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The relative burden of diabetes complications on healthcare costs: the population-based ARNO Diabetes Observatory, Italy

Pagano E[1], De Rosa M[2], Rossi E[2], Cinconze E[2], Marchesini G[3], Miccoli R[4], Vaccaro O[5], Bonora E[6], Bruno G[7], for the ARNO Diabetes Observatory

[1]Unit of Cancer Epidemiology, "Città della Salute e della Scienza" Hospital-University of Turin and CPO Piemonte, Turin, Italy

[2]CINECA Interuniversity Consortium, Health Department, Bologna, Italy

[3]Unit of Metabolic Diseases and Clinical Dietetics, Alma Mater Studiorum University, Bologna, Italy

[4]Department of Endocrinology and Metabolism, Section of Metabolic Diseases and Diabetes, University of Pisa, Italy

[5]Department of Clinical Medicine and Surgery, University of Napoli Federico II, Napoli, Italy

[6]Endocrinology, Diabetes and Metabolism, Department of Medicine, University and University Hospital of Verona, Italy

[7]Department of Medical Sciences, University of Turin, Italy

Corresponding author

Eva Pagano

Unit of Cancer Epidemiology

University of Turin, "Città della Salute e della Scienza" Hospital

Via Santena 7, 10126, Turin, Italy

Tel.: +39/011/6336855; Fax: +39/011/6706692; E-mail: eva.pagano@cpo.it

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ABSTRACT

Background and Aims: In the present population-based study, we aimed to describe the per patient annual healthcare cost of people with diabetes in 2007-2012, to assess the relative burden of diabetes complications and other potential determinants on healthcare costs in the 2012 cohort, and to describe and analyse the determinants of the cost of incident cases diagnosed in 2012.

Methods and Results: We analysed data from a retrospective cohort of residents in four Italian areas that were served by Local Health Units participating in the ARNO Observatory. Per patient annual healthcare costs (Euros) were estimated as the sum of all the resources supplied during that year (drugs, outpatient care, and hospitalisations). The mean per patient annual healthcare cost increased from €2752 in 2007 to €3191 in 2010, before decreasing to €2791 in 2012. The largest component of these costs was represented by hospitalisations (around €1550, on average; 51.7% of total cost), followed by outpatient care (€422; 14.6%) and drugs (€973; 33.7%). In 2012, the most relevant cost determinants were chronic diabetes complications, with an additional cost due to nephropathy/end stage renal disease (€4683), amputations (€5042), lower extremity revascularization (€4808), and cerebrovascular diseases (€3861). Costs associated with incidence cases were higher than those associated with prevalent.

Conclusion: The present study provides evidence on the excess of healthcare costs due to diabetes complications in both prevalent and incident cases.

Introduction

Diabetes determines a relevant economic burden on national healthcare systems. Direct healthcare costs related to diabetes accounted for 10.8% of the total health budget worldwide in 2013 [1] and for 144 billion US dollars in the European Union in 2014 [2]. As the prevalence of diabetes and its related complications are increasing, the direct costs of the disease, particularly for inpatient care, will continue to rise. The fourth edition of the International Diabetes Atlas indicated that in Europe, healthcare expenditures for diabetes will grow by around 20% between 2010 and 2030 [3]. The main determinants of this increase are the continuing growth in the prevalence of diabetes and its complications, as well as changing health care practices, technology, and cost of treatment, with a relevant increase in the use and price of prescription drugs [4].

People with diabetes have a higher lifetime healthcare expenditure than do those without diabetes [5], with an estimated cost ratio between average annual costs of 2.3 (range: 1.5-4.0, depending on the methodological approach) [6-12]. The average annual healthcare cost for a person with diabetes in the EU is around €2500, with some variations across countries [13], probably due to heterogeneity in the available data, as well as in adopted cost calculation methods. Studies from Europe [7-11, 13-15] and the United States [6] on the distribution of the drivers of these costs have shown strong agreement. They reported that inpatient costs are consistently higher than outpatient costs, accounting for around half of total costs in all examined countries [10]. Moreover, many direct costs are associated with long-term diabetes complications [14, 16, 17]. In a global scenario of limited economic resources, health care planners need long-term projections of outcome and cost. In this context, one of the major limitations in the knowledge of costs is the lack of data on the cost of diabetes complications [18-21] and of standardised long-term data that would allow for trend analysis and identification of relevant determinants [22].

The objective of this study was to analyse the healthcare costs in a large sample of Italian patients with diabetes covered by the National Health Service (NHS). The specific objectives were: 1) to describe the per patient annual healthcare cost of people with diabetes in 2007-2012; 2) to assess the

relative burden of diabetes complications and other potential determinants on healthcare costs in the 2012 cohort; and 3) to describe and analyse the determinants of the cost of incident cases diagnosed in 2012.

Methods

Data

The population-based multiregional ARNO Observatory is a healthcare monitoring system based on administrative data (demographics, disease-specific exemptions, outpatient drug prescriptions, inpatient hospital discharge records, lab tests prescriptions, and instrumental examination) from more than 30 Local Health Units (LHUs) in Italy. The ARNO Observatory was created by CINECA to provide local and national reports on the main epidemiological features and drug consumption of representative subgroups of the Italian population, such as children, the elderly, and those with chronic diseases [7, 23-26]. Data on drugs prescriptions are provided by all participating LHUs, whereas data on hospitalisations and health services utilisation are provided by only some LHUs. People using health care services in Italy can easily be identified through the Italian NHS, a universal system which allows all residents to receive health care, irrespective of their citizenship, social class or income. Moreover, individuals with diabetes receive free access (without any co-payment) to drugs, outpatient care, and hospitalisations within the NHS, making the use of private sector care negligible among people with diabetes.

This report includes data from the 2007-2012 population-based retrospective cohort of residents in four Italian area covered by LHUs participating to the ARNO Observatory, distributed as follows: 34% in the North, 39% in the Centre, and 27% in the South. All data referring to one subject were linked by means of a unique identification code. Subjects were considered to have diabetes if they satisfied at least one of the following criteria: 1) if they had received at least one prescription of glucose-lowering drugs (GLD), either oral agents or insulin (Anatomical

Therapeutic Chemical Classification System [ATC], code A10A and A10B), during the course of the year; 2) if they had one hospital admission with a diagnosis of diabetes (ICD9-CM 250); or 3) if they were exempt from co-payments due to a diagnosis of diabetes. Incident cases in 2012 were identified by excluding subjects identified as having diabetes during the previous 5 years (2007-2011).

Per patient annual healthcare costs were estimated as the sum of all resources supplied during the year. For examinations, consultations, and hospitalisations, we used regional tariffs, which represent the reimbursement paid by the LHUs to healthcare providers, as the standard cost. Drug prices were those reimbursed by the NHS. All costs were expressed in Euros. Annual costs were adjusted for inflation to 2012 Euro value, using the Consumer Price Index obtained by the Italian National Institute of Statistics – ISTAT (http://rivaluta.istat.it/Rivaluta/).

For the 2012 cohort, we also collected the following data for each patient: age, gender, GLDs (oral agents, insulin, oral agents and insulin associated, no GLD), presence of diabetes complications (hypertension, heart diseases, nephropathy/end stage renal disease (ESRD), cerebrovascular diseases, amputations, lower extremity revascularisations, retinopathy, neuropathy), presence of acute complications of diabetes (ketoacidosis, coma, hyperosmolarity), and presence of other comorbidities (chronic obstructive pulmonary disease, cancer, depression). Complications and comorbidities were identified using specific algorithms based on ICD9-CM codes of diagnosis (principal diagnosis) and procedures in hospital discharge records, and on outpatient examinations and specific drugs for the assessed diseases (Annex). Algorithms were developed based on published literature, the AHRQ Inpatient Quality Indicators, previous ARNO Observatory studies, and expert opinions. References are reported in the Annex.

The variable diabetes duration was defined as the duration a subject had diabetes during the study period, i.e., 0 (incident case) up to 5 years or more.

Statistical Analysis

In the final 2012 cohort, patients with no healthcare costs due to the absence of any episode of care were excluded. Patients identified by the algorithm on the basis of the exemptions for diabetes only and not receiving any healthcare treatment were thus excluded (on average N=653; 0.54%).

Per patient annual healthcare costs in 2007-2012 are described as mean overall costs (€), and by different resource categories (drugs, outpatient and hospitalisations). Per patient annual healthcare cost in 2012 were described by several patient and disease characteristics, separately for prevalent and incident cases. Absence of normality distribution of total cost was assessed by the Kolmogorov-Smirnov test ($p<0.0001$). Cost distribution was found to be highly skewed due to the presence of a small proportion of patients incurring extremely high costs. Thus in the analysis of determinants of annual cost, we chose models able to cope with this lack of normality and heteroscedasticity [27]. For this analysis, a generalised linear model (GLM) with log-link and gamma variance function was applied. First, we analysed all patients with diabetes in 2012, adjusting for age as a linear term, gender, year of prevalence, GLD, single diabetes complications, acute complication of diabetes, other single comorbidities, and diabetes duration. When compared to a disease duration of ≤1 year (incidence), coefficients for each year of disease duration between 1 year and ≥5 years (prevalence) were similar, therefore we decided to dichotomise this variable as prevalence versus incidence. The effect of each covariate, with the 95% confidence interval (CI), was estimated as a mean costs ratio (CR) between the cost of the category of interest and the reference category when all the other covariates were fixed, and obtained as exponential of model coefficients. For each covariate, marginal costs were also estimated, that is the absolute amount of additional Euros due to the covariate compared to the reference category. Using model coefficients, predicted cost for an average patient were estimated. For each covariate, marginal costs were then estimated as the difference between the predicted cost for an average subjects with the specific covariate set to one and the predicted costs when the covariate is set to zero.

Furthermore, using the same modelling approach and set of covariates, except for disease duration, determinants of cost were estimated for incident cases only. Statistical analyses were performed by using IBM-SPSS Statistics version 20.

Results

During the period 2007-2012, the observed cohort included an average of around 2.14 million inhabitants each year, with a prevalence of diabetes of 5.6%. Data for each year of the analysed time-frame is reported in table 1. Prevalence showed a constant increase, from 5.15% in 2007 to 6.11% in 2012. The mean per patient annual healthcare cost increased from €2752 in 2007, to €3191 in 2010 and decreased thereafter to €2791 in 2012. The largest component of costs was represented by hospital admissions (around €1550, on average; 51.7% of total cost), followed by outpatient care (€422; 14.6%), and drugs (€973; 33.7%). The distribution among the three resource categories showed a moderate reduction in drug expenditures from 2010 and a steady relative burden of hospitalisation costs.

In 2012, cost data were analysed for a cohort of 130,502 patients. Table 2 describes the mean annual cost by several patient and clinical characteristics. The mean age (± standard deviation, SD) of the analysed cohort was 67.8 (±14.3) years and 92% of subjects received at least one GLD. The mean per patient annual healthcare cost was €2792 (interquartile range, €542 - €2519). The distribution among the three resource categories - drugs, inpatient, and outpatient - varied slightly according to the age groups, with the burden of hospitalisations ranging from 43-44% between 35-64 years to 60% for the oldest patients (>79 years).

Table 3 presents the adjusted estimates of the effect on annual healthcare cost for the same variables, and the marginal cost expressed in Euros. All the analysed factors were significant predictors of major costs, excluding female gender, which was associated with a lower level of expenditure. After adjusting for age, gender, type of drug treatment and presence of other frequent comorbidities, the most relevant predictors (CR above 2.8) were several chronic diabetes complications, with an additional cost due to nephropathy/ESRD (€4683), amputations (€5042),

lower extremity revascularisation (€4808) and cerebrovascular diseases (€3861). Heart disease, retinopathy, neuropathy, and acute complications showed a CR between 1.6 and 2.2, with a marginal cost for each complication of around €1500 to €2000. Compared to patients treated with oral GLD, patients treated with insulin, both alone or combined with oral therapy, showed an extra annual cost of around €1500. Among the considered comorbidities, cancer was a strong predictor of extra costs (CR 4.37, 95% CI 4.16-4.59; marginal cost €6464). Incident cases (N=17,273), representing 13.2% of the 2012 cohort and corresponding to an incidence rate of 0.9%, had a positive marginal cost with reference to prevalent cases (CR 1.13, 95% CI 1.09-1.16), independently from prevalent diabetes duration (data not shown).

Among incident cases, the mean per patient annual healthcare costs were €3151 (interquartile range €387-€3010). Details on the annual cost of incident cases by several patient and clinical characteristics are available online. Table 4 describes the relevant predictors of annual healthcare costs for incident diabetes. For most of the diabetes complications considered, CRs were similar to those observed for prevalent cases.

Discussion

This study describes the healthcare costs of a population-based cohort of individuals with diabetes covered by the NHS. This approach allowed us to provide unbiased estimates, both in absolute and relative terms, of the relative burden of diabetes complications on healthcare costs. Such data are relevant as they can be used in economic evaluation studies and cost-of-illness modelling. As many of the healthcare costs in people with diabetes are associated with the long-term complications of the disease, actions to prevent their onset are a major study subject. In order to assess the economic impact of new healthcare strategies, cost data disaggregated for different diabetes-related complications are necessary. However, these data are very limited in the current literature [14, 18-20, 28].

Our results on per patient annual healthcare costs are consistent with previous European [13], and specifically Italian [9, 11, 29] data, and confirm that, for people with diabetes, annual healthcare costs are substantial and mainly due to hospital admissions [10], particularly in the elderly [6, 30]. During the study period, annual costs were rather stable with no relevant time trend. Considering the stability of the annual cohorts in regard to individual socio-demographic and clinical characteristics, this effect is probably attributable to the Italian policies implemented to reduce NHS expenditure in response to the economic crisis [31]; mostly the increase in market share for generic drugs and the more efficient use of the hospital admissions. In the US, direct costs increased from 2002 to 2011 and the bulk of the expenditure came from hospital inpatient and prescription expenditure [22].

Our study identified diabetes complications (nephropathy/ESRD, amputations, lower extremity revascularisation, and stroke) as major cost drivers, independently from other relevant determinants of cost, e.g., age and comorbidities. At a lower level of additional cost, relevant determinants of extra costs were heart disease, retinopathy, and neuropathy. Similar results were observed in the US [21] and Singapore [28], where diabetes-related complications were found to be strong determinants of costs. An American report using the Diabetes Complications Severity Index [18] - a score based on the number and severity of complications associated with diabetes, estimated from diagnostic and laboratory tests - showed that diabetes healthcare costs were incremental with increasing severity of complications. Our report, with a population-based multiregional study design, is one of the few European studies that provides healthcare costs of people with diabetes stratified by the presence of complications. Indeed, the major strength of this study is the population-based study design, which allowed us to include patients who received care from diabetes clinics and from general practitioners exclusively. This meant that our data were not affected by the selection bias of specialised centres. Still, the ARNO-CINECA Observatory is characterised by a high level of standardisation and reproducibility, allowing for an easy updating of the analyses and feasible time-trend assessments, and these data have been previously used for

several studies on diabetes care quality and costs [7, 26, 32]. Moreover, we examined a population using the services of the NHS, which provides services to people with diabetes free of charge, thus considerations regarding selection bias due to the impact of cost of the disease on people with a low socioeconomic level do not apply.

Compared to prevalent cases of diabetes, incident cases had higher direct costs (CR 1.13), independently of other examined factors. This finding has also been shown in Ontario, Canada [30, 33] and likely reflects higher health service use intensity at diabetes diagnosis. This should be properly taken into account in the economic modelling of diabetes prevention strategies to adequately allocate health resources.

In an American study based on a disease model that simulates the natural progression of diseases and the associated costs [34], the lifetime medical costs of diabetes complications accounted for 48%-64% of the overall lifetime costs. As a consequence, any reduction of diabetes cost burden will require early identification of people at risk, implementation of effective preventive strategies, and ongoing management of metabolic factors known to contribute to the development of diabetes complications. Electronic health records such as those employed in the ARNO Observatory are available in many countries now and would improve the monitoring of the prevalence of diabetes and its complications, quality of care, and outcome indicators. This process might help to reduce the survival gap between subjects with and without diabetes and, hopefully, the health-related costs of complications.

Limitations of the administrative data gathered in the Observatory should be taken into consideration. First, the absence of clinical details (such as glycated haemoglobin or cholesterol levels) and risk factors (such as body mass index and smoking) meant that we could not better describe disease severity or the presence of pre-clinical complications. Costs associated with each complication should then be considered as referring to a clinical phase of the disease, averaging its different levels of severity. For example, costs associated with nephropathy/ESRD should be

considered as the average cost of all the different stages of renal disease, chronic renal failure, dialysis, and transplantation.

Data used to identify people with diabetes from the entire population did not allow us to ascertain who was not pharmacologically treated and who did not require exemption to co-payments for diabetes, namely less severe cases. As these people are likely to have lower healthcare expenditures, an overestimation of the average costs could have affected our results. However, the estimated completeness of ascertainment for the ARNO Observatory is over 95%, thus this bias is likely very limited [35].

A residual confounding effect likely affected our results as the information on diabetes duration was available only up to 5 years. Indeed, previous studies have shown that costs increase most in people who have had diabetes for over 10-15 years [21].

The coding system available in the Observatory is based on ICD9-CM and does not distinguish between type 1 and 2 diabetes. Thus our results pertain to the entire diabetic population.

Our methods to identify patients with diabetes complications could have determined an underestimation of their prevalence, including only severe subjects. This could have led to an overestimation of the cost of diabetes complications. However, the prevalence of diabetes complications in the ARNO Observatory was similar to that reported in other Italian surveys based on individual data, thus the effect of this bias, if any, should be negligible [36, 37].

Finally, overall healthcare costs in the present study were also slightly underestimated, as some cost items, mainly diabetes-related medical devices, were not considered due to the lack of data homogeneity among the LHUs included in the analyses.

In conclusion, the present study provides evidence on the burden of healthcare costs due to diabetes complications. Strengthening programmes to improve diabetes management and to reduce the risk of these complications should be a high priority in order to control the expected future increase diabetes-related healthcare expenditures. This type of analytic data on the cost of different

episodes of care, complications, and treatment are needed for economic impact assessment and cost-effectiveness evaluations.

Duality of interest

No potential conflicts of interest relevant to this article were reported.

C**ontribution statement**

E.P. and G.B. contributed to the study concept and design, researched and interpreted the data. E.P. drafted the manuscript.

E.R. and E.C. contributed to data analysis and reviewed the manuscript. M.D.R., G.M., R.M., O.V., and E.B. oversaw the progress of the project, contributed to the discussion and reviewed the manuscript.

E.P. and G.B. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Table 1: Prevalence of diabetes and mean per patient annual healthcare cost (in Euros) in a cohort of residents in 4 Italian Local Health Units, by year of observation (2007-2012).

Years	**Population**	**Patients with diabetes**	**Prevalence of diabetes (%)**	**Drug costs (€)**	**%**	**Hospitalisations costs (€)**	**%**	**Outpatients costs (€)**	**%**	**Total costs (€)**
2007	2 090 783	107 120	5.12	942	34.2	1423	51.7	387	14.1	2752
2008	2 138 469	111 279	5.20	944	33.6	1499	53.4	366	13.0	2808
2009	2 160 703	117 069	5.42	1022	34.4	1522	51.2	427	14.4	2971
2010	2 157 691	122 671	5.69	1100	34.5	1652	51.7	440	13.8	3192
2011	2 148 836	127 517	5.93	948	33.6	1444	51.2	430	15.2	2821
2012	2 147 017	130 502	6.08	887	31.8	1433	51.3	471	16.9	2792
Average 2007-2012	2 140 583	119 360	5.58	973	33.7	1496	51.7	422	14.6	2891

Table 2: Mean per patient annual healthcare cost (in Euros) by several patient and disease characteristics in a cohort of prevalent cases of diabetes (year 2012).

			Mean annual costs (SD)			
Variables	**N**	**%**	**Drug**	**Outpatient**	**Hospitalizations**	**Total**
	13 0502		887 ± 1688	471 ± 1886	1433 ± 4523	2792 ± 5606
Age						
0-34	3619	2.8	442 ± 900	338 ± 753	746 ± 2634	1526 ± 3187
35-49	9781	7.5	604 ± 1091	377 ± 2060	739 ± 3330	1719 ± 4626
50-64	32 740	25.1	810 ± 2368	408 ± 1954	962 ± 3899	2179 ± 5377
65-79	57 319	43.9	980 ± 1596	555 ± 2053	1588 ± 4957	3123 ± 6073
>79	27 043	20.7	944 ± 965	423 ± 1404	2020 ± 4731	3387 ± 5266
Gender						
Female	65 150	49.9	852 ± 1401	438 ± 1384	1283 ± 4002	2573 ± 4823
Male	65 352	50.1	921 ± 1930	504 ± 2279	1583 ± 4983	3009 ± 6284
Drug treatment type						
Oral agents	91 597	70.2	733 ± 1554	379 ± 1153	941 ± 3389	2053 ± 4136
Insulin	13 478	10.3	1475 ± 2566	930 ± 4250	2968 ± 6968	5373 ± 9395
Oral agents + insulin	15 096	11.6	1476 ± 1346	555 ± 1281	2479 ± 5772	4510 ± 6396
No GLD	10331	7.9	619 ± 1441	569 ± 2612	2269 ± 6086	3457 ± 7224
Presence of diabetes related conditions and complications						
Hypertension	96 791	74.2	1026 ± 1853	515 ± 2070	1629 ± 4858	3169 ± 6038
Heart disease	21 587	16.5	1350 ± 1988	702 ± 2993	4093 ± 7389	6144 ± 8669
Nephropathy/ESRD	3017	2.3	1948 ± 2288	3212 ± 11 237	9968 ± 10 723	15 128 ± 16 123
Cerebrovascular disease	3196	2.4	1167 ± 1131	661 ± 3413	8347 ± 10 113	10 175 ± 11 049
Amputations	242	0.2	1804 ± 2457	2098 ± 6882	18 831 ± 13 635	22 733 ± 17 011
Lower extremity revascularization	240	0.2	1634 ± 1213	1098 ± 3162	12781 ± 10592	15 513 ± 11 814
Retinopathy	1012	0.8	1424 ± 1629	939 ± 2841	4301 ± 7484	6665 ± 8833
Neuropathy	666	0.5	1621 ± 1268	1372 ± 5568	8180 ± 10033	11 174 ± 12 691

			Mean annual costs (SD)			
Variables	**N**	**%**	**Drug**	**Outpatient**	**Hospitalizations**	**Total**
Presence of acute complications						
Hypoglycaemic coma	73	0.1	1658 ± 3300	1305 ± 4576	9040 ± 9929	12 003 ± 12183
Ketoacidosis	398	0.3	731 ± 1168	650 ± 1891	4655 ± 7871	6036 ± 9123
Other coma	77	0.1	1057 ± 839	452 ± 855	7699 ± 8540	9208 ± 8638
Hyperosmolarity	137	0.1	1285 ± 1331	917 ± 3417	8073 ± 8030	10 275 ± 10428
Presence of comorbidities						
COPD	11 459	8.8	1575 ± 1673	646 ± 2501	2764 ± 6245	4985 ± 7404
Cancer	5063	3.9	1925 ± 3646	1354 ± 2101	6854 ± 8386	10 132 ± 9940
Depression	19 820	15.2	1252 ± 2016	629 ± 2630	2318 ± 5817	4199 ± 7166
Disease duration						
Incident cases	17 273	13.2	633 ± 1219	495 ± 2138	2023 ± 5545	3151 ± 6613
Prevalent cases	113 229	86.8	925 ± 1745	468 ± 1845	1343 ± 4339	2737 ± 5434

SD=standard deviation; GLD=glucose lowering drugs; ESRD=end stage renal disease; COPD= chronic obstructive pulmonary disease.

Table 3: Impact of patients demographic and clinical characteristics on annual healthcare costs expressed as cost ratio 95% confidence interval and marginal cost (€) in a cohort of prevalent cases of diabetes (year 2012).

Variables (reference)	Cost ratio	95%CI	Marginal costs (€)
Age (every 10 increasing year)	1.04	1.04-1.05	651
Female gender (males)	0.95	0.93-0.97	-102
Drug treatment type (oral agents)			
Insulin	1.89	1.83-1.95	1689
Oral agents + insulin	1.72	1.67-1.78	1382
No GLD	1.42	1.37-1.48	837
Incident cases (Prevalent cases)	1.13	1.09-1.16	252
Diabetes related conditions and complications (absence)			
Hypertension	1.43	1.40-1.47	657
Heart disease	2.11	2.06-2.17	1996
Nephropathy/ESRD	3.37	3.16-3.60	4683
Cerebrovascular disease	2.95	2.77-3.14	3861
Amputations	3.49	2.81-4.40	5042
Lower extremity revascularization	3.37	2.72-4.25	4808
Retinopathy	1.78	1.60-1.99	1587
Neuropathy	1.85	1.62-2.13	1723
Acute complications (absence)	1.84	1.61-2.11	1704
Comorbidities (absence)			
COPD	1.49	1.44-1.54	957
Cancer	4.37	4.16-4.59	6464
Depression	1.45	1.41-1.49	859

GLD= glucose lowering drugs; ESRD=end stage renal disease; COPD= chronic obstructive pulmonary disease.

Table 4: Impact of patients demographic and clinical characteristics on annual healthcare costs expressed as cost ratio 95% confidence interval and marginal cost (€) in a cohort of incident cases of diabetes (year 2012).

Variable (reference)	Cost ratio	95%CI	Marginal costs (€)
Age (10 increasing year)	1.04	1.03-1.05	120
Female gender (males)	0.96	0.92-0.99	-23
Drug treatment type (oral agents)			
Insulin	2.76	2.60-2.94	612
Oral agents + insulin	2.09	1.93-2.27	427
No GLD	2.12	2.02-2.21	418
Diabetes related conditions and complications (absence)			
Hypertension	1.38	1.33-1.44	159
Heart disease	2.32	2.20-2.43	479
Nephropathy/ESRD	3.54	3.17-3.95	827
Cerebrovascular disease	2.95	2.69-3.24	678
Amputations	4.43	2.88-6.82	1041
Lower extremity revascularization	3.81	2.59-5.62	903
Retinopathy	2.09	1.59-2.76	432
Neuropathy	2.05	1.55-2.72	420
Acute complications (absence)	1.81	1.53-2.15	338
Comorbidities (absence)			
COPD	1.61	1.52-1.70	257
Cancer	4.69	4.36-5.05	1058
Depression	1.44	1.38-1.51	192

GLD= glucose lowering drugs; ESRD=end stage renal disease; COPD= chronic obstructive pulmonary disease.