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Research Paper

Comparison of all-cause and cause-specific mortality after myocardial infarction – a Hungarian registry study

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ABSTRACT

Study Objective: Despite advances, myocardial infarction remains a significant public health concern, with survival being a crucial outcome measure. While all-cause mortality is well-studied, less is known about causes of death following an infarction. This study aimed to analyse cause-specific mortality after myocardial infarction and to compare it with the analysis of all-cause mortality.

Design: Data from a nationwide Hungarian myocardial infarction registry from January 2020 to June 2022 were linked with official cause of death information. Cumulative incidence functions and multivariable modelling of subdistribution hazard were used for cause-specific survival analysis, accounting for competing risks. Standard all-cause survival analysis (Cox proportional hazards model) was also carried out as a comparison.

Results: Among 27,965 patients with acute myocardial infarction, 25.0 % died during follow-up (of a median of 661 days). Myocardial infarction was the primary cause of death in 38.6 % of cases, followed by other cardiovascular causes (37.5 %). Factors associated with higher cause-specific mortality for infarction included older age, male sex, ST-elevation infarction, diabetes, prior stroke, peripheral artery disease, and heart failure. Percutaneous coronary intervention and hypertension was associated with lower hazard. Results largely matched all-cause survival analysis, except for ST-elevation, where hazard was much higher in cause-specific analysis.

Conclusions: While overall and cause-specific analyses aligned in this large registry study, a notable difference was observed for ST-elevation infarction, where hazard was substantially higher in the cause-specific analysis. This highlights the potential relevance of distinguishing between causes of death for a more precise understanding of outcomes.

1. Introduction

Despite steady advances over recent decades, acute myocardial infarction (AMI) remains a major public health [1] and economic burden [2]. MI is also widely regarded as a "tip-of-the-iceberg" indicator for coronary artery disease—the leading cause of death globally [3]. These facts highlight the importance of adequately monitoring MI outcomes, as well as epidemiologic characteristics and details of care, and analysing the resulting data. Such analyses are essential not only for informing domestic health policy but also for enabling meaningful international comparisons [4].

Among the various outcome measures for MI [5,6], survival is arguably the most critical, as it reflects patient characteristics, quality of care, and the effectiveness of post-infarction rehabilitation. Extensive data are available on both short-term [7–10] and long-term [11–15] mortality, however, these studies typically rely on all-cause mortality and rarely distinguish between specific causes of death.

While cause-specific survival analysis presents challenges—particularly due to ambiguities and inaccuracies in death certificate data [16–21] —it remains a valuable approach: by isolating deaths unrelated to MI, this method could enable a more focused and meaningful assessment of infarction outcomes.

The present study aims to enhance our understanding by linking infarction data of post-infarction patients with cause-of-death information from death certificates and conducting cause-specific survival analyses on this integrated dataset. Additionally, it compares these

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findings with all-cause mortality outcomes from the same cohort to highlight the differences between the two approaches and to better assess the relative strengths of each analytical method.

2. Materials and methods

2.1. Patient data

The Hungarian Myocardial Infarction Registry (HUMIR) is a nationwide, comprehensive database established to systematically collect, analyse, and monitor clinical and epidemiological data on acute myocardial infarction in Hungary. The registry is maintained by the Gottsegen National Cardiovascular Center. Since 2014, reporting of all MI cases has been mandatory through an online platform, followed by rigorous validation procedures. A comparison between reported MI cases and the number of reimbursed cases recorded by the country's single national health insurance fund suggests a registration completeness rate of approximately 88–93 %, depending on the year [22]. Further details on HUMIR were described earlier [23].

Although HUMIR is linked to the national vital statistics, which provides mortality data, it does not include information on the cause of death (COD). To address this limitation, HUMIR partnered with the Hungarian Central Statistical Office (HCSO) to obtain statistical COD data for deaths occurring after January 1, 2020. These data were subsequently linked to the HUMIR database. For consistency, the present study includes only MI cases reported to HUMIR on or after January 1, 2020. The data collection period concluded on June 30, 2022, with mortality follow-up data available through June 30, 2023, thereby ensuring a minimum one-year follow-up for all included patients.

The COD data is based on the official death certificates and is obtained from the HCSO. Cause of death is coded according to the 10th revision of the International Classification of Diseases (ICD-10) [24]. This dataset includes both the ICD-10 chapter and the corresponding three-digit code, but for the purposes of this analysis, causes of death were categorized into four groups: acute myocardial infarction (AMI), other cardiovascular causes, cancer, and other causes. Deaths were classified as "cardiovascular other than AMI" if the underlying COD was coded under Chapter I (Diseases of the Circulatory System) in ICD-10, but not as AMI.

2.2. Statistical methods

Continuous variables are presented as lower quartile / median / upper quartile, mean +/− standard When analysing cause-specific survival—as opposed to overall survival—it is essential to account for competing risks. Simply treating events other than the event of interest as censored can lead to biased estimates from the Kaplan-Meier estimator, as the assumption of independence between event time and censoring is violated [25]. Therefore, the cumulative incidence function (CIF) was used to estimate event incidence while properly accounting for competing risks [26].

For multivariable modelling of (cause-specific) survival, the proportional subdistribution hazards approach of Fine and Grey [27] was applied using the weighted estimating equation method [28]. This approach directly models the subdistribution hazard, as opposed to methods modelling cause-specific hazard, and is usually used when developing clinical prediction models taking competing risks into account [29].

As a comparison, standard all-cause survival analysis was also carried out using usual Cox proportional hazards model.

2.3. Programs used

The calculations were carried out using R statistical program package version 4.5.1 [30] using package tidycmprsk version 1.1.0 [31] among others.

The source code of the script used for analysis is available at https://github.com/ferenci-tamas/cause-specific-infarction-mortality.

3. Results

3.1. Patient characteristics

From 1 January 2020 to 30 June 2022 a total of 29,374 infarctions were registered in the HUMIR database. Of those, 1409 could not be linked with the HCSO database, leaving a final sample size of 27,965. Characteristics of these patients are presented in Table 1.

In brief, the average age of the patients was 66.3 years, most of them were male (61.6 %) and 51.5 % of them had non-ST-elevation MI (NSTEMI). The majority had hypertension (78.9 %), 35.1 % had diabetes, and the prevalence of all other comorbidities was around 10 %. Of the ST-elevation MI (STEMI) cases, 86.7 % percent underwent percutaneous coronary intervention (PCI) during the acute care. The 30-day crude all-cause mortality was 12.9 % (11.4 % in the NSTEMI group, 14.4 % in the STEMI group), while the 1-year crude all-cause mortality was 21.3 % (22.0 % in the NTSEMI group, 20.5 % in the STEMI group).

Vital registration of the patients was complete until 30 June 2023. The median follow-up was 661 days (lower quartile: 401 days, upper quartile: 972 days). In this timespan, 25.0 % of the patients died (26.7 % in the NTSTEMI group, 23.1 % in the STEMI group), the majority of them (38.6 %) having MI as the cause of death. 37.5 % had cardiovascular cause of death other than MI. 7.4 % had cancer as the cause of death and 16.5 % had other cause of death. Comparing COD of STEMI and NSTEMI patients, AMI was more common COD in STEMI patients (50.0 % vs. 29.3 %), while cardiovascular other than AMI COD was more frequent in NSTEMI patients (44.1 % vs 29.3 %).

The median follow-up time was 679 days for STEMI cases and 647 days for NTSEMI cases.

3.2. Univariable survival analysis

The cumulative incidence of all-cause mortality, and cause specific mortality (with a breakdown of AMI, cardiovascular other than AMI, cancer, other) is shown on Fig. 1.

Numerical values for important time points are given in Table 2.

As expected, the incidence of deaths due to AMI increases very sharply early on and then reaches a plateau, while the remaining causes keep increasing, although with different rates.

Table 3 shows the distribution of deaths in those patients who died within 1 year according to the cause of death in both STEMI and NSTEMI patients, separated according to whether the death occurred within or beyond 30 days.

3.3. Multivariable modelling of survival

The multivariable survival model for AMI cause of death along with usual multivariable model for all-cause mortality is shown in Fig. 2.

In the cause-specific model for AMI cause of death, STEMI infarction (HR = 2.37 [95 % CI: 2.17–2.59], $p < 0.001$), higher age (HR = 1.05 [95 % CI: 1.05–1.06] for each year increase, $p < 0.001$), prior stroke (HR = 1.43 [95 % CI: 1.26–1.62], p < 0.001), the presence of peripheral arterial disease (HR = 1.58 [95 % CI: 1.42–1.76], $p < 0.001$), heart failure in medical history (HR = 1.53 [95 % CI: 1.37–1.71], $p < 0.001$) and the presence of diabetes mellitus (HR = 1.16 [95 % CI: 1.07–1.26], p < 0.001) were factors significantly associated with higher hazard, while female sex (HR = 0.87 [95 % CI: 0.80–0.94], p < 0.001), the performing of percutaneous coronary intervention (HR = 0.56 [95 % CI: 0.51–0.61], p < 0.001), and interestingly, the presence of hypertension (HR = 0.76 [95 % CI: 0.69–0.84], p < 0.001) were associated significantly with lower hazard.

Table 1
Characteristics of the included patients.

	N	NSTEMI (*N* = 14,413)	STEMI (*N* = 13,552)	Combined (*N* = 27,965)
Age	27,965	60.4/69.2/77.5 68.4±12.3	54.4/64.5/73.1 64.1±12.9	57.2/67.0/75.7 66.3±12.8
Sex: Female	27,965	39.5 % (5691)	37.2 % (5040)	38.4 % (10731)
Medical history				
Prior AMI	27,307	14.5 % (2037)	8.4 % (1118)	11.6 % (3155)
Heart failure	27,338	15.5 % (2184)	7.9 % (1043)	11.8 % (3227)
Stroke	27,305	8.8 % (1242)	6.2 % (820)	7.6 % (2062)
COPD	12,489	9.0 % (586)	6.2 % (368)	7.6 % (954)
Comorbidities				
Hypertension	27,594	84.1 % (12005)	73.2 % (9758)	78.9 % (21763)
DM	27,486	39.4 % (5588)	30.5 % (4058)	35.1 % (9646)
PAD	26,972	15.4 % (2135)	8.1 % (1060)	11.8 % (3195)
CKD	12,906	9.8 % (666)	5.1 % (313)	7.6 % (979)
Treatment and outcome				
PCI	27,965	62.6 % (9018)	86.7 % (11748)	74.3 % (20766)
30-day all-cause mortality	27,965	11.4 % (1644)	14.4 % (1956)	12.9 % (3600)
1-year all-cause mortality	27,965	22.0 % (3172)	20.5 % (2776)	21.3 % (5948)
Died	27,965	26.7 % (3850)	23.1 % (3128)	25.0 % (6978)
Primary COD: AMI	6978	29.3 % (1128)	50.0 % (1564)	38.6 % (2692)
Cancer		7.6 % (294)	7.1 % (223)	7.4 % (517)
Cardiovascular other than AMI		44.1 % (1699)	29.3 % (917)	37.5 % (2616)
Other		18.9 % (729)	13.6 % (424)	16.5 % (1153)

AMI: acute myocardial infarction, DM: diabetes mellitus, PAD: peripheral arterial disease, COPD: chronic obstructive pulmonary disease, CKD: chronic kidney disease, PCI: percutaneous coronary intervention, COD: cause of death.

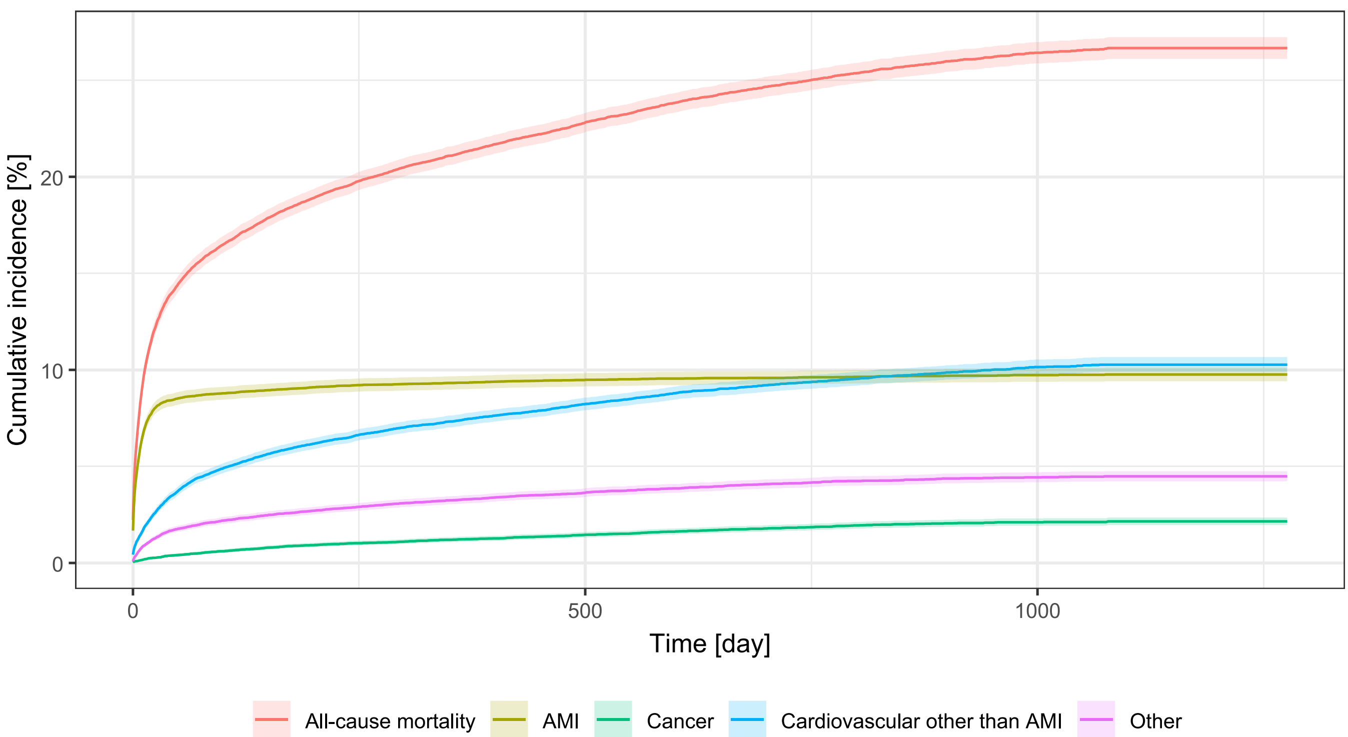

Fig. 1. Cumulative incidence of all-cause and cause-specific mortality.

Table 2
Cumulative incidence [%] of different causes of death and all causes for 30 days, 90 days and 1 year.

Time	AMI	Cardiovascular other than AMI	Cancer	Other	All-cause mortality
30	8.24 (7.92–8.56)	2.91 (2.72–3.12)	0.29 (0.24–0.36)	1.43 (1.29–1.57)	12.87 (12.48–13.27)
90	8.75 (8.43–9.09)	4.73 (4.49–4.99)	0.58 (0.49–0.67)	2.11 (1.95–2.28)	16.17 (15.74–16.61)
365	9.34 (9–9.68)	7.42 (7.11–7.73)	1.23 (1.1–1.36)	3.29 (3.09–3.5)	21.27 (20.79–21.75)

4. Discussion

In Hungary, the registration of births and deaths was initiated by the Catholic Church in 1625, following an order by Bishop Péter Pázmány. Other churches soon adopted similar practices. Since 1895, however, civil registration has become an exclusive responsibility of the state,

Table 3
Distribution of deaths among those who died within 1 year, according to diagnosis (STEMI/NSTEMI) and whether the death occurred within 30 days or later.

	All patients who died within 1 year ($n = 5948$)			
	STEMI (2776, 46.7 %)		NSTEMI (3172, 53.3 %)	
	Died within 30 day (1956, 70.5 %)	Died after 30 day (820, 29.5 %)	Died within 30 day (1644, 51.8 %)	Died after 30 day (1528, 48.2 %)
AMI	1430 (73.1 %)	111 (13.5 %)	874 (53.2 %)	196 (12.8 %)
Cardiovascular other than AMI	323 (16.5 %)	421 (51.3 %)	492 (29.9 %)	838 (54.8 %)
Cancer	33 (1.7 %)	116 (14.1 %)	49 (3.0 %)	145 (9.5 %)
Other	170 (8.7 %)	172 (21.0 %)	229 (13.9 %)	349 (22.8 %)

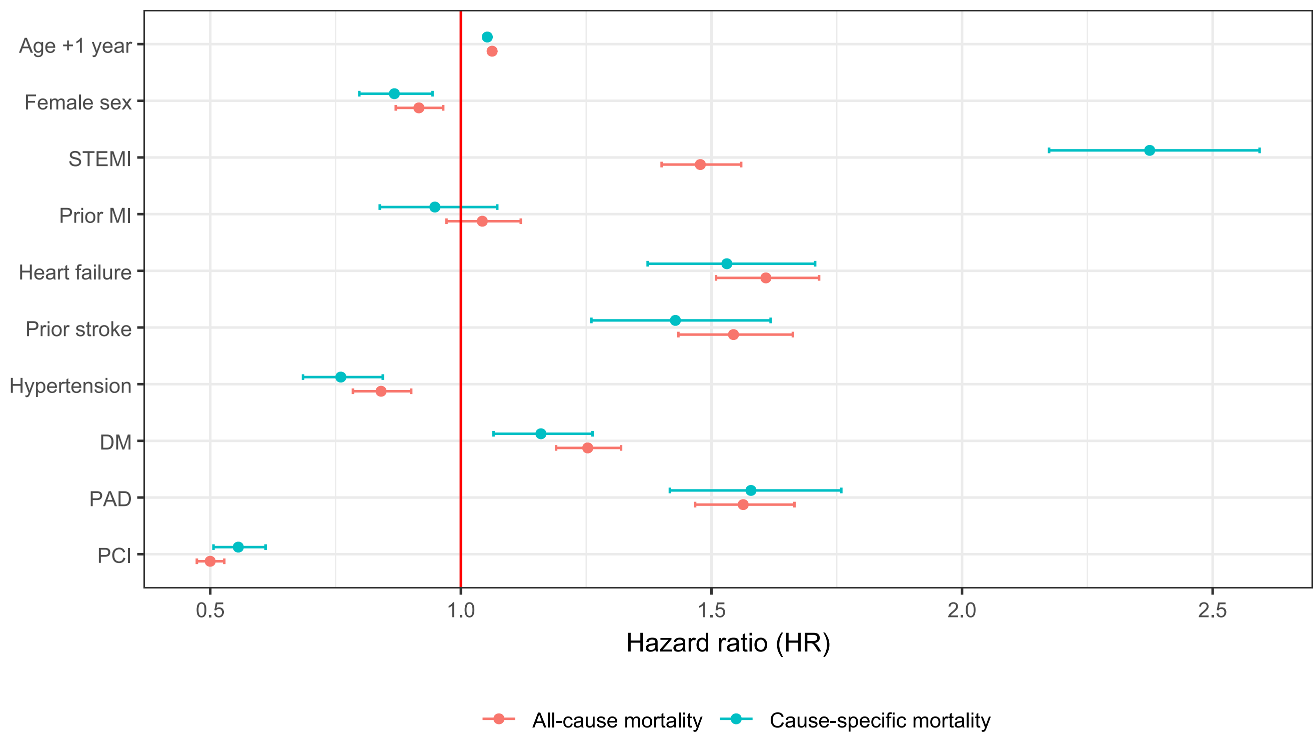

Fig. 2. Hazard ratios (HRs) obtained from the multivariable survival model for AMI cause of death along with multivariable Cox-model for all-cause mortality visualized with 95 % confidence intervals. DM: diabetes mellitus, STEMI: ST-elevation myocardial infarction, MI: myocardial infarction, PCI: percutaneous coronary intervention, PAD: peripheral arterial disease.

currently reported by the Hungarian Central Statistical Office (HCSO). To ensure international comparability, causes of death have been recorded according to a system developed by French statistician Alphonse Bertillon in the late 19th century [32]. Bertillon's classification grouped diseases based on anatomical data and initially comprised 164 categories. Since 1995, the HCSO has used the tenth revision of the International Classification of Diseases (ICD-10), maintained by the World Health Organization (WHO) [24]. Crucially, cause-of-death statistics are based on the underlying condition leading to death, along with any associated diseases noted on the death certificate.

Despite the importance of survival as an outcome metric in myocardial infarction, and despite the potential of cause-specific survival to increase the resolution of analysis, few studies have addressed cause-specific survival after MI [14,33–36].

One possible reason for this is the uncertainty inherent in cause-of-death classification—both in terms of the accuracy of data recording and the difficulty of categorization in patients with multiple comorbidities. These uncertainties may also change over time, as illustrated by diseases such as chronic obstructive pulmonary disease (COPD) [37,38] or diabetes [39], complicating longitudinal analyses such as survival studies. In addition to this, on the very long term, ICD itself gets expanded and revised from time to time, and bridging between different revisions is far from being trivial [40].

Despite these challenges, the present study undertook a cause-specific survival analysis based on the official statistical cause-of-death classification. A key strength of this work is its large sample size of nearly 30,000 patients, representing almost all MI cases in Hungary during a two-and-a-half-year period.

The cause-specific survival analysis identified several independent risk factors for AMI-specific mortality, including older age, male sex, ST-elevation index myocardial infarction (STEMI), diabetes, prior stroke, peripheral artery disease (PAD), and heart failure. Percutaneous coronary intervention (PCI) was confirmed as being associated with a lower hazard of mortality due to AMI. Interestingly, hypertension was also associated with a lower hazard—a finding that may seem counterintuitive at first glance. However, this phenomenon, often referred to as the "hypertension paradox" [41,42], is well-documented and is likely related to the medical therapy these patients typically receive—an aspect not controlled for in the regression model used in this study.

Our findings can also be compared to data from other countries in terms of risk of death itself. A recent registry-based study from the United Kingdom found that the 1-year all-cause mortality was 14.2 % in 2019 [43], substantially lower than what is reported here (21.3 %). While the lack of age-adjustment limits the comparability, this finding is in line with the overall European trends [44]. Conforming this, a Polish study from 2018 found a 1-year mortality more similar to ours (17.3 %)

[45].

A particularly noteworthy aspect of this study is the comparison between cause-specific and all-cause mortality during the follow-up. While both approaches yielded largely consistent findings, a notable exception was observed for STEMI: the hazard ratio (HR) for STEMI was substantially higher in the cause-specific analysis for AMI cause of death (2.38) compared to the all-cause analysis (1.48). This discrepancy is likely due to differences in how causes of death are distributed among patients with STEMI and non-STEMI (NSTEMI): deaths in NSTEMI patients were less frequently attributed directly to AMI. Nevertheless, they were still predominantly cardiovascular in nature, specifically, 1699 NSTEMI patients (44.1 %) had a cardiovascular cause of death other than AMI, compared to 29.3 % in the STEMI group. Among those 1699 patients, 1161 (68.3 %) were classified as having died from chronic ischaemic heart disease (ICD-10 code I25), with all other causes of death accounting for less than 5 %.

4.1. Study limitations

The study was restricted to a period of 2.5 years (although this still resulted in almost 30,000 patients due to the comprehensive nature of the used dataset). Also, patients all came from Hungary, potentially limiting the generalizability of the findings. Finally, as for any observational study, multivariable models might still have uncontrolled confounding.

5. Conclusions

While overall and cause-specific analyses aligned in this large registry study, a notable difference was observed for ST-elevation infarction, where hazard was substantially higher in the cause-specific analysis. This highlights the potential relevance of distinguishing between causes of death for a more precise understanding of outcomes.

Informed patient consent

No individual or a group of individuals can be identified from the manuscript.

CRediT authorship contribution statement

Tamás Ferenci: Writing – original draft, Visualization, Software, Methodology, Investigation, Formal analysis. **András Jánosi:** Writing – original draft, Investigation, Data curation, Conceptualization.

Ethical statement

It is thereby declared that the work submitted

- has not been published previously except in the form of a preprint, an abstract, a published lecture, academic thesis or registered report;
- it is not under consideration for publication elsewhere;
- its publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out;
- if accepted, it will not be published elsewhere in the same form, in English or in any other language, including electronically, without the written consent of the copyright-holder.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Analysis script underlying this article is available at https://github.com/ferenci-tamas/cause-specific-infarction-mortality.

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