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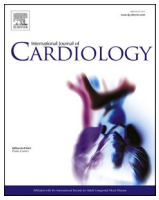

Mortality trend of ischemic heart disease (2008–2022): A retrospective analysis of epidemiological data

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ABSTRACT

Background: Age-sex specific trend analyses of ischemic heart disease (IHD)-related mortality and prevalent risk factors can improve our understanding and approach to the disease.
Methods: We performed a 15-year retrospective epidemiological analysis of acute and chronic IHD-related mortality and prevalent cardiovascular risk factors using administrative data from Veneto, a socio-economically homogeneous Italian region. Standard mortality statistics using the underlying cause of death (UCOD) and deaths with any mention of IHD in death certificates (MCOD) from ICD-10 codes I20-I25 was performed between 2008 and 2022.
Results: A total of 134,327 death certificates reported IHD-related deaths, representing 18.6% of all deaths. Proportional mortality decreased from 14.6% in 2008 to 7.8% in 2022 for deaths with IHD as the UCOD and from 23.5% to 14.6% for deaths with IHD among the MCOD. A more pronounced decline of proportionate and case-specific mortality rate was seen in women. The decline in mortality over the whole study period was larger for acute (vs. chronic) IHD. The COVID-19 pandemic led to a marked increase in mortality in 2020 (+12.2%) with a subsequent further decline. IHD-related deaths displayed a typical seasonal pattern with more deaths during winter. The prevalence of cardiovascular risk factors was higher in IHD (vs. no IHD) deaths: this association appeared more pronounced in younger adults.
Conclusions: We provided an analysis of epidemiological trends in IHD-related mortality and prevalence of risk factors. Our findings indicate a change in the pattern of cardiovascular deaths and may suggest a switch in death from acute to chronic conditions.

1. Introduction

Ischemic heart disease (IHD) is a prevalent cardiovascular disease and leading cause of death worldwide. [1] IHD consists of acute coronary syndrome (ACS) and chronic coronary syndrome (CCS), reflecting the different manifestations of disease, [2] which require different ad hoc therapies and prevention strategies. [3–5]

In 2019, nine million people died worldwide due to IHD, representing >15% of global deaths. [6–8] In Italy, almost 100,000 IHD-related deaths occurred in 2019, corresponding to a mortality rate of 160 per 100,000 inhabitants. [6] Over the past decades, the IHD-related incidence and mortality have been decreasing in Western countries [9,10]. In parallel, risk factors for IHD have been mutating together with ageing populations. [11,12]

In many countries, including Italy, IHD-related mortality increased significantly in 2020 compared to the pre-COVID-19 period, interrupting a long-term decline [13]. It remains to be assessed if such change of trends continued over more recent years. Further, analyses of mortality by stratification into the underlying and concomitant causes of death can improve our understanding of the mortality trends and their root causes.

The aim of the present retrospective epidemiological analysis is to

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investigate time trends in standardized mortality related to ACS and CCS in Veneto, a large and socio-economically homogeneous region located in Northern Italy.

2. Methods

2.1. Data source

We performed a retrospective epidemiological analysis of death certificates of all residents in the Veneto region, Italy. As of 2022, the region has approximately 4.9 million inhabitants. A copy of all certificates was collected by the Regional Epidemiological Department, which also takes care of coding in accordance with the International Classification of Diseases, 10th revision (ICD-10). Standard mortality statistics identify the underlying cause of death (UCOD) among all conditions reported in the death certificate. Usually, the UCOD corresponds to the cause of death chosen by the certifying physician, but in specific cases another condition can be selected based on rules set by the World Health Organization. [14] Automated designation of the UCOD is performed to standardize selection. Until 2017, the Automated Classification of Medical Entities software was used. Subsequently, the IRIS software was implemented, as in most European countries; the introduction of the IRIS software corresponded to the adoption of the 2016 version of the ICD-10, with slightly different coding rules. [15] All reported comorbidities at the time of death were collected to integrate the multiple causes of death (MCOD). The study is based on anonymized data; the analysis of mortality records is a mandatory activity of the Regional Epidemiological Department according to the regional law. Therefore, this study is exempt from Institutional Review Board approval.

2.2. Statistical analysis

All death certificates from January 1st, 2008 until December 31st, 2022 with any mention of IHD were retrieved from the regional mortality registry based on the ICD-10 codes I20-I25, in accordance with prior research. [16] The yearly number of deaths and the proportional mortality (share of annual total deaths) related to IHD was calculated for both deaths with IHD as the UCOD and deaths with any mention of IHD (MCOD). Age-standardized mortality rates (2013 European standard population) and proportional mortality were calculated for both sexes and for age classes (<65, 65–74, ≥75 years). [17] Further, a stratification into ACS (ICD-10 codes I21, I22, I24) and CCS only (all IHD excluding ACS) was performed. Changes in mortality trends over time and the average annual percent change (AAPC) in rates with 95% Confidence Intervals (CI) through the study period were estimated by means of the Joinpoint software. For the years starting from 2020, a sensitivity analysis was carried out by excluding IHD deaths mentioning an acute COVID-19 infection (U07.1, U07.2, U10.9).

The monthly number of deaths from 2008 to 2022 was plotted to visually check for changes in the mortality pattern. In a further investigation focusing on the period from January 2018 to December 2022, deaths with any IHD among the MCOD were further broken down by place of death (in-hospital or out of hospital), ACS or CCS, and presence of risk factors (diabetes, hypertensive disease) specifically associated to worse COVID-19 outcomes. [18]

Lastly, the share of IHD-related deaths with mention of common chronic comorbidities was assessed across three-year calendar periods (the pandemic, 2020–2022. compared with four previous periods of equal length): hypertensive diseases (I10-I15), atrial fibrillation (I48), cerebrovascular diseases (I60-I69), peripheral arterial diseases (PAD) (I70.2, I73.9, I74.3, I74.4), diabetes (E10-E14), obesity (E66), chronic kidney disease (N18), chronic obstructive pulmonary disease (COPD) (J40-J44, J47), neoplasms (C00-D48), and dementia/Alzheimer's disease (F00-F03, G30). To assess the association of IHD with major risk factors (hypertensive diseases, diabetes, obesity, and COPD as a marker of tobacco exposure), we applied, separately by sex and broad age classes, conditional logistic models (strata defined by age and calendar year at death) for the association of each risk factor mentioned in death certificates with IHD-related vs. non-IHD-related deaths. To test sex differences in the associations, further conditional regression models included an interaction term between sex and the investigated risk factor.

3. Results

Throughout the study period, 134,327 death certificates reported IHD ICD-10 codes in any position among the MCOD, representing 18.6% of all registered deaths (N = 723,240). The number of IHD-related deaths progressively decreased throughout the period. Proportional mortality decreased from 14.6% in 2008 to 7.8% in 2022 for deaths with IHD as the UCOD and from 23.5% to 14.6% for deaths with IHD among the MCOD (Table 1**)**. A decreasing trend was observed in both men and women, with a more pronounced decline in women (based on MCOD, from 24.0% to 17.7% in men and from 22.9% to 11.9% in women). Separate figures by gender and broad age class are provided in **Supplementary Tables 1–4**.

3.1. Mortality rate

In men, age-standardized rates were higher and showed a less prominent reduction over time than in women. For IHD as UCOD, the AAPC was −5.0% (CI -4.6,-5.4) in men and − 6.0% (CI -5.5,-6.6) in women. The corresponding figures for IHD as MCOD were − 3.9% (CI -2.9,-4.8) and − 5.3% (CI -4.7,-6.0), respectively. Notably, based on MCOD the Joinpoint software did not identify changes over time in the mortality trend among women, whereas in men rates initially declined at a similar pace (2008–2013: -5.8%, CI -3.4,-8.0), whereas subsequently the yearly decrease slowed down (2013–2022: -2.8%, CI -1.8, −3.8). At the beginning of the COVID-19 pandemic in 2020, the IHD-related mortality rate markedly increased for IHD as MCOD (2020 vs. 2019: +12.2%), whereas only a small excess was registered for IHD as UCOD (+3.7%). COVID-19 alone may explain the excess cardiovascular deaths: in fact, Fig. 1 shows that a consistent linear decrease over time could still be observed during the pandemic by excluding deaths with mention of COVID-19 in the death certificate. After the pandemic's first year, IHD-related mortality rates started to decline again. The transient growth in MCOD-based rates observed in 2020 compared to 2019 was larger among the elderly, with a change of +13.0% in the population aged ≥75 years, +10.3% in the 65–74 age class, and + 7.0% in people younger than 65 years (data not shown). The gender gap in mortality to the disadvantage of men was larger among younger subjects. In all age groups an increase of the gender gap was observed from 2008 to 2022: the men-to-women ratio of standardized mortality rates increased from 4.7 to 6.6 in the population aged <65 years, from 3.2 to 4.0 in the 65–74 years age group, and from 1.7 to 2.1 in those aged ≥75 years (**Supplementary Fig. 1**).

The decline in mortality over the whole study period was steeper for both ACS as the UCOD (AAPC -6.0%, CI -5.5,-6.5) and ACS as MCOD (AAPC -6.1%, CI -5.2,-6.9) than for CCS (UCOD: AAPC -4.8%, CI -4.3,-5.3; MCOD: AAPC -3.4%, CI -2.8,-4.0). Only a minor increase was observed in 2020 compared to 2019 for mortality with mention of ACS (+3.7%), while a 16.0% increase was registered for CCS (Fig. 2).

3.2. COVID-19 pandemic

Before the COVID-19 pandemic, IHD-related deaths displayed a seasonal pattern with higher values during winter months, in correspondence with cold spells and flu epidemics (Fig. 3). In contrast, for deaths with IHD among the MCOD, in 2020 the seasonal peak usually observed in January shifted to the first COVID-19 epidemic wave involving the region (March to April 2020, Fig. 4A). Monthly IHD-related deaths reached record numbers in correspondence with the

Table 1
Yearly number of deaths from IHD selected as the underlying cause of death (UCOD), or as any mention in death certificates (MCOD), and proportional mortality (share of annual total deaths): Veneto Region (Italy), 2008 to 2022.

	UCOD, n	MCOD, n	Proportional mortality (UCOD)	Proportional mortality (MCOD)
2008	6430	10,341	14.6%	23.5%
2009	6149	9969	14.0%	22.7%
2010	6090	9864	13.7%	22.2%
2011	5770	9537	12.9%	21.2%
2012	5836	9573	12.5%	20.5%
2013	5246	8795	11.5%	19.3%
2014	5190	8701	11.4%	19.2%
2015	5335	8977	10.9%	18.3%
2016	5138	8742	10.8%	18.4%
2017	5094	8633	10.4%	17.6%
2018	4659	8141	9.6%	16.7%
2019	4473	7780	9.2%	16.0%
2020	4771	8959	8.4%	15.7%
2021	4497	8237	8.5%	15.5%
2022	4325	8078	7.8%	14.6%
Total 2008–2022	79,003	134,327	10.9%	18.6%

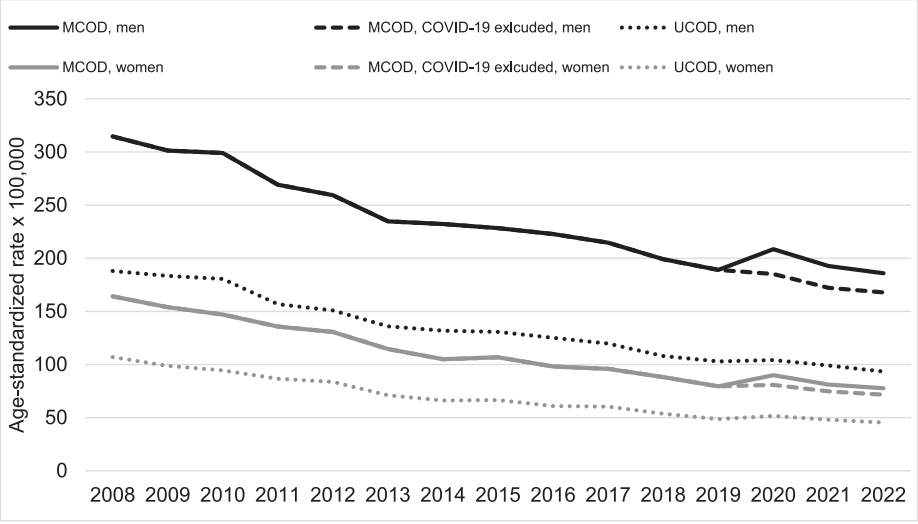

Fig. 1. Age-standardized mortality rates (European standard population) from IHD selected as the underlying cause of death (UCOD), or as any mention in death certificates (MCOD).

second, most deadly epidemic wave (December 2020 to January 2021) registered in Veneto. [16] After January 2021, epidemic waves had a less pronounced impact. The above pattern through different phases of the pandemic was evident for CCS and less pronounced for ACS (Fig. 4B). Notably, the impact of the first epidemic wave was evident for out of hospital IHD-related deaths, whereas no increase was found in in-hospital IHD-related deaths. During the second, larger epidemic wave, IHD-related mortality markedly increased irrespective of out- or in-patient setting and of presence of hypertensive heart disease or diabetes (Fig. 4C, Fig. 4D).

3.3. Concomitant diseases

The share of death certificates with mention of IHD also reporting hypertensive diseases, cerebrovascular diseases and COPD steadily decreased throughout the study period. The share of those reporting diabetes and obesity slightly increased, and a substantial growth could be observed in the proportion of IHD-related deaths associated with atrial fibrillation and chronic kidney disease (Table 2). **Supplementary Fig. 2** shows the association between deaths with mention of IHD and major risk factors. The association was more pronounced among population groups with lower baseline IHD-related mortality rates, especially younger women. In the <65 and 65–74 years age classes, associations were stronger in women compared to men; the heterogeneity between sexes was highly significant for diabetes, hypertension, and COPD ($p < 0.001$), and of borderline significance for obesity (<65 years $p = 0.070$, 65–74 years $p = 0.028$, data not shown).

4. Discussion

In this retrospective analysis, we provide epidemiological estimates of mortality trends related to IHD over the past 15 years. In the Veneto region, an Italian high-income area of around 4.9 million inhabitants, we found a decrease in the mortality rate due to IHD as the UCOD from 138 deaths per 100,000 inhabitants to 65 deaths per 100,000 in the period 2008–2022. Rates based on MCOD declined from 221 to 122 deaths per 100,000. The decrease was steeper among women, with a widening gender gap in IHD-related mortality. The proportional mortality fell steadily over the whole period, with 2020 being the notable exception. To our knowledge, this is the first study to break down long-term trends of IHD-related deaths by UCOD and MCOD and separately for ACS and CCS. Moreover, the present results demonstrate that after the pandemic's first year, mortality related to IHD continued the pre-existing decreasing trend.

In high-income Western European countries, the mortality rate of IHD as the UCOD decreased between the years 1990 and 2019. This

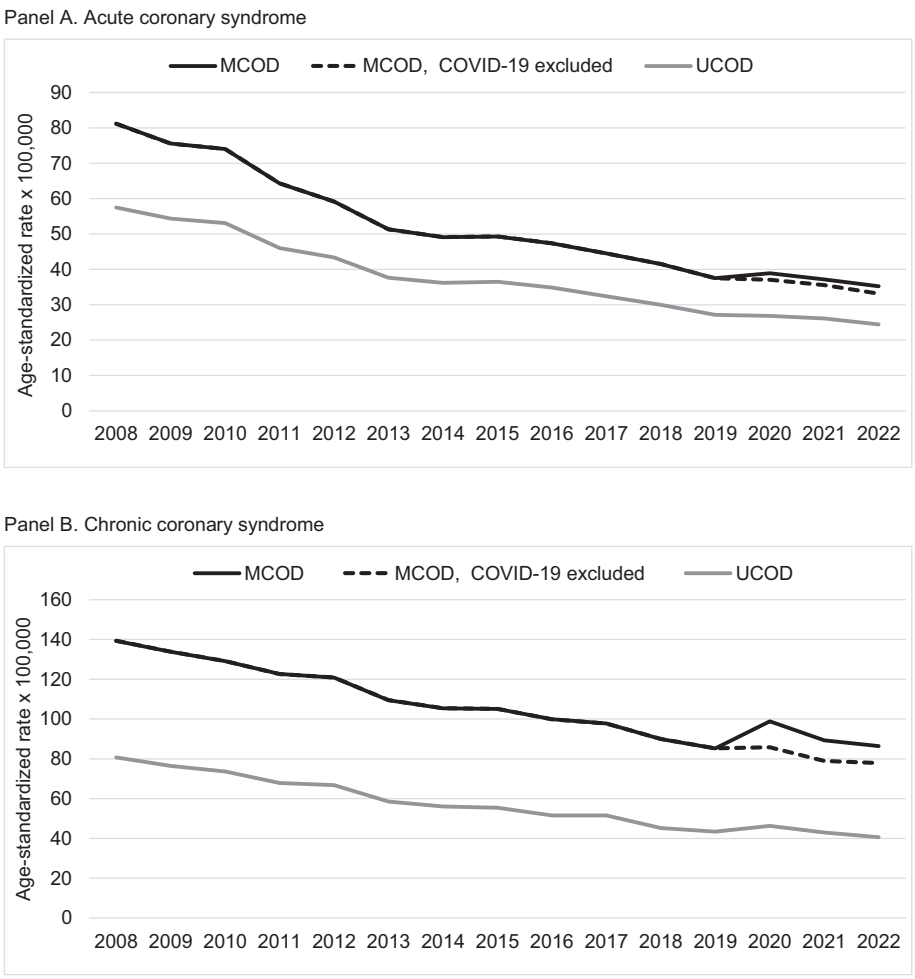

Fig. 2. Age-standardized mortality rates (European standard population) from acute coronary syndrome (Panel A) and chronic coronary syndrome (Panel B), selected as the underlying cause of death (UCOD), or as any mention in death certificates (MCOD).

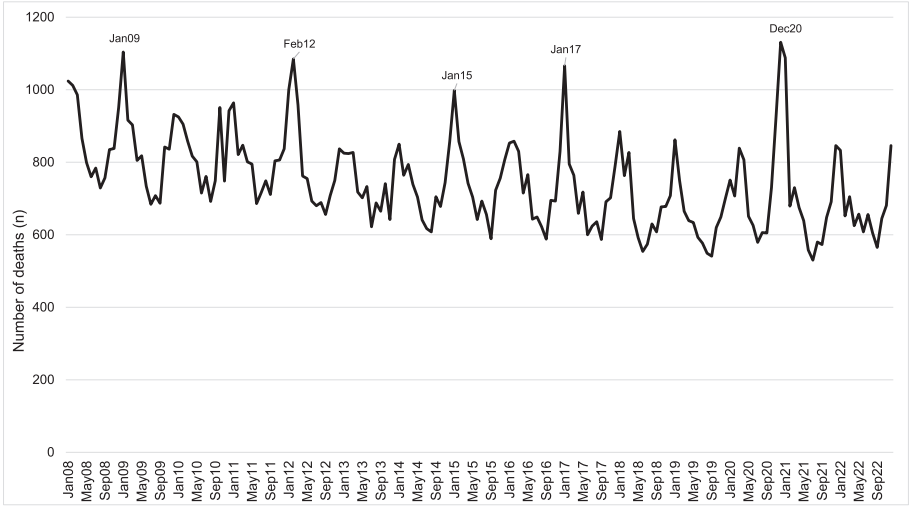

Fig. 3. Monthly number of deaths with any mention of IHD in death certificates. Veneto Region (Italy), January 2008–December 2022.

trend was shown in an analysis of aggregated data from the Global Burden of Disease initiative. For women, a slightly steeper decrease in mortality was observed compared to men. [10] Over the whole study period, 18.6% of deaths were related to IHD. In the Veneto region, IHD contributed to 23.5% of all deaths in 2008, but only 14.6% in 2022. The yearly decrease in age-standardized IHD-related mortality based on MCOD was about 4% in men and 5% in women. This decrease was even more pronounced for IHD as the UCOD, falling yearly by about 5% and 6%, respectively. These findings are consistent with known trends in the mortality rate of cardiovascular diseases in high-income countries. [4]

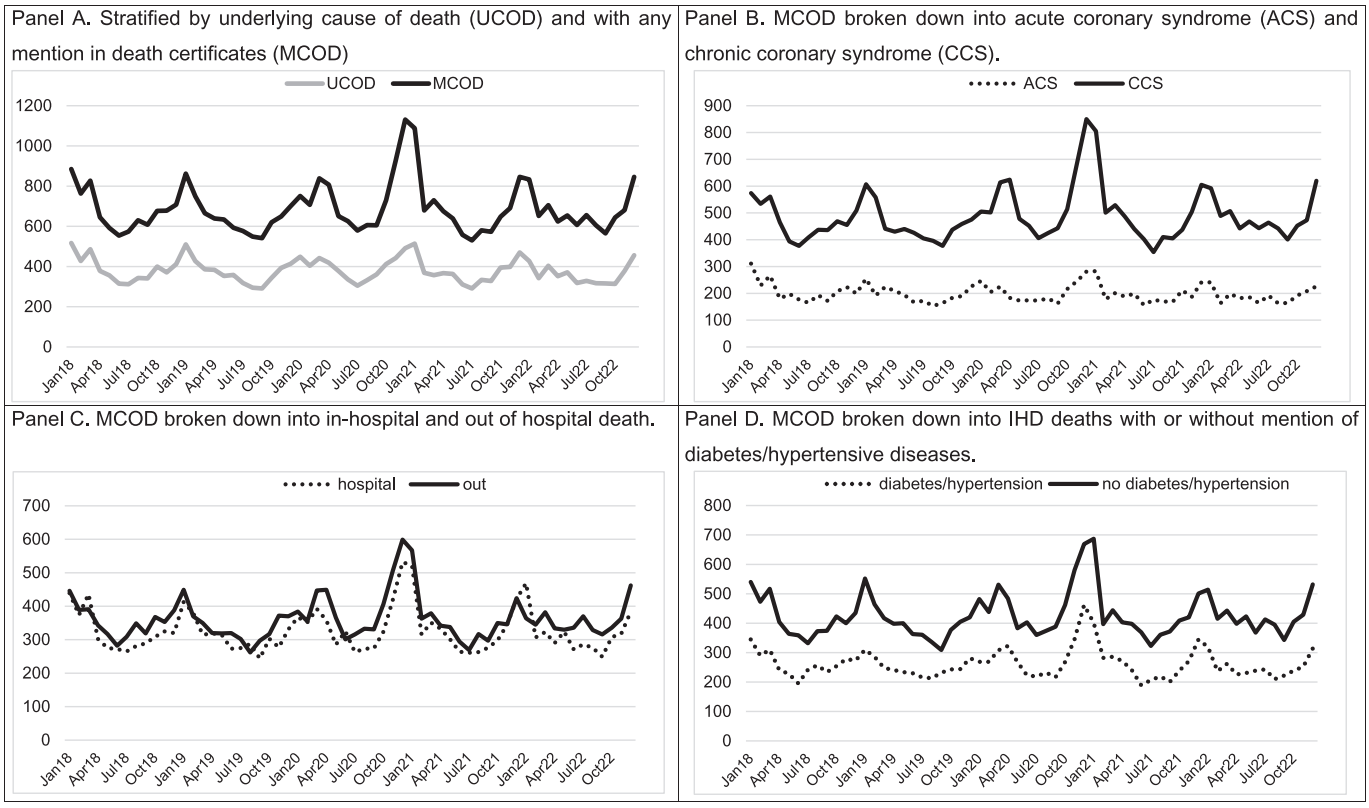

Fig. 4. Monthly number of deaths from IHD. Veneto Region (Italy), January 2018–December 2022.

Table 2
Proportion of deaths with mention of IHD reporting common chronic comorbidities by timeperiod: Veneto region (Italy), 2008 to 2022.

	2008–2010 (n = 30,174)	2011–2013 (n = 27,905)	2014–2016 (n = 26,420)	2017–2019 (n = 24,554)	2020–2022 (n = 25,268)
Hypertensive diseases	26.8%	25.2%	23.9%	24.1%	23.3%
Diabetes	19.0%	19.8%	19.8%	20.1%	20.4%
Cerebrovascular diseases	17.2%	16.1%	15.0%	13.6%	12.3%
Atrial fibrillation	12.8%	13.3%	14.6%	16.0%	17.0%
Chronic obstructive pulmonary disease	10.5%	10.4%	9.6%	9.1%	8.3%
Chronic kidney disease	6.7%	9.0%	10.5%	11.3%	11.5%
Peripheral arterial disease	2.3%	2.6%	2.8%	2.9%	2.6%
Obesity	1.2%	1.3%	1.3%	1.4%	1.6%

This decline has been previously attributed to improvements in prevention and treatment of cardiovascular diseases. [4,5] Risk factors for IHD are changing. Smoking, hypertension, dyslipidemia, and physical inactivity are well-recognized and are common targets of prevention strategies. [19,20] Other risk factors, such as diabetes, obesity, and age, are increasing in importance. [12] According to analyses based both on MCOD and on the UCOD, we found higher IHD mortality for men, with the gender gap becoming progressively wider, especially in younger individuals. Further research is warranted to investigate the reasons for this less favorable trend among men.

We found a sharper decrease in mortality for ACS than for CCS. Early identification and revascularization are key in ACS, thus focus lies on the improvement of diagnosis and treatment. [21–23] The improvement in treatment of ACS leads to a higher survival rate [4,5] with a consequent increasing proportion of CCS within the IHD spectrum. Besides the higher rate of ACS survival, the ageing population may also explain the higher prevalence of CCS. [24] In ACS, we found a similar decrease in its mortality as UCOD and MCOD. In CCS, we saw a greater decrease in its mortality as UCOD than MCOD. The similarities in ACS as UCOD and MCOD might stem from the acute nature of the condition, with ACS being more commonly identified as the underlying cause rather than a comorbidity or a complication. [25]

Compared to 2019, we observed an increase in mortality due to ACS of roughly 4% and an increase in mortality due to CCS of 16% in 2020. This increase can primarily be attributed to the impact of the COVID-19 pandemic on the Veneto region. Our findings align with previous reports that indicated a similar increase in mortality from ACS during the pandemic. [26]

In this analysis, we could once again confirm that IHD-related deaths peak in winter, [27,28] with five pronounced peaks in 2009, 2012, 2015, 2017, and 2020. The usual peak in winter shifted to the first COVID-19 epidemic wave involving the region (March–April 2020). In the second, most deadly epidemic wave (December 2020 to January 2021) registered in the Veneto region, we found a peak in deaths with IHD as MCOD far above the usual, while deaths for IHD as UCOD showed a less pronounced peak. For the first COVID-19 wave, we found a slight increase in mortality in out- patients, with no peak for in-hospital patients. We attribute this effect to the decrease in hospital admissions during the pandemic. [29,30] The second peak was more pronounced for CCS than for ACS. We associate this increase mainly to patients dying of COVID-19 as UCOD, while having a CCS diagnosis as a concomitant diagnosis; this would explain why only a small increase in mortality due

to ACS was observed. After the second epidemic wave and the implementation of the vaccination campaign, IHD-related mortality returned to pre-pandemic levels.

Throughout the study period, we found a decrease in the mention of hypertensive diseases, cerebrovascular diseases and COPD as diseases concomitant with IHD. We attribute this change to improvement in primary prevention. [3,12,19,20] We found only a slight increase in diabetes as concomitant disease, in contrast to what is expected based on previous studies that have described an increasing prevalence of diabetes among IHD patients [12,31]. In patients who died due to IHD (vs. other causes), the prevalence of major cardiovascular risk factors was higher among younger patients. Previous studies found a greater association of risk factors with heart failure in younger patients than in older patients. [32] In our cohort, this could be explained by a lower absolute risk in younger individuals, a higher attributable proportion for IHD, and fewer competing risk factors for death. [33] This finding appeared more pronounced in women.

Our findings suggest that preventive measures and improvements of care are affecting the mortality rate of IHD and are leading to a decreasing trend in the rate. However, despite these efforts, IHD remains the leading cause of death in Italy. [6] In the future, chronic cardiovascular syndromes are likely to play a progressively larger role among non-communicable diseases. Further measures, particularly focusing on secondary prevention, should be undertaken to address IHD with a special focus on cardiovascular risk factors with a growing prevalence, such as diabetes.

The present study has several limitations. Firstly, the study is based on the ICD-10 coding of death certificates, which are less reliable than autopsy results. Secondly, selection of the underlying cause is prone to subjective judgement of the treating physician; the use of MCOD allows this study to lessen the impact of this effect. Thirdly, pathologies might be omitted from the death certificate if considered not to contribute to death (e.g. obesity). Finally, the analysis was limited to the Veneto region in Italy. No generalization, especially to low- and middle-income countries, can be made.

5. Conclusions

Mortality due to IHD as the UCOD fell from 14.6% to 7.8% person-years of all deaths between 2008 and 2022 in the Veneto region in Italy; such a decrease was confirmed by IHD-related proportional mortality (with IHD among the MCOD) dropping from 23.5% to 14.6%. Mortality rates showed a marked seasonal pattern and a decreasing trend across the whole study period, with only a transient increase in 2020 due to COVID-19. The decline in mortality was more pronounced among women and was larger for ACS compared to CCS. Our findings may suggest that preventive measures and improvements of care are shifting IHD from an acute to a chronic disease.

CRediT authorship contribution statement

Simon Wolf: Project administration, Writing – original draft, Writing – review & editing. **Elena Schievano:** Writing – review & editing, Formal analysis. **Claudio Barbiellini Amidei:** Writing – review & editing, Formal analysis. **Nils Kucher:** Writing – review & editing, Supervision. **Luca Valerio:** Writing – review & editing. **Stefano Barco:** Writing – review & editing, Supervision. **Ugo Fedeli:** Writing – review & editing, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

We declare that we have no competing interests related to this work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2024.132042.

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