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Food, nutrition services and health system management: investigating the cost-disease relationship

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ENGLISH ABSTRACT

Background: During the past decade, rapid growth in several scientific fields of relevant interest and, in particular, in the area of population-based epidemiological evidence, has encouraged to better explaining the role of diet in the prevention and control of morbidity and mortality resulting from Non-Communicable Diseases (NCDs). Changes in daily eating patterns and lifestyles occurred with economic development, are having a noteworthy influence on the health and nutritional status of the populations.

As the availability of food expanded and become more assorted, there have been significant negative consequences in terms of inappropriate dietary patterns, decreased physical activities and a corresponding increase in chronic diet-related diseases. Chronic NCDs, such as diabetes, are becoming increasingly significant causes of disability among people, placing additional burdens on already overtaxed national health budgets.

Diabetes represents not only a major concern in terms of clinical care but also an immense public health challenge. In 2016, over 3 million and 200 thousand people in Italy reported suffering from diabetes, 5.3% of the total population. Eye, kidney, and cardiovascular diseases disproportionately affect people with diabetes, which involve significant healthcare costs. Although many interventions can reduce the health burden of diabetes, the economic management of health resources is still limited. Therefore, evidence is needed to inform healthcare professionals and policy-makers of the costs and benefits of these interventions, and thus help payers and patients establishing priorities for diabetes prevention and control interventions.

The aim of this population-based longitudinal study was to evaluate healthcare costs, diabetes prevalence, the onset of complications and the mortality of Diabetes Mellitus (DM) using the Cost-of-Illness (COI) approach on the combination of numerous administrative health databases. In other words, the model sought to estimate the average annual cost incurred by the Apulia Regional Health Service for the treatment of DM stratified by patients' comorbidities.

Methods: The Apulia region includes about 4 million individuals. Its DM population was identified through a combination of different databases: Hospital Discharge Registry (HDR), Cause of Death Registry (CDR), Outpatient Services Registry (OSR), User Fee Exempts Registry (UFER), and Drugs Prescription Registry (DPR). In order to estimate diabetes costs, a unique database matching the records extracted from data sources by using the personal ID number was created.
All individuals, who during the year 2005 had a hospital discharge with an ICD9-CM code 250.XX, and/or two consecutive prescriptions of drugs for diabetes (ATC code A10XXXX) within one year, and/or an exemption from co-payment healthcare costs specific for DM, were selected and followed up to 10 years. The prevalence, mortality, and healthcare costs (hospitalizations, drugs and outpatient examinations/visits) from the point of view of the Regional Health Service were calculated.

Results: A total of 264,126 eligible subjects in the year 2005 were identified. At the index date, the study population was aged 65-69 for age class on average and consisted of 15.47% male and 14.77% female, and 70-74 years (13.68% male and 15.67% female). Only 0.38% of the sample was < 15 years. It is possible to argue that different contributions of the three classes of costs (HDFs, pharmaceutical prescriptions and outpatient services) were found in different years. The percentage of hospital costs on total expenditure has recorded diverse phases over the years, ranging from € 2778.82 in 2006 (72.98%) of costs among diabetic patients, to € 4060.73 in 2016 (73.79%). Consequently, the relative contribution of the other costs decreased: pharmaceutical cost ranged from € 895.43 in 2006 (23.52%), to € 1144.70 in 2016 (20.8%), and outpatient costs ranged from € 133.63 in 2006 (3.51%), to € 297.77 in 2016 (5.41%) reaching the minimum value in 2014 (€ 86.05).

Conclusions: This study is the first that considers real Apulian data and COI model to estimate the economic burden of DM and its comorbidities from the Regional Health Service's perspective. Merging different administrative databases can provide many data from large populations observed for long periods. This study was effective for its ability to give, in a relatively short time, a quite big set of estimates of the burden of DM, punctually providing information to policy-makers for health planning. The

findings contained in this dissertation can be of interest to the sector involved in the control of public health, since economic evaluation is one of the most important components of studies focused on the management and control of public health. The model represents a valid decision support to evaluate the relative value of interventions that can improve the economic management of the health system and is effectively applicable to monitor the direct expense of the pathologies.

Keywords: Chronic Non-Communicable Diseases; NCDs; Diabetes; DM; Cost-of-Illness; COI; healthcare costs; evaluation model; Apulia Regional Health Service.

ITALIAN ABSTRACT

Background: Nell'ultimo decennio, l'accresciuto interesse manifestato in diversi ambiti scientifici e, in particolare, nell'ambito degli studi epidemiologici, ha contribuito a una più chiara definizione del ruolo della dieta nella prevenzione e nel controllo della morbilità e della mortalità derivanti da malattie croniche non trasmissibili (NCD). I mutamenti negli stili di vita, verificatisi a seguito dello sviluppo economico, stanno ancora notevolmente influenzando lo stato di salute e il comportamento alimentare di intere popolazioni.

Con l'aumento della disponibilità e dell'assortimento di cibo, sono state registrate conseguenze significativamente negative in termini di modelli dietetici inappropriati, diminuzione dell'attività fisica e un corrispondente aumento delle malattie croniche legate all'alimentazione. Le malattie croniche non trasmissibili (ad esempio, il diabete), essendo le principali cause di disabilità, pongono pesanti oneri sui bilanci sanitari nazionali già sovra-tassati.

Il diabete rappresenta ad oggi, non solo una delle maggiori preoccupazioni in termini di cure cliniche, ma anche una grande sfida per la salute pubblica. Nel 2016 oltre 3 milioni e 200 mila persone in Italia hanno riferito di avere il diabete; il 5,3% della popolazione totale. Le persone con diabete sono colpite in modo sproporzionato da malattie agli occhi, ai reni e da patologie cardiovascolari, le quali comportano costi sanitari significativi. Sebbene molti interventi possano ridurre il peso economico-sanitario del diabete, l'attività di gestione economica delle risorse sanitarie disponibili è ancora molto limitata. Pertanto, per informare gli operatori sanitari e i responsabili politici dei costi e dei benefici di nuovi e migliorati interventi, sono necessarie prove che possano abilmente stabilire quali sono le priorità per gli interventi di prevenzione e controllo del diabete.

Lo scopo di questo studio longitudinale basato sulla popolazione, è quello di valutare i costi sanitari, la prevalenza, l'insorgenza di complicanze e la mortalità del Diabete Mellito (DM) usando l'approccio Cost-of-Illness (COI) per la combinazione dei database sanitari amministrativi. In altri termini, il modello ha cercato di stimare il costo

medio annuo sostenuto dal Servizio Sanitario della Regione Puglia per il trattamento del DM stratificato per comorbidità.

Metodi: Gli abitanti della Regione Puglia sono circa 4 milioni. La popolazione diabetica pugliese è stata identificata attraverso una combinazione di diversi database: Registro di Dimissione Ospedaliera (HDR), Registro Mortalità (CDR), Registro Servizi Ambulatoriali (OSR), Registro Esenti (UFER) e Registro Prescrizioni Farmaceutiche (DPR). Al fine di stimare i costi del diabete, è stato creato un database univoco corrispondente ai record estratti dalle fonti di dati utilizzando un codice personale identificativo (ID).
Tutti gli individui che nel corso del 2005 hanno avuto una dimissione ospedaliera con un codice ICD9-CM 250.XX, e / o due prescrizioni consecutive di farmaci per il diabete (codice ATC A10XXXX), e / o un'esenzione dal pagamento dei costi sanitari specifici per diabete, sono stati selezionati e seguiti per un periodo di 10 anni. Seguendo la prospettiva del Servizio Sanitario Regionale sono stati calcolati la prevalenza, la mortalità e i costi sanitari (costi per ricovero, farmaci e visite / esami ambulatoriali).

Risultati: 264.126 soggetti che hanno risposto ai criteri di inclusione, sono stati identificati nel 2005. In tale data, la popolazione oggetto d'analisi aveva un'età media, identificata per classi di età di 65-69 anni ed era composta per il 15,47% di uomini e il 14,77% di donne e 70-74 anni (13,68% maschi e 15,67% femmine). Solo lo 0,38% del campione aveva meno di 15 anni.
È possibile sostenere che per diversi anni sono stati riscontrati differenti contributi delle tre classi di costo (costi per ricovero, prescrizioni farmaceutiche e servizi ambulatoriali). La percentuale dei costi per ricovero sulla spesa totale ha registrato diverse fasi, passando da € 2778,82 nel 2006 (72,98%) dei costi tra i pazienti diabetici, a € 4060,73 nel 2016 (73,79%). Di conseguenza, il contributo relativo degli altri costi è stato inferiore: il costo farmaceutico è variato da € 895,43 nel 2006 (23,52%), a € 1144,70 nel 2016 (20,8%), e i costi ambulatoriali da € 133,63 nel 2006 (3,51%), a € 297,77 nel 2016 (5,41%) raggiungendo il valore minimo nel 2014 (€ 86,05).

Conclusioni: Tale studio è stato il primo a definire un modello considerando dati reali provenienti dai registri sanitari della Regione Puglia e utilizzando l'approccio COI per stimare l'onere economico del DM e delle sue comorbilità dal punto di vista del Servizio Sanitario Regionale. La combinazione dei database sanitari-amministrativi, fornisce una grande quantità di dati provenienti da grandi popolazioni osservate per lunghi periodi di tempo. Il presente studio è stato efficace per la sua capacità di fornire, in tempi relativamente brevi, una serie piuttosto ampia di stime dell'onere del DM, fornendo informazioni puntuali ai responsabili politici per la pianificazione sanitaria.
I risultati contenuti in questa tesi possono essere di interesse per il settore impegnato nel controllo della salute pubblica in quanto, la valutazione economica, è una delle componenti più importanti degli studi focalizzati sulla gestione e sul controllo della salute pubblica. Il modello, oltre a risultare applicabile per monitorare la spesa diretta delle patologie, rappresenta uno strumento decisionale atto a migliorare la gestione economica del sistema sanitario.

Parole chiave: Malattie croniche non trasmissibili; Diabete; DM; Cost-of-Illness; COI; costi sanitari; modello di valutazione; Servizio Sanitario Regione Puglia.

CONTENTS

GLOSSARY OF ABBREVIATIONS

Abbreviation	Meaning
ADA	American Diabetes Association
AIC	Marketing Authorization Code (drugs field)
ATC	Anatomical Therapeutic Chemical Classification System
AUD	Australian Dollar
BMI	Body Mass Index
CDCP	Center for Disease Control and Prevention
CDR	Cause of Death Registry
CHD	Coronary Heart Disease
CI	Confidence Interval
COI	Cost-of-Illness
CVD	Cardiovascular Disease
DALY	Disability Adjusted Life Years
DDD	Defined Daily Dose
DM	Diabetes Mellitus
DPR	Drugs Prescription Registry
DPR	Drugs prescription registry
DRG	Diagnosis Related Group
ESRD	End-Stage Renal Disease
EURO-DURG	European Drug Utilization Research Group
FAO	Food and Agriculture Organization
GAD	Glutamic Acid Decarboxylase
HDF	Hospital Discharge Form
HDR	Hospital Discharge Registry
HRQoL	Health-Related Quality of Life
IARC	International Agency for Research on Cancer
ICD-9 CM	International Classification of Diseases, 9th revision - Clinical Modification
ICER	Incremental Cost-Effectiveness Ratio

ID	Identification Code
IDF	International Diabetes Federation
IFG	Impaired Fasting Glucose
IGT	Impaired Glucose Tolerance
IHME	Institute for Health Metrics and Evaluation
ISS	Italian Institute of Health
ISTAT	Italian National Institute of Statistics
IUGR	Intrauterine Growth Retardation
LEA	Essential Levels of Assistance
NCD	Non-Communicable Disease
NGO	Non-Governative Organization
NOP	National Outcome Program
NSP	Non-Starch Polysaccharides
OSR	Outpatient Services Registry
PUFA	Polyunsaturated Fatty Acids
QALY	Quality Adjusted Life Years
QOL	Quality Of Life
SD	Standard Deviation
SFA	Saturated Fatty Acids
SSN	National Health Service
T1D	Type 1 Diabetes
T2D	Type 2 Diabetes
UFER	User Fee Exempts Registry
WHA	World Health Assembly
WHO	World Health Organization

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1. INTRODUCTION

According to the world cultural diversity, the eating patterns characterize to a large extent people's wellness, growth, and development (Greenhalgh, 2016). Some unhealthy and risky behaviors, like physical inactivity and tobacco use, can alter the result for better or worse. The cultural, social, economic, and political environment can influence the health of populations except active actions are taken to make the environment a wellness-promoting one (Andermann, 2016).

Since the earliest WHO publications (1990 – 2002 (a - f)), there have been enormous improvements in the scientific research field, significant development of knowledge, and a deepened international awareness in the prevention and control of chronic illnesses. Moreover, the theory of the basic life course, the *continuum* of human lives from fetus to seniors, and the important mapping of the human genome have become part of any issue concerning chronic diseases (WHO, 2000). The influences in the womb and subsequently in the course of life, even if in a different way, clearly have a strong effect on the manifestation of chronic diseases. Both under- and over-nutrition, as well as the effects of both man-made and surrounding environments, are increasingly recognized as the main factors for the development of chronic diseases. The recognition of such elements not only give a comprehensible and clear frame of what is occurring but also offer diverse prospects to address them. To date, people most exposed to these diseases are better identified; those who are more disadvantaged in the richest countries, and the populations of developing and transitional countries.

Latest studies revealed that the influencing factors, contributing to chronic disease development, have permanence in the organism (Australian Institute of Health and Welfare, 2012; WHO, 2005(a)). These factors include the atomic environment of the genetic material; the macroscopic urban setting; the impact of social and political actions affecting the health and diet of people; and the way in which already stretched agriculture system will change the choices accessible and the recommendations to carry out a healthy lifestyle (Australian Institute of Health and Welfare, 2012).

As for chronic diseases, even if the risk occurs at all stages of the life, at the same time, all ages are full of opportunities for their prevention. Under- and over-nutrition negatively and, in a different way, influence disease growth; as a result, the developing world needs further targeting. Poor people need diverse preventive approaches from the

richer (Müller et al., 2005; Uwaezuoke, 2015; Shrimpton et al., 2012). The activity has to start with the deepening of the individual risk factors, and attempts at prevention and health promotion must also take account of the wider social, political and economic environment as well. Industry, commerce, buyers, and advertising have to be included in the prevention spiral (Kavaler et al., 2003).

The present dissertation starts with an overview to understand how the science of nutrition and nutritional services can affect the health of an individual to prevent and control non-communicable diseases, particularly, diabetes. Then, the study presents the findings of a comprehensive study carried out with health administrative databases of the Apulia region (Italy) from 2006 – 2016.

In the following paragraphs, a thorough analysis presents a critical review of both the existing lifestyle impacts and the role of diet in preventing and controlling morbidity and premature mortality resulting from diabetes. Moreover, some of the specific dietary components that increase the probability of diseases occurrence in individuals, and interventions to modify their impact, have also been identified. A major focus was upon both the emerging role and importance of valuing the whole range of costs associated with the treatment of diabetes from a Regional Health Service perspective, and the potential use of this information to create a model useful for the continuous monitoring of epidemiology and costs. Such a model could be applied also in other disease areas of interest for assisting the decision-making process in healthcare.

The *third section* presents an overview of the research methodology applied.

It gives a detailed account of the COI (Cost-of-Illness) approach used to evaluate the economic burden that diabetes imposes on society as a whole and on State's coffers. It also highlights how health administrative databases can be used as the primary data source to assess the costs of such pathology.

The *fourth section* is the main focal point of this thesis as it gives a detailed account of the disease-costing model. It is in three parts. The first one, after a brief description of the sample investigated, gives an overall view of the direct costs calculated using the Hospital Discharge Registry. The second one gives an overall vision about the direct costs calculated for Drugs Prescription Registry. Finally, the third one shows information on the outpatients' services costs.

In light of the above, the *last section* discusses aspects of the research findings, summarizes and concludes this dissertation. It gives a snapshot view of the research outcome by highlighting significant attributes made to frame the current direct expenses of diabetes incurred by the health system of the Apulia region.

1.1 The global burden of chronic diseases in the developed and developing countries

Nutrition represents an important factor for the promotion and preservation of good health throughout life. It is recognized as a determinant of chronic NCDs, and as an important element of the prevention activities as well (WHO, 2002(e)). The chronic diseases here considered are related to diet and nutrition and show the greatest public health burden, in terms of both direct cost to government, and disability adjusted life years (DALYs) (Cecchini et al., 2010; WHO, 2005(b)). These are osteoporosis, cancer, obesity, dental diseases, cardiovascular diseases and diabetes.

The burden of chronic diseases is quickly increasing worldwide. In 2001, chronic diseases contributed at 33.9 million of deaths in the world (60% of total reported deaths in the world) and 46% of the global burden of disease (WHO, 2002(f)). According to the last statistical estimates, the percentage of the burden of NCDs is estimated to increase to 57% by 2020 (Benziger et al., 2016). Almost 50% of the total chronic disease deaths are assignable to cardiovascular diseases. Diabetes and obesity are presenting troubling trends, not only for their rapid spreading but also because they have started to become visible from a young age (Benziger et al., 2016).

Contrary to what is usually thought, the chronic diseases are a persistent problem in several developed countries and, to date, developing countries are progressively more suffering from high public health burden caused by chronic diseases (Petersen et al., 2012). Among the regions included by the WHO, in 5 out of 6 the high percentage of deaths are provoked by chronic disease (WHO, 2002(c)). It is evident that the epithet "diseases of abundance" assigned to chronic diseases is a mistake since they affect both poorest countries and the poorer population in richer countries. This rapid shift in the pattern of disease is taking place at a faster rate in developing regions rather than it did in the industrialized regions (WHO, 2002(d)). By 2020, it has been estimated that

chronic diseases will account for approximately 75% of all deaths in the world, of which 75% due to stroke and more than 70% due to diabetes will appear in developing countries (Barker et al., 1993(a); Harris, 2019). In this latter region, it has been observed that the number of diabetics will increase by more than 2.5-times, up to 228 million in 2025 (Barker et al., 1993(b); Harris, 2019). Instead, the existing prevalence that has reached unprecedented levels concerns overweight and obesity. Annually, the rate constantly increases in most developing countries and the health implications of this are shocking (Hayes et al., 2019; Fanzo et al., 2019). For example, some of them have to face a double burden of disease becoming threatening challenges for the national health system. India has to address challenges posed by a group of communicable and chronic diseases together. Another problem is the obesity, which will become a serious issue in Latin America, Africa and Asia up to 2020, despite the common incidence of under-nutrition (Szwarcwald et al., 20219; Fanzo et al., 2019).

The actual scientific debate asserts that chronic diseases are mainly preventable illnesses. The currently available scientific evidence provides a strong starting point to give a good reason for taking action now even if scientific research is needed to clarify some mechanisms that link health and diet. For people already suffered, the drugs treatment is needed but the most cost-effective approach remains the primary prevention considered to be affordable and sustainable to cope with the chronic disease epidemic (Jakovljevic et al., 2019; WHO, 2013). Modern eating patterns are identified as risk behaviors that move across regions like an infectious disease, influencing diseases worldwide. Genetic predisposition, sex, and age are non-modifiable factors but many of the risks associated with human wellness are modifiable (Kruk, 2007). Such risks embrace behavioral factors (such as diet, tobacco use, alcohol consumption, physical inactivity, etc); biological factors (such as hyperinsulinemia, overweight, dyslipidemia, hypertension, etc); and societal factors, which take into account a complex group of interacting socio-economic, cultural and other aspects. For decades, the diet has been considered to play a key role as a risk factor for chronic diseases (Li et al., 2014; Odermatt, 2011). Since 1950, great changes at the international level have shaped the world inducing variations in eating patterns, firstly in developed regions and recently in developing countries. Traditional plant-based diets have been switched with fat- and energy-diets containing many animal-based foods. However, nutrition is only one of the

many risk factors; another important one is physical activity. It is recognized that the sedentary lifestyle has an important factor of influence on health and a recent study states that only in the city of São Paulo, in Brazil, sedentary behavior is followed by 70 - 80% of the population (Barker et al., 2001). The need for actions to address new control and prevention measures to stop the spread of chronic diseases is now widely accepted by many countries, but the developing regions are still behind in realizing such measures (Azevedo et al., 2019). Everywhere, efforts to prevent and neutralize the rise in chronic diseases are progressively assigned a higher priority. Indeed, the USA have shown a great interest giving birth to the bilateral agencies and no-profit organizations in addressing health promotion, food, and nutrition policies and strategy for the prevention of chronic diseases (Aboderin et al., 2002).

The need to face the challenges posed by the spreading of chronic diseases was recognized firstly by the International Conference on Nutrition in 1992 (WHO, 2002(a); Aboderin et al., 2002; Godfrey et al., 2000), secondly, by the World Health Assembly (WHA) in 1998 (Forsen et al., 2000(a); Eriksson et al., 1999). More recently, in 2002, the WHA approved a resolution that encouraged the USA to work together with the WHO in order to develop :*''...a global strategy on diet, physical activity and health for the prevention and control of non-communicable diseases, based on evidence and best practices, with special emphasis on an integrated approach..."* (Rich-Edwards et al., 1999).

Several factors have inhibited evolution in the prevention of chronic diseases. Underestimation of the productiveness of interventions, the conviction of a long delay in achieving measurable impact, commercial pressures, institutional issues and inadequate resources are some examples. The interrelation among these aspects can be seen by a study carried out in North Karelia, Finland. The rate of age-adjusted mortality for coronary heart disease dropped between 1970 and 1995 (Leon et al., 1998). Analyzing the three main risk factors, respectively smoking, high blood pressure, raised plasma cholesterol, indicated that diet represented the first element of this substantial decline in cardiovascular disease; the drugs treatments have shown a small role (Leon et al., 1998). In such context, the pressure of consumer demand on the food market carried out a very important function (Sun- Waterhouse, 2011).

Another significant experience is that of the Republic of Korea. Their eating pattern is prevalently based on the high-vegetable diet despite major social and economic changing (Mckeigue, 1997). Such a population has lower percentages of chronic diseases and a lower level of fat intake and obesity prevalence compared to the other industrialized countries with analogous economic growth (Lithell et al., 1996).

A solution to the global problem of nutrition would be to create a fruitful dialogue with the food companies in order to improve the effective food labeling, support the production of healthier products, spread the daily use of fruit and vegetables and encourage the production of food with less saturated fat (Cash et al., 2005). Planetary "health and nutrition literacy" demands an immense increase in investigation and resources (Charlton, 2016).

Finally, taking into account that the poor people are exposed to the social disadvantage in terms of incidence of chronic diseases, access to the care and considering their low rates of acceptance of health-promoting behaviors, national policies should support them as they are the most vulnerable at risk and have the least power to actuate change.

1.2 An integrated approach to diet-related and nutrition-related diseases

Poverty and discrimination are the principal causes of malnutrition. Removing such causes is necessarily a social and political commitment and nutritional programs represent only one aspect of this issue. Safety, attention to social aspects, various food supplies limit malnutrition and decrease the risk of chronic diseases as well. Nutritional scarcity increases the likelihood of contracting an infectious disease, in particular for the children and vice versa (Eriksson et al., 2000; Must et al., 1999). From a public health point of view, there is a strong interconnection between identified policies and programs to prevent both chronic diseases and other diet- and nutrition-related diseases (Must et al., 1999; Prentice et al., 2008). This approach is the essence of the countries that have substantial public health budget, but it remains, for the most part, dedicated to the prevention of deficits and infections (Prentice et al., 2008). Actually, there is no country in the developed regions, where the fight against deficit and infection is no longer the prerogatives of public health (Engl et al., 2019). Since rich countries are used to programming strategy in order to contrast the proliferation of chronic diseases, they can

intensify the effectiveness of strategies by applying them to the prevention of nutritional deficiencies and food-related illnesses.

An exemplary model could be that developed by Latin America countries (Singhal et al., 2001). In these countries' guidelines have been developed to assign the same prerogative to the prevention of nutritional shortage and chronic diseases. In Brazil, for example, the eating guidelines provided to the population, shown the same attention to the food-related diseases, chronic diseases and the prevention of nutritional scarcity (Ravelli et al., 2000).

1.3 Food, nutrition and prevention of chronic diseases through the life course

The burden of chronic diseases is quickly increasing. This issue represents a key determinant of global public health. Although almost 80% of deaths for chronic diseases happen in developing countries (WHO, 2002(c)), everywhere is evident that the risk of these diseases begins in the mother womb and continue till the elderly (Barker et al., 1989; 1993(a, b); 1995; 2000; 2001). For these reasons, the prevention strategies' have to base on a life-course approach in order to catch both the cumulative risk and the many intervention's opportunities. A possible phases' identification of the life-course approach can be: fetal development and infancy; childhood and adolescence; adulthood; and elderly (WHO, 2019; Kuh et al., 2004).

1.3.1 Fetal development and infancy

Among the researched factors in fetal life, intrauterine growth retardation (IUGR) has been detected in the developed regions as associated with a more likely risk of developing stroke, cardiovascular diseases, and diabetes (WHO, 2002(d); Aboderin et al., 2002; Godfrey et al., 2000; Forsen et al., 2000(b); Eirksson et al., 1999). More recently, macrosomia has been investigated as another factor implying an increased risk of cardiovascular disease and diabetes (Leon et al., 1998; McKeigue, 1997; Lithell et al., 1996; Martyn et al., 1996; Martyn et al., 1994; McCance et al., 1994; Plagemann et al., 2008; Yang et al., 2019). A research performed in India has showed a relation between impaired glucose acceptance and high ponderal index at birth (Fall et al.,

1998). High birth weight has also been investigated as connected to an increased risk of different type of cancers (Wojcik et al., 2019). Such studies should be considered not only for instantaneous mortality and/or morbidity data, but also for long-term results such as diet-related chronic diseases.

In the next phase of the life, infancy, the lack of normal weight and height growth, can be a symptom of the late appearance of chronic diseases. A connection between low growth in infancy and an elevated risk of coronary heart disease (CHD) without take into account the size at birth, has been investigated (Eriksson et al., 2001). Moreover, it has been revealed that abnormal height growth is linked to the risk of stroke and diabetes (Aboderin et al., 2002; Rich-Edwards et al., 1999; McCarron et al., 2001; Forsen et al., 2000(a); Hart et al., 2000; Jousilahti et al., 2000; McCarron et al., 2000; Owino et al., 2019; Garriga et al., 2019). The breast-feeding phase is often associated with the appearance of chronic diseases in the later stages of life (Singhal et al., 2001; Wilson et al., 1998). Some studies have revealed a positive correlation between being healthy and exclusive breast-feeding for a prolonged period. In particular, when the lactation is ensured, there is a low percentage to become obese in the future (Gillman et al., 2001; von Kries et al., 1999- 2000; Hawkins et al., 2019; Wambach et al., 2019).

Another issue regards the formula. The formula is baby food used by the mothers when they have difficulty in breast-feeding. Data from most observational studies of newborns, have generally recommended adverse effects of formula consumption on the risk factors for cardiovascular disease, but little knowledge to support this concept is available from evidence-based studies (Roberts, 2001). However, current researches indicate adverse effects of the formula on the risk factors of cardiovascular disease; this is consistent with the observations of a high mortality rate among elderly who, during the infancy, were fed with formula (Roberts, 2001; Wambach et al., 2019; Fall, 1992). Nonetheless, the appearances of celiac disease, some types of cancer, inflammatory bowel disease, and diabetes have been linked to some breast-milk surrogates (Davis, 2001).

1.3.2 Childhood and adolescence

A connection between low growth during childhood and an amplified risk of CHD has been investigated (Eriksson et al., 2001; Clayton et al., 2007). It is difficult to verify a self-determining effect of weight since infant overweight usually continues in the adult phase. A relative retrospective cohort study (Must et al., 1992), states that adolescence weight is significantly connected to colon cancer. Moreover, Frankel et al., (1998), found that after considering the confounding effects of social class, there was a significant positive association between adolescence energy intake and cancer mortality in adults. In support of such a concept, the International Agency for Research on Cancer (IARC), concluded that correlation evidence between obesity appearance and cancer risk was existing (IARC, 2002). Other studies demonstrated that low tallness during adolescence is not only linked to a socio-economic deficit but, also, with an elevated risk of CHD, stroke, and diabetes (Rich-Edwards, 1999; Aboderin et al., 2002; McCarron et al., 2001; Jousilahti et al., 2000; Wannamethee et al., 1998; Marmot et al., 2001; Jolliffe et al., 2007). Low tallness is a susceptible premature-socio-economic deprivation index and it reflects a connection among premature under-nutrition and infectious disease (Gunnell et al., 1998; Davey-Smith et al., 2000). Tallness is also a useful index of socio-economic and nutritional status in adolescence. Poor fetal and infancy growth have been connected with elevated risk of cardiovascular disease during the adult phase. On the other hand, a high calorie intake during infancy and adolescence may be correlated to an amplified risk of cancer (Berkey et al., 2019).

The presence of high blood pressure in adolescents happens on the background of unhealthy lifestyles, embracing excessive intakes of saturated fats, cholesterol, salt, and reduced physical activity followed by high levels of sedentary life (Aboderin et al., 2002). During adolescence, recurrent alcohol and tobacco consumption causes an increase in blood pressure (Berenson et al., 1991; Okasha et al., 2000). Moreover, the prevalence of elevated blood pressure is shown not only in adults with low socio-economic status (Bartley et al., 2000; Bao et al., 1995; Tan et al., 2000), but in children with low socio-economic conditions as well (Aboderin et al., 2002). During the infancy, higher blood pressure together with other risk factors, determine anatomical changes associated with cardiovascular risk, increased ventricular size and mass, and cutbacks in artery elasticity (Aboderin et al., 2002).

During adolescence, the increasing of unhealthy habits tending to raise risk factors, contributes to raising blood pressure and other risk factors in early life, most of which develop in the adult stage. The worst thing in the first appearances of chronic disease is that once they have appeared, they are prone to afflict the entire life of the human being. Nonetheless, there are demonstrated proofs that such risk factors can be redressed. For example, overweight and obesity are two factors that, even if are particularly hard to correct, could be removed bringing benefit to the individual. Some studies (Parsons et al., 1999; 2001) have revealed a greater persistence gave by the subsequent weight gain in adolescence. As mentioned by Dietz (2001), almost 65% of overweight adolescents have one extra risk factor for developing cardiovascular diseases and over 20% have two or more chronic diseases.

In light of the above, it is evident that a healthy eating pattern followed by the infant/adolescent has beneficial effects on the entire later body composition (Roberts, 2001). For example, increased birth weight amplifies the risk to develop obesity in the later stages of life, but children, who follow the right diet, presenting low weight, tend to remain thin into adulthood (Dietz, 2001; Strauss, 2000).

The world made up of wrong food choices is controlled by the adolescent market, making the right healthy options difficult to choose. Most of the reasons that implicate increased blood pressure, reduced glucose tolerance are linked to unhealthy eating pattern such diet with many saturated fats, sugar, salt, and low intake of healthy nutrients such as fiber, vitamins, potassium, etc (Aboderin et al., 2002). Such an unhealthy lifestyle is also the driver of the appearance of chronic diseases in life early stages.

1.3.3 Adulthood

During the entire life cycle the adult stage is the most important stage in which chronic diseases begin to appear and the preventive strategies to reduce the risk factors are implemented (Campisi et al., 2019). To improve treatments, control and preventive strategies deepen to what extent the risk factors continue to be important in the development of chronic diseases during the adult stage and, in addition, to what extent modifying such risk factors, with appropriate treatments, will make a difference to the

emergence of disease (Mann, 2002). In the academic literature, the most studied correlations are between hearth diseases and diabetes with an appearances peak recognized during the adult stage due to the unhealthy habits adopted; alcohol and tobacco use, obesity, physical inactivity (Elisaf, 2001). Some studies (Kannel, 1996; Mac Mahon et al., 1990; Hooper et al., 2003; Hu et al., 2000; Lopez, 1999; Nichols et al., 2019; Varghese et al., 2019) specifically revealed that high blood pressure and cholesterol, raise the risk of CHD and stroke. Instead, Davey-Smith et al., (2000), Farmer et al., (2019) and Coppola et al., (2019), assert that obesity, physical inactivity and intense alcohol use, increase the percentage of CHD, stroke and diabetes appearance. Such findings have been identified not only in the developed regions but evidence from developing countries is beginning to emerge as well (Gupta et al., 2000). Low socio-economic condition is often associated with a higher risk of cardiovascular disease and diabetes in rich countries (Davey-Smith, 1997). In addition, such a scenario will gradually move towards the most disadvantaged groups of society and some proofs are already present in some poor Brazilian and Moroccan groups (Aboderin et al., 2002, Monteiro et al., 2002; Benjelloun, 2002).

1.3.4 Older people

During the last stage of life, most chronic diseases are visible and there is a concrete need both in adopting health-promoting behaviors and in maximizing health by avoiding or delaying infirmities.

In the last decades, the "elderly" definition has been in transition. During the last century, when people reached 60 years, exceeded the average life expectancy (WHO, 2002(e)). To date, the spreading of healthy aging and the constant attention of the health national systems toward the elderly, have improved the elderly quality of life everywhere. Nonetheless, most chronic diseases appear in this stage of life (Darnton et al., 2001; Manton et al., 1997). Cancers, cardiovascular disease, type 2 diabetes, and the main burden of general chronic diseases reach the culmination in this stage. Recently, the elderly have been supported in following a healthy eating pattern respecting both a well-balanced diet and constant physical exercise (Darnton et al., 2001; WHO, 2002(e)). Finally, even if little attention for the elderly primary prevention has been dedicated, the

increase of rate in decline caused by external factors has been commonly assumed reversible at any age (WHO, 1999). Interventions to support the individual and to improve environments for ensuring healthier and active aging, will often lead to increased elderly independence (WHO, 1999).

1.4 Intervening throughout life

In the literature is common to find the application of the life-course approach to the prevention and control of chronic disease (Mikkelsen et al., 2019; Marmot et al., 2019). Such evidence is still inconsistent and sometimes ambiguous. In literature, it is clearly evident and it is possible to confirm with scientific studies that an unhealthy dietary pattern, smoking and alcohol habits and physical inactivity are proven risk factors for chronic diseases. Instead, the biological risk factors such as hypertension, obesity and dyslipidemia are recognized as causes for stroke, coronary heart disease and diabetes (Mochizuki et al., 2019). Trends confirm that many risk factors such as obesity, physical inactivity and, smoking habit in the developing world, are upwards. Studied interventions prove to be effective but should extend beyond risk factors and persist throughout life (Brown et al., 2019). In addition, some strategies of preventive interventions adopted in the first phases of life allow obtaining benefits for the entire life course. Secondary prevention, through improving daily eating patterns and physical activity, represents a harmonious strategy both to delay the progression of chronic diseases and to reduce the disease burden and mortality from such illnesses. As such, it is fundamental that risk factors have to be faced and modified during the life course. In this sense, the role of primary prevention is to direct the populations towards a healthier direction. Even little modifications in the lifestyle of most people who are exposed to moderate risk, can reflect a huge impact in terms of population-related risk of infirmity, death, and costs (Rukavina et al., 2014). For example, reductions in cholesterol, blood pressure and other risk factors have a great effect on reducing healthcare costs. Some studies have shown as a better lifestyle than the one previously followed, can reduce the risk of developing diabetes by 58% (WHO, 2002(b); Tuomilehto et al., 2001). Other studies have revealed that almost 81% of cases of coronary heart disease and almost 91% of type 2 diabetes, could be avoided only by modifying lifestyle factors, as well as

one-third of cancers could be avoided by following a healthy eating pattern (Stampfer et al., 2000; Hu et al., 2001; Key, 2002).

To date, the nutritional guidelines should guarantee that the overall benefit produced by such recommendations, prevails over any possible negative impacts on the determined population's subgroups. For example, the spread of campaigns to control the obeseness may cause panic and apprehension about fat and, thus, could begin a spiral of under-nutrition problems in adolescent girls (Raisborough, 2016). The main objectives of the national guidelines are to contrast and/or reduce the effect of adverse dietary changes that have happened during the past century in the developed regions and, recently, in many developing countries. The actual nutritive goals should consider the effects of environmental change (Swinburn et al., 2004; Béné et al., 2019). Indeed, the scarcity of food that occurs periodically in the under-developed countries no longer constitute a selective advantage but increase the exposition to develop chronic diseases. Huge food supply is a recent phenomenon and it did not represent a positive solution considering the exponential growth of the diet-related diseases. A combination of physical activity, healthy foods such as fruits, vegetables and fish, and frequent social interactions, is the most probable lifestyle profile to improve health, to the detriment of the present habit that moves towards increasing consumption of animal proteins (Ashton et al., 2019; Thomson et al., 2019). Such mechanism of doing so, confirms that increasingly national dietary guidelines are not followed and often the population does not know its existence. In the British case, only 2 - 4% of the population are currently consuming the recommended level of saturated fat, and 5% of them are achieving the recommended levels of fiber consumption (Praagman et al., 2019). This trend is more or less the same in many other developed countries, where most of people are not aware of what exactly the dietary guidelines suggest.

Based on what abovementioned, the most important need to address in short time is to modify the risk factors that affect the adult stage of life. With all populations aging, the numbers and potential cost savings would be enormous and realizable. In addition, revolutions in health promotion contexts need to be amplified and considered as an essential part of whichever intervention. Actions to reduce the use of sugary drinks and of high-energy-density foods, as well as techniques to restrain and control smoking, will have an influence both on the society and, specifically, on the economic burden of the

diet-related diseases (Fedacko et al., 2019). These changes representing the "humanity challenge" require the joint participation of politicians, communities, consumer representatives, health systems, municipalities, as well as economists as a whole.

1.5 Dietary goals for preventing diet-related chronic diseases

The population's dietary goals specify the average intake of people identified as consistent with the preservation of health in the population as a whole. In this context, a low prevalence of food-related diseases is evident (Fedacko et al., 2019). Even if in the literature often specific information is missing, in a theoretical model to define and to observe whether the percentage of a risk factor increases or decreases, it would be necessary to constantly check the relationship established by the multiple-randomized-control tests of interventions on population that represents a representative sample. This practice should adapt the referable risk of the adverse exposure in that population. Such theoretical model use the following criteria to illustrate in which way the "evidence" of the social and environmental factors can leads to behavioral changes and, thus, modify risks. As established by the World Cancer Research Fund the principles are reported (FAO/WHO, 1998).

- "Convincing evidence", epidemiological studies show consistent associations between risk factors and disease. The presented evidence descends from diverse studies that embrace randomized controlled trials of sufficient size and prospective observational studies.
- "Likely evidence", epidemiological studies show adequately consistent relationships between risk factors and disease, but there are deficiencies in the available evidence or contrary-evidence that can preclude a clear and definite judgment. Such deficiencies can be insufficient trials available; insufficient duration of trials; inadequate sample sizes; incomplete follow-up.
- "Hypothetical evidence", case-control and cross-sectional studies show potential evidences. Randomized controlled trials with some deficiency, observational studies or non-randomized controlled trials are available. Evidence based on non-epidemiological studies gives support.

- "Insufficient evidence", the case-studies offer few results compared to the few studies identified in the literature and the latter are not sufficient to establish an association between risk factors and disease. Limited or no evidence is available from randomized controlled trials. Temporary associations need more well designed research.

National and local institutions have established dietary recommendations for the prevention of diet-related chronic diseases. As shown by Nishida et al., (2004), some recommendations are presented in Table 1. The specificity of these suggestions is that they are expressed in numerical terms, rather than as increases or decreases of some foods. The following table highlights the latest recommendations provided by the WHO and FAO Joint Consultation in 2002 compared to those provided by WHO in 1989. They show no particular differences, but the previous report issued by WHO provided an incomplete direction in terms of proportions of various energy sources, particularly for certain fats. Instead, the latest report integrates the previous one reporting the correct nutritional requirements as stated by FAO and WHO (FAO/WHO, (1998 – 2003)).

Table 1. Population nutrient-intake goals for the prevention of diet-related NCDs

Dietary factor	1989 WHO Study Group recommendations[2]	2002 Joint WHO/FAO Expert Consultation recommendations[1]	Rationale for Joint WHO/FAO Expert Consultation recommendations
Total fat	15–30%	15–30%	Obesity/CVD/diabetes
Saturated fatty acids (SFAs)	0–10%	<10%	Diabetes/CVD
Polyunsaturated fatty acids (PUFAs)	3–7%	6–10%	CVD
n-6 PUFAs		5–8%	CVD
n-3 PUFAs		1–2%	CVD
Trans fatty acids		<1%	CVD
Monounsaturated fatty acids (MUFAs)		By difference*	
Total carbohydrate	55–75%	55–75%†	
Free sugars‡	0–10%	<10%	Obesity/dental diseases
Complex carbohydrate	50–70%	No recommendation	
Protein	10–15%	10–15%§	
Cholesterol	0–300 mg/day	<300 mg/day	CVD
Sodium chloride (Sodium)‖	<6 g/day	<5 g/day (<2 g/day)	CVD
Fruits and vegetables	≥400 g/day	≥400 g/day	CVD/cancer
Pulses, nuts and seeds	≥30 g/day (as part of the 400 g of fruit and vegetables)		
Total dietary fibre	27–40 g/day	From foods	
NSP	16–24 g/day	From foods	Obesity/diabetes/CVD/Cancer

* This is calculated as: total fat - (SFAs saturated fatty acids + PUFAs polyunsaturated fatty acids + trans fatty acids).

† The percentage of total energy available after taking into account that consumed as protein and fat, hence the wide range.

‡ The term ‘‘free sugars’’ refers to all monosaccharides and disaccharides added to foods by the manufacturer, cook or consumer, plus sugars naturally present in honey, syrups and fruit juices.

§ The suggested range should be seen in the light of the Joint WHO/FAO/UNU Expert Consultation on Protein and Amino Acid Requirements in Human Nutrition, held in Geneva from 9 to 16 April 2002.

‖ Salt should be iodized appropriately. The need to adjust salt iodization, depending on observed sodium intake and surveillance of iodine status of the population, should be recognized.

Source: Nishida et al., 2004.

To decipher these recommendations in dietary guidelines, some considerations are needed.

The rates of “total fats” express the diverse habits of the different populations. Indeed, there are some regions where the typical fat intake is above 30% as well as those where the typical intake may be low, less than 15%. 20% of fat exactly contributes to maintain good health (FAO/WHO, 2003).

As for the “free sugars”, studies revealed that they are responsible to increase the risk of unhealthy weight gain (Stubbs et al., 2000; Rolls et al., 2000). Eating patterns that are restricted in free sugars have been shown to decrease total energy intake and encourage weight loss (Mann et al., 1970; Smith et al., 1996). A research carried out by Raben et al., (2002) has shown that when a sugary soft drink is consumed there is elevated energy intake and a progressive increase in body weight when compared with energy-free drinks. Children fall into being overweight if they use a high quantity of sugary drinks compared to their peers who use in minor terms (Ludwig et al., 2001; Hale et al., 2019). Fruits, vegetables, and not-refined grains contain the largest number of non-starch polysaccharides (NSP). The recommended use of not-refined grains and fruits and vegetables is > 20 g per day of NSP (> 25 g per day of total dietary fiber) (Table 1).

Although physical activity is not included in Table 1, it represents one of the most important factors to contribute to maintaining healthy body weight and, a general human-being wellness. International guidelines suggest playing physical activity one hour per day on most days during the week of moderate-intensity activity, such as walking. In particular, such recommendation is addressed to people with sedentary professions. The advice is based on the analysis of what reported in the literature on the relationships between body weight and physical activity and, more practically, on the estimates of energy balance (Collese et al., 2019; Caballero, 2007).

1.6 Recommendations for preventing overweight and obesity

The obesity epidemic is rapidly spreading in developed and developing regions with differences between and within countries. In developing regions, the epidemic is widespread between women, people who live in an urban setting and who have good socio-economic conditions, whereas, in developed regions, this problem is common among younger adults and children. It has been detected that the estimated annual healthcare costs of obesity-related illness are a staggering $190.2 billion or almost 21% of annual medical spending in the United States (Cawley et al., 2012). Considering only the childhood obesity, it has been revealed that it is responsible for $14 billion in direct medical costs. In general, obesity-related medical costs are projected to rise considerably; today's obese children are likely to become tomorrow's obese adults (Marder et al., 2006; Wang et al., 2008). Even if the direct costs in other developed countries are lower, they still consume a considerable amount of national health budgets (ADA, 2010(b)). Instead, with indirect costs is meant a type of cost much higher than direct cost, which embrace medical visits, lost working days, disability pensions and premature mortality, while intangible costs include compromised quality of life (ADA, 2010(b)).

Because the risk factors of cardiovascular disease, hypertension, and diabetes, grow with increasing weight, there are many intersections between the prevention of both overweight and of chronic diseases, especially type 2 diabetes (Alberti et al., 2007). To improve the population education strategies will need changes based on the new health policies. The increasing globalization and industrialization are correlated to the changes in dietary model and behavior; especially eating patterns are directed towards diets rich in fats, proteins, and high-energy foods. Such new paths represent the reasons behind the growth of the obesity followed by a dramatic rise in the prevalence of diabetes (CDCP, 2008).

As measured by the BMI, mortality rates increase in parallel with the increase in overweight levels. Therefore, as the BMI grows, so too does the percentage of people with one or more comorbidity conditions.

Other “obesogenic” effects (word-for-word: obesity-promoting) are the environmental ones. Physical activity, for example, is a crucial determining factor for body weight. It is an important modifier of mortality and morbidity related to overweight. There is consistent evidence that moderate physical activity provides a significantly decreased risk of developing cardiovascular disease and it has a protective effect against mortality at all BMI levels in men with diabetes (Gill et al., 2008).

Another factor that could influence overweight in the course of life is the environment attended by children (Anzman et al., 2010; Dunton et al., 2009). Home and school are the first ones environments known by the children, promoting a healthy lifestyle that includes healthy food and physical activity. Despite its understandable importance in the development of the child, there is still low evidence to support this idea. Indeed, it has been demonstrated that the exposition and the easy access to fruits and vegetables in the home is vital for the improvement of individual preferences for these foods (Davies et al., 2004). As for the effect of the school environment on nutrition knowledge, the research carried out by the CDCP, (2008) has shown a positive implication of school-based interventions on obesity control and prevention.

The food composition, energy-rich and micronutrient-poor foods, represents another factor involved in the development of overweight and obesity (Baothman et al., 2016; Wang et al., 2019). Fast foods, identified in the “eat least” category of the common national dietary guidelines, are among the most marketed and widespread products. Often, the target customers are the children. Due to the advertising of such products, they influence the grocery purchased by the parents (Huang et al., 2009). Children are not able to understand television program contents from the persuasive purpose of advertising. For this reason, it is considered that there is enough evidence to warrant interventions to limit the negative effects of advertising on such target customer (Hogan et al., 2003; Huang et al., 2009; Engelgau et al., 2004; Zhang et al., 2004).

Socio-economic conditions are considered a contributory effect on the development of the overweight. Many studies highlighted that there is a strong relationship between the progression of obesity and poor socio-economic conditions (Conklin et al., 2019; Fuentes et al., 2019; Monteiro et al., 2004). The development of obesity begins with women in developed regions and in high-income groups but as the endemic progresses, overweight and obesity are more common in people with poor socio-economic status.

Such a connection can also be two-way; more unfavorable socio-economic condition supports obesity, and obese people are more probable to be included in the low socio-economic status group. The procedures by which socio-economic conditions have an impact on lifestyle models are numerous and need detailed explanations. Nonetheless, people with poor socio-economic conditions are more exposed to the obesogenic context, since their lifestyle and behaviors are completely subject to the offer linked to their economics possibilities. Some evidence-based studies that prove the effects of low socio-economic status on influencing people to obesity are consistent particularly in higher income countries (Zajac et al., 2010).

1.6.1 General strategies for obesity prevention

Obesity rates are increasing in all parts of the world (International obesity task force, 2005). Despite growing identification of the threat to global public health, few interventions have been started to decrease the prevalence of obesity on a population- wide scale. Obesity represents a global issue and there is an imperative need to develop international strategies to address it.

Many attempts to address obesity have been unproductive (Committee on Evaluating Progress of Obesity Prevention Effort, 2014). This is because most actions aim at preventing or treating obesity, focus primarily on producing individual variations in eating and physical activity patterns. What has been lacking is a strategy that, at the same time, recognizes and deals with the economic, environmental and cultural forces stimulating and supporting positive energy balance. If on the one hand, interventions that have been successful in producing short- term improvements in diet, physical activity and weight have been recognized, on the other, few interventions to effectively change sustainable behaviors have been found (Foster et al., 2005; Crawford et al., 2000). Strategically, it could be interesting to marshal intense resources to help people from the early stages of life. The prevention of obesity in young children should be considered a priority in every national political agenda. Summerbell et al., (2012), assert that some strategies for children could be:

- promoting exclusive use of home-made food;
- promoting an active lifestyle;

- avoiding the use of added sugars;
- promoting the intake of fruits and vegetables;
- instructing mothers to accept the requests of his/her child to regulate energy intake rather than feeding until the plate is empty;
- assuring the correct micronutrient use needed to promote optimal growth.

In developing countries, nutritional programs designed to control or prevent food-related problems, need to assess physical standards to prevent excess or low energy supplies to children. Instead, in economic transition regions, as people become constantly more inactive and able to consume large amounts of energy-dense foods, it is necessary to ensure the intake of healthy components of traditional diets.

Globally, poor populations often replace healthy foods by heavily marketed, sugary beverages and energy-dense fatty, salty and sugary foods. Such a tendency is linked to the regular growth of obesity. The planned actions are considered necessary to improve the quality of eating patterns by increasing consumption of fruits and vegetables, in addition to increasing physical activity to reduce the epidemic of obesity and associated diseases.

1.7 Diabetes and strategies to control and prevent it

1.7.1 Background

Diabetes represents a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of different organs, especially eyes, kidneys, nerves, heart, and blood vessels (ADA, 2010(a)). Diabetes, as a chronic illness, can be responsible of severe complications and premature death (CDCP, 2009) and needs continuing medical care and constant programs of education and support for patients to prevent acute complications and to reduce the risk of long-term disabilities (ADA, 2010(a)). In addition, some conditions, such as impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), are considered ‘pre-diabetes notifications’. They should not be referred at clinical entities

but rather as risk factors for diabetes, cardiovascular disease and premature mortality (ADA, 2010(a); Leu et al., 2010; de Courten 2010). A right lifestyle, with physical activity, producing 5-10% loss of body weight, can control or delay the development of diabetes in people with pre-diabetes conditions (ADA, 2010(b)).

Diabetes is classified into four categories: type 1 diabetes (T1D), type 2 diabetes (T2D), gestational diabetes mellitus and other types of diabetes due to other causes. The first two categories are the most common forms (ADA, 2010(b); Bennett et al., 2005).

T1D is principally due to pancreatic islet β-cell destruction and is characterized by absolute insulin deficiency. A person affected by T1D is completely dependent on insulin therapy for the preservation of life. Individuals with T1D have a normal metabolism before the disease is clinically manifest, but the process of β-cell destruction can be discovered earlier by the presence of certain auto-anti-bodies. This type of diabetes is often characterized by the presence of anti-GAD, anti-islet cells, or anti-insulin antibodies, which reveals the autoimmune processes that lead to β-cell destruction. T1D represents about 5-15% of all diagnosed cases of diabetes (Stene et al., 2008). The appearance of β-cell autoimmunity is linked in a proportional way, to the incidence of T1D in various regions; indeed, Sweden and Finland recorded the highest prevalence of islet cell antibody and they are associated with the highest frequency of T1D (Triplitt et al., 2008). As for the T1D risk factors, they can be genetic, environmental and for the autoimmune deficiency (CDCP, 2008).

T2D is identified by disorders of insulin action and secretion (ADA, 2010(a)). Both are usually present when diabetes occurs clinically. Although the specific etiology of T2D is not clearly known, autoimmune destruction of the β-cells does not occur (Bennett et al., 2005). People with T2D usually have insulin resistance and relative insulin deficiency. At the time of the first diagnosis of diabetes, patients do not need insulin treatment to survive, although many require it for glycemic control (Home et al., 2014). Most of the people with T2D are obese when diabetes appears, and such a condition aggravates insulin resistance. T2D is often undiagnosed for many years since T2D in the earlier stages is not severe enough; however, patients are at increased risk of developing micro- and macro-vascular complications. The effects of insulin resistance may be restricted with weight reduction or pharmacotherapy; this evolves in the normalization of glycemia. Moreover, such type of diabetes is frequent in women who

have a previous history of gestational diabetes and in subjects with characteristics of insulin resistance syndrome, such as hypertension or dyslipidemia (Bennett et al., 2005). T2D accounts for over 90% of all diabetes cases globally (CDCP, 2008; Zimmet et al., 2001). T2D is increasingly common in both adults and children mainly due to the increases in the prevalence of a sedentary lifestyle and obesity (Zimmet et al., 2001; Carlisle et al., 2008). Some epidemiological studies affirm diabetes that develops in adults may be directly considered as T2D, although this result in some misclassification of the type of diabetes (Kenny et al., 1995; Warram et al., 2005). The prevalence and incidence of T2D increase with age, and, in particular, its prevalence varies among different ethnicity as well (Carlisle et al., 2008). A healthy lifestyle, constant glycemic control, and correct pharmacotherapy interventions can control or prevent T2D from developing in high-risk populations and can slow its devastating complications (Carlisle et al., 2008).

1.7.2 T1D incidence

There is a solid increase in the incidence of T1D in most populations investigated. A research carried out in Austria showed that the incidence of T1D doubled from 7.3/100,000 in 1979-1984 to 14.6/100,000 in 2000-2005 (Schober et al., 2008). Moreover, studies from Germany, Finland, Croatia, France, and China show that T1D is growing at 2-5% per annum (Ali, 2010). Such incidence depends on different reasons: age, geographical and migration.

T1D can appear at the age of 4-6 and 10-14 years (Haller et al., 2005). The T1D first appearance is comparable in several European countries, but the average age has a tendency to be higher in African and Asian populations. These results may coincide with greater exposure to infectious actors and a greater insulin demand due, for example, to insulin resistance at the puberty stage of life. A study confirms that almost half of people with T1D are adults and that new cases continue to occur around the age of 70 years old (Ali, 2010).

One of the most surprising problems of T1D is its wide variation in the world. The appearance of T1D in the infancy phase can occur differently up to 400 times (Stene et al., 2008). In an Italian region, Sardinia, it has been recorded the highest incidence rates

in the world of T1D, while oriental and equatorial populations have the lowest ones (Stene et al., 2008). Moreover, although in the Scandinavian peninsula, Finland, Sweden and Denmark populations are genetically homogenous and are equally developed societies living at the same latitude, incidence rates vary from a maximum of 45 per 100,000 in Finland to 28 in Sweden and 20 in Denmark. While incidence rates are much higher in European populations, the absolute number of new cases is almost the same in Asia and Europe as the Asian population is much larger. It is estimated that out of 400,000 new T1D that occur each year in children under the age of 14, about half of them appear in Asia, although incidence rates are much lower (Ali, 2010).

Migration is another effect affecting T1D incidence. A research confirms, in some populations, migrants tend to take on the incidence rates of the host countries within one or two generations. In a study performed in United Kingdom, incidence rates of T1D among children in South Asia were almost identical to those in the United Kingdom and were more than 20-fold higher than those who still lived in South Asia. This may indicate that children moving from low-incidence areas to high-incidence areas may get a higher risk due to environmental factors (Ali, 2010).

1.7.3 T2D incidence

Prospective studies about population-based T2D incidence that perform a diagnostic diabetes test are few and carried out on populations that are often not nationally representative (Warram et al., 2005; Geiss et al., 2008). Most of the American evidence-based studies use medical records, registries, Hospital Discharge Forms (HDF), cross-sectional survey data and general health care administrative data to categorize which are the newly diagnosed cases of diabetes (Geiss et al., 2008). Medicare, a federal health insurance program for people who are 65 or older, younger people with disabilities and people with end-stage renal disease (ESRD), indicated that the T2D incidence was also increasing among the elderly (McBean et al., 2004).

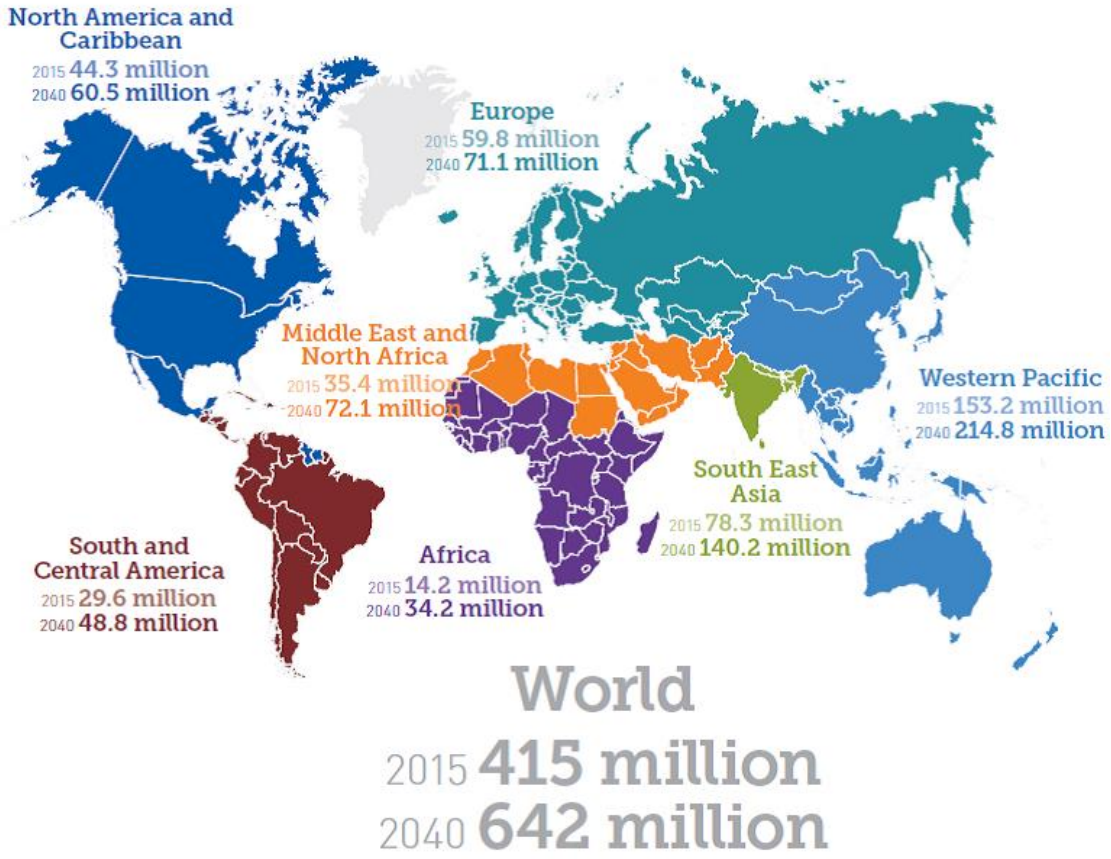
In recent times, in 2015, 30.3 million Americans, 9.4% of the population, had diabetes and of the 30.3 million adults, 23.1 million were diagnosed and 7.2 million were undiagnosed (CDCP, 2017). Each year, the number of newly diagnosed cases of diabetes exceeds the number of deaths among adults with diabetes (McBean et al., 2004; Green et al., 2003). This disproportion between the number of deaths among

people with diabetes and the number of people entering the prevalent pool will probably continue to grow (Geiss et al., 2008). In addition to age, the growth in body mass index (BMI) also coincides with the growing trend of the incidence of T2D in the United States (Warram et al., 2005; Geiss et al., 2008).

Increases in BMI and obesity are the most common factors in the development of diabetes. In addition, a number of other lifestyle factors are associated with incidence, such as smoking, physical inactivity, excessive alcohol consumption, and various aspects of diet (Geiss et al., 2008; Warram et al., 2005). During the last decade, in infancy and adolescence phases, the incidence of T2D has increased dramatically especially in poor groups of the populations (ADA, 2010(b)). An earlier study asserts that the majority of children and adolescents with diabetes had T2D, and only 1-2% of them were considered to have T1D or other rare forms of diabetes (ADA, 2000). Another old report suggested that between 8% and 45% of newly diagnosed diabetes cases in children and adolescents in the United States presented T2D and the variation in these percentages seemed to depend on age group, ethnicity and strategy of sampling (Fagot-Campagna et al., 2001).

Nowadays, it is estimated that 415 million people are living with diabetes in the world, which is estimated to be 1 out of 11 of the world's adult population. 46% of people with diabetes are undiagnosed. This data is expected to rise to 642 million people living with diabetes worldwide by 2040 (Ogurtsova et al., 2017) (Figure 1).

Figure 1: estimated number of people with diabetes worldwide and per region in 2015 and 2040 (20 – 79 years).



Source: IDF Diabetes Atlas

1.7.4 Diet, physical activity and diabetes

The dietary suggestions for the T1D aim to reduce excessive postprandial glycemia and fluctuations in blood glucose levels (ADA, 2001). The hypoglycemia control is a fundamental aim. For people with diabetes, dietary recommendations and nutrition therapies are designed to decrease the risk of long-term complications both by improving glycemic control and by reducing other risk factors linked to vascular disease (Evert et al., 2014). Food choice and dietary advice for people with T2D and T1D are similar, and the main principles seem similar to those for entire high-risk CHD populations. Thus, it is not necessary to differentiate food for diabetics by the rest of the family.

The rapid increase in T2D incidence rates suggests an important role for environmental factors for arresting the global diabetes epidemic. The most dramatic increases are recorded in those societies most exposed to rapid changes in the type of diet consumed, reductions in physical activity, and increases in overweight and obesity (Popkin et al., 2004). These daily dietary patterns are typically rich in saturated fatty acids, poor in NSP (non-starch polysaccharides) as well as energy-dense. Around the world, overweight and obesity are associated with an increased risk of T2D. Some studies state that BMI-categories are often not suitable for identifying the risk of developing T2D in individuals of the entire population due to ethnicity differences and the different distribution of excess adiposity (Vistisen et al., 2014; Oktay et al., 2017). To this end, pieces of evidence demonstrated by some nutrients such as saturated fatty acids that increase the risk of T2D, and NSP that has a protective effect, are more realistic rather than those proofs for many other nutrients that have been implicated.

As regards physical activity, longitudinal studies confirmed that increasing physical exercise decreases the risk of the T2D appearance without considering the adiposity degree (Bennett et al., 2005; Kriska et al., 1993; Helmrich et al., 1991). Intense exercise can substantially improve insulin sensitivity (Wranik, 2008). Nevertheless, to improve insulin sensitivity, the minimum intensity and duration of exercise required have not been investigated yet. The recent scientific literature concerning the association between NSP intake and T2D is complex due to the ambiguity of the definitions adopted; often, ‘fibre’ and ‘NSP’ are used in an interchangeable way.

A study conducted in Uganda revealed that the scarcity of diabetes cases in Africa could stem from the generous use of NSP in the diet. The NSP and a wide use of minimally-processed or unprocessed carbohydrates have a protective effect. In the study, it was also hypothesized that the worldwide development of diabetes was supported by the rising intakes of extremely-processed carbohydrate, poor in NSPs (Trowell, 1975). In other experimental, evidence-based studies, high intakes of NSP have contributed to decreasing blood glucose and insulin levels in people with T2D and impaired glucose tolerance (Mann, 2001; O’Connor et al., 2018). In addition, the increased use of fruits, vegetables, and cereals, was an element of the dietary patterns associated with a reduced risk of evolution of impaired glucose tolerance to T2D into two controlled trials (Tuomilehto et al., 2002; Knowler et al., 2002). In light of these results, there is

evidence of a probable protective effect of NSP. Substantially, a low glycemic index does not give health benefits as a food rich in fat or sugar can also result in a reduced glycemic index (Augustin et al., 2002; Rilstone et al., 2019). Therefore, although this capacity of carbohydrate-content foods can positively influence the risk of developing T2D, evidence is accorded to a lower level of strength than to evidence related to NSP-content foods.

The dietary recommendation for diabetics often involves a great change in lifestyle and physicians are usually not able to suggest the right advice, even if their support is essential to encourage compliance with the medical advice given by them and specifically by nutritionists. The actual implementation of nutritional therapy is now easier than in the past because the "healthy-rules" of the diet are recommended for diabetics but can also be appreciated by all family members.

In conclusion, for the most of diabetics, nutritional guidelines will increasingly highlight nutritional changes to ensure the right energy intakes, reductions of fatty acids, sodium and sugar and satisfactory daily use of fruit and vegetables. Specialized dietary advice from dieticians, taking into account individual preferences and metabolic characteristics, are desirable for all diabetics, but this is not universally available for all populations. Many people with T2D are able to effectively cope with advice on nutritional and dietary principles as long as they obtain the support of other health professionals such as diabetes nurses or trained community members and family members. Regular follow-up encourages compliance with the diet and has been shown to support weight loss over the time (Folsom et al., 1996; Hunter, 2019).

1.7.5 General trend of diabetes

Diabetes is one of the globally major public health threats and, to date represents an increasingly prevalent and costly cause of morbidity and mortality (Harris et al., 1998; Flegal et al., 1991; Mokdad et al., 2001(a); Mokdad et al., 2001(b)). Recent studies evaluated that in 2000 and 2010 the estimated prevalence of diabetes among people more than ≥ 20 years old was 2.8% (171 million people) and 6.4% (285 million people) respectively. Such prevalence is projected to increase reaching 7.7% and affecting 439 million people by 2030 (Harris et al., 1998; Flegal et al., 1991).

According to the International Diabetes Federation (IDF) statistics, presently every seven seconds someone is estimated to die from diabetes or its complications, with 50% of those deaths (4 million in total per year) occurring under the age of 60 years (IDF, 2017). This is against the background of a global diabetes prevalence of 8.8% (95% confidence interval 7.2-11.3%) of the world population in 2017, standardized for the age group 20-79 years (ESC, 2019). Such prevalence is expected to increase to 9.9% (95% CI 7.5-12.7%) by the year 2045. In general words, this replicates a population of 424.9 million (95% CI 346.4-545.4 million) people with diabetes worldwide in 2017 with an estimate of a 48% increase to 628.6 million people (95% CI 477.0-808.7 million) for the year 2045. The general trend has shown continuous growth; 151 million in 2000, 285 million in 2009 and 382 million in 2013. Disturbingly in this context, some 50% of all individuals with diabetes are undiagnosed, especially in developing countries (IDF, 2017).

Diabetes is expensive not only to the healthcare system but also to the society. 285 billion adults with diabetes in 2010 have been recorded. This number will continue to rise globally due to a growth of unhealthy eating patterns, an aging population, a spreading of urbanization and high prevalence of obesity and sedentary lifestyle (Shaw et al., 2010).

Expected healthcare costs for diabetes should increase to $ 490 billion in 2030 worldwide (Mokdad et al., 2001 (b)). The high economic burden of diabetes represents an urgent health policy issue (Colditz et al., 1990) and highlights the importance both of improving knowledge about new diabetes-prevention interventions and of investigating whether or not they can reduce healthcare costs.

Taking into account the global evolution of the disease burden of diabetes, actions to prevent and / or control and / or delay the diabetes' complications or the development of the diabetes itself, are urgently needed (Despres et al., 2001 (a)). Policy-makers and health professionals facing the growing demand for limited resources, have to look for new actions on how to prioritize healthcare resources in an efficient way (Chan et al., 1994). The cost-effectiveness analysis can help the decision-makers to effectively allocate resources across challenging needs to expand health outcomes from a limited budget (Boyko et al., 2000; Despres, 2001 (b)). Efficiency can be estimated using cost-benefit, cost-effectiveness or cost-utility analysis. Only the latter two methods are

adopted in healthcare field since the economic evaluation of health benefits is not acceptable on ethical and on practical matter (Mc Auley et al. 2002; Tuomilehto et al., 2002). Currently, in the decision-making process, economic analysis has not often been involved but it may increase in importance as healthcare costs continue to increase (Mc Auley et al., 2002). The use of the economic framework to inform and guide political decisions about resource allocation in diabetes prevention and control is important for some reasons. First, diabetes is expensive and the resources can be dedicated to diabetes prevention and control, are limited. Finally yet importantly, the demand for complete care and new interventions will continue to increase due to the increasing prevalence of diabetes (Mc Auley et al., 2002).

1.8 Health resources and economic burden of diabetes

Resource's use and health expenditure are associated with both clinical consequences of diabetes and modification of its risk factors such as, obesity (Hoerger et al., 2008). American Heart Association (2017), states that direct medical costs related to CVD are more extensive than medical costs related to any other disease, including Alzheimer and diabetes. Such costs embrace money spent on medical services via a physician, hospital or health care system, and corresponding or follow-up costs, such as prescription drugs, home health or nursing home care. According to a 2016 study, annual expenditure related to CVD is projected to increase to $749 billion in 2035 (AHA, 2017) and the annual cost of CVD can range from $8,200 to $13,100 per person depending on the presence or absence of diabetes (Stephens et al., 2006).

1.8.1 Health resources used for diabetes care

Several providers and system level factors influence health resources used for diabetes care. Diabetes, poor health, morbidity, and preventative care, result in incrementally more health services use (Ali et al., 2010). More in detail, it has been revealed that significant amounts of health services are used for chronic complications of diabetes. In particular, CVD, neurological, and renal complications are associated with high resource utilization due to diabetes (ADA, 2008). Some American statistics investigated that 24.3 million hospital inpatient days, 5.6 million emergency visits and 64.7 million

physician office visits are attributed to diabetes annually. In addition, the diabetes population aged 65 years or more uses a large amount of health resources, reflecting the high burden of diabetes placed on the Medicare program (ADA, 2008). Other studies reveal that diabetics have greater use of emergency visits, hospital inpatient care, outpatient and physician office visits, visits with health professionals, home health visits, and prescription drugs and medical supplies than their peers without such pathology (ADA, 2008; Hoerger et al., 2008; Ali et al., 2010; Killilea, 2002). In a study carried out by ADA (2008), it was shown that men with diabetes aged 60 to 64 years, record 8-fold the number of hospital inpatient days, 7-fold the number of emergency visits, and 6-fold the number of specialist medical and outpatient visits for heart failure more than their peers without that condition. In addition, people with such pathology double the risk of hospitalization compared to people without diabetes, and this risk is augmented by the presence of diabetes-related complications (Ali et al., 2010; ADA, 2008). Although most of the studies in this sector report macro- or micro-vascular complications as the main cause of diabetes-related hospitalizations, lower-income countries such as Ethiopia confront a greater proportion (2/3) of hospitalizations due to acute episodes of dysglycemia (Ali et al., 2010).

A population-based study (Evans et al., 2008) to compare prescription's utilization between patients with T2D and those who did not have diabetes was performed. In such study, it was revealed that the average number of drug prescriptions excluding anti-diabetic agents, was higher for patients with diabetes of all age groups. After data-adjusting for age, T2D' patients had a greater probability of 1.7-fold receiving a drug than patients who did not have diabetes. Cardiovascular drugs accounted for 28.8% of total prescriptions for T2D' patients. Furthermore, patients with diabetic complications are called "high users"; they use more expensive services than patients without complications do. For example, the Centers for Disease Control and Prevention Diabetes, group in the Managed Care Work Group, explains that diabetics with multiple complications use much more specialist care services (5.8-6.3 fold), more emergency visits (3.3-5.5 fold) and record more hospitalizations (3.3-11.9 fold) than those without complications (CDCD, 2001).

1.8.2 Economic burden of diabetes: different perspectives

Whatever way to assess and quantify the economic impact of any health condition is the perspective. In other terms, it means when costs are classified according to the viewpoint of the single individual, or his / her family, or health system, or, still, society as a whole. The International Diabetes Federation (IDF) represents the most important agency of research that publishes recent studies on diabetes healthcare expenditures (IDF, 2011). These different perspective shave been embraced by some studies in which evaluation methods have been developed. Specifically, in the literature they are considered the principal models: Jönsson (1998), Hex (2012) and 3C Study (McGuire et al., 2011).

The method studied by Jönsson requires understanding of diabetes prevalence, total healthcare budget, and a hypothesis of the percentage of the total cost of medical care for diabetics compared to the cost of care for people without diabetes, identified as "diabetes cost ratio" (R). Such a procedure is useful to calculate the total cost of care attributable to diabetics. Early evaluations of these costs (Williams, 2003) and the most recent evaluations (IDF, 2011) have lower and upper bounds of R of 2 and 3.

Some recent statistics have revealed that, in 2011, almost USD 465 billion was globally spent in treating diabetes and preventing its complications (IDF, 2011). In other words, this is 11% of the world's total health expenditure and for each diabetic the average cost was USD 1274. In addition, 20% of the total global costs of diabetes is at expense of low- and middle-income countries in which 80% of diabetics live (IDF, 2011). Instead, in high-income countries the average per person annual cost is USD 5063 compared with USD 271 in low- and middle-income countries. Such a type of estimation uses a "top-down" approach to assess expenditures on individuals using epidemiologic and financial data from populations. These IDF estimates do not make a distinction between T1D and T2D; however, the greatest burden of the expenditures will be attributable to the latter. Moreover, hospital admission is known to be the principal driver of expenditures and it has been recognized that the greatest difference in admissions between diabetics and those without, is seen in the young.

Hex et al. (2012), instead, elaborated a more commonly used top-down approach to separately evaluate T1D and T2D costs. Routine data on prescriptions, hospital admissions, primary care consultations, and some estimates of premature mortality

derived from epidemiological literature both to quantify the cost of T1D and T2D in the UK in 2010/2011 and to predict their evolution in 2035/2036 have been used by this method. Evaluations for informal care, productivity's loss caused by premature mortality, potential productivity's loss for those diabetics who remain at work (more known as "presenteeism" (Johns, 2010), and work's sickness absence, specifically called "absenteeism", have been considered. Results contained in the Table 2 shown the estimates of the economic burden of diabetes.

Table 2. Estimates of the economic burden of diabetes in the UK for 2010/2011 and projections to 2035/2036

Costs		2010/2011			2035/2036		
		All diabetes	Type 1 diabetes	Type 2 diabetes	All diabetes	Type 1 diabetes	Type 2 diabetes
Direct	Screening & testing	[a]0.1%	[a]0.2%	[a]0.2%	[a]0.1%	[a]0.2%	[a]0.1%
	Treatment & management	[a]20.9%	[a]28.7%	[a]20.0%	[a]20.2%	[a]30.7%	[a]19.0%
	Complications	[a]78.9%	[a]71.1%	[a]79.8%	[a]79.7%	[a]69.1%	[a]80.9%
	Total	£9.8 bn*	£1.0 bn	£8.8 bn	£16.9 bn	£1.8 bn	£15.1 bn
		[b]41.4%	[b]52.6%	[b]40.4%	[b] 42.5%	[b]42.9%	[b]42.4%
Indirect	Premature mortality	[c]34.4%	[c]62.3%	[c]32.4%	[c]27.8%	[c]30.9%	[c]27.4%
	Sickness absence	[c]6.8%	[c]10.5%	[c]6.6%	[c]6.2%	[c]5.9%	[c]6.2%
	Presenteeism	[c]21.9%	[c]10.1%	[c]22.7%	[c]16.4%	[c]15.7%	[c]16.5%
	Informal care	[c]36.9%	[c]17.1%	[c]38.3%	[c]49.6%	[c]47.5%	[c]49.9%
	Total	£13.9 bn	£0.9 bn	£13.0 bn	£22.9 bn	£2.4 bn	£20.5 bn
		[b]58.6%	[b]47.4%	[b]59.6%	[b]57.5%	[b]57.1%	[b]57.6%
Total		**£23.7 bn**	**£1.9 bn**	**£21.8 bn**	**£39.8 bn**	**£4.2 bn**	**£35.6 bn**

[a] Proportion of direct costs for that type of diabetes at that time.
[b] Proportion of all costs for that type of diabetes at that time.
[c] Proportion of indirect costs for that type of diabetes at that time.
* £1 ≈ USD 1.23
Source: Adapted from Hex et al., (2012).

Although these features are calculated in the UK context, they show important elements that can be applied also in other contexts. Forecasts for 2035/2036 make use of demographic projections on changes in prevalence and outcomes and within the category of direct assistance, the relative contributions of the sub-areas do not change. Instead, in the category of indirect costs, it is expected that the contributions of premature mortality costs will decrease, while those of informal care will increase. In general, in all sub-areas, costs rise, determined by higher complications costs, higher

prevalence, and higher treatment costs. Moreover, the authors state that "*whatever treatment to improve the way diabetes is treated that leads to both better glycemic control and fewer complications, could have a significant impact on these costs, but this remains to be assessed*" (Hex et al., 2012).

Primary prevention contributes significantly to the reduction in prevalence and the goals of treatment should be expanded to include other parameters such as blood pressure and lipids.

The bottom-up approach used in the 3C Study (McGuire et al., 2011) considers data on individual expenses to determine population-level costs and facilitates the estimates to be made for T1D or T2D without the need for diabetes cost ratio assumptions. 3C Study carried out into two regions of China, Beijing and Shantou, aims to describe coverage, cost, and care of T1D. The inclusion criterion was the person with T1D recruited from the outpatient and inpatient hospitals' reports. Interviews, data collection from medical discharge forms, and government sources were considered as "tools" of the methodology. They have been used in a combination of bottom-up and top-down approaches in order to evaluate direct medical and nonmedical costs, and indirect costs from point of views of health systems, families, patients, insurers, and society. Finally, other ongoing studies yet unpublished well prove that the diabetes cost ratio, in some regions, is going to significantly increase than the previously statistical ratios evaluated.

Hospitalization for diabetes represents a fundamental factor for health expenditure and, therefore, the possible complications of this pathology will strongly influence healthcare costs. Some studies have confirmed this trend.

The Cost of Diabetes in Europe – Type 2 study (CODE-2 study) (Williams et al., 2002) used the same bottom-up procedure in eight European countries and shown that the cost of standard healthcare per patient was 3.5-fold greater in patients with both micro- and macro-vascular complications than in those without such a type of complication. After the CODE-2 study, the CODEIRE research (Nolan et al., 2006) revealed that both micro- and macro-vascular complications contribute to raising the annual cost of care by 3.8 compared to diabetics without complications. Both micro- and macro-vascular complications were correlated in increments of 1.8 and 2.9, respectively. In recent times, Clarke et al. (2008) used a method to quantify the costs of diabetic complications in Western Australia. The following complications were considered: lower limb

amputation, ischemic heart disease, renal failure, chronic leg ulcer, heart failure, nonfatal stroke, and nonfatal myocardial infarction. The economic estimates varied from the average costs in the year the event occurred for the first time to a 60-year-old man. Thus, they ranged from AUD 28.66 (95% CI 22,989–34,202) for renal failure to AUD 11.66 (95% CI 10,931–12,450) for a non-fatal myocardial infarction (1 AUD ≈ 1.04 USD).

In light of this, it is possible to argue that it is true that initiatives to improve the quality of care reduce the currently high expenses of providing care to diabetics, but this is not entirely true since it is recognized as one of the principal aims of these initiatives. Indeed, health resources deriving from the reduction in complications that are not used, are not saved, but are used for other purposes. The principal aim of the health system is not to save money, but rather to improve the quality of life and the conditions that have the greatest impact on life through effective and efficient use of resources.

1.8.3 Economic comparisons of preventive alternatives

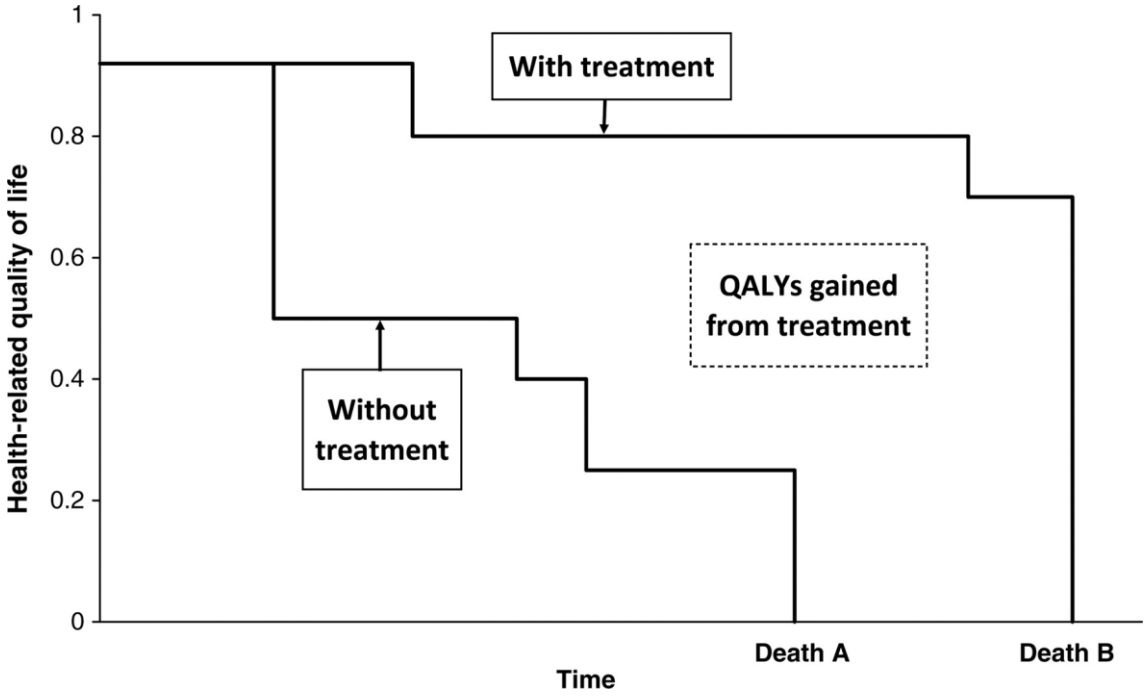
There are three main type of analyses for preventive and therapeutic alternatives; cost-benefit, cost-utility and cost-effectiveness analyses.

Cost-benefit analyses categorize the costs of operations and their probable benefits, giving an economic value and comparing the total amount of costs with the total amount of benefits in order to assign a cost-benefit ratio (Frew, 2010). Depending on the size of the numerator and denominator (cost-benefit ratio), it is more or less probable that the intervention is acceptable. Such a type of analysis is particularly useful for its feasibility and clarity, but there are problems when it is necessary to assign a valid economic value to the benefits; e.g. assessing the reduction of disability, extended life, or, still, better wellbeing.

Cost-utility analysis relies on the QALYs (quality adjusted life years) notion (Joish et al., 2005). The QALY combines "*the effects of health interventions on mortality and morbidity into a single index*" (Kind et al., 2009), thereby providing a common currency to compare different disease areas. During life, people face different health conditions and these health conditions are weighted on the utility score. The QALY concept combines the survival function of a person with his HRQoL (Figure 2). This shows the

QALYs can be gained from receiving treatment rather than receiving no treatment. The area under the curve represents the total QALY value.

Figure 2: QALYs gained from treatment



Source: Whitehead et al., (2010).

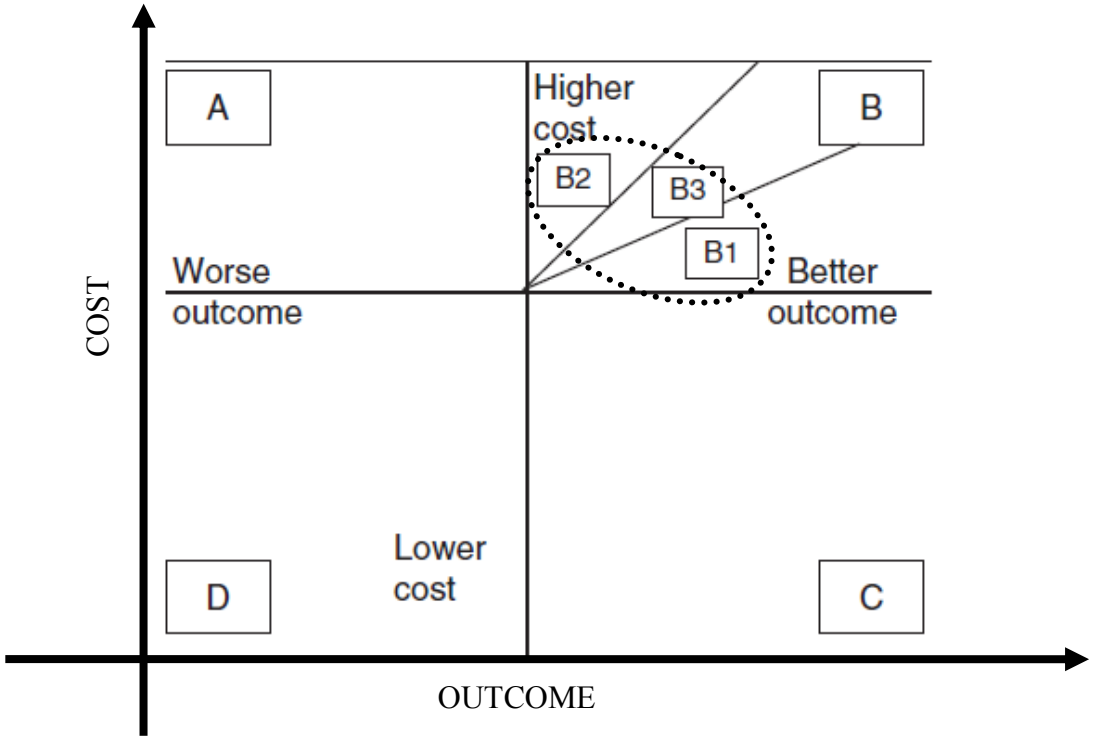
In other words, QALY joins the concepts of length and quality of life and requires assessments of "utility" which people attribute to different health states, such as dependency on renal dialysis.

Cost-effectiveness analysis is a method for assessing the gains in health relative to the costs of different health operations. This method allows decisions to be easily made on how to allocate resources as it directly relates to the financial and scientific implications of different interventions. The evaluation procedure is based on dividing the cost of an intervention expressed in economic units by the expected health gain expressed in natural units, such as the number of lives saved (Jamison, 2006). Such analysis bypassing the requirement to assign monetary values to all the benefits, faces the main disadvantage; interventions that lead to different types of benefits cannot be compared. For example, the cost-effectiveness of an intervention aimed at preventing end-stage renal disease (ESRD) cannot be compared with an intervention aimed at preventing

lower limb amputation, using this type of analysis. It can only be compared with similar ESRD interventions.

The only useful way to compare alternatives is the incremental cost-effectiveness ratio (ICER). This explains the ratio between the difference in costs and effectiveness for two interventions. Morris et al. (2012), Black (1990) and Laupacis et al (1992) deepened the validity of this measure. Indeed, as shown in Figure 3, the cost-effectiveness is seen as a diagram in which two intersecting axes, one relating to the cost, the other to the outcome, form four quadrants.

Figure 3: Cost-effectiveness diagram



Source: Laupacis et al. (1992), Morris et al., (2012)

"A" area embraces interventions that generate worse outcome at a higher cost. Practically, these are unacceptable. In "B" area, interventions generate better outcome but at higher costs; this is the most common case. In "C" area, the interventions are cost saving, in terms of a better outcome and lower cost; the most desirable situation. Ultimately, in "D" area, interventions are cheaper but produce worse outcomes.

Morris et al. (2012) assert that in "B" and "D" areas the acceptability of interventions must be addressed in terms of trade-offs. Specifically, in "B", there are improved

outcomes though at higher costs; in “D”, there is a cost reduction even if with a worse outcome.

In the study carried out by Laupacis et al. (1992), “B” area is divided into three sub-areas:

- “B1”, interventions are considered cost-effective because enhanced effects are achieved at little extra cost.
- “B2”, only a small improvement of effect requires comparatively large costs; interventions can be considered unacceptable.
- “B3”, is an intermediate zone in which the acceptability of the interventions is subjected to debate on the trade-off.

In situations where health resources are limited, moving to less expensive and less effective interventions can be beneficial to the population to an extent as to mitigate the losses that some individuals will suffer due to reduced effectiveness.

2. RATIONALE OF THE STUDY

This study is justified and rationalized by the increase in the economic burden of diabetes mellitus worldwide.

The incidence of diabetes was estimated to grow each year and in 2030, it will reach 7.7% (Shaw et al., 2010). Such estimation is higher than the prediction made only a few years ago (Gnavi et al., 2008). Nowadays, 90% of cases have T2D, which is the predominant form (WHO, 2014). According to the estimation of the Italian National Institute of Statistics (ISTAT, 2013) in 2010 in Italy, there were more than 3 million people with T2D diagnosed and 1 million people with the same type of diabetes undiagnosed. This trend is associated with populations' aging, improved health status, urbanization, and with worse lifestyle, and reduced physical activity (Astrup, 2001; Hu, 2011; Davis et al., 2006).

Estimates of diabetes costs give information to better define which are the priorities for: allocating scarce resources, attracting additional resources and managing assets to control diabetes. These analyses could help healthcare organizations, governments, legislators and national authorities in formulating strategies, policies, and programs for the control of diabetes and its complications. If these entities know what the economic impact of diabetes is in the population, they could be more willing to allocate resources efficiently.

The economic aspects of diabetes and its care persist to engage worldwide attention as the diabetes epidemic rises and health systems remain under pressure to satisfy most of the global needs within constrained resources (IDF, 2018). Its economic burden is one of the main concerns for many developed and developing countries. A recent study revealed that medical cost is two to three-fold higher (Barcelo et al., 2003) and economic cost is two to five-fold higher in diabetics compared to those without this pathology (ADA, 2003). The increasing healthcare cost, thus, causes the feeling that there is an urgent need for attention and action to develop prevention programs to reduce the cost burden to society. Diabetes associations, NGOs, health professionals, and diabetics need to know which is the current and future economic impact of this disease on the individual, family, society and healthcare systems (IDF, 2018).

In light of this, monitoring diabetes is crucial in public health inspection for planning health services, for defining the general burden of disease, for evaluating strategies in

prevention, control and outcome assessment. Administrative databases can be a useful and efficient tool for that aim, in particular, if they are able to provide accurate data from a large number of people observed over long periods.

The objective of this longitudinal population-based study was to evaluate healthcare costs, diabetes prevalence, the onset of complications and the mortality of diabetes mellitus through the application of the Cost-of-Illness (COI) approach on the combination of numerous administrative health databases.

3. METHODOLOGY

3.1 Cost-of-Illness approach: what it is and why to perform it

Cost-of-Illness (COI), also known as the Burden-of-Disease (BOD), is a notion that includes diverse characteristics of the disease effect on the health outcomes in a country, specific areas or communities. The categories of COI range from the incidence or prevalence of illness to its effect on morbidity, longevity and Quality of Life (QoL), and, also, financial facets such as direct and indirect costs deriving from premature death, disability or injury due to disease and/or its comorbidities (Jo, 2014).

The origins of today's COI approach rely on the works of Fein (1958), Mushkin et al., (1959), Weisbrod (1961), Rice et al., (1967) developed in the late 50s and early 60s. At the beginning, several public health measures were widespread and of public interest; just note the developments in the methods to limit polio with the advent of the Salk and Sabin vaccines. Later, in 1966, after debates on the most appropriate manner to further improve health, the first study to propose a method for estimating costs from the information available in existing databases, was that of Rice et al., (1967). This study became a *de facto* standard for future COI studies. It addressed the economic cost of illness taking into account direct and indirect costs' points of view.

More recently, Jefferson et al. (2000) stated "*the aim of COI studies is descriptive: to itemize, value, and sum the costs of a particular problem with the aim of giving an idea of its economic burden*". Therefore, in performing COI studies, researchers should recognize, identify, categorize and evaluate the costs that disease and its comorbidities can cause (Jefferson et al., 2000). Clabaugh and Ward (2008) recognize that "*COI presents useful opportunities for communicating with the public and policy makers on the relative importance of specific diseases and injuries*".

Nowadays, the increase in health costs, the limits of healthcare resources, the modification of refund models and theories on the effectiveness of health treatments have meant that COI estimates were defined as an important element in the choices made about diabetes care and management. COI studies have received much attention over time. As abovementioned, Mushkin et al., (1959) and Weisbrod (1961) developed a framework to identify the costs related to the disease as one part of a broader effort to

identify appropriate health programs for implementation. Since that time, COI estimates have also been proposed for use in identifying the burden of disease, possible areas for future improvements, and possible areas for priority setting in healthcare and research. At the core, COI estimates are a descriptive economic method (Tarricone, 2006). These estimates give information on the resources used related to a disease. Many researchers assert that together with prevalence, incidence, morbidity, and mortality data, economic appraisals represent the impact that society faces from a disease (Tarricone, 2006). An added benefit of the method is the ability of COI estimates to combine a variety of disease characteristics into one general statement regarding the burden of disease (Rice, 1967).

Economic COI perspectives consider, among others, two cost categories: direct and indirect costs (Jo, 2014).

The resources used in treating a disease, including expenditures for medical care (e.g. hospital care, physician services, nursing home care, drugs and other medical needs), produce direct economic costs. Recently, the inclusion of non-medical direct costs has also been supported, including the costs of transporting patients and assistance costs by family members (Ama et al., 2010; Sherman et al., 2001).

As for the indirect economic costs, they address the potential resources that are lost as a result of a disease. They incorporate the societal costs of morbidity, disability, and premature mortality. These non-medical costs represent the impact, present and future, of opportunities lost as an effect of the disease in question (e.g., diabetes) (Afroz et al. 2018).

Most early COI studies used one of two computational methods to determine the direct costs of the disease: “top-down” or “bottom-up” approach (Tolpin et al., 1983).

In the present study, a “bottom-up” approach to evaluate the direct costs was used. This is based on the costs of individual units of service performed. It uses the average cost of service and applies these data to the total number of healthcare encounters related to the disease to arrive at a global estimate of the disease healthcare costs (Rosen et al., 2018). For example, the costs of hospital care in diabetes would be calculated by multiplying the average cost of a hospital stay per day by the total number of hospitalized days attributed to the diabetic population.

3.2 Overview of longitudinal population-based study

The core of longitudinal population-based studies is represented by the continuous and repeated nature of the measures adopted. The sample of individuals selected is followed for prolonged periods (usually years or decades). These measures are often observational, the data can be quantitative or qualitative and no external influence is exercised.

Such type of study is useful to evaluate the association between diseases, risk factors and the outcomes of diverse procedures over different periods. Furthermore, since data is collected for specific individuals within a defined group, proper statistical test can be used to analyze changes over time for the group as a whole or for a particular person (Van Belle et al., 2004; Caruana et al., 2015).

3.2.1 Advantages and disadvantages of longitudinal study

Longitudinal population-based studies, if conducted prospectively, offer different benefits, such as:

- implementing a sequence of events;
- identifying and correlating events to particular risk factors, and better defining these factors in terms of presence, timing, and chronicity;
- eliminating recall bias in participants, by collecting data in a prospective way and prior to knowing that a subsequent event probably occurs;
- eliminating the cohort effect; this makes it possible to analyze the individual temporal components of the cohort (e.g. range of birth dates), period (e.g. current time), and age and to consider for the impact of each one.

Few disadvantages are implicit in the study design, such as:

- increased temporal and financial requests;
- trouble in separating the impact of exposure to risk factor and outcome; and particularly wherein the induction period between exposure and occurrence is prolonged;
- insufficient and discontinued follow-up with loss of continuity over time;
- threats to the representative nature of the sample potentially resulting from a particular exposure or occurrence.

3.3 Data sources

The study aims to assess the incidence of hospitalization for diabetes mellitus and to quantify its costs, using administrative databases of the Apulia region (4 million inhabitants). The use of administrative databases is a very flexible and accessible information source for the continuous monitoring of both morbidity and resource consumption related to diabetic disease. These databases allow producing timely information on the questions that arise continuously in the scientific context. Diabetes is an ideal model for this type of evaluation, since the identification of people with pharmacologically treated diabetes takes place thanks to the supply of antidiabetic drugs in the healthcare context.

The Hospital Discharge Registry (HDR) allows the data collection relating to all hospitalizations and represents a valid tool for clinical-epidemiological assessments regarding the use of resources and care needs. Therefore, HDRs are an important information source both for identifying the events linked to the pathology that requires hospitalization and for assessing the impact of the therapies prescribed on the incidence of such hospitalizations. The study was conducted starting from the data of the ASL of the Apulia region in the years 2006 - 2016.

In order to obtain an integrated database, different registries were used.

- Regional Hospital Discharge Registry (HDR);
- Cause of Death Registry (CDR);
- Outpatient Services Registry (OSR);
- Regional User Fee Exempts Registry (UFER);
- Drugs Prescription Registry (DPR).

In this study, a deterministic record linkage among diverse administrative databases of the Apulia region was carried out to identify subjects with diabetes mellitus and the main comorbidities associated with this pathology. The connection among the different administrative databases took place through an anonymous Identification code (ID), on the data related to a 10-years period (2006–2016). The selection process of comorbidities per patient and the codes used to calculate pharmaceutical costs could be deepened in the following Tables 3 and 4.

Table 3. Inclusion criteria used for subjects identified as diabetic

Disease	ICD9-CM	Exemption	ATC	Drug description	Specialist care
Diabetes	250	013	A10	Hypoglycaemic drugs	-
Cardiac diseases	310- 459 (excluding 390- 392)	002	C01	Cardiac therapy	
			C02	Antihypertensive drugs	
			C03	Diuretics	
			C07	Beta blockers	
			C08	Calcium channel blockers	
			C09	bstances acting on the renin angio tensin system	-
			C10AA	Inhibitors of the *HMG CoA reductase*	
Neuropathic diseases	-		N02A	Opiates – in the diabetic neuropathy	
			N02BE01	Paracetamol – in the diabetic neuropathy	
			N03AX12	Gabapentin – in the diabetic neuropathy	
			N03AX16	Pregabalin – in the diabetic neuropathy	-
			N06AX21	Duloxetine – in the diabetic neuropathy	
			N07BC02	Methadone – in the diabetic neuropathy	
			J01	Antibacterials for systemic use – in the diabetic foot	
Kidney diseases - nephropathy	582 - 588 (excluding 584;588.1)	023	A02AD	Associations among compounds of aluminium, calcium and magnesium	
			A12AA04	Calcium carbonate	
			A12AA12	Calcium acetate anhydrous	
			B03A	Iron- based preparations	-
			B03BB	Folic acid and derivatives	
			B03X	Other anti- anaemic preparations	
			H05BX	Other antiparathyroid substances	
			V03AE	Drugs for hyperkalaemia and hyperphosphataemia	
Retinal diseases	362.0- 362.6	-	-	-	Fluoroscein_angiography (code 95.12)

Source: Marcellusi et al., 2016.

Table 4. Services associated with the treatment of diabetes or comorbidities

Code	Description
91.49.2	Venous blood test
90.27.1	Glucose /s /u
89.01	Medical history and assessment, brief description
90.28.1	Glycosylated haemoglobin (hba1c) /Sg
90.62.2	Blood count cytometric and morphological test /sg
90.16.3	Creatinine /s /u
89.7	General check up
90.44.3	Complete urine analysis
90.14.3	Total cholesterol /s
90.04.5	Glutamic pyruvate transaminase (gpt- alt) /s
90.09.2	Glutamic oxaloacetic transaminase (got- ast) /s
90.43.2	Triglycerides /s
90.14.1	Hdl cholesterol /s
90.37.4	Potassium /s /u
90.44.1	Urea /s /u
90.25.5	Gamma glutamyl transpeptidase (gamma –gt) /s
90.40.4	Sodium /s /u
90.33.4	Microalbumin /u
93.82.1	Educational therapy of the patient with diabetes
89.52	Electrocardiogram
1.49.1	Capillary blood sample
90.42.1	Thyrotropin (tsh) /s
90.22.5	Iron /s
90.10.4	Total biilurubin /s
90.10.5	Direct bilurubin /s
90.11.4	Calcium /s /u
90.15.4	Creatine kinase (ck) /s
90.72.3	Quantitative c- reactive protein /s
90.23.5	Alkaline phosphatase /s /u
89.03	Complete medical history assessment
90.22.3	Ferritin /s

95.02	Comprehensive eye examination
96.59	Other wound cleansing
90.94.2	Urine culture for aerobic/mycete bacteria and bacterial count
90.13.3	Chloride /s /u
89.39.3	Evaluation of vibration perception threshold
93.56.1	Bandaging
39.95.4	Bicarbonate hemodialysis and biocompatible membranes
88.77.2	Regional or upper or lower limbs eco (color) doppler
90.38.5	Total proteins /s /u
90.29.2	Lactate dehydrogenase (ldh) /s
88.73.5	Eco (color) doppler of supra aortic trunks
88.76.1	Complete abdominal ultrasound
90.06.4	Amylase /s /u
95.12	Fluorescein angiography or angioscopy of eye
90.24.3	Inorganic phosphate /s /u
90.30.2	Lipase /s
90.82.3	Troponin I and T /S /P
88.74.1	Upper abdominal ultrasound
95.09.1	Fundus oculi examination
89.13	Neurological examination
54.98.1	Automated peritoneal dyalisis (ccpd)
86.22	Debiridement of wound, infection or burn
90.05.1	Albumin /s /
88.28	Foot and ankle x- ray
90.85.2	Sensitivity test bacteria from mic culture (at least 10 antibiotics)
90.35.5	Parathormone (pth) /s intact molecule
90.86.1	Biochemical identification of nas bacteria
90.69.4	Immunoglobuline (igg- iga- igd- igm) /S /U (each)
88.72.3	Doppler echocardiography
90.13.5	B12 vitamin /s
90.23.2	Folate /s
90.24.5	Phosphorous/phosphates /s

90.33.5	Myoglobin /s /u
90.51.4	Antithyroid peroxidase antibodies
90.54.4	Anti thyroglobulin antibodies /s
93.20.1	Outpatient care services

Source: Marcellusi et al., 2016.

3.3.1 Description of the databases

3.3.1.1 Hospital Discharge Registry

Hospital Discharge Registry (HDR) collects data on discharge diagnoses (one main and up to five secondary diagnoses) and procedures of all patients admitted to hospitals in Apulia region. Discharge diagnosis and procedures are coded using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD9-CM). Hospital discharge data are usually used to address issues of public safety, including the identification of disease rates, patient characteristics, hospitalization costs, and outcomes for specific disease, and spreading the development of disease prevention and control programs. Moreover, discharge data can be useful to better understanding hospitalizations patterns for an exact area, planning for better allocation of resources, identifying services that are lacking in a population, and assessing the potential impact of hospital changes. In some National Health Services, hospital discharge data are also used in health assessment systems. They integrate data from other health facilities, as well as data on vital statistics, morbidity, behavioral risk factors, health resources, and socio-economic characteristics. In addition, they embrace a range of critical information for a variety of public health uses, such as chronic disease prevention and control programs, disease surveillance, and public health reports (Gliklich et al., 2014; Mennuni et al., 2017).

As for the benefits of hospital discharge data, they are inexpensive to obtain and can easily be used for a set of activities. Their advantages are:

- usefulness to compare them with the cost of similar data collected through surveys or abstraction of medical records;
- reliability than other data sources, such as patient self-reporting of medical expenses or physician reporting of specific conditions for disease supervision;
- greater validity compared to data obtained from third-party payers because they are generally available for several years and support trend analyses;
- usefulness for analyses of rare conditions or for specific conditions of population subgroups.

In spite of these substantial advantages, there are two threats that may limit their utility for certain purposes. Firstly, inconsistencies across providers in the way they report

specific data elements, as well as hospital-specific mistakes in data reporting, can produce data with quality problems. Secondly, other elements that would support more advanced and innovative analyses are lacking.

These elements include detailed information such as clinical test results, the presence or absence of a condition at the time of hospital admission, patient functional status, severity of illness, behavioral risk factors, and a unique ID for patients and for all physicians involved in the episode.

3.3.1.2 Cause of Death Registry

Mortality is one of the most solid epidemiological indicators and can be used for geographical and temporal comparisons: mortality data are collected in the various countries, divided per territory and classified in a historical series by the statistical institutes that code them based on internationally accepted rules (ICD9-CM) and periodically updated according to the so-called "Revisions". The description of mortality therefore represents an element of great importance for the knowledge of population health status; the temporal analysis and the geographical comparison of general mortality provide useful indications on the lengthening of populations' life expectancy. In Italy, to provide recommendations and public health information at institutions (central and local), operators of health services and citizens, mortality data are collected, codified, and processed by the National Institute of Statistics (Istat) and Institute of Health (ISS).

The management of a mortality register is articulated and is expressed in the reception and control of the quality of the data, in the codification for epidemiological purposes, in the insertion in the database and archiving, in the management of the dissemination of health information on mortality and, finally, in the analysis of the data for epidemiological, planning and evaluation purposes. In particular, the mortality registers perform their functions only if they are complete, that is if they contain the data relating to all dead residents. Thus, a mortality register is complete only if the death records are, in turn, complete as a number and as information contained. A good management of mortality registers therefore derives from the completeness of the archive and the form. Therefore, register operators are periodically required to verify these requirements, with

appropriate investigations in collaboration with the municipalities and local health authorities (EpiCentro, 2019).

3.3.1.3 Outpatient Services Registry

Database of Outpatient Services collects prescriptions for specialist outpatient services coded according to the Italian tariff (Italian Ministry of Health, 2012).

"Specialized outpatient care" means the intra- or extra-hospital structure responsible for providing health services for prevention, diagnosis, therapy, and rehabilitation, in situations that do not require hospitalization. The Italian regulatory sources prior to the Prime Ministerial Decree of 29.11.2001 do not provide a definition of what is meant by outpatient specialist assistance but provide (directly and indirectly) a list of services related to this level of assistance. A detailed list of services is defined only with Ministerial Decree 22.7.1996; according to this decree, the deliverability of services coincides with the level of assistance.

The objective of such a registry is to regulate the criteria and methods of access to specialist outpatient services in order to ensure the organizational and clinical-care management of the outpatient sick. This registration procedure allows the rationalization of outpatient specialist assistance activities, the simplification of access procedures and the facilitation of care procedures in a suitable context that allows compliance with the principle of equity and uniformity of waiting times in the society. The qualifying element of outpatient specialist assistance is the patient's organizational and clinical-assistance care for the provision of:

- specialized examinations;
- laboratory services;
- instrumental diagnostic services;
- therapeutics care (Traversa, 2015).

3.3.1.4 User Fee Exempts Registry

The ticket, introduced in Italy since 1982, represents the way in which the citizens contribute to the cost of the health services they receive. The benefits included in the Essential Levels of Assistance (LEA), defined by Decree of the President of the Council of Ministers 12 January 2017, for which the cost of the ticket is paid, are:

- specialist visits, instrumental, and laboratory diagnostic tests;
- services performed in the emergency room that are not emergency (e.g. white codes), not followed by hospitalization;
- spa treatments.

Instead, the services for which the ticket's payment is not considered are:

- instrumental, laboratory diagnostic exams, and other specialist assistance services included in collective prevention programs promoted or authorized by the Region (e.g., mammography for the early diagnosis of breast cancer, the PAP cancer test cervix uteri, exams for occult blood in the stool for colorectal cancer);
- instrumental, laboratory diagnostic exams, and other specialist assistance services necessary for the protection of collective health;
- services provided by general practitioners and pediatricians;
- treatments provided during a hospitalization, ordinary or in day-hospital, including admissions to rehabilitation and post-acute long-stay wards or facilities and the examinations strictly connected to the planned hospitalization, previously provided by the same structure;
- foods for particular categories (e.g. gluten-free foods for people with celiac disease) and medical devices for people with diabetes (needles, test strips, lancing pens, blood glucose meters, etc);
- prostheses and technological aids for people with disabilities.

Moreover, for health services that require the payment of a ticket, clients are entitled to an exemption (for some or all services) in the following cases:

- specific income situations associated with age or social status;
- presence of certain pathologies (chronic or rare);
- disability status:

- special cases (pregnancy, early diagnosis of some cancers, HIV detection).

According to the WHO, chronic diseases are "*health problems that require continuous treatment over a period of time from years to decades*". For some of them, the National Health Service (SSN) provides the possibility of exempting certain outpatient specialist services from the ticket, aimed at monitoring the disease and preventing complications and further aggravations (Ministerial Decree 329/99 and subsequent amendments).
Illnesses and conditions that give the right to the exemption are identified based on the criteria dictated by the Legislative Decree 124/98 (Ministero della Salute, 2018).

3.3.1.5 Drugs Prescription Registry

Drugs prescription registry (DPR) store information on drugs prescribed to patients by the health services. Drugs are coded according to the Anatomical Therapeutic Chemical Classification System (ATC). ATC is the coding system used for the systematic classification of drugs and is created and managed by the WHO Collaborating Center for Drug Statistics Methodology. The Italian version is edited by DURG - Italy, reference center for the ATC / DDD system, a scientific association affiliated to the European Drug Utilization Research Group (EURO-DURG) that since 1995 manages and distributes an archive of drugs on the Italian market with ATC and DDD (Defined Daily Dose).
According to the Technical Disciplinary attached to the 1996 Italian Ministerial Decree on the ESF, the ATC codes together with the AIC code must be used within the PSS for the coding of:

- adverse reactions to drugs and/or food with regard to therapeutic, pharmacological or chemical class;
- drug therapies;
- vaccinations (Ministero della Salute, 2010).

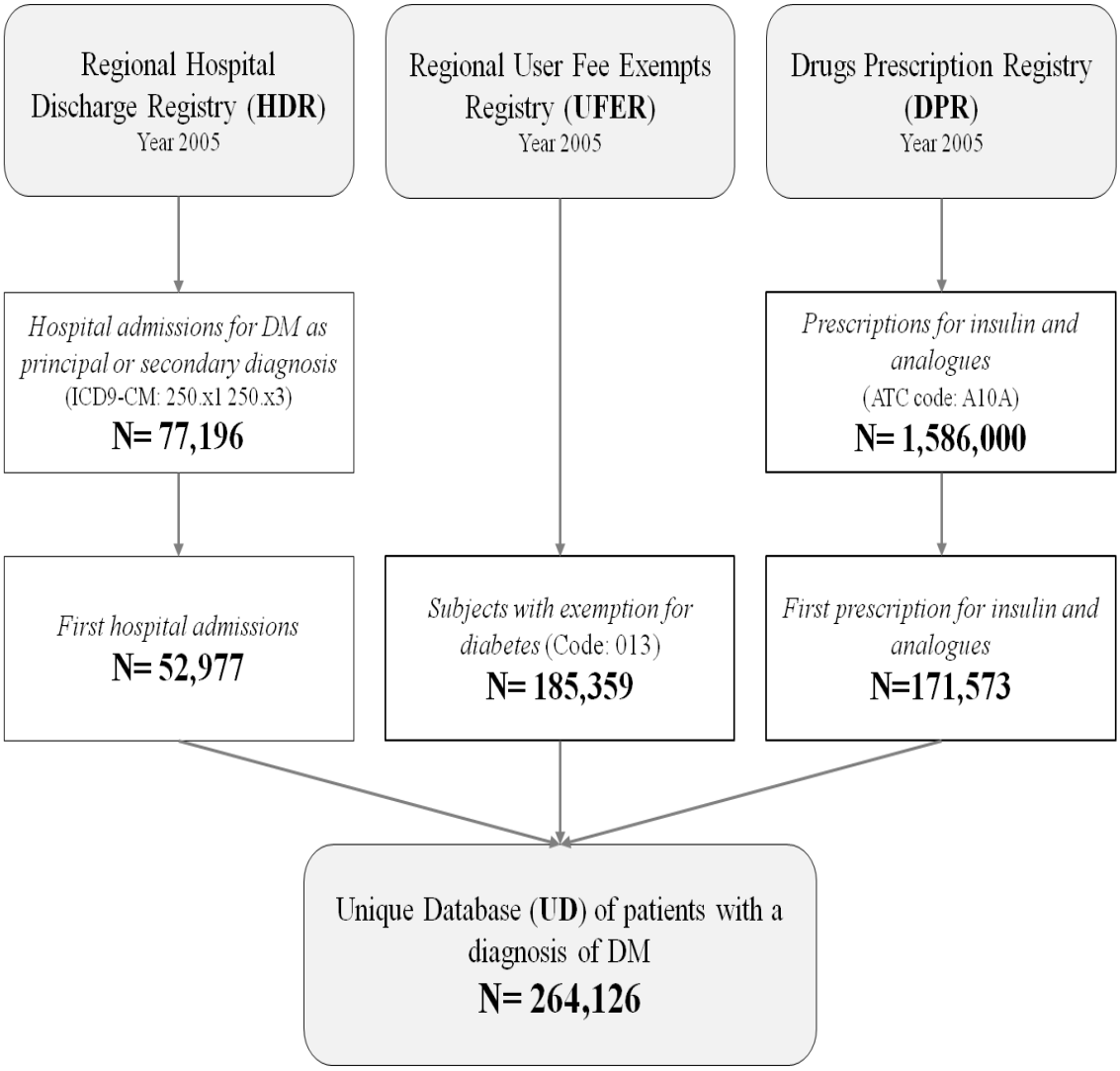
3.4 Sampling method

For each year, all subjects met at least one of the following criteria were considered:

- hospital discharge with a ICD9-CM code 250.XX in at least one of the six discharge diagnosis fields;
- two consecutive prescriptions of drugs for diabetes within one year of observation, classified with the ATC classification system (code A10XXXX);
- an exemption from co-payment healthcare costs specific for diabetes mellitus (code 13.250).

The index date was defined as the date of occurrence of the first criterion above.
All identified individuals, regardless of age, sex and type of diabetes, were followed up to death, cancellation from the chargeable registry or at the end of the period considered (December 31st, 2016).
Both the main and secondary diagnoses were considered. The cases of diabetic subjects pharmacologically treated have been identified in the DPR. Incidence rates per 1,000 person-years of hospitalization were estimated based on age groups. In addition to the entire observation period, the incidence was estimated over each of the years under examination to highlight any temporal trends.
In order to estimate diabetes incidence, a unique database matching the records extracted from the data sources by using personal ID number was created (Figure 4).

Figure 4 Flowchart of the total number of patients with DM. Apulia, Italy, 2005.



Source: personal elaboration

3.5 Data and analyses

The characteristics of the study population were expressed with absolute, relative numbers and with minimum, maximum, mean and Standard Deviation (SD). Diabetes prevalence was evaluated dividing the number of subjects meeting the eligibility criteria at the index date by the number of Apulia region inhabitants on January, 1st 2005, stratified by sex and age classes.

Once the cohort of patients with DM was identified, a detailed analysis of the sample with DM was carried out with the support of a board of clinical experts. According to the comorbidities treated during the years of investigation within the Apulia region, the diabetics were split by cardiovascular, kidney, neuropathic and retinal diseases. Fundamentally, a patient selected in each year of analysis was identified with one or more comorbidities if he/she had used at least one of the considered services.

Mortality rates, stratified by sex and age, were estimated by dividing the number of deaths up to recorded death. In particular, mortality rates were reported along with their 95% CI, calculated by dividing the number of deaths by the number of people identified in the sample per age-class multiplied 100,000.

Healthcare costs were analyzed from the Regional Health Service point of view. Costs were computed using expenses that the Health Information System of the Apulia region reimbursed to the providers of care. The main cost categories were identified in: hospitalizations (cause of death registry and hospital discharge forms), pharmaceutical prescriptions and outpatient claims.

According to the following main diagnosis, hospitalizations were stratified into four groups identified with the Diagnosis Related Group (DRG) code and related tariff:

- group 1, diabetes (ICD9-CM codes: 250.X);
- group 2, cardio- or cerebro-vascular events (ICD-9 CM codes: 40X.X; 41X.X; 42X.X; 43X.X; 44X.X; 451.X; 452.X; 453.X);
- group 3, other possible DM related complications (ICD-9 CM codes: 337.X, 354.X, 355.X, 357.X, 358.X, 362.X, 365.X, 366.X, 369.X, 459.X, 581.X-589.X, 707.X, 713.X, 785.X, 895.X-897.X);
- group 4, any other main diagnosis (Scalone et al., 2014).

According to the ATC system, pharmaceutical claims were grouped in order to differentiate costs related to the drugs purely for diabetics (A10), drugs for cardiovascular system (C), for neuropathic diseases, for kidney diseases (nephropathy) and for retinal diseases (Marcellusi et al., 2016).

Finally, the cost of outpatient specialist services was calculated selecting from the information system of the specialist service of the Apulia region the services potentially associated with the therapy (see Appendix B). These were valued through the regional tariffs in force. The selection was made taking into account the expert opinion of the clinical board.

As for the economic analyses, the central tendency parameter was expressed as a mean cost per patient per year. Hospital admissions were also shown as the frequency of utilization related to the main diagnosis. Due to the highly skewed distribution of cost variables, the distribution of costs per patient per year, instead of standard deviations, was used as a variability indicator. All analyses were performed with STATA version 14.2 (StataCorp LP, USA).

The study was approved by the Institutional Review Board of the Apulian Observatory for Epidemiology. It was conducted in accordance with the Guidelines for Good Clinical Practice and the ethical principles originating in the Declaration of Helsinki.

4. RESULTS

4.1 Study population

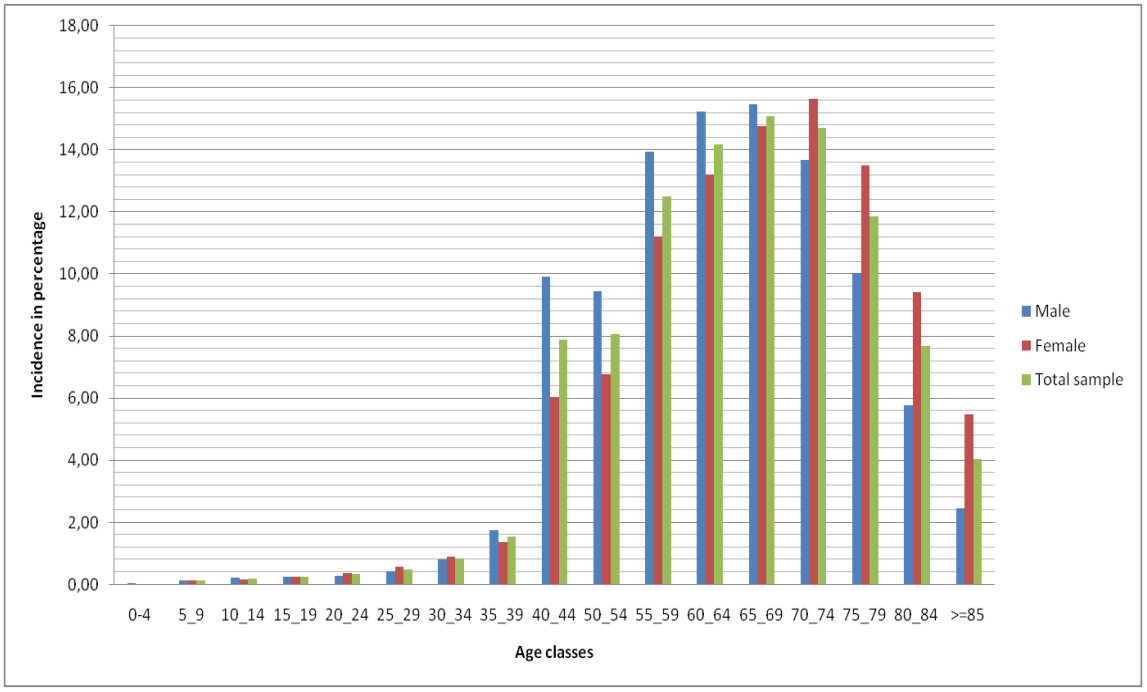
264,126 eligible subjects were identified in the year 2005. The study population was aged, at the index date, 65-69 for age class on average and consisted of 15.47% male and 14.77% female and 70-74 years (13.68% male and 15.67% female). Only 0.38% of the sample were < 15 years (Table and Figure 5).

Table 5 Description of the sample (sex and age classes)

Age classes	Male		Female		Total	
	(n.)	%	(n.)	%	(n.)	%
0-4	58	0.05	46	0.03	104	0.04
5_9	190	0.15	183	0.13	373	0.14
10_14	288	0.23	252	0.18	540	0.20
15_19	323	0.26	385	0.28	708	0.27
20_24	386	0.31	509	0.37	895	0.34
25_29	547	0.44	803	0.58	1350	0.51
30_34	1015	0.81	1252	0.90	2267	0.86
35_39	2209	1.76	1915	1.38	4124	1.56
40_44	12472	9.93	8384	6.05	20856	7.90
50_54	11889	9.46	9409	6.79	21298	8.06
55_59	17541	13.96	15528	11.21	33069	12.52
60_64	19152	15.24	18299	13.22	37451	14.18
65_69	19441	15.47	20449	14.77	39890	15.10
70_74	17184	13.68	21692	15.67	38876	14.72
75_79	12614	10.04	18717	13.52	31331	11.86
80_84	7264	5.78	13043	9.42	20307	7.69
>=85	3082	2.45	7605	5.49	10687	4.05
Total	**125655**	**100.00**	**138471**	**100.00**	**264126**	**100.00**

Source: personal elaboration

Figure 5 Age classes by sex and relative incidence



Source: personal elaboration

4.2 Mortality and comorbidity analyses

During the observational period 64,752 deaths (24.52% of study population) occurred, with an average mortality rate compared to the Apulia population of 1.44% deaths per 1,000 patients per year (Table 6). Analyzes showed that men had statistically significant lower mortality rates than women, although the difference was minimal (46.85% males; 53.15% females), and that the mortality rate increases with increasing age (Table 6.1). Moreover, during the period 2006 – 2016 causes of death and related incidences have been investigated (Figure 6.1). Cardiovascular diseases, different types of cancer and endocrine, nutritional and metabolic diseases, have been found to be the most frequent causes of death (39.6%, 17.4%, and 15.1% respectively). Instead, the less incidences causes were: malformations and congenital deformations, chromosomal abnormalities (0.1%), diseases of the skin and subcutaneous tissue (0.1%) and diseases of the musculoskeletal system and connective tissue (0.3%).

Table 6. Description of the sample (mortality)

	Total deaths		Dead males		Dead females		Males resident in Apulia region	Females resident in Apulia region	Apulia population	Mortality rate * 1000 (95% CI)
Year	(n.)	%	(n.)	%	(n.)	%	(n.)	(n.)	(n.)	%
2006	4309	6.65	2006	6.61	2303	6.69	1,977,338	2,094,180	4,071,518	1.06
2007	4815	7.44	2257	7.44	2558	7.43	1,976,125	2,093,744	4,069,869	1.18
2008	4816	7.44	2249	7.41	2567	7.46	1,978,216	2,098,330	4,076,546	1.18
2009	4587	7.08	2138	7.05	2449	7.12	1,979,254	2,100,448	4,079,702	1.12
2010	4853	7.49	2247	7.41	2606	7.57	1,980,902	2,103,133	4,084,035	1.19
2011	4532	7.00	2068	6.82	2464	7.16	1,984,310	2,106,949	4,091,259	1.11
2012	6038	9.32	2909	9.59	3129	9.09	1,962,375	2,087,697	4,050,072	1.49
2013	7815	12.07	3673	12.11	4142	12.04	1,963,041	2,087,762	4,050,803	1.93
2014	7582	11.71	3670	12.10	3912	11.37	1,983,757	2,106,509	4,090,266	1.85
2015	7465	11.53	3457	11.39	4008	11.65	1,984,227	2,105,878	4,090,105	1.83
2016	7940	12.26	3665	12.08	4275	12.42	1,979,253	2,097,913	4,077,166	1.95
TOTAL	**64752**	**100.00**	**30339**	**100.00**	**34413**	**100.00**	**21,748,798**	**23,082,543**	**44,831,341**	**15.89**

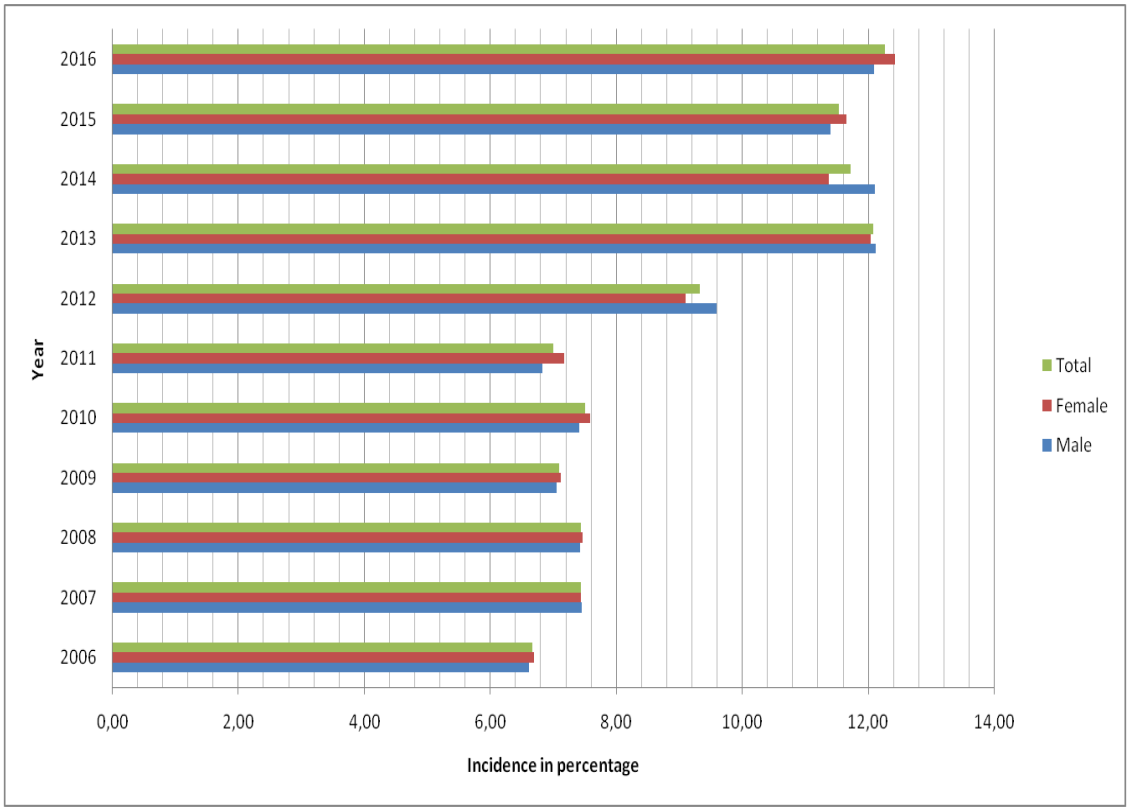
Source: personal elaboration

Table 6.1. Mortality rate by age classes

Age classes	N. deaths	Mortality rate x100,000
0-4	1	0
5_9	0	0
10_14	0	0
15_19	1	0
20_24	4	0.1
25_29	7	0.2
30_34	16	0.5
35_39	34	1
40_44	111	3.2
45_49	253	7.7
50_54	574	19.4
55_59	1138	40.7
60_64	2451	94.8
65_69	4564	197.9
70_74	7178	353.6
75_79	11359	659.1
80_84	14661	1166
>=85	22400	2261
TOTAL	**64752**	

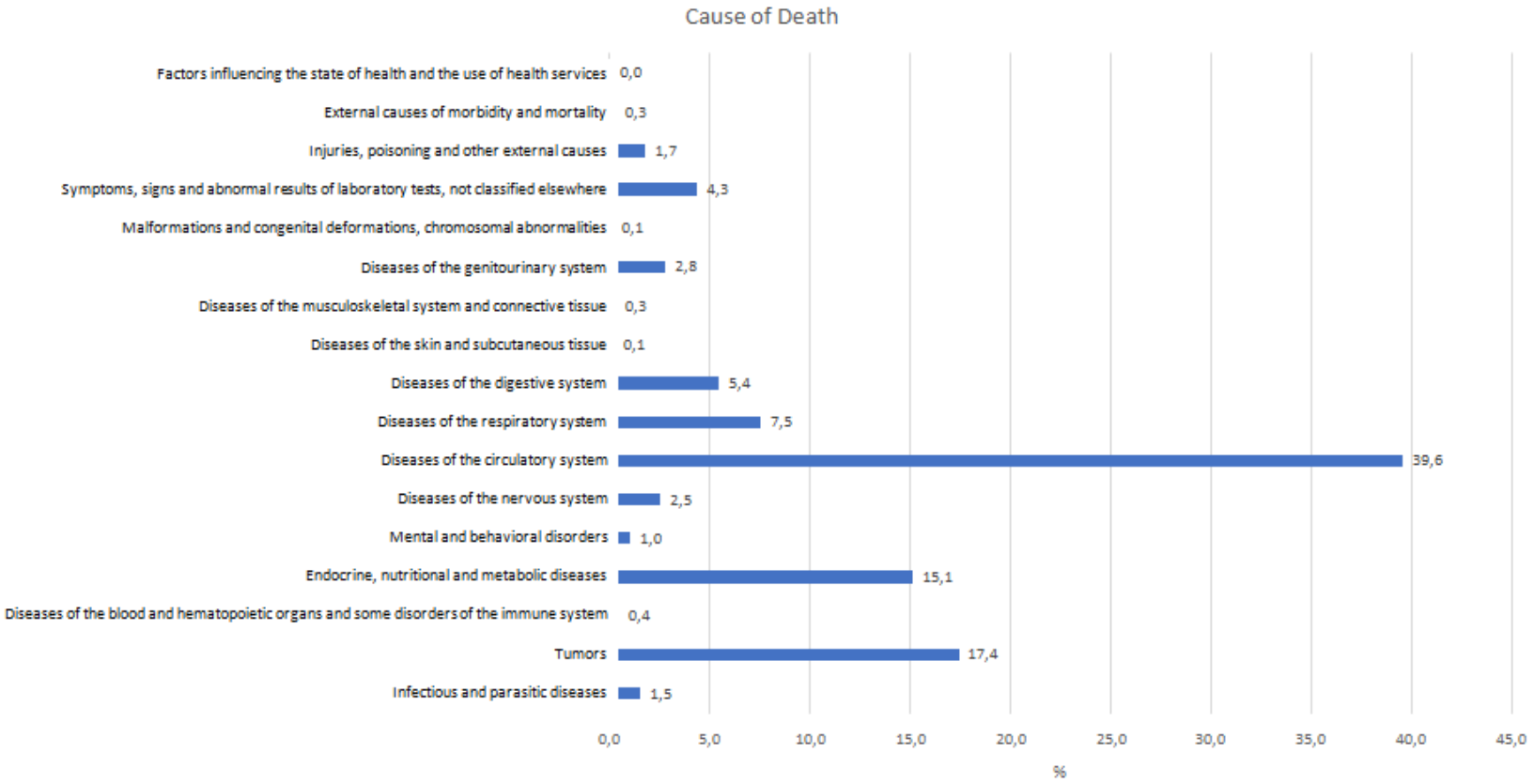
Source: personal elaboration

Figure 6 Mortality by year, gender and relative incidence



Source: personal elaboration

Figure 6.1 Causes of death and related incidences



Source: personal elaboration

4.3 Costs analyses of Hospital Discharge Forms

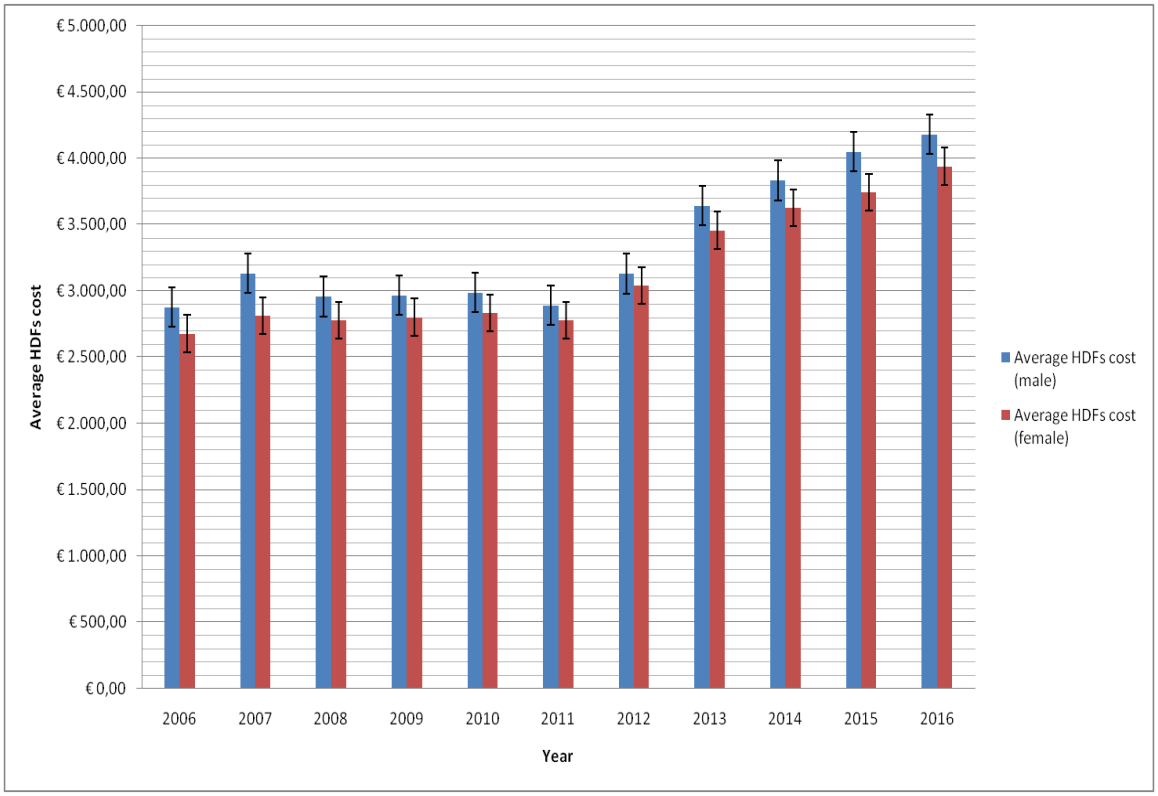
Hospital Discharge Registry is the tool for collecting information related to all hospitalizations provided in public and private hospital facilities.

HDR was developed for purely administrative purposes of the hospital setting, and, to date, thanks to the numerous administrative and clinical information contained, it has become an indispensable tool for a wide range of analysis and processing: health planning activities, monitoring of the provision of hospital assistance, monitoring of Essential Assistance Levels (LEA), proxy analysis of other levels of assistance, and for clinical-epidemiological and outcome analyzes. In this regard, the HDR is a fundamental element of the National Outcome Program (NOP). The economic evaluation of the HDR is given by the economic value assigned to each DRG.

"*Apart from their use in reimbursement systems, case-mix systems such as DRG were designed for planning, budgeting, management, and financing inpatient care*" (Serden et al., 2003).

Currently, the DRG system benefits mainly the National Health Fund. Hospitals are implementing DRG-based system for planning, budgeting, and management. In addition, there is a huge potential for improving hospital management and profitability using the known economic value of DRG. To this end, the average economic value associated with each DRG (HDFs) was evaluated by dividing the amounts per gender and per year. During the period 2006 – 2016, the mean value of the HDR recorded for diabetics' females was € 3135.25 and for diabetics' male was € 3331.83 (Table and Figure 7).

Figure 7 Average HDFs cost by year and gender



Source: personal elaboration

Table 7 Average HDF cost

Year	Observations		Average HDF cost		std. error		[95% conf. interval]			
	(n.) female	(n.) male	€ female	€ male	(n.) female	(n.) male	(n.) female		(n.) male	
2006	59916	59812	2678.52	2879.111	12.77454	15.73087	2653.482	2703.558	2848.279	2909.944
2007	61590	64362	2813.628	3133.871	13.76774	54.47741	2786.643	2840.613	3027.095	3240.647
2008	58613	61380	2778.716	2957.434	13.32283	14.93878	2752.604	2804.829	2928.154	2986.714
2009	56953	60033	2800.423	2968.955	13.72772	15.56106	2773.516	2827.329	2938.455	2999.455
2010	57661	62583	2833.368	2988.581	13.09349	15.6089	2807.704	2859.031	2957.987	3019.174
2011	51332	56725	2778.237	2889.762	13.53776	14.65595	2751.703	2804.771	2861.037	2918.488
2012	41676	45816	3041.263	3128.224	16.80261	17.37265	3008.33	3074.197	3094.174	3162.275
2013	35045	39117	3455.762	3643.093	20.24038	21.33941	3416.09	3495.434	3601.268	3684.919
2014	32069	35601	3624.819	3831.95	23.05819	25.42368	3579.624	3670.014	3782.119	3881.781
2015	29588	33184	3743.23	4047.51	23.66857	63281.48	3696.84	3789.622	-56704.96	191362.9
2016	27742	31569	3939.818	4181.65	24.88217	26.48142	3891.048	3988.589	4129.746	4233.555

Source: personal elaboration

4.4 Costs analyses of Pharmaceutical prescriptions

The cost of the pharmacological therapy was calculated as the sum of the prescriptions made during the reference year, based on the prices identified by the information system of the Apulia region. The costs of concurrent drugs per comorbidity treatment were considered as the ATC codes reported in the Table 3. All costs calculated with the ATC codes identified (Marcellusi et al., 2016) can be deepened in the supplementary Appendix A.

As regards pharmaceutical claims,24.35% of costs were attributable to diabetes drugs (ATC: A10), 54.77% to cardiovascular drugs ATC Class C, 11.06% of costs were spent for neuropathic diseases and for nephropathy 9.82% of pharmaceutical costs. Specifically, as regards cardiac diseases' drugs, 290 million euro (42.15% of total costs of cardiovascular drugs) were the highest type of cardiovascular drugs' cost attributable to agents acting on the renin–angiotensin system (Table 8).

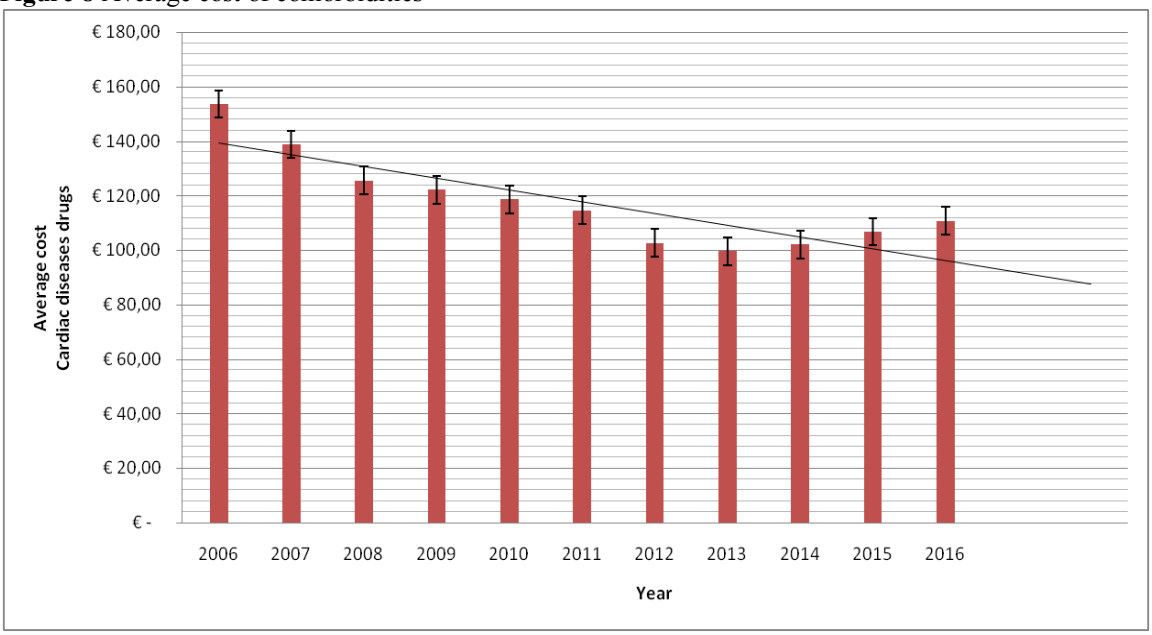
Table 8 Pharmaceutical total costs

Diabetes and comorbidities	Total cost	%
Diabetes	€ 306'292'524.00	24.35
Cardiac diseases	€ 689'007'034.00	54.77
Neuropathic diseases	€ 139'145'545.40	11.06
Kidney diseases - nephropathy	€ 123'542'934.31	9.82
	€ 1'257'988'037.71	**100**

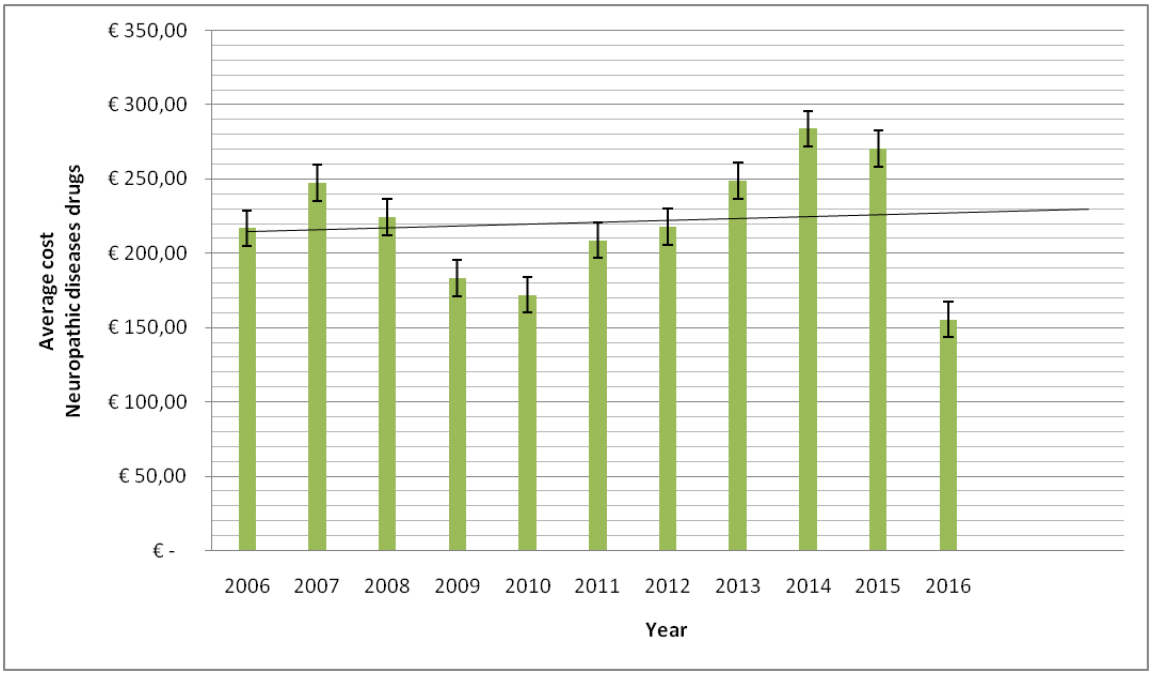
Source: personal elaboration

In 10 years of observations, the average expenditure on drugs for the treatment of cardiac disease related to diabetes was € 117.76, of neuropathic diseases was € 220.88, of nephropathy was € 845.52 and, in Figure 8 (A, B, C), it is possible to identify each linear trend of prediction.

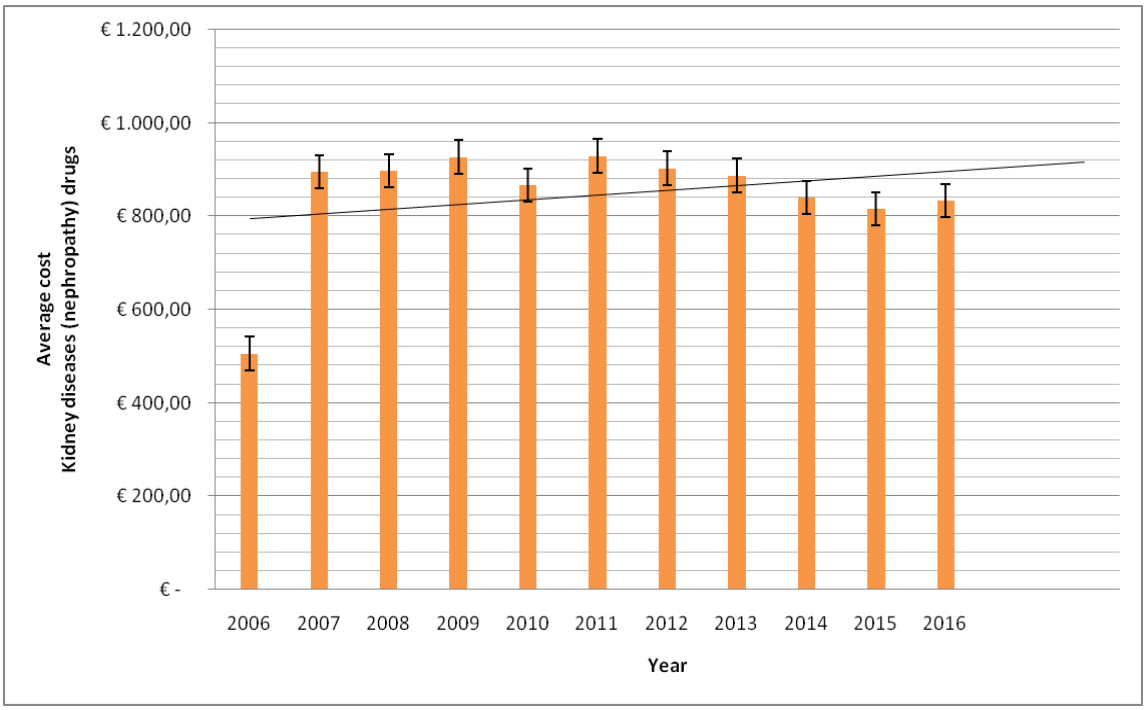
Figure 8 Average cost of comorbidities



(A)



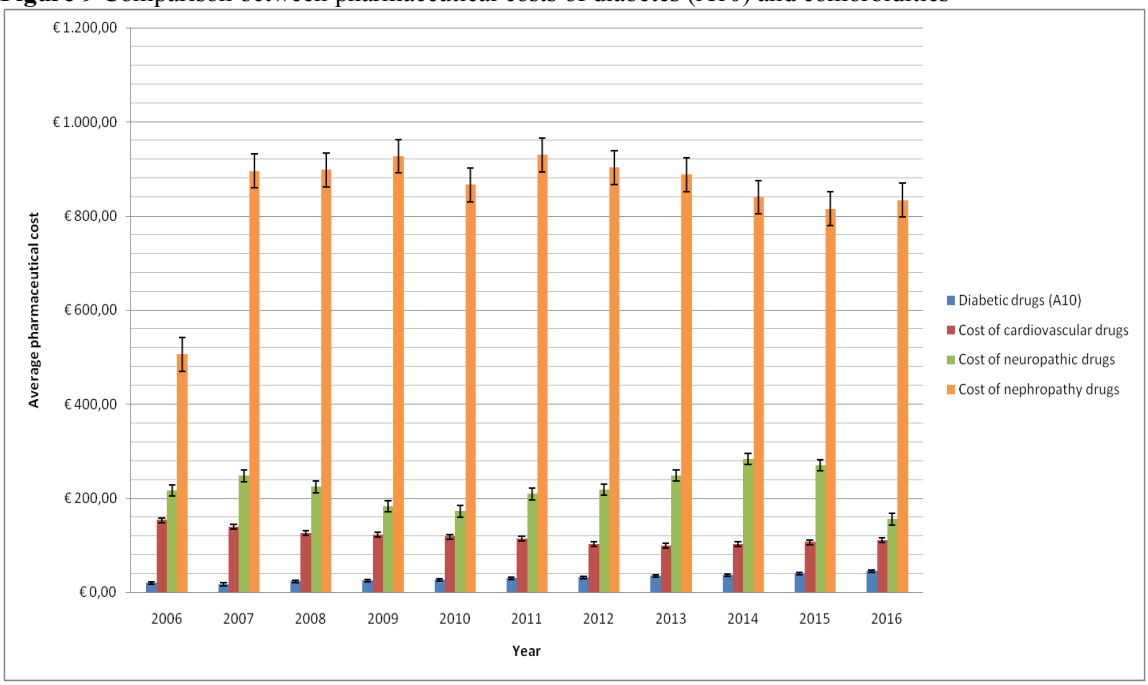
(B)



(C)
Source: personal elaboration

Diabetes is the most common cause of chronic kidney disease, with a high economic impact on health systems (Ene-Iordache et al., 2016). Indeed, the cost of drugs for the treatment of nephropathy attributable to diabetes is, in general, very expensive, and in this sample, during the period 2006 –2016 it was more than €123 million and a slight trending upward is recorded. As shown in Figure 9, the average cost of drugs for the treatment of nephropathy in people with diabetes is the highest average pharmaceutical cost.

Figure 9 Comparison between pharmaceutical costs of diabetes (A10) and comorbidities



Source: personal elaboration

In summary, Table 9 shows all average pharmaceutical costs that the Apulia healthcare system has incurred for drugs provided to an Apulian diabetic patient in the period 2006 - 2016. Specifically, the cost of drugs' trend for the treatment of diabetes (ATC: A10) has been steadily increasing. The cost of drugs for the treatment of cardiovascular pathology in diabetic patients peaked in 2006 (€ 153.68) and, contrary to the previous trend, was constantly decreasing. The cost of drugs for neuropathy reached the highest value in 2014 (€ 283.82) and, finally, the treatment of nephropathy was more expensive in 2011 (€ 929.49).

In summary, the trend of these costs was almost constant, the highest amount was recorded in 2007 (€ 1299.38) and, in 10 years, the average total pharmaceutical cost was € 1214.08.

Table 9 Pharmaceutical costs divided per diabetic, cardiovascular, neuropathic and nephropathy comorbidity

Year	Cost of diabetic drugs	Cost of cardiovascular drugs	Cost of neuropathic drugs	Cost of nephropathy drugs	Total pharmaceutical cost
2006	€ 19.39	€ 153.68	€ 216.69	€ 505.67	€ 895.43
2007	€ 17.23	€ 138.89	€ 247.58	€ 895.68	€ 1299.38
2008	€ 23.21	€ 125.53	€ 224.54	€ 897.80	€ 1271.08
2009	€ 25.27	€ 122.14	€ 183.41	€ 926.79	€ 1257.61
2010	€ 26.44	€ 118.57	€ 172.12	€ 866.20	€ 1183.33
2011	€ 29.55	€ 114.61	€ 208.76	€ 929.49	€ 1282.41
2012	€ 32.11	€ 102.64	€ 218.00	€ 902.65	€ 1255.40
2013	€ 34.73	€ 99.65	€ 248.73	€ 887.50	€ 1270.61
2014	€ 36.14	€ 102.11	€ 283.82	€ 840.04	€ 1262.11
2015	€ 40.26	€ 106.78	€ 270.49	€ 815.33	€ 1232.86
2016	€ 44.84	€ 110.74	€ 155.50	€ 833.62	€ 1144.70

Source: personal elaboration

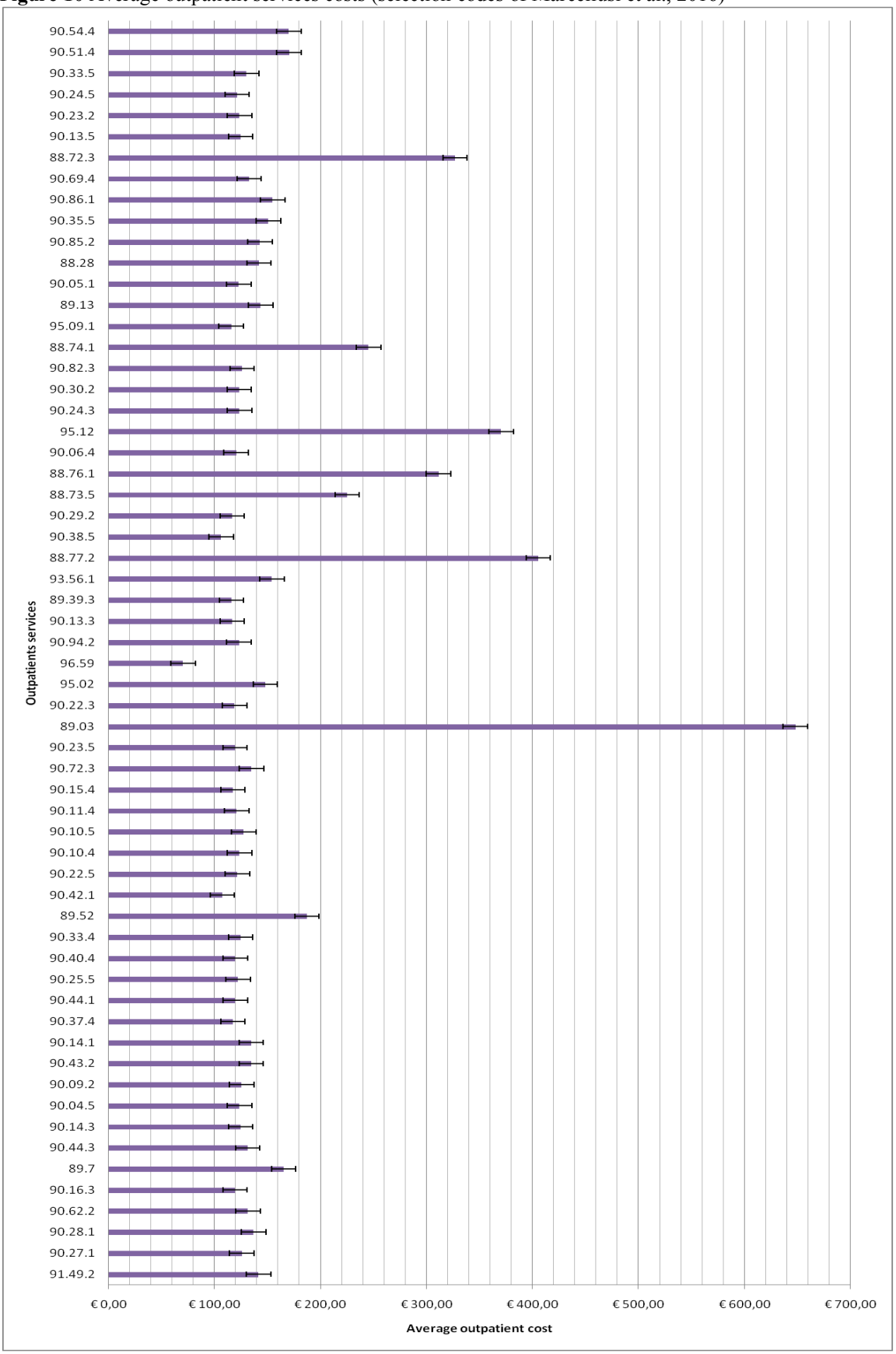
4.5 Costs analyses of Outpatient services

Some different considerations have to be made in order to calculate the costs of services associated with the treatment of diabetes and comorbidities. In the database of outpatient services, some codes selected in the analysis by Marcellusi et al., (2016), 89.01, 93.82.1, 1.49.1, 39.95.4, 54.81 and 86.22 were not observed (see Appendix B).

The average costs in Figure 10 indicate the cost (expressed in thousands of Euros) divided by the number of outpatient services provided in the years analyzed (see Appendix C). Thanks to the average costs calculated in the 2006 – 2016 period, it is possible to demonstrate that the highest costs are those incurred for the "complete medical history assessment" (€ 648.10) and represent 6.9% of all outpatient services costs considered. Costs for "regional or upper or lower limbs eco (color) Doppler" are the second type of higher costs (€ 405.56) and represent 4.3% of all the outpatient services costs considered. Instead, the lowest measured cost was for "other wound cleansing" (€ 70.79), 0.8% of the costs considered. In general, in 10 years, the healthcare system in the Apulia region has incurred € 147.95, on average, for outpatient services provided to a diabetic patient (Table 10).

The reason why some costs are greater than others is linked not only to the amount itself but it is also related to the fact that some services for the diabetic patient are provided much more often than others (see Appendix C).

Figure 10 Average outpatient services costs (selection codes of Marcellusi et al., 2016)



Source: personal elaboration

Table 10 Average outpatient services costs by years

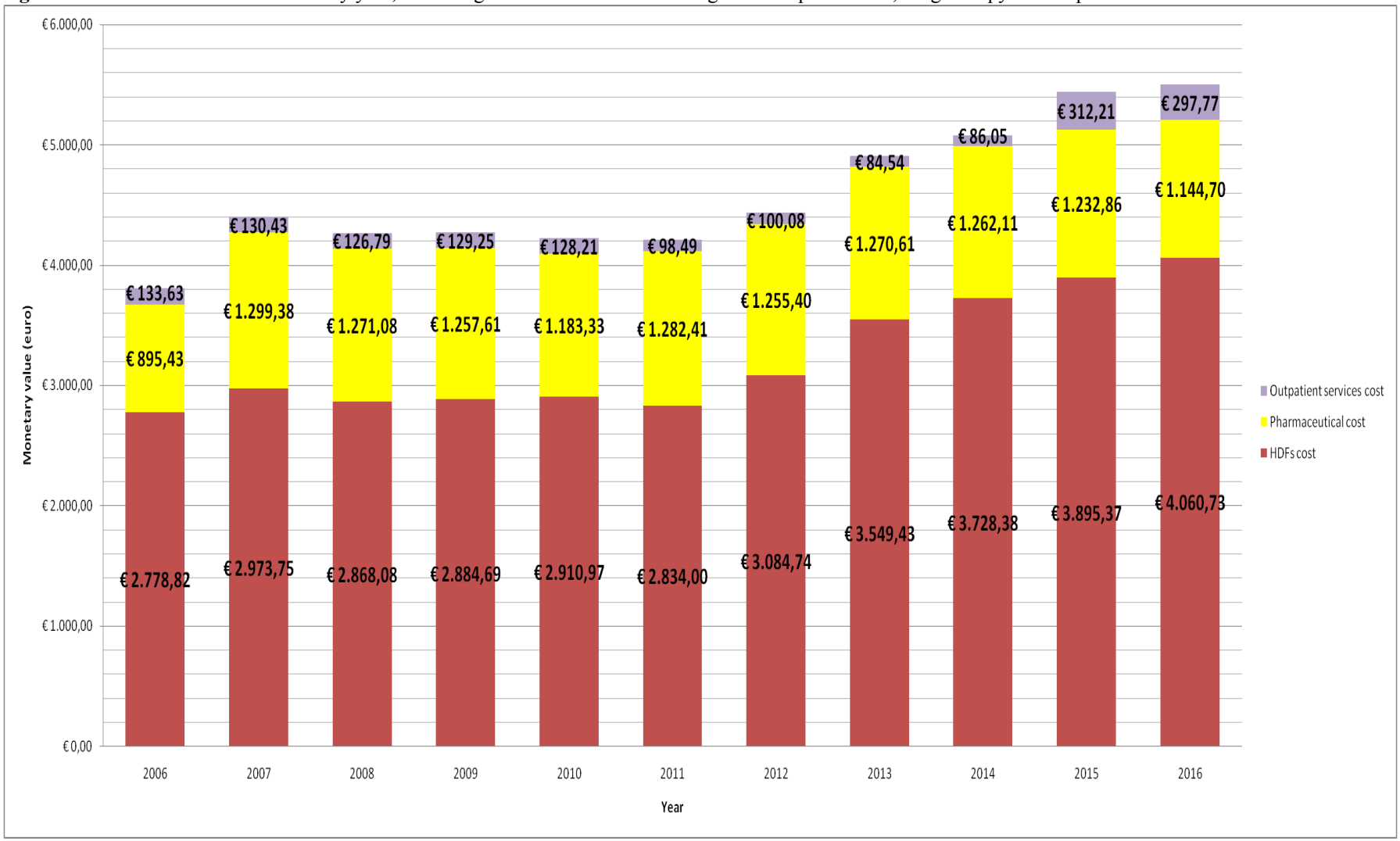
Year	Total outpatient services cost
2006	€ 133.63
2007	€ 130.43
2008	€ 126.79
2009	€ 129.25
2010	€ 128.21
2011	€ 98.49
2012	€ 100.08
2013	€ 84.54
2014	€ 86.05
2015	€ 312.21
2016	€ 297.77
	€ 147.95

Source: personal elaboration

In light of these results, it is possible to assert that different contributions of the three classes of costs (HDFs, pharmaceutical prescriptions and outpatient services) were found in different years (Figure11).

The percentage of hospital costs on total expenditure has recorded diverse phases over the years, ranging from € 2778.82 in 2006 (72.98%), to € 4060.73 in 2016 (73.79%) and this HDFs amount has reached the minimum value in 2008 (67.23%). Consequently, the relative contribution of the other costs decreased: pharmaceutical cost ranged from € 895.43 in 2006 (23.52%), to € 1144.70 in 2016 (20.8%), and outpatient costs ranged from € 133.63 in 2006 (3.51%), to € 297.77 in 2016 (5.41%) reaching the minimum value in 2014 (€ 86.05) (see Appendix D).

Figure 11 Distribution of overall costs by year, according to the three main cost categories: hospitalization, drug therapy and outpatient services



Source: personal elaboration

5. DISCUSSION AND CONCLUSION

Nowadays, many national studies have been performed with the aim of identifying the epidemiological and social weight of diabetes in Italy (ARNO, 2011; Kanavos et al., 2012; Marcellusi et al., 2016; Scalone et al., 2014).

The present research represented one of the most extensive study conducted on the burden of diabetes, focusing on prevalence, mortality and healthcare costs assessed on a large population of diabetes patients observed in Apulia region from 2006 to 2016. This study was possible with the use of several administrative databases combined together after a major effort to review and reorganization all of them.

The scientific work has tried to assess the economic burden of the patients affected by diabetes in Italy reporting the data recorded in Apulia, a region of Southern Italy, and showing the results by type and number of comorbidities associated with the patients with DM. Moreover, applying scenario analyses discussed with a board of experts, the model has calculated the expense impacts of the healthcare direct costs deriving from this combination of databases. The procedure has been carried out both to guarantee an improvement of diabetes management indicators, and an improvement of the therapeutic management and care and, consequently, effectiveness (reduction of comorbidities and hospitalizations direct costs).

In order to estimate the DM incidence, the databases were combined in an unique database matching the records extracted by using personal ID number as linkage key. In the target population, extracted from administrative databases in 2005, a 6.48% prevalence of diabetes was consistent with the data obtained by the Italian National Institute of Statistics according to which the prevalence in Southern Italy was around 5% until 2005, the highest prevalence recorded in Italy (3.9% in North and 4.1% in Central Italy) (Lombardo et al., 2007).

An average amount of € 4500 per patient-year was spent in healthcare costs by the Regional Health Service, higher during the last year of analysis (2014, 2015, 2016). More than half of costs were attributable to HDFs value [67.23% - 73.79%] and only a small range of these costs [1.69% - 5.74%] was attributable to outpatient services value. Pharmaceutical costs generated almost 30% of total patient-year costs and more than half of these were attributable to the use of drugs for cardiovascular reasons.

Such findings were comparable with those shown in the studies of Marchesini et al., (2011) and Scalone et al., (2014) even if their analyses were carried out in different Italian regions with territorial, social and demography differences. Specifically, Marchesini et al., (2011) constructed a database with almost 7-million of Italian citizens and according to their estimation the diabetes' costs were around € 2600 of which 50% per hospital admission, 30% per pharmaceutical therapies and 20% per outpatient services (Marchesini et al., 2011).

Another similar study was carried out by Jonsson (1998), who using a bottom-up prevalence-based design, evaluated more than 7000 patients with T2D in eight countries (Belgium, France, Germany, Italy, the Netherlands, Spain, Sweden and the United Kingdom). During the 6-month evaluation period, he found that the total direct medical costs of T2D were estimated at € 29 billion a year (1999 values) and the estimated average yearly cost per patient was € 2834 a year. Of these costs, hospitalizations accounted for the main driver (55%, range 30-65%) totaling € 15.9 billion and, in contrast, drug costs for managing T2D were relatively low, with antidiabetic drugs and insulin accounting for only 7% of the total healthcare costs. This research clearly proves that though the health administrative databases were not born to assess the epidemiological or economic impact of diseases in the population, they can be efficiently used also for these purposes, since they can provide in a relatively short time period, correct information directly from the target populations investigated for relevant follow up (Ayanian, 1999; Schneeweiss et al., 2005; Mantovani et al., 2011; Newgard, 2006). Moreover, the health administrative databases are a good source of population-based information for research about disease and for public health surveillance (James et al., 2004; Virnig et al., 2001; Elliott et al., 2012).

The combination of sources in the present study was fairly original when compared to the other experiences cited in the literature (Ballotari et al., 2014; Carstensen et al., 2011; Gudbjörnsdottir et al., 2003; Karter et al., 2001; Asghari et al., 2009). An Italian study by Ballotari et al., (2014) showed that several data sources made a meaningful contribution to assess the burden of diabetes (HDR, CDR, OSR, biochemistry lab and outpatient clinics), capturing cases not otherwise identified (Ballotari et al., 2014).

The present research has some limitations.

Firstly, people without diabetic exemption and not hospitalized during the reference year, 2005, could not be included in the study population. However, the probability that a consistent portion of people with a diagnosis of diabetes was not involved in any of the selection criteria in one year is low.

Additionally, it was not possible to make a distinction between T1D and T2D, since neither the exemption code nor the other criteria used, identified in the study of Scalone et al., (2014), were specific to the type of diabetes. Hypothesize in the source of data, a distinction code between the two types of DM, should allow a reduction of this boundary for future research.

Thirdly, healthcare costs may have been probably underestimated, due to the lack of some information in the administrative databases, such as costs for medical devices (needles, syringes, tests, intravenous feeding (IV)), costs for integrated home care and telemedicine, admission in residence for assisted health care; data that, to date, are not available through the administrative databases. In particular, costs of visits to general practitioners were not considered; all inhabitants residing in Italy are registered at a general practitioner, from whom they receive primary care in case of need. General practitioners are paid on a capitation basis, regardless of the care provided to their patients, thus it is not possible to measure the costs attributable to the visits for diabetes reasons (Age.na.s., Lgs. Decree 502/92).

Fourthly, another limitation consists in the association of specialist visits (outpatient services) and hospitalizations related to the illnesses investigated. It was not possible to associate them in a different way because each patient and related access cannot be analyzed in detail. Consultation with the board of experts and the deepening of the analysis carried out by Marcellusi et al., (2016), represented the only ways to identify the codes of services potentially associated with the care and management of patients with DM.

In general, since administrative databases were not originally intended for the epidemiological purpose, there could be several limitations in their use for the assessment of the incidence of the disease, including errors at each step of the coding process (O'Malley et al., 2005). Ultimately, the different probability of a case being included on each source, making it inappropriate to adopt the capture-recapture

methodology as a means to monitor the diabetes epidemic, could be counted among the limitations (Bruno et al., 1994; Fernàndez-Ramos et al., 2017; Rawshani et al., 2014).

The estimation of other indicators of the diabetes burden like loss of productivity, Disability Adjusted Life Years (DALYs) and Quality Adjusted Life Years (QALYs), could be the next step of the present research obtaining data related to absenteeism, impossibility to perform usual activities, causes of death, in order to calculate both loss of productivity for DALYs indicators, and quality of life expressed as utility index for QALYs calculation.

Institute for Health Metrics and Evaluation (IHME), an independent global health research center, in 2017 has calculated the top 10 causes of death and disability (DALYs) everywhere. In Italy, diabetes represents the fourth cause of death and disability and around 601.0 DALYs were attributable to such pathology in the year 2017 (IHME, 2017). Therefore, as a future aim, it could be valuable integrating the health administrative databases with new ones in which other kinds of data, such as causes of death, loss of productivity and quality of life, should be collected and registered, so as to develop more complete sources of data for the global assessment of the burden of diseases.

Nevertheless, this study was effective for its ability to give, in a relatively short time, a quite set of estimates of the burden of DM, punctually providing information to policy-makers for health planning. Although it could be improved, the model demonstrated to be an important source in terms of immediate availability and convenience since it is relatively cheap to obtain large amounts of good quality data on general population for the continuous monitoring of epidemiology and costs, which can be applied also in other disease areas of interest for the decision-making process in healthcare (Shahian et al., 2007; Suissa et al., 2007).

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APPENDICES

Appendix A - Pharmaceutical costs calculated with the ATC-code selection of Marcellusi et al., (2016).

Year	Obs	Total cost (€)	Average cost (€)	Std dev	[95% CI]	
A10						
2006	1732830	3.38E+07	219.39	705.02	216.86	221.93
2007	1979014	3.58E+07	370.23	938.76	367.52	372.93
2008	2094768	4.86E+07	23.21	31.05	23.16	23.25
2009	1996232	5.05E+07	25.27	33.78	25.23	25.32
2010	2139421	4.10E+07	26.44	35.24	26.39	26.48
2011	1885945	4.20E+07	29.55	39.4	29.5	29.6
2012	1967617	4.37E+07	32.11	42.14	32.05	32.17
2013	1923667	4.61E+07	34.73	44.72	34.67	34.79
2014	1838821	4.52E+07	36.14	47.97	36.07	36.2
2015	1731857	4.73E+07	40.26	50.22	40.19	40.33
2016	1357458	4.17E+07	44.84	54.12	44.75	44.93
C01						
2006	398596	4464013	11.2	7.53	11.18	11.22
2007	411550	4502465	10.94	7.12	10.92	10.96
2008	398724	4481233	11.24	7.8	11.21	11.26
2009	346035	3970236	11.47	10.24	11.44	11.51
2010	335511	4388612	13.08	15.25	13.03	13.13
2011	285931	4475607	15.65	20.72	15.58	15.72
2012	282418	4998704	17.7	24.93	17.61	17.79
2013	264478	5351476	20.23	29.1	20.12	20.34
2014	247816	5919657	23.89	33.94	23.75	24.02
2015	223539	6003203	26.86	37.56	26.7	27
2016	166648	5116169	30.7	41.16	30.5	30.89
C02						
2006	143749	3746964	26.07	10.79	26.01	26.12
2007	154976	3324226	21.45	8.78	21.41	21.49

Year	Obs	Total cost (€)	Average cost (€)	Std dev	[95% CI]	
2008	151025	2819637	18.67	6.46	18.64	18.7
2009	134249	2349760	17.5	6.07	17.47	17.53
2010	131904	2212470	16.77	5.77	16.74	16.8
2011	114629	1766225	15.41	5.62	15.38	15.44
2012	115295	1688618	14.65	5.25	14.62	14.67
2013	111134	1629999	14.67	5.22	14.64	14.69
2014	106217	1576720	14.84	5.32	14.81	14.87
2015	97278	1472607	15.14	5.66	15.1	15.17
2016	73353	1096511	14.95	5.52	14.91	14.98
C03						
2006	404759	2202650	5.44	5.09	5.43	5.45
2007	442013	2281588	5.16	4.9	5.15	5.17
2008	452566	2323480	5.13	4.98	5.12	5.14
2009	425394	2105455	4.95	4.81	4.93	4.96
2010	444434	2195636	4.94	4.79	4.93	4.95
2011	392812	2013820	5.13	4.96	5.11	5.14
2012	414503	2143510	5.17	5	5.16	5.18
2013	408087	2120400	5.2	5.19	5.18	5.21
2014	405227	2199813	5.43	6.85	5.41	5.44
2015	387837	2105101	5.43	5.85	5.41	5.44
2016	298379	1630508	5.46	5.82	5.44	5.48
C07						
2006	260272	3408642	13.1	7.19	13.07	13.12
2007	311340	3800729	12.21	6.83	12.18	12.23
2008	343542	4199107	12.22	6.92	12.2	12.24
2009	340168	4061010	11.94	7.05	11.91	11.96
2010	374869	3990008	10.64	6.57	10.62	10.66
2011	352564	3270284	9.28	4.56	9.26	9.29

Year	Obs	Total cost (€)	Average cost (€)	Std dev	[95% CI]	
2012	393729	3581224	9.1	4.3	9.08	9.11
2013	410155	3737000	9.11	4.36	9.1	9.12
2014	420803	3917756	9.31	4.57	9.3	9.32
2015	415574	3964653	9.54	4.86	9.53	9.55
2016	330423	3171285	9.6	4.98	9.58	9.61
C08						
2006	476132	1.03E+07	21.7	10.49	21.67	21.72
2007	510029	1.08E+07	21.15	10.19	21.12	21.17
2008	510635	8779798	17.19	9.68	17.17	17.22
2009	461590	7602879	16.47	9.61	16.44	16.49
2010	462150	6948608	15.04	8.65	15.01	15.06
2011	394570	5341860	13.54	8.21	13.51	13.56
2012	383170	4753390	12.41	7.77	12.38	12.43
2013	366157	4516738	12.34	7.73	12.31	12.36
2014	339518	4268008	12.57	7.95	12.54	12.59
2015	301747	3835175	12.71	8.04	12.68	12.74
2016	219990	2835545	12.89	8.23	12.86	12.92
C09						
2006	1249511	3.36E+07	26.93	14.7	26.9	26.95
2007	1379019	3.67E+07	26.59	14.57	26.57	26.62
2008	1407163	3.58E+07	25.47	16.69	25.44	25.49
2009	1280621	3.26E+07	25.49	17.62	25.46	25.51
2010	1296747	3.14E+07	24.2	17.38	24.17	24.22
2011	1127619	2.76E+07	24.5	17.92	24.47	24.53
2012	1154366	2.44E+07	21.11	16.19	21.08	21.13
2013	1110597	2.11E+07	19.03	14.88	19	19.05
2014	1052885	1.77E+07	16.77	11.84	16.75	16.79
2015	961147	1.68E+07	17.47	12.53	17.45	17.49

Year	Obs	Total cost (€)	Average cost (€)	Std dev	[95% CI]	
2016	721278	1.27E+07	17.55	12.8	17.53	17.58
C10AA						
2006	464895	2.29E+07	49.24	23.27	49.17	49.3
2007	552999	2.29E+07	41.39	21.77	41.33	41.44
2008	607044	2.16E+07	35.61	23	35.55	35.66
2009	609453	2.10E+07	34.32	24	34.26	34.38
2010	658577	2.23E+07	33.9	24.47	33.84	33.95
2011	591184	1.84E+07	31.1	22.7	31.05	31.16
2012	629843	1.42E+07	22.5	18.26	22.46	22.54
2013	624496	1.19E+07	19.07	15.96	19.03	19.11
2014	606678	1.17E+07	19.3	16.2	19.26	19.33
2015	575998	1.13E+07	19.63	16.58	19.59	19.67
2016	441359	8646262	19.59	16.74	19.54	19.64
N02A						
2006	34772	666662.1	19.17	31.4	18.84	19.5
2007	41002	759382.5	18.52	26.72	18.26	18.78
2008	45237	863649.8	19.09	29.99	18.82	19.37
2009	51795	928233	17.92	25.42	17.7	18.14
2010	89652	1330799	14.84	21.89	14.7	14.98
2011	82926	1415422	17.07	24.97	16.9	17.23
2012	91506	1882192	20.57	30.02	20.37	20.76
2013	89665	2129229	23.75	35.47	23.51	23.98
2014	77582	2229680	28.74	37.86	28.47	29
2015	80017	2454177	30.67	41.93	30.38	30.96
2016	65265	2010883	30.81	39.1	30.51	31.11
N02BE01						
2006	257	1898.14	7.39	4.07	6.89	7.89
2007	268	1832.93	6.84	3.47	6.42	7.25

Year	Obs	Total cost (€)	Average cost (€)	Std dev	[95% CI]	
2008	291	1970.23	6.77	3.71	6.34	7.19
2009	247	1796.07	7.27	3.79	6.8	7.74
2010	263	2029.13	7.72	4.14	7.21	8.21
2011	261	2143.09	8.21	3.89	7.74	8.68
2012	226	1853.59	8.2	5.27	7.51	8.89
2013	202	1599.36	7.92	3.65	7.41	8.42
2014	176	1415.93	8.05	3.86	7.47	8.61
2015	175	1523.26	8.7	4.47	8.04	9.37
2016	125	1105.16	8.84	4	8.13	9.54
N03AX12						
2006	21817	626701	28.73	12.11	28.56	28.89
2007	18119	498422.3	27.51	11.66	27.34	27.67
2008	16521	456455.6	27.63	11.83	27.45	27.8
2009	14211	361992.7	25.47	11.47	25.28	25.66
2010	14257	353474.9	24.79	11.35	24.61	24.97
2011	11897	305558.3	25.68	11.65	25.47	25.89
2012	12275	292518.1	23.83	11.2	23.63	24.02
2013	11921	285101.4	23.92	11.36	23.71	24.11
2014	11633	274216.2	23.57	11.31	23.37	23.77
2015	10655	250301.8	23.49	11.64	23.27	23.71
2016	8127	188676	23.22	11.44	22.97	23.46
N03AX16						
2006	31380	1361315	43.38	32.83	43.01	43.74
2007	29173	1406575	48.21	34.14	47.82	48.6
2008	32883	1649209	50.15	34.98	49.78	50.53
2009	35397	1772519	50.08	35.63	49.7	50.44
2010	41787	2052520	49.12	35.2	48.78	49.45
2011	38450	1971144	51.27	37.37	50.89	51.63

Year	Obs	Total cost (€)	Average cost (€)	Std dev	[95% CI]	
2012	42147	2243640	53.23	39.11	52.86	53.6
2013	43545	2325262	53.4	39.86	53.02	53.77
2014	45342	2441744	53.85	40.71	53.48	54.22
2015	46087	2486103	53.94	42.27	53.56	54.32
2016	38061	1954359	51.35	41.7	50.93	51.76
N06AX21						
2006	2815	181300.7	64.41	22.22	63.58	65.22
2007	5811	392115.3	67.48	24.08	66.86	68.1
2008	8423	581018.9	68.96	24.58	68.43	69.48
2009	10615	672856.2	63.39	29.3	62.83	63.94
2010	14360	777742.5	54.16	32.86	53.62	54.69
2011	13105	716754.9	54.69	34.75	54.09	55.28
2012	14775	836384	56.61	35.19	56.04	57.18
2013	15312	895041.3	58.45	34.44	57.91	58.99
2014	14733	897951	60.95	33.41	60.41	61.48
2015	13864	709062.6	51.14	30.51	50.64	51.65
2016	10649	275110.4	25.83	11.33	25.62	26.04
N07BC02						
2006	20	626.62	31.33	36.34	14.32	48.33
2007	76	4425.14	58.23	47.75	47.31	69.14
2008	74	2299.87	31.8	34.42	23.11	39.05
2009	no obs					
2010	11	32.98	3	3.84	0.42	5.57
2011	no obs					
2012	4	160.05	40.01	7.27	28.44	51.58
2013	21	1382.86	65.85	18.02	57.65	74.05
2014	15	1396.8	93.12	8.64	88.34	97.9
2015	25	2170.74	86.83	28.43	75.09	98.56

Year	Obs	Total cost (€)	Average cost (€)	Std dev	[95% CI]	
2016	no obs					
J01						
2006	498108	11100000	22.28	17.35	22.23	22.32
2007	543405	11300000	20.79	16.69	20.75	20.83
2008	557109	11200000	20.14	16.03	20.09	20.18
2009	498603	9612369	19.28	15.83	19.23	19.32
2010	483712	8944594	18.49	15.72	18.45	18.53
2011	425395	7609514	17.89	15.64	17.84	17.93
2012	423363	6581231	15.55	14.76	15.5	15.58
2013	423035	6530363	15.44	14.2	15.39	15.48
2014	415810	6462513	15.54	14.54	15.5	15.58
2015	395324	6213307	15.72	14.81	15.67	15.76
2016	284523	4396503	15.45	14.44	15.4	15.5
A02AD						
2006	51154	234643.2	4.59	2.93	4.56	4.61
2007	53943	253516.6	4.7	2.99	4.67	4.72
2008	50126	238608	4.76	3.01	4.73	4.78
2009	43300	207191.8	4.79	3	4.76	4.81
2010	41804	205442.8	4.91	3.06	4.89	4.94
2011	19617	147044.6	7.5	2.94	7.45	7.54
2012	20361	156781.1	7.7	3.01	7.66	7.74
2013	19856	154837.5	7.8	3.06	7.76	7.84
2014	20312	164877.7	8.12	3.16	8.07	8.16
2015	24497	196296.5	8.01	3.17	7.97	8.05
2016	18302	151181.1	8.26	3.2	8.21	8.3
A12AA04						
2006	3795	30545.71	8.05	3.09	7.95	8.14

Year	Obs	Total cost (€)	Average cost (€)	Std dev	[95% CI]	
2007	4166	31794.11	7.63	2.94	7.54	7.72
2008	4099	31135.53	7.6	2.92	7.51	7.68
2009	3873	28644.87	7.4	2.92	7.3	7.48
2010	4259	30874.97	7.25	2.83	7.16	7.33
2011	3870	30327.6	7.84	3.06	7.74	7.93
2012	4122	31585.1	7.66	3.02	7.57	7.75
2013	4065	31246.29	7.69	3.02	7.59	7.78
2014	3730	29113.78	7.81	3.18	7.7	7.9
2015	3553	28092.06	7.91	3.16	7.8	8.01
2016	2775	22330.95	8.05	3.24	7.93	8.16
A12AA12						
2006	no obs					
2007	no obs					
2008	no obs					
2009	1	33.1	33.1			
2010	4	165.5	41.38	16.55	15.04	67.7
2011	no obs					
2012	3	165.5	55.17	19.11	7.69	102.63
2013	3	165.5	55.17	19.11	7.69	102.63
2014	no obs					
2015	no obs					
2016	no obs					
B03A						
2006	24738	145483.9	5.88	2.68	5.85	5.91
2007	27714	165656	5.98	2.86	5.94	6.01
2008	31440	195555.9	6.22	3.15	6.19	6.25

Year	Obs	Total cost (€)	Average cost (€)	Std dev	[95% CI]	
2009	31293	203788.2	6.51	3.05	6.48	6.54
2010	35035	226798.1	6.47	3	6.44	6.5
2011	31818	226652.5	7.12	3.25	7.09	7.15
2012	35830	266790.8	7.45	3.46	7.41	7.48
2013	37269	273663.1	7.34	3.41	7.31	7.37
2014	38976	282737.6	7.25	3.4	7.22	7.28
2015	37273	271434.6	7.28	3.46	7.25	7.32
2016	27843	235186.2	8.45	3.7	8.4	8.49
B03BB						
2006	3286	11169.19	3.4	1.53	3.35	3.45
2007	4902	20101.47	4.1	1.53	4.06	4.14
2008	6483	29008.5	4.47	1.73	4.43	4.51
2009	7176	36688.54	5.11	2.26	5.06	5.16
2010	7634	46228.64	6.06	2.18	6	6.1
2011	8213	50933.12	6.2	2.26	6.15	6.25
2012	12128	74103.84	6.11	2.19	6.07	6.15
2013	15619	95526.66	6.12	2.13	6.08	6.15
2014	18809	116042.6	6.17	2.09	6.14	6.19
2015	20493	128809.7	6.29	2.29	6.25	6.32
2016	17018	104616.9	6.15	2.48	6.11	6.18
B03X						
2006	22148	6512462	294.04	325.66	289.75	298.33
2007	27775	7547365	271.73	304.86	268.15	275.32
2008	33938	8756775	258.02	279.22	255.05	260.99
2009	34484	9018051	261.51	267.35	258.69	264.34
2010	37196	1.02E+07	273.38	271.8	270.62	276.14

Year	Obs	Total cost (€)	Average cost (€)	Std dev	[95% CI]	
2011	36020	1.05E+07	291.75	270	288.96	294.54
2012	39569	1.13E+07	286.67	272.03	283.99	289.35
2013	40769	1.20E+07	293.7	273.58	291.04	296.36
2014	39681	1.15E+07	290.37	259.14	287.82	292.92
2015	39478	1.10E+07	279.1	244.52	276.68	281.5
2016	33287	9212212	276.75	233.75	274.24	279.26
H05BX						
2006	no obs					
2007	56	23552.38	420.58	229.41	359.14	482.01
2008	365	155296.3	425.47	170.55	407.91	443.02
2009	500	202490.1	404.98	195.2	387.83	422.13
2010	1346	406771.1	302.21	156.04	293.86	310.55
2011	1502	461461.3	307.23	183.56	297.94	316.52
2012	1497	476321.6	318.18	173.74	309.38	326.99
2013	1873	561477	299.77	169.57	292.09	307.46
2014	2003	604680.3	301.89	172.26	294.34	309.44
2015	1914	614732.8	321.18	4.44	312.46	329.89
2016	1577	525599.1	333.29	200.96	323.36	343.21
V03AE						
2006	2186	414696.7	189.71	153.93	183.25	196.16
2007	2513	454743.8	180.96	156.15	174.85	187.06
2008	2764	528654.5	191.26	168.27	184.99	197.54
2009	2498	508069.7	203.39	172.62	196.62	210.16
2010	2573	577746.8	224.54	172.85	217.86	231.22
2011	2666	628254.3	235.65	186.99	228.55	242.76
2012	2948	630025.8	213.71	191.48	206.8	220.63

Year	Obs	Total cost (€)	Average cost (€)	Std dev	[95% CI]	
2013	3244	680949.2	209.91	191.05	203.33	216.49
2014	3420	747015.4	218.43	188.66	212.1	224.75
2015	3368	624957.9	185.56	177.98	179.54	191.57
2016	2724	524823.3	192.67	187.84	185.61	199.72

Source: personal elaboration

Appendix B - Services cost associated with the treatment of diabetes or comorbidities based on the code selection of Marcellusi et al., (2016).

Year	Obs	Total cost (€)	Average cost (€)	Std dev	[95% CI]	
91.49.2						
2006	160663	2.29E+07	141.87	91.97	141.42	142.31
2007	150698	2.16E+07	143.46	93.73	142.99	143.94
2008	123020	1.78E+07	144.77	96.06	144.24	145.31
2009	132631	1.85E+07	139.59	95.66	139.08	140.1
2010	118945	1.65E+07	138.34	97.37	137.78	138.89
2011	no obs					
2012	no obs					
2013	no obs					
2014	no obs					
2015	no obs					
2016	no obs					
90.27.1						
2006	195448	3.34E+07	170.99	96.68	170.56	171.45
2007	181055	3.11E+07	171.57	99.19	171.11	172.02
2008	166640	26300000	157.9	98.85	157.43	158.38
2009	164415	2.75E+07	167.34	102.03	166.85	167.83
2010	149641	2.47E+07	164.91	106.95	164.36	165.45
2011	475013	3.38E+07	71.09	132.66	70.71	71.46
2012	475013	3.02E+07	63.61	126.18	63.25	63.96
2013	475013	2.18E+07	45.8	100.26	45.52	46.08
2014	475013	1.73E+07	36.52	77.53	36.29	36.73
2015	106026	1.70E+07	160.8	81.86	160.31	161.29
2016	98087	1.72E+07	175.22	78.74	174.73	175.71
89.01						
no obs						
90.28.1						
2006	81048	1.32E+07	163.07	126.85	162.2	163.94

Year	Obs	Total cost (€)	Average cost (€)	Std dev	[95% CI]	
2007	88419	1.42E+07	161.06	128.94	160.21	161.91
2008	79738	1.23E+07	154.68	124.42	153.82	155.54
2009	99027	1.42E+07	143.38	132.72	142.55	144.21
2010	98792	1.40E+07	141.52	134.51	140.68	142.35
2011	362162	3.19E+07	88.08	167.45	87.54	88.62
2012	362162	3.21E+07	88.74	168.46	88.19	89.29
2013	362162	2.44E+07	67.39	138.36	66.94	67.84
2014	362162	2.00E+07	55.12	109.48	54.76	55.47
2015	85593	1.96E+07	227.4	103.64	226.76	228.14
2016	84953	1.86E+07	218.94	99.03	218.27	219.6
90.62.2						
2006	148841	2.48E+07	166.93	111.07	166.37	167.5
2007	143249	2.31E+07	161.38	114.2	160.79	161.97
2008	147294	2.23E+07	151.5	116.05	150.9	152.09
2009	141287	2.06E+07	145.89	119.41	145.26	146.51
2010	132668	1.93E+07	145.7	120.38	145.05	146.34
2011	446321	3.70E+07	82.87	157.97	82.41	83.33
2012	446321	3.56E+07	79.66	158.26	79.2	80.12
2013	446321	2.63E+07	59	127.86	58.63	59.38
2014	446321	2.23E+07	49.87	101.6	49.57	50.17
2015	105137	2.14E+07	203.67	106.7	203.03	204.31
2016	100390	2.02E+07	200.79	104.1	200.15	201.43
90.16.3						
2006	102513	1.77E+07	172.82	93.85	172.25	173.39
2007	101856	1.72E+07	168.53	95.07	167.94	169.11
2008	114307	1.75E+07	153.38	100.33	152.8	153.9
2009	99213	1.66E+07	167.48	94.91	166.89	168.07
2010	95003	1.56E+07	164.18	99.6	163.55	164.82
2011	332415	2.15E+07	64.56	125.98	64.13	64.98
2012	332415	2.03E+07	61.11	122.83	60.69	61.52

Year	Obs	Total cost (€)	Average cost (€)	Std dev	[95% CI]	
2013	332415	1.43E+07	43.02	95.2	42.69	43.34
2014	332415	1.15E+07	34.69	72.3	34.45	34.93
2015	80147	1.12E+07	139.61	82.56	139.03	140.1
2016	73829	1.07E+07	145.03	87.72	144.4	145.6
89.7						
2006	13077	2774204	212.14	76.4	210.83	213.45
2007	13664	2825083	206.75	77.56	205.45	208.05
2008	33030	6716342	203.34	72.05	202.56	204.11
2009	18266	3701146	202.62	71.01	201.59	203.65
2010	17150	3555276	207.3	70.02	206.26	208.35
2011	54307	3969178	73.09	181.63	71.56	74.61
2012	54307	3562668	65.6	151.82	64.33	66.87
2013	54307	3594588	66.19	168.36	64.77	67.6
2014	54307	3344898	61.59	170.16	60.16	63.02
2015	12723	3363544	264.37	229.04	260.39	268.34
2016	12006	3080363	256.57	238.11	252.31	260.82
90.44.3						
2006	155745	2.66E+07	171.11	101.58	170.61	171.61
2007	145071	2.46E+07	169.55	106.38	169.01	170.1
2008	145860	2.36E+07	161.53	110.27	160.97	162.1
2009	134512	2.17E+07	161.26	110.98	160.67	161.86
2010	123670	1.95E+07	157.72	116.28	157.07	158.36
2011	407487	3.12E+07	76.48	142.83	76.04	76.91
2012	407487	2.83E+07	69.54	135.32	69.13	69.95
2013	407487	2.13E+07	52.18	110.23	51.84	52.5
2014	407487	1.76E+07	43.23	87.85	42.96	43.49
2015	93831	1.74E+07	185.4	87.46	184.84	185.96
2016	88673	1.75E+07	197.44	92.68	196.83	198.05
90.14.3						
2006	136494	2.49E+07	182.5	93.36	182	183

Year	Obs	Total cost (€)	Average cost (€)	Std dev	[95% CI]	
2007	131326	2.37E+07	180.6	95.16	180.09	181.12
2008	126773	2.14E+07	169.1	96.78	168.6	169.6
2009	126454	2.21E+07	174.89	96.74	174.36	175.43
2010	116771	2.01E+07	171.88	102.63	171.29	172.46
2011	379804	2.53E+07	66.71	123.53	66.32	67.1
2012	379804	2.46E+07	64.66	122.9	64.27	65.05
2013	379804	1.68E+07	44.34	95.07	44.04	44.64
2014	379804	1.25E+07	32.88	69.86	32.66	33.1
2015	82077	1.17E+07	143	80.39	142.47	143.57
2016	69493	9.87E+06	141.99	81.85	141.38	142.59
90.04.5						
2006	124663	2.26E+07	181	94.59	180.47	181.52
2007	120443	2.12E+07	175.87	96.41	175.33	176.41
2008	244583	4.21E+07	172.28	97.92	171.89	172.6
2009	118556	2.01E+07	169.96	98.44	169.4	170.5
2010	112364	1.89E+07	168.26	103.36	167.66	168.86
2011	365492	2.49E+07	68.16	124.32	67.76	68.56
2012	365492	2.39E+07	65.32	124.73	64.92	65.72
2013	365492	1.65E+07	45.03	96.48	44.72	45.34
2014	365492	1.30E+07	35.61	72.86	35.37	35.84
2015	82407	1.20E+07	146.06	85.1	145.48	146.64
2016	66058	8.93E+06	135.24	93.09	134.53	135.95
90.09.2						
2006	124277	2.26E+07	181.91	93.7	181.39	182.42
2007	119886	2.14E+07	178.46	95.21	177.92	179
2008	133668	2.32E+07	173.84	97.12	173.32	174.35
2009	118399	2.05E+07	173.09	96.67	172.54	173.64
2010	111946	1.92E+07	171.5	101.86	170.9	172.09
2011	364619	2.48E+07	68	123.77	67.61	68.41
2012	364619	2.38E+07	65.23	124.41	64.82	65.63

Year	Obs	Total cost (€)	Average cost (€)	Std dev	[95% CI]	
2013	364619	1.65E+07	45.16	96.4	44.84	45.47
2014	364619	1.32E+07	36.15	73.29	35.91	36.38
2015	82789	1.22E+07	147.38	78.93	146.84	147.9
2016	65844	9.37E+06	142.35	84.6	141.7	142.99
90.43.2						
2006	127377	2.28E+07	178.99	106.12	178.41	179.57
2007	123180	2.18E+07	176.62	109.67	176.01	177.23
2008	110024	1.89E+07	171.78	114.55	171.11	172.46
2009	120165	1.98E+07	164.55	116.44	163.9	165.2
2010	111596	1.85E+07	165.63	118.04	164.94	166.32
2011	364157	2.88E+07	79.15	141.5	78.69	79.6
2012	364157	2.88E+07	79.05	147.28	78.57	79.52
2013	364157	2.10E+07	57.54	118.42	57.16	57.92
2014	364157	1.59E+07	43.77	88.99	43.48	44.05
2015	79262	1.48E+07	186.19	82.25	185.62	186.76
2016	66468	1.19E+07	179.74	76.67	179.16	180.32
90.14.1						
2006	93072	1.62E+07	174.31	110.68	173.6	175
2007	95891	1.64E+07	171.28	114.76	170.56	172.01
2008	154026	2.51E+07	162.93	117.33	162.35	163.52
2009	104837	1.65E+07	157.53	121.53	156.79	158.26
2010	99215	1.56E+07	157.46	124.03	156.69	158.24
2011	337418	2.75E+07	81.41	148.12	80.91	81.91
2012	337418	2.75E+07	81.45	150.46	80.94	81.96
2013	337418	2.02E+07	59.88	121.3	59.47	60.28
2014	337418	1.54E+07	45.59	91.25	45.28	45.89
2015	74378	1.45E+07	195.48	81.03	194.89	196.06
2016	61259	1.20E+07	195.14	78.63	194.52	195.76
90.37.4						
2006	64664	1.08E+07	167.05	98.31	166.3	167.81

Year	Obs	Total cost (€)	Average cost (€)	Std dev	[95% CI]	
2007	64374	1.06E+07	164.15	97.55	163.39	164.89
2008	57926	8403145	145.06	96.03	144.28	145.84
2009	67041	1.08E+07	161.04	99.22	160.28	161.79
2010	65302	1.06E+07	161.6	100.17	160.83	162.37
2011	230121	1.53E+07	66.54	128.18	66.02	67.06
2012	230121	1.49E+07	64.71	129.76	64.18	65.23
2013	230121	1.05E+07	45.64	100.26	45.23	46.04
2014	230121	8.63E+06	37.48	76.34	37.17	37.79
2015	56362	8.14E+06	144.48	87.71	143.76	145.2
2016	46677	6.23E+06	133.47	91.92	132.64	134.3
90.44.1						
2006	94841	1.67E+07	175.65	90.52	175.07	176.22
2007	91521	1.56E+07	170.87	92.86	170.27	171.47
2008	85463	1.43E+07	167.85	95.47	167.21	168.48
2009	86987	1.46E+07	167.58	92.36	166.97	168.19
2010	81510	1.37E+07	167.81	95.71	167.15	168.47
2011	269184	1.74E+07	64.67	123.02	64.2	65.13
2012	269184	1.54E+07	57.03	116.29	56.59	57.46
2013	269184	1.05E+07	38.87	88.61	38.53	39.2
2014	269184	8.68E+06	32.23	68.67	31.97	32.49
2015	63217	8.45E+06	133.64	80.38	133	134.26
2016	46808	6.57E+06	140.3	82.29	139.55	141.04
90.25.5						
2006	74304	1.30E+07	174.59	92.02	173.92	175.24
2007	74028	1.28E+07	173.37	91.54	172.71	174.02
2008	60574	9978498	164.73	94.33	163.98	165.4
2009	77544	1.33E+07	170.93	90.82	170.3	171.57
2010	74788	1.27E+07	169.16	96.3	168.47	169.84
2011	249918	1.64E+07	65.62	123.28	65.14	66.1
2012	249918	1.50E+07	60.19	121.11	59.71	60.66

Year	Obs	Total cost (€)	Average cost (€)	Std dev	[95% CI]	
2013	249918	1.05E+07	42.11	93.83	41.74	42.48
2014	249918	8.58E+06	34.32	72.11	34.04	34.6
2015	58560	8.36E+06	142.78	79.93	142.13	143.42
2016	47017	7.02E+06	149.22	80.78	148.49	149.95
90.40.4						
2006	61697	1.04E+07	167.98	96.11	167.22	168.74
2007	61401	1.02E+07	165.98	96.34	165.22	166.74
2008	54341	8848164	162.82	97.8	162	163.64
2009	63763	1.04E+07	163.19	98.29	162.43	163.95
2010	62298	1.02E+07	164.14	99.56	163.36	164.92
2011	220184	1.48E+07	67	128.68	66.47	67.54
2012	220184	1.44E+07	65.38	130.45	64.83	65.92
2013	220184	1.02E+07	46.3	101.5	45.88	46.72
2014	220184	8.42E+06	38.25	77.49	37.93	38.57
2015	54089	7.83E+06	144.72	87.84	143.98	145.46
2016	44676	5.96E+06	133.42	89.53	132.59	134.24
90.33.4						
2006	26302	3738963	142.15	126.5	140.63	143.68
2007	30304	4267886	140.83	128.81	139.38	142.28
2008	29370	3840806	130.77	127	129.32	132.22
2009	39661	4693963	118.35	130.64	117.07	119.63
2010	170271	1.27E+07	74.7	153.32	73.97	75.42
2011	170271	1.27E+07	74.7	153.33	73.97	75.42
2012	170271	1.55E+07	91.09	166.18	90.3	91.88
2013	170271	1.29E+07	75.67	142.93	75	76.35
2014	170271	9.65E+06	56.69	109.33	56.17	57.2
2015	38104	8.96E+06	235.25	90.3	234.34	236.15
2016	34920	8.12E+06	232.5	89.4	231.56	233.43
93.82.1						

Year	Obs	Total cost (€)	Average cost (€)	Std dev	[95% CI]	
no obs						
89.52						
2006	5687	1382512	243.1	96.25	240.6	245.6
2007	6332	1506432	237.9	93.1	235.61	240.2
2008	6383	1400239	219.37	101.04	216.89	221.84
2009	4660	1089352	233.77	107.13	230.69	236.84
2010	4929	1160783	235.5	108.56	232.47	238.53
2011	16776	1470860	87.68	170.38	85.1	90.25
2012	16776	1286220	76.67	152.47	74.36	78.98
2013	16776	1249365	74.47	160.19	72.05	76.89
2014	16776	1098790	65.5	145.38	63.3	67.69
2015	3770	1115138	295.79	162.15	290.6	300.9
2016	3610	1049405	290.69	158.61	285.52	295.86
1.49.1						
no obs						
90.42.1						
2006	30110	399691.3	13.27	57.31	12.63	13.92
2007	30733	442521.4	14.39	59.87	13.72	15.06
2008	36087	548294.9	15.19	60.45	14.57	15.82
2009	34377	423109.8	12.31	55.83	11.72	12.89
2010	33042	453191.6	13.72	59.37	13.08	14.36
2011	113545	1.77E+07	155.73	278.9	154.1	157.34
2012	113545	1.69E+07	148.85	277.08	147.24	150.46
2013	113545	1.16E+07	101.98	214.74	100.73	103.22
2014	113545	9.30E+06	81.87	159.86	80.94	82.8
2015	27758	8.94E+06	322.23	151.52	320.45	324
2016	24488	7.41E+06	302.76	144.93	300.94	304.57
90.22.5						
2006	41722	6248004	149.75	116.07	148.64	150.86

Year	Obs	Total cost (€)	Average cost (€)	Std dev	[95% CI]	
2007	40497	5992642	147.97	116.11	146.84	149.1
2008	38783	5309632	136.9	115.04	135.76	138.05
2009	42916	6102968	142.21	117.36	141.1	143.3
2010	41899	5752974	137.31	118.1	136.17	138.43
2011	150570	1.25E+07	82.86	159.92	82.05	83.66
2012	150570	1.18E+07	78.11	156.41	77.32	78.9
2013	150570	8308988	55.18	121.81	54.57	55.79
2014	150570	7006188	46.53	94	46.06	47
2015	37219	6745628	181.24	102.35	180.2	182.28
2016	28579	5121753	179.21	101.63	178.04	180.39
90.10.4						
2006	9758	1695674	173.77	97.23	171.84	175.7
2007	8417	1459167	171.32	98.68	169.23	173.42
2008	11240	1867260	166.13	100.77	164.26	167.98
2009	6169	1041621	168.85	97.57	166.41	171.28
2010	5570	939276.3	168.63	97.51	166.07	171.19
2011	16021	1281914	80.01	136.68	77.9	82.13
2012	16021	1083993	67.66	132.88	65.6	69.7
2013	16021	665959.9	41.57	94.48	40.1	43
2014	16021	480720.1	30	68.42	28.95	31.05
2015	3073	440526.7	143.35	80.96	140.49	146.22
2016	2467	369446.8	149.76	87.58	146.3	153.21
90.10.5						
2006	34551	5722659	165.62	108.62	164.48	166.77
2007	35632	5846108	164.07	110.48	162.92	165.21
2008	54562	8301093	152.14	115.73	151.16	153.11
2009	39130	5968273	152.52	114.38	151.39	153.66
2010	37885	5831160	153.92	115.99	152.75	155.08
2011	133333	1.07E+07	80.15	149.82	79.34	80.95
2012	133333	1.01E+07	75.47	145.13	74.69	76.24

Year	Obs	Total cost (€)	Average cost (€)	Std dev	[95% CI]	
2013	133333	7124040	53.43	113.9	52.82	54
2014	133333	6031350	45.24	89.59	44.75	45.7
2015	31801	5746746	180.71	85.61	179.77	181.6
2016	25906	4759498	183.72	84.79	182.69	184.75
90.11.4						
2006	24119	3910796	162.15	98.63	160.9	163.39
2007	24443	3884081	158.9	98.66	157.67	160.14
2008	42828	6619922	154.57	100.4	153.62	155.5
2009	27880	4495484	161.24	96.94	160.11	162.38
2010	28982	4582956	158.13	98.75	156.99	159.26
2011	113140	7621145	67.36	136.11	66.57	68.15
2012	113140	7610488	67.27	138.64	66.46	68.07
2013	113140	5464487	48.3	110.58	47.65	48.94
2014	113140	4776560	42.22	86.88	41.71	42.72
2015	30259	4734091	156.45	104.5	155.27	157.6
2016	23087	3590799	155.53	109.25	154.12	156.94
90.15.4						
2006	15148	2253325	148.75	106.41	147.06	150.44
2007	16082	2352516	146.28	107.88	144.62	147.95
2008	21302	2681893	125.89	108.09	124.44	127.35
2009	19164	2727182	142.31	111.47	140.73	143.88
2010	18436	2549316	138.28	112.76	136.65	139.9
2011	66270	4868766	73.47	149.42	72.33	74.61
2012	66270	4725098	71.3	145.78	70.19	72.41
2013	66270	3411841	51.48	115	50.6	52.35
2014	66270	2908870	43.89	90	43.21	44.58
2015	15989	2793495	174.71	101.61	173.14	176.28
2016	12368	2166305	175.15	105.95	173.29	177.02
90.72.3						

Year	Obs	Total cost (€)	Average cost (€)	Std dev	[95% CI]	
2006	16984	2363530	139.16	123.07	137.31	141.01
2007	16326	2185388	133.86	123.68	131.96	135.75
2008	16236	2022568	124.57	124.39	122.66	126.48
2009	17490	2019905	115.49	124.96	113.64	117.34
2010	16601	1969579	118.64	124.47	116.75	120.53
2011	54787	5577905	101.81	194.82	100.17	103.44
2012	54787	5252915	95.88	195.34	94.24	97.51
2013	54787	3880370	70.82	157.38	69.51	72.14
2014	54787	3624922	66.16	133.16	65.05	67.27
2015	13396	3549822	264.99	136.46	262.68	267.3
2016	10826	2775703	256.39	129.48	253.95	258.83
90.23.5						
2006	29221	4745421	162.4	108.05	161.16	163.63
2007	27682	4409842	159.3	108.69	158.02	160.58
2008	22085	3224438	146	111.17	144.53	147.46
2009	26390	4142068	156.96	108.92	155.64	158.27
2010	25479	3914192	153.62	109.13	152.28	154.96
2011	82665	6544531	79.17	149.14	78.15	80.18
2012	82665	6045912	73.14	145.33	72.15	74.12
2013	82665	4088434	49.46	112.74	48.69	50.22
2014	82665	3335042	40.34	85.61	39.76	40.92
2015	19034	2915665	153.18	101.67	151.74	154.62
2016	11964	1668254	139.44	102.21	137.61	141.27
89.03						
2006	no obs					
2007	126	2000543.8	20.19	62.71	9.13	30
2008	253	4132	16.33	55.85	9.42	23.24
2009	135	2272.6	16.83	56.73	7.18	26.49
2010	345	3705.7	10.74	45.85	5.89	15.59
2011	4039	1256833	311.17	1234.72	273.08	349.26

Year	Obs	Total cost (€)	Average cost (€)	Std dev	[95% CI]	
2012	4039	2105014	521.17	2126.19	455.58	586.76
2013	4039	2895517	716.89	2273.7	646.75	787.03
2014	4039	3938798	975.19	248.52	898.52	1000.8
2015	1798	3585317	1994.06	2430.9	1881.62	2006.4
2016	1907	3620357	1898.46	2150.44	1801.89	1990.03
90.22.3						
2006	15562	1037553	66.67	117.59	64.82	68.51
2007	16429	1073356	65.33	116.8	63.55	67.11
2008	22063	1618983	73.38	118.17	71.82	74.9
2009	20011	1119162	55.93	110.21	54.4	57.45
2010	20973	1239265	59.09	113.37	57.55	60.62
2011	81743	9910258	121.24	237	119.61	122.86
2012	81743	9758717	119.38	238.6	117.75	121
2013	81743	7444800	91.08	193.25	89.75	92.4
2014	81743	6544604	80.06	152.18	79.02	81.1
2015	22050	6577504	298.3	149	296.33	300.26
2016	19562	5473639	279.81	136.87	277.89	281.72
95.02						
2006	1951	343681	176.15	78.89	172.65	179.65
2007	2295	440834	192.08	57.18	189.74	194.42
2008	3892	752645.4	193.38	53.57	191.7	195.06
2009	1966	373328	189.89	63.1	187.1	192.68
2010	1707	327204	191.68	59.21	188.87	194.49
2011	6626	399016	60.22	131.28	57.06	63.38
2012	6626	363390.7	54.84	111.4	52.16	57.52
2013	6626	353556	53.36	116.91	50.54	56.17
2014	6626	422594.2	63.78	118.03	60.94	66.62
2015	1849	418383.9	226.28	125.4	220.55	231.99
2016	1772	400589	226.07	124.47	220.27	231.8
96.59						

Year	Obs	Total cost (€)	Average cost (€)	Std dev	[95% CI]	
2006	293	13676.4	46.67	62.77	39.46	53.89
2007	235	9005.2	38.32	55.32	31.21	45.43
2008	271	9094.9	33.56	30.34	29.93	37.18
2009	147	4671.3	31.78	41.09	25.08	38.47
2010	115	5535.1	48.13	42.18	40.34	55.92
2011	546	9096.2	16.66	97.52	8.47	24.85
2012	546	25204.9	46.16	155.64	33.08	59.24
2013	546	36322.3	66.52	179.32	51.45	81.5
2014	546	6629.9	12.14	66.97	6.51	17.77
2015	57	10425.4	182.9	272.78	110.52	255.28
2016	58	14840.1	255.86	335.52	167.64	344.08
90.94.2						
2006	27992	3570015	127.53	110	126.25	128.83
2007	27566	3433527	124.55	110.55	123.25	125.86
2008	29167	3370270	115.55	103.57	114.36	1016.7
2009	28733	3395878	118.18	109.83	116.92	119.46
2010	27309	3234254	118.43	110.4	117.12	119.74
2011	90622	7037564	77.66	156.65	76.64	78.67
2012	90622	6581513	72.63	153.3	71.63	73.62
2013	90622	5518170	60.89	132.48	60.03	61.75
2014	90622	5536829	61.1	122.37	60.3	61.89
2015	21385	5209110	243.59	126.99	241.88	245.28
2016	20868	4935960	236.53	126.06	234.82	238.24
90.13.3						
2006	4687	791908.2	168.96	84.43	166.54	171.37
2007	4458	754677.7	169.28	85.48	166.77	171.79
2008	6393	1044940	163.45	88.11	161.29	165.61
2009	5247	907545	172.96	80.94	170.77	175.15
2010	5412	915668	169.19	85.56	166.91	171.47
2011	21433	1267371	59.13	114.4	57.6	60.66

Year	Obs	Total cost (€)	Average cost (€)	Std dev	[95% CI]	
2012	21433	1161485	54.19	111.43	52.7	55.68
2013	21433	826042.5	38.54	83.94	37.42	39.66
2014	21433	716503	33.43	66.78	32.54	34.32
2015	5529	694317.4	125.58	75.23	123.59	127.56
2016	3646	474687.6	130.19	78.06	127.66	132.72
89.39.3						
2006	487	90533.3	185.9		185	185.93
2007	no obs					
2008	762	141655.8	185.9			
2009	760	68968.9	185.9			
2010	251	46660.9	185.9			
2011	275	16731	60.84	87.38	50.47	71.21
2012	275	16916.9	61.52	87.63	51.11	71.91
2013	275	11154	40.56	76.91	31.43	49.69
2014	275	6320.6	22.98	61.3	15.71	30.26
2015	no obs					
2016	no obs					
93.56.1						
2006	no obs					
2007	no obs					
2008	no obs					
2009	24	4837.5	201.56	74.82	169.97	233.15
2010	56	11404	203.64	59.59	187.69	219.59
2011	830	4907.3	5.91	33.37	3.64	8.18
2012	830	11517.4	13.87	59.94	9.79	17.96
2013	830	27839.9	33.54	91.35	27.32	39.76
2014	830	171594.7	206.74	118.36	198.68	214.8
2015	1470	403899.4	274.76	49.26	272.24	277.28
2016	1949	572540.9	293.76	55.78	291.28	296.23
39.95.4						

Year	Obs	Total cost (€)	Average cost (€)	Std dev	[95% CI]	
no obs						
88.77.2						
2006	no obs					
2007	no obs					
2008	no obs					
2009	no obs					
2010	no obs					
2011	24704	6803545	275.4	466.62	269.58	281.22
2012	24704	5739859	232.34	420.33	227.1	237.58
2013	24704	4521170	183.01	378.66	178.29	187.73
2014	24704	3958642	160.24	355.14	155.81	164.67
2015	4299	3420389	795.62	316	786.18	805.07
2016	4651	3659246	786.77	303.85	778.03	795.5
90.38.5						
2006	6982	991782.9	142.04	97.2	139.77	144.32
2007	7773	1084921	139.57	96.59	137.43	141.72
2008	7301	923953.1	126.55	97.06	124.32	128.78
2009	7497	1068979	142.59	96.82	140.4	144.77
2010	7622	1100948	144.44	99.41	142.21	146.68
2011	26833	1576597	58.76	125.03	57.26	60.25
2012	26833	1407479	52.45	118.71	51.03	53.87
2013	26833	1076472	40.12	96.71	38.96	41.27
2014	26833	993946.9	37.04	81.21	36.07	38
2015	7012	966518.4	137.84	105.73	135.36	140.3
2016	5301	788463.4	148.74	116.78	145.59	151.88
90.29.2						
2006	8792	1315024	149.57	104.54	147.38	151.76
2007	8823	1303015	147.68	104.51	145.5	149.86
2008	7750	1117129	144.15	103.91	141.83	146.45
2009	10078	1470853	145.95	104.05	143.92	147.97

Year	Obs	Total cost (€)	Average cost (€)	Std dev	[95% CI]	
2010	10128	1460602	144.21	104.57	142.18	146.25
2011	34914	2622531	75.11	149.16	73.55	76.67
2012	34914	2535970	72.63	149.11	71.07	74.19
2013	34914	1754127	50.24	116.56	49.02	51.46
2014	34914	1405541	40.26	87.58	39.34	41.17
2015	8376	1336038	159.51	106.45	157.22	161.79
2016	5395	836650.9	155.08	107.84	152.2	157.95
88.73.5						
2006	5276	68.1	0.01	0.94	-0.01	0.04
2007	no obs					
2008	no obs					
2009	no obs					
2010	no obs					
2011	31011	4812180	155.18	299.26	151.85	158.5
2012	31011	4677484	150.83	288.06	147.63	154.03
2013	31011	3963241	127.8	261.99	124.89	130.7
2014	31011	3712579	119.72	250.14	116.93	122.5
2015	6237	3197399	512.65	219.55	507.2	518.1
2016	6384	3262095	510.98	203.7	505.98	515.97
88.76.1						
2006	no obs					
2007	no obs					
2008	no obs					
2009	no obs					
2010	no obs					
2011	13591	2250926	165.62	286.12	160.81	170.42
2012	13591	2179035	160.33	289.12	155.47	165.19
2013	13591	2057836	151.41	271.32	146.85	155.97
2014	13591	2040385	150.13	271.08	145.57	154.68
2015	3503	2171807	619.98	103.84	616.54	623.42

Year	Obs	Total cost (€)	Average cost (€)	Std dev	[95% CI]	
2016	3692	2296165	621.93	121.67	618	625.86
90.06.4						
2006	4934	718226.8	145.57	109.69	142.51	148.62
2007	4888	689587.1	141.07	111.3	137.96	144.2
2008	8718	1157579	132.78	111.19	130.45	135.11
2009	5388	764948.6	141.97	110.69	139.02	144.92
2010	5402	728035.3	134.77	112.5	131.77	137.77
2011	19768	1531242	77.46	160.35	75.23	79.69
2012	19768	1398783	70.76	150.46	68.66	72.85
2013	19768	1032019	52.21	120.14	50.53	53.88
2014	19768	964383.4	48.79	99.51	47.4	50.17
2015	5131	954564.5	186.04	114.59	182.9	189.17
2016	2897	567713.6	195.97	111.05	191.92	200
95.12						
2006	no obs					
2007	no obs					
2008	no obs					
2009	no obs					
2010	no obs					
2011	no obs					
2012	33	7333.3	222.22	329.47	105.4	339
2013	33	5293.5	160.41	348.92	106.69	284
2014	33	5831.4	176.71	336.13	57.52	295.89
2015	4	3692.3	923.08	193.65	614.93	1001.2
2016	no obs					
90.24.3						
2006	1384	215940.3	156.03	100.4	150.73	161.3
2007	1386	211734.1	152.76	98.41	147.58	157.95
2008	1181	171215.1	144.97	98.97	139.32	150.63

Year	Obs	Total cost (€)	Average cost (€)	Std dev	[95% CI]	
2009	1682	274802.7	163.38	95.56	158.81	167.95
2010	1743	270895.2	155.42	94.8	150.97	159.87
2011	7138	456944.7	64.02	132.26	60.95	67.08
2012	7138	442877.7	62.05	133.1	58.96	65.13
2013	7138	346237.8	48.51	107.68	46	51
2014	7138	332768.3	46.62	96.84	44.37	48.87
2015	1911	333229.3	174.37	119.36	169	179.72
2016	1406	270893.2	192.67	123.68	186.2	199.13
90.30.2						
2006	1993	255552.2	128.22	114.98	123.17	133.27
2007	2173	270563.1	124.51	116.04	119.63	129.39
2008	2028	245179.6	120.89	114.21	115.92	125.87
2009	2746	340772.8	124.1	119.17	119.64	128.55
2010	2928	367964.9	125.67	119.68	121.33	130
2011	12387	1018214	82.2	173.75	79.14	85.26
2012	12387	986494.4	79.64	172.1	76.61	82.67
2013	12387	784741	63.35	141.72	60.86	65.84
2014	12387	820137	66.21	122.02	64.06	68.36
2015	3749	837782.9	223.47	123.33	219.52	227.42
2016	2505	549718.5	219.45	118.38	214.81	224.09
90.82.3						
2006	429	32156.6	74.96	121.34	63.44	86.47
2007	482	25450.3	52.8	107.77	43.16	62.44
2008	568	31277.4	55.07	105.74	46.35	63.78
2009	597	34406.3	57.63	112.32	48.6	66.6
2010	631	35917.1	56.92	111.46	48.21	65.63
2011	2379	303759.4	127.68	236.01	118.19	137.17
2012	2379	266912.2	112.2	224.95	103.15	121.23
2013	2379	205076.7	86.2	185.67	78.74	93.67
2014	2379	214130	90	171.95	83.1	96.92

Year	Obs	Total cost (€)	Average cost (€)	Std dev	[95% CI]	
2015	599	214336.4	357.82	170.61	344.13	371.51
2016	464	146815	316.41	154.19	302.35	330.47
88.74.1						
2006	no obs					
2007	no obs					
2008	no obs					
2009	no obs					
2010	no obs					
2011	13517	1821930	134.79	227.7	130.95	138.62
2012	13517	1686876	124.8	222.39	121.05	128.54
2013	13517	1507694	111.54	215.96	107.9	115.18
2014	13517	1535101	113.57	215.4	109.94	117.2
2015	2916	1451551	497.79	158.62	492.03	503.55
2016	2598	1271020	489.23	147.44	483.56	494.9
95.09.1						
2006	2190	240236.5	109.7	71.21	106.71	112.68
2007	2200	251368.7	114.25	64.31	111.57	116.94
2008	2667	299185.8	112.18	61.7	109.84	114.52
2009	1069	179976.5	168.36	75.92	163.8	172.9
2010	974	164668.4	169.06	74.42	164.38	173.74
2011	5126	230464.9	44.96	105.96	42.06	47.86
2012	5126	334856.5	65.33	139.13	61.52	69.13
2013	5126	219319	42.79	108.32	39.82	45.75
2014	5126	272071.5	53.08	120.25	49.78	56.36
2015	1284	251044.1	195.52	146.09	187.52	203
2016	1225	246230.1	201	158.89	192.1	209.9
89.13						
2006	261	50410.4	193.14	51.08	186.92	199.36
2007	200	37497.9	187.49	61.33	178.93	196.05
2008	396	74376	187.81	59.47	181.94	193.69

Year	Obs	Total cost (€)	Average cost (€)	Std dev	[95% CI]	
2009	180	33262.6	184.79	63.66	175.43	194.15
2010	152	30163.6	198.44	40.36	191.98	204.91
2011	853	48137.7	56.43	98.75	49.8	63.07
2012	853	35638.4	41.78	85.87	36	47.55
2013	853	42223.6	49.5	96.97	43	56
2014	853	56737.5	66.52	101.18	59.72	73.3
2015	332	68823.6	207.3	12.75	205.92	208.67
2016	315	65311.4	207.34	13.09	205.88	208.78
54.98.1						
no obs						
86.22						
no obs						
90.05.1						
2006	2198	314888.8	143.26	110.84	138.62	147.89
2007	2282	333638.4	146.2	113.02	141.56	150.84
2008	4548	636283.8	139.9	113.93	136.59	143.21
2009	2625	372442	141.88	114.54	137.5	146.26
2010	2719	384691.6	141.48	114.07	137.19	145.77
2011	13337	901885.4	67.62	143.93	65.18	70
2012	13337	1024564	76.82	151.8	74.24	79.39
2013	13337	803985.7	60.28	127.69	58.12	62.44
2014	13337	711985.7	53.38	106.45	51.58	55.19
2015	3466	681514.7	196.63	127.38	192.38	200.87
2016	2822	523208.3	185.4	117.31	181.07	189.73
88.28						
2006	2017	136139.2	67.5	87.75	63.66	71.32
2007	2146	141165	65.78	87.11	62.09	69.47
2008	3773	301653.6	79.95	89.04	77.11	82.79
2009	2161	135997.2	62.93	86.3	59.29	66.57

Year	Obs	Total cost (€)	Average cost (€)	Std dev	[95% CI]	
2010	2060	113296.2	55	83.14	51.41	58.59
2011	7158	743318.1	103.84	231.94	98.47	109.2
2012	7158	806029.3	112.61	236.74	107.12	118.09
2013	7158	766938.5	107.14	228.34	101.85	112.43
2014	7158	695235.7	97.13	221.84	91.99	102.26
2015	1535	623973.6	406.5	270.83	392.94	420
2016	1704	690031.5	404.95	256.51	392.76	417.13
90.85.2						
2006	5079	569546.2	112.14	130.28	108.55	115.72
2007	5432	619568.4	114.05	130.31	110.59	117.5
2008	7030	950983.5	135.27	131.09	132.21	138.34
2009	5784	620667.4	107.31	126.04	104.06	110.55
2010	5618	622477.4	110.8	127.99	107.45	114.15
2011	19326	1785791	92.4	182.24	89.83	94.97
2012	19326	1718624	88.93	178.34	86.41	91.44
2013	19326	1559754	80.71	160.85	78.44	82.97
2014	19326	1766667	91.41	160.82	89.15	93.68
2015	5348	1738497	325.07	123.17	321.77	328.38
2016	5709	1804760	316.13	121.57	312.97	319.27
90.35.5						
2006	1288	64657.6	50.2	101.66	44.64	55.75
2007	1454	72633	49.95	104.25	44.59	55.31
2008	1486	88752	59.73	106.18	54.32	65.12
2009	2144	93095.1	43.42	97.39	39.3	47.54
2010	2579	115489.1	44.78	99.87	40.92	48.64
2011	12067	1447773	119.98	253.1	115.46	124.4
2012	12067	1472848	122.06	252.66	117.55	126.56
2013	12067	1454346	120.52	232.72	116.37	124.67
2014	12067	1704069	141.22	229.97	137.11	145.32
2015	3849	1782892	463.21	167.98	457.9	468.5

Year	Obs	Total cost (€)	Average cost (€)	Std dev	[95% CI]	
2016	3453	1546231	447.79	154.91	442.62	452.96
90.86.1						
2006	5005	643472.4	128.56	145.57	124.53	132.6
2007	4990	614000.3	123.05	144.76	119.03	127.06
2008	4712	592635.2	125.77	144.06	121.66	129.88
2009	4200	499674	118.97	144.74	114.59	123.34
2010	4083	486988.7	119.27	145.14	114.82	123.72
2011	13424	1312421	97.77	184.4	94.65	100
2012	13424	1277940	95.2	181.18	92.13	98.26
2013	13424	1151924	85.81	166.4	83	88.6
2014	13424	1334254	99.39	171.25	96.5	102.29
2015	3501	1253012	357.9	105.18	354.42	361.38
2016	3387	1201855	354.84	104.11	351.34	358.35
90.69.4						
2006	2216	177908	80.31	120.18	75.3	85.32
2007	2393	161573.5	67.52	113.95	62.95	72.08
2008	2108	162432.3	77.06	113.15	72.22	81.88
2009	2746	181692.9	66.17	112.54	61.96	70.37
2010	2514	175248.6	69.71	116.06	65.17	74.24
2011	7716	1016179	131.7	240.59	126.33	137.06
2012	7716	913850.3	118.44	226.15	113.39	123.48
2013	7716	693920.7	89.93	202.51	85.41	94.45
2014	7716	661172.7	85.69	172.61	81.84	89.54
2015	2310	786489	340.47	156.35	334.09	346.85
2016	1683	562768.9	334.38	146.69	327.37	341.39
88.72.3						
2006	no obs					
2007	no obs					
2008	no obs					
2009	no obs					

Year	Obs	Total cost (€)	Average cost (€)	Std dev	[95% CI]	
2010	no obs					
2011	6302	1312240	208.22	317.73	200.38	216.07
2012	6302	1058724	167.99	293.32	160.75	175.24
2013	6302	981717	155.78	288.96	148.64	162.91
2014	6302	810481.1	128.61	267.87	121.99	135.22
2015	1234	804169	651.68	107.54	645.67	657.68
2016	1180	766378.8	649.47	105.26	643.46	655.48
90.13.5						
2006	1190	46496.7	39.07	97.48	33.53	44.61
2007	1378	42420.5	30.78	88.23	26.12	35.44
2008	2827	70156	24.82	78.75	21.91	27.72
2009	2171	49944.4	23	76.47	19.79	26.22
2010	2699	62505.3	23.16	77.17	20.25	26.07
2011	14019	1799061	128.33	269.53	123.87	132.7
2012	14019	1887640	134.65	275.69	130.08	139.21
2013	14019	1581084	112.78	227.27	109.02	116.54
2014	14019	1664096	118.7	190.2	115.55	121.85
2015	5250	1978840	376.92	151.15	372.83	381.01
2016	4901	1762833	359.69	141.42	355.73	363.64
90.23.2						
2006	1267	46226	36.48	94.54	31.27	41.69
2007	1511	50535.1	33.44	90.12	28.9	37.9
2008	1450	51543.6	35.54	90.09	30.91	40.18
2009	2399	58837.4	24.53	79	21.36	27.68
2010	2887	69527	24.08	77.87	21.24	26.92
2011	13948	1844861	132.27	271.29	127.76	136.77
2012	13948	1880645	134.83	272.92	130.31	138.36
2013	13948	1520787	109.03	221.37	105.36	112.71
2014	13948	1561841	111.98	183.47	108.93	115.02
2015	4851	1786497	368.27	146.52	364.15	372.4

Year	Obs	Total cost (€)	Average cost (€)	Std dev	[95% CI]	
2016	4398	1550399	352.52	134.58	348.55	356.5
90.24.5						
2006	5634	878056.9	155.85	99.15	153.26	158.43
2007	6016	914947.6	152.08	99.44	149.57	154.59
2008	5595	774598.1	138.44	99.74	135.83	141.05
2009	7144	1074814	150.45	98.89	148.16	152.74
2010	7371	1079006	146.39	98.59	144.13	148.63
2011	28010	1711163	61.09	129.22	59.58	62.6
2012	28010	1698353	60.63	129.35	59.12	62.14
2013	28010	1315525	46.97	106.49	45.72	48.21
2014	28010	1275858	45.55	94.68	44.44	46.65
2015	7893	1420654	179.99	123.2	177.27	182.71
2016	6023	1192449	197.98	132.41	194.64	201.33
90.33.5						
2006	378	36028.7	95.31	121.16	83.06	107.56
2007	414	40292	97.32	120.62	85.67	108.97
2008	424	34480.2	81.32	116.22	70.23	92.41
2009	523	46122.4	88.19	123.06	77.62	98.75
2010	622	53425.2	85.89	121.74	76.31	95.47
2011	2458	243208.3	98.95	195.13	91.23	106.66
2012	2458	247269.1	100.59	198.48	92.75	108.44
2013	2458	180208.5	73.32	162.13	66.9	79.73
2014	2458	222954.8	90.71	160.9	84.34	97
2015	703	224790.6	319.76	155.58	308.24	331.28
2016	383	116173.5	303.33	138.28	289.43	317.2
90.51.4						
2006	4411	47095.6	10.67	53.81	9.09	12.26
2007	4338	42840.3	9.88	51.47	8.34	11.4
2008	3626	67009.3	18.48	70.46	16.19	20.77
2009	4658	39138.1	8.4	48.36	7.01	9.79

Year	Obs	Total cost (€)	Average cost (€)	Std dev	[95% CI]	
2010	4170	38637.7	9.27	50.26	7.74	10.79
2011	11850	2784117	234.95	386.13	227.99	241.89
2012	11850	2494896	210.54	374.46	203.8	217.2
2013	11850	1749880	147.67	298.49	142.29	153.04
2014	11850	1495995	126.24	244.58	121.84	130.64
2015	2411	1339151	555.43	180.91	548.21	562.66
2016	1528	831921.5	544.45	176.54	535.59	553.3
90.54.4						
2006	4536	40674.1	8.97	49.83	7.52	10.41
2007	4420	36882.7	8.34	48.73	6.9	9.78
2008	4344	36529.8	8.41	48.06	6.98	9.83
2009	4751	38990.7	8.21	48.56	6.83	9.58
2010	4289	34241.5	7.98	47.78	6.55	9.41
2011	12272	2925836	238.42	389.3	231.53	245.3
2012	12272	2621937	213.65	377.42	206.97	220.33
2013	12272	1826548	148.84	300	143.52	154.15
2014	12272	1554784	126.69	246.36	122.33	131
2015	2551	1420889	556.99	169.11	550.43	563.55
2016	1694	924316.7	545.64	172.11	537.44	553.84
93.20.1						
no obs						

Source: personal elaboration

Appendix C - Average outpatient services costs

Code	Description	Average cost (2006 - 2016)
91.49.2	Venous blood test	€ 141.61
90.27.1	Glucose /s /u	€ 125.98
90.28.1	Glycosylated haemoglobin (hba1c) /Sg	€ 137.22
90.62.2	Blood count cytometric and morphological test /sg	€ 131.57
90.16.3	Creatinine /s /u	€ 119.49
89.7	General check up	€ 165.41
90.44.3	Complete urine analysis	€ 131.40
90.14.3	Total cholesterol /s	€ 124.78
90.04.5	Glutamic pyruvate transaminase (gpt- alt) /s	€ 123.89
90.09.2	Glutamic oxaloacetic transaminase (got- ast) /s	€ 125.73
90.43.2	Triglycerides /s	€ 134.82
90.14.1	Hdl cholesterol /s	€ 134.77
90.37.4	Potassium /s /u	€ 117.38
90.44.1	Urea /s /u	€ 119.68
90.25.5	Gamma glutamyl transpeptidase (gamma –gt) /s	€ 122.46
90.40.4	Sodium /s /u	€ 119.93
90.33.4	Microalbumin /u	€ 124.79
89.52	Electrocardiogram	€ 187.31
90.42.1	Thyrotropin (tsh) /s	€ 107.48
90.22.5	Iron /s	€ 121.57
90.10.4	Total biilurubin /s	€ 123.73
90.10.5	Direct bilurubin /s	€ 127.91
90.11.4	Calcium /s /u	€ 121.10
90.15.4	Creatine kinase (ck) /s	€ 117.41
90.72.3	Quantitative c- reactive protein /s	€ 135.25
90.23.5	Alkaline phosphatase /s /u	€ 119.36
89.03	Complete medical history assessment	€ 648.10

Code	Description	Average cost (2006 - 2016)
90.22.3	Ferritin /s	€ 119.12
95.02	Comprehensive eye examination	€ 147.98
96.59	Other wound cleansing	€ 70.79
90.94.2	Urine culture for aerobic/mycete bacteria and bacterial count	€ 123.33
90.13.3	Chloride /s /u	€ 116.81
89.39.3	Evaluation of vibration perception threshold	€ 116.19
93.56.1	Bandaging	€ 154.22
88.77.2	Regional or upper or lower limbs eco (color) doppler	€ 405.56
90.38.5	Total proteins /s /u	€ 106.38
90.29.2	Lactate dehydrogenase (ldh) /s	€ 116.76
88.73.5	Eco (color) doppler of supra aortic trunks	€ 225.31
88.76.1	Complete abdominal ultrasound	€ 311.57
90.06.4	Amylase /s /u	€ 120.67
95.12	Fluorescein angiography or angioscopy of eye	€ 370.61
90.24.3	Inorganic phosphate /s /u	€ 123.71
90.30.2	Lipase /s	€ 123.43
90.82.3	TROPONIN I and T /S /P	€ 126.15
88.74.1	Upper abdominal ultrasound	€ 245.29
95.09.1	Fundus oculi examination	€ 116.02
89.13	Neurological examination	€ 143.69
90.05.1	Albumin /s /	€ 122.99
88.28	Foot and ankle x- ray	€ 142.12
90.85.2	Sensitivity test bacteria from mic culture (at least 10 antibiotics)	€ 143.11
90.35.5	Parathormone (pth) /s intact molecule	€ 151.17
90.86.1	Biochemical identification of nas bacteria	€ 155.14
90.69.4	Immunoglobuline (igg- iga- igd- igm) /S /U (each)	€ 132.85
88.72.3	Doppler echocardiography	€ 326.96

Code	Description	Average cost (2006 - 2016)
90.13.5	B12 vitamin /s	€ 124.72
90.23.2	Folate /s	€ 123.91
90.24.5	Phosphorous/phosphates /s	€ 121.40
90.33.5	Myoglobin /s /u	€ 130.43
90.51.4	Antithyroid peroxidase antibodies	€ 170.54
90.54.4	Anti thyroglobulin antibodies /s	€ 170.19

Source: personal elaboration

Appendix D - Distribution of hospitalization, drug therapy and outpatient services costs by year

Year	HDFs cost		Pharmaceutical cost		Outpatient services cost		Total
	(€)	(%)	**(€)**	(%)	**(€)**	(%)	
2006	€ 2778.82	72.98%	€ 895.43	23.52%	€ 133.63	3.51%	€ 3808.84
2007	€ 2973.75	67.53%	€ 1299.38	29.51%	€ 130.43	2.96%	€ 4404.53
2008	€ 2868.08	67.23%	€ 1271.08	29.80%	€ 126.79	2.97%	€ 4266.91
2009	€ 2884.69	67.53%	€ 1257.61	29.44%	€ 129.25	3.03%	€ 4272.52
2010	€ 2910.97	68.94%	€ 1183.33	28.02%	€ 128.21	3.04%	€ 4223.48
2011	€ 2834.00	67.24%	€ 1282.41	30.43%	€ 98.49	2.34%	€ 4215.87
2012	€ 3084.74	69.47%	€ 1255.40	28.27%	€ 100.08	2.25%	€ 4441.20
2013	€ 3549.43	72.37%	€ 1270.61	25.91%	€ 84.54	1.72%	€ 4905.56
2014	€ 3728.38	73.44%	€ 1262.11	24.86%	€ 86.05	1.69%	€ 5077.52
2015	€ 3895.37	71.60%	€ 1232.86	22.66%	€ 312.21	5.74%	€ 5441.38
2016	€ 4060.73	73.79%	€ 1144.70	20.80%	€ 297.77	5.41%	€ 5504.15
Total	€ 35568.96		€ 13354.92		€ 1627.45		€ 50561.98

Source: personal elaboration