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Time trends in first hospitalization for heart failure in a community-based population

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ABSTRACT

Background: This study aims to assess time trends in first hospitalization for heart failure (HF) in a community-based population over the period from 1977 to 2014.
Methods: Population-based cohort study using resources from the "Martignacco project" started in 1977 and promoted by the WHO. Three thousand and sixty-six subjects were involved in the project with follow-up through December 2014. Estimates were made for age-specific incidence rates for the first hospitalization for HF by birth cohort, calendar period, and gender. To disentangle the effects of age, calendar period, and birth cohort on the overall temporal trend in HF, we performed an age-period-cohort (APC) analysis.
Results: An incident hospitalization for HF was reported for 427 subjects. In the APC model, a cohort effect with a turning point in 1930 was observed. After 1930, a sharp decrease in the rate ratios (RRs) occurred in among both genders. The estimated RR in the 1940 birth cohort decreased to 0.43, (95% CI 0.19–0.92), in men and to 0.45, (95% CI 0.16–1.26), in women. A residual effect of calendar period on RR was observed with a plateau in 1995 for women and in 2000 for men, followed by a decline.
Conclusions: The current findings showed that HF hospitalization incidence has declined over the period considered in subjects over 65 years living in a geographically defined community in Northeast Italy. Moreover, the age of birth, calendar period of diagnosis, and birth cohort play an important role in the incidence of the first hospitalization for HF.

1. Introduction

Heart Failure (HF) is a severe and potentially life-threatening condition frequently encountered in everyday clinical practice. Despite recent advances in HF management [1], it continues to represent a large public health burden [2]; it has been estimated to affect approximately 26 million people worldwide [3], and from an economic standpoint, it is associated with high healthcare expenditures [4–7].

Analysing HF epidemiology is crucial to characterize the disease better. In fact, HF represents a complex chronic condition with an onset that is influenced by heterogeneous factors. Understanding HF predictors might help in the development of ad hoc prevention strategies, resulting in a reduction in the burden of such disease. Considering this framework, analysing time trends of HF incidence is crucial, since the analysis of changes in HF incidence over time may assist in better understanding HF contributors. However, epidemiological data on HF incidence trends are sparse and controversial, given the lack of community-based studies on secular trends in HF incidence. The analysis of data from the Framingham study (which enrolled people aged 28–62 years in Framingham, Massachusetts, in 1948) [8] has shown that HF incidence has stabilized among men over the period considered, while it has decreased among women. Survival was found to be improved in both genders. Similarly, a study of HF trends among the population of Olmsted County, Minnesota [9] has shown that HF incidence remained stable over two decades (1979–2000) in both genders, while the 5-year survival rate improved (exception made for the elderly). Conversely, Jhund et al. [10] analysed HF incidence between 1986 and 2003 in Scotland and found that rates of the first hospitalization for HF had increased until 1994 and declined thereafter.

Findings from these studies suggest that the incidence of HF over the last 30 years may have stabilized. These observed trends might be the joint result of several factors affecting the onset of HF over time, such as the progressive demographic shift (age effect), the improvement of clinical management of HF (period effect), and the improvement in population well-being (cohort of birth effect). However, the common

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approach to the study of age, period of diagnosis, and birth cohort effects on HF incidence has not fully explored the separate roles of these time dimensions. Few studies have reported on the use of combined analyses to disentangle the age-period-cohort (APC) effects. The age effect in HF incidence has been well described, showing that the risk of HF increases exponentially in the elderly [11]. However, period and cohort effects are more difficult to understand separately. Improvements in healthcare over time, particularly the introduction of angiotensin-converting enzyme (ACE) inhibitors, spironolactone, and β-blockers, may be period effects, which can modify the time trends in incidence rates. Cohort effects can result from changes in well-being between generations.

To obtain a reliable explanation for the time trends in first hospitalization for HF, the APC dimensions are addressed using a unique analysis that can provide a separation of the individual effects. Using a combined approach of estimating APC effects, the aim of this study is to unravel the separate effects of age, period and cohort on first hospitalization for HF within a geographically defined community in Northeast of Italy that was enrolled in the "Martignacco project" [12] in 1977 and followed up for 37 years.

2. Methods

2.1. Study population

The "Martignacco project", promoted by the World Health Organization (WHO), was started in 1977 with the aim of evaluating the impact of health promotion interventions on cardiovascular health in middle-aged (40–59 years) subjects. Two comparable communities in the Friuli Region of Northeastern Italy were selected: Martignacco was chosen as the intervention area, and San Giorgio di Nogaro was designated the control area. The intervention consisted of both the development of initiatives aimed at promoting healthy lifestyles among the community (e.g., cooking classes, smoking cessation support programs) and the regular follow-up of subjects with increased cardiovascular risk at the time of enrolment. The project is ongoing, and details are available elsewhere [12, 13].

The cohort data for the present analysis refers to the 3066 subjects (1324 and 1742 drawn from the geographical area of Martignacco and San Giorgio di Nogaro, respectively) enrolled in 1977 and followed up through December 31, 2014, by means of a computerized record linkage system with administrative sources on healthcare use.

2.2. The Italian National Health Service

The principle of universal provision of services, regardless of ability to pay, was introduced in 1978 by the first health care reform, which established the Italian National Health Service (NHS). In Italy, the NHS provides health services free of charge (in-patient care and general practitioner consultations) or at a minimal charge (outpatient care and prescription drugs). Some particular circumstances such as disability, chronic diseases, the status of inability, low income (based on the previous year's gross income) or >65 years of age entitle patients to co-payment fee exemption. It is worthwhile to note that the exemption is not a deterministic function of age, since from one hand individuals can be exempted before age 65 in case of chronic health problems or unemployment status and, on the other hand, are not entitled to the exemption after 65 if their family income is above the threshold level.

Since the Italian NHS provides universal coverage with standard care to all Italian citizens, the inequality in health care access is not a matter of insurance status. However, the universal coverage does not necessarily imply an equitable health care access. In fact, in Italy, it has been observed that the health care access could be affected by the socioeconomic status [14–16].

All exemptions from co-payment were retrieved for the study participants. Since exemptions may have a different period of validity (lifetime or periodically renewed), those referring to the same subject and condition were considered as a single one with an overall duration given by sum of the single pieces. Conversion of former or regional coding to the current nomenclature (http://www.salute.gov.it/BancheDati/anagrafi/MCR) was performed.

2.3. Heart failure identification

A HF event is defined as the first occurrence in the study period of a hospitalization with a primary diagnosis of HF (428) or hypertensive HF (402.01, 402.11, and 402.91), according to the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). As reported in a literature review [17], this choice ensures a high positive predictive value (97%) in identifying incident HF.

2.4. Statistical analysis

The number of first hospitalizations for HF and the incidence rate (per 1000 person years), along with 95% confidence intervals (95% CI), were calculated both overall and stratified by gender, age, period, and geographic area. Denominators for these rates were measured in years of observation time for each cohort member, beginning in June 1977 until the occurrence of an HF event or the end of follow-up. Subjects who died before experiencing an HF event were censored at that time.

Age-specific incidence rates of first hospitalization for HF by birth cohort and gender were estimated. For this purpose, age at hospitalization was split into six 10-year increment age groups, from 45 to 95+ years, and birth cohort was split into five 5-year increment age groups, from 1915 to 1940.

To try to disentangle the effect of age, calendar period, and birth cohort on the overall temporal trend for HF during the period from 1977 to 2014, we fitted an APC model [18] to the data.

To overcome the identifiability problem of APC analysis, we set the cohort function at zero at 1930 (median of birth date) and constrained the period effects to be zero, on average, with zero slope. Different parameterizations can be chosen; however, they do not affect the effect curve. With the chosen parameterization, age effects can be interpreted as incidence rates for the first hospitalization for HF in the reference cohort of 1930, cohort effects as the rate ratios (RRs) relative to the reference cohort and period effects as the residual rate ratios relative to the age-cohort estimation. This approach assesses whether period has the same effect on all age groups and/or whether all birth cohorts have similar patterns (decreasing, increasing or stable incidence rates).

Computations were implemented with R software [19] (version 3.4.0) using the "rms", "EPI", and "PopEpi" packages.

3. Results

The study cohort included 3066 subjects. Two thousand seven hundred and fifty-two subjects were entitled to a co-payment exemption during the follow-up. Of these, 422, 615 and 958 were exempted for diabetes, neoplasms, and hypertension, respectively. In addition to that, such analysis showed a high proportion of low-income exemptions (Table S1 Supplementary material).

3.1. HF incidence

A total of 427 individual patients in the study cohort ($n = 3066$) were discharged from the hospital for the first time with HF over the 37-year time span. One thousand six-hundred and thirty-four subjects (52%) died during the follow-up period. Of these, 123 also had a hospitalization for HF.

Table 1 shows that the incidence of first hospitalization for HF increases with age and is higher for males. For the calendar period component, a crude increase in HF incidence from 2000 onwards was evident

Table 1
Number of first hospitalizations for heart failure (HF), person-years (P-years), incidence rates (IR) (×1000), and 95% confidence intervals (95% CI) according to age at first hospitalization, gender, period of first hospitalization and geographic area.

	HF	P-years	IR (×1000)	95% CI
Age at first hospitalization for HF (years)				
45–55	1	5299	0.2	0–1.3
55–65	26	20,323	1.3	0.9–1.9
65–75	116	26,285	4.4	3.7–5.3
75–85	208	16,240	12.8	11.2–14.7
85–95	75	3509	21.4	17.0–26.8
95+	1	23	43.8	6.2–311.0
Gender				
Female	212	38,630	5.5	4.8–6.3
Male	215	33,049	6.5	5.7–7.4
Period				
1985–1990	9	15,302	0.3	0.3–1.1
1990–1995	37	14,573	2.5	1.8–3.5
1995–2000	69	13,205	5.2	4.1–6.6
2000–2005	117	11,500	10.2	8.5–12.2
2005–2010	93	9646	9.6	7.9–11.8
2010–2014	102	7453	13.7	11.3–16.6
Geographical area				
Martignacco	182	31,087	5.9	5.1–6.8
San Giorgio Di Nogaro	245	40,592	6.0	5.3–6.8
Overall	427	71,679	6.0	5.4–6.5

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Table 2
Incidence rate of first hospitalization for HF by age and birth cohort overall, for the male and female populations.

	Cohort of birth				
	1915–1920	1920–1925	1925–1930	1930–1935	1935–1940
Age at first hosp. for HF (years)					
Males					
45–55	–	–	0 (0)	0.7 (1)	0 (0)
55–65	–	–	1.9 (6)	2.2 (8)	1.8 (3)
65–75	3.0 (4)	5.0 (17)	8.5 (26)	3.9 (12)	6.5 (9)
75–85	17.2 (16)	18.2 (39)	13.2 (26)	10.9 (16)	8.9 (3)
85+	14.1 (6)	29.6 (20)	15.2 (3)	–	–
Females					
45–55	–	–	0 (0)	0 (0)	0 (0)
55–65	–	0.7 (1)	0.8 (3)	0.8 (4)	0.3 (1)
65–75	3.3 (5)	3.2 (12)	4.8 (9)	3.3 (11)	0.7 (1)
75–85	18.2 (2)	11.7 (35)	10.2 (31)	10.9 (19)	2.5 (1)
85+	16.5 (10)	25.8 (32)	12.9 (5)	–	–
Total					
45–55	–	–	0 (0)	0.4 (1)	0 (0)
55–65	0 (0)	0.4 (1)	1.3 (9)	1.6 (12)	1.2 (4)
65–75	3.1 (9)	4.0 (29)	6.4 (45)	3.6 (23)	3.5 (10)
75–85	17.7 (38)	14.4 (74)	11.4 (57)	10.9 (35)	5.4 (4)
85+	15.5 (16)	27.1 (52)	13.7 (8)	–	–

as the cohort aged. The Martignacco intervention area exhibits HF rates comparable to those in the San Giorgio di Nogaro control area.

The analysis of age-specific HF rates according to gender and birth cohort showed that HF incidence was generally higher in men compared to women. In both genders, the incidence decreased with time for the 65–75 and 75–85 age groups, whereas it remained stable for those below 65 years of age (Table 2).

3.2. APC analysis

Table 3 shows all possible models with APC effects. By comparing the deviance between adjacent lines (a lower *p*-value indicates a better fit), it was possible to identify which model provided a better fit. In both genders, the best model for HF incidence turned out to be the full APC model. For the parameterization used, a cohort effect with a turning point in 1930 was observed. After 1930, a sharp decrease in the RRs occurred among both genders (statistically significant only in men). The estimated RR in the 1940 birth cohort decreased to 0.43 (95% CI 0.19–0.92) in men and to 0.45 (95% CI 0.16–1.26) in women. A residual effect of calendar period on RR was observed with a plateau in 1995 for women and in 2000 for men (statistically significant only in men), followed by a decline.

Fig. 1 is divided into three plots, where the effects are displayed for both genders. The left plot presents the age effect with the display of age-specific incidence rates per 1000 person years. The centre plot is the graphic display of the cohort effect. Finally, the right plot presents the period effect as residual RRs.

Table 3
Age-period-cohort (APC) deviance table of the model fitted for males and females, separately.

	Residual deviance (degrees of freedom, df)	Deviance difference (df difference)	*p*-Value
Males			
Age	92.4 (75)		
Age-drift	92.4 (74)	0.0 (1)	0.962
Age-cohort	88.4 (72)	3.9 (2)	0.136
Age-period-cohort	71.9 (69)	16.5 (3)	<0.001
Age-period	76.9 (71)	−5.1 (−2)	0.079
Age-drift	92.4 (74)	−15.5 (−3)	0.001
Females			
Age	62.9 (75)		
Age-drift	59.9 (74)	3.0 (1)	0.081
Age-cohort	56.9 (72)	3.0 (2)	0.224
Age-period-cohort	49.8 (70)	7.1 (2)	0.029
Age-period	53.2 (72)	−3.4 (−2)	0.182
Age-drift	59.9 (74)	−6.6 (−2)	0.036

4. Discussion

The current study described trends in the first hospitalization for HF within a community-based cohort in Northeast Italy. The findings confirm that age, period and birth cohort play an important role in the incidence of the first hospitalization for HF.

Incidence rates were similar to those reported in the Framingham study [8], while they were found to be slightly higher compared to those reported in the studies by Roger and Jhund [9, 10, 20]. However, comparing HF incidence with international literature is often a struggle, since criteria and data sources (e.g., hospital discharge records, administrative databases, death records) employed for HF identification may vary [20].

Consistent with the literature [21, 22], APC analysis showed that HF incidence increased markedly with age. Referring to gender differences, men were found to be significantly more likely to suffer from HF compared to women. This finding is consistent with the literature in the field [23]. Generally, female subjects are less likely to suffer from cardiovascular diseases, even if, in recent years, they have experienced a small increase in cardiovascular diseases [24]. It cannot be excluded that such finding may be related to the fact that HF could be misdiagnosed or neglected in women (it has been shown that women are more likely to receive a misleading cardiovascular diagnosis [25]). However, if this phenomenon had actually occurred, we could hypothesize that it may have affected other epidemiological studies on HF to a similar extent.

Similar to population trends observed in Europe [10], we report a plateau in the late nineties and subsequent declines in HF hospitalization rates up to 2010. We cannot rule out that the peak in HF incidence observed for the 1930 cohort may be related to left truncation [26] for the older birth cohorts (i.e., the exclusion of the presumably small portion of subjects from the 1915–1920 and 1920–1925 birth cohorts who experienced HF and died before the study started may potentially lead to underestimation of HF rates). The decline in HF hospitalizations has continued in the new century at a time when relevant advances have taken place in both primary and secondary prevention of HF. In Italy, the new century has seen a progressive decrease in tobacco smoking [27] and alcohol consumption [28]. Data from recent Italian surveys [29] have also shown a slight decrease in rates of hypertension (even if hypertension prevalence remains high among the Italian population). Furthermore, an improvement in coronary heart disease (CHD) survival has been identified thanks to both advances in medical treatment (e.g., the introduction in the nineties of angioplasty for the treatment of acute myocardial infarction [30]) and reductions in major risk factors for CHD [31]. Not least, since the mid-1980s, additional HF disease-modifying therapies have been introduced into clinical practice, including drug therapy (ACE-inhibitors, spironolactone, and β-blockers) and more recently pacing therapy [1]. Unfortunately, in the present study, drug prescriptions' data were available only from 2000. A supplementary analysis (Fig. S1, Supplementary material) on HF disease-modifying therapies' prescriptions showed an evident increasing trend, especially for the younger birth cohorts compared to the older ones. However, given the lack of data about prescriptions before 2000, we might just hypothesize that this factor could be related to the cohort effect.

Looking at the analyses conducted on the exemptions, even if they have increasingly been used to map comorbidities in HF patients [32], present results should be interpreted with caution since the accuracy of the exemption code in identifying the disease is disease-dependent. As to co-existing cancer, the positive predictive value of the corresponding exemption code is estimated to be 86% [33].

Although an evaluation of the effectiveness of the health promotion intervention was beyond the scope of this study, a crude comparison

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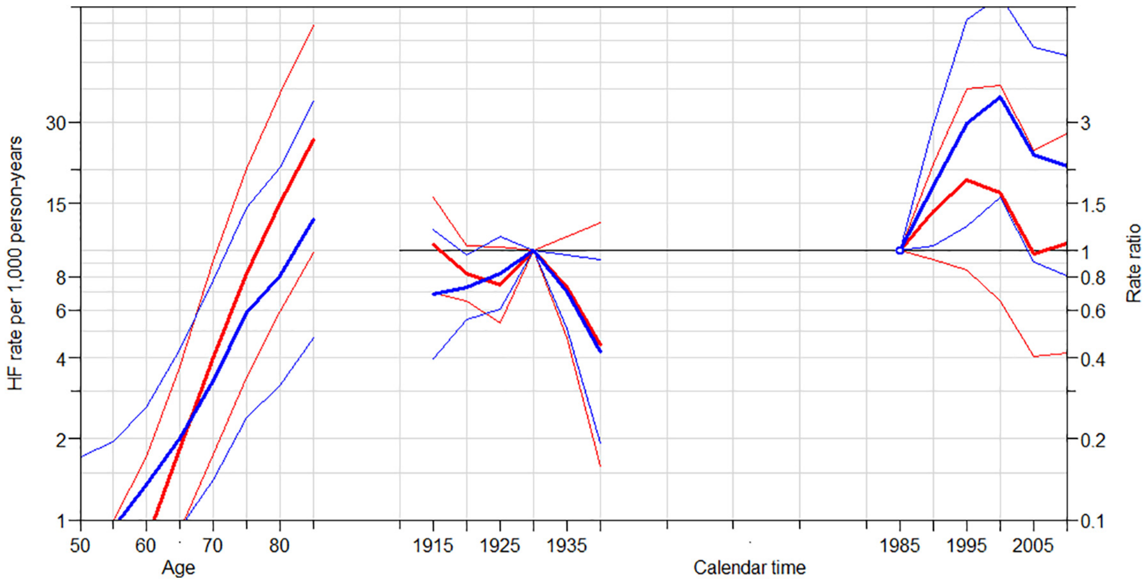

Fig. 1. Estimated effects and 95% confidence intervals for the incidence rate of first hospitalization for HF based on the APC models (women = red lines, men = blue lines). The age effect is on the left, the cohort effect is in the centre plot, and the period effect is on the right. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

between the area of Martignacco (exposed) and San Giorgio di Nogaro (control) seems to suggest the absence of significant differences in HF incidence rates. Recently, a reduction in the incidence rates for cardiovascular diseases due to advancement in prevention strategies and diagnosis [34] has been demonstrated, but HF disease seems to be an exception. This is probably because HF is a multifaceted disease affected by heterogeneous risk factors (e.g., concomitant heart and cardiovascular diseases, concomitant medications, genetics) in addition to lifestyle.

With an ultimate goal of providing information that can guide policy decisions, study results could be integrated in a microsimulation approach [35, 36], aimed at forecasting the use of hospital resources by patients with HF - in terms, for example, of number of beds to be allocated to the Cardiology and Medicine wards - in the long run and under different hypothetical scenarios (i.e., policy changes, shifts in risk factors, …).

4.1. Strengths

To our knowledge, this is one of the few studies to assess such a trend within a cohort and not through hospital episode-based statistics. The analysis of a cohort represents an added value of the present research because it allows to estimate the incidence of the condition under study and to relate its onset to specific exposures. Moreover, this type of study allows to capture changes over time and to evaluate the impact on the cohort of its individual components (age, calendar period, birth cohort) as in this case. The adoption of the APC approach to untangle the effects of age, period and cohort of birth (which are not yet fully understood) has allowed a better understanding of the incident trends in HF. Such trends are understudied, despite the severe burden represented by the disease and the need to better characterize its epidemiology in order to develop ad hoc prevention strategies and to allow a cost-effective allocation of healthcare resources in the context of heath planning.

4.2. Limitations

Referring to study limitations, we relied on a definition of an HF event known to have the highest positive predictive value and specificity [17]. However, a possible underestimation cannot be ruled out. In addition to that, the set-up of the NHS in Italy occurred in 1978 and took about two years to be fully applied [37], and electronic administrative sources were not available before 1985. Therefore, a limited bias might have occurred in the first study years.

Not least, the cohort was enrolled in a geographically defined community in Northeast Italy, potentially representing specificities (e.g., eating habits, lifestyle) that we cannot rule out as affecting HF incident trends.

5. Conclusions

The present study is one of the few works that have analysed secular trends of HF incidence within a community setting. HF incidence was found to be higher among men compared to women and to decrease with time over the age of 65. In the APC analysis, age, calendar period of the first hospitalization, and cohort of birth were found to have a significant influence on HF incident trends.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.05.132.

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Conflicts of interest

None.

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