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### ► To cite this version:

Aline Meirhaeghe, Michèle Montaye, Katia Biasch, Samantha Huo Yung Kai, Marie Moitry, et al.. Coronary heart disease incidence still decreased between 2006 and 2014 in France, except in young age groups: Results from the French MONICA registries. *European Journal of Preventive Cardiology*, 2020, 27 (11), pp.1178-1186. 10.1177/2047487319899193 . hal-02896567

**HAL Id: hal-02896567**

**<https://hal.science/hal-02896567>**

Submitted on 17 Nov 2020

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**CHD incidence still decreased between 2006 and 2014 in France, except in young age groups. Results from the French MONICA registries.**

**Aline Meirhaeghe<sup>a</sup>, Michèle Montaye<sup>a</sup>, Katia Biasch<sup>b</sup>, Samantha Huo Yung Kai<sup>c,d</sup>,**

**Marie Moitry<sup>b,e</sup>, Philippe Amouyel<sup>a</sup>, Jean Ferrières<sup>c,f</sup>, Jean Dallongeville<sup>a</sup>**

<sup>a</sup> INSERM UMR1167, RID-AGE, Risk Factors and Molecular Determinants of Aging-Related Diseases, Université de Lille, Centre Hosp. Univ Lille, Institut Pasteur de Lille, Lille, France.

<sup>b</sup> Department of Epidemiology and Public Health, Faculty of Medicine, University of Strasbourg, Strasbourg, France.

<sup>c</sup> UMR 1027, INSERM, Paul Sabatier University Toulouse III, Toulouse, France.

<sup>d</sup> Department of Public Health, Toulouse University Hospital, Toulouse, France.

<sup>e</sup> Department of Public Health, Strasbourg University Hospital, Strasbourg, France.

<sup>f</sup> Department of Cardiology, Toulouse University School of Medicine, Rangueil Hospital, Toulouse, France.

**Corresponding author:**

Aline Meirhaeghe, PhD

INSERM UMR1167, Institut Pasteur de Lille

1 rue du Pr Calmette - BP 245

F-59019 Lille Cedex, France

Tel.: +33-320-877-257

Fax: +33-320-877-894

E-mail: [aline.meirhaeghe@pasteur-lille.fr](mailto:aline.meirhaeghe@pasteur-lille.fr)

## **Abstract**

### **Background**

Over the last few decades, decreases in coronary heart disease morbidity and mortality rates have been observed throughout the western world. We sought to determine whether the acute coronary event (ACE) rates had decreased between 2006 and 2014 among French adults, and whether there were sex- and age-specific differences.

### **Methods**

We examined the French MONICA population-based registries monitoring the Lille urban area in northern France, the Bas-Rhin county in north-eastern France, and the Haute Garonne county in south-western France. All ACEs among men and women aged 35-74 were collected.

### **Results**

Over the study period, the age-standardized attack rates decreased in both men (annual percentage change (APC):-1.5%,  $p=0.0006$ ) and women (APC:-2.1%,  $p=0.002$ ). Also, the age-standardized incidence rates decreased in both men (APC:-0.9%,  $p=0.03$ ) and women (APC:-1.8%,  $p=0.002$ ), due to decreases in the 65-74 age group. In men, age-standardized mortality rates decreased by 3.5% per year ( $p=0.0004$ ), especially in the 55-64 and 65-74 age groups. In women, these rates decreased by 4.3% per year ( $p=0.0009$ ), particularly in the 35-44 and 65-74 age groups. We also observed significant decreases in case-fatality among both men (APC:-1.7%,  $p<0.0001$ ) and women (APC:-1.9%,  $p=0.009$ ).

### **Conclusions**

Downward trends in ACE attack, incidence and mortality rates were observed between 2006 and 2014 in men and women. This effect was age-dependent and primarily due to decreases in the 65-74 age group. There were no substantial declines in the younger age groups except for mortality in young women. Prevention measures still need to be strengthened, particularly in young adults.

**Word count: 249 words**

### **Keywords**

Registries, CHD, acute coronary event, incidence, mortality, trends, standardized rates

## **Introduction**

Mortality rates from coronary heart disease (CHD) generally rose during the 20<sup>th</sup> century but started to decline in some countries during the 1960s, in both men and women. Reductions in exposure to risk factors and improvements in treatment have all contributed to the observed reductions in CHD mortality, although estimates of the relative impacts of prevention and treatment vary from one country to another [1–3]. Despite the observed decline in CHD mortality, the World Health Organization (WHO) reported that this condition is still the leading cause of death worldwide and accounted for 9.5 million deaths in 2016 alone [4].

In France, our studies of population-based registries have shown that attack rates for myocardial infarction (MI) and coronary death (CD) decreased continuously between 1997 and 2007 in both men and women [5–7]. Between 2000 and 2007, the decreases in the MI and CD rates were greatest in people aged over 54 [6]. The incidence rates for MI and CD also decreased over this period (-16% in men, and -19% in women) [6].

The objective of the present study of three population-based registries was to determine whether acute coronary event (ACE) rates and the associated mortality rates had decreased between 2006 and 2014 among French adults aged 35-74, and whether there were sex- and age-specific differences in the rates.

## **Methods**

### ***Population***

The French MONICA registries cover three geographical areas of about 1 million inhabitants each: Lille urban area in northern France, the Bas-Rhin county in north-eastern France, and the Haute Garonne county in south-western France. The registries record data on all ACEs among men and women aged 35-74 of each geographical area.

### ***Data collection***

All fatal and non-fatal hospitalized ACEs (including acute myocardial infarction, acute coronary syndrome, and unstable angina) and all in-hospital and out-of-hospital coronary deaths (sudden deaths of people with a history of CHD, or deaths with ischemic symptoms) were recorded. The events were classified as being fatal or non-fatal at 28 days. If several events occurred within 28 days, only the most serious event was selected for analysis. In line with the same registry rules, fatal cardiac events that occurred less than 28 days after an index acute ischemic event were classified as a single fatal coronary event.

Cases were identified from several overlapping sources of case ascertainment (discharge letters, computerised lists covering the diagnosis upon discharge from hospital, emergency department case lists, death certificates, etc.) in all public- and private-sector hospitals and emergency departments in the study areas [5]. To ensure exhaustiveness, the sources were reviewed and cross-checked. Hospitalised cases of ACE were documented on the basis of hospital files. Diagnoses were obtained from the hospital discharge letters. For each fatal case outside hospital, the coronary event was documented by contacting general practitioners and/or mobile emergency medical services, examining the death certificate, and screening the subject's medical records and the registry database for any history of an ACE. For each hospitalised case, the registry investigators collected information regarding symptoms (chest pain, acute pulmonary edema, cardiogenic shock, syncope, successfully resuscitated cardiac arrest), ECGs (ST elevation, Q wave appearance, apparition of a left bundle branch, other repolarization abnormalities, uncodable ECG), troponins (troponins peak value and laboratory cut-off value, regardless of the type of troponins measured). In this work, we did not

directly use these data as we used the clinician diagnoses and we pooled together all acute coronary episodes (MI + ACS + unstable angina + coronary deaths occurring outside of hospitals for which we did not have clinical, ECG or biological information).

The causes of death were checked by reviewing hospital and autopsy records and by interviewing general practitioners [7]. The registry staff analysed the data and then, depending on the subject's medical history and the circumstances of death, classified the event in one of the four following categories: (i) coronary death (including fatal MI), whether sudden or not, (ii) probable CD (death with the symptoms and/or a history of CHD, and lacking another cause of death), (iii) possible CD (rapid death in less than 24 hours but with no history of CHD), or (iv) unknown cause of death (insufficient data). Only cases of unknown cause of death were excluded in the present study.

### **Indicators**

All participants were classified into four 10-year age groups (i.e. 35-44, 45-54, 55-64, and 65-74 years of age). To estimate the event rates, we used the person-years at risk for people in the same age group and of the same sex in the area covered by the registries over the corresponding time period (provided by the French National Institute of Statistics and Economic Studies, *Institut national de la statistique et des études économiques* (Paris, France)) as the denominator. The incidence rate was calculated with the number of *de novo* events as the numerator. The attack rate was calculated with the total number of events (both *de novo* and recurrent events) as the numerator. The 28-day mortality rate was calculated with the number of deaths as the numerator. Rates were expressed per 100,000 inhabitants per year. The 28-day case-fatality (expressed as a percentage) was calculated with the number of deaths at 28 days as the numerator and the total number of events as the denominator.

Direct age-standardization was performed using the corresponding 10-year age group in the standard world population [8].

### **Statistical analyses**

Trends in age-standardized rates were tested by sex, using Boyle & Parkin's method [9]. Regression coefficients were obtained using log-linear Poisson regression models (the *genmod* procedure in SAS (version 9.1, SAS Institute Inc., Cary, NC, USA) adjusted for centre and age group in which the year was the continuous predictor variable. Year x age group interactions were tested by including the corresponding interaction term in the regression models. The annual percentage change (APC) was calculated as (regression coefficient) x 100. The 95% confidence interval (CI) of the APC was calculated from the standard error of the regression coefficient.

Non linear trends and the changes in a given trend was analysed using the Joinpoint Regression Program (Version 4.7.0.0 - February 2019; Statistical Methodology and Applications Branch, Surveillance Research Program, National Cancer Institute, Bethesda, MA, USA), with a maximum of one joinpoint. The Bayesian information criterion was used to select the model that best fitted the data.

With the exception of joinpoint regression, all statistical analyses were performed using SAS software. The threshold for statistical significance was set to  $p < 0.05$ .

## Results

In the period from 2006 to 2014, a total of 35,975 ACEs were recorded: 27,603 (77%) in men, and 8,372 (23%) in women (**Supplementary Table 1 & Supplementary Table 2**). Of these, 24,465 (68%) were incident events (18,368 in men (67%) and 6,097 (73%) in women), and 10,605 (29%) were fatal (7,830 (28%) in men and 2775 (33%) in women).

The crude annual average attack, incidence and fatal ACE rates increased exponentially with age in both men and women ( $p < 0.0001$  for all) (**Figure 1**).

**Table 1** and **Figure 2** show the year-by-year age-standardized attack rates for ACEs by sex. Over the period studied, the overall APC was -1.5% in men ( $p$  trends=0.0006); the attack rate fell from 396 per 100,000 in 2006 to 351 per 100,000 in 2014. The overall APC was -2.1% in women ( $p$  trends=0.002), with a fall in the attack rate from 106 per 100,000 in 2006 to 91 per 100,000 in 2014. Similar decreases over time were observed for age-standardized incidence rates (APC = -0.9% in men,  $p$  trends=0.0072, and -1.8% in women,  $p$  trends=0.0015). The decrease over time was more pronounced for mortality rates. The APC for the mortality rate was -3.5% in men ( $p$  trends=0.03), with a fall in the rate from 114 per 100,000 in 2006 to 89 per 100,000 in 2014, and -4.3% in women ( $p$  trends=0.002), with a fall from 38 per 100,000 in 2006 to 29 per 100,000 in 2014.

**Figure 3** and **Supplementary Table 3** show the year-by-year, age-specific, crude ACE rates (attack, incidence, and mortality).

In men, significant year x age interactions were detected for the attack rate ( $p=0.0035$ ) and the mortality rate ( $p < 0.0001$ ). Indeed, significant decreases over time were observed only in the two oldest age groups (55-64 and 65-74 years) for the attack rate (APC: -1.1% and -2.9%, respectively) and the mortality rate (APC: -3.0% and -4.3%, respectively). Concerning incidence rates, the year x age interaction was not significant ( $p=0.14$ ) but the decrease over time was solely due to a decline in the 65-74 age group (APC: -2.7%).

In women, significant year x age interactions were detected for the attack rate ( $p < 0.0001$ ), incidence rate ( $p=0.0006$ ), and mortality rate ( $p < 0.0001$ ) (**Figure 3** and **Table 3**). A decrease over time was observed for the attack and incidence rates in the 65-74 age group only (APC: -4.6% and -4.3%, respectively). A decrease over time in the mortality rate was observed in both the 35-44 and 65-74 age groups (APC: -6.4% and -11.3%, respectively).

We also calculated case-fatality for the period. In women aged 35-74, one of three events was fatal at 28 days (33%); the rate was slightly lower in men (28%,  $p < 10^{-6}$ ). Time trends in case-fatality revealed a significant decrease in both men (APC: -1.7% per year,  $p < 0.0001$ ) and women (APC: -1.9% per year,  $p=0.009$ ) over the period (**Figure 4**). In men, the decrease over time was significant in the 45-54, 55-64 and 65-74 age groups (**Supplementary Table 4**). In women the decrease over time was significant in the 35-44 age group only.

It is noteworthy that the jointpoint regression analysis, which allows testing for changing direction of trends during the observed period [10], did not reveal any significant changes in time trends over the period for any of the calculated rates (data not shown), meaning that the changes were constant and linear over the 9-year period from 2006 to 2014.

## Discussion

Our analysis of data from three population-based registries, from northern to southern France, showed that ACE attack, incidence, mortality rates and case-fatality in France decreased between 2006 and 2014 in both men and women (APC: -1.5%, -0.9%, -3.5%, and -1.7% respectively in men; -2.1%, -1.8%, -4.3%, -1.9% respectively in women). Earlier reports on the MONICA registries in France (between 1985 and 2000, and between 2000 and 2007) also showed downward trends in these indicators for MI and coronary heart disease [5,7]. The persistence of these favourable trends over a 30-year period [5,6] suggest that primary and secondary prevention measures continue to have beneficial effects. Our present data are in line with the decreases over time in cardiovascular risk factors observed in France since 1985 – especially for hypertension, dyslipidaemia and (only in men) smoking [11–14].

The downward trends observed here are consistent with those recorded by several other European registries. The Swedish national registry showed that overall mortality rates from CHD have been declining since the 1980s [15,16]. Between 1987 and 2009, CHD mortality rates decreased by 67.4% in men and by 65.1% in women aged 35-84 [16], and the decrease was observed in all age groups. In the Czech Republic, Bruthans et al. showed that the CHD mortality rates had decreased by 66% in men and 65% in women aged 25-74 years between 1985 and 2007; 52% of this decrease was attributed to a reduction in major CV risk factors, and 43% was attributed to improvements in care [17]. In a large study of six European registries, MI attack and mortality rates decreased in most populations in both sexes and all age groups between 1985 and 2010 [18]. Last, the Italian MONICA/CAMUNI registry also showed a 3% annual decrease in the incidence rate for MI in both sexes during the 1985-2004 period [19]. Lastly, in the USA, CHD mortality rates between 1979 and 2011 clearly declined in over-65 adults and stagnated in younger men and women (<55 years of age) [20].

Other more recent studies, based on mortality statistics, reported a slowdown since 2010 in CVD (cardiovascular disease)-mortality decline in adults aged 35-74 in high-income countries such as France and even an increase in CVD-mortality in the most recent years in the USA and Canada [21]. As these authors reported combined mortality for both ischaemic heart disease and stroke (CVD), it is difficult to compare their data with ours. Another study, based on hospital admissions from the national French hospitalization database, described that from 2004 to 2014, the annual rates of age-standardized admissions for acute coronary syndromes in women aged less than 65 years increased by 6.3% over the period whereas they decreased by 23% in women aged 65 years or more [22]. These data could appear very different from ours in women below 65 but our population-based registries included both hospitalized and non-hospitalized data and are therefore very different from those coming from a national hospitalization database only. Complementary analyses, separating hospitalized from non-hospitalized patients, are needed to explore these trends.

The observed decrease in ACE mortality rates in both men and women in our registries is quite spectacular. This decrease might be due to a concomitant decrease in incidence rate and case-fatality, since both phenomena were observed over the period in our registries. Hence, the combination of a decrease in new events and a reduction in the proportion of fatal outcomes after an acute event might contribute to the favourable trend in mortality rates seen during the follow-up period. There are several possible explanations for these favourable trends in case-fatality. Firstly, better awareness of the CHD risk could result in earlier interventions by paramedics during the acute phase of the event, which would probably reduce the extent and/or severity of coronary lesions. Secondly, improvements in managing the acute phase of a CHD-related event could also result in better outcome. Lastly, and although secondary prevention is not optimal after an event, these efforts have improved significantly over the last decade [23,24].

The overall decrease in CHD rates concealed some age-group disparities. In men, the decrease in the incidence rate was solely observed in the oldest age group (65-74), whereas the decrease in the mortality rate was detected in the 65-74 and 55-64 age groups. In women, the decrease in the incidence rate was also observed in the oldest age group (65-74), whereas the decrease in mortality was found in the oldest (65-74) and youngest (35-44) age groups. Studies of earlier periods (2000-2007) found a major decrease in the oldest age group in both men and women, and a stagnation in CHD mortality among young women (aged 35-44 or 45-54) [6,7]. In contrast, we observed a clear decrease in the mortality rate in women aged 35-44; this might be due to a decline in both the incidence rate and case-fatality in this group. The reasons for these changes are not clear. Given the small number of events in this age group (510 events and 142 deaths over the 9-year period), these trends need to be confirmed on a longer time scale. However, it is possible that information campaigns about the CHD risk might have improved awareness among young women [25]. Furthermore, owing to increasing awareness on the risk of smoking for foetal development, women aged 35-44 may have stopped smoking because of pregnancy; the average age at first pregnancy in France is 28 [26] and the effect of smoking cessation can therefore be seen in this age group. In this respect, antismoking campaigns and measures have flourished in France since 2003, with a steady increase in the pack price, a total ban on smoking in public places, and the adoption of a less attractive "neutral" pack format. The reduction in the prevalence of smoking [11] probably had a beneficial impact on the ACE incidence rate.

The decrease in CHD incidence rates among the oldest individuals studied here might be related to favourable trends in CHD prevention in the population. It may also be easier to detect favourable trends in older adults than in younger adults, owing to the much larger number of ACEs in the 65-74 age group (n=13,317, accounting for 37% of all ACEs) than in the 35-44 age group (n=2,740, accounting for 8% of all ACEs). Given that risk factors are more prevalent in the oldest ages, progress in CHD prevention may have a greater impact in this group - leading to a decrease in CHD rates. Furthermore, the absence of a decrease in incidence in the youngest age group may be due (at least in part) to smoking - one major cardiovascular risk factor that is more frequent in younger adults than in older adults and that is strongly associated with CHD events among young individuals [27]. This phenomenon could also be attributed to the increasing prevalence of overweight / obesity (and consequently type 2 diabetes) observed in many countries. However, we previously showed that the prevalence of being overweight increased in men but was stable in women over the 1986-2013 period in northern France [11]. A combination of all these risk factors is more likely to explain stagnation among young individuals. Efforts are required to better understand the causes of this stagnation and then to reverse it.

Our study has several limits. Our data relied on contemporary but relatively short-term (9y) period. It would have been interesting to report long-time (30y) trends in ACE incidence but the change of definition of the outcome during that period (MI then ACE) makes it impossible to perform. However, since 1985, we have already periodically reported trends in rates of MI and coronary deaths [5,7]. Then, these data have been observed in three geographical areas in France and may not be generalized to the whole country. Finally, our study might have limited statistical power to detect trends in youngest age groups.

## **Conclusion**

A clear decline in ACE attack, incidence, mortality rates and case-fatality was observed between 2006 and 2014 in both sexes, and especially in the 65-74 age group, documenting the persistence of favourable trends in ACE rate over the past 3 decades in the French population. Primary and secondary prevention measures still need to be strengthened - particularly in young adults to further lower these trends.

## **Ethical approval**

The study 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: 97002.A) and the French National Data Protection Commission (*Commission Nationale de l'Informatique et des Libertés*; reference: 986001v3) and the French National Registry Committee (reference: 2016/11/9).

## **Competing interests**

The authors have no competing interests and no conflicts of interest in relation to this work.

## **Acknowledgments**

We would like to thank the Investigators of the three French centers for their valuable contribution to the careful collection and validation of the data, the physicians and the cardiologists who helped in this process.

## **Funding**

This work was funded by Santé Publique France, INSERM and the Institut Pasteur de Lille.

## **Author contributions**

MA, MM, BK, HYKS, MoiM, AP, FJ and DJ contributed to the conception or design of the work. MA, MM, BK, HYKS, MoiM, AP, FJ and DJ contributed to the acquisition, analysis, or interpretation of data for the work. MA drafted the manuscript. MM, BK, HYKS, MoiM, AP, FJ and DJ critically revised the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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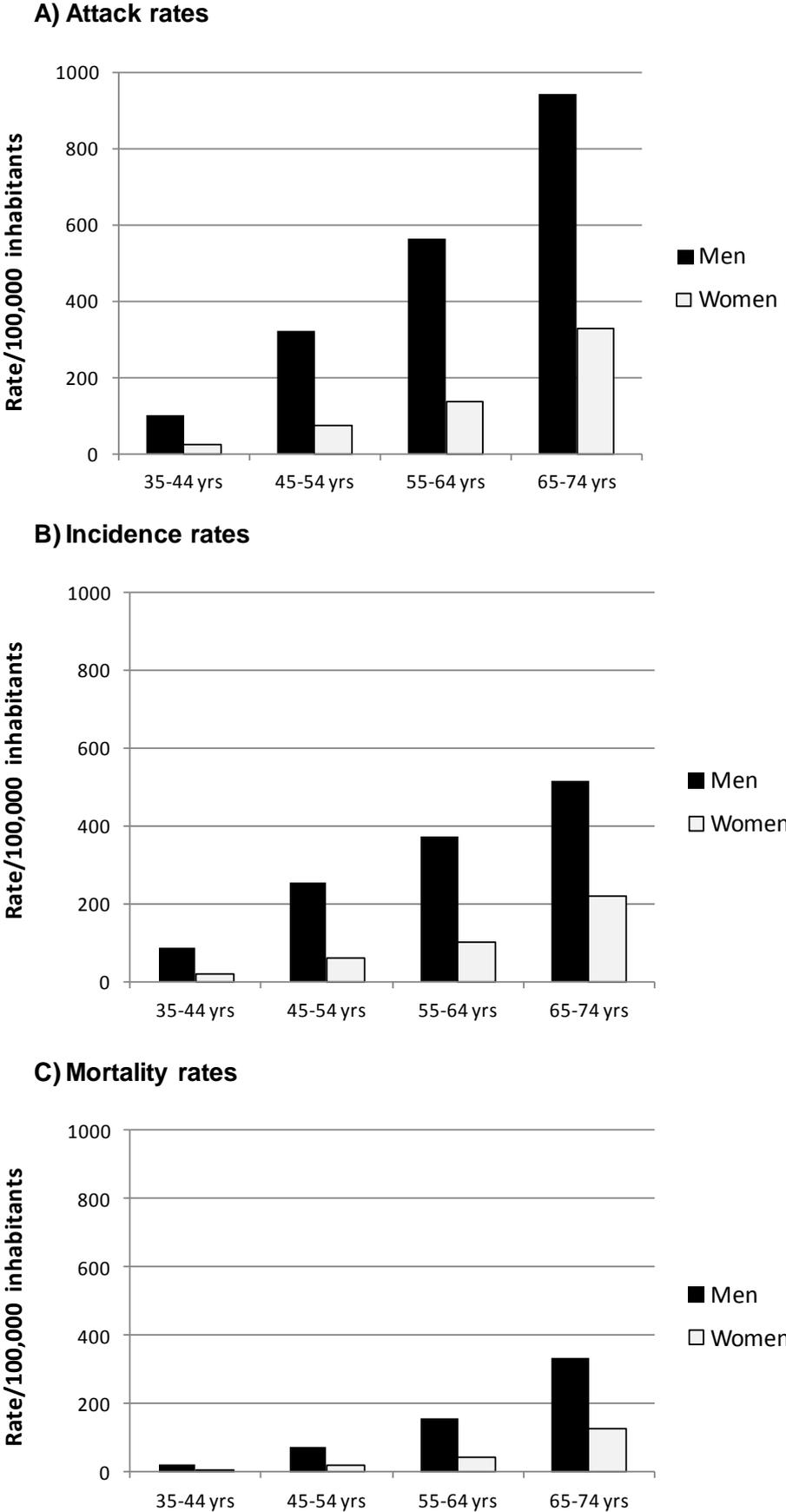
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**Table 1.** Age-standardized annual event rates per 100,000 inhabitants between 2006 and 2014 in adults aged from 35 to 74.

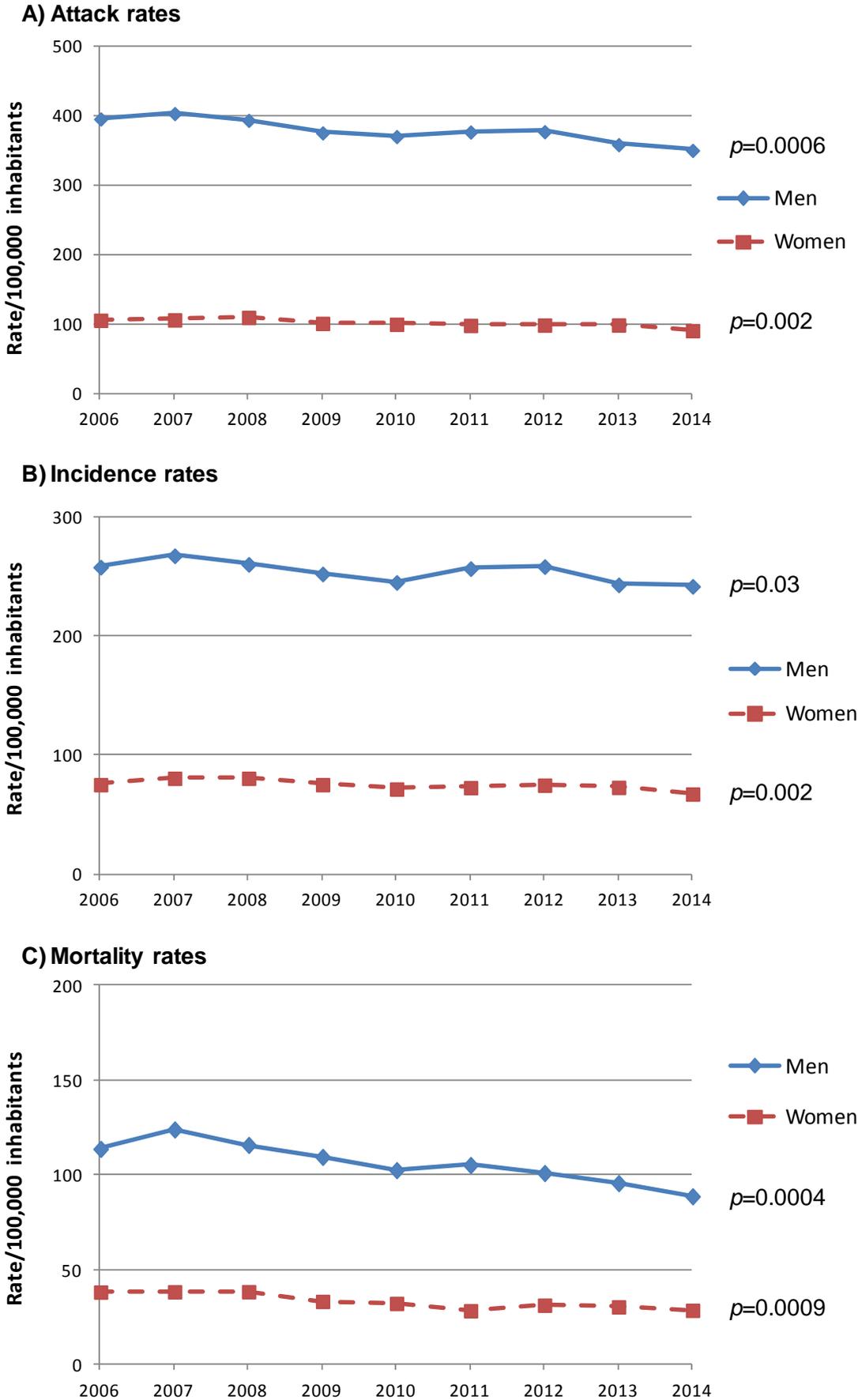
		2006	2007	2008	2009	2010	2011	2012	2013	2014	<i>p</i> trends	Annual percentage change (95%CI)
<b>Attack rate</b>	<b>Men</b>	396	404	394	376	371	377	378	359	351	<b>0.0006</b>	-1.5 (-2.1 to -1.0)
	<b>Women</b>	106	107	110	102	100	99	99	99	91	<b>0.002</b>	-2.1 (-3.1 to -1.1)
<b>Incidence rate</b>	<b>Men</b>	258	268	261	253	245	257	259	243	242	<b>0.03</b>	-0.9 (-1.5 to -0.2)
	<b>Women</b>	76	81	81	76	72	73	75	73	68	<b>0.002</b>	-1.8 (-2.9 to -0.7)
<b>Mortality rate</b>	<b>Men</b>	114	124	116	109	102	105	101	96	89	<b>0.0004</b>	-3.5 (-4.4 to -2.5)
	<b>Women</b>	38	38	38	33	32	28	31	30	29	<b>0.0009</b>	-4.3 (-6.0 to -2.5)

Significant *p* values are indicated in bold.

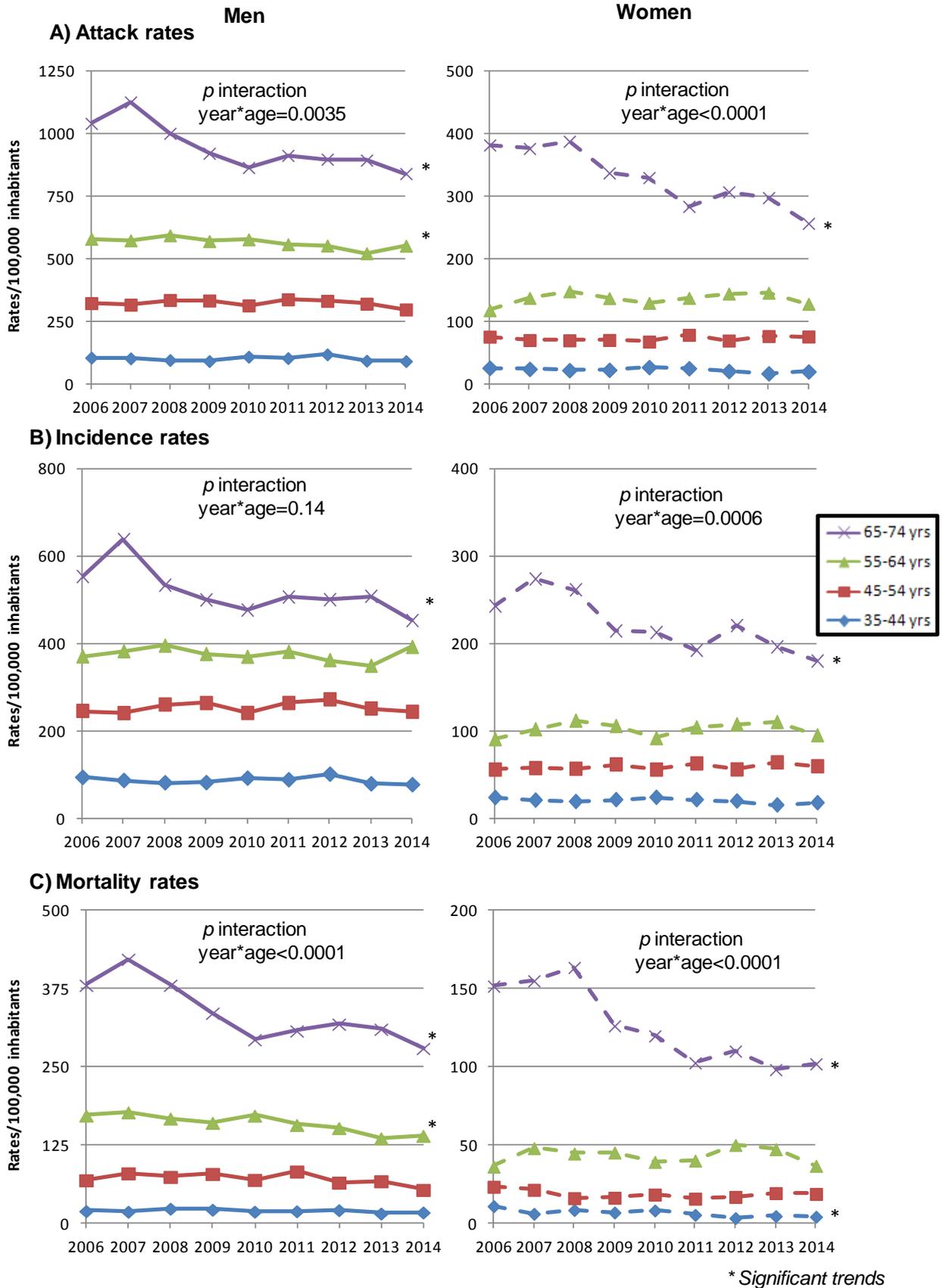
**Figure 1.** Crude annual average event rates (per 100,000 inhabitants) by sex and by age group between 2006 and 2014, in adults aged 35 to 74.



**Figure 2.** Trends in age-standardized rates between 2006 and 2014 by sex, in adults aged 35 to 74.



**Figure 3.** Trends in crude rates between 2006 and 2014, by age group in adults aged from 35 to 74.



**Figure 4.** Trends in case-fatality (%) between 2006 and 2014 by sex, in adults aged from 35 to 74.

