Department of Statistics and Quantitative Methods

Division of Biostatistics, Epidemiology and Public Health, Laboratory of Healthcare Research and Pharmacoepidemiology

PhD program in Public Health
XXXII Cycle

Curriculum in Decision Making Process based on Effectiveness Evidence

MONITORING AND ASSESSING DIAGNOSTIC-THERAPEUTIC PATHS WITH HEALTHCARE UTILIZATION DATABASES: EXPERIENCES, CONCERNS AND CHALLENGES

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ACADEMIC YEAR 2018/2019

Contents

Abstract

The aim of this thesis is to provide the methodology used to develop and validate population-based prognostic scores, and to assess the effectiveness and cost-effectiveness of the diagnostic-therapeutic path of diabetes, using the healthcare utilization databases (or administrative databases) of Italian regions. Thus, the thesis is structured into the following three main parts.

First, the reasons to justify the need of real-world studies in addition to evidence from randomized controlled trials, the definitions of real-world data and real-world evidence, and an overview of the Italian healthcare utilization databases are given.

Second, because patients should be monitored according to their risk to experience adverse outcomes (e.g., all-cause mortality, hospital admissions), prognostic scores could be used. However, the main limitation in the use of pre-existing score is that they are usually developed in countries different from Italy and from hospital-based or pharmacy-based surveys, so hindering their applicability to all beneficiaries of the National Health Service. Therefore, two population-based prognostic scores were developed and validated using data from some Italian regions. The usefulness of one of these scores (i.e., the so-called Multisource Comorbidity Score) in the risk adjustments and as a tool for health policy planning is also shown.

Third, tracing the work carried out from the "Monitoring and assessing care pathways" working group of the Italian Ministry of Health, a description of the following activities is provided:

I. the development of process indicators to monitor and assess the quality of care of patients suffering from some chronic disease;
II. the comparison of care quality between regions;
III. the validation of the diabetes care indicators with respect to selected outcomes (i.e., the assessment of their effectiveness);

IV. the assessment of the costs from the National Health Service perspective (calculated by the amount that the Regional Health Authority reimbursed to health providers) according to different levels of adherence to the diagnostic-therapeutic path of diabetes.

Finally, the Beaver® regional research platform, able to compute the set of process and outcome indicators defined by the Health Ministry and to generate evidence on effectiveness and cost-effectiveness profile, is described.

List of abbreviations

AIFA: Agenzia Italiana del Farmaco (Italian Medicines Agency)
ATC: Anatomical Therapeutic Chemical
AUC: Area Under the (ROC) curve
CCI: Charlson Comorbidity Index
CDS: Chronic Disease Score
CedAP: Certificato di Assistenza al Parto (Certificates of Delivery Assistance)
CReSc: Chronic Related Score
DQIP: Diabetes Quality Improvement Project
DRG: Diagnosis-Related Group
EHR: Electronic Health Record
EI: Elixhauser Index
FDA: Food & Drug Administration
GDP: Gross Domestic Product
HCU: Healthcare Utilization (database)
ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification
ISS: Istituto Superiore di Sanità (National Institute of Health)
ISTAT: Istituto Nazionale azionale di Statistica (Italian National Institute of Statistics)
LASSO: Least Absolute Shrinkage and Selection Operator
LEA: Livelli Essenziali di Assistenza (Essential Level of Care)
MCS: Multisource Comorbidity Score
MSD: Mixed-Source Database
NHS: National Health Service
NRI: Net Reclassification Improvement
PY: Person-Years
RCT: Randomized Controlled Trial
ROC: Receiver Operating Characteristic
SAS: Statistical Analysis System

Introduction

Why RCTs are no longer enough?

Randomized Controlled Trials (RCTs) are the best way to study the efficacy of new treatments. The random allocation (i.e., the randomization) of patients into the intervention and control groups ensures of assessing the efficacy and safety profile of the treatment removing the chance of systematic differences between groups [1]. Because RCTs are designed to be unbiased and have less risk of systematic errors, they are given the highest level in the hierarchical system of classifying evidence [2] and they are mandatory for governmental regulatory bodies for approval decisions.

However, RCTs have also some significant limitations. First, strict eligibility criteria are usually applied during patients' recruitment, and vulnerable patients are usually excluded. Albeit the inclusion of a homogeneous patient population increases internal validity, the exclusion of several categories of patients that would be eligible for the treatment compromises the external validity of the findings. A literature review showed that that RCT samples are highly selected and have a lower risk profile than real-world populations, with the frequent exclusion of elderly patients and patients with co-morbidities [3]. For example, the proportion of patients with type 2 diabetes in the general population who met the eligibility criteria of four RCTs ranging from 4% to 40% [4].

Second, how the treatment performs in a controlled clinical environment (i.e., the efficacy) could be very dissimilar from its impact under the routine practice (i.e., the effectiveness). This gap could be explained by the highly controlled settings in which RCTs are performed, which are very different from the context of clinical practice. Characteristics of the health care settings, including the "behaviour" of caregivers, patients' adherence to treatment and disparity in resource and access, affect the treatment effect [5].

Third, due to the high costs [6], RCTs usually enrol a relatively small number of patients for short follow-up periods. However, the low sample size limits the statistical power of RCTs to detect rare adverse events [7] and the assessment of the efficacy at a brief-term (i.e., usually few years only) requires to extrapolate the results to much longer follow-up (e.g., chronic drug therapies should be assumed for the entire life).

Finally, RCTs are usually designed to evaluate the efficacy of a single treatment. However, patients with a compromised clinical status and those suffering from chronic diseases should follow a multidisciplinary clinical pathway that ensures the overall response to their needs as well as the continuity of care, which cannot be evaluated in a controlled setting [8].

Real-world data and real-world evidence

Although RCTs should still be the gold standard to guide the regulation process and to assess the causal effect of a treatment on an outcome, there is a growing interest in observational studies, which could accompaniment the RCTs' findings with results from the context of clinical practice in order to take into account the above-mentioned limitations.

The U.S. Food & Drug Administration (FDA) defines *real-world data* as "data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources", including , e.g., electronic health records (EHRs), medical claims, drug and disease registries, patient lifestyle-related activities and health-monitoring devices (https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence). Albeit the definition of real-world data is debated in the literature, there is a consensus on that they are data collected in a non-randomized controlled trial setting [9].

Real-world evidence is defined as that information on health care that is derived from the analysis of real-world data [10]. The usefulness of real-world evidence gathers from its potential for complementing findings obtained from RCTs, whose generalizability of the results is weak. For example, real-world evidence can be gained on treatments in special populations, such as pregnant

women [11], children [12] and elderly [13]. In addition, real-world data allow assessing phenomenon that cannot be investigated in RCTs, like the patient's adherence [14] and the therapeutic inertia [15]

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D0espite these data have no major issue of generalizability, the lack of random assignment of patients to treatment and control groups (i.e., randomization) makes the results exposed to confounding. This explains why building reliable evidence from real-world data requires planning the study according to a logical-formal process aimed at justifying every choice (the target population, the definition of exposure and outcome, selection of covariates), according to approaches that minimizing the risk of bias, with the attempt to answer the question with credible results [16].

The Italian Healthcare Utilization Databases

There are two broad categories of databases that include health data: (i) EHRs databases, in which data are collected by general practitioners during their routine activity and (i) the Healthcare Utilization (HCU) databases, or administrative databases, recording data for administrative purposes [17].

The UK General Practice Research Database is one of the most important EHRs database, covering about 3 million patients [18]. In Italy, the Health Search database involves almost 1,000 general practitioners and more than 1 million patients [19].

The HCU databases were established for recording all payments of health care providers in order to obtain reimbursement. They include data on several services supply to patients, such as hospital admissions, drugs dispensed, outpatients visits, laboratory examinations, etc. In the United States, the HCU databases funded by the government (i.e., Medicare, Medicaid, and Veteran Administration) are usually used to perform clinical studies [20].

All Italian citizens have equal access to healthcare services as part of the National Health Service (NHS). The Italian NHS is decentralised and is organised into 21 administrative units (19 regions and 2 autonomous provinces), who provide healthcare providers, called local health units. Because

Regional Authorities reimburse their healthcare providers, administrative databases were established to collect these data [21]. In each administrative unit, at least the following information is recorded:

1. an archive of NHS beneficiaries, reporting demographic and administrative data, other than the dates in which the condition of NHS beneficiary started (because he/she was born or immigrated) or stopped (because he/she died or emigrated);
2. hospital discharge database reporting information about primary diagnosis, coexisting conditions, and provided procedures (coded according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), classification system, (http://icd9.chrisendres.com/) and the official Italian diagnosis-related group (DRG) (http://www.gazzettaufficiale.it/eli/gu/2010/01/05/3/sg/pdf));
3. drug prescription database providing information on all the drugs reimbursed by the NHS dispensed by territorial pharmacies and medicaments directly administered in the outpatient setting and day-hospital (coded according to the Anatomical Therapeutic Chemical (ATC) classification system, (https://www.whocc.no/atc_ddd_index/));
4. outpatient database, including visits in specialist ambulatories and diagnostic laboratories accredited from the NHS (coded according to the regional outpatients services coding);
5. copayment exception database, including exception for chronic disease (coded according to the national exceptions coding);
6. emergency room accesses, providing ICD-CM-9 codes of causes of access to general and specialized emergency/acceptance departments of public and private hospitals;
7. Certificates of Delivery Assistance (i.e., the so-called CedAP) providing information on the mother's socioeconomic traits, as well as medical information on pregnancy, childbirth, and child presentation at delivery.

As a unique identification code was used for all databases, their record linkage allowed searching out the complete care pathway of NHS beneficiaries.

During the last years, the use of HCU databases as data source to carry out investigations with the aim of assessing the burden of diseases [22], measuring the performance of various functions of the NHS [23] or monitoring the quality of care [24], has grown.

The usefulness of the risk scores in public health

Risk scores can be used in several ways by different actors of Public Health.

First, researchers use prognostic scores for control of confounding in epidemiological studies [25]. Among the scores proposed in the literature, the most applied are the Charlson Comorbidity Score [26], the Elixhauser [27] and the Chronic Disease score [28]. These scores are usually developed from hospital-based or pharmacy-based surveys and, despite they are extensively used, convincing evidence suggesting the superiority of an approach in predicting health outcomes are not currently available [25,29].

Second, clinicians could use the risk scores to manage their patients according to the risk of experience specific outcomes. For example, the calculation of the individual risk score for assessing the probability of developing a first major cardiovascular event (risk charts) was performed by means of the development of risk score in the CUORE Cohort [30].

Finally, policy-makers might use prognostic scores to stratify beneficiaries of the health system according to the risk level, i.e., for identifying those to address towards primary and secondary prevention programs, systems of long-term healthcare by integrating primary and specialist services, and short-term intensive inpatients care.

The case of the Multisource Comorbidity Score [1]

Introduction

Comorbidity has been defined as the total burden of illnesses unrelated to the patient's principal diagnosis [31]. Ideally, in any given individual assessment of comorbidity should be based on complete information on his/her clinical and demographic profile. However, this is so time-consuming and costly that for large populations attention has been directed to measures that make use of data available via computerized information systems [32]. The Charlson Comorbidity Score [26], and the Chronic Disease Score [28], i.e., two popular indices respectively based on diagnostic coding system and prescribed medications, are extensively used comorbidity scores based on available computerized data [33].

Most diagnosis-based comorbidity scores have been developed from hospital-based surveys reviewing inpatients medical records and only later they were adapted for use with population-based administrative data [26,28,33–41]. Conversely, few instruments have been developed from administrative data [27], without however providing a weighting system for scoring comorbidity indices [33]. As sick people are likely to receive pharmacotherapy and because the number of prescribed drugs has been shown to increase with the number of chronic disease conditions [42], medication-based scores offer an alternative tool for measuring comorbidities . However, convincing evidence suggesting the superiority of an approach (e.g., of medication-based towards diagnosis-based comorbidity scoring) in predicting health outcomes are not currently available [25,29,33,43].

[1] Results reported in this chapter have been published in Corrao G, Rea F, Di Martino M, De Palma R, Scondotto S, Fusco D, Lallo A, Belotti LMB, Ferrante M, Pollina Addario S, Merlino L, Mancia G, Carle F. Developing and validating a novel multisource comorbidity score from administrative data: a large population-based cohort study from Italy. BMJ Open. 2017;7:e019503. doi: 10.1136/bmjopen-2017-019503

This population-based study aimed to develop and validate a novel comorbidity score predictive of mortality, hospital admissions and health care costs using multiple source information from the administrative Italian NHS databases.

Methods

The HCU database of Lombardy, Emilia-Romagna, Lazio and Sicily were used for empirically developing a risk-prediction model, using the methods described by May et al. [44], Royston et al. [45] and Riley [46].

Candidate predictors

Starting from the lists included under the Charlson, Elixhauser and Chronic Disease Scores (respectively denoted CCI, EI and CDS), a list of 46 diseases and conditions classified as infectious and parasitic diseases (2), neoplasms (4), endocrine, nutritional and metabolic diseases, and immunity disorders (6), diseases of the blood and blood-forming organs (2), mental disorders (7), diseases of the nervous (5), circulatory (9), respiratory (2), digestive (3), genitourinary (3) systems, diseases of the musculoskeletal system and connective tissue (1), and other conditions (2), was developed. Of the 46 included conditions, 18 were traced from inpatients diagnostic codes only, 6 from outpatients prescribed drugs only, and the remaining 22 from both, diagnostic and therapeutic codes, depending on availability of specific diagnostic codes and drug therapies supplied free of charge from the Italian NHS.

The entire list of candidate predictors, and the corresponding codes, are reported in the **Table 1**.

Table 1. List of diseases and conditions candidate to be tested as predictors of one-year mortality.

Diagnostic category	Disease/condition	ICD-9 CM code	ATC code
Infectious and parasitic diseases	HIV infection	042.x-044.x	Zidovudine (AZT) (J05AF01, J05AR01, J05AR04, J05AR05), Didanosine (DDI) (J05AF02), Zalcitabine (DDC) (J05AF03), Pentamidine (P01CX01), Clarithromycin (J01FA09), Rifabutin (J04AB04), Atovaquone (P01AX06)
	Tuberculosis	010.x - 018.x	Anti-tuberculosis antibiotics (J04AB)
Neoplasms	Lymphoma	200.00-202.38, 202.50-203.01, 203.8x, 238.6x, 273.3x, V10.71, V10.72, V10.79	
	Metastatic cancer	196.0x-199.1x	
	Cancer, without metastasis	140.0x-172.9x, 174.0x-175.9x,179.x-195.8x, V10.0x-V10.9x	
	Malignancy medication		Antineoplastic (L01), Taxol (C07AB05), Interleukins (L03AC), Colony-stimulating factors (L03AA), Antinausea misc, ondansetron (A04)
Endocrine, nutritional and metabolic diseases, and immunity disorders	Diabetes	250.x, 357.2, 362.0	Antidiabetic agents (A10)
	Hypothyroidism	243.x-244.2, 244.8x, 244.9x	Thyroid replacement (H03A), Antithyroid agents (H03B)
	Obesity	278.00-278.01	
	Weight loss	260.0x-263.9	
	Disorders of fluid, electrolyte, and acid-base balance	276.0x-276.9x	
	Gout	274.x	Colchicine (M04AC01), Uric acid inhibitors (M04AA, M04AB)
Diseases of the blood and blood-forming organs	Coagulation defects	286.0x-286.9x, 287.1x, 287.3x-287.5x	
	Anaemias	280.0x, 280.1x-281.9x, 285.9x	Marrow stimulants (L03AA), Erythropoietin (B03XA01)
Mental disorders	Dementia	290.x	
	Psychosis	295.x-298.9x, 299.10-299.11	Butyrophenone derivates (N05AD), Phenothiazines (N05AA, N05AB, N05AC), Antipsychotic misc (N05AX), Tiotixene (N05AF04)
	Depression	300.4x, 301.12, 309.0x, 309.1x, 311.x	Tricyclic antidepressants (N06AA), Monoamine oxidase inhibitors (N04BD, N06AF, N06AG), SSRI, fluoxetine (N06AB03, N06CA03)
	Bipolar disorders	296.0	Lithium (N05AN)
	Alcohol abuse	291.1x, 291.2x, 291.5x, 291.8x, 291.9x, 303.90-303.93, 305.00-305.03, V11.3x	
	Drug addition	292.0x, 292.82-292.89, 292.9x, 304.00-304.93,305.20-305.93	

	Anxiety medication		Benzodiazepine derivatives (N05BA, N05CD), Meprobamate (N05BC01), Meprobamate combinations (N05BC51), Other anxiolytics (N05BX), Benzodiazepine related drugs (N05CF), Hypnotics and sedatives in combination, excl. barbiturates (N05CX01), Other psychostimulants and nootropics (N06BX)
Diseases of the nervous system	Hemiplegia and hemiparesis	342.00-342.12, 342.9x-344.9x	
	Other neurological diseases	331.9x, 332.0x, 333.4x, 333.5x, 334.0x-335.9x, 340.x, 341.1x-341.9x, 345.00-345.11, 345.40-345.51, 345.80-345.91, 348.1x, 348.3x, 780.3x, 784.3x	
	Glaucoma	365.x	Ophtalmic miotics (S01E)
	Epilepsy	345.x	Anticonvulsants barbiturates and congeners (N03AA), Phenytoin and combinations (N03AB02, N03AB05, N03AB52), Misc anticonvulsants (N03AX)
	Parkinson's disease	332x	Autononics L-Dopa (N04B), Selegiline (N04BD01)
Diseases of the circulatory system	Acute myocardial infarction	410.x-412.x	
	Heart failure	398.91, 402.11, 402.91, 404.11, 404.13, 404.91, 404.93, 428.x	Disopyramide (C01BA93), Vasodilator nitrates (C01DA), Digitalis glycosides (C01AA), Diuretic, loop (C03C), Procainamide (C01BA02), Quinidine (C01BA01, C01BA51, C01BA71)
	Arrythmia	426.10, 426.11, 426.13, 426.20-426.53, 426.60-426.89, 427.0x, 427.2x, 427.31, 427.60,427.9x, 785.0x, V45.0x, V53.3x	Class 1 A antiarrhythmics (C01BA), Class 1 C antiarrhythmics (C01BC), Class 1 I antiarrhythmics (C01BD)
	Valvular diseases	093.20-093.24, 394.0x-397.1x, 424.00-424.91, 746.3x-746.6x, V42.2x, V43.3x	
	Vascular diseases	440.0x-440.9x, 441.2x, 441.4x, 441.7x, 441.9x, 443.1x-443.9x, 447.1x, 557.1x, 557.9x, 785.4x, V43.4x	
	Cerebrovascular diseases	430.x-438.x	
	Hypertension	401.x-405.x	ACE inhibitors (C09A, C09B), Alpha blockers (C04AX02, C04AB01, C04AB02, C02CA, C02LE), Antihypertensive vasodilators (C04, C01D, C07E), Beta-adrenergic blockers (C07), Calcium channel blockers (C08), Clonidine (C02AC01, C02LC01, C02LC51), Diuretics, thiazides (C03A, C07B, C07D), Ganglionic blockers (C02B), Guanethidine (C02CC02, C02LF01), Methyldopa (C02AB, C02LB), Rauwolfia alkaloids (C02AA, C02LA)
	Coronary and peripheral vascular disease		Anticoagulants (vitamin K antagonists, Factor Xa inhibitors, direct thrombin inhibitors, other) (B01AA, B01AB, B01AF,

			B01AE, B01AX01, B01AD10, B01AD12), Pentoxifylline (C04AD03), Ticlopidine (B01AC05)
	Hyperlypidemia		Lipid lowering agents (C10)
Diseases of the respiratory system	Chronic pulmonary diseases	490.x-492.8x, 493.00-493.91, 494.x, 495.0x-505.x, 506.4x	Beta agonist bronchodilators (R03AA, R03AB, R03AC), Xanthines (R03DA, R03DB, R03DA20), Cromolyn (R01AC01, R03BC01, R01AC51, S01GX01, S01GX51), Inhaled corticosteroids (R03BA)
	Cystic fibrosis	277.0	Mucolytics (R05CB, R05FB01, R05FA01), Pancreatic enzymes (A09AA02)
Diseases of the digestive system	Peptic ulcer	531.x-534.x	Histamine H2 blockers (A02BA), Prostaglandin, Misoprostil (A02BB), Proton pump inhibitors, Omeprazole (A02BC01, A02BD05, A02BD01)
	Liver diseases	070.32, 070.33, 070.54, 456.0x, 456.1x, 456.20, 456.21, 571.0x, 571.2x, 571.3x, 571.40-571.49, 571.5x, 571.6x, 571.8x, 571.9x, 572.3x, 572.8x, V42.7x	Ammonia detoxicants (A06AD)
	Crohn's and ulcerative colitis	555.x-556.x	Sulfasalazine (A07EC01), Olsalazine (A07EC03), Mesalazine (A07EC02)
Diseases of the genitourinary system	Kidney diseases	582.x, 583.0, 583.1, 583.4, 583.7, 583.8, 584.6, 585.x, 586.x, 588.x	Potassium removing resins, Kayexalate (V01AE01)
	Kidney dialysis	V56.0	
	Kidney transplantation	55.6 (procedure)	
Diseases of the musculoskeletal system and connective tissue	Rheumatologic conditions	390.x, 391.x, 714.0x, 714.1, 714.3, 714.9x, 720.0x-720.9x, 725.x	Systemic corticosteroids (M01BA), Gold salts (M01CB), Hydroxychloroquin (P01BA02)
Other conditions	Transplantation		Cyclosporine-A (L04AD01), Azathioprine (L04AX01)
	Pain and inflammation		Narcotics (N02), NSAIDs (M01A)

ICD-9 CM: International Classification of Diseases, Ninth Revision, Clinical Modification; primary or secondary diagnosis fields
ATC: Anatomical Therapeutic Chemical classification system

Score development

With the aim of selecting conditions independently able to predict one-year mortality (i.e., the main outcome of interest), the following steps were performed. First, a training (derivation) set of 500,000 individuals was randomly selected from individuals who in 2008 were (i) aged 50 years or older, (ii) NHS beneficiaries, and (iii) resident in Lombardy from at least two years. Data were retrieved from the databases of Lombardy, a region of Italy that accounts for about 16% of its population, being almost 4 million those aged 50 years or more. Second, the relationship between the selected covariates and the time to death was investigated by fitting parametric survival models based on the Weibull distribution. Covariates included into the model were gender, age (in January 1th, 2008), and the 46 above reported diseases or conditions which were made available, respectively, by patient hospitalizations and outpatient prescriptions in the years 2006 and 2007. These data entered as dichotomous variables into the model, with value 0 or 1 according to whether the specific condition was not or was recorded at least once within two-years prior to baseline (2006-2007). Third, the least absolute shrinkage and selection operator (LASSO) method was applied for selecting the diseases / conditions able to predict one-year mortality [47]. LASSO selects variables correlated to the measured outcome by shrinking coefficients weights, down to zero for the ones not correlated to outcome. Finally, the coefficients estimated from the model were used for assigning a score at each selected covariate. In particular, the coefficients were converted into scores by multiplying them by 10 and rounding them to the nearest whole number [48], which were sequentially summed to produce a total aggregate score. To simplify the system, i.e., with the aim of accounting for excessive heterogeneity of the total aggregate score, the latter was categorized by assigning increasing values of 0, 1, 2, 3 and 4 to the categories of the aggregate score of 0-4, 5-9, 10-14, 15-19 and $\geq$ 20, respectively. The index so obtained was termed Multisource Comorbidity Score (MCS).

Model validation

Internal and external validity of MCS was investigated by applying the score developed from individuals belonging to the training set, to several validation sets. These latter were selected by applying the same inclusion/exclusion criteria of the training set.

The following two-stage validation procedure was applied. First, the MCS performance was explored with respect to other prognostic scores by applying the current Multisource Comorbidity, the Charlson Comorbidity, the Elixhauser, and the Chronic Disease scores to an internal validation set of 500,000 NHS beneficiaries from Lombardy. Two approaches were used with this aim. One, the discriminatory power was assessed by constructing the receiver operating characteristic (ROC) curve and calculating the area under the ROC curves (AUCs). Two, the net reclassification improvement (NRI) was calculated to assess the improvement of risk classification of MCS with respect to CCI, EI and CDS [49]. The NRI measures the net proportion of subjects correctly reclassified by MCS by evaluating the predicted probability among those who experienced and those who did not experience the outcome.

Second, three external validation sets, each consisting of 500,000 NHS beneficiaries were selected from a Northern (Emilia-Romagna), Central (Lazio) or Southern (Sicily) Italian region and considered jointly with the internal validation set. The total population of these regions amount to about 21.4 million NHS beneficiaries, i.e., more than one third of the Italian population (35.3%). Due to the heterogeneity of data availability, different periods had to be considered for different regions, i.e., 2008 for Lombardy, 2010 for Emilia-Romagna and Lazio, and 2013 for Sicily. Between regions consistence of MCS performance, was tested by comparing AUC estimates and Kaplan-Meier one-year survival probabilities stratified by MCS.

Sensitivity analysis and secondary outcomes

Because of the arbitrary nature of score categorization (see the above reported description of the score development), in a secondary analysis the MCS robustness in predicting one-year mortality was verified by comparing the probability of survival (Kaplan-Meier curves) of the internal validation sample as stratified according to MCS categories alternative to that used in the main analysis.

Further analyses were performed for evaluating whether MCS may predict other secondary outcomes including: (i) the five-year all-cause mortality, (ii) the one-year and five-year hospital admissions for all causes, and (iii) the two-year hospital costs measured from the perspective of the Italian NHS. Secondary outcomes were referred to 1,000 person-years (PY) and calculated along the categories of MCS within the internal validation set.

Results

MCS score

Factors which mostly contributed to the total aggregate score were metastatic cancer, alcohol abuse, cancer without metastasis and tuberculosis, while arrhythmia, obesity and hypothyroidism provided small, although significant, contributions (**Table 2**).

Table 2. Assignment of weights in building the Multisource Comorbidity Score (MCS) through a time-to-death multivariate Weibull model.

Disease/condition	Weight
Metastatic cancer	18
Alcohol abuse	11
Cancer, without metastasis	10
Tuberculosis	10
Psychoses	8
Liver disease	8
Anxiety medication	6
Weight loss	6
Dementia	6
Malignancy medication	5
Parkinson's disease	5
Lymphoma	5
Hemiplegia and hemiparesis	5
Coagulation defects	5
Disorders of fluid, electrolyte, and acid-base balance	4
Kidney diseases	4
Kidney dialysis	4
Heart failure	4
Other neurological diseases	3
Rheumatoid arthritis	3
Anaemias	3
Cerebrovascular diseases	3
Diabetes	2
Vascular diseases	2
Gout	2
Epilepsy	2
Chronic pulmonary diseases	2
Peptic ulcer	2
Acute myocardial infarction	1
Coronary and peripheral vascular disease	1
Valvular diseases	1
Arrhythmia	1
Obesity	1
Hypothyroidism	1

Overall, 86.4% and 1.2% of NHS beneficiaries respectively had the lowest (0) and the highest (4) MCS value. The less favourable prognosis of men and elderly people with respect to women and young people was caught by the novel prognostic score. The prevalence of NHS beneficiaries belonging to the lowest MCS category progressively decreased with the increasing categories of age from 94% to 64% in men and from 95% to 72% in women (**Figure 1**).

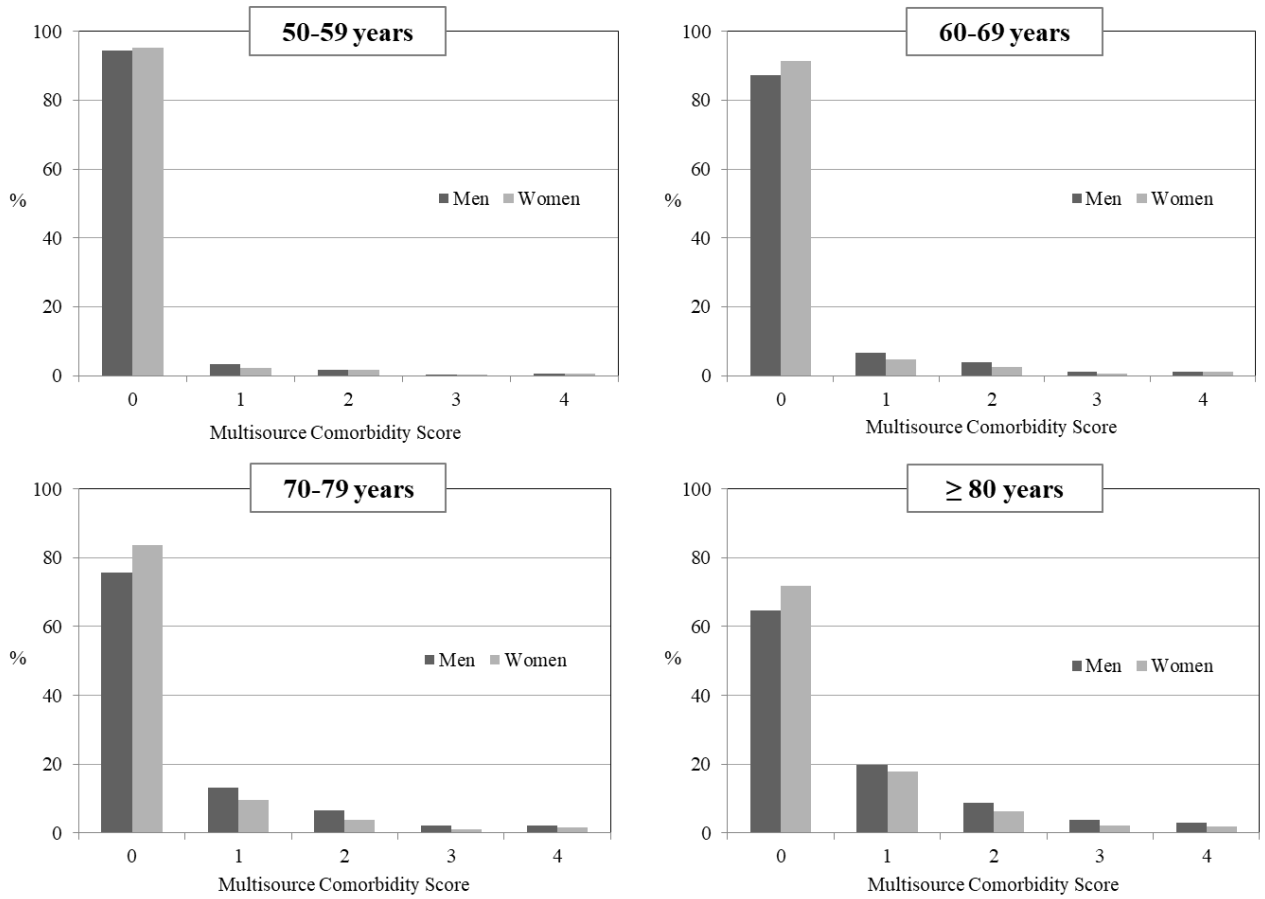


Figure 1. Multisource Comorbidity Score distribution among NHS beneficiaries (internal validation set) according to their gender and age category

MCS compared to other comorbidity Scores

The AUC values (95% Confidence Interval, CI) of MCS, CCI, EI and CDS were 0.78 (0.77, 0.79), 0.69 (0.68, 0.70), 0.65 (0.64, 0.66), and 0.69 (0.68, 0.70), respectively (**Figure 2**).

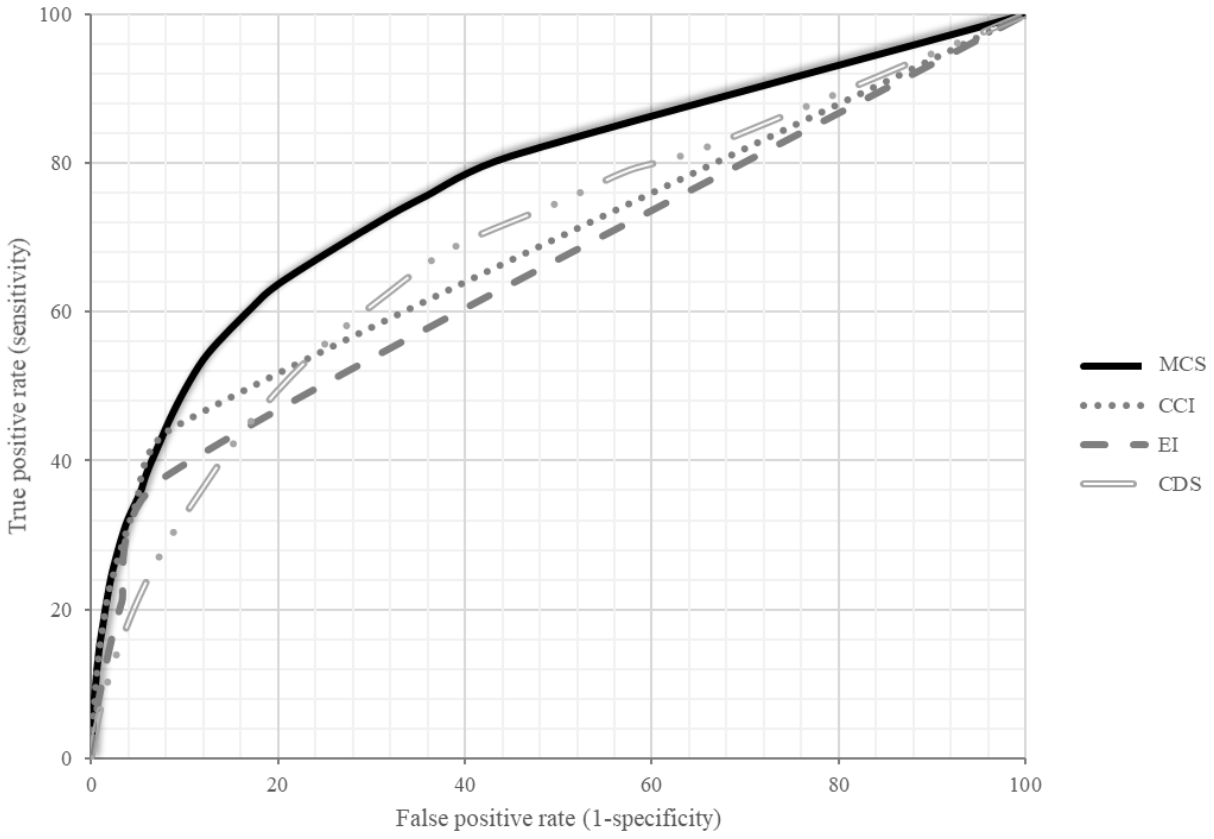


Figure 2. Receiver Operating Characteristics (ROC) curves comparing discriminant power of Multisource Comorbidity Score (MCS) Charlson Comorbidity Index (CCI), Elixhauser Index (EI) and Chronic Disease Score (CDS) in predicting one-year survival among NHS beneficiaries (internal validation set)

Performance analyses using NRI showed that MCS significantly improved the net one-year mortality reclassification by all other scores, the magnitude of the improvement being 38.8% (95% CI, 36.9, 40.7; $p < 0.0001$) when compared to the CCI, 68.8% (66.8, 70.7; $p < 0.0001$) when compared to the EI, and 27.2% (25.3, 29.1; $p < 0.001$) when compared to the CDS. With respect to the CDS (the medication-based score), MCS improved by 17% the sensitivity of the correct reclassification of individuals who experienced the outcome (the deceased ones), whereas with respect to CCI and EI (i.e., the diagnosis-based scores), it improved the correct reclassification of individuals who did not experience the outcome (the survivors), by 37% and 67%, respectively.

MCS model performance across Italian regions

The AUC values (95% CI) of MCS showed superimposable values in the four regions, i.e. 0.78 (0.77, 0.79), 0.78 (0.77, 0.79), 0.77 (0.76, 0.78), and 0.78 (0.77, 0.79) in Lombardy, Emilia-Romagna, Lazio and Sicily, respectively (**Figure 3**). In addition, in all four regions there was a progressively reduction of one-year survival as MCS increased (**Figure 4**).

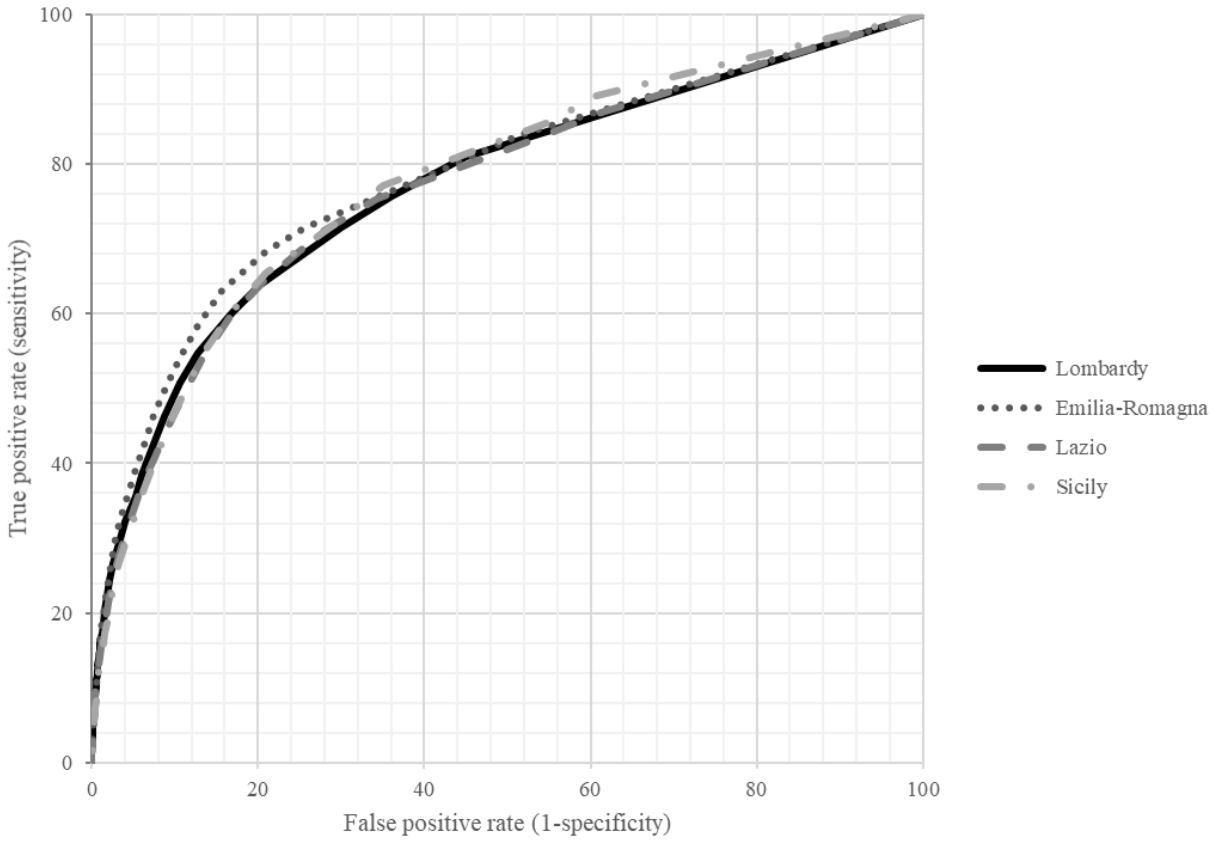


Figure 3. Receiver Operating Characteristics (ROC) curves comparing discriminant power of Multisource Comorbidity Score (MCS) in predicting one-year survival in four Italian regions (internal and external validation sets)

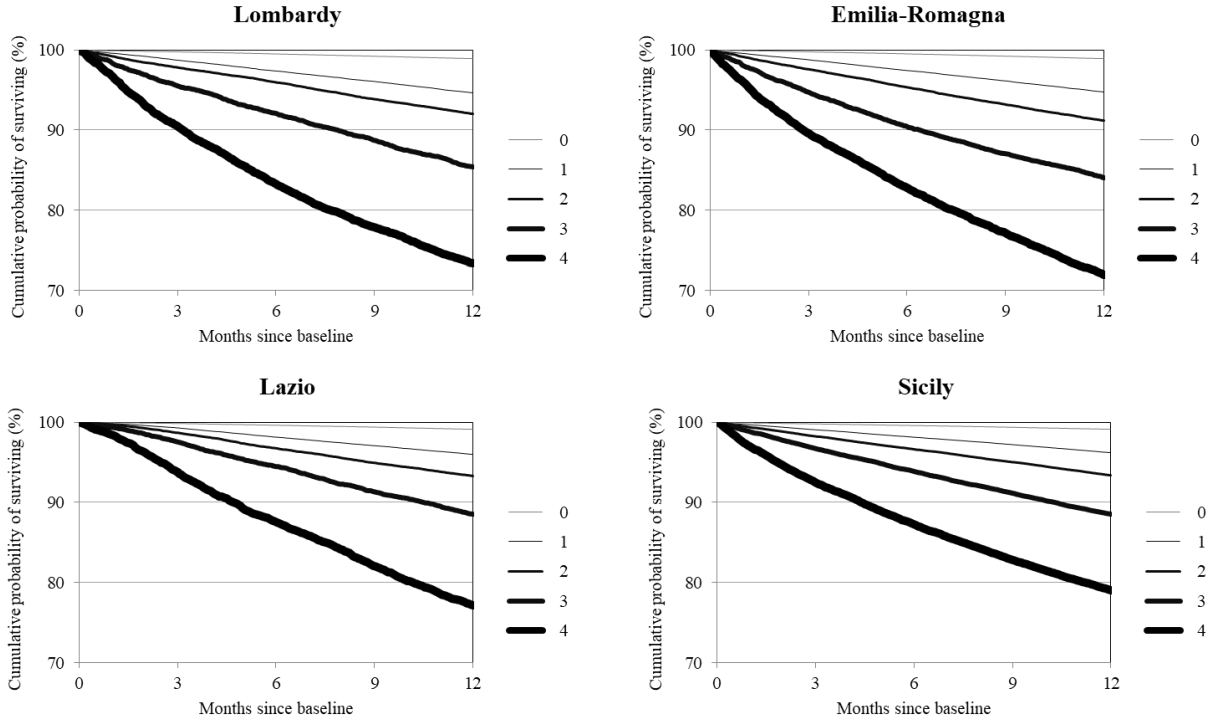


Figure 4. One-year Kaplan-Meier survival curves according to the value of the Multisource Comorbidity Score (MCS) in four Italian regions (internal and external validation sets)

Sensitivity Analyses and other secondary outcomes

A reduced one-year survival with increasing MCS values was observed also when alternative criteria for categorizing the multisource comorbidity score were employed (**Figure 5**). This was the case also when secondary outcomes, rather the one-year mortality, were considered (**Figure 6**), the NHS beneficiaries with the highest MCS score (MCS=4) exhibiting five year mortality rates, one-year and five-year hospital admission rates and two-year hospital costs respectively 9-fold, 8-fold, 6-fold and 8-fold higher than NHS beneficiaries with the lowest MCS score (MCS=0).

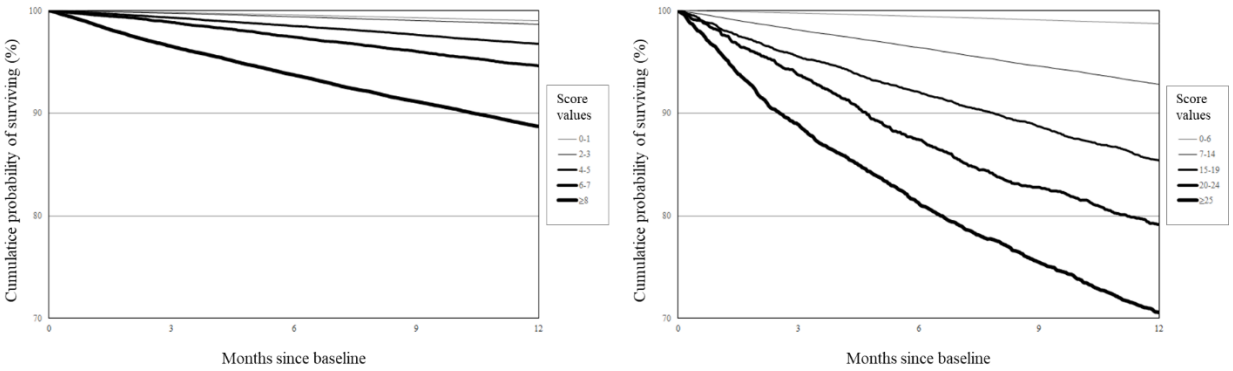


Figure 5. One-year Kaplan-Meier survival curves according to different categorizations of the Multisource Comorbidity Score values. Lombardy, internal validation set

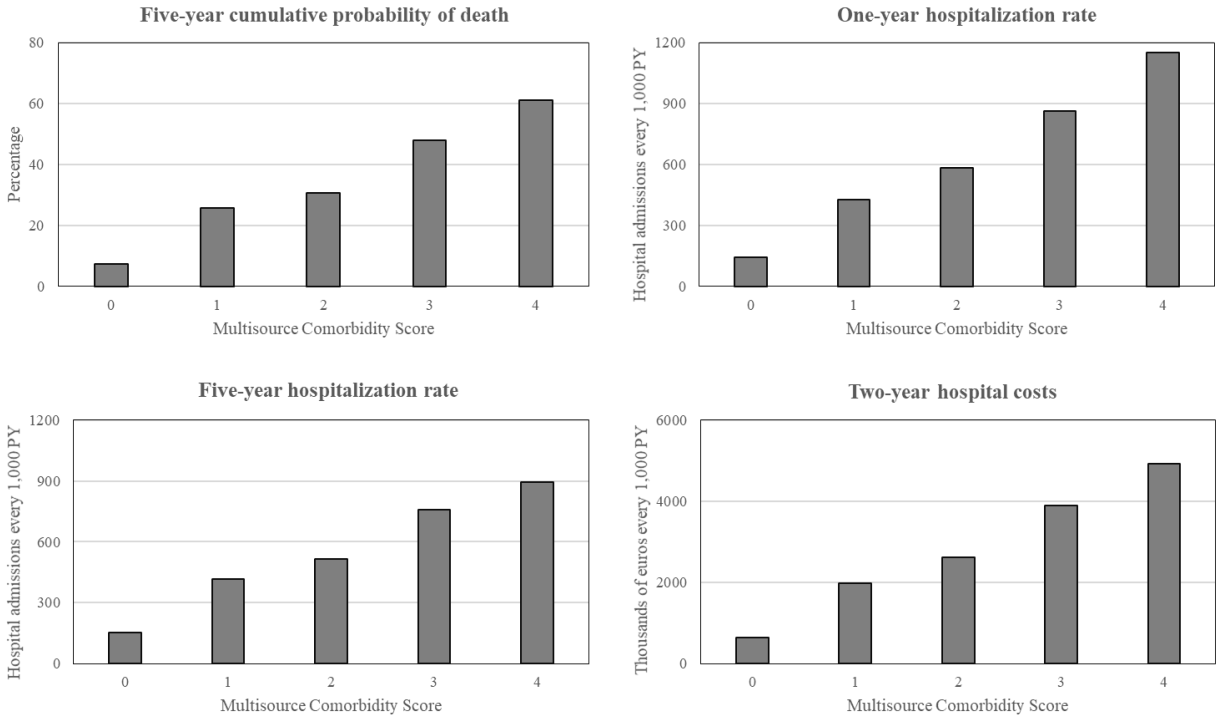


Figure 6. Five-year mortality, and hospital admissions and hospital costs annual rates according to the value of the Multisource Comorbidity Score (MCS) of NHS beneficiaries (internal validation set)

Discussion

Thid study shows that a simple score based on hospital diagnoses and drug prescriptions derived from current administrative data is able to stratify beneficiaries of Italian NHS according to their one-year risk of death. It further shows that this score significantly improves the discriminatory power and net reclassification of commonly used prognostic scores, such as the Charlson Comorbidity Index, the Elixhauser Index, and the Chronic Disease Score. It finally shows that the score performance 1) was comparable in northern, central and southern Italian general populations and 2) was similarly valid for predicting long-term mortality, short- and long-term number of hospital admissions, and two-year cost of hospitalizations as calculated from the NHS perspective.

Although MCS was derived from the entire list of 46 diseases and conditions already used for developing CCI, EI and CDS, our score used more information that any of the previously validated comorbidity scores. In general, our MCS identified more individuals at higher risk of experiencing clinical outcomes than the CDS, another comorbidity score that integrates information about medications into its scoring. The MCS also was able to exclude more individuals at low risk of adverse outcomes than the other diagnosis-based comorbidity scores.

The present study has several strengths. First, although previous studies already identified predictors of mortality and other health outcomes [33], to our knowledge MCS is the first combining inpatient diagnoses and outpatient drug prescriptions to stratify NHS beneficiaries according to comorbidities related to relevant clinical outcomes. Second, this study was based on a very large unselected population, which was made possible because in Italy a public funded healthcare system involves virtually all citizens. Third, MCS was validated and tested on 2 million of NHS beneficiaries, a sample not only very large, but also representative of the entire Italian population. Fourth, because pharmacists are required to report drug prescriptions in detail in order to obtain reimbursement, and incorrect reports about the dispensed drugs have legal consequences the drug prescription database provided highly accurate data [50]. Finally, the selection of comorbidities based on opinion of experts

[51,52] was avoided and prevalence data [46,53,54]. Moreover, with the aim of overcoming the limitation of conventional stepwise selection when several predictors must to be analysed[55,56] , the LASSO model has been adopted. By shrinking variables with very unstable estimates towards zero, the LASSO model can effectively exclude some irrelevant variables generating sparse estimations [57].

Several potential limitations must also be taken into account. First, predictors are restricted to those routinely collected in all regions of Italy. This means that some data potentially relevant to clinical outcomes and healthcare costs such as outpatient services (including visits and diagnostic tests performed by specialized physicians and laboratories accredited by the NHS, payment exemptions, drugs directly delivered to inpatients, and emergency room visits) were not considered because not ubiquitously available. Furthermore, the administrative databases did not contain information on the educational level, the functional patient's status, the caregiver availability and the markers of social instability, which have been shown to have a predictive value for the outcomes explored in our study [58]. This emphasizes the interest of future research on additional predictors, and implies that there is potential for scores that predicts outcomes even more accurately than ours.

Second, the proposed scoring system did not capture health services supplied from private providers. For example, the lack of evidence that depression predicts comorbidity-related outcomes, might be due by our inability of capturing patients who are not treated from public mental health services. However, given that the Italian NHS covers entirely essential healthcare needs, it is unlikely that diseases strongly affecting mortality escape its databases.

Third, misdiagnosis (due to poor accuracy in reporting diagnoses and comorbidities [59]) and upcoding (in pursuit of higher reimbursements [60]) of hospital records might have generated a conservative estimate of MCS performance. However, these diagnostic errors would affect similarly all diagnosis-based comorbidity scores, thereby failing to question the main result, i.e. that MCS had a better performance than both the Charlson and Elixhauser scores.

Fourth, since outcomes are markedly influenced by the nature and quality of the health care system [61], our scoring system might perform differently in countries other than Italy, which means that its applicability elsewhere in Europe will have to be tested. In this context, however, it is important to emphasize that the MCS performance showed an impressive stability throughout Italian regions where important differences in quality of, and accessibility to, healthcare services have been reported [62]). This suggests that its predictive value for mortality and other outcomes of medical relevance may persist under different settings.

Finally, MCS may not apply to every relevant outcome and quantify the role of all conditions that may increase patients' risk of death. For example, this score cannot take into account of (i) conditions that do not affect one-year mortality, (ii) NHS beneficiaries suffering a given condition who did not leave 'footprints' of routine medical care able to detect that condition (e.g., untreated hypertensions), and (iii) patients who did not survive at least two years after the onset of an acute condition (e.g., fatal myocardial infarction).

Conclusions

In summary, a simple multisource prognostic score derived from data usually used for health system management was developed and validated. Because MCS is useful for predicting short-term and long-term risk of death, hospitalization and high health costs of each individual NHS beneficiary, this score can represent a useful tool for risk adjustment in clinical and epidemiological studies, for assessing and health system performance and health policy planning, as well as an instrument for the identification of patients in need of a focused approach in everyday medical practice.

MCS as a tool for health policy planning [2]

Introduction

Measuring inequality in the prevalence of multimorbidity is requested for proper resources allocation, particularly in systems universally covered by a NHS. However, despite the well-established evidence base highlights the impact and costs associated with multimorbidity among patients suffering from a given chronic disease [63–66], measures of healthcare needs are usually built around single diseases [67]. Alternatively, comorbidity scores that consider the set of diseases and conditions independently predicting outcomes that clinicians and patients would like to avoid (e.g., mortality and hospital admission) or costs that the NHS policy makers would like to save (e.g., reimbursements to accredited health providers) can be used [26–28,34–37,40,68,69]. However, most of the scores were developed from hospital-based or pharmacy-based surveys, so hindering their applicability to all beneficiaries of the NHS and/or to diseases unrequiring hospital admission.

A simple Multisource Comorbidity Score (MCS) combining population-based administrative data of healthcare utilization from the NHS beneficiaries has been recently developed and validated in Italy [70]. As MCS showed impressive stability of between-region performance in predicting clinical outcomes, its utilization for measuring regional differences in the impact of multimorbidities should be suitable. With these premises, a very large real-world investigation covering 63.1% of the Italian population aged 50-85 years was then conducted under the auspices of the Italian Health Ministry with the aim of measuring between-region differences in the multimorbidity distribution.

[2] Results reported in this chapter have been submitted in Corrao G, Rea F, Carle F, Di Martino M, De Palma R, Francesconi P, Lepore V, Merlino L, Scondotto S, Garau D, Spazzafumo L, Montagano G, Clagnan E, Martini N. Measuring multimorbidity inequality across Italy through the Multisource Comorbidity Score: A nationwide study

Methods

Setting

This study is based on computerized healthcare utilization databases from ten of the twenty Italian regions, which voluntarily adhered to the initiative. Three regions are located in the northern (Lombardy, Friuli-Venezia-Giulia and Emilia-Romagna), three in central (Marche, Tuscany and Lazio) and four in the southern Italy (Puglia, Basilicata, Sicily and Sardinia). Overall, these data cover more 38 million beneficiaries of the NHS, just under two-thirds of the entire Italian population.

Selecting the study population and data processing

Beneficiaries of the NHS who in the index year (i.e., in 2018) were aged from 50 years to 85 years, and were resident in one of the ten participant Italian regions from at least two years (i.e., were recorded as beneficiaries of the regional NHS before the year 2016), formed the study population. The latter included 15.7 million NHS beneficiaries of the 24.9 million overall resident in Italy in the index year (63.1% of the Italian population aged 50-85 years).

Although databases did not substantially differ across regions for several aspects, a between regions data harmonization was performed, thus allowing data extraction processes to address the same semantic concepts (e.g., information were uniformly encoded by using the same names, values and formats). Anonymized data were extracted and processed locally by using common Statistical Analysis System (SAS) codes according to protocol previously approved by the Italian Health Ministry working group.

Data analysis

The list of predictors used for calculating MCS, and the corresponding weights, is reported in the previous chapter ("*The case of the Multisource Comorbidity Score*"). Briefly, the presence of 34 diseases and conditions was traced from footprints left by NHS beneficiaries in hospital discharge and drug prescription databases. A string with 34 morbidity values was built for each beneficiary, so that each disease was indexed as 1 whether a footprint suggestive of its presence was left at least once

within two years prior to the index year (i.e., in the years 2016 and 2017), 0 otherwise. A weight was assigned to each disease according to how much it predicted the outcome. Finally, MCS was calculated by categorising the individual sum of the string values into 1 of the 6 categories denoting a progressive worsening comorbidity status (i.e., with values 0, 1-4, 5-9, 10-14, 15-19 and ≥ 20). With respect to the original version [70], the first category (originally with values 0-4) was divided in order to take into account for beneficiaries without signs of comorbidities.

With the aim of comparing the MCS distribution in women and men belonging to geographic partitions (i.e., between north, centre and south Italy, and across the 10 regions), the following steps were followed. The percentage of beneficiaries belonging to the MCS categories was calculated for each individual age, and the corresponding distributions stratified according to gender and geographic partitions were represented. Each distribution, which was denoted as age-specific MCS distribution, consisted in a rectangle (with the 35 ages as base and 1 as height) within which the area was portioned into sub-areas with different shades of grey which gradually become darker according to progressively increasing values of the MCS.

Three approaches were used for synthesizing and comparing the age-specific MCS distributions. One, the age above which half of the beneficiaries suffered from at least one comorbidity was calculated and denoted as MCS median age. Two, the portion of the rectangle area covered by beneficiaries suffering from at least one comorbidity was also calculated and denoted as percentage of comorbid population. Three, the ridit transformation of the MCS was finally performed [71]. In the current study, for each individual age, the ridit–transformed MCS was used to compare the comorbidity profile for NHS beneficiaries from a given geographic partition, with respect to NHS beneficiaries of the entire Italian population covered by the current investigation [72,73]. A ridit score with value lower, equal and higher to 0.5 is obtained respectively according to whether comorbidity profile of a given geographical partition is better, the same or worse than the entire Italian population does.

Finally, the relationship between indexes of MCS profile and per capita gross domestic product (GDP) was investigated by means of an ecologic approach. A plot displaying regional distribution of per capita GDP (abscissa) against a given index of MCS (ordinate) was built, and the corresponding Pearson's correlation coefficient (ρ) was calculated.

Results

Figure 7 shows that MCS median age ranged from 60 years (centre and south) to 68 years (North) in women and from 63 years (centre and south) to 68 years (north) in men. The percentage of comorbid population was lower than 50% for northern population, while it was around 60% for central and southern populations.

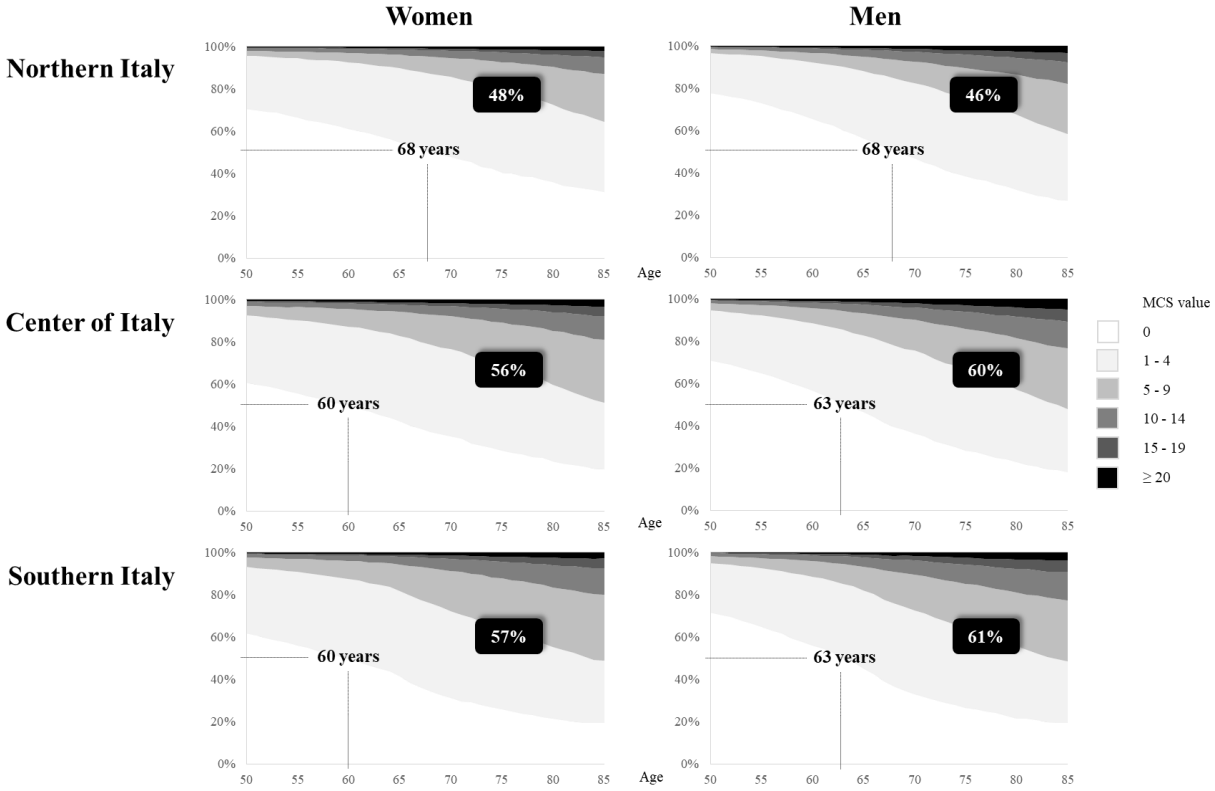


Figure 7. Multisource Comorbidity Score (MCS) distribution among National Health Service beneficiaries of North, Center and South of Italy according to their gender and age

Figure 8 shows that, compared with NHS beneficiaries from central and southern Italy, those from northern Italy always showed better comorbidity profile for both women and men. Starting from age of 65 years or older, NHS beneficiaries from southern Italy showed worse comorbidity profile than those from central Italy. Among men aged 80 years or older, however, this trend is reversed with a worse profile in central Italy.

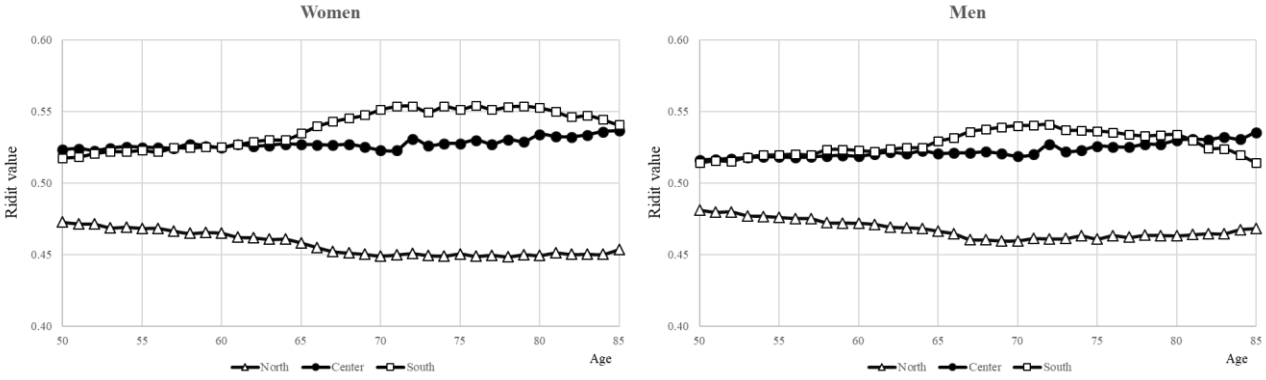


Figure 8. Trend of mean ridit values of the MCS distribution among National Health Service beneficiaries of North, Center and South of Italy according to their gender and age

Regional comparisons are shown in **Table 3**. The geographic gradient towards worsening comorbidity profile from north to south was confirmed. The best comorbidity profile was always obtained for Lombardy, so that the best profile observed in northern Italy was clearly dragged from this region. The worst comorbidity profile was usually observed for Lazio, so that the not optimal profile obtained for central Italy was clearly worsened by this region. Elderly from Sicily had the worst comorbidity profile for both women and men.

Table 3. MCS median age, percentage of comorbid population, and ridit values at 50, 65 and 80 years of age in women and men of ten Italian region

	Women						Men					
	NHS beneficiaries	MCS median age (years)†	Percentage of comorbid population‡	Mean ridit at age (years) § 50	65	80	No. NHS beneficiaries	MCS median age (years)†	Percentage of comorbid population‡	Mean ridit at age (years) § 50	65	80
Lombardia	2,164,592	70	47%	0.462	0.444	0.433	1,937,724	70	47%	0.476	0.457	0.450
Friuli Venezia Giulia	286,397	67	51%	0.480	0.464	0.465	255,640	68	50%	0.485	0.475	0.485
Emilia Romagna	985,388	65	54%	0.495	0.488	0.486	875,678	67	51%	0.492	0.486	0.489
Marche	343,071	62	59%	0.509	0.508	0.528	305,771	64	57%	0.510	0.519	0.534
Toscana	862,003	65	55%	0.493	0.487	0.504	757,224	66	53%	0.496	0.492	0.502
Lazio	1,279,276	56	65%	0.546	0.558	0.559	1,101,596	62	61%	0.531	0.540	0.551
Puglia	864,071	58	63%	0.529	0.546	0.557	760,319	63	59%	0.520	0.536	0.539
Basilicata	123,944	59	59%	0.531	0.529	0.515	111,612	63	52%	0.524	0.518	0.474
Sicilia	1,048,743	62	63%	0.505	0.535	0.582	917,475	64	60%	0.510	0.536	0.561
Sardegna	376,457	60	58%	0.517	0.509	0.491	339,812	65	53%	0.505	0.503	0.488
Total	8,333,942	64	56%				7,362,851	66	53%			

Three regions are located in the northern (Lombardy, Friuli-Venezia-Giulia and Emilia-Romagna), three in central (Marche, Tuscany and Lazio) and four in the southern Italy (Puglia, Basilicata, Sicily and Sardinia).

† Age above which half of the beneficiaries suffered from at least one comorbidity

‡ Portion of the age-specific MCS distribution covered by beneficiaries suffering from at least one comorbidity

§ Mean ridit measures the relative probability that a randomly selected NHS beneficiary among those of a given region had worse comorbidity score than a randomly selected NHS beneficiary among those of the entire Italian population

Figure 9 shows that MCS median age tendentially increases as raising GDP per capita (ρ = +0.6), while the opposite occurred for comorbid population (ρ = -0.6). Interesting, among the 10 investigated regions, only Lazio deviates from linear trends, since it has high GDP and poor comorbid profile.

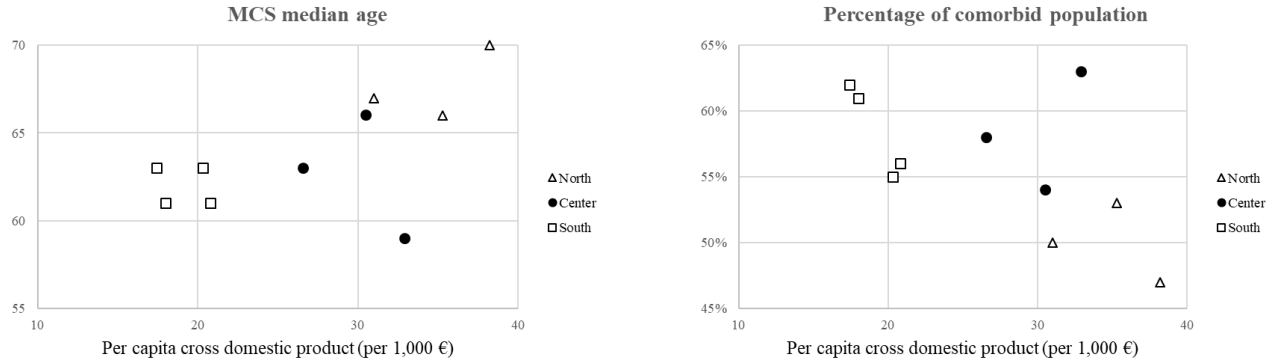


Figure 9. Plots of regional per capita gross domestic product versus comorbidity MCS median age (left plot) and percentage of comorbid population (right plot)

Discussion

Deep differences in age-specific MCS distribution were observed across Italy with a clear worsening gradient from north to south. The between-geographic partition differences were not trivial because, compared to NHS beneficiaries from northern Italy, those of central and southern Italy had MCS median age lower than 5 years (men) and 8 years (women) and percentage of comorbid population higher than 8-9% (men) and 14-15% (women). At the age of 70 years, a beneficiary randomly selected from southern Italy had a 4.2% (man) and 5.1% (woman) probability of having worse comorbid profile than a NHS beneficiary randomly selected from Italy as a whole. Of course, even higher inequalities were observed among regions, so that the distance between the best (Lombardy) and worst (Lazio) region was of 8 years (men) and 15 years (women) in MCS median age, and 14% (men) and 19% (women) in percentage of comorbid population.

Three issues need to be discussed to fully appreciate and weigh strengths and weaknesses of our approach in measuring comorbidity. First, as healthcare utilization databases have regional management, geographic heterogeneity of data quality might explain the observed difference in MCS distribution. Second, misclassification due to out-of-pocket provided services, i.e., healthcare from private services, might fully or partially explain such differences. Third, because administrative data on care receipted were used for building MCS, the latter measures demand rather than unmet healthcare need. However, as an impressive overlapping predictive ability of the MCS score across regions was observed [70], these concerns should be downsized. This, in fact, may suggest that regional heterogeneity in data quality and use of private services minimally concerns our ability to capture patients with chronic conditions highly predictive of the risk of death. For these conditions, moreover, demand and health needs likely almost coincide. These considerations taken together suggest that MCS represents a very useful tool for measuring regional inequalities in healthcare needs.

Higher multimorbidity prevalence has been observed among people on low socioeconomic profile [74], even in countries with universal access to healthcare [75]. This is consistent with our findings that showed a progressively worse comorbidity profile as GDP lowering. On the other hand, multimorbidity should be considered as a major source of healthcare inefficiency with a higher risk of avoidable inpatient admission, suboptimal disease management, inadequate treatment and communication barriers [76]. This might explain why not always higher average income leads better comorbidity profile.

Policy implications of these findings fit into the current debate on how to assign appropriate resources and plan suitable services to meet demand according to comorbidity profiles. In particular, decision makers need validated tools for stratifying beneficiaries of the health system according to the risk level, i.e., for identifying those to address towards primary and secondary prevention programs, systems of long-term healthcare by integrating primary and specialist

services, and short-term intensive inpatients care. MCS score seems to fit these needs since it represents a tool for resources assignment according to health demands.

On the central government point of view, monetary incentive for regions agreeing with proactive management of high-risk patients (i.e., the collaborative process assessing, planning, implementing, coordinating, monitoring and evaluating the options and services required to meet an individual's health needs, using communications and available resources to promote quality, cost-effective outcomes [77,78]) might have clinically and operationally major implications [79]. Of course, MCS may be used for monitoring the effect of such or other policies.

In summary, MCS may be easily derived from data usually used for health system management, and has relevant value for conducting population-based investigations aimed to compare multimorbidity prevalence and assessing health policy implications. These results support the usefulness of MCS at the central level (e.g. the Ministry of Health) to monitor the health needs of the population in order to guide national health planning and to point out the differences between sub-national areas (e.g. the Italian Regions). Providing this information to local policy makers and healthcare managers would allow them to make the necessary specific and more complete assessments of multimorbidity, exploring accessibility to health services, costs and outcomes for specific health conditions.

From the Chronic Related Groups to the Chronic Related Score: the Lombardy experience [3]

Introduction

The ageing population with rising prevalence of chronic conditions makes unprecedented demands on healthcare services [80,81]. Patients with chronic conditions are more likely to experience hospital admissions for potentially avoidable causes, resulting in a 'triple fail event' of suboptimal health outcomes, significant health costs and poor patient experience [82,83].

Through detecting high-risk individuals who require more careful care [84], risk stratification models are expected to improve patient outcomes and provide economic value to healthcare [85,86]. This proactive targeting of services at people at defined risk has retained prominence by the Italian Health Ministry since, notably with the recently adopted national plan of chronicity, efforts to introduce integrated care mainly addressed to high-risk individuals have been recommended [http://www.salute.gov.it/imgs/C_17_pubblicazioni_2584_allegato.pdf].

In estimating individual risk scores, models typically include predictors relating to past use of healthcare, diagnoses and medications [28,33–36]. However, most of the available scores have been developed from hospital-based surveys reviewing inpatients medical records and only later they were adapted for risk stratification of whoever beneficiary of the health system [41]. A simple population-based comorbidity score (i.e., the called Multisource Comorbidity Score, MCS) has been recently validated in the setting of the Italian National Health System [70]. Because MCS was developed to be applied everywhere, only data on inpatient diagnoses and outpatient drug prescriptions were used.

[3] Results reported in this chapter have been published in Rea F, Corrao G, Ludergnani M, Cajazzo L, Merlino L. A new population-based risk stratification tool was developed and validated for predicting mortality, hospital admissions, and health care costs. J Clin Epidemiol. 2019;116:62-71. doi: 10.1016/j.jclinepi.2019.08.009

However, other healthcare utilization data, although not ubiquitously collected, may contribute to explain relevant clinical and economic outcomes.

Recognising such challenges and opportunities, welfare authority from the Lombardy Region of Italy developed an 'evidence-based' framework involving the building of algorithms able of capturing patients who suffer from 65 chronic diseases and conditions through all the available healthcare utilization databases, thus realizing the so-called Chronic Related Groups, CReG.

Herein, taking advantage from several sources of healthcare data routinely collected for NHS beneficiaries from Lombardy, a score based on the CReG list, just called Chronic Related Score (CReSc), was developed and validated. The association of the CReSc with five-year mortality, hospital admissions and health care costs, as well as, the relationship between CReSc distribution and household income were investigated.

Methods

Healthcare utilization data from Lombardy

The data used for the present study were retrieved from the HCU databases of Lombardy, a Region of Italy that accounts for about 16% of its population. Costs associated with the provided healthcare services were measured from the NHS perspective using the amount that the Regional Health Authority reimbursed to health providers.

As a unique identification code was used for all databases, their record linkage allowed searching out the complete care pathway of NHS beneficiaries. In order to preserve privacy, identification codes were automatically converted into pseudo-anonymized codes, and the inverse process was prevented by deletion of the conversion table.

Score development

A list of 65 chronic conditions (that is the CReG list that is reported in the **Table 4**) was carefully chosen by a regional working group appointed for identifying those conditions, which mostly affect expenditure of regional health authority. For each of the 65 conditions, an algorithm was developed for capturing patients who suffer from it through the above-mentioned databases.

Table 4. List of the 65 diseases and conditions candidate to be tested as predictors of five-year mortality

	Disease/condition
1	Active transplant recipients
2	Dialysis
3	Symptoms, signs and morbid conditions unspecified
4	Acromegaly and gigantism
5	Diseases of the blood and of the hematopoietic organs
6	HIV positive and full-blown AIDS
7	Non-active transplant recipients
8	Type 1 diabetes mellitus, complicated
9	Respiratory insufficiency / oxygen therapy
10	Neoplasia, active
11	Neuromyelitis optica
12	Immune haemolytic anaemias
13	Multiple sclerosis
14	Arterial vasculopathy
15	Certain conditions originating in the perinatal period
16	Type 2 diabetes mellitus, complicated
17	Chronic kidney failure
18	Endocrine, nutritional and metabolic diseases, and immunity disorders
19	Liver cirrhosis
20	Heart failure
21	Cushing's syndrome
22	Systemic sclerosis
23	Cerebral vasculopathy
24	Ankylosing spondylitis
25	Valvular heart disease
26	Chronic pancreatitis
27	Venous vasculopathy
28	Dementias
29	Ischaemic cardiopathy
30	Arrhythmic miocardiopathy
31	Diabetes insipidus
32	Cardiomyopathy (not arrhythmia-induced)
33	Parkinson's disease
34	Epilepsy
35	Pituitary dwarfism
36	Diseases of the circulatory system
37	Myasthenia gravis
38	Addison's disease
39	Chronic obstructive pulmonary disease
40	Rheumatoid arthritis
41	Psoriasis and psoriatic arthropathy
42	Diseases of the nervous system and sense organs
43	Chronic hepatitis
44	Type 1 diabetes mellitus
45	Systemic lupus erythematosus
46	Crohn's disease and ulcerative colitis
47	Alzheimer's disease
48	Hypercholesterolemia
49	Disease of the musculoskeletal system and connective tissue
50	Type 2 diabetes mellitus
51	Infectious and parasitic diseases
52	Sjögren's disease
53	Hyperparathyroidism and hypoparathyroidism
54	Diseases of the genitourinary system
55	Congenital anomalies
56	Hypertension
57	Neoplasia, follow-up

58	Diseases of the skin and subcutaneous tissue
59	Neoplasia, remission
60	Hypothyroidism
61	Rare cancer
62	Basedow's disease
63	Asthma
64	Hashimoto's disease
65	Diseases of the digestive system

With the aim of selecting conditions independently able to predict five-year mortality (i.e., the main outcome of interest), the following steps were adopted.

First, two out of three of the 8.1 million citizens aged 18 years or older who in the year 2013 were beneficiaries of the Lombardy health system from at least two years (i.e., almost 5.4 million citizens) was randomly selected to form the so-called training (derivation) set. These patients were followed until the earliest date between death and censoring (emigration or 31 December 2017). Second, the Cox proportional hazard regression model was fitted to compute the hazard ratios estimating the relationship between the selected covariates and the time of death. Covariates included into the model were gender, age (at January 1th, 2013), and the 65 candidate predictors. The latter entered into the model as dichotomous variables, with value 1 or 0 according to whether the specific condition was or was not recorded at least once within two years prior to baseline (2011-2012). Third, the least absolute shrinkage and selection operator (LASSO) method was applied for selecting the diseases / conditions able to independently predicting five-year mortality [47]. LASSO selects variables correlated to the measured outcome by shrinking coefficients weights, down to zero for the ones not correlated to outcome. Finally, the coefficients estimated from the model were used for assigning a weight at each selected covariate. In particular, a weight was assigned to each coefficient by multiplying it by 10 and rounding it to the nearest whole number [48]. The weights thus obtained were then summed to produce a total aggregate score. To simplify the system, i.e., with the aim of accounting for excessive heterogeneity of the total aggregate score, the latter was categorized by assigning increasing values of 0, 1, 2, 3 and 4 to the categories of the aggregate score of 0, 1-10, 11-20, 21-30 and ≥31, respectively. The so obtained index was denoted Chronic Related Score (CReSc).

Model performance

Performance of CReSc was explored with respect to other prognostic scores such as the Charlson Comorbidity Index (CCI) and the Multisource Comorbidity Score (MCS). With this aim, the corresponding weights were applied to the so-called validation set consisting of the beneficiaries of NHS who did not enter into the training set (i.e., 2.7 million).

Predictive performance was assessed through discrimination and calibration. Discrimination indicates how well the model can distinguish individuals with the outcome from those without the outcome. Two approaches were used for assessing discrimination. One, discriminatory powers were compared by the receiver operating characteristic (ROC) curves and the corresponding area under the ROC curves (AUCs) [49]. Two, the net reclassification improvement (NRI) was calculated for assessing the 'net' number of individuals correctly reclassified using CReSc over a comparator index (i.e., CCI or MCS) [87].

Calibration ascertains the concordance between the model's predictions and observed outcomes, which was evaluated using a calibration plot. The plot displays predicted versus observed 5-year survival probabilities for increasing predicted risk. Ideally, the plot follows a 45° line, showing that the predicted risks are equal to the observed outcome frequencies. The difference in predicted and observed frequency in the total cohort, indicating the extent to which predictions are systematically too high or too low (referred to as calibration-in-the-large), and the recalibration slope, reflecting the slope of the calibration plot and ideally equal to 1, were assessed [88]. Finally, the Hosmer-Lemeshow goodness-of-fit test modified by Yu et al [89] was used for testing the null hypothesis of agreement between observed and predicted survival probabilities.

Other than for the entire sample, performance of CReSc was calculated according to age (three classes of 18 until 50 years, 51 until 85 years, and 86 years or older) and gender.

Secondary outcomes

Secondary analyses were performed for verifying the CReSc robustness in predicting outcomes other than the cumulative five-year all-cause mortality. With this aim, cumulative healthcare costs, rates of hospital admissions and cumulative days of hospital stays were calculated along the CReSc increasing categories for the entire 5-year time-window. Cumulative healthcare costs were calculated by means the Bang & Tsiatis estimator [90], a method that takes into account censored cost data. Finally, the rates of hospital admissions and cumulative days of hospital stays, both expressed as average number every 1,000 person-years (PY), were considered.

Exploring the effect of income on the Chronic Related Score

Because of the well-known association between income inequality and health [91] and with the aim to verify whether income affects CReSc profiles, data were further processed as follows.

One, the individual income from the household taxable income data (regional tax registry) was calculated. To take into account the household size and composition, the formula that is frequently applied in income inequalities studies was used, which consists of dividing the household income by the square root of the number of household members [92]. When counting the number of household members, the first adult of a family was weighted as 1.0, other adults as 0.7, and children less than 18 years old as 0.5. The equivalent income measures the net income per year that is available for one person.

Two, NHS beneficiaries were classified according to their income. Low- and high-income categories were defined according to 10th and 90th percentile of equivalent income distribution, being intermediate-income category otherwise. Because the income is expected to be related to age and gender, the equivalent income distribution for each stratum of gender and five-year intervals of age was used for categorizing individuals in low-, intermediate- and high-income.

Three, with the aim of assessing whether income categories affected the CReSc value, the ridit analysis was used. Ridit transformation is a method based on the assumption that the ordered categorical variable approximates an underlying continuous variable [93]. In the current study, within each stratum of gender and five-year intervals of age, the ridit–transformed CReSc was used to calculate the mean ridit for NHS beneficiaries on low- and high-income with respect to those on intermediate-income. Mean ridit measures the probability that a randomly selected NHS beneficiary among those on low or high income had higher CReSc value than a randomly selected NHS beneficiary among those on intermediate income [72]. The resulting ridit score represents a probability that ranges from a minimum of 0 to a maximum of 1, with a value of 0.5 assigned to the reference category. For example, whether a trend towards worsening CReSc as income get worse, then ridit values higher and lower than 0.5 would be respectively expected among NHS beneficiaries on low and high income. The statistical significance of differences in mean ridit was evaluated with a Z-test.

Finally, since the CReSc score could have different performances according to the income categories (e.g., because NHS beneficiaries with low income could have worse access to services), the ROC curves, and the corresponding AUCs, among categories of equivalent income were compared. Of course, overlapping ROC curves, and similar AUC values, are expected. Otherwise, the ridit values among the income categories should be interpreted as an effect of the different performance between the income categories, rather than the income action in differentiating the level of chronicity.

Results

Chronic Related Score

The 31 conditions significantly contributing to the CReSc, the corresponding codes, jointly with a schematic explanation on how the score must to be calculated, are reported in the **Table 5**.

Table 5. Diseases and conditions that contribute to the Chronic Related Score.

Disease/condition	ICD-9 CM code	DRG code	ATC code	Outpatient services code	Exemption code
Dialysis				39.95, 54.98 (at least 70 records)	
Acromegaly and gigantism	253.0		H01CB (DDD > 50%)		001
HIV positive and full-blown AIDS	042, V08	488, 489, 490	J05AB14, J05AE, J05AG, J05AR, J05AX07 (DDD > 30%)		020
Respiratory insufficiency / oxygen therapy		518.83, 518.84	V03AN01 (at least 400 €)		024.518.81, 024.518.83
Neoplasia, active	140–208, V58.0, V58.1 99.25 (procedure)		L01	38.99.1, 38.99.2, 89.01.M, 89.7C.1, 92.24, 92.25.1, 92.27.1, 92.27.3, 92.27.5, 92.28.3, 92.28.4, 92.28.5, 92.28.6, 92.29.H, 92.29.J, 92.29.K, 92.29.L, 92.29.M, 99.25, MAC01, MAC02, MAC03, MAC04	046.340, 047.710.1, 048, RM0120
Immune haemolytic anaemias	283.0				003
Arterial vasculopathy	440, 441, 442, 443.1, 443.2, 444, 445, 447 39.24, 39.25, 39.26, 39.50, 39.51, 39.52, 39.54, 39.56, 39.57, 39.58, 39.71, 39.72, 39.73, 39.74, 39.79, 39.90 (procedure)				002.440, 002.441.2, 002.441.4, 002.441.7, 002.441.9, 002.442, 002.444, 002.447.0, 002.447.1, 002.447.6
Type 2 diabetes mellitus, complicated	250.40, 250.42, 250.50, 250.52, 250.60, 250.62, 250.70, 250.72, 250.80, 250.82, 250.90, 250.92, 357.2, 362.01-363.07	285	N03AX12, N03AX16 (DDD > 30%)	14.33, 14.34, 14.75, 96.59.1–96.59.6	

Chronic kidney failure	V56, 585, 586	316, 317	H05BX01, H05BX02, V03AE01, V03AE02, V03AE03 (DDD>50%)		023, 031.403, 031.404, 0031.403, 0031.404, 061, 062
Liver cirrhosis	456.0, 456.1, 456.2, 571.2, 571.5, 571.6, 571.8, 572.3				008
Heart failure	428		C09A, C09C (DDD>50%) and [C03CA, C03CB, C03EB (DDD>50%) or C07AG02 C07AB02 C07AB07 (DDD>50%)]		021.428
Systemic sclerosis	710.1				047, RM0120
Cerebral vasculopathy	430-438				002.433, 002.434, 002.437
Valvular cardiopathy	394-397, 745-747, V42.2, V43.3 35 (procedure)				002.394, 002.395, 002.396, 002.397, 002.424, 002.745, 002.746, 002.747, 002.V42.2, 002.V43.3
Chronic pancreatitis	577.1		A09AA (DDD>50%)		042
Venous vasculopathy	452, 453, 459.1				002.452, 002.453, 002.459.1
Dementias	290, 294				011.290.0, 011.290.1, 011.290.2, 011.290.4, 011.291.1, 011.294.0
Ischaemic cardiopathy	410-414 36 (procedure)		C01DA (DDD>50%)		002.414
Arrhythmic miocardiopathy	426, 427, V45.0		C01B (DDD>50%)	89.48.1	002.426, 002.427, 002.V45.0

	37.65, 37.66, 37.68, 37.70, 37.87, 37.89, 37.96 (procedure)			
Cardiomyopathy (not arrhythmia-induced)	402, 404, 415-417, 425, 429.4		C02KX01, C02KX02, C02KX03, G04BE03, G04BE08, B01AC09 (DDD>50%)	031.402, 031.403, 002.416, 002.417, 002.429.4, 0031.402, 0031.403
Parkinson's disease	332.0, 332.1		N04 (DDD> 30%)	038
Epilepsy	345		N03AB02, N03AX14 (DDD>50%)	017.345
Myasthenia gravis	358.0		N07AA02 (DDD>50%)	034.358.0, RFG101
Addison's disease	255.4			022
Chronic obstructive pulmonary disease	491, 492, 494, 496		R03 (DDD>30%, Age ≥45)	057
Diseases of the nervous system and sense organs				RF (except RFG101), 0031.362.11
Chronic hepatitis	070		L03AB04, L03AB05, L03AB06, L03AB09, L03AB10, L03AB11, L03AB12, L03AB60, L03AB61 (DDD>50%) J05AE14, J05AX14, J05AX15, J05AX16, J05AX65, J05AX67, J05AX68	016
Alzheimer's disease	331.0		N06D (DDD >30%)	029.331.0
Type 2 diabetes mellitus	250.00, 250.02, 250.10, 250.12, 250.20, 250.22, 250.30, 250.32	294	A10B (DDD>50%)	013.250 (Age ≥35)
Hypertension	401, 403, 405	134	C02AC01, C02CA04, C03, C07, C08C, C09 (DDD > 50%)	031.401, 031.405, D31.401, D31.405, 0031, 0031.405.0

Neoplasia, follow-up	140-208, V58.0, V58.1 99.25 (procedure)	L01, L02	38.99.1, 38.99.2, 89.01.M, 89.7C.1, 92.24, 92.25.1, 92.27.1, 92.27.3, 92.27.5, 92.28.3, 92.28.4, 92.28.5, 92.28.6, 92.29.H, 92.29.J, 92.29.K, 92.29.L, 92.29.M, 99.25, MAC01, MAC02, MAC03, MAC04	046.340, 047.710.1, 048, RM0120

ICD-9 CM: International Classification of Diseases, Ninth Revision, Clinical Modification; DRG: Diagnosis-Related Group; ATC: Anatomical Therapeutic Chemical classification system; DDD: Defined Daily Dose; EX: exemption code

A NHS beneficiary is classified as suffering from a given condition according to whether within two years before the index year (that is, in the years 2011 and 2012 in the current validation set, since the 2013 was considered the index year) at least one of these events occurred at least once:

- inpatients primary diagnosis, or co-existing condition, recorded according to at least one of the corresponding ICD-9 CM and/or DRG codes
- outpatient drug prescription, recorded according to at least one of the corresponding ATC codes; with the aim of avoiding that a sporadic drug dispensation lead to classify a patient affected by the considered condition (false positive diagnoses) a restraint was introduced, that is the proportion of days covered (ratio between the total amount of the Defined Daily Dose dispensed packing in the previous two years and 730 days) has to be greater than 30% (e.g., Parkinson's disease) or 50% (e.g., heart failure) for classifying the beneficiary affected from the condition;
- outpatient services, recorded according to the corresponding regional nomenclator;
- exemption to co-payment for chronic disease, recorded according to the corresponding national exceptions coding

Notes:

- Diabetes. Type 1 (T1DM) and type 2 (T2DM) diabetes mellitus are mutually exclusive categories. The following rules established the condition for each patient.
    - if T2DM_ATC = 1 then T2DM
    - if T2DM_ATC = 0 and T1DM_ATC = 0 and (T1DM_DRG = 1 or T1DM_ICD9 = 1 or T1DM_EX = 1 or T2DM_DRG = 1 or T2DM_ICD9 = 1 or T2DM_EX = 1) then T2DM
    - if (T1DM_EX = 1 or T1DM_DRG = 1 or T1DM_ICD9 = 1) and T1DM_ATC = 1 then T1DM
    - if T1DM_ATC = 1 and T2DM_EX = 1 then T2DM
    - if (T2DM_DRG = 1 or T2DM_ICD9 = 1) and T1DM_ATC = 1 then T2DM
    - if T1DM_ATC = 1 then T1DM

- Neoplasia (active, follow-up and remission). ATC codes L01AB01 and L01AA01 should not be considered if there is an exemption with the following codes: 006.710, 045.696, 028.710, 047.710.1, 046.340
- Respiratory insufficiency / oxygen therapy, Chronic obstructive pulmonary disease, Asthma are mutually exclusive categories. The following rules established the condition for each patient.
    - if ASTHMA_EX = 1 then ASTHMA
    - if ASTHMA_ATC1 = 1 then ASTHMA
    - if ASTHMA_ICD9 = 1 then ASTHMA
    - if ASTHMA_ATC2 = 1 then ASTHMA
    - if COPD_ATC = 1 then COPD
    - if COPD_ICD9 = 1 then COPD
    - else if Respiratory insufficiency / oxygen therapy.
- According to the following table, the right condition (condition 2) was set to “absent” if patient suffered from the left one (condition 1)

Condition 1	Condition 2
Arrhythmic miocardiopathy	Hypercholesterolemia
Arrhythmic miocardiopathy	Hypertension
Type 2 diabetes mellitus, complicated	Type 2 diabetes mellitus
Type 2 diabetes mellitus, complicated	Hypercholesterolemia
Type 1 diabetes mellitus, complicated	Type 1 diabetes mellitus
Type 1 diabetes mellitus, complicated	Hypercholesterolemia
Cardiomyopathy (not arrhythmia-induced)	Hypercholesterolemia
Cardiomyopathy (not arrhythmia-induced)	Hypertension
Cerebral vasculopathy	Hypertension
Cerebral vasculopathy	Hypercholesterolemia
Dementias	Cerebral vasculopathy
Dementias	Parkinson's disease
Dementias	Epilepsy
Dementias	Alzheimer's disease
Dementias	Hypertension
Dementias	Hypercholesterolemia
Dialysis	Chronic kidney failure
Dialysis	Hypertension
Type 1 diabetes mellitus	Hypercholesterolemia

Ankylosing spondylitis	Psoriasis and psoriatic arthropathy
Respiratory insufficiency / oxygen therapy	Chronic obstructive pulmonary disease
Respiratory insufficiency / oxygen therapy	Asthma
Heart failure	Ischaemic cardiopathy
Heart failure	Valvular heart disease
Heart failure	Arrhythmic miocardiopathy
Heart failure	Cardiomyopathy (not arrhythmia-induced)
Heart failure	Hypercholesterolemia
Heart failure	Hypertension
Ischaemic cardiopathy	Hypercholesterolemia
Ischaemic cardiopathy	Hypertension
Chronic kidney failure	Hypertension
Systemic sclerosis	Disease of the musculoskeletal system and connective tissue
Valvular heart disease	Hypercholesterolemia
Valvular heart disease	Hypertension
Rheumatoid arthritis	Psoriasis and psoriatic arthropathy
Rheumatoid arthritis	Sjögren's disease
Neoplasia, active	Neoplasia, follow-up
Neoplasia, active	Neoplasia, remission
Arterial vasculopathy	Hypertension
Arterial vasculopathy	Hypercholesterolemia
Neoplasia, follow-up	Neoplasia, remission
Liver cirrhosis	Chronic hepatitis
Systemic lupus erythematosus	Disease of the musculoskeletal system and connective tissue
Chronic obstructive pulmonary disease	Asthma
Active transplant recipients	Non-active transplant recipients
Hypothyroidism	Basedow's disease
Hypothyroidism	Hashimoto's disease
Alzheimer's disease	Cerebral vasculopathy
Alzheimer's disease	Parkinson's disease
Alzheimer's disease	Epilepsy
Alzheimer's disease	Hypercholesterolemia
Alzheimer's disease	Hypertension
Sjögren's disease	Disease of the musculoskeletal system and connective tissue
Type 2 diabetes mellitus	Hypercholesterolemia

Almost 30% of NHS beneficiaries had at least a condition contributing to the CReSc. **Table 6** shows that Alzheimer's disease, dementia and heart failure most contributed to the total aggregate score.

Table 6. Weights, prevalence and burden of conditions contributing to the Chronic Related Score (CReSc)

	Disease/condition [(a)]	CReSc Weight [(b)]	Prevalence rate (%)	Per-capita annual cost (€)	Burden ranking [(c)]
1	Alzheimer disease	22	0,26	9,026	29
2	Dementia	20	0,17	9,684	23
3	Heart failure	18	1,80	20,345	2
4	Neoplasia, active	14	2,10	20,828	1
5	Parkinson diseases	14	0,40	18,246	6
6	Dialysis	14	0,09	140,824	10
7	Arrhythmic miocardiopathy	11	2,15	14,650	7
8	Liver cirrhosis	10	0,30	27,862	3
9	Respiratory insufficiency / Oxygen therapy	10	0,10	21,971	11
10	Hypertension	9	15,47	9,203	18
11	Ischaemic cardiopathy	9	2,47	15,078	4
12	Chronic obstructive pulmonary	9	1,86	17,187	5
13	Cerebral vasculopathy	9	1,04	15,430	9
14	Immune haemolytic anaemias	9	0,01	23,377	28
15	Neoplasia, follow up	8	1,21	14,746	12
16	Diseases of the nervous system and the sense organs	7	0,10	14,609	21
17	Cardiomyopathy (no arrhythmia-induced)	6	2,67	13,977	13
18	Chronic kidney failure	6	0,75	24,513	8
19	Acromegaly and gigantism	6	0,02	52,394	24
20	Type 2 diabetes mellitus	5	5,58	13,659	15
21	Epilepsy	5	0,44	12,395	25
22	Venous vasculopathy	5	0,22	14,927	19
23	Systemic sclerosis	5	0,06	28,637	17
24	Chronic pancreatitis	5	0,05	25,327	22
25	Myasthenia gravis	5	0,03	18,299	27
26	Arterial vasculopathy	4	0,56	22,986	14
27	Type 2 diabetes mellitus, complicated	4	0,40	28,095	16
28	Addison's diseases	4	0,02	12,909	31
29	HIV positive and full-blown AIDS	3	0,30	54,036	20
30	Chronic hepatitis	1	0,94	18,217	26
31	Valvular cardiopathy	1	0,45	13,862	30
	Beneficiaries with at least one selected disease/condition	-	29,94	-	

(a) Disease/condition selected as independent predictor of 5-year mortality

(b) Weight calculated by multiplying by 10 the specific coefficient of the survival model and rounding it to the nearest whole number

(c) Ranking obtained by multiplying ranking of CReSc weight, ranking of prevalence rate and ranking of per-capita annual cost of each selected disease/condition

As expected, with respect to the other listed conditions, hypertension, type 2 diabetes and no arrhythmia-induced cardiomyopathy had higher prevalence rates, while dialytic treatment, HIV/AIDS, and acromegaly and gigantism had higher per-capita healthcare cost. By considering prognosis, prevalence and costs, in a unique proxy of disease burden, active neoplasia, heart failure and liver cirrhosis showed a higher impact in our setting.

Figure 10 shows that the worst clinical status expected for men and elderly with respect to women and young people was clearly caught through the CReSc, being the prevalence of NHS beneficiaries with at least a chronic disease contributing to the score progressively increased with age both in women (from 6.6% to 74.6%) and even more in men (from 7.7% to 79.1%).

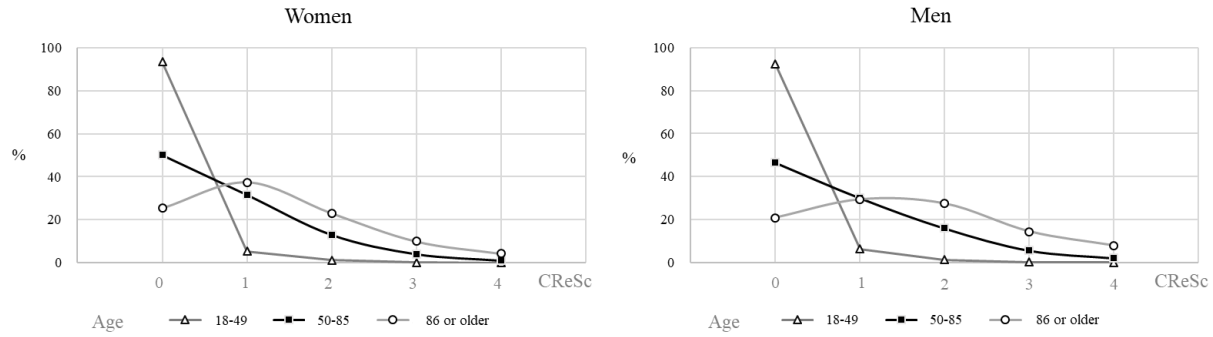


Figure 10. Chronic Related Score (CReSc) distribution among NHS beneficiaries of Lombardy, Italy, according to their gender and age category

CReSc performance

AUC of CReSc, MCS and CCI had values of 0.793, 0.761 and 0.623 respectively (**Figure 11**). It should be emphasized that, because the very large sample size, AUC and confidence limits practically coincided, so that confidence intervals were not reported.

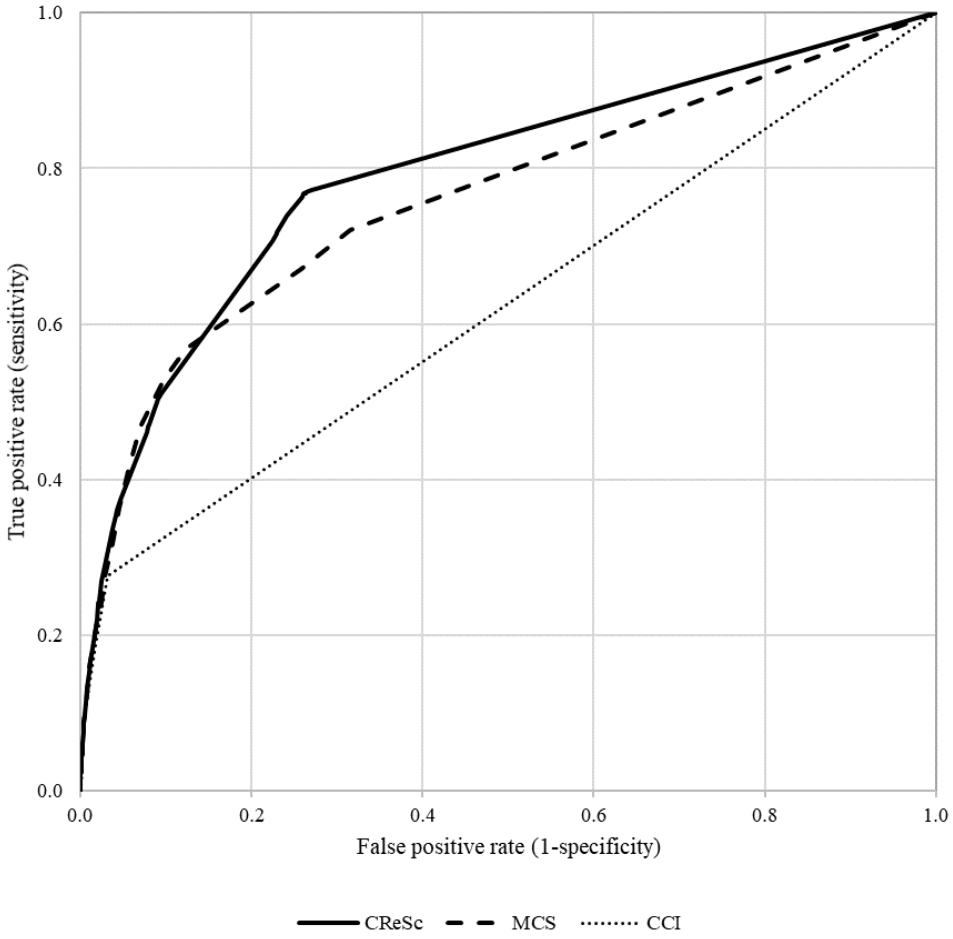


Figure 11. Receiver Operating Characteristics (ROC) curves comparing discriminant power of Chronic Related Score (CReSc), Multisource Comorbidity Score (MCS) and Charlson Comorbidity Index (CCI) in predicting five-year mortality among NHS beneficiaries of Lombardy, Italy

Figure 12 shows that our score had good performance among both women and men belonging to the intermediate age category (50 until 85 years) being the corresponding AUC 0.730 and 0.731. Conversely, among younger and even more among older beneficiaries, our score had a poor predictive ability (being the corresponding AUC 0.687 and 0.570 in women and 0.637 and 0.627

in men). For this reason, further analyses were performed by excluding NHS beneficiaries younger than 50 years and those older than 85 years.

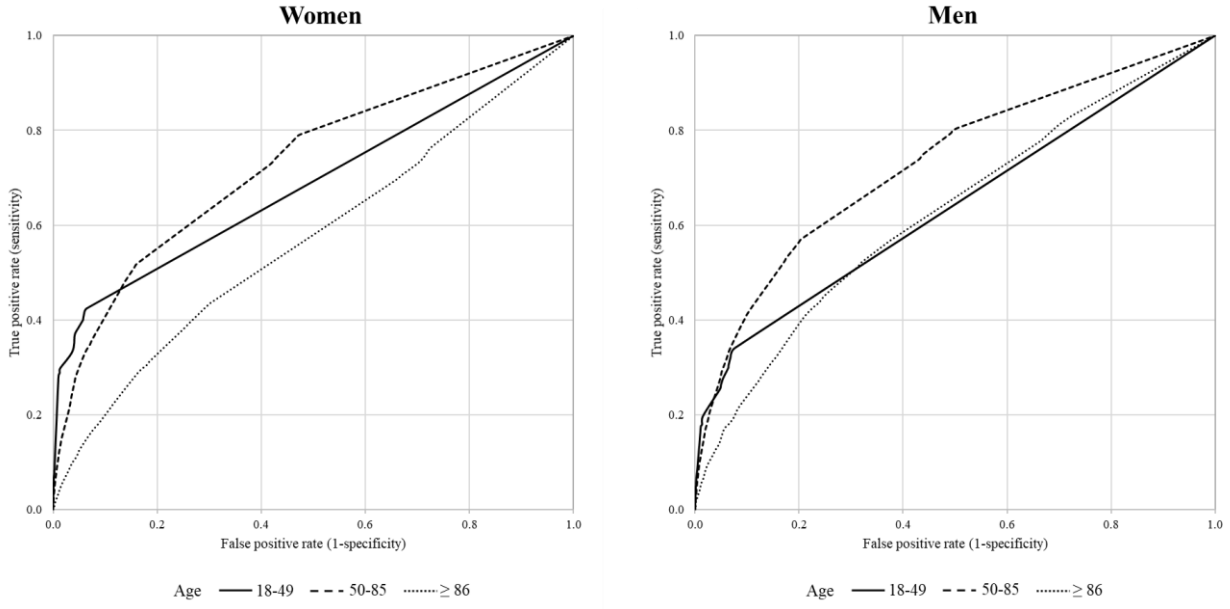


Figure 12. Receiver Operating Characteristics (ROC) curves comparing discriminant power of Chronic Related Score (CReSc) according to age strata and gender in predicting five-year mortality among NHS beneficiaries of Lombardy, Italy

Performance analyses using NRI showed that CReSc significantly improved the net five-year mortality reclassification. In particular, CReSc improved MCS classification of 44% (95% CI 43% to 45%) both in men and in women. Of interest, the improvement mainly concerned sensitivity (25%) than specificity (18%). As expected, CReSc even more improved the classification of CCI, being the corresponding NRI 50% (49% to 51%) and 52% (51% to 53%) in men and women respectively.

Figure 13 shows that there was a good agreement between the observed and the predicted survival probabilities, with values of the calibration-in-the-large close to the ideal value of 0 (-0.03) and

values of the recalibration slopes close to the ideal value of 1 (1.03). Adequate goodness of fit was also confirmed by the modified Hosmer-Lemeshow test, according to which the null hypothesis of agreement between observed and predicted frequencies could not be rejected either in women or in men.

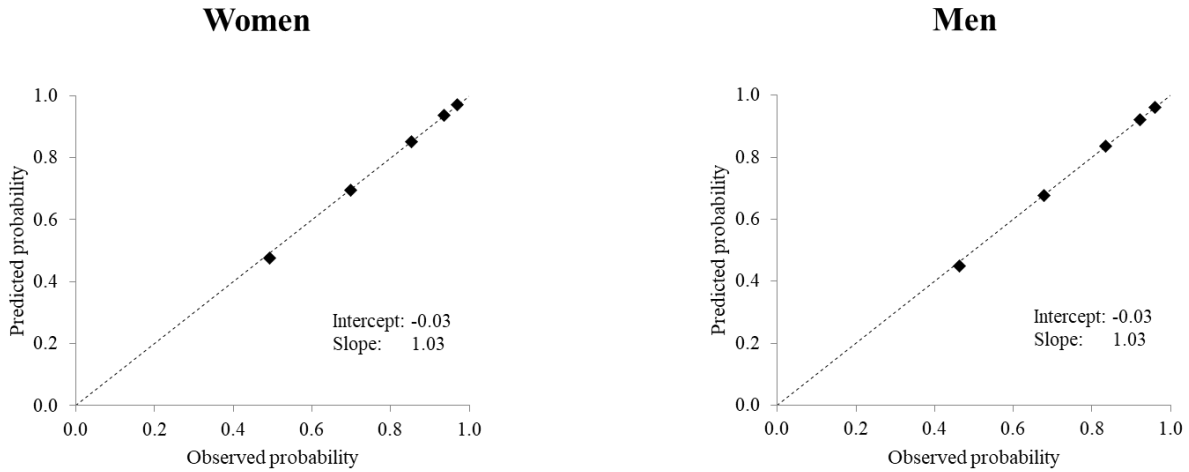


Figure 13. Calibration plots comparing observed and predicted five-year survival probabilities of the Chronic Related Score (CReSc) according to gender of NHS beneficiaries of Lombardy, Italy

CReSc predictability

A clear positive trend towards increasing rates of all the considered outcomes as CReSc increases was observed (**Figure 14**). In particular, with respect to NHS beneficiaries with the lowest score (CReSc=0), those on the highest score (CReSc=4) had one-year risk of death, five-year risk of death, five-year healthcare costs, rate of hospital admissions, and rate of cumulative hospital stay respectively 36-fold (from 0.43% to 15.5%), 15-fold (from 3.43% to 52.6.21%), 6-fold (from 4,236 € to 26,882 €), 9-fold (from 113 to 761 hospital admissions every 1,000 PY) and 7-fold (from 849 to 8,839 days of stay every 1,000 PY) higher.

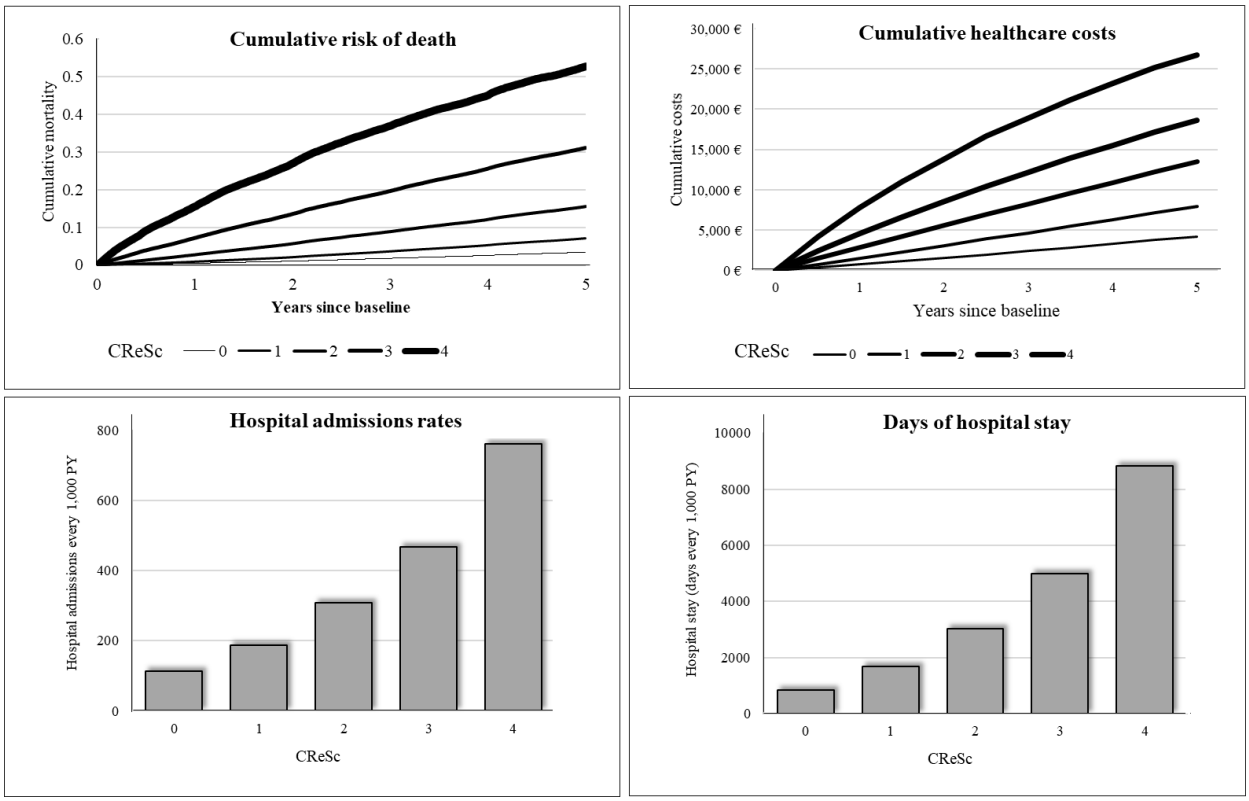


Figure 14. Five-year cumulative mortality and healthcare costs, and rates of hospital admission and days of hospital stay, according to the Chronic Related Score (CReSc) distribution among NHS beneficiaries of Lombardy, Italy

CReSc and income relationship

AUC for NHS beneficiaries with low-, intermediate- and high-income had values of 0.726, 0.723 and 0.727 respectively (**Figure 15**, left box). Starting from the age category of 61-65 years, a trend towards ameliorating CReSc profile with income category augmenting was observed both in women and in men (**Figure 15**, right boxes). Compared with individuals on low-intermediate income, NHS beneficiaries on the highest income always showed better CReSc profile irrespectively from age and gender.

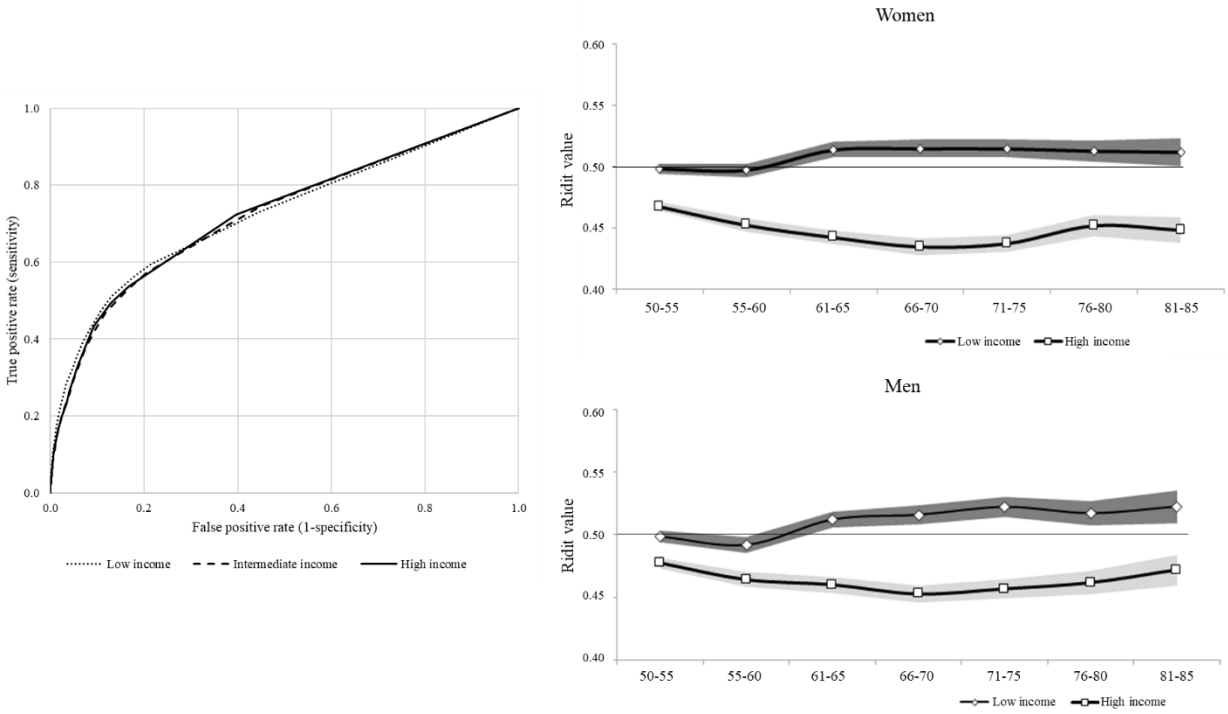


Figure 15. Receiver Operating Characteristics (ROC) curves comparing discriminant power of Chronic Related Score (CReSc) in predicting five-year mortality according to income category (left box) and age specific values of mean ridit values of the CReSc distributions in women and men according to their income category, with corresponding 95% confidence intervals (right boxes)

Discussion

This study shows that a score based on healthcare utilization data currently used for managing NHS from Italian Lombardy health authority is able to stratify NHS beneficiaries according to their short-term (one-year) and long-term (five-year) outcomes such as mortality, healthcare costs and hospital admissions. This new score significantly improved discriminatory power and net reclassification of the Charlson Comorbidity Index (CCI), undoubtedly the most worldwide used comorbidity score [26]. In addition, because our score used much more information than the Multisource Comorbidity Score (MCS), CReSc outperformed the previous population-based comorbidity score validated by means of Italian HCU databases in which only data on inpatient diagnoses and outpatient drug prescriptions were used [70]. Compared with MCS, and even more CCI, CReSc showed better ability to identify NHS beneficiaries at higher risk (so allowing better identification of patients who need medical care), and even more to exclude those at low risk of experiencing adverse outcomes. It follows that CReSc may be useful to epidemiologists, clinicians and policy-makers who now have a tool for risk adjustment, management and stratification characterized by improved performances with respect to the available scores.

This study provides the following additional results. One, among the 31 conditions considered, Alzheimer's disease, dementia and heart failure most contributed to the total aggregate score. Of interest, our data confirmed that in our setting most persons live with hypertension and/or type 2 diabetes (roughly one in five NHS beneficiaries live with one or both the conditions), and that dialytic treatment and positivity to HIV and full-blown AIDS had high financial burden (being healthcare costs associated with these conditions 140,000 € and 54,000 € respectively). By including prognostic weight, prevalence and costs in a unique proxy of disease burden, active neoplasia, heart failure and liver cirrhosis showed a higher impact in our population.

Two, CReSc showed good performance in predicting 5-years mortality among men and women aged between 50 and 85 years, while it failed in NHS beneficiaries younger than 50 years and in those older than 85 years. It is not surprising that the few individuals aged 50 years or younger who suffered from chronic diseases mainly experienced death in later life, so the model had poor performance in this age group [94]. On the other hand, the almost total absence of prognostic score specifically developed to predict mortality and other outcomes in elderly people is even not surprising [95], given that almost all people aged 85 or over suffer from chronic diseases.

Three, consistently with the reported socio-economic health inequality [96], even observed in countries with universal access to essential health care services such as Italy [97], worse CReSc among NHS beneficiaries who have the lowest income were observed. As low healthcare accessibility is expected among the most disadvantaged social class, it may be speculated CReSc worse capture health needs among beneficiaries with low socio-economic status. However, impressive stability of CReSc in predicting mortality regardless of the income was found. This suggests that, at least among NHS beneficiaries of intermediate age, our score reflects comorbidities of the population covered by the NHS, rather than the accessibility to healthcare services. By accepting this hypothesis, the observed worse health status associated with low and low-to mild income may aid the identification of vulnerable subgroups who may benefit from tailored health education and management [98].

The present study has several strengths. First, because in Italy a public funded healthcare system involves virtually all citizens, our sample included all the NHS beneficiaries so resulting for an unselected population (i.e., ours is a population-based investigation) and very large sample size. Second, CReSc was validated and tested on a random sample of almost 3 million of NHS beneficiaries, a sample so large that random uncertainty slightly affected our estimates. Third, the selection of comorbidities based on the opinion of experts [52] and prevalence data [54] was

avoided. Finally, as the selected diseases were detected through the use of health services, our data overcome the artificial positive socioeconomic inequalities in chronic disease prevalence when using self-reports [99].

Potential limitations must take into account for interpreting or findings. First, our scoring system did not capture health services supplied by private providers. However, due to the universal coverage for essential healthcare, it is unlikely that diseases strongly affecting mortality may escape from the Italian NHS. Second, misdiagnosis (often due to poor accuracy in reporting diagnoses and comorbidities [59]) and upcoding (sometimes in pursuit of higher reimbursements [60]) in hospital records might have generated too conservative estimates of CReSc performance. However, because diagnostic errors alike affect the compared diagnosis-based comorbidity scores, this issue does not question our main result that CReSc had better performance than both CCI and MCS. Third, since the included outcomes can be considered proxies of the quality of care (that is unsuccessful discharge processes or inadequate social care [61] influence mortality and hospital readmissions), this new scoring system might not be generalizable to other settings of Italy. Fourth, Lombardy has a long tradition in the management of several healthcare databases. However, data on outpatient services (including visits and diagnostic tests respectively performed in specialist ambulatories and laboratories accredited by the NHS), payment exemptions, drugs directly administered in the inpatient setting, and emergency room visits, are not yet available in several Italian regions. Fifth, generalizability may be also limited by the split approach used in our study since randomly splitting the whole dataset into a training and a validation set raised concerns from some authors [100]. External validations in other settings (e.g., other Italian regions, countries outside Italy, and different calendar times) should be carried out for ensuring external validity of CReSc. Finally, CReSc may not apply to every relevant outcome and cannot really predict the individual conditions in increasing patients' relative risk of death. For example, this score cannot take into account (i) conditions that do not affect five-year mortality, if nor marginally (e.g., type

1 and type 2 diabetes), (ii) NHS beneficiaries suffering a given condition who did not leave 'footprints' of routine medical care able to detect that condition (e.g., untreated hypertension), or who mostly escape capture with administrative data (e.g., chronic obstructive pulmonary disease), and (iii) patients who did not survive at least two years after the onset of an acute condition (e.g., fatal myocardial infarction).

In summary, a prognostic score derived from data usually used for health system management of Lombardy and useful for predicting short-term and long-term mortality, hospitalization and health costs of each individual NHS beneficiary was developed and validated. CReSc can represent a useful tool for epidemiologists (who need an instrument for risk adjustment in clinical and epidemiological studies), clinicians (who need detecting and managing frail patients in everyday medical practice), and policy-makers (who need assessing health system performance and health policy planning). In particular, clinically and operationally important effects are expected with the introduction of the CReSc risk stratification tool, jointly of monetary incentive for services agreeing with proactive management of high-risk patients.

The care pathways in clinical practice

Several terms are used in literature to refer to *care pathway*, including “clinical pathway”, “integrated care pathway” and “care map”. Care pathway can be defined as a structured multidisciplinary care plan, with a detailed sequence of actions, of patients with a specific clinical problem. The aims of their application are (i) to translate the guidelines or evidence into local structures and clinical practice, (ii) to standardize the care (i.e., reduce variation), (iii) to improve quality of care and (iv) to maximize the outcomes, for a specific clinical problem [101].

A cross-sectional survey published in 2006 and carried out in 23 countries on care pathways highlighted their main use in acute hospitals [102]. At the time of the investigation, clinical pathways were viewed as a multidisciplinary tool to improve the quality and efficiency of evidence-based care. A few years later, a review of twenty-seven studies evaluated the effect of clinical pathways on professional practice, patient outcomes, length of stay and hospital costs [103]. These studies showed a reduction in in-hospital complications, length of stay and hospital costs, whereas there was no evidence of differences in readmission to hospital or in-hospital mortality.

Although clinical pathways have been widely applied in different settings of hospitals (e.g., emergency, elective surgery, and pre-post-surgery) [104], the use of these tools is growing in outpatient care. Studies aiming at monitoring the quality of care of patients suffering from chronic diseases in the clinical practice has been carried out in several fields, e.g., respiratory disease[8], cardiological disease [105] and among those patients suffering from multiple diseases [106].

In this section of the thesis, a description of the working group established at the Ministry of Health whose aim is to monitor and assess care pathways for specific care problems is given. In particular, the following chapters deal with the following issues: (i) which indicators could be used to assess the quality of care? (ii) how to measure these indicators? (iii) does a better process profile, as measured

by these indicators, translate into better outcomes? (iv) what are the costs associated with these pathways? (v) how standardize the calculation of the indicators with the aim to compare them between regions?

“Monitoring and assessing care pathways” working group (Italian Ministry of Health)

According to the Agreement between the Government, Regions and Autonomous Provinces of Trento and Bolzano, the Ministry of Health should carry out a system to assess the quality of health care and its homogeneity among the entire country, with the aim to monitor the effectiveness and efficiency of services. This system ought to also monitor and assess the diagnostic-therapeutic paths for specific conditions and health needs using the HCU databases stored in each region.

With these premises, a working group of the Ministry of Health was established with the following purposes:

1. developing a system of indicators for assessing care pathways across different levels in order to identify the best strategy according to effectiveness, cost-effectiveness and economic sustainability;
2. developing a research platform containing HCU data able to compute the above-mentioned indicators and to generate evidence useful for the decision-making process.

The methodology used to develop the system of indicators is suitable for:

- identifying the patients who suffer from the conditions of interest (i.e., prevalent patients);
- identifying the newly taken in-care patients who suffer from the conditions of interest (i.e., incident patients);
- evaluating the complete care pathway experienced by patients and defining suitable measures of it;
- defining the outcomes of interest and some indicators of them;
- estimating the economic burden of care pathways;
- assessing the effectiveness and efficiency of care pathways.

The working group began its activity starting from some clinical conditions characterized by a high impact on health care: diabetes, heart failure, chronic obstructive pulmonary disease, breast, colon or rectum cancer. The following table shows the proposed process indicators for each condition.

Condition	Process indicators
Diabetes	• The proportion of patients who had at least two glycated haemoglobin evaluations every year • The proportion of patients who had at least one lipid profile evaluation every year • The proportion of patients who had at least one urine albumin excretion evaluation every year • The proportion of patients who had at least one serum creatinine evaluation every year • The proportion of patients who had at least one dilated eye exam every year
Heart failure	• The proportion of patients adherent to pharmacological treatment with ACE inhibitors • The proportion of patients adherent to pharmacological treatment with beta-blockers • The proportion of patients who had at least one echocardiogram every year
Chronic obstructive pulmonary disease	• The proportion of patients adherent to pharmacological treatment with long-acting bronchodilators

	• The proportion of patients having at least one respiratory visit every year
Breast cancer	• The proportion of patients in which the surgery is timeliness • The proportion of patients in which the medical therapy is timeliness • The proportion of patients who started the complementary radiotherapy within twelve months from the surgery • The proportion of patients who had at least one mammography within eighteen months from the surgery
Colon cancer	• The proportion of patients in which the surgery is timeliness • The proportion of patients who had at least one endoscopy within eighteen months from the surgery
Rectum cancer	• The proportion of patients in which the first treatment is timeliness • The proportion of patients who had at least one endoscopy within eighteen months from the surgery

In addition, evaluations on selected mental disorders, myocardial infarction, stroke and pregnancy are under review.

As far as the diabetes is concerned, (i) the methods and main findings of the validation study, (ii) the assessing of the care pathway in a specific population (i.e., pregnant women with pre-existing diabetes) and (iii) the economic impact of the care, are reported in the following chapters.

The diagnostic-therapeutic path of diabetes [4]

Introduction

Evidence exists that microvascular and cardiovascular complications may be appreciably reduced in patients with type 2 diabetes when multifactorial, intensive lifestyle modifications are implemented [107]. Accordingly, evidence-based clinical practice guidelines have been published [108], with specific recommendations for managing patients with type 2 diabetes. Nevertheless, studies investigating the success of guidelines on the management of diabetes have shown that treatment goals are often not met in 'real-life' practice, and implementation of strategies preventing the onset of complications in patients with type 2 diabetes remains suboptimal [109].

Several initiatives have been implemented for monitoring the quality of care for patients with diabetes in 'real-life' practice, while controlling costs [110]. The Diabetes Quality Improvement Project (DQIP), which was designed to influence the care of patients with diabetes from United States [111], developed a set of indicators for monitoring care quality. Among these, the so-called accountability indicators consisting in verifying the percentage of diabetic patients who regularly receive clinical evaluations (e.g., glycaemic and lipid profiles, kidney functioning and dilated eye exams) are focused to compare health systems and plans or providers [112]. Although improvements in the process of diabetes care have been documented though these indicators, their effectiveness is largely untested [113], making evaluation essential.

Taking inspiration by the above-mentioned DQIP accountability indicators, a working group of the Italian Health Ministry developed a set of process indicators for quality of diabetes care. Because a better process profile, as measured by these indicators, not necessarily translate into better outcomes,

[4] Results reported in this chapter have been published in Corrao G, Rea F, Di Martino M, Lallo A, Davoli M, De Palma R, Belotti L, Merlino L, Pisanti P, Lispi L, Skrami E, Carle F; working group 'Monitoring and assessing diagnostic-therapeutic paths' of the Italian Heath Ministry. Effectiveness of adherence to recommended clinical examinations of diabetic patients in preventing diabetes-related hospitalizations. Int J Qual Health Care. 2019;31:464-472. doi: 10.1093/intqhc/mzy186

a study for validating the set of indicators through their relationship with measurable clinical outcomes was designed.

Methods

Data sources

This study is based on HCU databases from three Italian regions (Lombardy, Emilia-Romagna and Lazio). Overall, these data covered almost 20 million beneficiaries of the Italian NHS, nearly one third of the entire Italian population.

Harmonization and data processing

Although databases did not substantially differ across all regions for several aspects, a between regions data harmonization was performed, thus allowing data extraction processes to be targeted the same semantic concepts (e.g., information were uniformly encoded by using the same names, values and formats). Anonymized data were extracted and processed locally by using a common SAS program according to protocol previously approved by the Italian Health Ministry working group.

Capturing "prevalent" and "incident" diabetic patients

Beneficiaries of the NHS who in the index year (i.e., in 2014) had aged 18 years or older and were resident in three Italian regions (Lombardy, Emilia-Romagna and Lazio) formed target population. With the aim of ensuring enough time back for capturing diabetic patients, subjects were excluded if they were recorded as beneficiaries of the regional NHS after the year 2011.

Subjects belonging to the target population were considered prevalent diabetic patients if they left 'footprints' of diabetes through supplied services from the NHS within a specified time-window. In particular, NHS beneficiaries who (i) from 2012 until 2014 had at least two prescriptions of antidiabetic agents in two distinct dates over 365 days, and/or (ii) in the same time-window experienced at least one hospital admission with primary or secondary diagnosis of diabetes, and/or (iii) in the year 2014 took advantage on co-payment exemption for diabetes, were considered to be affected by diabetes (i.e., prevalent cases). Among these latter, those who during the period 2011 until

2013 did not experience any specific drug prescription, hospital admission, and co-payment exemption were considered newly taken in care for diabetes (i.e., incident cases).

Diabetes prevalence and incidence rates were separately calculated for each participant region and for the whole population of all the regions taken together. Rates were standardised (direct method) according to gender and twenty-year intervals of age of the Italian population. Between-region differences in prevalence and incidence rates were evaluated by testing the null hypothesis of homogeneity.

Incident cohort features and follow-up

In order to have enough time to appreciate the effect of adherence to recommendations on the selected outcomes (see below), subjects who were detected as incident diabetic patients during 2010 were included in the study cohort: in other words, the clock was brought back four years with respect to the above reported time interval used for detecting incident diabetic patients.

Baseline characteristics of cohort members (i.e., those recorded at the date of cohort entry or during the previous three years) included gender, age, drug therapies and comorbidities. Drug therapies included antiplatelet, digitalis glycosides, organic nitrates, antiarrhythmics, blood pressure- and lipid-lowering agents, antidepressants, non-steroidal anti-inflammatory drugs, anti-gout agents and drugs for chronic obstructive pulmonary disease. Comorbidities were measured through previous hospitalizations for cancer, heart failure, and ischaemic heart, cerebrovascular, respiratory and kidney disease. In addition, the so-called MCS was considered [70].

Cohort members accumulated person-years of follow-up starting from the date of cohort entry until the occurrence of one of the following events, whichever came first: the study outcome (hospital admission for selected diagnoses, see below), death, emigration, or end-point of follow-up, i.e., December 31, 2015.

Adherence to recommendations

Outpatient visits, including assessments of glycated haemoglobin, lipid profile (total and HDL cholesterol and triglycerides), urine albumin excretion, serum creatinine and dilated eye exams dispensed to cohort members during follow-up were identified. A patient was considered adherent to recommendations whether he/she every year was submitted to at least two glycated haemoglobin assays, and at least one of the other evaluations [114].

Other than for each individual recommendation, the cumulative number of recommendations was calculated. A score of increasing adherence was developed by categorizing each cohort member according whether almost none (0 or 1), just some (2 or 3) or almost all (4 or 5) recommendations were followed in a given year.

Outcome

A composite outcome was developed to take into account complications of diabetes potentially avoidable. A cohort member was considered to experience the outcome whether during follow-up at least one hospital admission occurred with primary or secondary diagnosis, or correlated procedures, of: (i) brief-term diabetes complications, (ii) uncontrolled diabetes, (iii) long-term vascular outcomes, and (iv) no traumatic lower limb amputation. The date of first hospitalization with one of these diagnoses was considered as the date of outcome onset.

Association between adherence and outcome

The following two-stage procedure for generating pooled meta-analytic estimates of adherence-outcome association were used.

In the first stage, a Cox proportional hazard regression model was fitted within each participant region for separately estimating the hazard ratio (HR) and its 95% confidence interval (CI), for the association between adherence to each recommendation taken individually, as well as to the total adherence score, and the risk of experiencing the outcome. Adjustments were made for above listed covariates (i.e. gender, age, drug therapies, comorbidities and Multisource Comorbidity Score). A

time-dependent covariate was built by considering the adherence to recommendations experienced during the one-year period before each risk set forms itself up, i.e., by the patient who experience the outcome at a given moment of the follow-up (case) and the cohort members who until then have not experienced it, having accumulated the same observation period of the case. In this way, the brief-term effect of adherence on the outcome onset (close adherence) was investigated. However, as more careful and frequent evaluations might be requested because of worsening clinical profile, a paradoxical positive adherence–outcome association might be observed by considering adherence so close to the outcome. To account for such a bias, which can be considered a form of protopathic bias [115], a time-dependent adherence delayed of one year with respect to the close adherence was also considered (delayed adherence).

In order of obtaining the summarized adherence-outcome relationship estimate, in the second stage a random effect meta-analysis [116] was performed for combining the HRs obtained from the considered regions. Between-region heterogeneity was tested by Cochran's Q test and measured with the I^2 statistics that is the proportion of between-region variability due to heterogeneity [117].

For all hypotheses tested, 2-tailed p-values less than 0.05 or, in an equivalent manner, 95% CI of HR that does not contain the value expected under the null hypothesis was considered significant.

Results

Prevalent and incidence diabetic patients

Table 7 shows that, among the nearly 16 million NHS beneficiaries forming the whole target population, 1,139,043 and 76,490 subjects respectively met our algorithm for capturing prevalent and incident diabetic patients in the year 2014, being the corresponding standardised rates 6.7 diabetic patients every 100 persons and 4.5 new diabetic patients every 1,000 person-year. There was evidence that prevalence and incidence standardised rates significantly differed between regions, being higher rates observed for the population from Lazio.

Table 7. Diabetes prevalence (patients who in the index year and/or in the previous 2 years left 'footprints' of disease presence) and incidence (newly taken in care patients) among beneficiaries of the National Health Service (NHS) of three Italian regions

	Lombardy	Emilia-Romagna	Lazio	Total
NHS beneficiaries aged 18 years or older [a]	8,277,623	3,734,707	4,902,165	16,914,495
All known diabetic patients (prevalent) [b]	516,547	256,670	365,826	1,139,043
Prevalence rate (every 100 persons)				
Crude	6.2	6.9	7.5	6.7
Standardized	6.2	6.6	7.7	6.7
Newly taken in care diabetic patents (incident) [c]	37,462	15,904	23,124	76,490
Incidence rate (every 1,000 PY)				
Crude	4.5	4.3	4.7	4.5
Standardized	4.4	4.1	4.8	4.5

Baseline characteristics of the cohort of 77,285 patients newly taken in care during 2010 are shown in **Table 8**. At baseline, more than one half of cohort members were men, almost one third of them were aged 70 years or older, most patients had signs of cardiovascular disorders, mainly because they were in treatment with blood pressure- and lipid-lowering medicaments or previous ischaemic heart or cerebrovascular disease or heart failure. Although beneficiaries from Lazio showed lower values of the Multisource Comorbidity Score, they had higher prevalence of drug users.

Table 8. Baseline characteristics of diabetic patients newly taken in care (incident cases) in three Italian regions

	Lombardy	Emilia-Romagna	Lazio	Total
Male gender	18,987 (54.5%)	9,225 (53.4%)	12,353 (49.1%)	40,565 (52.5%)
Age (years)				
18-30	547 (1.6%)	314 (1.8%)	760 (3.0%)	1,621 (2.1%)
31-50	5,472 (15.7%)	2,778 (16.1%)	4,313 (17.2%)	12,563 (16.3%)
51-70	17,759 (50.9%)	7,654 (44.3%)	12,063 (48.0%)	37,476 (48.5%)
70-90	10,624 (30.5%)	6,210 (36.0%)	7,755 (30.8%)	24,589 (31.8%)
>90	460 (1.3%)	317 (1.8%)	259 (1.0%)	1,036 (1.3%)
Medications [a]				
Antiplatelet	10,005 (28.7%)	4,386 (25.4%)	8,297 (33.0%)	22,688 (29.4%)
Digitalis glycosides	1,265 (3.6%)	453 (2.6%)	1,052 (4.2%)	2,770 (3.6%)
Organic nitrates	2,267 (6.5%)	653 (3.8%)	1,641 (6.5%)	4,561 (5.9%)
Antiarrhythmics	1,099 (3.2%)	272 (1.6%)	856 (3.4%)	2,227 (2.9%)
Blood-pressure lowering agents	20,651 (59.2%)	7,837 (45.4%)	16,072 (63.9%)	44,560 (57.7%)
Lipid lowering agents	7,113 (20.4%)	3,490 (20.2%)	7,730 (30.7%)	18,333 (23.7%)
Antidepressants	3,456 (9.9%)	1,889 (10.9%)	3,089 (12.3%)	8,434 (10.9%)
NSAIDs	10,417 (29.9%)	4,295 (24.9%)	12,870 (51.2%)	27,582 (35.7%)
Anti-gout drugs	2,457 (7.1%)	1,147 (6.6%)	1,761 (7.0%)	5,365 (6.9%)
Drugs for COPD	4,254 (12.2%)	2,057 (11.9%)	5,310 (21.1%)	11,621 (15.0%)
Comorbidities [b]				
Cancer	3,474 (10.0%)	1,801 (10.4%)	2,258 (9.0%)	7,533 (9.7%)
Ischemic heart disease	2,788 (8.0%)	1,426 (8.3%)	1,625 (6.5%)	5,839 (7.6%)
Cerebrovascular disease	1,984 (5.7%)	1,138 (6.6%)	1,313 (5.2%)	4,435 (5.7%)
Heart failure	1,551 (4.5%)	1,063 (6.2%)	933 (3.7%)	3,547 (4.6%)
Respiratory disease	3,195 (9.2%)	1,888 (10.9%)	1,997 (7.9%)	7,080 (9.2%)
Kidney disease	938 (2.7%)	601 (3.5%)	574 (2.3%)	2,113 (2.7%)
Multisource comorbidity score				
0	21,859 (62.7%)	10,022 (58.0%)	12,783 (50.8%)	44,664 (57.8%)
1	5,933 (17.0%)	3,476 (20.1%)	6,683 (26.6%)	16,092 (20.8%)
2	3,630 (10.4%)	1,926 (11.2%)	3,176 (12.6%)	8,732 (11.3%)
3	1,367 (3.9%)	758 (4.4%)	1,230 (4.9%)	3,355 (4.3%)
4	2,073 (6.0%)	1,091 (6.3%)	1,278 (5.1%)	4,442 (5.8%)

NSAIDs: Non-steroidal anti-inflammatory drugs; COPD: chronic obstructive pulmonary disease

Adherence to recommendations

During the first year after diagnosis, newly taken in care patients (incident cases) had poor adherence to the considered recommendations, being only 16% of them submitted to dilated eye exam, little bit more than 30% to glycated haemoglobin and urine albumin excretion evaluations, and more than half to lipid profile and serum creatinine assays (**Table 9**). It is noteworthy that 20% and 44% of newly taken in care diabetic patients respectively adhered to almost all (4 or 5) or almost none (0 or 1) recommendations. Again, there was evidence that patients from Lazio were less adherent than those from Lombardy and Emilia-Romagna ($p < 0.001$).

Table 9. Diabetic patients newly taken in care (incident cases) who during the first year after diagnosis adhered to selected recommendations in three Italian regions

	Lombardy	Emilia-Romagna	Lazio	Total
Individual recommendations				
Glycated haemoglobin	13,881 (39.8%)	6,349 (36.8%)	5,997 (23.8%)	26,227 (33.9%)
Lipid profile	19,297 (55.4%)	9,365 (54.2%)	11,575 (46.0%)	40,237 (52.1%)
Urine albumin excretion	11,976 (34.4%)	6,565 (38.0%)	4,841 (19.3%)	23,382 (30.3%)
Serum creatinine	21,176 (60.7%)	11,000 (63.7%)	14,314 (56.9%)	46,490 (60.2%)
Dilated eye exam	4,204 (12.1%)	3,888 (22.5%)	3,936 (15.7%)	12,028 (15.6%)
Categories of cumulative number of recommendations				
0 or 1	14,015 (40.2%)	6,702 (38.8%)	13,249 (52.7%)	33,966 (44.0%)
2 or 3	13,350 (38.3%)	6,108 (35.4%)	8,309 (33.0%)	27,767 (35.9%)
4 or 5	7,497 (21.5%)	4,463 (25.8%)	3,592 (14.3%)	15,552 (20.1%)

Women, patients aged 70 years or older and those with more cotreatments and comorbidities were on average less adherent to recommendations (**Table 10**).

Table 10. Baseline characteristics of diabetic patients according to cumulative number of recommendations

	Cumulative number of recommendations			
	None or almost none (0 or 1) (n=33,966)	Just some (2 or 3) (n=27,767)	All or almost all (4 or 5) (n=15,552)	p-trend [c]
Male gender	17,313 (51.0%)	14,583 (52.5%)	8,669 (55.7%)	<0.001
Age (years)				
≤70	21,650 (63.7%)	18,492 (66.6%)	11,518 (74.1%)	<0.001
>70	12,316 (36.3%)	9,275 (33.7%)	2,447 (25.9%)	
Medications [a]				
Antiplatelet	9,973 (29.4%)	8,553 (30.8%)	4,162 (26.8%)	<0.001
Digitalis glycosides	1,502 (4.4%)	904 (3.3%)	364 (2.3%)	<0.001
Organic nitrates	2,253 (6.6%)	1,636 (5.9%)	672 (4.3%)	<0.001
Antiarrhythmics	1,085 (3.2%)	817 (2.9%)	325 (2.1%)	<0.001
Blood-pressure lowering agents	19,197 (56.5%)	16,671 (60.0%)	8,692 (55.9%)	0.286
Lipid lowering agents	6,773 (19.9%)	7,588 (27.3%)	3,972 (25.5%)	<0.001
Antidepressants	3,839 (11.3%)	3,093 (11.1%)	1,502 (9.7%)	<0.001
NSAIDs	11,851 (34.9%)	10,385 (37.4%)	5,346 (34.4%)	0.512
Anti-gout drugs	2,228 (6.6%)	2,150 (7.7%)	987 (6.3%)	0.490
Drugs for COPD	5,397 (15.9%)	4,066 (14.6%)	2,158 (13.9%)	<0.001
Comorbidities [b]				
Cancer	4,136 (12.2%)	2,372 (8.5%)	1,025 (6.6%)	<0.001
Ischemic heart disease	2,875 (8.5%)	2,052 (7.4%)	912 (5.9%)	<0.001
Cerebrovascular disease	2,526 (7.4%)	1,401 (5.0%)	508 (3.3%)	<0.001
Heart failure	2,222 (6.5%)	1,011 (3.6%)	314 (2.0%)	<0.001
Respiratory disease	4,152 (12.2%)	2,065 (7.4%)	863 (5.5%)	<0.001
Kidney disease	1,202 (3.5%)	697 (2.5%)	214 (1.4%)	<0.001
Multisource comorbidity score				
0	17,927 (52.8%)	16,248 (58.5%)	10,489 (67.4%)	<0.001
≥1	16,039 (47.2%)	11,519 (41.5%)	5,063 (32.6%)	

NSAIDs: Non-steroidal anti-inflammatory drugs; COPD: chronic obstructive pulmonary disease

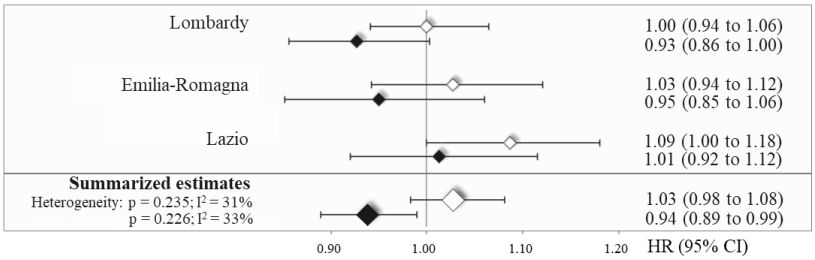
Outcome

During follow-up, cohort members accumulated 322,645 person-years and experienced 875 hospital admissions for brief-term diabetes complications (incidence rate, 2.4 cases every 1,000 person-years (PY)), 4,372 uncontrolled diabetes (12.0 every 1,000 PY), 18,319 long-term vascular outcomes (55.7 every 1,000 PY), and 262 no traumatic lower limb amputation (0.7 every 1,000 PY). The first occurring hospital admission for one of these causes (i.e., the composite outcome of interest) happened for 20,363 cohort members with incidence rate of 63.1 cases every 1,000 PY. The first cause of hospitalization for the composite outcome was long-term vascular outcomes (87%), following by uncontrolled diabetes (12%) and brief-term diabetes complications (1%). No patient experience no traumatic lower limb amputation as the first occurring hospital admission among those considered for building the composite outcome.

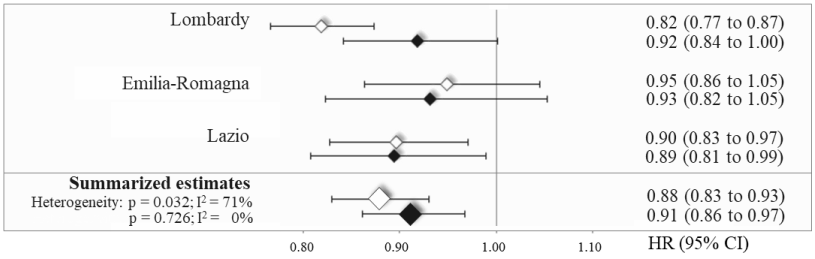
Association between adherence and outcome

Forrest plots for the adherence-outcome relationship for each participant region, as well as for summarizing national data, are shown in **Figure 16**. There was evidence than both close and delayed adherence to urine albumin excretion and lipid profile evaluations, exerted protective effect on the outcome occurrence. The protective action for glycated haemoglobin and serum creatinine was better highlighted by the delayed adherence than by the close one. For example, patients who adhered to serum creatinine during the one-year period before the outcome occurs, had a paradoxical 50% higher risk than those who did not adhere to it during the same time-window. Conversely, adherence to serum creatinine (as well as to glycated haemoglobin) delayed of one year, was significantly associated with reduced outcome risk. Although usually significant (with the exception of dilated eye exam), adherence to each individual recommendation was weakly associated with the outcome, being summarized risks of adherent diabetic patients reduced of around 10% or less with respect to no adherent ones. It is noteworthy that there was never evidence of between regions heterogeneity of the estimated delayed adherence-outcome associations.

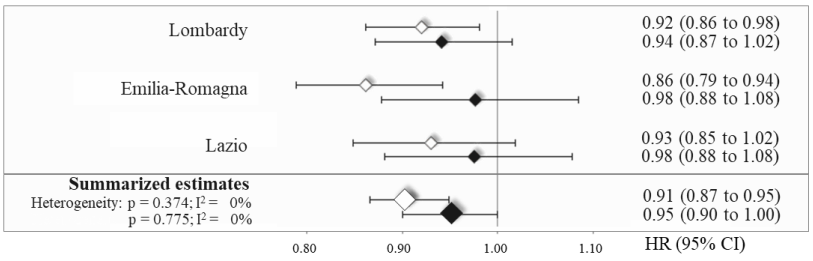
Glycated haemoglobin



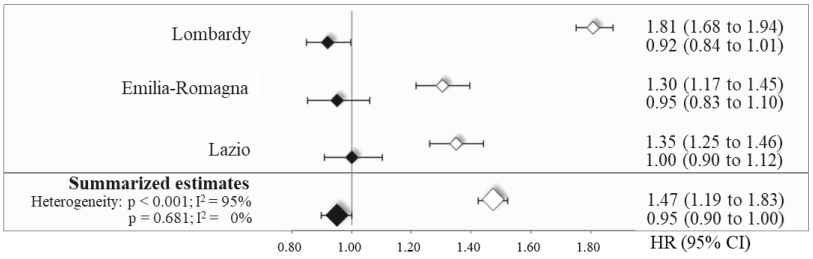
Lipid profile



Urine albumin excretion



Serum creatinine



Dilated eye exam

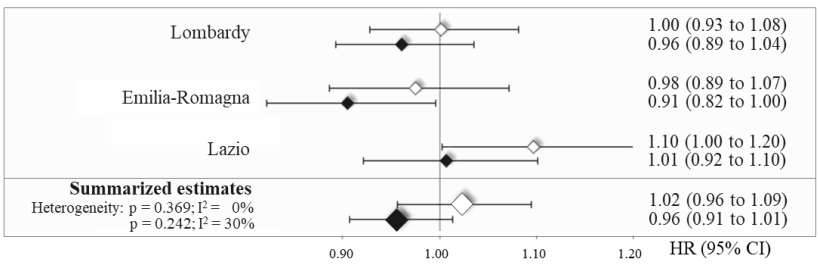


Figure 16. Forest plots of region-specific (smaller diamonds) and summarized (larger diamonds) hazard ratios (HR) for the association between time-dependent close (white diamonds) and delayed (black diamonds) adherence to selected recommendations, and the risk of hospital admission for selected causes, including brief-term diabetes complications, uncontrolled diabetes, long-term vascular outcomes, and no traumatic lower limb amputation

Figure 17 reports the trend in HRs according to increasing level of delayed adherence within each participant region, as well as for summarizing national data. A clear trend towards decreasing outcome risk as the total adherence score increases was observed for all regions, albeit with between-region differences. According to summarized estimates, compared to patients who adhered to none or almost none recommendation, significant risk reductions of 16% (95% CI, 6% to 24%) and 20% (7% to 28%) were observed for those who adhered to just some (2 or 3) and almost all (4 or 5) recommendations, respectively.

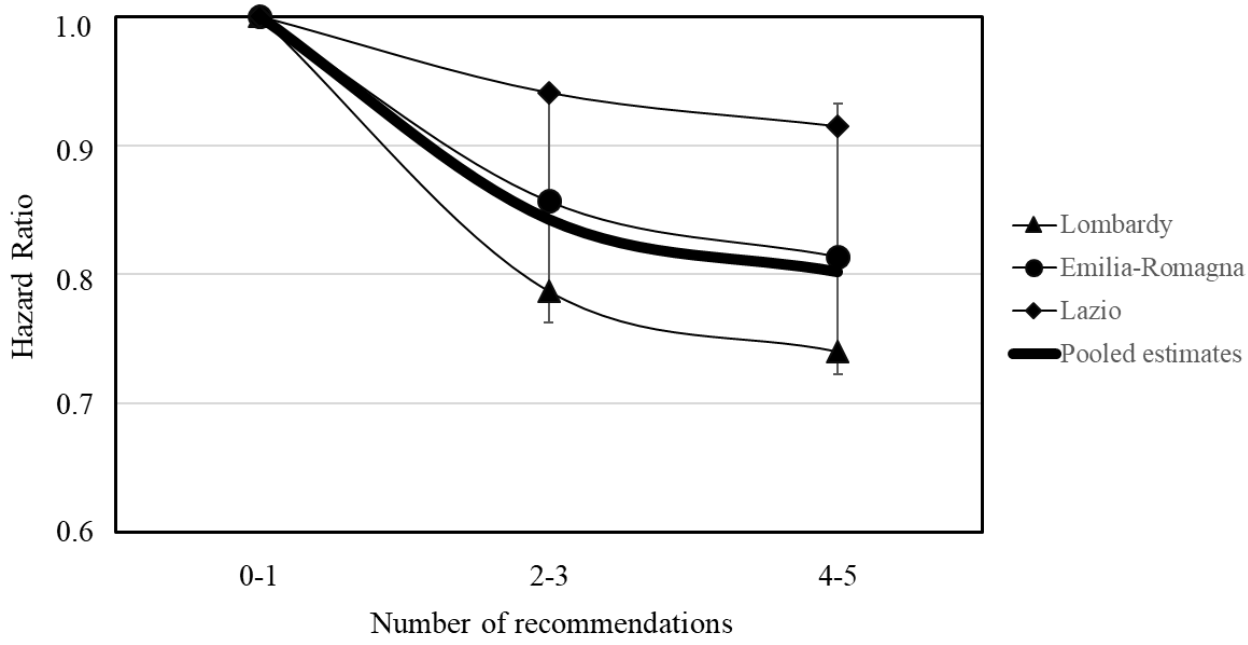


Figure 17. Trends in region-specific and summarized hazard ratios (HR) for the association between categories of total adherence to recommendations and the risk of hospital admission for selected causes, including brief-term diabetes complications, uncontrolled diabetes, long-term vascular outcomes, and no traumatic lower limb amputation

Discussion

The present study confirms previous observations that guidelines for the management of diabetes are often not met in the 'real-life' practice [112], even in the Italian setting [110]. In addition, evidence of regional variations in the management of diabetes within the same country [118] was confirmed from our study. The new important finding, however, is that diabetic patients who regularly received all or almost all the recommended clinical evaluations had a 20% reduction of the risk of hospitalization for selected outcomes compared to patients who received none, or almost none evaluation. Assuming that these estimates are unbiased, the proportion of complication of diabetes attributable to suboptimal adherence to recommendations was of 9.8%, i.e., nearly 1,990 of the 20,363 hospital admissions occurred among cohort members could have been avoided if all they had adhered to the considered recommendations [119]. This finding is very important for reaching a consensus in how to measure and compare the quality of care of diabetic patients, to develop process improvements, and to reduce practice heterogeneity [110].

This study was designed under the auspices of the Italian Health Ministry with the aim to obtain a simple tool for appreciating regional variations in the management of patients with diabetes. This implies the availability of good quality data useful for (i) capturing prevalent diabetic patients; (ii) identifying those who are newly taken in care; (iii) characterizing they as far as possible for their features; (iv) outlining their use of recommended clinical services; and (v) identifying those who experience relevant clinical outcomes. This was made possible because in Italy, an automated system of databases providing information on essential healthcare, including those for diabetes care, was available in each of the 19 regions for the management of the public funded healthcare system virtually involving all citizens. Because of constraints limiting the free movement of electronic health data even within the same country [120], a two-stage procedure allowing for local data processing and subsequent pooling aggregate data, was adopted. Admitting comparability in data quality, guarantees of privacy respect and estimates accuracy are provided by the procedure [121].

Existing figures pertaining to general adult population showed prevalence rates ranging from 6% (England) to 8% (USA) [122], and incidence rates ranging from 2 cases every 1,000 PY (Ireland) to 7 cases every 1,000 PY (USA) [123]. In this study, prevalence and incidence rates respectively being 7% and 5 cases of every 1,000 PY were found, i.e., within the expected range according to the worldwide figures.

Routine laboratory tests of glycosylated haemoglobin, lipid profile, serum creatinine and urinary albumin are recommended for patients with diabetes [114]. Consistently with other reports [124], some of which refer to the Italian setting [125], a wide gap between guidelines-driven recommendations and their clinical application was found. In fact, only 34% of the included incident diabetic patients controlled at least twice glycosylated haemoglobin, while only 20% of them adhered to all, or almost all, the recommended controls within the first year after they were taken in care. This finding is of particular concern given that (i) nearly one-fifth of participants had a history of major cardiovascular outcomes and three out five of them had comorbidities related to increasing mortality risk and (ii) patients on worse clinical profile, that is the older ones and those with more cotreatments and comorbidities, were less adherent to the recommendations.

Few and inconsistent evidence is available regarding the generally assumed relationship between adherence to recommendations and patient outcomes [126]. Inconsistency is likely due to serious difficulties inherent systematic uncertainty of observational evaluations. For example, in this application adherence to recommendations in a given year, particularly to serum creatinine and glycosylated haemoglobin evaluations, was found to be associated with increased risk of outcome. Protopathic bias might explain this paradoxical finding. In fact, the symptomatic onset of diabetic complications in the outpatient setting (unobserved true outcome) may have led to changing therapeutic regimen and then to increasing clinical evaluations for monitoring its effect. In these conditions, a paradoxical positive association between exposure and detected outcome (hospital admission) could be observed [115]. To address this possibility, a one-year delayed lag-time period

preceding the detected outcome was applied. As suspected, by this stratagem following the considered recommendations were found to exert a protective action on the outcome onset.

Rather than with each individual recommendation, the cumulative number of followed recommendations predicted the outcome onset, that is, the higher is its value, the better the protective action on diabetes related hospitalizations. Among the possible explanations for this finding, the more reasonable is that the speed of diabetes progression might be reduced by structured care of which regular control might be a proxy.

Limitations of the study should be taken into account for correctly interpreting our results. One, as individuals aged less than 18 years were excluded from the considered target population, patients affected by, and taken in care for type 2 diabetes mellitus should have been mainly captured. Nevertheless, it cannot be excluded that some patients with type 1 diabetes may have been included. This however, does not modify our main conclusion that diabetics, both type 1 and type 2, should benefit of more careful adherence to recommendations. Two, information about health service outpatient facilities supplied by private organizations are not available from our databases. Three, the length of follow-up might be insufficient to appreciate the effect of disease progression on clinical outcome. Four, adherence to pharmacological therapy (i.e. to antidiabetic agents) was not taken into account in our analysis. However, antidiabetic agents available in the Italian market at the time of our patients' follow-up have shown only modest beneficial effects on macrovascular complications [127], which are the main cause of hospital admission among those considered for building the composite outcome. In addition, not all diabetic patients need drug therapy since some of them achieve glycaemic control with diet and exercise alone. Finally, because patients with frequent controls are expected to have different clinical characteristics than those with less intensive examinations, our results could be affected by confounding by indication. That is, the reduction in diabetes-related hospitalization associated with better adherence to recommendations might have been generated by uncontrolled factors, accompanying but different from a better adherence. For example, less frequent

controls might had been requested for patients who reached good glycaemic target. However, as the latter are at lower baseline risk of experiencing the outcome, the protective action of regular controls is expected to be higher than that observed in our study. Of course, this does not entirely eliminate the problem of confounding, one aspect of which is that because adherence may be a surrogate for overall health-seeking behaviour, patients more adherent might also have more regularly followed healthy lifestyle advices, more effectively treated or dealt with diabetes more frequently as out- rather than in-hospital. Further evidence are thus urgently needed to confirm the protective role of adherence to recommendations among diabetic patients.

Conclusion

In the meantime, because benefits for patients and health care system are expected from improving adherence to guidelines-driven recommendations, tight control of diabetic patients through regular clinical examinations must to be considered the cornerstone of national guidance, national audits, and quality improvement incentives schemes.

Adherence to clinical recommendations in special populations: the case of pregnant women with pre-existing diabetes [5]

Introduction

Globally, the prevalence of hyperglycaemia in pregnancy in women aged 20–49 years is 17% [128]. In Italy, from 6% to 7% of women are affected by diabetes during pregnancy [129], making diabetes the most frequent gestational complication. Maternal diabetes is classified in pregestational diabetes mellitus (type 1 diabetes or type 2 diabetes already diagnosed before pregnancy), and gestational diabetes mellitus (high blood glucose level during pregnancy without signs of pre-existing diabetes). Although gestational diabetes mellitus is still the more common form of diabetes during pregnancy, both type 1 and type 2 diabetes are progressively increasing in women of childbearing age, and, consequently, among pregnant women.

Although evidence-based recommendations for managing diabetes during gestation are currently available [114] and several initiatives have been implemented for improving pregnancy preparation among women with type 1 and type 2 diabetes [130], pregnancies complicated by pre-existing diabetes still frequently generate adverse outcomes [131] such as spontaneous abortions, pregnancy complications, neonatal deaths and congenital malformations [132]. As such, improved care for women with pregestational diabetes mellitus presents a growing clinical challenge and priority during pregnancy [133]. Ideally, pregnancies should be carefully planned and optimal glycaemic control should be achieved prior to, during and after pregnancy among women with pregestational diabetes mellitus.

[5] Results reported in this chapter have been published in Cantarutti A, Rea F, Locatelli A, Merlino L, Lundin R, Perseghin G, Corrao G. Adherence to clinical evaluations in women with pre-existing diabetes during pregnancy: A call to action from an Italian real-life investigation. Diabetes Res Clin Pract. 2019;154:1-8. doi: 10.1016/j.diabres.2019.06.006

The purpose of this population-based study is to investigate the quality of diabetes mellitus monitoring and care before, during and after pregnancy in a large cohort of women with signs of diabetes who experienced childbirth in the Italian Region of Lombardy. To achieve this aim, a set of indicators developed and validated by a working group of the Italian Health Ministry to estimate the management of diabetes was adopted.

Methods

Study Cohort

The data used for the present study were retrieved from the HCU databases of Lombardy, a Region of Italy that accounts for about 16% (~10,000,000) of its population.

As shown in **Figure 18**, all 653,416 NHS beneficiaries in Lombardy from January 1st 2009 until December 31th 2012 with healthcare system utilization suggestive of diabetes were selected. In particular, beneficiaries who during this period (i) had at least two prescriptions of antidiabetic agents in two distinct dates over 365 days, and/or (ii) experienced at least one hospital admission with primary or secondary diagnosis of diabetes, and/or (iii) took advantage of co-payment exemption for diabetes, were considered suffering from diabetes. Among the 50,053 diabetic women aged 18 to 55 years identified, 3,299 women who experienced at least a birth from January 1st 2011 until December 31st 2015 were identified and the first birth occurred during this period was considered the index delivery. Eligible diabetic women with first pregnancies two years into the data collection period to allow assessment of their clinical history in the two years preceding the index pregnancy were identified. Women who in the period between 3 years before and 2 years after the date of the index delivery (i) were not NHS beneficiaries (to ensure the complete ascertainment of exposure along the entire period of interest, see below) and/or (ii) experienced another pregnancy other than that index (to ensure complete ascertainment of exposure in the pre- and post-pregnancy time period and that exposure to antidiabetic care was not affected by other pregnancies, see below), were excluded. The final study cohort, therefore, consisted of 1,913 diabetic women.

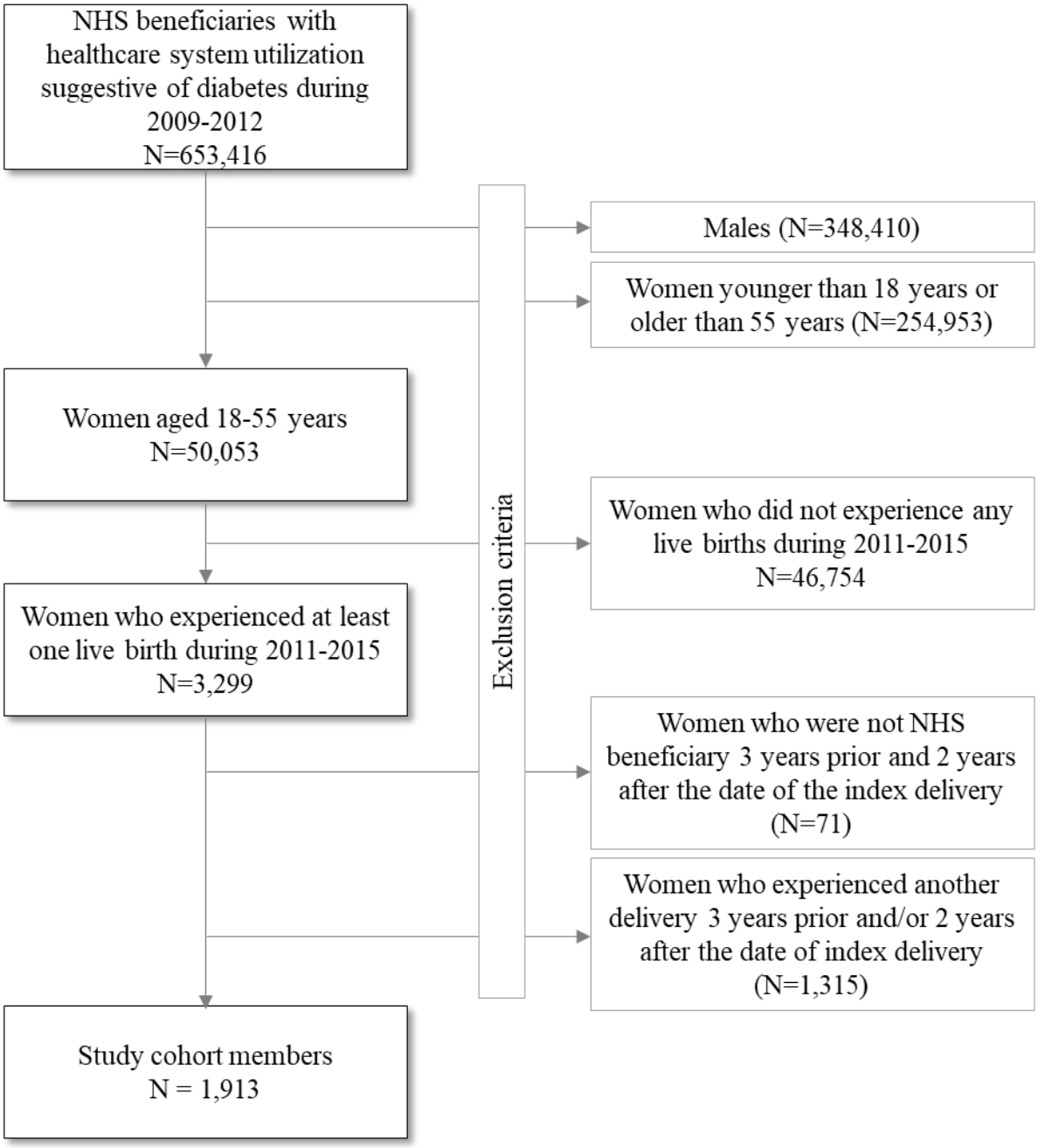


Figure 18. Flow-chart of inclusion and exclusion criteria

Exposure to recommendations and care

Antidiabetic care was identified in two ways. First, outpatient examinations, including assessments of glycated haemoglobin, lipid profile (total and HDL cholesterol and triglycerides), urine albumin excretion, and serum creatinine and dilated eye exams were evaluated. A woman was considered adherent to recommendations if she had at least two glycated haemoglobin evaluations and at least one of the other assessments annually. Second, dispensations of antidiabetic drugs, both insulin and oral hypoglycaemic agents, were assessed. Both adherence to recommendations and prescriptions for both types of antidiabetic drugs were independently assessed during three one-year timeframes: (i) during pregnancy (i.e. the year before the date of index delivery), (ii) before pregnancy (i.e. the year before the pregnancy period), and (iii) after pregnancy (i.e. the year after the date of index delivery).

Data analyses

The null hypothesis that adherence to recommendations and prescription of antidiabetic drugs did not change between each possible pair of time-windows (i.e., before and during pregnancy, during and after pregnancy, and before and after pregnancy) was tested by means of the non-parametric McNemar's test with Bonferroni correction, performing a within-woman (between-periods) comparison (**Figure 19, box A**). The same analyses were restricted to women younger than 35 years who used insulin before the index pregnancy, namely to women likely suffering from type 1 diabetes.

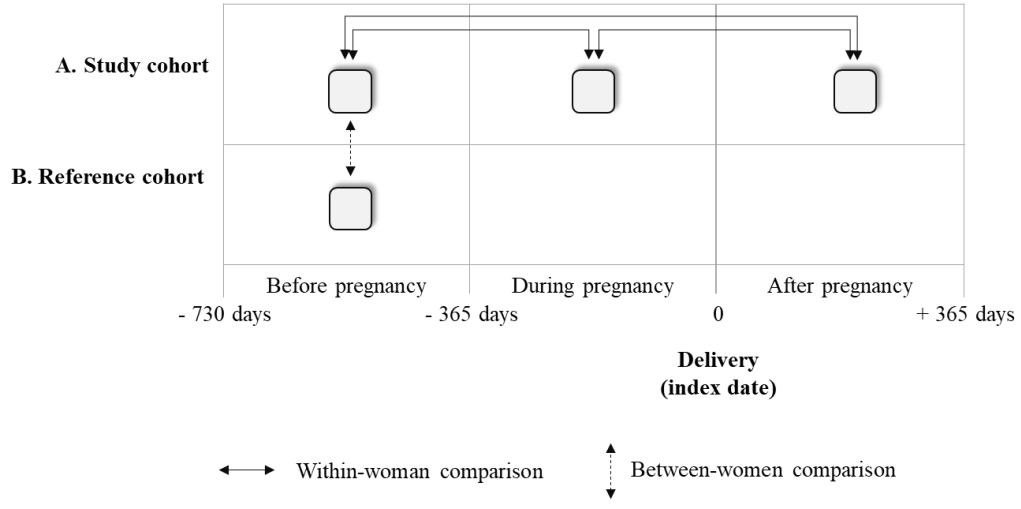


Figure 19. Graphical representation of the performed comparisons (within- and between-women)

Sensitivity analysis

To understand whether our results for pre-pregnancy period reflect real-world care of childbearing age women in general, a reference cohort of diabetic women who did not experience a live birth during the considered period was created. The 46,754 women who did not experience any birth during 2011-2015 were subjected to the same exclusion criteria as the 3,299 women with births (**Figure 18**) to form the eligible reference cohort. For each study cohort member, a reference woman was matched for age at the index delivery and date of first evidence of diabetes. Adherence to recommendations and antidiabetic drug prescriptions during the one-year pre-pregnancy period of the matched study cohort member were measured for each member of the reference cohort. Again, the null hypothesis that study and reference women did not differ in adherence to recommendations and antidiabetic drug prescriptions during the pre-pregnancy period was tested by means of the non-parametric McNemar's test with Bonferroni correction (**Figure 19, box B**).

Results

The mean age of the diabetic women included in the study cohort was 35 years (interquartile range, 32-38). Four out of five women were identified by co-payment exemption (82%), with 40% identified by antidiabetic drug dispensations and 24% by hospital admission with diagnosis of diabetes.

Before pregnancy, study cohort members showed poor adherence to recommendations, with only a portion of them ranging from 13% to 42% undergoing dilated eye and serum creatinine exams respectively (**Table 11**). During or just before pregnancy a significant portion of women increased adherence to all recommendations, with the exception of lipid profile control, which was less controlled during pregnancy. Despite the gain, it should be noted that adherence continued to be low during or just before pregnancy, as during this period only a portion of women ranging from 19% to 61% underwent dilated eye and serum creatinine exams respectively. After pregnancy, the prevalence of women adhering to considered recommendations dropped to pre-pregnancy levels, or even lower for lipid profile and serum creatinine (data not showed). Use of antidiabetic drugs roughly followed the same trends seen for recommended adherence. Less than one woman in three received drug therapy before pregnancy, with a significant increase of insulin during pregnancy and return to pre-pregnancy levels afterwards (**Table 11**). A significant reduction of oral hypoglycemic agents was seen across the periods during and post- pregnancy.

Table 11. Adherence to recommendations and use of antidiabetic drugs of the 1,913 study cohort mothers before, during and after pregnancy. Italy, Lombardy region, 2011-2015

	Peri- pregnancy periods [a]						Between-period comparisons [b]	
	Before pregnancy (A)		During pregnancy (B)		After pregnancy (C)		A vs. B	B vs. C
Recommended examinations								
Glycated haemoglobin	390	(20.4%)	902	(47.2%)	375	(19.6%)	<0.001	<0.001
Lipid profile	673	(35.2%)	523	(27.3%)	524	(27.4%)	<0.001	0.962
Urine albumin excretion	365	(19.1%)	564	(29.5%)	363	(19%)	<0.001	<0.001
Serum creatinine	803	(42%)	1157	(60.5%)	665	(34.8%)	<0.001	<0.001
Dilated eye exam	251	(13.1%)	364	(19%)	219	(11.5%)	<0.001	<0.001
Antidiabetic drug therapy								
Insulin	382	(20.0%)	646	(33.8%)	442	(23.1%)	<0.001	<0.001
Oral hypoglycaemic agents	212	(11.1%)	173	(9.0%)	137	(7.2%)	<0.001	0.001

[a] Before pregnancy: within the year before the 3 months prior the expected date of conception. During pregnancy: within the year before the date of index delivery. After pregnancy: within the year after the date of index delivery

[b] According to the non-parametric McNemar's test with Bonferroni correction for multiple comparisons

As shown in **Table 12**, study cohort members likely affected by type 1 diabetes showed better adherence to recommendations. With the exception of the dilated eye exam, more than half of women with type 1 diabetes adhered to treatment recommendations. Adherence further increased during pregnancy in this sub-group, reaching almost optimal levels for urine albumin excretion, serum creatinine and above all glycated haemoglobin testing, returning to pre-pregnancy levels afterwards (data not showed).

Table 12. Adherence to recommendations of the 253 study cohort mothers aged ≤35 years and in treatment with insulin (before pregnancy) before, during and after pregnancy. Italy, Lombardy region, 2011-2015

	Peri- pregancy periods [a]						Between-period comparisons [b]	
	Before pregnancy (A)		During pregnancy (B)		After pregnancy (C)		A vs. B	B vs. C
Recommended examinations								
Glycated haemoglobin	190	(75.1%)	244	(96.4%)	165	(65.2%)	<0.001	<0.001
Lipid profile	174	(68.8%)	169	(66.8%)	166	(65.6%)	0.600	0.753
Urine albumin excretion	170	(67.2%)	222	(87.8%)	152	(60.1%)	<0.001	<0.001
Serum creatinine	191	(75.5%)	227	(89.7%)	169	(66.8%)	<0.001	<0.001
Dilated eye exam	106	(41.9%)	150	(59.3%)	72	(28.5%)	<0.001	<0.001

[a] Before pregnancy: within the year before the 3 months prior the expected date of conception. During pregnancy: within the year before the date of index delivery. After pregnancy: within the year after the date of index delivery

[b] According to the non-parametric McNemar's test with Bonferroni correction for multiple comparisons

Figure 20 shows that in the one-year period coinciding with the pre-pregnancy period of study cohort members, referent women did not differ in adherence to recommendations and antidiabetic drug prescriptions, with the exception of the lipid profile exam.

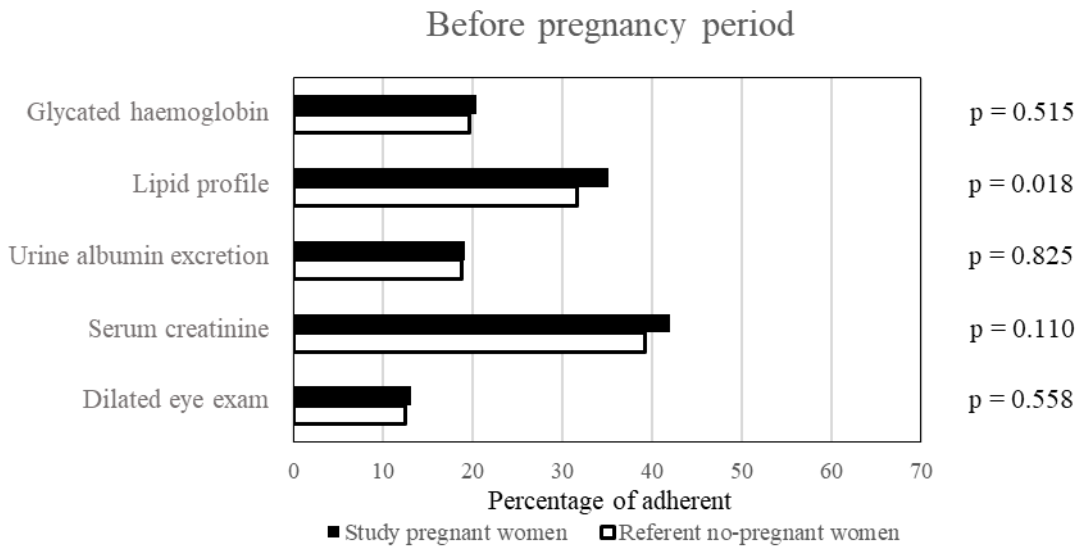


Figure 20. Adherence to recommendations of the 1,913 study cohort mothers and the corresponding 1,913 matched study cohort members during the one-year pre-pregnancy period

Discussion

Planning for diabetes care during pregnancy and optimization of metabolic control in the preconception period and during pregnancy are recognized pillars of the health care of diabetic women and their children. This study, which was focused on diabetic women with a birth during 2011-2015 in Lombardy (Italy), aimed to establish in a retrospective fashion the adherence to recommended clinical monitoring and prescription of antidiabetic drugs in these women in the preconception period, during pregnancy and after birth. These results clearly demonstrate that, although the efforts of health care practitioners improved the indicators of clinical adherence and prescription of antidiabetic drugs during pregnancy, the pre-pregnancy period was characterized by

lack of a proper pre-conception clinical monitoring and in a similar fashion the after-birth period demonstrated a returned to pre-conception poor adherence to treatment recommendations and low rates of antidiabetic drug prescription. However, much higher adherence to treatment recommendations was observed among women likely affected by type 1 diabetes (i.e., those aged less than 35 years and on treatment with insulin), probably because of the difficulty of management of this condition.

The Italian Society of Diabetes recommends careful monitoring during pregnancy including physical and laboratory evaluations at least once every two months for women with pre-existing diabetes [134]. Although looser criteria were adopted (i.e., those validated from a working group of the Italian Health Ministry for clinical examinations of diabetic patients), these results are disconcerting for several reasons. First, adherence to recommendations was very low in all the considered periods, even if during pregnancy women appeared to be more adherent to the clinical monitoring, especially in the assessments of glycated haemoglobin and serum creatinine. Second, only a small proportion of women were on treatment with oral antidiabetic drugs or insulin, although the prevalence of insulin use increased during pregnancy. It cannot, however, be excluded that in women with pre-gravidic type 2 diabetes, metabolic control could be achieved by diet and physical activity alone [135].

This is the first study that assesses the quality of diabetes care by means of these outpatient examinations in pregnant women with pregestational diabetes. Charlton et al. [136] evaluated antidiabetic medicine prescribing to women before, during and after pregnancy. Although the patterns were similar to ours (i.e., increase of insulin prescriptions during pregnancy and return to pre-pregnancy levels after pregnancy), the authors carried out the investigation among all pregnant women rather than those with pre-existing diabetes. Therefore, a comparison of drug use between studies cannot be performed. However, our results could be explained by the tendency to avoid drug therapies other than insulin during pregnancy. Lower adherence to oral hypoglycaemic agents during

the post- pregnancy period could be interpreted as poor care but also as the desire for planning a second pregnancy relying on alternative monitoring care of diabetes rather than drug-based care.

Pregestational diabetes mellitus can represent a danger for the foetus. High blood sugar in the gestation period, particularly during the first trimester, is in fact an established risk factor for congenital anomalies, especially those of cardiovascular and nervous systems [137]. Nonetheless, a diabetic woman who receives careful diabetes care from the stage before conception may reduce the risk of congenital anomalies and neonatal events to the same risk levels of non-diabetic women [114]. For this reason, it is important that diabetic women plan their pregnancy with optimal care of diabetes for at least six months before conception [138]. Despite these recommendations, the results of our study indicate insufficient antidiabetic care in diabetic women before and after pregnancy and, most importantly, document a lack of sufficient improvement in diabetes care during pregnancy.

This study has several strengths. First, the investigation was based on data from a large unselected population, which was made possible by the fact that the publicly funded Italian healthcare system involves virtually all citizens. Second, the drug prescription database provided highly accurate data because pharmacists are required to report prescriptions in detail to obtain reimbursement, and incorrect reports about the dispensed drugs have legal consequences. Three, the results were not affected by the presence of a temporal trend in recommendation adherence among the periods of interest because the findings were replicated by matching the cohort members to non-pregnant women of the same age.

However, our study also had some limitations. First, the exclusion of miscarriages might have excluded less healthy women from our study cohort. Second, information about health service outpatient facilities supplied by private organizations are not available from our databases. Therefore, a portion of examinations might have been lost. However, an Italian investigation showed that administrative data and medical records had good concordance in detecting microalbuminuria, glycated haemoglobin, lipid profile and creatinine controls, while eye exams were often not captured

[139]. Third, as mentioned above, not all diabetic patients need drug therapy since some of them achieve glycaemic control with diet and exercise alone. Nevertheless, these two limitations do not affect the main finding of this study, i.e., the increase of adherence during pregnancy and the drop afterwards. Finally, the lack of clinical information (above all, haemoglobin A1c and folic acid intake) recorded in our database did not allow complete ascertainment of the patients (i.e., determining the glycaemic control and the whole care quality of the women). In addition, the lack of socioeconomic and educational background of the mother did not allow to assess their impact on the adherence to medical recommendations and clinical evaluations, especially in the observed difference between the type 1 and type 2 diabetes patients. Future researches on this topic are needed.

In conclusion, the results of this study provide convincing evidence for the need to improve education of all health care professionals involved in diabetes care, and of diabetic women of childbearing age, to improve management of the disease and prevent the excess of spontaneous abortions, fetal congenital anomalies and pregnancy complications related to diabetes. These efforts would most likely also substantially reduce health care cost. Since this process takes time from the preconception period but it also must last after-birth, it is of paramount importance that a multidisciplinary team of health care professionals (general practitioner, nurses, diabetologist, obstetrician/gynecologist) develop specific community-based pre- and post-pregnancy programmes of prevention and care in all women within gestational age.

The economic burden of the health care: cost-effectiveness analysis of the clinical pathway for diabetes [6]

Introduction

Type 2 diabetes, a major challenge to human health in the 21st century, requires continuous medical care and appropriate risk reduction strategies to reduce its macro and microvascular complications. Scientific societies, such as the American Diabetes Association, the European Society of Cardiology, and the European Association for the Study of Diabetes, regularly report and adapt clinical guidelines to achieve these goals and reduce diabetes-related outcomes as effectively as allowed by trial-based outcome evidence.

Although the benefits of adherence to diabetes guidelines have been widely investigated, at least three pitfalls characterize the studies so far performed. First, these studies mainly focus on medication adherence, while other aspects of adherence to guidelines, such patients' regular follow-up and periodic clinical examinations have rarely been considered. Second, attention has been mainly directed to the association between adherence to treatment and intermediate outcomes, such as glycemic control, and few data are available on the impact of adherence to guidelines on the onset of diabetes complications and the resulting costs. Third, to avoid diabetes-related complications and reduce health-care related costs, guidelines always recommend risk stratification-based management of patients with diabetes. However, studies investigating the benefits of adhering to guidelines according to patients' clinical complexity are lacking.

The quality and costs of health care in patients with diabetes has been monitored in a 'real-life' setting in several countries. In particular, the U.S. DQIP has monitored the care quality of patients with diabetes by verifying the percentage of patients who regularly receive clinical evaluations, using a

[6] This project is ongoing.

number of so-called accountability indicators, e.g. glycaemic and lipid profiles, kidney function, dilated eye examination etc. This has allowed by comparing different health-care systems as well as different healthcare plans or providers for their health care quality in relation to their costs.

Following the DQIP experience, a Working Group was appointed by the Italian Minister of Health to develop a set of indicators that would allow comparing the quality of diabetes care among the Italian regions. However, to ensure that adherence to these indicators would translate into better outcomes and costs reduction, a validation study was required .This was the aim of the present study that explored the impact of adherence with recommended clinical evaluations on hospital admissions for complications of diabetes. The relationship between adherence with clinical recommendations and healthcare costs was also investigated overall and according to patient's clinical complexity.

Methods

Selection of a cohort of newly "taken-in-care" diabetic patients

This study is based on the computerized healthcare utilization databases from the Italian Region of Lombardy.

Beneficiaries of the NHS from the Lombardy Region who in 2012 (the index year) were aged 18 years or older, constituted the target population. Subjects belonging to the target population were considered eligible to be admitted into the cohort if in the index year they left specific 'footprints' on services supplied by the NHS, i.e., if they 1) had at least two prescriptions of antidiabetic agents in two distinct dates over the year, 2) experienced at least one hospitalization with diabetes as primary or secondary diagnosis and/or 3) took advantage of exemption from co-payment of antidiabetic management. Patients were excluded if in the previous three years they had already experienced at least one dispensation of antidiabetic drug(s), hospitalization reporting diabetes or diabetic complications as primary or secondary diagnosis, and/or exemption from co-payment the management of diabetes. Because a three-year medical history was not available, patients recorded as beneficiaries of the NHS after 2007 were excluded, and exclusion was extended to patients who

did not reach at least one-year follow-up period after the index year. The remaining patients were considered newly "taken- in-care", and were then included into the study cohort. The taken in-care date was assumed to be that of the second antidiabetic drug prescription, the first hospitalization for diabetes, or the documentation of co-payment exemption, whichever came first.

Adherence with recommendations

Measurements of glycated haemoglobin, lipid profile (serum total cholesterol, HDL cholesterol and triglycerides), urine albumin excretion, serum creatinine and dilated the eye fundus examination dispensed to the cohort members within the first year after a patient was taken-in-care, were identified. A patient was considered adherent to guideline recommendations if during a year he or she had at least two glycated haemoglobin measurements, plus at least one of the other above mentioned measurements. Cohort members were categorized into three levels of adherence to the guideline recommendations, i.e. whether none or almost none (0 or 1), some (2 or 3), or all or almost all (4 or 5) recommendations were followed within the first year of follow-up.

Additional measurements

Baseline characteristics of cohort members included gender, age, as well as drug therapies and comorbidities recorded within the three previous years. Drug therapies included antiplatelet agents, digitalis glycosides, nitrates, antiarrhythmics, blood pressure- and lipid-lowering agents, antidepressants, non-steroidal anti-inflammatory drugs, anti-gout agents and drugs for chronic obstructive pulmonary disease. Comorbidities were identified by hospitalization for cancer, heart failure, and ischaemic heart, cerebrovascular, respiratory and kidney diseases. Patients were also categorized by the MCS. To simplify calculations and comparisons, three rather than the original five categories of worsening clinical profile (0,1,2,3 and 4) of the MCS were reduced to three, i.e., good (MCS=0), intermediate ($1 \leq MCS \leq 2$) and bad ($3 \leq MCS \leq 4$) .

Clinical outcomes

Cohort members accumulated person-years of follow-up starting from one year after the patient was "taken in care", until the occurrence of the clinical outcome of the study (see below), death, migration, or end of follow-up, i.e., December 31, 2017, regardless of which of these events came first. A composite clinical outcome was developed to take into account potentially avoidable complications of diabetes. A cohort member was considered to experience the outcome if during the follow-up there was at least one hospitalization in which at least one of the following events was mentioned at discharge: (i) short-term diabetes complications, (ii) uncontrolled diabetes, (iii) long-term vascular outcomes, and (iv) traumatic lower limb amputation of non-traumatic origin. The date of the first hospitalization with one of these diagnoses was considered as that of the outcome.

Healthcare costs measurement

Healthcare costs accumulated by each cohort member were recorded starting from the date when the member was "take in-care" until death, migration or December 31, 2017. Costs were calculated from the amount that the Regional Health Authority reimbursed to health providers and included hospitalizations for diabetic complications or other causes, dispensed antidiabetics or other drugs, and other outpatient services such as specialist visits, laboratory examinations and instrumental examinations including radio or echo imaging. The period over which costs were calculated ranged, from the cohort entry (i.e., when he/she was taken in care) to after a hospitalization, thus being longer than that used to assess clinical outcomes. The average annual healthcare cost per patient was calculated by dividing costs and person-years accumulated from the cohort.

Statistical analyses

A 1:1:1 matching design was used to ensure that patients classified according to their adherence with recommendations had similar baseline characteristics. For each patient who adhered to all or almost all recommendations, one subject who adhered to none or almost none and one who adhered to some recommendations were randomly selected from the cohort to be matched for sex, age at cohort entry and clinical complexity (i.e., MCS). Furthermore, with the aim to limit the potential for healthy user

bias, patients were also matched for the number of NHS contacts (including hospital admissions, drugs dispensed, diagnostic imaging, laboratory analyses, etc.) in the previous three years.

To assess the impact of adherence with recommended clinical evaluations on the clinical endpoint (i.e., hospital admissions for complications of diabetes), Cox regression models were fitted to estimate the hazard ratio (HR), and 95% confidence interval (CI), of the outcome in relation to the categories of overall adherence index, using patients on none or almost none recommendation as reference. Cumulative incidence curves for composite outcome were estimated with the Kaplan–Meier method according to adherence with recommended clinical evaluations.

With the aim of investigating the adherence-cost relationship, the average annual cost per patient for 1:1:1 matched cohorts was compared along categories of overall adherence index.

Finally, the incremental cost-effectiveness ratio (ICER) was computed as the difference in costs between two adherence levels (using patients on none or almost none recommendation as reference), divided by the difference in their effects. In this analysis, cumulative health care costs were calculated for each patient at 5 year of follow-up, whereas restricted mean survival time (RMST) at the same time-point was used as outcome measure. ICERs for some and or all or almost all recommendations were computed in the whole cohort as well as according to increasing levels of clinical complexity (i.e., MCS). To assess the uncertainty of the estimates, 1,000 bootstrap samples were drawn and the ICER was calculated again.

All analyses were performed on an intention-to-treat basis. All the analyses were performed using SAS 9.4 (Cary, NC). A 2-sided p-value of 0.05 or less was considered significant.

Results

Newly taken in-care patients with diabetes

Among the NHS beneficiaries forming the whole target population, 36,098 subjects met the criteria for the definition of newly taken–in-care patients with diabetes in the year 2012, the standardised rate being 4.4 newly taken-in-care diabetic patients every 1,000 person-year. Among the 36,098 newly taken-in-care patients with diabetes, 20,635 reached at least one year of follow-up and were included into the study cohort.

Adherence with recommendations

During the first year of observation, only 28% of the cohort members had a dilated eye examination, 32% had an evaluation of glycated haemoglobin and urine albumin excretion, and more than 50% had lipid profile and serum creatinine assessments (**Table 13**). On average, more than 43% of the cohort members did not adhere to any or almost any recommendation.

Table 13. Adherence to selected recommendations among cohort members during the first year after they were taken in care in the Lombardy Region. Italy, 2012-2017

	Adherence
Glycated haemoglobin	6,571 (32%)
Lipid profile	10,744 (52%)
Urine albumin excretion	7,409 (36%)
Serum creatinine	10,477 (51%)
Dilated eye exam	5,793 (28%)
Overall adherence index †	
0-1	8,880 (43%)
2-3	7,332 (36%)
4-5	4,423 (21%)

The baseline characteristics of newly taken in-care diabetic patients are shown in **Table 14** according to their adherence index to guidelines. Women, patients on co-treatments and patients with co-morbidities were at higher risk of low adherence. There was only a marginal difference in demographic, clinical and therapeutic profiles between matched cohort members.

Table 14. Baseline characteristics of cohort members newly taken in care for diabetes from the NHS

	Adherence (number of recommendations)[#] before matching[##]				Adherence (number of recommendations)[#] after matching[##]			
	None or almost none (0 or 1) N = 8,880 (43%)	Just some (2 or 3) N = 7,332 (36%)	All or almost all (4 or 5) N = 4,423 (21%)	p-trend	None or almost none (0 or 1) N = 4,151 (33%)	Just some (2 or 3) N = 4,151 (33%)	All or almost all (4 or 5) N = 4,151 (33%)	p-trend
Male gender	3,981 (44.8%)	3,866 (52.7%)	2,626 (59.4%)	<0.001	4,700 (56.4%)	4,567 (54.8%)	4,634 (55.6%)	MV
Age ≥ 65 years	3,411 (38.4%)	3,342 (45.6%)	1,710 (38.7%)	0.020	1,647 (39.7%)	1,647 (39.7%)	1,647 (39.7%)	MV
Multisource comorbidity score[††]								
0	6,959 (78.4%)	5,691 (77.6%)	3,658 (82.7%)	<0.001	3,527 (85.0%)	3,527 (85.0%)	3,527 (85.0%)	MV
1-2	1,627 (18.3%)	1,474 (20.1%)	704 (15.9%)		591 (14.2%)	591 (14.2%)	591 (14.2%)	
3-4	294 (3.3%)	167 (2.3%)	61 (1.4%)		33 (0.8%)	33 (0.8%)	33 (0.8%)	
Medications [†]								
Antiplatelet	1,875 (21.1%)	1,824 (24.9%)	989 (22.4%)	0.007	934 (22.5%)	885 (21.3%)	914 (22.0%)	0.596
Digitalis glycosides	128 (1.4%)	107 (1.5%)	41 (0.9%)	0.032	40 (1.0%)	45 (1.1%)	39 (0.9%)	0.912
Organic nitrates	234 (2.6%)	205 (2.8%)	92 (2.1%)	0.121	82 (2.0%)	83 (2.0%)	85 (2.1%)	0.814
Antiarrhythmics	123 (1.4%)	128 (1.8%)	57 (1.3%)	0.969	67 (1.6%)	60 (1.5%)	54 (1.3%)	0.233
Anti-hypertensive drugs	4,161 (46.9%)	4,145 (56.5%)	2,371 (53.6%)	<0.001	2,377 (57.3%)	2,238 (53.9%)	2,219 (53.5%)	0.001
Lipid lowering agents	1,541 (17.4%)	1,898 (25.9%)	1,031 (23.3%)	<0.001	976 (23.5%)	1,007 (24.3%)	961 (23.2%)	0.698
Antidepressants	764 (8.6%)	726 (9.9%)	352 (8.0%)	0.655	394 (9.5%)	360 (8.7%)	322 (7.8%)	0.005
NSAIDs	1,783 (20.1%)	1,794 (24.5%)	1,026 (23.2%)	<0.001	970 (23.4%)	947 (22.8%)	968 (23.3%)	0.959
Anti-gout drugs	323 (3.6%)	340 (4.6%)	155 (3.5%)	0.689	147 (3.5%)	165 (4.0%)	140 (3.4%)	0.681
Drugs for COPD	882 (9.9%)	805 (11.0%)	416 (9.4%)	0.726	423 (10.2%)	419 (10.1%)	381 (9.2%)	0.121
Comorbidities [††]								
Cancer	376 (4.2%)	268 (3.7%)	125 (2.8%)	<0.001	113 (2.7%)	114 (2.8%)	98 (2.4%)	0.302
Ischemic heart disease	269 (3.0%)	283 (3.9%)	148 (3.4%)	0.133	114 (2.8%)	127 (3.1%)	125 (3.0%)	0.475
Cerebrovascular disease	272 (3.1%)	178 (2.4%)	81 (1.8%)	<0.001	67 (1.6%)	57 (1.4%)	61 (1.5%)	0.586
Heart failure	172 (1.9%)	99 (1.4%)	44 (1.0%)	<0.001	36 (0.9%)	42 (1.0%)	38 (0.9%)	0.819
Respiratory disease	458 (5.2%)	311 (4.2%)	126 (2.9%)	<0.001	157 (3.8%)	133 (3.2%)	115 (2.8%)	0.009
Kidney disease	75 (0.8%)	36 (0.5%)	10 (0.2%)	<0.001	17 (0.4%)	11 (0.3%)	9 (0.2%)	0.107

NSAIDs: Non-steroidal anti-inflammatory drugs; COPD: chronic obstructive pulmonary disease

Outcome incidence

During the follow-up, cohort members accumulated 84,312 person-year of observation and experienced 69 hospitalizations for short-term diabetes complications (incidence rate, 0.8 cases every 1,000 PY), 453 for uncontrolled diabetes (5.1 every 1,000 PY), 2,643 for long-term vascular outcomes (31.2 every 1,000 PY), and 43 for non-traumatic lower limb amputation (0.5 every 1,000 PY). Overall, hospitalization (the composite outcome involved 2,870 cohort members, with an incidence of 34.0 cases every 1,000 person-year.

Association between adherence with recommendations and outcome

Figure 21 compares the Kaplan-Meier cumulative incidence of outcomes for the categories of the overall adherence index. Compared to diabetic patients who did not adhere to any or almost any recommendation, the patients who adhered to just some or all (or almost all) recommendations showed a risk reduction of 13% (95% CI, 2%-22%) and 16% (95% CI, 6%-26%), respectively.

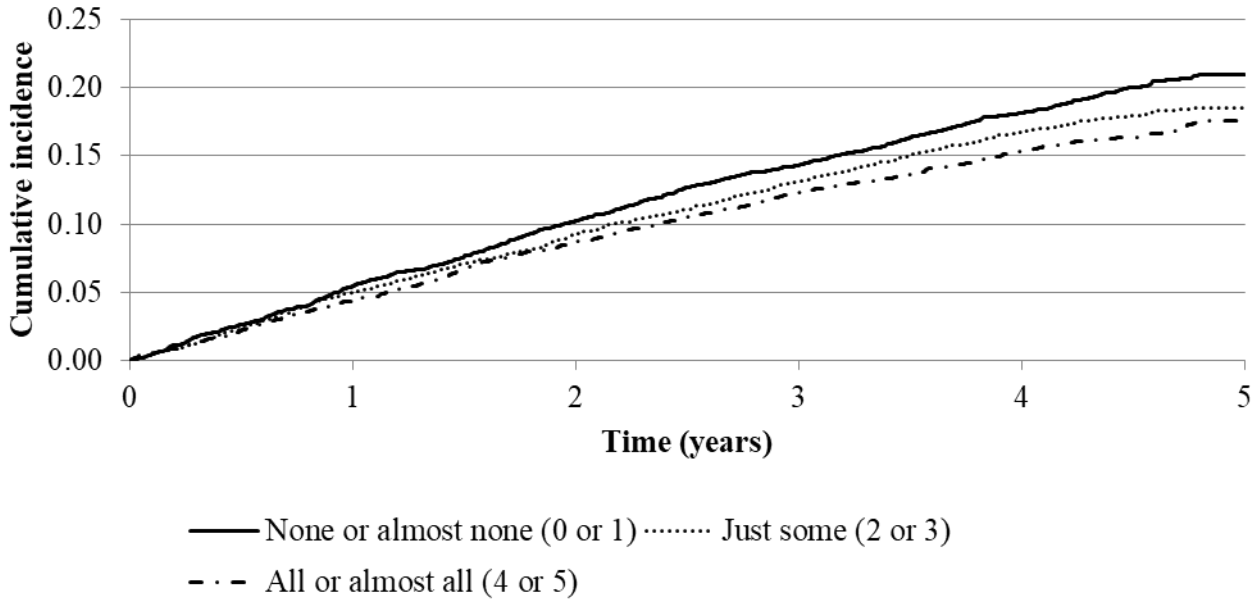


Figure 21. Cumulative incidence of the composite clinical outcome among matched cohorts differentiated according whether none or almost none, just some or all or almost all recommendations were followed.

Association between adherence with recommendations and healthcare costs

Table 15 compares the average annual cost per patient according to the overall adherence index. Although an increase of adherence was associated with an increase of outpatient drug and service costs, hospitalization costs were clearly reduced among well adherent diabetic patients. The overall costs showing a trend towards a reduction with an increase in adherence to recommendations also when hospital and outpatient costs were considered together. Annual healthcare costs per diabetic patients who did not adhere to any or almost any recommendations, adhered just to some recommendations or adhered to all or almost all recommendations were, respectively, 953, 940 and 855 Euros.

Tables 15. Relationship between average annual healthcare cost per patient and adherence to recommendations

	None or almost none (0 or 1)	Just some (2 or 3)	All or almost all (4 or 5)
Hospital admissions for diabetes	244	187	203
Hospital admissions for other causes	521	425	414
Antidiabetic drugs	51	73	103
Other drugs	343	333	352
Diabetes recommendations	16	27	37
Other laboratory exams or specialist visits	341	346	371
Total	1516	1391	1480

With respect to patients adherent to none or almost none recommendations, those adherent to just some and to all or almost all recommendations showed ICERs of -1,092 (RMST: 55.2 vs 55.7 months, costs: 8,164 vs 7,534 EUR) and -156 (RMST: 55.2 vs 55.8 months, costs: 8,164 vs 8,063 EUR). The ICER scatterplot is shown in **Figure 22**. Almost all the ICER estimates regarding patients adherent to just some recommendations exhibited better outcomes and fewer costs compared to patients adherent to none or almost none recommendations (left panel). Conversely, the strength of costs reduction associated with the highest level of adherence was weaker, as displayed by a significant portion of ICER estimates in the first quadrant of the graph (right panel).

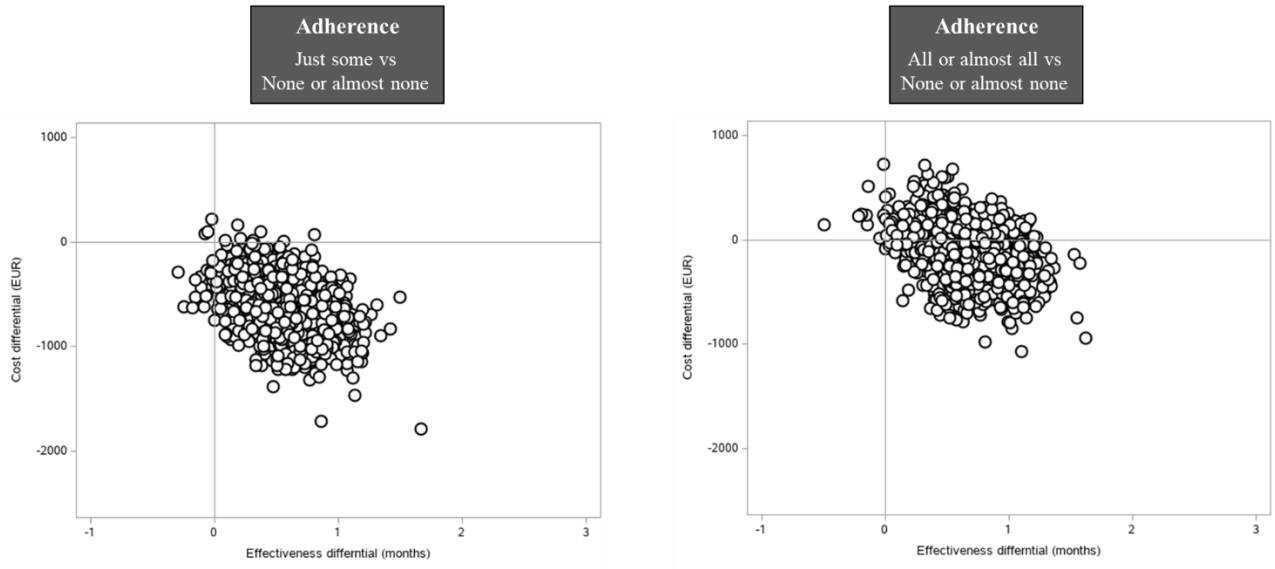


Figure 22. ICER scatterplot comparing patients adherent to just some and to all or almost all recommendations, with respect to those adherent to none or almost none recommendations.

Figure 23 shows that good adherence with recommendations favourably affected outcomes and costs especially among patients with bad clinical status. There was a clear trend in the clinical and economic benefits from patients with good to those with bad clinical status. The ICER estimates ranged from -701 and 186 EUR among the former group (good clinical status) to -15,064 and -10,289 EUR in the latter (bad clinical status). It is noteworthy to report that the average cost ranging from about 7,000 in patients with good clinical status to about 20,000 EUR in patients with bad clinical status.

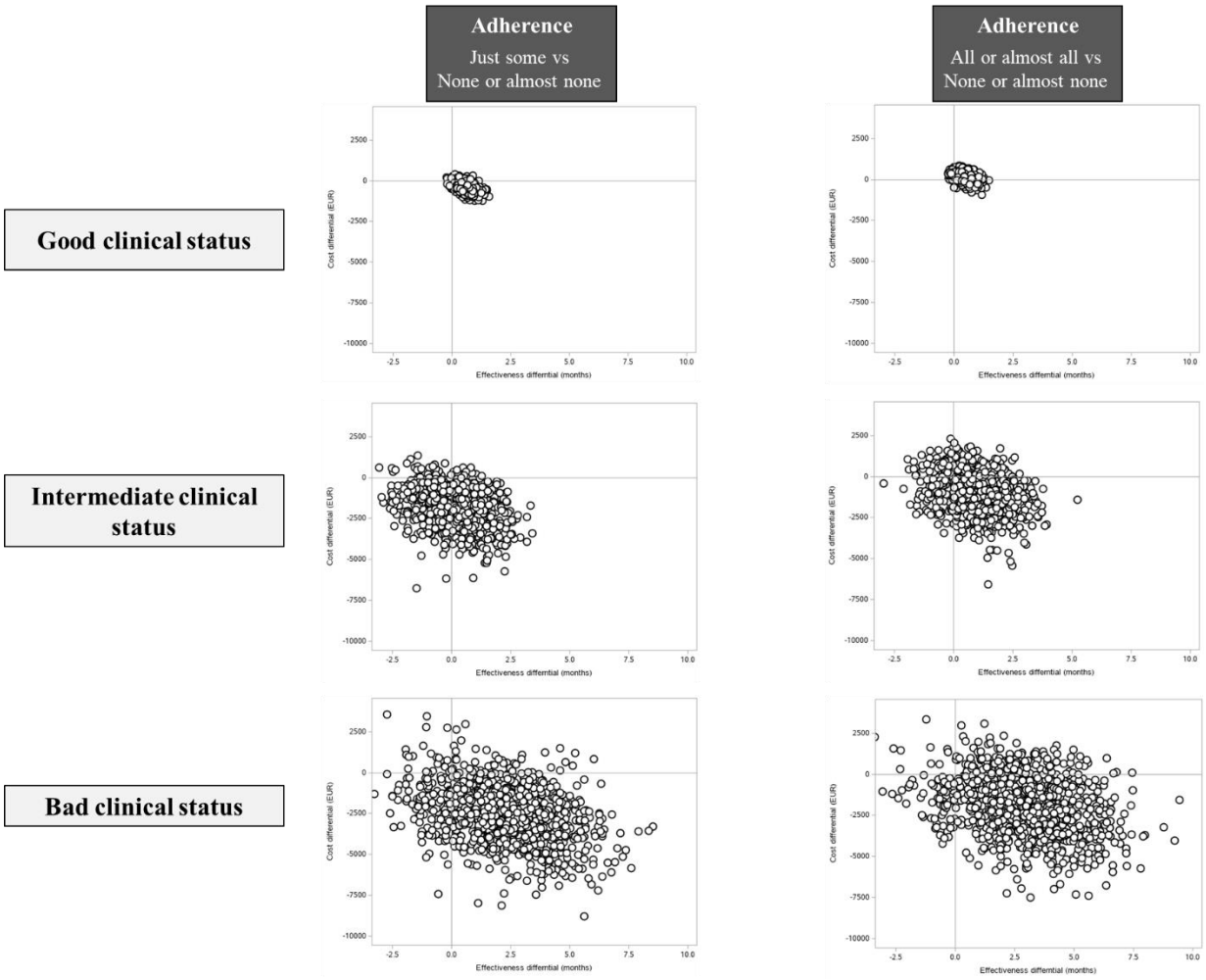


Figure 23. ICER scatterplot comparing patients adherent to just some and to all or almost all recommendations, with respect to those adherent to none or almost none recommendations according to clinical profile.

The results substantially did not change by applying the HDPS algorithm.

Discussion

The present study extends to the Italian population the evidence that guidelines for the management of diabetes are often not adhered to in 'real-life' practice. It further provides, however, three new important findings. First, diabetic patients who received all or almost all the clinical evaluations recommended by guidelines had a 16% reduction in the risk of hospitalization for diabetes complications compared to patients in whom all or almost no recommended clinical evaluations were received. Second, adherence to the clinical evaluations recommended by guidelines benefits not only

patients, but also the health care system because, based on our data, 36 Euros per patient could be saved every year by adhering to the recommended clinical evaluations. Third, although the economic saving included both patients with milder and those with more severe clinical complexities, the economic benefit was much greater for the latter patient. Thus, protection of diabetic patients depends not only on adherence to drug treatment but also depends on recommendations on periodical patient assessment by specialist visits and medical examinations that make adherence to the entire management strategies clinically important. Of special interest is that greater adherence to recommended specialist visits and even complex medical examinations does not lead to increased health care costs, but on the contrary it allows, by reducing hospitalizations cost savings that in patients with greater clinical complexities appear to be considerable.

In diabetic patients, routine evaluations of glycosylated haemoglobin, lipid profile, serum creatinine and urinary albumin are recommended by all guidelines. Some guidelines e.g., the American Diabetes Association and the American Academy of Ophthalmology also recommend periodical dilated eye examinations for all people with diabetes at baseline. Consistently with other reports, we found a wide gap between these guidelines-driven recommendations and their clinical implementation in real life. This is exemplified by the observation that in only 32% of the patients glycosylated haemoglobin was controlled twice a year as recommended by guidelines, while only 21% of the diabetic population adhered to all or almost all the recommended controls. This finding is of particular concern given that nearly one-fifth of participants had a history of hospitalization for CV disease and three out five of them had comorbidities related to an increased risk of mortality.

Few and inconsistent reports are available on the relationship between adherence to individual recommendations and clinical outcomes. Inconsistency is likely due to serious difficulties inherent systematic uncertainty of observational evaluations. For example, these estimates could be very sensitive to differential exposure misclassification and unmeasured confounding. In fact, patients who had more severe diabetes (i.e., those expected to more likely experience the outcome) could be more careful treated by the NHS service (so generating a differential misclassification), as well as more adherent to recommendations (so generating an unmeasured confounding).

However, rather than each individual recommendation, the number of recommendations as a whole should be interpreted as a proxy of the quality of care for patients with diabetes in 'real-life' practice. It was showed that the better was the adherence with recommendations, the higher the costs for medications and outpatient services, while reducing incidence and costs for inpatients services. This suggests that progression of diabetes might be mitigated by structured care, of which regular control might be a proxy. It should be emphasized, however, that the latter sentence is a speculation not directly investigated in this study. The effect of the continuity of care of chronic patients, including those with type 2 diabetes, is a topic of great interest that deserves to be extensively explored.

This study has several strengths. First, the study was based on a very large unselected population, which was made possible because in Italy the healthcare system extends free or almost free of cost to virtually all citizens. Second, data from electronic healthcare utilization records provided a valuable insight into clinical outcome and healthcare cost, which may be saved by better adherence with recommended clinical evaluations. Third, both the hospital and out-patient based data included in the database are very accurate because all services claimed by the health providers to obtain reimbursement by the Regional Health Authority are checked, and incorrect reports may have legal consequences. Fourth, the adopted incident users design reduced the potential for selection bias. Finally, the consistency of estimates between the main results and the data provided by the sensitivity analysis are in favour of the robustness of our findings.

There are also some limitations that need to be taken into account. One, the age of patients included in this cohort make our data representative of type 2 diabetes. Nevertheless, a limited number of patients with type 1 diabetes was presumably also included.

Two, although this incidence figure (4.4 cases of every 1,000 PY) was within the expected range according to the worldwide figures (ranging from 2 to 7 cases every 1,000 PY in Ireland and USA respectively), a questionable sensitivity for detecting patients with type 2 diabetes has been showed from a recent Italian survey. In addition, because patients undetected from administrative data showed to be less compliant than those who were detected, adherence to recommendations may actually be even worse than the concerning one found in our cohort.

Three, exposure misclassification likely affected our findings through several ways. In fact, the above-mentioned Italian survey showed that administrative data and medical records had at least good concordance in detecting patients who adhered to microalbuminuria, glycated hemoglobin, lipid profile and creatinine controls, while eye exams were often not captured. Adherence observed during the first year after the patient was taken in care was implicitly considered as a proxy of the adherence accumulated during follow-up, which may not be invariably the case. For example, diabetic patients who initially followed recommendations might be less carefully controlled afterwards. It has been however speculated that the initial period after diagnosis of type 2 diabetes may be critical for early glycaemic control and for applying weight loss interventions, of which adherence of recommendations is likely a proxy.

Four, outcome misclassification not even can be excluded. For example, incorrect diagnostic codes might be opportunistically used for receiving higher reimbursement from the Regional Health Authority. Yet, only complication of diabetes requiring hospital admission were capture by our study, so that our conclusions should be limited to severe adverse outcomes.

Five, adherence to pharmacological therapy (i.e. to antidiabetic agents) was not taken into account in our analysis. However, as costs for drug therapy was observed for patients on better adherence, we could speculate that a portion of the benefits observed in these patients may be attribute to the unobserved better adherence with antidiabetic drugs, of which the considered clinical examinations should be considered a proxy.

Finally, because patients with frequent controls are expected to have different clinical features than those with less intensive examinations, our results could be affected by confounding by indication. That is, the reduction in diabetes-related hospitalization associated with better adherence might have been generated by uncontrolled factors, accompanying but different from adherence. To minimize the potential for residual confounding, the use of HDPS matching design was employed. According to this sensitivity analysis, furthermore, an observed protective action of adherence was never annulled. Of course, this does not entirely avoid the problem of confounding, one aspect of which is that because adherence may be a surrogate for overall health-seeking behaviour, more adherent

patients might also have more regularly followed healthy lifestyle advices, more effectively treated or dealt with diabetes as out- rather than in-hospital.

Conclusions

Because benefits for patients and health care system are expected from improving adherence to guidelines-driven recommendations, tight control of diabetic patients through regular clinical examinations must to be considered the cornerstone of national guidance, national audits, and quality improvement incentives schemes.

The Beaver software: a research platform to compute indicators of healthcare utilization and clinical outcomes [7]

What real-world data are we talking about?

Beaver® is at least powered by data accounting for healthcare services delivered by the Italian regions, and the associated expenditures, of which, since the early 2000s, the National Government has made it mandatory for regional governments to collect. The resulting regional databases, i.e., the HCU databases, represent the minimum set available in each region and that alone justifies / supports the implementation of a regional platform. However, other data may be integrated within a given Beaver® platform, depending on the availability of relevant data, and the specific regional concerns. For example, it is possible to feed a Beaver® regional platform with other institutional sources (e.g., drug and therapeutic plan registries instituted by the Drug Agency -AIFA-, national registry of rare diseases instituted by the Health Institute -ISS-, health surveys and population census instituted by the Central Institute of Statistics -ISTAT-), as well as non-institutional ones (e.g., population-based cancer registries, medical records from primary healthcare and specialist clinics), provided that data is recorded using the same identification code already used for recording NHS administrative data (e.g., the national fiscal code).

Privacy and other ethical issues

In order to ensure a high level of protection of natural persons, rights and rules, ratified by the European Parliament and Council in the recently issued Directive 95/46/EC, represented the milestone for designing and managing Beaver®. In particular, because there "… *are circumstances under which it may be reasonable and economical ensuring data protection to be broader than a single project*…", a common processing platform may be established by public authority (in our

[7] [7] Results reported in this chapter have been published in Rea F, Pugni P, Pescini D, Palmieri L, Giampaoli S, Carle F, Corrao G. Real-world assessment of healthcare provided by the National Health Service: The network of regional Beaver research platforms. EBPH. 2017;Vol 14, Num 3, Supp. 2:e12862-1-8

case regional government), so realizing an environment where data may be processed "… *in a manner that ensures appropriate security and confidentiality of the personal data, including for preventing unauthorized access ...*".

Beaver® architecture and functioning

The above-mentioned general principles drove the design of the Beaver® platform and led to a two layers architecture: the platform administration layer and the remote user layer (**Figure 24**).

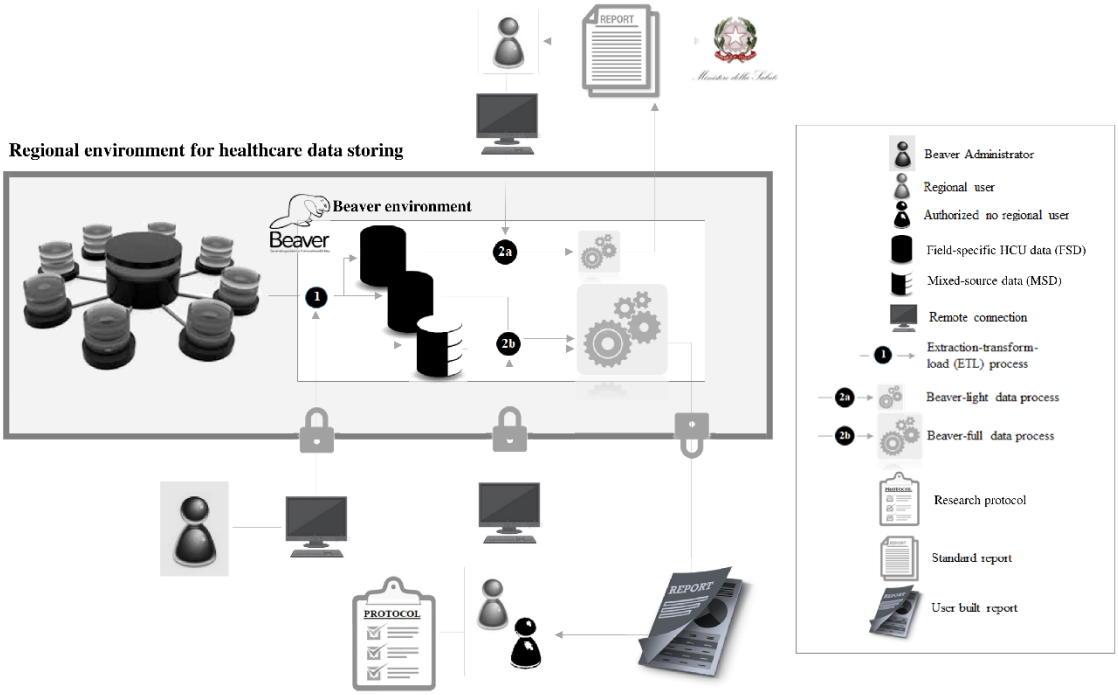


Figure 24. General architecture for the regional Beaver® research platform

The **administrator** is the physical person authorized by the Regional Authority for accessing to the regional environment where healthcare data is stored and protected and is in charge of the first layer. Other than for setting and managing Beaver® into a dedicate fully secured system within the regional environment, the administrator has the tasks of (i) extracting data relating to specific fields

of interest, (ii) harmonizing them according to definite protocols, and (iii) allocating each of them in a dedicated database within the Beaver® environment. Two types of databases may be installed within the platform.

The first type, i.e., the so-called field-specific database (FSD), concerns a specific diagnostic-therapeutic area and provides only data extraction from each administrative regional database of the information that is common to all regions. For example, for achieving the "diabetes FSD", a two-step procedure of data extraction is carried out. The NHS beneficiaries who leave their 'footprints' suggestive of diabetes through specific services (i.e., at least one antidiabetic drug prescription, one hospital admission with primary or secondary diagnosis of diabetes, and/or co-payment exemption for diabetes) provided in a definite time-window, are identified in the first step. Their identification code represents the key for grabbing services provided to patients likely affected by diabetes as recorded from administrative archives in the second step. FSD covering areas of oncology, cardiovascular and respiratory diseases, mental disorders, and pregnancy-child health, are designed and achieved with analogous procedures. Data extract-transform-load (the so-called ETL procedure) for each FSD is designed uniformly through all the Italian regions participating to the Beaver® network. Differences regarding the time-window depth covered by administrative recording may depend on data availability.

The second type of database, i.e., the so-called mixed-source database (MSD), concerns the covering of specific data available in a given region. Experiences of linking administrative data with information from population-based sampling surveys (e.g., the health examination survey managed for Italy by the National Institute of Health) and hospital-based disease registries (e.g., cancer registry from the National Cancer Institute of Milan) are ongoing in Lombardy. Analogously to FSD, the identification code of subjects included into the survey/registry (first step) serves for linking with administrative data (second step).

The second layer of the Beaver® is devoted to the **users** who are the physical persons belonging to either the regional administration or an accredited agency who obtained the credentials for

accessing a database (FSD or MSD) after the Regional Authority approved the protocol. Two distinct solutions may be adopted.

The first solution (the so-called **Beaver® Light** front-end, attainable by regional administration personnel only) allows to automatically compute the set of process and outcome indicators defined by the Health Ministry. Indicators are those reported in the official manual for LEAs (Livelli Essenziali di Assistenza) monitoring through the assessment of pathways experienced by the NHS beneficiaries suffering from chronic diseases (i.e., diabetes, heart failure, chronic obstructive pulmonary disease, breast, colon or rectum cancer, selected mental disorders), experiencing acute episodes (e.g., myocardial infarction, stroke), or who are going through a physiologic experience (e.g., pregnancy). By choosing a given FSD (e.g., the diabetes FSD), and a reference year (e.g., 2017), a standard report is generated containing size and rates of the prevalent cohort (e.g., all diabetic patients), incident cohort (e.g., patients newly taken in care for diabetes), process indicators (e.g., prevalent cohort members who adhered to selected recommendations, such as assessments of glycated haemoglobin, lipid profile, urine albumin excretion, serum creatinine and dilated eye exams) and outcome indicators (e.g., incident cohort members who experienced at least one hospital admission for brief-term diabetes complications, uncontrolled diabetes, long-term vascular outcomes, and no traumatic lower limb amputation). Findings stratified for gender, age class, and possibly geographical area of residence (for example local health unit if present), may be obtained using Beaver® Light.

The second solution (the so-called **Beaver® Full** front-end, available for every authorized user), involves an eight-step procedure entirely driven by the protocol approved by the Regional Authority. An easy-to-use interface articulated in a sequence of queries and drop down menus for specifying (i) FSD (or MSD) from which data must to be processed, (ii) inclusion and (iii) exclusion criteria, defining for (iv) exposure(s), (v) covariates, (vi) outcome(s) and (vii) follow-up, allows of choosing time window(s), demographics (age and gender), diagnostics (ICD-9-CM codes), therapeutics (ATC codes), outpatient services (National Tariff Nomenclator), and other

data useful for carrying out the study. The output of these first seven steps is a master table, still not accessible to users, which may be used for data analysis (i.e., the eighth and last step of the sequence). Usually, data analysis is made through another sequence of queries specifying variables of interest (possible transformed with respect to their original form) which must be used for obtaining descriptive statistics, as well as for fitting selected models (e.g., logit, log-binomial, Poisson, or Cox ones). However, in order to make Beaver® Full as flexible as possible and to apply other and more tailored models and algorithms, data may be directly processed through R or SAS (the latter admitted that the licence is available in the regional environment). Finally, a report including results of data processing is obtained in the form of lists, tables and figures are returned to the user, admitted that the regional administrator approves it.

Discussion

In light of the increasing demands for low-cost real-world healthcare data and evidence, the new opportunity arising from the Beaver® regional research platform, a web-based system for integrating and processing healthcare data, is described in this chapter.

Beaver® has several strengths. First, because the platform was designed and achieved by means of grants from institutional public agencies, it is free of charge to the regions concerned. The contractual form defining intellectual property and the rules for installation, updating and maintenance of Beaver® is currently being studied.

Second, the rules established by the new European regulation for protection of natural persons in relation to the processing of personal data limiting the free movement of electronic health data, are fully complied. In other terms, because each Italian region must be considered the owner of data on healthcare provided to NHS beneficiaries of that region, data should be stored and processed within a regional secured environment and its movements should be limited to few and exceptional needs (such as those of Health Ministry or for legal questions). Accordingly, Beaver® was designed in order to (i) locally process data, (ii) prevent regional data from leaving the platform that hold it

and (iii) allow users to see only the aggregate results of the analysis without any possibility to override the citizens' right to privacy.

Third, because evidence appropriately addressing knowledge-based policy improving effectiveness of healthcare and efficiency of health services are expected for processing real-world data, Beaver® has been designed as a technologic tool (i.e., the Beaver® platform) attendant the rules for scientific research, at which the Beaver® network is required to comply. For example, the platform implements algorithms for automatically computing adherence to recommended clinical examinations of NHS beneficiaries suffering from selected disease and conditions. It should be emphasized that the algorithms implemented in the platform were designed according to the Health Ministry official manual for LEA indicators, the latter being validated for their relationship with measurable clinical outcomes. Other than for monitoring healthcare, the Beaver® platform has been designed for allowing users, external to the regional administration, to generate solid evidence. However, physical persons may be authorized to access platform whether (i) they belong to a public agency (e.g., academy, or other research institutions), (ii) they have documented experience on generating evidence from secondary data, and (iii) a detailed study protocol complying with good practice of epidemiological research using secondary data [16] have been submitted to and approved from the Regional Authority. In other words, the reports which the Beaver® platform is able to produce, i.e., both the standard report with official data on process and outcome indicators of LEA monitoring, as well as the report expressly built for answering a specific research question, are generated accordingly with a predefined, approved protocol.

Finally, as regions where the platform is up and running are connected to the Beaver® network, and a common protocol always drives the data process, aggregated data generated within each region may be compared and/or summarized by means meta-analytic techniques [121]. This is very important because assessments of between-regions healthcare homogeneity (equity), as well as summarized evidence of healthcare implications, may be obtained with comparable data and methods.

Discussion

The studies included in this thesis show how the analyses of HCU databases of Italian regions (i.e., real-world data) can generate real-world evidence in Public Health useful to decision-makers.

Albeit several prognostic scores have been proposed in literature, most of them were developed from hospital-based or pharmacy-based surveys, so hindering their applicability to all beneficiaries of the NHS. Starting from the data recorded into the HCU databases, two population-based scores have been proposed: MCS and CReSc. The strengths of the MCS, based on hospital diagnoses and drug prescriptions, are (i) the chance to be applied in each Italian region, so making easy its calculate, and (ii) the comparable performances in northern, central and southern Italian general populations. Conversely, CReSc outperforms MCS using other HCU data, which, however, are not ubiquitously collected in all Italian regions. Hence, generalizability to other regions is doubtful at this time. Nevertheless, these scores can be used with different purposes. First, the researchers could use these tools for risk adjustment (as performed in the studies of diabetes with MCS). Second, clinicians can use them to manage their patients according to the risk to experience several outcomes. Third, they represent tools for resources assignment according to health demands ("MCS as a tool for health policy planning" chapter).

Care pathways, defined as a structured multidisciplinary plan of care, can improve patients' outcomes, reducing the heterogeneity of care. In this thesis, the quality of diabetes care, as measured by five recommended clinical evaluations, has been found to translate into a better outcome. Indeed, patients who adhered to all or almost all recommendations showed a reduction in the risk of hospital admission for diabetes complications. In addition, also the NHS seems to benefit from the application of this diabetes management, according to the economic analysis. In particular, the economic benefit was much greater for patients with bad clinical status, as showed by MCS.

Finally, the Beaver® regional research platform is a promising tool to combine HCU data (and other data sources) (i) for computing the set of process and outcome indicators defined by the Health Ministry as well as (ii) for generating evidence on effectiveness and cost-effectiveness profile. The

use of standardized and validated algorithms enables to obtain regional estimates that, being obtained by employing regional platforms containing data extracted with standardized procedure, may be compared and possibly summarized by using common meta-analytic techniques.

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