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Twenty-year trend in comorbidity score among adults aged 50–85 years in Lombardy, Italy: Age-Cohort-Period analysis and future trends

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ABSTRACT

Objectives To assess the effects of age, birth cohort, and period on comorbidity rates as well as project their future trends over the next 25 years.

Design Population-based retrospective observational study.

Setting Record linkage from the population-based healthcare utilisation database of Lombardy, Italy, between 2004 and 2023.

Participants All beneficiaries of the Italian National Health Service (NHS) aged 50–85 years residing in Lombardy. Data were separately analysed for each year from 2004 to 2023, with thus the availability of 20 study populations.

Primary outcome measures Comorbidities were traced via the medical services provided by the NHS, and the overall quantification was obtained by the Multisource Comorbidity Score, which was developed and validated for the Italian population. The temporal analysis of the 20 yearly temporal comorbidity rates was obtained by the Age-Cohort-Period models. The comorbidities prevalence trends were forecasted from 2025 to 2050.

Results From 2004 to 2023, the prevalence of comorbidities declined from 46% to 40% in men and from 47% to 42% in women. An increase in prevalence between the ages of 50 and 85 years was observed for both women (from 33% to 63%) and men (from 29% to 67%). A declining prevalence was observed among cohorts born from 1922 to 1970 for both women (by 33%) and men (by 50%). A continued decline in the absolute number and prevalence rate of comorbidities is expected for both women and men until 2050.

Conclusions The decline in ageing-related comorbidity prevalence over time may persist up to 2050. Improved medical care and public health initiatives benefiting individuals born in more recent years may counterbalance the expected trend of increasing comorbidity prevalence due to population ageing.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study was based on population-based data referred to about 10 million inhabitants.
⇒ We were able to evaluate the trend in the prevalence of comorbidities over a long period including the last 20 years and to forecast the trend over the next 25 years.
⇒ The generalisability of our findings should be evaluated in other countries.

INTRODUCTION

Over the past century, the age of the population has shown a progressive increase in most high-income countries. It has been estimated that, due to progressive ageing, by 2030 half of the population of Western Europe will be older than 50 years, with a predicted average life expectancy at the age of 50 years of further 40 years.[1 2] These demographic changes have obvious fundamental implications for healthcare policies. However, the magnitude of several ageing-related modifications on the population health has never been satisfactorily studied.[3] For example, as they age, people accumulate health deficits that eventually become clinically manifest as multimorbidity.[4] On the other hand, throughout the entire past century, there have been progressive favourable changes in many health-related behaviours, healthcare accessibility and availability of critically important diagnostic and treatment improvements. This favourable 'birth-cohort effect' may amplify, mitigate or even override the negative 'ageing effect' on a population's health status, including the progression of the multimorbidity prevalence. Overall, population-based evidence regarding trends in comorbidity across birth cohorts is limited and produces discordant results.[5–7] Moreover, to the best of our knowledge, no studies have evaluated the impact of birth cohort on comorbidity trends in recent years and forecast future trends in comorbidity.

With the aim to reduce this gap, we conducted a population-based investigation using the healthcare data from Lombardy, the most populated region of Italy, known

for its strong economic performance among European regions.[8] The objectives of the study were to (i) measure the changes in the prevalence of comorbidities that have occurred over time, (ii) investigate the effects of age and year of birth on comorbidity rates and (iii) predict the prevalence of comorbidities over the next 25 years. The comorbidity rate and clinical profile complexity were measured using the Multisource Comorbidity Score, which has been recently developed and validated in the Italian population.[9 10]

METHODS

Target population and data sources

Residents of Lombardy aged 50–85 years who on 1 January of each year from 2004 to 2023 were beneficiaries of the Regional Health Service (RHS) for at least 2 years formed the 20 target populations of interest. By design, each citizen can be included in multiple target populations. In Italy, all citizens have equal access to the healthcare provided by the National Health Service (NHS). Lombardy uses an automated system of healthcare utilisation databases to manage health services. Databases include demographic information (sex, year of birth, dates of start and end of the condition of RHS beneficiary, vital status, and date of death) and healthcare-related data, including diagnoses and interventions (coded through the International Classification of Diseases, ninth revision, Clinical Modification—classification system) by all hospitals of the region, and drugs prescribed by the RHS physicians to outpatients, directly dispensed by territorial pharmacies (coded through the anatomical therapeutic chemical—classification system) and completely or almost completely reimbursed by the RHS. These databases can be interconnected using a unique individual identification code assigned to each NHS beneficiary. This system allowed us to characterise each citizen in the 20 target populations based on demographic and clinical information provided by their use of healthcare services.

Comorbidity assessment

The Multisource Comorbidity Score (MCS) was used in this study to evaluate comorbidities. For each citizen belonging to each target population, the 34 diseases or conditions contributing to the MCS were identified using inpatient diagnostic codes and records of drugs dispensed in community pharmacies at least once within 2 years prior to the baseline information (ie, in 2002–2003 for the population entering on 1 January 2004, and in 2021–2022 for the population entering on 1 January 2023). In accordance with the original validation study,[9] each of the 34 diseases or conditions was assigned a weight based on its ability to predict 1-year mortality. The MCS for each citizen was then calculated as the sum of these weights. The aggregate scores were categorised into five levels: 0, 1–4, 5–9, 10–14 and ≥15, corresponding to increasing severity of comorbidity profiles denoted with MCS values of 0, 1, 2, 3 and 4, respectively. Tables detailing the number of beneficiaries, categorised by MCS aggregate scores, sex and year of birth, were generated for each of the 20 target populations studied.

Statistical analyses

Comorbidity prevalence. The primary outcome of interest was the prevalence rate of at least one disease or condition contributing to the MCS (ie, an MCS value ≥1). This measure is referred to as the comorbidity prevalence rate throughout the study.

Prevalence trends. The average comorbidity prevalence rates were calculated for 4-year periods corresponding to 9 age groups (50–53, 54–57,…, and 82–85 years), 13 categories of birth cohorts (1922–1925, 1926–1929,…, and 1970–1973) and 5 grouped calendar periods (2004–2007, 2008–2011,…, and 2020–2023). Additionally, over the 20-year period of interest, we calculated the trends in comorbidity prevalence rates standardised to the age-specific regional population in 2023 (using direct standardisation), graphically reporting the results as a smooth curve, distribution of MCS values and age above which half of the beneficiaries had at least one disease or condition (ie, the MCS median age).

Modelling the effects of age, cohort and period. We modelled the effects of age, cohort and period on the comorbidity prevalence rate. Since an individual's birth cohort is a perfectly linear function of the study calendar year and the individual's age (ie, cohort=period age), standard models cannot uniquely estimate the effects of these three temporal factors simultaneously due to collinearity.[11] To address this, we adapted the classic Age-Cohort-Period (ACP) model to our setting.[12] Briefly, the data were modelled such that the effects of age were represented as the age-specific rates of the reference cohort (1946–1949 birth cohort), adjusted for the period effects. The cohort effect was measured as prevalence ratios relative to the reference cohort, which was set to 1. The period effect was represented as residual prevalence ratios relative to the fitted values for age and cohort effects, standardised to have an average of 1 and a slope of 0. This model can be interpreted as showing the longitudinal effect of ageing for the reference cohort and how this effect varies across different birth cohorts.[13]

Predicting upcoming trends. Trend forecasting is a technique used to predict health outcomes, such as comorbidity prevalence, based on historical trends and current data. In our study, we applied the coefficients of the age, period and cohort effect estimated from the ACP model to the forecasted population of the Lombardy region from 2025 to 2050.[14] This forecasting was based on projected changes in fertility, mortality and migration, as provided by the National Institute of Statistics, over 4-year periods from 2025 to 2050. The median values and 80% CIs of population projections were used in the current study.[15]

Secondary analysis. MCS was initially tested on a cohort of NHS beneficiaries in 2008.[9] Given the potential for changes in the MCS's ability to predict 1-year mortality

over the 20-year period under consideration, it is possible that variations in comorbidity prevalence may reflect changes in the MCS's performance rather than shifts in the clinical complexity of the target population. To address this, we assessed whether the performance of the MCS changed over time. We conducted an analysis using receiver operating characteristic (ROC) curves and calculated the corresponding areas under the ROC curves to evaluate the discriminant power of the MCS in predicting 1-year mortality from 2004 to 2023.

Analyses were performed separately for men and women. Computation, modelling and plotting were executed using the R statistical software V.4.3.2 (R Foundation for Statistical Computing, Vienna, Austria).

Privacy-by-design issues

Privacy-by-design principles were adopted for this study to ensure the protection of individual data.[16 17] The study adhered to regional infrastructures that provided a secure environment for storing health data and prevented unauthorised imports and exports of individual records. Data safety was maintained through the pseudo-anonymisation of identification codes, the inverse process being allowed only to the Regional Health Authority on request from judicial authorities. Data safety was ensured by restricting data analysis to a few authorised investigators (AT under the supervision of MF) who complied with ethical data usage requirements and legal agreements. These investigators submitted R codes to the database prepared by regional staff and exported the outputs without directly accessing or viewing individual records. The Regional Health Authority of Lombardy endorsed the project, recognising its potential public benefits. A comprehensive overview of the 'privacy-by-design research environments' method, which is the most common approach for guiding the use and interconnection of secondary data in the United Kingdom and mainland Europe, is available elsewhere.[18]

Patient and public involvement

The study analysed secondary data without patient involvement. Patients were not invited to be involved in the study design, development of outcomes, interpretation of the results or drafting of the manuscript.

RESULTS

Time trends in comorbidity prevalence

From 2004 to 2023, both crude and age-standardised comorbidity prevalence rates steadily declined from 46% to 40% in men (figure 1). This trend was also observed in women, with an overall decline from 47% to 42%, except for a temporary increase in prevalence between 2012 and 2015.

Figure 2 confirms the improving MCS profile. Over the study period, the proportion of citizens with a worse clinical complexity (MCS ≥4) decreased from 2.5% to 1.6% in women and from 3.4% to 1.8% in men. Concurrently, the MCS median age increased by 5 years (from 66 to 71 years) in men and by 6 years (from 67 to 73 years) in women, indicating that half of citizens have at least one disease/condition at higher age. This improvement in

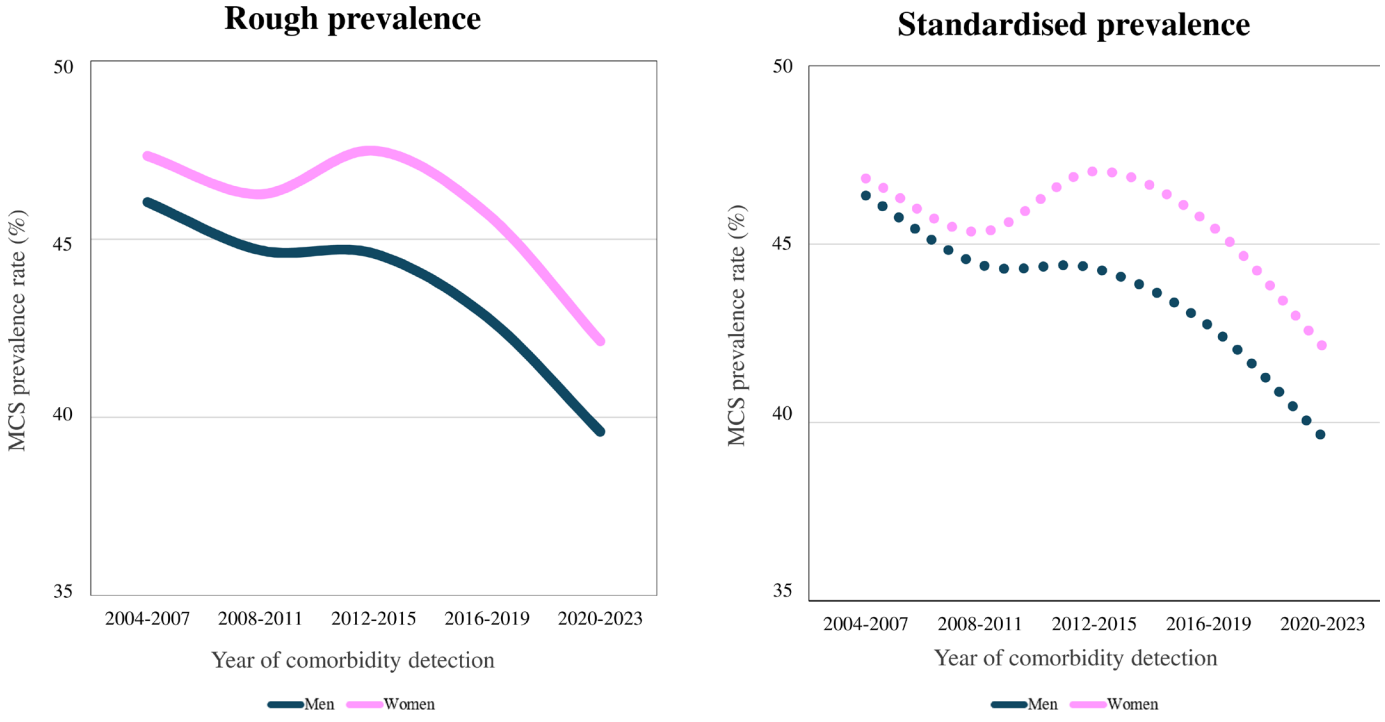

Figure 1 Trends in the crude and age-standardised comorbidity prevalence rates in men and women with a MCS of at least one among the Italian National Health Service beneficiaries who were residents in the Lombardy region and were aged 50–85 years between 2004 and 2023. Prevalence rates were standardised based on the age-specific regional population in 2023 (direct standardisation). MCS, Multisource Comorbidity Score.

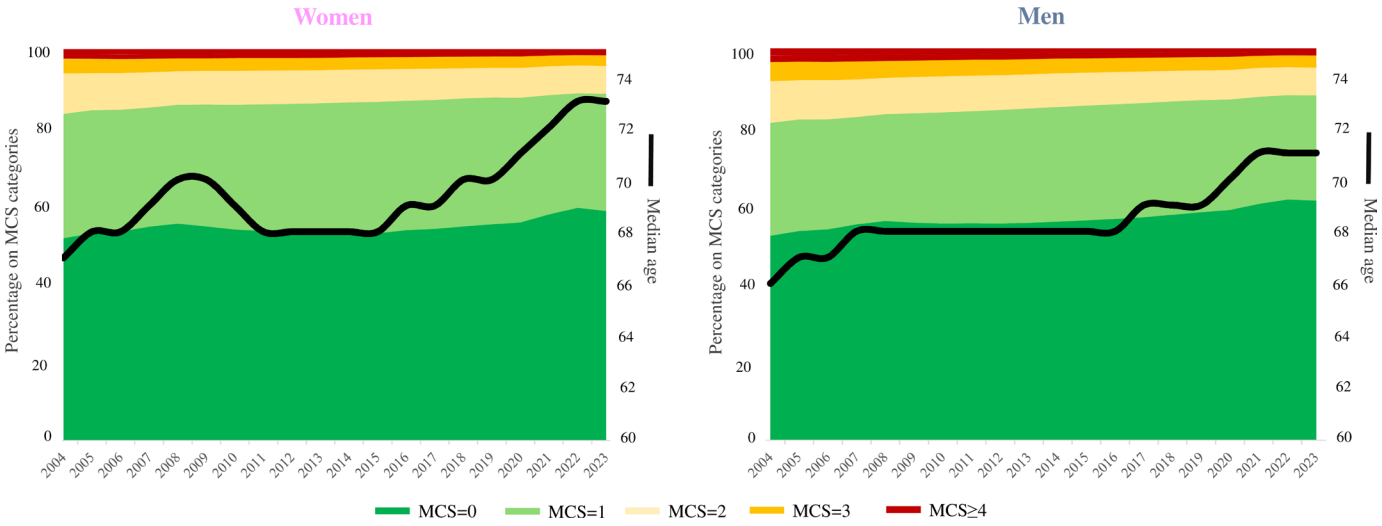

Figure 2 The MCS distribution and MCS median age (ie, the age above which half of the beneficiaries suffered from at least one disease/condition) among men and women who were beneficiaries of the Italian National Health Service, residents in the Lombardy region and aged 50–85 years between 2004 and 2023. MCS, Multisource Comorbidity Score.

the MCS median age was observed not only over time but also across birth cohorts, being the median age increased from 67 years for those born in 1935 to 72 years for those born in 1951.

Effects of age and birth cohort on the comorbidity prevalence

The MCS prevalence rates generally decreased with year of birth (figure 3). This trend was observed across all age groups and for both sexes. For example, women aged 66–69 years born between 1938 and 1941 had comorbidity prevalence rates of 49%, compared with 43% for those born between 1954 and 1957. The corresponding figures for men were 52% and 44%, respectively.

Modelled effects of age, cohort and period on the comorbidity prevalence

Figure 4 illustrates the effects of age, cohort and period on comorbidity prevalence. Among citizens born between 1946 and 1949 (the reference birth cohort), comorbidity rates increased progressively from 50 to 85 years, rising from 33% to 63% in women and from 29% to 67% in men. Compared with the reference birth cohort, prevalence ratios declined progressively from those born around 1922 to those born around 1970, with a 33% decrease in women and a 50% decrease in men. Regarding the period effect, the residual relative risks remained stable until 2008, increased until 2012 and then declined steadily by 10% per year over the last decade for both men and women.

Predicted future trends

Figure 5 depicts the projected trends in the MCS prevalence until 2050. A continued decline in comorbidity prevalence is anticipated for both women and men (figure 5A), with an average annual decrease of 2.8% in women and 3.6% in men. Similarly, the absolute number of individuals with comorbidities is expected to decrease by approximately 6000 women and 6400 men each year on average (figure 5B).

Online supplemental tables S1–S5 report the values graphically depicted in figures 1–5.

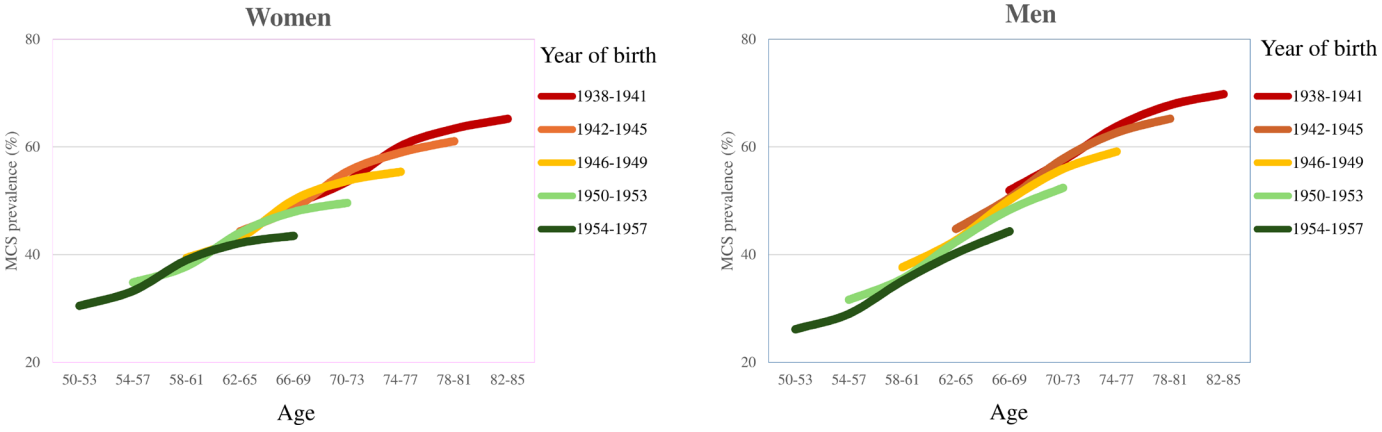

Figure 3 Influence of age and birth cohort on the MCS-based comorbidity prevalence rates among men and women who were beneficiaries of the Italian National Health Service, residents in the Lombardy region and aged 50–85 years between 2004 and 2023. MCS, Multisource Comorbidity Score.

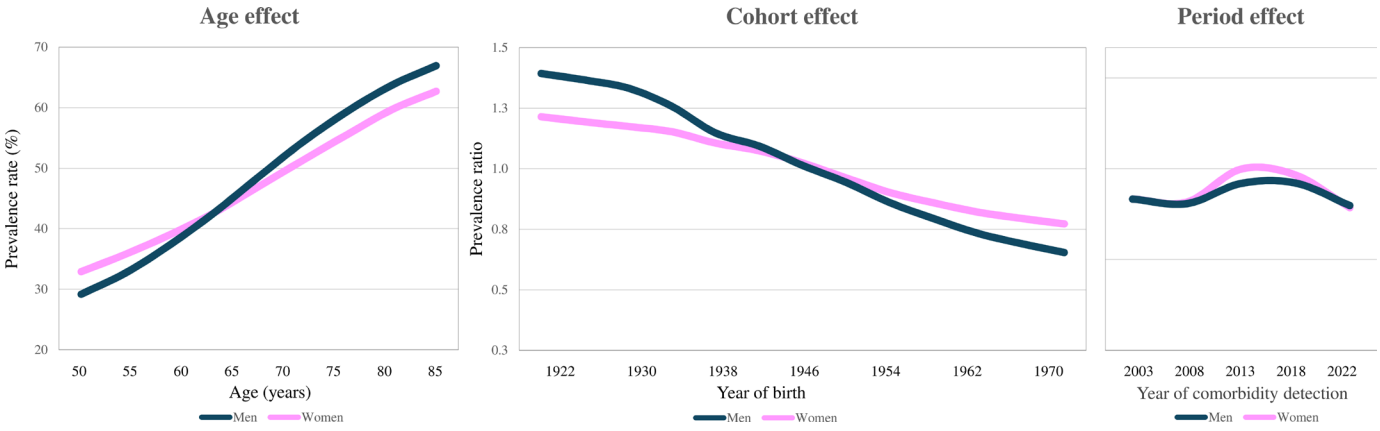

Figure 4 Modelling of the effects of age, cohort and period on the MCS-based comorbidity prevalence among men and women who were beneficiaries of the Italian National Health Service, residents in the Lombardy region and aged 50–85 years between 2004 and 2023. The confidence bands were too narrow to be represented. The Age-Cohort-Period model showed a large and significant decline in the residual deviance, changing from 92 864 for the model including age alone to 8109 for the model including age and birth cohort (–84 755 with 9 degrees of freedom, p<0.001), to 1830 for the model including age and period (–91 034 with 4 degrees of freedom, p<0.001) and to 182 for the model including age, birth cohort and period (–92 862 with 12 degrees of freedom, p<0.001). The corresponding values for women were 62 937, 3536 (–59 401 with 9 degrees of freedom, p<0.001), 23 065 (–39 872 with 4 degrees of freedom, p<0.001) and 785 (–62 152 with 12 degrees of freedom, p<0.001). MCS, Multisource Comorbidity Score.

Time trends in MCS discriminatory power

Online supplemental figure S1 shows that, except for a slight reduction in 2020, the areas under the ROC curves remained relatively stable throughout the 20-year period, ranging from 0.774 in 2004 to 0.754 in 2023.

DISCUSSION

A fundamental question in ageing research is whether increased life expectancy (i) leads to more years spent with chronic health problems, the expansion of morbidity theory[19] or (ii) older individuals spend fewer years in poor health due to the delayed onset of diseases, the compression of morbidity theory.[20] Online supplemental figure S2 provides a graphical representation of expected comorbidity prevalence based on these two theories. While due to socioeconomic disparities and other factors, both theories can coexist within a country, understanding the prevailing trend in a given country is crucial for shaping appropriate health policies. Our study aimed to investigate time trends in comorbidity prevalence among NHS beneficiaries in Lombardy aged 50–85 years from 2004 to 2023. We observed a decline in the proportion of comorbid citizens during the study period. At first glance, this finding may seem counterintuitive given the progressive ageing of the population and the expectation that clinical complexity would worsen with age. However, we also noted a decrease in comorbidity prevalence among

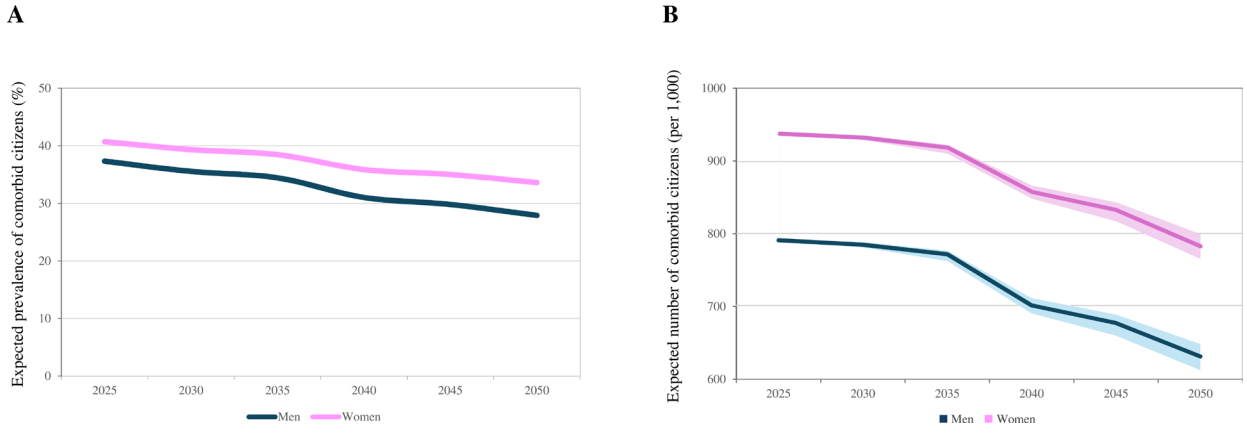

Figure 5 Expected number of comorbid citizens (2025–2050) who are beneficiaries of the Italian National Health Service, residents in the Lombardy region and aged 50–85 years. The base population used by the Italian National Institute of Statistics for population projections is the one that is stratified by sex and single age groups as of 1 January 2022. The margins of the uncertainty of the population projections (CIs) depend on the uncertainty inherent in the future levels of mortality, fertility and migration. The median values and 80% CIs of population projections were used in the current study.

individuals belonging to more recent birth cohorts; individuals of the same age from newer generations had better clinical status compared with those born in the early 20th century. These observations, combined with the increase in the median age of comorbidity over time and across birth cohorts, support the expansion of morbidity theory for the investigated population. If these trends continue, we anticipate a further reduction in the number of comorbid citizens as more recent generations age over the next 25 years.

Overall, evidence regarding trends in comorbidity across birth cohorts at the population level is limited. Our findings contrast with population-based studies in England and the United States, which have reported that more recent cohorts experience worse frailty and comorbidity compared with earlier cohorts.[5 6] This may reflect the heterogeneity in study design and study populations (ie, a respondent sample of the population vs entire population), period of observation and definitions of frailty (ie, frailty index vs comorbidity index). Conversely, a study from Sweden observed similar levels of frailty in the 1901–1902 and 1930 birth cohorts at the age of 70 years.[7] To the best of our knowledge, no other study besides ours has specifically investigated the impact of birth cohort on comorbidity trends in recent years or forecast future trends in comorbidity.

The so-called sex paradox[3] refers to the phenomenon where, despite being more likely to live to older ages than men,[21 22] women experience a greater burden of comorbidities, disability, frailty and poorer functioning at advanced ages.[23–25] Research has shown that women exhibit a dramatic linear increase in chronic illness from their 60s to their 80s, whereas men tend to show a nonlinear trajectory with a sharp increase just before death.[26] Our study findings align with this sex paradox, as we observed that women are more likely to be comorbid compared with men. However, our findings extend this understanding by suggesting that men benefit more from the birth-cohort effect. Consequently, the reduction in comorbidity prevalence over time is expected to occur more rapidly in men, potentially widening the sex difference in comorbidity rates in the coming years.

Several possible explanations could account for the observed decline in MCS prevalence, which underscores the uncertainty regarding the public health implications of our results. One hypothesis is that the MCS may be progressively losing its ability to predict clinical outcomes. However, this is countered by the fact that MCS performance did not significantly change over time, with only a minor decrease in discriminant power in 2020, coinciding with the onset of the COVID-19 pandemic. The decline in prevalence began before the pandemic, and no significant changes in the trend were noted during the pandemic. This suggests that the MCS remains relatively robust, with its predictive performance only slightly varying over time.

Another hypothesis is that the observed decline in prevalence might be due to reduced exposure to risk factors over the past 20 years. Consistent with this, a systematic analysis from the Global Burden of Disease Study reported a reduction in age-standardised disability-adjusted life year rates attributable to leading risk factors (such as smoking, uncontrolled systolic blood pressure, high body mass index, high fasting plasma glucose and alcohol use) in high-income countries from 2000 to 2021.[27] However, since changes in exposure to these factors require several decades to show their impact, they should have occurred at least since the second half of the last century to hypothesise their effect on the observed results.

A more plausible explanation is that the declining prevalence might result from a weaker effect of ageing compared with the stronger influence of the birth cohort. As new generations replace older ones, the birth-cohort effect may outweigh the impact of ageing. This hypothesis is supported by the notion that cohorts born after World War II, particularly in developed countries, were raised in healthier environments with better hygiene, improved diets, and access to prevention and treatment programmes. Evidence shows that developed populations have experienced a reduction in smoking prevalence[28] and increased access to antihypertensive agents and statins[29 30] starting with cohorts born after 1950. Conversely, there is a concerning trend of increasing obesity prevalence among children and adolescents, particularly in high-income countries.[31] If this trend continues without effective interventions, the cohort effect observed in our study may reverse when the current generations of adolescents reach adulthood.

Over the past 50 years, healthcare expenditure has significantly increased in high-income countries.[32] Despite this, there is limited consensus on the factors driving this increase and even less information on how these factors vary by health condition.[33] Common opinion, sometimes supported by 'ecological' cross-sectional correlation data,[34–36] suggests that population ageing is a major driver of increased healthcare expenditure. However, data from the United States indicate that increases in healthcare spending from 1996 to 2013 were primarily driven by rising healthcare service prices and intensity, rather than population ageing, and were even negatively associated with disease prevalence or incidence.[37] Similarly, a study combining data from the United States and Canada found that medical technology innovation was the main factor behind healthcare expenditure growth, with population ageing having a relatively minor impact.[38] Our findings align with these observations. Despite a significant increase in healthcare expenditure in our setting, this rise was not attributable to worsening clinical complexity due to ageing. This suggests that policies aimed at controlling healthcare spending should focus on modifiable factors, such as the appropriateness of care, rather than attributing rising costs solely to inevitable population ageing.

The present study has several strengths, including its use of population-based data and a 20-year observation period. However, there are notable limitations. First, the MCS estimates relied solely on inpatient diagnoses and

outpatient drug therapies. Conditions treated in primary care or other outpatient settings were not considered, and this may lead to an underestimation of comorbidity prevalence and future trends. However, we observed a decline in the prevalence of comorbidities also among patients with a worse clinical complexity, that is those patients suffering from more severe conditions, which are unlikely treated in primary care. Second, comorbidity prevalence only included diseases independently associated with 1-year mortality, thereby focusing on severe and potentially lethal conditions. Less severe conditions were not assessed, which may limit the comprehensiveness of the prevalence estimates. Third, the increasing use of out-of-pocket healthcare services[39] could reduce our ability to evaluate comorbid citizens. However, our findings show a declining trend in comorbidity prevalence alongside a reduction in severe and clinically complex diseases. Because the use of out-of-pocket services is expected to decrease with increasing clinical complexity,[40] this factor alone is unlikely to fully explain the observed trends. Fourth, our predictions were based on several scenarios involving changes in survival, fertility and migration.[12] However, they did not account for potential changes in social policies (eg, fertility interventions), healthcare advancements (eg, new effective medical technologies) or the onset of catastrophic events (eg, wars, terrorist attacks and severe pandemics), which could influence future trends. Fifth, there are concerns about the external validity of our findings, highlighting the need for further research to verify their generalisability to other high-income regions and countries.

In conclusion, this large population-based study observed a declining comorbidity prevalence rate over time, a trend expected to continue at least until 2050. Improved medical care and public health initiatives, particularly those benefiting more recent generations, may counterbalance the anticipated rise in comorbidity prevalence due to population ageing.

Contributors GC led the study conceptualisation and the development of the research question, supported by MF, OL, GZ and GB; MF, AT and VB developed the statistical analysis plan and performed the analyses; GC supervised the analyses and wrote the first draft of the paper; GM supervised manuscript for its clinical implications; all authors contributed to the interpretation and discussion of the results, critically revised the manuscript for intellectual content, and approved the final version and the submission of the manuscript. GC is the guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Competing interests GC received research support from the European Community (EC), the Italian Agency of Drugs (AIFA) and the Italian Ministry for University and Research (MIUR). GC and GM took part in a variety of projects that were funded by pharmaceutical companies and received to them honoraria as a member of the advisory boards. All other authors have no completing interest to declare.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval According to Italian law, studies entirely based on registry data do not require approval from an ethics review board. All data were completely anonymized. All procedures were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available. The data that support the findings of this study are available from the Lombardy region, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the Lombardy region upon reasonable request.

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