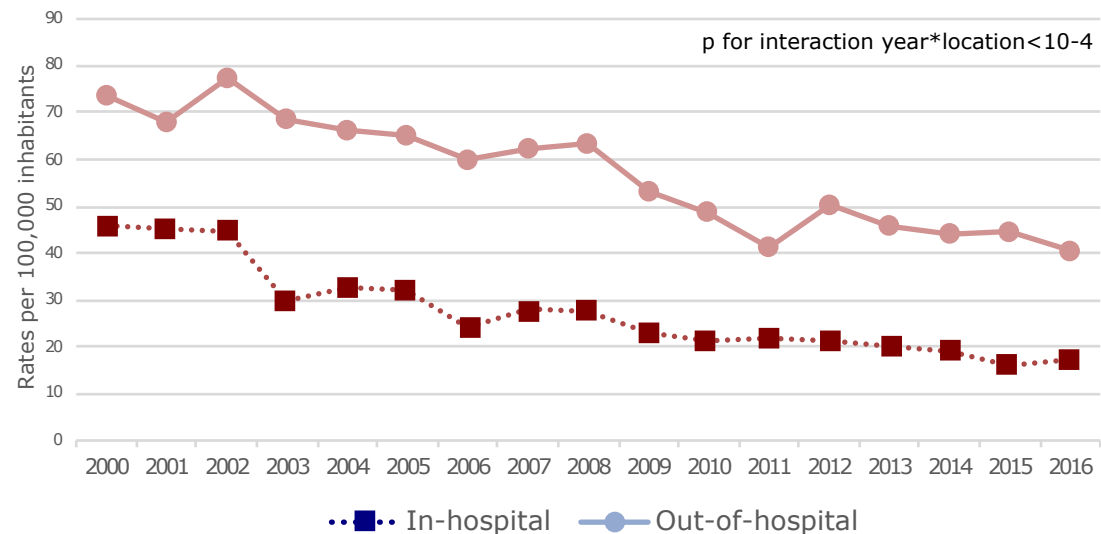


Table 1. Characteristics of fatal events according to in- or out-of-hospital location

	In-hospital		Out-of-hospital		p
	N	%	N	%	
	6,366	30.6	14,456	69.4	
Sex					
Men	4,667	73.3	10,604	73.4	0.9
Women	1,699	26.7	3,852	26.7	
Age*	67	[59 - 71]	63	[54 - 70]	
35 - 54 y	979	15.4	3,630	25.1	<10 ⁻⁴
54 - 74 y	5,387	84.6	10,826	74.9	
Past CHD history[†]					
No	3,035	48.5	10,465	74.2	<10 ⁻⁴
Yes	3,226	51.5	3,645	25.8	
Time between symptom onset and death^{††}					
<1h	1,086	17.1	7,779	54.1	<10 ⁻⁴
1-24h	2,255	35.6	6,378	44.3	
>24h	3,000	47.3	225	1.6	
Location of death					
Emergency Room	491	7.7%	-	-	
Intensive care - cardiology department	4,189	65.8%	-	-	
Other medical department	1,686	26.5%	-	-	-
Home	-	-	12,905	89.3%	
Public place	-	-	1,409	9.7%	
Ambulance	-	-	142	1.0%	

*Median, interquartile range

†Missing N =451

††Missing N=99

Table 2. Trends in in- and out-of-hospital CHD mortality rates by sex and 20-year age group, adults age 35 to 74 years – 2000 to 2016

		Total		Men		Women	
		APC (95% CI)	P Trends	APC (95% CI)	P Trends	APC (95% CI)	P Trends
Total†	In-hospital	-4.5 (-4.9 to -4.1)	<10 ⁻⁵	-4.3 (-4.9 to -3.7)	<10 ⁻⁵	-5.0 (-6.0 to -4.0)	<10 ⁻⁵
	Out-of-hospital	-2.9 (-3.4 to -2.4)	<10 ⁻⁵	-2.9 (-3.4 to -2.4)	<10 ⁻⁵	-3.2 (-3.9 to -2.4)	<10 ⁻⁵
35 - 54††	In-hospital	-1.9 (-3.1 to -0.8)	0.002	-1.4 (-2.6 to -0.2)	0.02	-3.5 (-6.2 to -0.8)	0.02
	Out-of-hospital	-1.9 (-2.6 to -1.2)	<10 ⁻³	-1.6 (-2.4 to -0.8)	<10 ⁻³	-3.0 (-4.6 to -1.4)	0.001
55 - 74††	In-hospital	-5.4 (-6.1 to -4.8)	<10 ⁻⁵	-5.2 (-6.0 to -4.5)	<10 ⁻⁵	-6.3 (-7.3 to -5.3)	<10 ⁻⁵
	Out-of-hospital	-3.6 (-4.1 to -3.2)	<10 ⁻⁵	-3.6 (-4.0 to -3.1)	<10 ⁻⁵	-3.9 (-4.6 to -3.1)	<10 ⁻⁵

APC: Annual Percentage Change

CI: Confidence Interval

†APCs for age-standardized CHD mortality rates

††APCs for crude CHD mortality rates