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ORIGINAL RESEARCH ARTICLE

The economic impact of multimorbidity in Italy: evaluation of direct costs and scenario analysis of patients with type 2 diabetes, heart failure, and chronic kidney disease using real-world data

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ABSTRACT

Objectives: This study aimed to evaluate the healthcare costs associated with managing type 2 diabetes (T2D), chronic kidney disease (CKD), and heart failure (HF) in Italy. Specifically, the research investigated the economic impact on the Italian National Health System due to the increased clinical complexity and multimorbidity among patients with these conditions.

Methods: A predictive model was developed to estimate the costs of managing patients with T2D, CKD, and HF, either as standalone diseases or in combination. Epidemiological data were derived from real-world data, analyzing a sample corresponding to approximately 10% of the Italian population. The model stratified patients into seven groups based on disease combinations and estimated direct healthcare costs, resulting from hospitalizations, medications, and outpatient services. Scenario analyses were performed to forecast costs based on the expected progression of single diseases to multimorbid conditions.

Results: The analysis estimated a total annual healthcare expenditure of approximately €18.7 billion for the 5.77 million Italian patients with at least one of these diseases. Patients with T2D, CKD, and HF had an average yearly cost of €2,002, €4,322, and €5,061, respectively, with multimorbid patients incurring significantly higher costs. Scenario analyses predicted a potential increase in total healthcare expenditures to €19.5 billion, with an additional burden of €775 million.

Conclusions: The findings underscore the substantial economic burden of T2D, CKD, and HF, exacerbated by multimorbidity. The results highlight the need for early diagnosis, targeted prevention, and optimized treatment strategies to mitigate rising healthcare costs and improve patients' outcomes.

Keywords: Chronic kidney disease, Healthcare costs, Heart failure, Multimorbidity, Scenario analysis, Type 2 diabetes

Introduction

The increased life expectancy has resulted in a growing proportion of older adults in the global population (1-5). Since 2007, the World Health Organization (WHO) has extensively documented the correlation between the demographic shift and the increased prevalence of chronic diseases such as type 2 diabetes (T2D), chronic kidney disease (CKD), and heart failure (HF), together with hypertension, obesity, and mental health conditions like depression. As individuals age, physiological changes and prolonged exposure to risk factors contribute to the development of these non-communicable diseases (NCDs) (1-5). The rising numbers in age-related conditions have become a pressing issue, in view of the substantial burden on individuals, families, and society due to the necessity of long-lasting therapeutic interventions, rehabilitation, and stress, with the related costs for the healthcare systems (6,7).

Nowadays, T2D, CKD, and HF represent a major area of concern in public health and clinical practice, not only as single pathological entities, but more importantly for their close interconnection, especially in the elderly, in whom their co-occurrence is common (8). Real-world clinical practice, evidence-based management guidelines, and clinical research support the view that single-disease approaches are becoming inadequate in an increasingly aging community with complex multimorbidity profiles (9).

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A large multinational study of approximately 500,000 diabetics across 12 countries, including Italy, reported that T2D patients free from cardiovascular and renal comorbidities have an increased lifetime risk of incurring CKD and HF of 54% and 29%, respectively (10). Hence, the clinical and economic impact of each single disease is even more enhanced when two or all three conditions among T2D, CKD, and HF coexist (10).

In Italy, approximately 24 million individuals are affected by chronic diseases, with over 85% of them aged over 75 years suffering from at least one chronic condition (11). The prevalence of diabetes in Italy is estimated at 6.4% (12). A study analyzing data during the year 2018 identified 697,208 individuals with diagnosed diabetes, corresponding to a prevalence of 6.2%. The average age of these patients was 69 years, highlighting the higher occurrence among the older subjects (13).

Consistent with other European countries (14,15), and data from overseas (16,17), in Italy, HF has a reported prevalence of approximately 1.7%, higher in older people, and represents the first cause of hospitalization and rehospitalization, with considerable implications for the costs sustained by the national and regional systems (18).

Likewise, CKD prevalence in Italy is notably higher among the elderly population, reflecting the global trend. Italian data have confirmed that the risk of CKD increases after 50 years of age and is most common among adults older than 70 years (19). Moreover, prevalence is different between sexes, as CKD stages 3-5 range from 5.7 to 7.5% in men and 6.2% to 6.5% in women (19).

Efforts to implement timely and valuable prevention measures against chronic diseases and multimorbidity require a deeper knowledge of the characteristics, risk factors, and clinical history of patients with overlapping T2D, CKD, and HF. The cumulative burden of such diseases might be ideally alleviated by focusing on the modifiable risk factors, promoting the attainment of blood pressure target levels, LDL-cholesterol lowering, glucose control, and lifestyle interventions on smoking habits, physical activity, diet, and body mass index (BMI) (20). Besides, the availability of therapies able to provide benefits across the individual diseases, like sodium-glucose cotransporter-2 inhibitors (SGLT2i or gliflozins), lipid-lowering agents, and renin–angiotensin system inhibitors (RAASi) has the potential to improve clinical outcomes for T2D, CKD, and HF (21).

To date, there are poor data from the real clinical practice in Italy on the epidemiology, demographic characteristics, healthcare resource utilization, and costs of patients with different patterns of T2D, CKD, and HF, viewed as single pathological entities or coexisting diseases.

The present study was conducted to quantify the prevalence of multimorbidity, specifically the coexistence of T2D, HF, and CKD in the Italian population, and to estimate the associated burden on healthcare costs. Additionally, a scenario analysis was applied to explore the increase in expenditures for the Italian National Health System (Servizio Sanitario Nazionale—SSN) resulting from greater clinical and therapeutic complexity.

Methods

Study design and data source

A retrospective observational analysis was conducted using administrative healthcare data collected from a network of Local Health Units (LHUs) across nine Italian regions: Piemonte, Liguria, Veneto, Umbria, Lazio, Molise, Abruzzo, Puglia, and Sicilia. The dataset spans from January 2010 to March 2023, with variations in data availability across regions. Overall, the population covered includes approximately six million individuals, about 10% of the Italian population, providing broad geographic representation and strengthening the generalizability of the findings. The primary purpose of the study was to evaluate healthcare resource use and economic burden, relying on anonymized patient-level data captured through routinely collected administrative flows maintained by the SSN. Administrative databases in Italy are designed to track economic flows between the SSN and healthcare providers.

For the purposes of this analysis, the following databases were browsed: (a) beneficiaries' database, which contains demographic details such as age, sex, and date of death, when applicable; (b) pharmaceutical database, providing data on prescribed medications, including the Anatomical Therapeutic Chemical (ATC) classification, prescription dates, and quantity of dispensed packages; (c) hospitalization database, for information on inpatient admissions, including admission dates, primary and secondary diagnoses coded according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), and Diagnosis Related Groups (DRG); (d) outpatient specialist services database, which reports laboratory tests, diagnostic procedures, and specialist consultations, including their type and date; (e) exemption database, which includes records of payment exemption codes granted to patients with specific health conditions that entitle them to receive care without incurring charges. For the purpose of this analysis, the laboratory databases, when available from the participating LHUs, were integrated to capture the values of eGFR. This level of granularity is not universally available in all administrative datasets, but was accessible in our case due to the integration of laboratory records within the regional data systems.

The dataset used consists solely of anonymized data. All the results of the analyses were produced and presented as aggregated summaries. Approval has been obtained from the ethics committees of the participating healthcare entities.

Study population

The study population included patients who met at least one of the following inclusion criteria: (a) hospitalization discharge diagnosis for HF at the primary or secondary level (ICD-9-CM: 428), or (b) estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73 m^2, or (c) hospitalization discharge diagnosis for T2D at the primary or secondary level (ICD-9 codes: 250.x0; 250.x2), or (d) prescription for medications indicated for T2D.

Exclusion criteria were age under 18 years, lack of continuous inclusion during the study period (for instance, patients who moved to another LHU), or death at the time of inclusion. Among patients aged 40 years or older who had prescriptions for insulins and analogues (ATC code A10A), those diagnosed with type 1 diabetes (ICD-9 codes: 250.x1; 250.x3) at any point during the available study period were excluded.

The inclusion period for the study spanned from January 2018 to December 2019. The index date was defined as the first occurrence matching the inclusion criteria. The follow-up period was defined as 12 months of post-index data for each subject.

Epidemiology estimates

The number of patients in each of the seven cohorts, defined by the presence of one, two, or all three conditions among T2D, CKD, and HF, was first calculated based on the study sample. These counts were then projected to the national population of Italy (N = 58,989,749 as of 1st January 2024), according to data from the Italian Institute of Statistics (22), to estimate the prevalence at the national level.

To assess the representativeness of the study sample, we compared the disease prevalence estimates derived from our dataset with national-level epidemiological data.

Demographic characteristics

Demographic information was collected for all patients included in the study. This included age at index date, distribution by age groups (18-39,40-59,60-79, and ≥80 years), and sex distribution (given as percentage of male patients).

Healthcare resource utilization and direct healthcare costs

Healthcare resource utilization (HCRU) and the corresponding direct costs were assessed for patients with HF, T2D, and CKD in the follow-up period. For the purpose of the cost analysis, only healthcare resource utilization and corresponding costs accrued during the first 12 months following the index date were considered. This provided a standardized and punctual estimate of per-patient costs.

These evaluations focused on drug therapies, hospital admissions, and outpatient specialist services. For the cost analysis, direct medical expenses were calculated based on the HCRU variables, reporting both individual cost categories and the total healthcare cost per patient at one-year follow-up, expressed in Euros (€). Drug costs were derived from the SSN purchase prices, hospitalization costs were based on DRG tariffs representing SSN reimbursements to providers, and costs of diagnostic and laboratory services were determined according to regional tariffs. Outliers, namely patients with total costs exceeding the mean by more than three times the standard deviation, were excluded from the cost analysis.

Scenario analyses

For each of the three pathologies, T2D, CKD, and HF, a simulation was developed to estimate the impact on the costs related to the greater clinical and therapeutic complexity in multimorbid patients. The percentages of patients who started with only one disease and then developed other concomitant diseases were defined to build a scenario reflecting an enhanced progression of these conditions. The percentages used in the scenario analysis are purely random hypotheses; they are reported only to provide a metric to better visualize the possible progression and its impacts (Fig. 1). The scenario analysis provides a point-in-time estimate based on a standardized 12-month follow-up period after the index date, without projecting future trends over multiple years. The costs for each population in the scenario analysis were calculated by multiplying the number of patients, adjusted with the percentages applied (Fig. 1), by the average costs. The impact on costs was calculated as the difference between the total costs of the scenario analysis and the base scenario (real-world data). Data were presented separately for each of the three diseases, and an overall scenario analysis on all patients was performed.

This calculation provided the necessary basis to estimate the cost increase associated with the transition to a greater clinical and therapeutic complexity (Fig. 1).

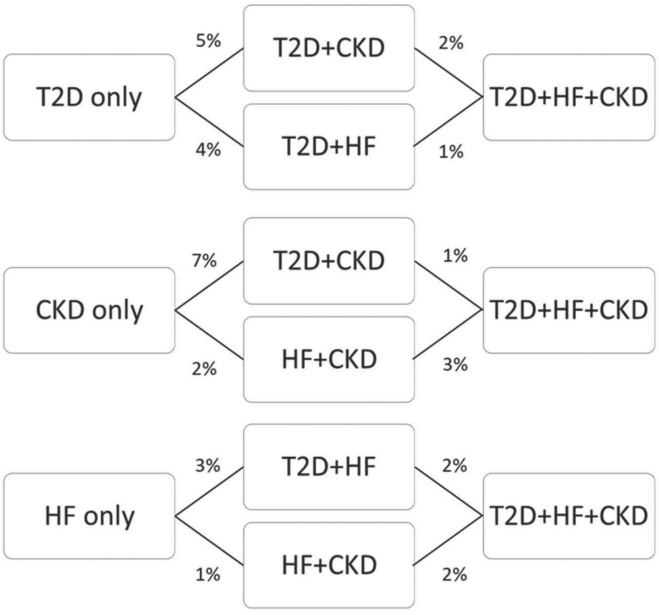

FIGURE 1 - Simulation of patient transitions from single to multiple chronic conditions and the estimated economic impact for each primary disease cohort.

Results

Epidemiology

The study estimated approximately 3,118,352, 1,319,013, and 121,232 Italian patients with only T2D, only CKD, and only HF, respectively. Those with two concomitant pathologies were estimated at 1,043,614 distributed across the different combinations, and the patients affected by all three diseases were estimated at 172,687 (Table 1). Our estimate of a 7.0% prevalence of T2D in the Italian population (calculated

considering total patients with T2D) is consistent with data from ISTAT (https://www.istat.it/en/archive/health) and from recent analyses also using the ARNO Diabetes Observatory (12,13). Similarly, the prevalence of CKD and HF identified in our projections (4.1% and 1.1%) corresponds well with prior national estimates, particularly among the elderly population, as reported by Turchetti et al. (19) and Piccinni et al. (18). This alignment supports the external validity of our findings and confirms the representativeness of the study population.

TABLE 1 - Estimates of patients with one, two or three diseases among T2D, CKD, and HF projected on the Italian population

	Estimated number of patients*
T2D only	3,118,352
CKD only	1,319,013
HF only	121,232
HF+CKD	209,907
T2D+CKD	714,865
T2D+HF	118,842
T2D+HF+CKD	172,687

*Estimates on 58,989,749 Italian citizens (ISTAT, demographic dataset: resident population on 1st January 2024).
Abbreviations: CKD, chronic kidney disease; HF, heart failure; T2D, type 2 diabetes.

Patients' characteristics

The main demographic variables of the populations in the previous analysis are reported in Table 2. Mean age tended to increase along with clinical complexity. Patients with T2D only were the youngest (mean age: 66.9 years; 57.5% in the range 60-79 years), and those with CKD + HF were the oldest (mean age: 82.4 years; 70.0% above 80 years), followed by the cohort with T2D + CKD + HF (mean age: 79.4 years; 55.6% above 80 years). CKD appeared to be more common among female subjects.

Direct healthcare costs

Table 3 shows the mean direct costs per patient at one-year follow-up for all the study cohorts, presented as total costs and by cost item (drugs, hospitalizations, and outpatient specialist services). Outliers, namely values exceeding the mean value by more than 3 times the standard deviation, were excluded from the cost analysis. Considering the patients with one disease, the total cost per patient at one-year follow-up was estimated to be 2,002€ for T2D, 4,322€ for CKD, and 5,061€ for HF. In patients with two concomitant diseases, the total cost per patient at one-year follow-up was 4,419€ for T2D + CKD, 4,284€ for T2D + HF, and 6,021€ for CKD + HF. The total cost per patient by T2D, CKD, and HF concomitantly was estimated to be 6,893€. The main cost drivers were drugs for T2D patients (accounting for 57% of total expenses), and hospitalizations for T2D + HF (47%), CKD + HF (56%), and T2D + CKD + HF (49%).

Scenario analysis

In the scenario analysis on T2D, it was assumed that 155,918 (5%) T2D patients also had CKD, and 124,734 (4%) also had HF. Similarly, 2,377 (2%) of patients with T2D and CKD and 7,149 (1%) of patients with T2D and HF switched to a greater complexity with all three diseases. Based on this pattern, patients with T2D were expected to be 2,837,700 (68.8%), patients with T2D and CKD were estimated at 868,406 (21.1%), patients with T2D and HF at 236,427 (5.7%), and patients with all three diseases at 182,212 (4.4%). The total cost of the 4,126,746 Italian patients with T2D was estimated at approximately 11.1 billion Euros, of which 6.2 billion Euros was for patients with T2D only, 3.2 billion Euros for patients with T2D and CKD, 509 million Euros for patients with T2D and HF, and 1.2 billion Euros for patients with the three diseases (Table 4A). According to the percentages of patients that were set, the total cost of the Italian patients with T2D would become 11.8 billion Euros, with an increase for the SSN equal to 685,976,761 Euros (Table 4A).

The scenario analysis on patients with CKD assumed that 92,331 (7%) CKD patients also had T2D, and 26,380 (2%) also had HF. Similarly, 2,099 (1%) of patients with T2D and CKD, and 21,446 (3%) of patients with CKD and HF, switch to a greater complexity with all three diseases concomitantly. According to this count, patients with CKD were estimated at 1,200,302 (49.7%), patients with T2D and CKD at 805,097 (33.3%), patients with CKD and HF at 214,841 (8.9%), and patients with all three diseases at 196,232 (8.1%).

The total cost of the 2,416,472 Italian patients with CKD is estimated at approximately 11.3 billion Euros, of

TABLE 2 - Baseline demographic characteristics in each study cohort

	T2D only	CKD only	HF only	T2D+CKD	T2D+HF	CKD+HF	T2D+CKD+HF
	N = 314,350	N = 132,965	N = 12,221	N = 72,063	N = 11,980	N = 21,160	N = 17,408
Age (years), mean ± SD	66.9 ± 12.8	76.0 ± 13.0	76.5 ± 13.3	76.1 ± 10.2	75.2 ± 10.6	82.4 ± 9.6	79.4 ± 9.2
Age group, n (%)							
18-39 years	8,393 (2.7%)	1,740 (1.3%)	164 (1.3%)	141 (0.2%)	21 (0.2%)	43 (0.2%)	7 (0.0%)
40-59 years	74,292 (23.6%)	13,863 (10.4%)	1,332 (10.9%)	4,415 (6.1%)	988 (8.2%)	575 (2.7%)	563 (3.2%)
60-79 years	180,695 (57.5%)	55,627 (41.8%)	4,598 (37.6%)	38,347 (53.2%)	6,382 (53.3%)	5,726 (27.1%)	7,157 (41.1%)
≥80 years	50,970 (16.2%)	61,735 (46.4%)	6,127 (50.1%)	29,160 (40.5%)	4,589 (38.3%)	14,816 (70.0%)	9,681 (55.6%)
Male, n (%)	167,705 (53.3%)	54,498 (41.0%)	6,368 (52.1%)	33,799 (46.9%)	6,812 (56.9%)	9,659 (45.6%)	8,806 (50.6%)

Abbreviations: CKD, chronic kidney disease; HF, heart failure; T2D, type 2 diabetes; SD, standard deviation.

TABLE 3 - Mean direct costs per patient at one-year follow-up in each study cohort

	T2D only	CKD only	HF only	T2D+CKD	T2D+HF	CKD+HF	T2D+CKD+HF
	N = 304,906	N = 114,564	N = 9,451	N = 62,833	N = 9,892	N = 14,706	N = 12,534
Total costs (€)	2,002€	4,322€	5,061€	4,419€	4,284€	6,021€	6,893€
Drugs	1,147€	1,332€	1,555€	1,857€	1,897€	1,655€	2,343€
Hospitalizations	545€	2,186€	3,160€	1,658€	2,023€	3,401€	3,347€
Outpatient services	310€	804€	346€	904€	364€	965€	1,203€

Abbreviations: CKD, chronic kidney disease; HF, heart failure; T2D, type 2 diabetes.

TABLE 4 - Expected differences in patients and costs with growing complexity in the T2D setting **(A)**, in the CKD setting **(B)**, and in the HF setting **(C)**

					Scenario analysis				
A. T2D	**N. of patients**	**% on T2D patients**	**Total costs**	**% of patients from the previous stage**	**N. of patients**	**% on T2D patients**	**Total costs**	**Delta patients**	**Delta costs**
T2D only	3,118,352	75.6%	6,242,379,401€		2,837,700	68.8%	5,680,565,255€	-280,652	-561,814,146€
T2D+CKD	714,865	17.3%	3,158,673,894€	5%	868,406	21.1%	3,837,102,955€	153,541	678,429,061€
T2D+HF	118,842	2.9%	509,084,664€	4%	236,427	5.7%	1,012,786,546€	117,585	503,701,883€
T2D+CKD+HF	172,687	4.2%	1,190,345,306€	3%	182,212	4.4%	1,256,005,271€	9,525	65,659,965€
Total T2D	**4,124,746**	**100.0%**	**11,100,483,265€**		**4,124,746**	**100.0%**	**11,786,460,026€**		**685,976,761€**
B. CKD	**N. of patients**	**% on CKD patients**	**Total costs**	**% of patients from the previous stage**	**N. of patients**	**% on CKD patients**	**Total costs**	**Delta patients**	**Delta costs**
CKD only	1,319,013	54.6%	5,700,576,334€		1,200,302	49.7%	5,187,524,464€	-118,711	-513,051,870€
T2D+CKD	714,865	29.6%	3,158,673,894€	7%	805,097	33.3%	3,557,368,693€	90,232	398,694,799€
HF+CKD	209,907	8.7%	1,263,894,127€	2%	214,841	8.9%	1,293,604,644€	4,934	29,710,517€
T2D+HF+CKD	172,687	7.1%	1,190,345,306€	4%	196,232	8.1%	1,352,643,012€	23,545	162,297,706€
Total CKD	**2,416,472**	**100.0%**	**11,313,489,662€**		**2,416,472**	**100.0%**	**11,391,140,814€**		**77,651,152€**
C. HF	**N. of patients**	**% on HF patients**	**Total costs**	**% of patients from the previous stage**	**N. of patients**	**% on HF patients**	**Total costs**	**Delta patients**	**Delta costs**
HF only	121,232	19.5%	613,574,549€		116,383	18.7%	589,031,567€	-4,849	-24,542,982€
T2D+HF	118,842	19.1%	509,084,664€	3%	118,281	19.0%	506,680,731€	-561	-2,403,932€
CKD+HF	209,907	33.7%	1,263,894,127€	1%	208,742	33.5%	1,256,882,308€	-1,165	-7,011,819€
T2D+CKD+HF	172,687	27.7%	1,190,345,306€	4%	179,262	28.8%	1,235,667,169€	6,575	45,321,863€
Total HF	**622,668**	**100.0%**	**3,576,898,646€**		**622,668**	**100.0%**	**3,588,261,776€**		**11,363,129€**

Abbreviations: CKD, chronic kidney disease; HF, heart failure; T2D, type 2 diabetes.

which 5.7 billion is for patients with CKD only, 3.2 billion for patients with T2D and CKD, 1.3 billion for patients with CKD and HF, and 1.2 billion for patients with the three diseases (Table 4B). According to the proportion of patients previously estimated in the simulation, the total cost of the Italian patients with CKD would become 11.4 billion Euros, with an increased spending for the SSN equal to 77,651,152 Euros (Table 4B).

The scenario analysis on patients with HF assumed that 3,637 (3%) HF patients also had T2D, and 1,212 (1%) also had CKD. Similarly, 4,198 (2%) of patients with T2D and HF, and 2,377 (2%) of patients with CKD and HF switched to a greater complexity with all three diseases. In accordance with this scenario, patients with HF were estimated at 116,383 (18.7%), patients with T2D and HF at 118,281 (19.0%), patients with CKD and HF at 208,742 (33.5%), and patients with all three diseases at 179,262 (28.8%).

The total cost of the 622,668 Italian patients with HF is estimated at approximately 3.6 billion Euros, of which 614 million Euros is for patients with HF only, 509 million Euros for patients with T2D and HF, 1.3 billion Euros for patients with CKD and HF, and 1.2 billion Euros for patients with the three diseases (Table 4C). According to the percentages of patients set in the simulation, the total cost of patients with HF would become 3.6 billion Euros, with a cost increase for the SSN equal to 11,363,129 Euros (Table 4C).

Scenario analysis on all patients

The results on all patients with one, two, or three diseases, including T2D, CKD, and HF, are summarized in Table 5. In total, 12%, 7%, and 3% of the patients from previous stages fell within the T2D+CKD, T2D+HF, and CKD+HF, respectively. Furthermore, 72,994 patients (19%) from previous stages switched to a greater complexity with all three diseases. The total cost of the 5,774,898 Italian patients with at least one of the diseases is estimated at approximately 18.7 billion Euros, of which 6.2 billion for patients with T2D only, 5.7 billion for patients with CKD only, 614 million for patients with HF only, 3.2 billion for patients with T2D and CKD, 509 million for patients with T2D and HF, 1.3 billion for patients with CKD and HF, and 1.2 billion for patients with all the three diseases.

According to the percentages of patients computed in the simulation, the total cost of the Italian patients with at least one of the diseases would become 19.5 billion Euros, with an increased spending for the SSN equal to 775 million Euros.

TABLE 5 - Expected differences in patients and costs in all subjects

	SCENARIO ANALYSIS								
	N. of patients	**% on overall patients**	**Total costs**	**% of patients from the previous stage**	**N. of patients**	**% on overall patients**	**Total costs**	**Delta patients**	**Delta costs**
T2D only	3,118,352	54.0%	6,242,379,401€		2,837,700	49.1%	5,680,565,255€	-280,652	-561,814,146€
CKD only	1,319,013	22.8%	5,700,576,334€		1,200,302	20.8%	5,187,524,464€	-118,711	-513,051,870€
HF only	121,232	2.1%	613,574,549€		116,383	2.0%	589,031,567€	-4,849	-24,542,982€
T2D+CKD	714,865	12.4%	3,158,673,894€	12%	958,638	16.6%	4,235,797,754€	243,773	1,077,123,860€
T2D+HF	118,842	2.1%	509,084,664€	7%	235,866	4.1%	1,010,382,614€	117,024	501,297,950€
CKD+HF	209,907	3.6%	1,263,894,127€	3%	213,677	3.7%	1,286,592,825€	3,770	22,698,697€
T2D+CKD+HF	172,687	3.0%	1,190,345,306€	19%	245,681	4.3%	1,693,497,202€	72,994	503,151,896€

Abbreviations: CKD, chronic kidney disease; HF, heart failure; T2D, type 2 diabetes.

Discussion

This analysis provided an estimation of the increase in healthcare expenses sustained by the SSN associated with the management of patients affected by the most common age-related diseases, namely T2D, CKD, and HF, by simulating the impact of progression toward multimorbidity at a fixed point in time, without adopting a specific time horizon. The scenario analysis was based on hypothetical percentages to reflect an increased prevalence of coexisting conditions, particularly in older patients, in line with the age distributions observed in the real-world datasets. It is acknowledged that the number of possible scenarios is virtually infinite and that the values used in our analysis are illustrative rather than predictive. The primary objective of this exercise was to provide a conceptual and quantitative framework to demonstrate how even small increases in multimorbidity prevalence could disproportionately impact healthcare expenditures. This type of ling, although simplified, might support decision-makers in stress-testing potential trends and initiating cost-containment strategies before clinical complexity becomes widespread. We also recognize that the scenario is not based on actual trends over the 13-year observation period, despite the broader temporal availability of data. This was due to incomplete longitudinal consistency across all LHUs prior to 2018 and the intrinsic limitations of administrative data in capturing the precise timing of disease progression. Therefore, rather than extrapolating from historical incidence, we adopted a static linear approach with hypothetical progression rates to explore the potential economic impact under predefined assumptions. Importantly, the same scenario modelling framework could be inverted to estimate the potential cost savings associated with reducing the incidence of multimorbidity. This perspective would more directly support health policy decisions aimed at prevention, screening, and early intervention. For example, estimating the economic benefit of reducing multimorbidity prevalence by a given percentage (e.g., through improved disease management or public health investment) could help quantify the value of such preventive strategies. Future analyses should explore this alternative formulation to guide more proactive resource allocation.

Global population ageing poses increasingly greater pressure on healthcare systems with an inexorable growth of the related expenditures. Multimorbidity implies substantial healthcare resource consumption and costs due to hospitalizations, readmissions, polypharmacy regimens, outpatient services, and financial burdens on families, society, and healthcare systems. However, the actual economic burden of multimorbidity is not fully elucidated (23). The most recent health economic or risk prediction models from different countries are progressively exploring disease combinations rather than approaches targeted on single pathologies, reflecting a more comprehensive approach to patients' care (24-27). By acknowledging the interplay between various chronic conditions, these scenario analyses aim to enhance the precision of risk assessments and the efficiency of healthcare resource allocation. This paradigm shift is crucial for developing effective interventions and policies tailored to the needs of patients with complex clinical profiles.

The close pathogenetic link between T2D, CKD, and HF can be explained by some shared mechanistic pillars that principally converge on age and inflammation, a state currently known as "inflammaging" (28). It is estimated that in industrialized countries, the proportion of deaths for age-related causes reaches 90% (29,30).

Using the approach of scenario analysis for each of the three diseases, this analysis indicated that the costs for the management of patients with T2D, CKD, and HF are expected to rise along with the transition from a single disease to a multimorbidity status, as the increasing clinical and therapeutic complexity resulted in higher medical costs. Thus, efforts to optimize healthcare planning should rely on the careful assessment of increasingly old and frail patients, whose needs, in terms of chronic therapies, hospitalizations, examinations, and outpatient specialist visits, represent a considerable burden in terms of sustainability from a health services perspective (31,32). In this context, various strategies might be implemented to alleviate the clinical and economic burden for the management of patients with T2D, CKD, and HF.

One main point relies on early diagnosis. In the nephrology setting, CKD is known to have a silent progressive onset and usually remains undetected until advanced stages, although timely identification and management might be critical in delaying renal function impairment and loss (33). Therefore, prevention programs have been made to include early detection of CKD among national public health priorities (34). Underdiagnosis of HF is also a critical issue, due to the non-specific nature of symptoms, which can be caused by a range of medical conditions, and for the thin line of demarcation between the chronic phase and the acute phase (35,36). Currently, HF represents the first cause of hospitalization and re-hospitalization, with a further notable impact on the costs of the national and regional systems (37). A recent analysis from our research group analyzed the clinical and economic burden of HF in Italian clinical practice between January 2012 and March 2021. The results showed that HF patients were characterized by common cardiovascular comorbidities, mainly hypertension (88.6%), cardiovascular disease (61.3%), and diabetes (32.1%), resulting in a larger necessity of hospital access and a 1.7-fold increase in total healthcare costs compared to the non-HF controls (38).

Regarding the therapeutic management of patients with chronic diseases, in recent years, innovative drugs have been made available to patients with a strong impact on the treatment of various pathologies and their comorbidities (39,40). Thus, one essential step might be to facilitate access to care with rapid approval processes. In addition, strategies to improve adherence to therapies and patients' awareness might also be essential, since an informed patient is able to know the pathology, recognize the symptoms, and strictly respect treatment schedules (41).

Moreover, the compliance with international and national guidelines is also a central aspect: recommendations that are updated by panels of experts on a recurring basis need immediate implementation and adaptation to achieve a strong improvement in patients' care and quality of life, with subsequent benefits on public health and costs (42).

The main strength of this analysis lies in its novelty, which might represent a template for cost prediction in settings where the interplay of concomitant conditions is known to amplify the disease burden with substantial repercussions on public health expenses. Despite not being initially intended for research purposes, administrative databases serve as powerful tools for epidemiological and health economics studies due to their comprehensive, structured, and continuously updated nature. They enable the analysis of real-world patient journeys, resource utilization, drug consumption, and outcomes. Information is recorded chronologically and linked to anonymized patient identifiers, allowing for integration across multiple healthcare domains while maintaining data privacy.

On the other hand, some limitations should be acknowledged. The data in administrative databases are primarily designed to trace economic flows between the SSN and healthcare providers rather than clinical research. As such, these datasets do not fully capture clinical detail, such as disease severity, risk profiles, or lifestyle-related information. The identification of patients was based on hospitalization discharge diagnoses, diagnostic codes, and (for T2D) pharmacological prescriptions. While this method is consistent with prior Italian administrative research, it may underrepresent individuals managed exclusively in primary care or with undiagnosed or untreated conditions. For example, patients with stable HF who were not hospitalized during the observation period and were not taking specific medications may have been missed, potentially resulting in an underestimation of prevalence. Furthermore, the inclusion of patients based predominantly on hospitalization or pharmacological records may result in a population with more advanced or clinically significant disease, potentially leading to an overestimation of average healthcare costs compared to a more general patient population that includes milder cases. Similarly, some T2D patients who are not yet on pharmacological therapy may not be captured. These limitations should be considered when interpreting prevalence data and extrapolations. Nonetheless, the use of validated algorithms and alignment of observed prevalence with national-level estimates (e.g., ISTAT) suggest that the sample remains broadly representative of the Italian population. Furthermore, the scenario analysis remains valid for assessing the economic impact of increasing disease complexity. Additionally, the hypothetical nature of scenario assumptions means that our cost projections are illustrative rather than predictive. Indirect costs (e.g., productivity loss, informal care) were not considered. Finally, generalizability may be limited outside of Italy, where health system structures differ.

Conclusion

This study, based on real-world administrative data from Italian healthcare bodies, enabled the assessment of epidemiological patterns and healthcare costs associated with T2D, HF, and CKD, either as individual conditions or in various multimorbidity combinations. By leveraging these comprehensive datasets, an integrated methodological approach of retrospective analysis and scenario analysis was developed. This allowed us to explore the potential economic impact

of increasing clinical complexity in multimorbid patients. The results projected a substantial increase in healthcare expenditures along with the progression from single diseases to multimorbid conditions. The scenario-based projections, though hypothetical in nature, serve as a valuable exploratory tool to support health policy planning and decision-making. This simulation highlights the urgent need to address the growing burden of chronic disease through integrated care strategies, early diagnosis, and the adoption of cost-effective interventions tailored to complex patient profiles. Real-world data, when used in a methodologically rigorous and privacy-compliant manner, provides a powerful foundation for understanding current and future healthcare dynamics and can inform the development of public health policies that better respond to the challenges of population aging and multimorbidity.

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