CEIS Centre for Economic and International Studies
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CEIS Tor Vergata

RESEARCH PAPER SERIES

Vol. 12, Issue 7, No. 321 – August 2014

Direct and Indirect Cost of Diabetes in Italy: a Prevalence Probabilistic Approach

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Running head: Cost of Illness of Diabetes in Italy

Keywords: cost of illness; diabetes mellitus; direct cost; indirect cost; Italy.

Acknowledgments: The study was partially supported with unrestricted funding from ABBOTT, Italy

ABSTRACT

Introduction: Diabetes Mellitus (DM) is a chronic-degenerative disease associated with a high risk of chronic complications and co-morbidities. However, very few data are available on the associated cost. The objective of this study is to identify the available information on the epidemiology of the disease and estimate the average annual cost incurred by the National Health Service (NHS) and society for the treatment of diabetes in Italy.

Methods: A probabilistic prevalence Cost of Illness model was developed in order to calculate an aggregate measure of the economic burden associated with the disease, in terms of direct medical costs (drugs, hospitalizations, monitoring and adverse events) and indirect costs (absenteeism and early retirement). A systematic review of the literature was conducted to determine both the epidemiological and economic data. Furthermore, a one-way and probabilistic sensitivity analysis with 5,000 Monte Carlo simulations was performed, in order to test the robustness of the results and define a 95% CI.

Results: The model estimated a prevalence of 2.6 million of patients under drug therapies in Italy. The total economic burden of diabetic patients in Italy amounted to € 20.3 billion/year (95% CI 95%: € 18.61 - € 22.29 billion), 54% of which are associated with indirect costs (95% CI :€ 10.10 - € 11.62 billion) and 46% with direct costs only (95% CI: € 8.11 - € 11.06 billion).

Conclusions: This is the first study being conducted in Italy aimed at estimating direct and indirect cost of diabetes with a probabilistic prevalence approach. As it might be expected, the lack of information involves that the real burden of Diabetes is partly underestimated, especially with regard to indirect costs. However, this is a useful approach for policy makers, in order to understand the economic implications of the diabetes treatment in Italy.

INTRODUCTION:

Diabetes Mellitus (DM) is a chronic-degenerative disease associated with a high risk of chronic complications and co-morbidities, with a significant impact on both life expectancy and quality of life [1]. It is well established that DM-related complications involve debilitating consequences, affecting the functioning of vital organs that may cause cardiovascular disease, hypertension, dyslipidemia, diabetic nephropathy, diabetic neuropathy, diabetic retinopathy, diabetic foot and erectile dysfunction [2, 3]. The consequences of DM cannot be overlooked due to their potential multiple economic impact : on the one hand, the direct medical costs including the costs for hospitalization, physician office visits, specialist services, drugs, self-monitoring of blood glucose (SMBG) and treatment of hypoglycemic events; on the other, a patient with diabetes is subject to the inability to work at full capacity or at all, resulting in absenteeism or early retirement [4]. Despite the importance of this disease, comprehensive studies on diabetes cost are limited, particularly those including complications, type 1 and type 2 diabetes, at all ages, as well as direct and indirect costs [4].

An epidemiological survey conducted in Italy describes DM as a widespread disease in the population (prevalence of 5.8% in 2010) with an increasing trend (+13% compared to 2007 analysis) [1]. The information concerning direct costs at national level is limited. ARNO Observatory estimates that the average annual cost per patient amounted to € 2,756 in 2010, 57% of which were due to hospitalization, 29% to drugs, and 14% to specialist services. However, the analysis did not take into account SMBG, a very important component of direct costs in diabetes therapy [5]. Furthermore, there is no standard diabetes therapy for all patients, but it is diversified into various types of treatment: Oral Therapy (OT), Basal Supported Oral Therapy (BOT) and Basal-bolus Insulin Therapy (BBT).

A European study published in 2010 comparing the national cost of diabetes in 5 EU countries reports a total direct medical cost of approximately € 7.92 billion in Italy [4]. As far as 2010 indirect costs of diabetes are concerned, they amount to € 12.64 billion totally in Italy, and they

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include € 5.36 billion for Absenteeism, € 7.19 billion for Early retirement and € 0.97 billion for Social Benefits.

The objective of this study is to identify the available information on the epidemiology of the disease and estimate the average annual cost incurred by the National Health Service (NHS) and society for the treatment of diabetes in Italy.

METHODS:

Study Design

A probabilistic prevalence Cost of Illness (COI) model was developed in order to calculate an aggregate measure of the economic burden associated with DM in Italy. The model aims at estimating both the *direct medical costs and the indirect costs of* the disease in Italy. In our approach direct costs measure the value of the resources used for treating a particular illness (drugs, hospitalizations, monitoring and AE), whereas indirect costs measure the value of lost resources due to the illness condition (absenteeism and early retirement) [6].

In order to estimate the direct medical costs, a Bottom-up approach was used. It estimates the cost by calculating the average cost of treatment multiplied by the illness prevalence in Italy. The average cost of treatment is calculated by adding up the various treatments[7]. For the estimation of the indirect costs, the Human Capital method was used. It measures the lost productivity in terms of lost earnings of a patient or caregiver [8].

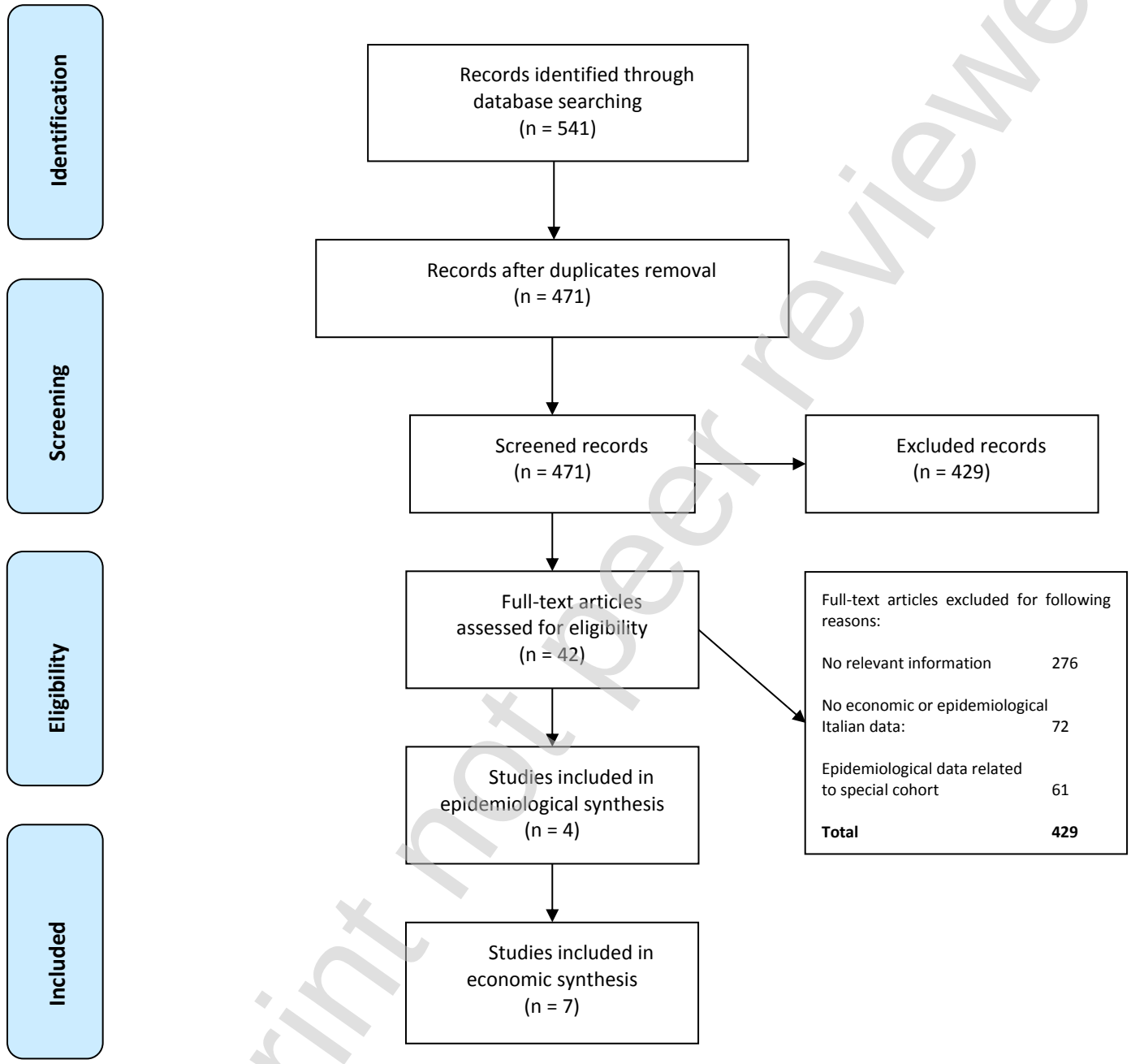
The data used in the model were estimated through a systematic literature review at national and international level [9]. A one-year time horizon and social perspective were considered.

Systematic Literature Review

As mentioned above, the secondary data used to inform estimates were identified via a literature review. The flow of information through the different phases of the systematic review is shown in Figure 1.

Search Strategy and Selection Criteria. In order to collect related secondary data, we carried out a systematic search in the following electronic databases: MEDLINE (PubMed), ISTAT (Italian National Institute of Statistics) and EpiCentro (Italian Epidemiology Portal). The systematic literature review included four steps: identification, screening, eligibility and inclusion [9]. The research was limited in time (articles published over the last 5 years) and space (articles about

Figure 1 - PRISMA 2009 Flow Diagram[1]



[1] *From:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

Italy). The keywords used for the search were: cost of illness, cost, burden of disease, burden of illness, diabetes, diabetes mellitus.

All the studies used in the epidemiologic and economic synthesis were required to meet at least one of the following inclusion criteria:

1. epidemiological data on diabetes (with particular attention to the illness prevalence and its treatments) resulting from population databases, such as national surveys or registries;
2. data on the direct medical costs of the illness evaluated from the perspective of the payer, and expressed in monetary values;
3. an observational study of epidemiological data on diabetes and their connected direct costs, simultaneously observed in the same cohort of patients;
4. studies containing indirect cost data of the illness or data on lost productivity associated with diabetes.

541 studies totally were identified and 42 of them were eligible for inclusion, 32 of which were excluded because they did not meet economic or epidemiologic inclusion criteria. 10 studies were used for the implementation of the model: 3 for the epidemiological analysis, 6 for the economic parameter and one for both. The main items identified by the systematic review of the literature were reported in Appendix A.

Model Parameters

The data extrapolated from the records identified through the systematic review were aggregated to obtain estimates including inside intervals (minimum and maximum available data from the literature). This approach was based on the assumption that differences found in various sources could indicate a probability distribution reflecting the available information in real world data. The average value of the distribution was estimated from a particularly reliable source in literature, or from the average minimum and maximum values, assuming an equal distribution at the two extremes. The probability distribution of the parameters was attributed by the common

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practice of health economics modelling. For cost parameters a gamma distribution was assigned, while the epidemiological parameters (prevalence or proportions) were modelled as a beta distribution [10]. The parameters used for the implementation of the model are reported in Table 1.

Epidemiologic Synthesis

In 2012 the Italian population was approximately 60 million people [11]. The diabetes prevalence provided by ISTAT [12] was equal to 5.5% in 2012. However, other sources estimated diabetes prevalence within a range between 4.9 % [3] and 5.8% [1] in 2011. On average, 79% of diabetic patients (between 70% [1] and 88% [13]) were on treatment, while the remaining 21% were able to control the disease thanks to a healthy lifestyle, diet and physical activity [1, 13]. Treated patients were divided into three groups: Oral Therapy (OT-about 76%), BOT (about 11%) and Basal-Bolus Therapy (BBT-approximately 13%) [1]. The proportion was assumed steady over time, as indicated in the ARNO estimates where the variation between 2007 [14] and 2011 [1] reports was about 1%. This variability estimated the variation range.

Economic Synthesis: Direct Medical Cost

The selection of direct cost parameters was based on the "2009-2010 Italian standard treatment of diabetes mellitus" published by the Diabetologists Medical Association (AMD) [2]. The selected parameters to estimate the total direct cost of diabetes treatment were: costs of drugs, costs of hospitalizations, costs of specialist services, costs of SMGB and costs of treatment and care of hypoglycemic events. If the costs were referred to different years before 2012, they were amended with the "ISTAT Compound Consumer Price Index rate (CCPI rate)" and expressed in Euros (2012 values) [15]. Specifically, the costs have been estimated as follows:

Costs of Drugs: this cost per patient was calculated as the ratio of gross pharmaceutical expenditure associated with the diabetic population compared to the total diabetic population. The maximum and minimum values were drawn from the Arno Report [1] and an Emilia-Romagna publication respectively [16].

Costs of Hospitalizations: this cost per patient was calculated as the ratio of gross hospitalization expenditure associated with the diabetic population compared to the total diabetic population. Hospital expenditure refers to monetary values for hospital Disease-Related Groups (DRGs) and outpatient tariffs. The DRG system aggregates all activities, including surgical interventions, administered drugs, materials, and health personnel, for each individual diagnosis. Furthermore, it establishes the reimbursement rate, corresponding to the sum of all provided interventions to be paid to the hospital [17]. Like the cost of drugs, the maximum and minimum values were drawn from the Arno Report and an Emilia-Romagna study respectively [1, 16].

Costs of Health Specialist Services: this cost per patient was calculated as the ratio of specialist service gross expenditure associated with the diabetic population compared to the total diabetic population. Specialist service gross expenditure is the amount of total expenditure of each specialist service. The specialist services include: non-hospital services (outpatient), specialist visits, cycles of rehabilitation services, laboratory tests and diagnostic imaging. Also in this case, the maximum and minimum values were drawn from the Arno Report [1] and the Emilia-Romagna study respectively [16].

Costs of SMBG: this cost depends on the use of daily tests for glycemic control. The cost of SMBG per patient was calculated as the average single test cost [5, 18] multiplied by the average of daily tests used for glycemic control [2]. The number of tests is not the same in the different treatments: patients under BBT use on average from 4 to 7 tests per day [2, 17], those under BOT use from 3 to 4 tests per day [2, 5] and patients under oral therapy use from 0.6 to 2.3 tests per day [2, 5].

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Table 1 – Average values, range and distribution of parameters

Parameters	Average Value	MIN	MAX	Distribution	Reference
Resident population in Italy on January 1, 2012	59.394.207	-	-	-	[11]
Prevalence of Diabetes	5,5%	4,9%	5,8%	BETA	[12, 3, 1]
Patients in Treatment	79,8%	70%	88%	BETA	[1, 13]
OT Patients Treated	77%	76%	77%	BETA	[14, 1]
BOT Patients Treated	11%	10%	11%	BETA	[14, 1]
BBT Patients Treated	13%	13%	13%	BETA	[14, 1]
Cost parameters	Average Annual Expenditure per Patient	MIN	MAX	Distribution	Reference
Direct medical costs					
Drugs	€ 796	€ 754	€ 838	GAMMA	[1, 16]
Hospitalizations	€ 1.919	€ 1.616	€ 2.223	GAMMA	[1, 16]
Health Specialist Services	€ 422	€ 384	€ 459	GAMMA	[1, 16]
SMBG-Oral therapy	€ 345	€ 77	€ 613	GAMMA	[2, 5, 17, 18]
SMBG-BOT	€ 769	€ 486	€ 1.051	GAMMA	[2, 5, 17, 18]
SMBG-Basal-Bolus Therapy	€ 1.190	€ 540	€ 1.840	GAMMA	[2, 5, 17, 18]
Hypoglycemic Events DM 1	€ 4,9	€ 4,5	€ 5,2	GAMMA	[2, 19]
Hypoglycemic Events DM 2	€ 2,9	€ 2,7	€ 3,2	GAMMA	[2, 19]
Indirect costs					
Absenteeism	€ 2.892	€ 2.892	€ 2.748	GAMMA	[3,20, 21, 22]
Early Retirement	€ 15.957	€ 15.957	€ 15.159	GAMMA	[20, 23]

Costs of Hypoglycemic Events: the model considered two types of hypoglycemic events: mild/moderate and severe. For moderate hypoglycemic events it was assumed that there was no additional use of any other drugs, but a simple injection of glucose followed by a glycemic control after a few minutes [2]. Therefore, these costs were already included in the SMBG costs. If a patient had one severe event, the model assumed that he took Glucagon plus 6 additional daily tests with respect to patients making normal blood glucose controls [2]. The cost of an event (6 tests + Glucagon [2, 19]) was then multiplied by the annual probability of such event [2]. Table 1 shows the costs associated with severe hypoglycemic events.

Economic Synthesis: Indirect Cost

Due to the lack of information on indirect costs, it was possible to estimate the absenteeism and early retirement costs only. In order to estimate them, a study from Danish population registries was used [20], thus assuming that the Italian diabetic population has the same behaviour as the Danish one. In order to calculate costs caused by absenteeism, the following elements have been taken into account: the average daily earnings in 2011 in Italy [21, 22] multiplied by the diabetic population in active employment [3]; the average lost working days in a year because of the disease [20]. For the costs resulting from early retirement, an average gross income at retirement [23] was used, multiplied by the probability of early retirement of the diabetic population [20]. All the parameters used for the estimation of indirect costs are summarized in Table 2.

Table 2 - Parameters used to estimate the indirect costs

Parameter	Value	SOURCE
Average working days lost in a year	41.50	[20]
Average daily earnings per person	€ 124.9	[21, 22]
Employment rate	55.80%	[23]
Working Age of Diabetic Population	20%	[3]
Probability of early retirement	17.38%	[20]
Average gross income at retirement	€ 15,957	[24]

Sensitivity Analysis

Sensitivity analysis is recommended any time there is uncertainty [25]. In order to verify the uncertainty of the model results, a deterministic one-way and probabilistic Sensitivity Analysis (DSA and PSA respectively) [26] was performed. In DSA, each sensible parameter of the model was subject to a variation of ± 25% and the model results were compared to the value of the base case. The DSA results were represented by a tornado diagram.

Probabilistic sensitivity analysis provides a useful technique to quantify the level of confidence of a decision-maker in drawing the conclusions of an economic evaluation [26]. At each model parameter a probability distribution (Table 1) used to make 5,000 Monte Carlo simulations was assigned, in order to test the robustness of the results and define a 95% CI.

RESULTS

3.3 million diabetic people were estimated in Italy in 2012. With reference to patients under pharmacological treatment, the model estimated about 2.6 million patients totally in Italy in 2012 (Table 3). The majority of these patients were treated with oral therapy (2,0 million people), while only a small part of them was treated with BOT and Basal Bolus (273,681 and 338,843 respectively). In Italy about 1.2 million people had to prematurely retire or lost working days (567,749 and 620,662 respectively) due to the disease in 2012. The average annual expenditure per treated patient is € 3,640. Obviously, it depends on the considered therapy group: OT has an average cost per patient equal to € 3,487, BOT € 3,909 and BBT € 4,330 (Table 3).

Regarding the indirect costs, the estimated average annual expenditure per patient is equal to € 4,098. The average annual expenditure of absenteeism per patient is € 2,612, while early retirement amounts to € 15,957 per patient yearly.

Table 3 - COI Results: Annual Expenditure per patient and number of patient in relation to direct and indirect costs

	Direct Medical Costs				Indirect Costs		
	a-Oral Therapy	b-BOT	c-Basal-bolus	**Total (a+b+c)**	d-Absenteeism	e- Early Retirement	**Total (d+e)**
Number of treated patients	1,993,961	273,681	338,843	**2,606,485**	620,669	567,749	**1,188,418**
	A- Oral Therapy	B-BOT	C-Basal-bolus	**Weighted Average (a,b,c)**	D- Absenteeism	E- Early Retirement	**Average (D*d+E*e)/ (a+b+c)**
Annual Expenditure per treated patient	**€ 3,485**	**€ 3,909**	**€ 4,330**	**€ 3,640**	**€ 2,612**	**€ 15,957**	**€ 4,098**

The model estimated that the total expenditure for the treatment and care of DM amounted to € 20.2 billion in Italy, ranging from € 18.3 to € 22.0 billion (Table 4). Approximately 53% of this total expenditure is due to indirect costs and 47% to direct medical costs.

The direct medical costs to the Italian NHS amount to € 9.6 billion (95% CI: €8.09 - €11.07). Table 4 shows the total expenditure related to drugs, SMBG, Specialist Services and Hypoglycemic

Events. The most important direct cost is hospitalization: € 3.83 billion associated with patients under Oral Therapy (95% CI: € 3.09 - € 4.64), € 530 million with BOT patients (95% CI: € 0.42; € 0.64) and € 650 million with patients under Basal-Bolus Therapy (95% CI: € 0.52 - € 0.72), for a total expenditure of € 5.05 (95% CI: € 4.1 - € 6.0). The model estimated a total indirect cost caused by diabetes in Italy of € 10.7 billion (95% CI: €9.94 - €11.42), € 9.0 billion of which are due to early retirement and € 1.62 billion to absence from work, with a corresponding 95% confidence interval of € 8.39 - € 9,74 billion and € 1.50 - € 1.74 billion respectively.

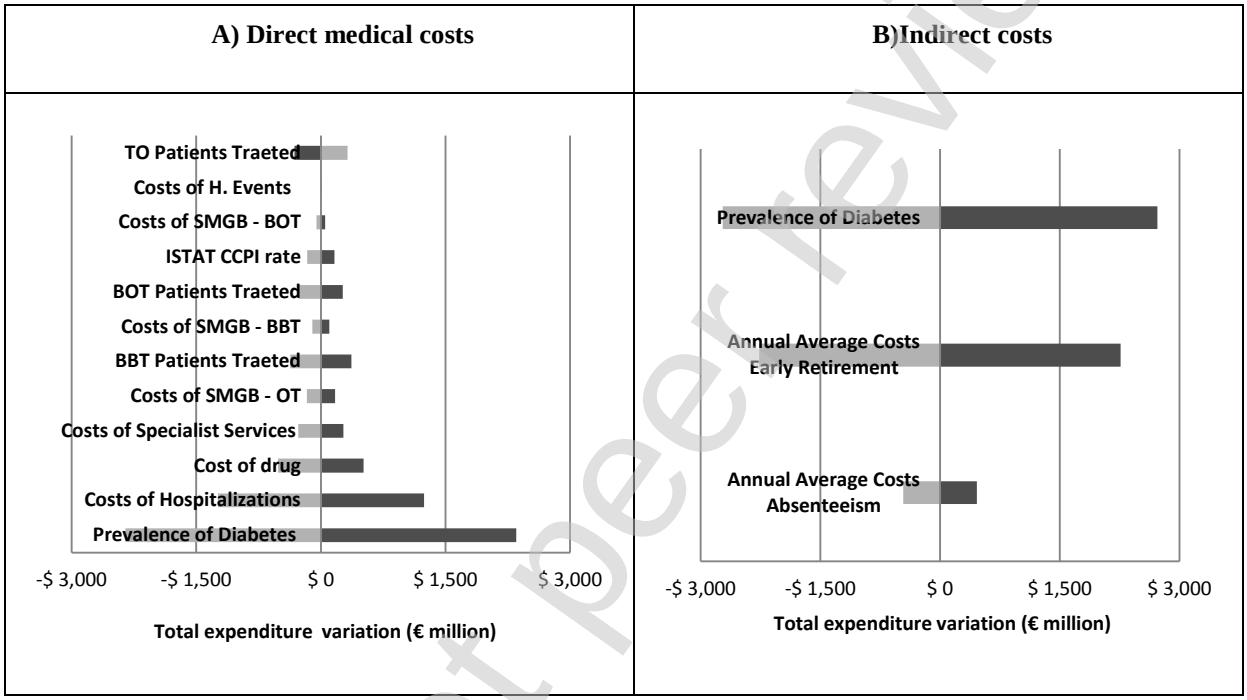
Table 4 - COI Results: Estimated direct medical costs and indirect costs

Cost Item	Expenditure on OT (€ billion)	Expenditure on BOT (€ billion)	Expenditure on BBT (€ billion)	Total
Costs of Drugs 95% CI (MIN-MAX)	**€ 1.59 (€1.39- €1.81)**	**€ 0.22 (€0.19-€0.25)**	**€ 0.27 (€0.23-€0.31)**	**€ 2.09 (€1.84-€2.34)**
Costs of Hospitalizations 95% CI (MIN-MAX)	**€ 3.83 (€3.09-€4.64)**	**€ 0.53 (€0.42-€0.64)**	**€ 0.65 (€0.52-€0.79)**	**€ 5.05 (€4.1-€6.0)**
Costs of Specialist Services 95% CI (MIN-MAX)	**€ 0.84 (€0.73-€0.97)**	**€ 0.12 (€0.1-€0.13)**	**€ 0.14 (€0.12-€0.17)**	**€ 1.11 (€0.95-€1.26)**
Costs of SMBG 95% CI (MIN-MAX)	**€ 0.69 (€0.14-€1.27)**	**€ 0.21 (€0.09-€0.5)**	**€ 0.40 (€0.34-€0.47)**	**€ 1.31 (€0.67-€1.95)**
Costs of Hypoglycemic Events 95% CI (MIN-MAX)	**€ 0.006 (€0.01-€0.01)**	**€ 0.001 (€0.0007-€0.001)**	**€ 0.001 (€0.0009-€0.0012)**	**€ 0.008 (€0.007-€0.009)**
Total 95% CI (MIN-MAX)	**€ 6,95 (€5,88-€8,17)**	**€ 1,07 (€0,73-€1,42)**	**€ 1,47 (€1,28-€1,69)**	**€ 9,58 (€8,09- €11,07)**
a – Total Average Expenditure on Direct Costs CI 95% (MIN-MAX)		**€ 9.58 (€8.09- €11.07)**		
Absenteeism CI 95% (MIN-MAX)		**€ 1.62 (€1.50-€1.74)**		
Early Retirement 95% CI (MIN-MAX)		**€ 9.06 (€8.39-€9.72)**		
b - Total Average Expenditure on Indirect Costs 95% CI (MIN-MAX)		**€10.68 (€9.94- €11.42)**		
a+b - Total Average Expenditure 95% CI (MIN-MAX)		**€ 20.26 (€18.42- €22.10)**		

Figure 1A shows how the deterministic variation of each parameter affects the estimate of total expenditure on direct medical costs associated with diabetes. As a result, the prevalence of diabetes

is the parameter which requires the highest level of variation in expenditure. The second sensitive parameter of the model is the cost of hospitalizations. The prevalence of diabetes is, again, the most important parameter to estimate the total indirect costs (Figure 1 B). However, the probability of early retirement involves an equally relevant variation.

Figure 1 - One-way Sensitivity Analysis Results: Tornado Diagram



DISCUSSION

Chronic non-communicable diseases are one of the most difficult challenges for the health systems, due to their steady and relentless growth. Undoubtedly, the most paradigmatic example is diabetes mellitus [27]. However, many governments and health programmes are unaware of the consequences of diabetes increase and its serious complications.

To our knowledge, the present study is the first attempt to evaluate the annual economic burden of diseases associated with Diabetes in both NHS and social perspectives, with a probabilistic model considering the heterogeneity and scarcity of the information available in Italy.

The study showed that DM is a widespread disease in the population (prevalence of 5.5% in 2012), with an average annual expenditure of € 20.45 billion (95% CI: € 18.61 - € 22.29 billion). This result includes both the expenditure of the Italian NHS (direct costs) and that incurred by social welfare (indirect costs). For the latter a total expenditure of € 10.7 billion was estimated, € 9.0 billion of which are associated with early retirement caused by the disease, and € 1.62 billion with absenteeism caused by the severity of the disease. These results are different from the study of Kavanos et al. [4] estimating a total expenditure of € 5.36 billion in 2010 associated with absenteeism and € 7.19 billion with early retirement. With reference to early retirement, the difference can be attributed to a higher estimate of early retirees (+12.3%), which can be caused by a higher prevalence of the disease in 2012., This study too used the average annual income at retirement, instead of the average annual pension considered in the study of Kanavos et al., which is slightly higher (+9.5%). As far as absenteeism is concerned, the difference between the two approaches is due to a lower number of diabetics in active employment (our estimation is 53.5% less). This difference is due to the different data source. In fact, while in this study the estimate was made using the data reported by ISTAT [3, 23], Kanavos et al. reported a survey developed by the author. In our opinion ISTAT data [3, 23] seem to be the most reliable source available in Italy.

However, the study confirms that the expenditure on indirect costs should never be overlooked. In fact, more than half of the total disease expenditure is linked to this cost item. It should be noted

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that the expenditure on indirect costs can be estimated only for absenteeism and early retirement, therefore our approach may underestimate these type of costs.

The expenditure on the estimated direct medical cost to the Italian NHS was approximately € 9.59 billion (95% CI: € 8.11 - € 11.06). In this case, the estimated expenditure was in line with the value identified by Kanavos et al [4] (€ 8.5 billion) that was included within the confidence interval estimated by our study. With reference to 2012, the total health care expenditure of the Italian NHS was € 114.5 billion [28]. Our study estimated that the COI related to diabetes care in Italy absorbs 8,3% of total public health expenditure.

The estimated average annual cost associated with direct medical costs was € 3,640 for each diabetic patient. This estimation not only includes the costs of hospitalizations, medications and specialist services, but also costs of SMBG and hypoglycemic events, not taken into account in other studies [1, 2]. In addition to this, the study pointed out the various costs associated with the therapies used to keep diabetes under control: Oral Therapy, BOT and Basal-Bolus Therapy. Although the information was not totally exhaustive, the study demonstrated that the Oral Therapy is the least expensive and the most widespread; BB and BOT therapies have much higher costs with respect to oral therapy (BB +24% and BOT +12).

The cost of hospitalization was the main item of health care costs for the treatment of diabetes in Italy. Hospitalizations can be caused by a high prevalence of the disease, but also by deficiencies in the management of patient care [3]. The opportunity to reduce this cost could be the main objective of economic and health policies in the future years. In fact, pursuing a policy of appropriate drug treatment and diabetes monitoring could allow a better allocation of resources and potential savings to the NHS.

Finally, several studies [29] showed that in a large part of people suffering from diabetes, the disease is diagnosed a few years after its onset. Even if the disease does not show any clear symptoms, the risk of vascular complications is already present . Therefore, it may be assumed that prevention and screening policies are the right actions to reduce the costs of diabetes.

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However, this study has some limitations. Firstly, it was not possible to identify a single national source collecting all data related to costs of the epidemiological disease. This issue has been approached carrying out a systematic literature review following specific guidelines accepted by the scientific community [9]. In this way, it was possible to organize the available data in a clear and scientific way, in order to extract as much evidence as possible. Secondly, the epidemiological data are poor and heterogeneous, particularly regarding the patient distribution by type of treatment and associated costs. It is often necessary to depend on sample data or data based on a single Italian region. Furthermore, the detected data by ARNO Diabetes Observatory are based on a enrolled patient population of 9.465.492 subject of 29 ASL in the sample ARNO, then it is a survey of objective data reporting clinically diagnosed diseases. Instead the data collected by ISTAT are based on questionnaire Survey Multiscopo, this means that reference subjectively reported diagnosis. The difference sources for the prevalence of diabetes between sources that report medically diagnosed pathologies and subjectively reported diagnosis since the two sources may lead to different results. However, the probabilistic sensitivity analysis has made it possible to take the heterogeneity of the different available data into account. Finally, the cost parameter considered in the model did not come from a single source, and it was not possible to clearly distinguish the different costs of diabetes. In particular, hypoglycemia and glucose monitoring costs are exposed to a risk of double counting and information on indirect costs was provided by Danish population registers [20]. Eventually, it should be noted that the COI are evaluated just for treated patients and nothing was assumed regarding patients without a drug therapy.

In conclusion, this work has not been devised to be a perfect instrument for estimating the economic burden of Diabetes. It will be a good tool for policy makers to properly understand the economic implications of diabetes treatment and care in Italy.

Appendix A

Publication	Analysis	Methodology	Key Findings
Annuario Statistico Italiano 2012- ISTAT	Repertory of official statistics on important topics for public life	The data of interest belong to "Istat-Indagine multiscopo: Aspetti della vita quotidiana" (annual sample) Year 2012	Prevalence of major chronic diseases including diabetes
Il diabete in Italia 2012- ISTAT	Collection of epidemiological data related to the pathology of diabetes and its complications	The data of interest belong to "Istat-Indagine multiscopo: Aspetti della vita quotidiana" (annual sample) Year 2011.	Prevalence of diabetes
VII REPORT HEALTH SEARCH Year 2011/2012	Monitoring of the disease has the greatest impact on the territory	A sampling model was validated by 700 General Practitioners (representatives on a regional basis), which included their patients within the database.	Proportion of diabetic patients under treatment
Rapporto ARNO - November 2011	Monitoring of the disease and its costs	Analysis conducted on a population of 9,465,492 serviceable by 29 ASL sample ARNO.	Prevalence of diabetes; spending for drug therapy, hospitalization and health specialist services

Publication	Analysis	Methodology	Key Findings
ADM-Standard Italiani per la cura del Diabete Mellito 2009-2010	Guidelines for the treatment of diabetes and the care of diabetic patients in Italy	Care lines drawn from the two scientific associations of Italian diabetologists (AMD and SID)	Daily use of test-routine conditions in the event of severe hypoglycaemia
Dossier n. 179/2009 Profili di assistenza e costi del diabete in Emilia-Romagna. (2005-2007).	Collection of data on the diabetic population under treatment resident in Emilia-Romagna	Empirical Analysis of diabetes in Emilia-Romagna through administrative data	Average annual cost per patient for: drug therapy, hospitalization and specialist services
Ravasio et al.2008	Analysis of cost-effectiveness between two alternative therapies (exenatide vs. Insulin Glargine)	Longitudinal survey in which two cohorts of patients received exenatide or insulin glargine. Follow-up Duration: 1 year.	Daily use of tests for each treatment and associated costs
Sorensen et al. 2009	Estimate of the lost productivity associated with diabetes in Denmark	Estimates of 2.2 million Danish randomly selected, approximately 40% of the adult population aged 18-70	Lost workdays/year for absenteeism and early retirement probability for the diabetic population
Tunis et al. 2010	Projection of long-term costs of self-monitoring of blood glucose (SMRG) in the diabetic population in France, Germany, Italy and Spain.	Review of the literature to identify country-specific estimates of glucose monitoring	Average annual tests used for oral therapy and associated costs

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