

Direct Medical Costs of Type 2 Diabetes in France: An Insurance Claims Database Analysis

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Abstract

Objectives Our objects was to estimate the direct health-care costs of type 2 diabetes mellitus (T2DM) in France in 2013.

Methods Data were drawn from a random sample of $\approx 600,000$ patients registered in the French national health insurances database, which covers 90% of the French population. An algorithm was used to select patients with T2DM. Direct healthcare costs from a collective perspective were derived from the database and compared with those from a control group to estimate the cost of diabetes and related comorbidities. Overall direct costs were also compared according to the diabetes therapies used throughout the year 2013.

Results Cost analysis was available for a sample of 25,987 patients with T2DM (mean age $67.5 \pm$ standard deviation

12.5; 53.9% male) matched with a control group of 76,406 individuals without diabetes. Overall per patient per year medical expenditures were $\text{€}6506 \pm 10,106$ in the T2DM group as compared with $\text{€}3668 \pm 6954$ in the control group. The cost difference between the two groups was $\text{€}2838$ per patient per year, mainly due to hospitalizations, medication and nursing care costs. Total per capita annual costs were lowest for patients receiving metformin monotherapy ($\text{€}4153 \pm 6170$) and highest for those receiving insulin ($\text{€}12,890$). However, apart from patients receiving insulin, costs did not differ markedly across the different oral treatment patterns.

Conclusion Extrapolating these results to the whole T2DM population in France, total direct costs of diagnosed T2DM in 2013 was estimated at over $\text{€}8.5$ billion. This estimate highlights the substantial economic burden of this condition on society.

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Key Points for Decision Makers

In 2013, the average overall direct healthcare expenditure for a patient with type 2 diabetes mellitus (T2DM) in France was €6506.

The direct cost of diabetes and related morbidities was estimated at €2838 per patient per year.

Patients receiving insulin incurred the highest costs (€12,890).

Costs did not differ markedly across the different oral treatment patterns.

1 Introduction

As in most Western countries, the prevalence of diabetes in France has risen sharply over the last two decades, reaching 4.7% of the adult general population in the French national survey conducted in 2013 [1] (updated to 5% in 2015 [2]). Over 2009–2013, the growth rate of the diabetic population was estimated at 2.3% each year [2]. On this basis, it can be estimated that around 3.3 million people had diabetes in France at the beginning of 2015. The majority of these cases correspond to type 2 diabetes mellitus (T2DM), and this population continues to grow because of the aging population and lifestyle factors. In the 2007 ENTRED study [3], 92% of all cases of diabetes were T2DM, and this proportion may have risen with the increases in obesity to reach 95% or more.

Given the large number of individuals affected and the high cost of managing the complications of diabetes, the economic burden from diabetes is considerable. Data from the 2007 ENTRED study provided an estimate of €12.5 billion for the total healthcare costs reimbursed by the National Sickness Fund for people with diabetes, whatever the type. However, this figure is likely to have evolved since then because of the increase in the treated population, the introduction of new treatments since 2007—notably glucagon-like peptide-1 (GLP-1) analogues and dipeptidylpeptidase-4 (DPP-4) inhibitors (gliptins)—and the impact of treatment guidelines recommending more intensive treatment regimens earlier in the disease course [4]. More recent estimates were also published by the National Sickness Fund, but these only considered reimbursed expenditure. The total healthcare costs reimbursed for people with diabetes was estimated at €19 billion in 2012. Several methods were then used to estimate the burden of diabetes, resulting in estimates varying between €7.7 billion and €10 billion [5].

Thus, we considered it timely to reassess the economic burden of T2DM in France. Recently, a number of public health insurance databases have become available in France, which have made it possible to collect quasi-exhaustive information on healthcare resource utilisation in representative samples of the French general population. The EGB (Echantillon Généraliste des Bénéficiaires) database is a representative sample of French National insurance funds that covers around 95% of the French population [6]. This database has been used in several recent studies to document medication prescription, costs or outcomes in different disease groups in the French general population [7–9], including in patients with diabetes [10]. The objective of this study was to describe the characteristics of patients with T2DM in France and their treatments and to estimate their total direct healthcare expenditure as the cost directly related to diabetes care and related comorbidities.

Although some of the well-known diabetes drugs are modestly priced generics, new brand-name drugs continue to be introduced at higher prices. Their mechanisms of action differ: some induce fewer side effects and others have greater efficacy. It is therefore interesting to compare total direct costs according to the antidiabetic agents prescribed in a real-life setting. The cost of a drug is one criterion that may guide treatment choice among available glucose-lowering agents for a patient with T2DM [11, 12]. However, the cost of treatment alone does not reflect the budget consequences of the drug choice. Therefore, we were also interested in reporting hospital and community costs for different pharmacological therapy options (monotherapy, dual, other) and to use an example to illustrate how a simple comparison of the direct costs of diabetes treatment may result in misinterpretation.

2 Methods

This was a retrospective study of healthcare resource consumption and associated costs generated by a representative sample of patients with T2DM identified in the French general health insurance claims database in 2013. Direct healthcare costs were estimated from a collective perspective regardless of the institution or individual.

2.1 The EGB Database

The EGB (Echantillon Généraliste des Bénéficiaires) database is a random sample of beneficiaries of the principal French public health insurance scheme, which covers approximately 95% of the total French population (66 million individuals) [6]. The sample of 1/97 randomly selected individuals included in the EGB database

corresponds to around 600,000 individuals. All information in the database is anonymous. The EGB database contains limited sociodemographic and medical data on healthcare users but comprehensive reimbursement records on healthcare consumption in community and hospital care. Sociodemographic information is restricted to age, sex, and place of residence. All items of medical consumption in the public or private sector that are eligible for reimbursement are documented, notably consultations, paraclinical tests, medication, devices and, since 2005, hospitalisations [6]. Items ineligible for reimbursement, such as over-the-counter drugs, are absent from the database and cannot be identified. In addition, information on inpatient rehabilitation is not available. For costing purposes, hospitalisations in acute care facilities (medicine, surgery or obstetrics) are coded in the EGB database through a specific diagnosis-related group (DRG). Medication is identified in the database through the relevant Anatomical Therapeutic Chemical (ATC) classification code. Date of death is documented in the database but not the cause of death.

The only types of data in the EGB database associated with an explicit diagnosis are hospitalisation and eligibility for full insurance coverage due to a severe chronic disease (Affection de Longue Durée [ALD] status). In the case of hospitalisations, the diagnosis can be identified since each hospital stay is valued on the basis of a unique DRG, which is coded using the International Classification of Disease, tenth revision (ICD-10) codes [13]. The reasons for hospitalisation are coded either as primary diagnoses (PD; the condition for which the patient was hospitalised), related diagnoses (RD; any underlying condition that may have been related to the PD) or as associated diagnoses (AD; comorbidities that may affect the course or cost of hospitalisation). In the case of ALD status, eligible diseases are identified on a restrictive list established by the French public health insurance schemes that specifies the equivalent ICD-10 disease code.

2.2 Subjects

2.2.1 Identification of Patients with T2DM

Patients with diabetes were identified in the EGB database according to a criterion usually applied in France [14]. This criterion was EITHER reimbursement for three distinct prescriptions for antidiabetic medication (including insulin), or two prescriptions when large packs were delivered, on three different dates within 2 consecutive years or ALD status for diabetes. All adult patients (aged ≥ 18 years) fulfilling this criterion during 2012 or 2013 were retained.

Additionally, a decision tree was used to distinguish patients with type 1 diabetes mellitus (T1DM) from those with T2DM (Fig. 1) [15]. This was based on hospitalisation

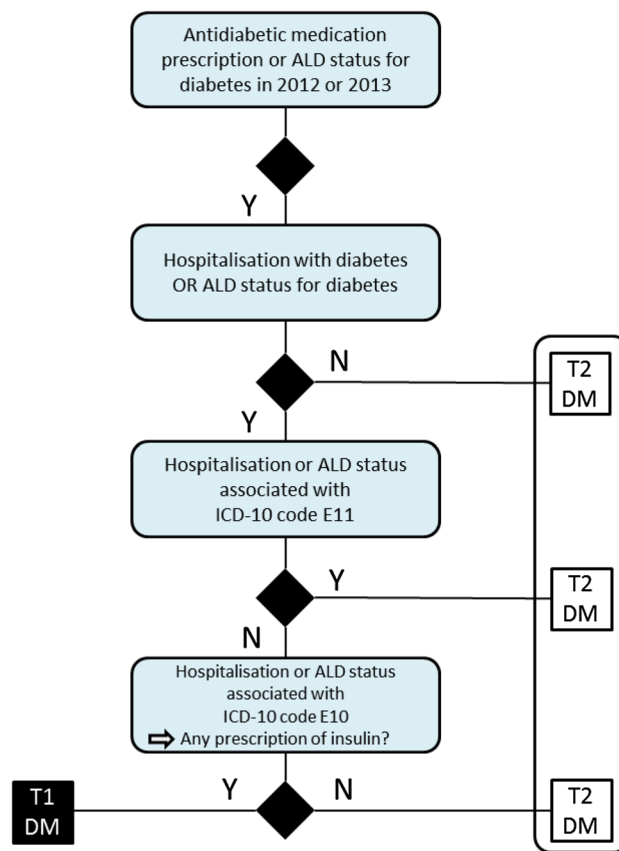


Fig. 1 Decision tree for identifying patients with T1DM and T2DM. ALD affection de longue durée (full insurance coverage due to a severe chronic disease), ICD-10 International Classification of Diseases, tenth revision, N no, T1DM type 1 diabetes mellitus, T2DM type 2 diabetes mellitus, Y yes

history with diabetes as an identified diagnosis (PD, RD or AD), ALD status for diabetes through the associated ICD-10 code and insulin treatment history. The relevant ICD-10 codes for diabetes applied in this decision tree were E10 for T1DM and E11 for T2DM. We assumed that all patients with T1DM had an ALD status or were hospitalized at least once over a 2-year period for diabetes.

2.2.2 Identification of Controls

Beyond the cost of care for people with diabetes, the cost of diabetes care was estimated using a case-control approach [16, 17].

A control sample was built, matched for age, sex, and region of residence to the index diabetes case sample using the quota method. The overall demographic structure of the diabetes sample was determined and quotas allocated for each age, sex, and geographic area class. Subjects without diabetes were then selected randomly from the EGB database and assigned to each quota until three controls had been identified for each case in each age, sex, and geographic area class.

2.3 Data Collection

For each eligible patient, information was extracted from the database on demographics (sex and age in 2013), ALD status for diabetes or other chronic diseases, and comorbidities or complications.

Comorbidities and complications of interest were ischaemic heart disease, stroke, cardiac failure, treated hypertension, treated dyslipidemia, kidney transplantation, chronic kidney failure, haemodialysis, retinopathy, hyperglycaemia, sleep apnoea and cancer. These were identified from three sources: hospitalisations in which these comorbidities were identified as a diagnosis through the relevant ICD-10 disease classification code, the presence of serial reimbursements for prescription of relevant specific medications, and ALD status identified through the relevant ICD-10 disease classification code.

All healthcare resource consumption documented in the EGB database between 1 January and 31 December 2013 were identified. Healthcare resource variables of interest were medication (for diabetes and other conditions) and other reimbursed pharmacy products, hospitalisations, consultations (specialists, general practitioners and dentists), paramedical care (nurses and physiotherapists), laboratory tests, medical devices, medical transport and other community care costs.

Costs presented for reimbursement were identified for each item in the EGB database. Ambulatory costs were directly estimated using reimbursement data from the EGB database. For hospitalisations, cost per DRG was estimated using the National Cost database per DRG [18]. All costs were estimated using a collective perspective (collective perspective limited to direct healthcare costs) according to the current guidelines for health economic evaluation in France [19].

2.4 Statistical Analysis

Two main analysis populations were considered in this study. For the description of the study population, all patients with T2DM identified in the EGB database were considered. For the cost analysis, patients with T2DM and controls who had died before the end of the cost assessment period (31 December 2013) were excluded to avoid bias due to differences in follow-up duration. A third population used to identify antidiabetic medication delivered during the last quarter of 2013 (the last period assessable in the study) was evaluated considering patients diagnosed with T2DM by the third quarter of 2013 at the latest.

Our presentation of the study population is principally descriptive. Continuous data are presented as mean values \pm standard deviation (SD) or as median values, and

categorical data are presented as frequency counts and percentages. The occurrence of comorbidities and complications was compared between the diabetes cases and the matched controls using the Chi-squared (χ^2) test or Fisher's exact test as appropriate.

Costs were compared between cases and controls for each individual cost component and for total costs using the Mann–Whitney *U* test. The differential cost between the cases and controls was calculated as a measure of the health economic burden of T2DM, including complications and related comorbidities. This burden was extrapolated to the whole French population using national diabetes prevalence data [1].

The cost of diabetes was reported for the different pharmacological therapy options (monotherapy, dual, other) according to hospital and community costs. Furthermore, an exploratory analysis of average annual consumption of care in patients with T2DM was conducted in patients receiving dual therapy throughout the year 2013 (quarters 1–4) depending on the type of dual therapy (metformin + DPP-4 inhibitor and metformin + sulfonylurea). For this analysis, patients treated with the same dual therapy throughout the year 2013 (same regimen during the quarters 1–4) were selected. Overall direct costs of healthcare were compared between the two groups.

As patients may have different characteristics according to their treatment group, we conducted an adjusted analysis (see Appendix I in the Electronic Supplementary Material [ESM]). A regression analysis (generalized linear model fitted with a Gamma distribution, after logarithmic transformation) was set up to explain the total healthcare consumption. Only patients who were treated throughout 2013 were analysed. The model took into account the following variables:

- Dual therapy in the last quarter of 2013: metformin + DPP-4 inhibitor or metformin + sulfonylurea
- Age in four groups (<55, 55–64, 65–75, \geq 75 years)
- Sex
- Presence of full coverage for a longstanding illness (ALD status)
- Simplified Charlson Comorbidity Index score based on diseases requiring hospitalizations in 2012–2013 (without taking into account patients age, which was already considered in the model)
- Patient area of residence
- Dual therapy duration (from the initial prescription of the dual therapy to the end of 2013).

All statistical analyses were performed using SAS software, version 9.2 (Cary, NC, USA). A bilateral probability threshold of 0.05 was used to determine statistical significance.

2.5 Ethical Considerations

Since this was a retrospective study of an anonymised database and had no influence on patient care, ethics committee approval was not required.

3 Results

3.1 Study Population

Overall, 30,155 patients with diabetes were identified in the EGB database. After application of the decision tree rules, 28,708 (95.2%) were considered to have T2DM. The majority of these patients ($N = 23,182$; 80.8%) were classified on the basis of an explicit ICD-10 code for T2DM associated with a hospitalisation record or ALD status; 5244 patients (18.3%) were identified on the basis of a prescription for antidiabetic medication alone. Among this T2DM population, 19.4% were receiving insulin. After 2721 patients who had died by 31 December 2013 were excluded from the study population, 25,987 (90.5%) remained for the cost analysis. The distribution of subjects across the analysis populations is presented in Fig. 2.

Overall, 54.1% of patients with T2DM were men, and the mean age of the sample was 67 years (Table 1). The majority (74.4%) benefited from ALD status (full reimbursement of all related care) for their diabetes (64% for <6 years), and 42.1% were classed as such for another pathology, most frequently hypertension ($N = 3723$; 13.0%) and ischaemic heart disease ($N = 1847$; 6.4%).

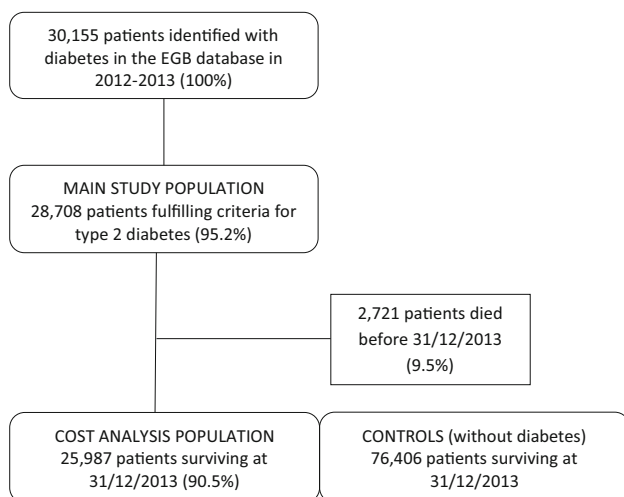


Fig. 2 Patient distribution and analysis populations. Percentages were calculated with respect to the previous line. EGB Echantillon Généraliste des Bénéficiaires database

Table 1 Study population demographics

Characteristic	Main study population ($N = 28,708$)	Cost analysis population ($N = 25,987$)
Age (years)	67.2 ± 12.9	67.3 ± 12.5
Median (range)	67 (18–112)	67 (18–104)
<45 years	1246 (4.4)	987 (3.8)
Sex		
Men (%)	15,538 (54.1)	14,001 (53.9)

Data are presented as mean \pm standard deviation or n (%) unless otherwise indicated

3.2 Comorbidities and Complications

The 2013 prevalence of complications and comorbidities was analysed using the cost analysis population in both diabetes cases and controls (Table 2). The proportion of subjects with an ischaemic complication, heart failure, kidney disease or retinopathy or who were receiving medication for the treatment of hypertension or dyslipidemia was markedly higher for cases than for controls (Table 2). No difference was observed for all cancers combined, but the frequency of hepatobiliary cancers and pancreatic cancers was higher in cases, whereas the frequency of prostate cancers was higher in controls.

3.3 Antidiabetic Medication

Antidiabetic medication delivered during the last quarter of 2013 (the last period assessable in the study) was evaluated by class (Table 3) among patients diagnosed with T2DM by the third quarter of 2013 at the latest. Among the 27,829 patients with T2DM considered in this cross-sectional analysis, 3777 patients (13.6%) had no medication delivered. Around half of the patients receiving treatment (48.9%) were prescribed a monotherapy (including insulin monotherapy), principally metformin (27.3%), and 25.6% were prescribed dual therapy. Insulin (alone or in combination) was prescribed for 19.4% of patients, and a GLP-1 analogue (alone or in combination) was prescribed for 3.5% of patients [20].

3.4 Costs

The total annual per capita cost incurred by patients with T2DM was €6506. These costs were 1.77 times higher than those incurred by the matched control group (€3668). The specific cost associated with T2DM and its related comorbidities or complications (difference between the two groups) was €2838 per patient per year (pppy). Ambulatory costs accounted for around two-thirds of costs, and hospital costs accounted for the remaining third

Table 2 Comorbidities and complications in diabetes cases and controls

Comorbidities and complications	Cases (<i>N</i> = 25,987)	Controls (<i>N</i> = 76,406)	<i>p</i> value
Ischaemic heart disease	3160 (12.2)	4977 (6.5)	<0.0001
Incident stroke in 2013	141 (0.5)	298 (0.4)	0.0011
Heart failure			
ALD	481 (1.9)	953 (1.2)	<0.0001
Hospitalisation 2009–2013 main diagnosis	851 (3.3)	983 (1.3)	<0.0001
Hospitalisation 2009–2013, secondary diagnosis	332 (1.3)	449 (0.6)	<0.0001
Either ALD or hospitalisation	1471 (5.7)	2068 (2.7)	<0.0001
Treated hypertension in 2013	20,192 (77.7)	36,773 (48.1)	<0.0001
Treated dyslipidemia in 2013	15,441 (59.4)	21,853 (28.6)	<0.0001
Kidney transplantation in 2013	2 (<0.1)	2 (<0.1)	0.2681
Chronic kidney disease	249 (1.0)	415 (0.5)	<0.0001
Haemodialysis (≥45 sessions per year)	118 (0.5)	96 (0.1)	<0.0001
Terminal kidney disease	120 (0.5)	98 (0.1)	<0.0001
Retinal laser treatment in 2013	87 (0.3)	28 (<0.1)	<0.0001
Retinopathy in 2013	609 (2.3)	734 (1.0)	<0.0001
Hypoglycaemia			
In 2013	162 (0.6)	–	<0.0001
Between 2009 and 2013	477 (1.8)	3 (<0.1)	<0.0001
Sleep apnoea			
Hospitalisation in 2013	581 (2.2)	485 (0.6)	<0.0001
Reimbursement for CPAP in 2013	1470 (5.7)	1587 (2.1)	<0.0001
Either hospitalisation or CPAP in 2013	1732 (6.7)	1835 (2.4)	<0.0001
Cancer	3174 (12.2)	9000 (11.8)	0.0615
Prostate	593 (18.7)	1964 (21.8)	0.0002
Breast	523 (16.5)	1595 (17.7)	0.1118
Colon	237 (7.5)	622 (6.9)	0.2931
Bladder	206 (6.5)	521 (5.8)	0.1517
Lung	131 (4.1)	353 (3.9)	0.6112
Other skin cancers	126 (4.0)	359 (4.0)	0.9622
Rectum	99 (3.1)	231 (2.6)	0.0994
Liver or biliary cancer	68 (2.1)	71 (0.8)	<0.0001
Kidney	87 (2.7)	232 (2.6)	0.6206
Mouth	71 (2.2)	200 (2.2)	0.9615
Pancreas	54 (1.7)	54 (0.6)	<0.0001
Thyroid	68 (2.1)	160 (1.8)	0.1926
Melanoma	70 (2.2)	180 (2.0)	0.4829

Data are presented as *n* (%) unless otherwise indicated

ALD Affection de Longue Durée, CPAP continuous positive airway pressure

(Table 4). The highest individual costs incurred related to hospitalisations (33.2% of total cost), medications (23.7%) and nursing care (10.9%). For each individual cost component, expenditure for diabetes cases was significantly higher ($p < 0.0001$) than for controls by a factor ranging from 1.2-fold (for physician consultations, interventions and physiotherapy) to fourfold (for nursing costs).

Costs were reported between the principal therapeutic patterns delivered in the last quarter of 2013 (Fig. 3). Total per capita annual costs were lowest in patients receiving metformin monotherapy (€4153 ± 6170) and highest in those receiving insulin (€12,890 ± 14,735). However, apart from patients receiving insulin, costs did not differ markedly across the different treatment patterns.

Table 3 Medications delivered during last quarter of 2013

Treatment	<i>N</i> = 27,829
No documented treatment	3777
Monotherapy	
Metformin	6568 (27.3)
Sulphonylurea	2120 (8.8)
Other	1228 (5.1)
Dual therapy	
Metformin + sulphonylurea	2381 (9.9)
Metformin + DPP-4 inhibitor	2399 (10.0)
Sulphonylurea + DPP-4 inhibitor	431 (1.8)
Other	943 (3.9)
Triple therapy	
Metformin + sulphonylurea + DPP-4 inhibitor	2019 (8.4)
Other	1031 (4.3)
Other multi-therapies, excluding insulin	243 (1.0)
Insulin regimens	
Insulin alone	1864 (7.7)
Insulin + metformin	741 (3.1)
Insulin + DPP-4 inhibitor	91 (0.4)
Insulin + metformin + DPP-4 inhibitor	247 (1.0)
Insulin + sulphonylurea	131 (0.5)
Other	1615 (6.7)

Data are presented as *n* (%) unless otherwise indicated. Percentages are calculated with respect to the 24,052 patients with a documented treatment

DPP-4 dipeptidylpeptidase-4

3.5 Costs According to Treatment Pattern: Patients Treated with Dual Therapy

A specific analysis of average annual consumption of care in patients with T2DM was conducted in patients receiving dual therapy throughout the year 2013 (quarters 1–4), comparing patients treated with metformin + DPP-4 inhibitor (*N* = 1846) and those receiving metformin + sulphonylurea (*N* = 1811).

In the real-life setting, the average cost of dual therapy with metformin + a DPP-4 inhibitor was estimated at €605 pppy (all taxes included), and the average cost of dual therapy with metformin + a sulphonylurea was estimated at €270 pppy, a significant difference of €335 pppy ($p < 0.0001$, +124%).

When considering average overall direct healthcare costs, the gap between patients treated with metformin + a DPP-4 inhibitor and those treated with metformin + a sulphonylurea reduced to €167 per year ($p < 0.0001$; +4%). The difference in costs for hypoglycaemic agents was partially offset by the reduced need for paramedics ($p = 0.0131$), including nursing ($p = 0.0004$), and a non-significant reduction in inpatient costs ($p = 0.1436$) (Table 5).

Finally, patients treated throughout 2013 with metformin + a DPP-4 inhibitor were younger than those treated with metformin + a sulphonylurea (65.0 ± 10.6 vs. 67.7 ± 11.0 years; $p < 0.0001$); their geographical distribution ($p < 0.0001$) and ALD status coverage (83 vs. 86%,

Table 4 Per capita costs presented for reimbursement by diabetes cases and controls

Costs	Cases (<i>N</i> = 25,987)	Controls (<i>N</i> = 76,406)	<i>p</i> value
Hospital costs	2159 (33.2) ± 6502	1304 (35.5) ± 4632	<0.0001
Ambulatory costs			
Medication	1541 (23.7) ± 2057	731 (19.9) ± 1693	<0.0001
Physician consultations	233 (3.6) ± 213	191 (5.2) ± 198	<0.0001
Home visits	58 (0.9) ± 159	33 (0.9) ± 110	<0.0001
Interventions	319 (4.9) ± 735	275 (7.5) ± 634	<0.0001
Nursing care	712 (10.9) ± 2468	182 (4.9) ± 1120	<0.0001
Physiotherapy	150 (2.3) ± 506	122 (3.3) ± 420	<0.0001
Medical devices	583 (8.9) ± 1146	309 (8.4) ± 744	<0.0001
Dental care	145 (2.2) ± 489	179 (4.9) ± 556	<0.0001
Laboratory tests	201 (3.1) ± 247	119 (3.2) ± 191	<0.0001
Transportation	236 (3.6) ± 1325	107 (2.9) ± 612	<0.0001
Total ambulatory costs			
Total community costs	4347 (66.8) ± 5230	2364 (64.5) ± 3421	<0.0001
Total costs	6506 (100) ± 9955	3668 (100) ± 6854	<0.0001
Median (IQR)	3093 (1627–7069)	1530 (665–558)	

Costs are presented in €, year 2013 values, as mean (%) ± standard deviation unless otherwise indicated
IQR interquartile range, SD standard deviation

Fig. 3 Per capita annual costs by patients with diabetes according to the principal therapeutic patterns (last 2013 quarter only). The numbers at the end of the horizontal columns represent total costs, the filled bars hospital costs and the open bars community costs. DPP-4-I inhibitor of dipeptidylpeptidase-4, SU sulphonylurea

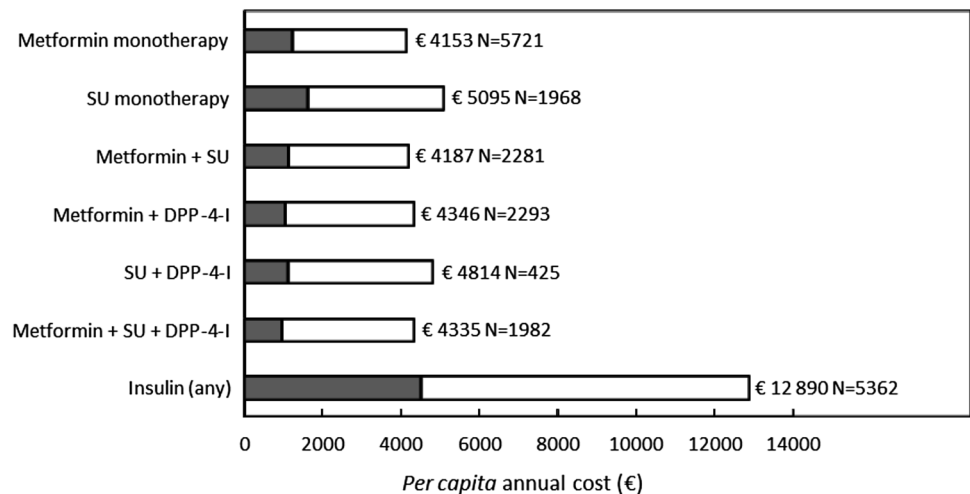


Table 5 Per capita costs presented for reimbursement per dual therapy (entire year)

Costs per item per year	Patients treated with metformin + a sulphonylurea	Patients treated with metformin + a DPP-4 inhibitor	<i>p</i> value
<i>N</i>	1811 (100.0)	1846 (100.0)	
Total amount presented for reimbursement	3969 ± 5337	4136 ± 5693	<0.0001
Hospitalisations	1002 ± 3228	917 ± 3270	0.1436
Ambulatory care			
Medications	1181 ± 1697	1542 ± 1998	<0.0001
Hypoglycaemic agents	605 ± 231	270 ± 204	<0.0001
Medical fees	660 ± 847	633 ± 777	0.1561
Paramedics	373 ± 1476	257 ± 1024	0.0131
Nursing care	262 ± 1344	143 ± 815	0.0004
Medical devices	353 ± 693	352 ± 724	0.2466
Transportation	91 ± 494	99 ± 764	0.0003
Laboratory tests	164 ± 160	165 ± 166	0.3762
Dental care	138 ± 479	162 ± 499	0.0013

Costs are presented in €, year 2013 values as *N* (%) or mean ± standard deviation

DPP-4 dipeptidylpeptidase-4

$p = 0.0052$) also differed, and these results suggest the two populations are not strictly comparable in a real-life setting. Therefore, we used a multivariate regression model to compare costs according to the dual therapy prescribed during 2013 as described in the methodology: analyses were adjusted on age, sex, a simplified Charlson Comorbidity Index score, ALD status and area of residence (Appendix 1 in the ESM).

The adjusted average overall healthcare costs of patients treated with metformin + a DPP-4 inhibitor were 6.3% (95% confidence interval [CI] 0.4–12.6%) higher than the average overall healthcare costs of patients treated with metformin + a sulphonylurea in 2013 ($p = 0.0348$). Goodness of fit of the adjusted model was estimated to be acceptable (χ^2 statistic [or the deviance] divided by the degrees of freedom was 0.82).

No significant difference in hospitalisations was observed between the groups of patients treated with a dual therapy ($p = 0.98$). Although using a DPP-4 inhibitor was more expensive, this was partly offset by reduced medical fees (honoraria) (−5.8%; $p = 0.04$) and need for paramedics (−25.5%; $p < 0.0001$) in patients treated with metformin + a DPP-4 inhibitor.

4 Discussion

In this study, we analysed direct healthcare costs accrued by patients with T2DM in 2013 from a collective perspective using a bottom-up approach in a representative sample of the national health insurance claims database (EGB). A sample of 28,708 patients fulfilling criteria for

T2DM using a decision tree was identified. Both selection and classification algorithms used in this study have their own limitations. The selection process excluded the least severe cases (without both antidiabetic medication and ALD status). The classification algorithm is likely to be imperfect. However, this will have only a marginal impact on the quality of the results.

Direct costs identified were those figuring in the national health insurance database. Some costs supported by patients and their families were not considered, such as some over-the-counter drugs. However, such costs are usually considered to be very low [21], especially for patients with diabetes who have 100% reimbursement status or are covered by a supplementary mutual health insurance.

The cost analysis was performed for all patients alive at 31 December 2013 and thus took into account expenditure for a full 12-month period. The mean annual per capita cost accrued by patients with T2DM was €6506, which was nearly twice as high as that of a matched sample of control subjects without diabetes. These data can be compared with a previous estimate of the cost of T2DM in France determined in the 2007 ENTRED survey [22], which was €4890 (€10,413 in patients treated with insulin and €3625 in patients not using insulin). The costs of diabetes would thus have increased by 30% between 2007 and 2013. This increase concerned all individual cost components. However, differences in methodologies between the two studies may introduce bias in the comparison (i.e. costing in the ENTRED survey was not conducted using the methodological guidelines for economic evaluation published in 2012 [19]; as an example, hospital stays were valued using tariffs and not costs, and the cost perspective was that of the National Sickness Fund).

We observed little change in the pattern of antidiabetic medication use since the 2007 ENTRED study [23], with the exception of the appearance of a significant proportion of patients receiving a DPP-4 inhibitor, which reached 25.3% in 2013. This was accompanied by a fall in prescriptions for sulphonylureas, from 49 to 30%. The proportion of patients receiving insulin remained stable at 19%, and the proportion of patients receiving monotherapy with an oral antidiabetic drug was also stable, at 42%. The use of metformin increased.

Patients with diabetes generated an additional per capita cost of €2838 compared with the matched controls in 2013. This cost represents both the cost of T2DM care and the costs of diabetes-related comorbidities and complications. Extrapolated to the estimated total French population with treated T2DM of nearly 3 million individuals (4.7%), this represents a total annual cost of €8.5 billion, corresponding to around 5% of all healthcare expenditure in France (estimated at €186.7 billion in 2013 [24]). The overall

healthcare expenditure for people with diabetes reaches €19.5 billion. Such results were remarkably close to those of de Lagasnerie et al. [5] despite methodological differences (e.g. this study considered both T1DM and T2DM, and estimates are based on 2012 reimbursed expenditures only).

The diabetes burden is likely to have increased since 2013, mainly due to the rising prevalence (in France, the average annual increase in diabetes prevalence was +2.3% between 2009 and 2013 [2]). A series of pricing measures has limited the pace of price increase.

In general, patients with diabetes tended to be more ill than controls, with significantly higher rates of a broad range of comorbidities. Furthermore, as the analysis considered only patients who did not die during the year, estimates provided in Table 2 may underestimate the full burden of these comorbidities. As such, it is interesting that the two most frequent reasons for hospitalisation for patients with diabetes were haemodialysis and cancer chemotherapy. Both kidney disease in general and regular haemodialysis (≥ 45 sessions/year) in particular were more frequent in diabetes cases than in controls, consistent with the well-characterised renal complications of diabetes [25]. On the other hand, although certain cancers were more frequent in diabetes cases (hepatobiliary and pancreatic cancers), the most frequent cancer type, prostate cancer, was in fact more frequent in controls. Again, this is consistent with the known association of these cancers with diabetes [26].

Excluding patients who died during the study period may have introduced a bias. Some evidence suggests that patients at the end of life drive healthcare spending, but this remains controversial [27]. Conversely, regardless of the period considered (year, month, etc.), including the costs of people who died early in the period would underestimate the costs of illness. Finally, we consider that end-of-life care is an important and challenging issue that needs to be addressed independently. A specific study on the cost of care at the end of life among people with diabetes is necessary.

The largest individual cost components were related to hospitalisations, medications and nursing care. This raises many questions, both about the organisation of care and about medication prescribing practices in France.

With regards to the healthcare system, it is well known that patients with diabetes in France are often referred to hospital even for issues that could be managed in an ambulatory setting. In the French Healthcare system, private nursing care is often used to provide an answer to social and medical issues encountered by patients with diabetes.

In our analysis, medication costs included those related both to antidiabetic therapy and to other drugs that may be prescribed to treat comorbidities or related cardiovascular

risk factors. In the USA [28], the cost of antidiabetic agents and diabetes supplies was estimated to represent 12% of the total direct medical costs, and prescription medications for the complications of diabetes or comorbidities was estimated at 18%. In France, 23.7% of diabetes costs are related to medications. However, when comparing the costs of antidiabetic agents, it is interesting to consider not only the price of drugs but also the budget impact of total care associated with the use of the drug. Our analysis provides an exploratory illustration of this based on a cost analysis of two dual therapies. The yearly cost of dual therapy with metformin + a DPP-4 inhibitor appears to be more than double that of metformin + a sulfonylurea when considering only the costs of the antidiabetic therapy. This estimate may be debatable because it was based on the public price of drugs, all taxes included, in France in 2013. Unknown rebates and paybacks are negotiated between payers and pharmaceutical companies for licensed drugs, resulting in lower prices in practice. However, considering the overall annual healthcare expenditure, the adjusted difference among the two populations was only 6% in 2013. Higher costs of treatment are partially offset by savings on other cost items.

Health-related retrospective databases, particularly claims databases, continue to be an important data source for outcomes research. A search of PubMed ((claims analysis[MeSH Terms]) OR (Claims[Title/Abstract]) AND (“2015/01/01”[Date-MeSH] : “2015/12/31”[Date-MeSH])) indicated that analyses of insurance claims data were published in at least 500 articles in 2015. In France, EGB contains exhaustive information on reimbursement claims for a representative sample of the national health insurance database covering 95% of the French population. Nevertheless, like other databases, EGB has some limitations: diagnoses rely on algorithms instead of adjudicated events, some patient subgroups, such as students and civil servants, are not well represented in the database; diagnoses are only documented if the patient was hospitalised or eligible for full reimbursement for an ALD. Other limitations include the absence of information on medications, tests or interventions that were prescribed but never delivered; limited documentation of sociodemographic and clinical characteristics of the insuree; and the risk of incomplete or inaccurate coding of medical events.

5 Conclusion

This insurance claims database study estimated the total cost of T2DM (including related comorbidities and complications) in France in 2013 to be €8.5 billion, corresponding to 5% of total public expenditure on healthcare. This large economic burden from diabetes highlights the

importance of public health programmes aimed at reducing the incidence of T2DM through the promotion of healthy lifestyles and at the prevention of diabetic complications (better glycaemic control, less therapeutic inertia and better compliance with lifestyle measures and drugs) and of developing integrated care programmes for patients with diabetes that may be less costly for society.

Author Contributions BC, SD and LLB conceptualized the study idea. BD designed the study, developed the data analysis plan and provided critical feedback at the design stage, wrote the first version of the manuscript, and is the guarantor of the study. IB performed all the analyses. All authors critically reviewed the manuscript and approved the final version.

Compliance with Ethical Standards

Data Availability Statement Data that supported these analyses are available from Dr. Bruno Detournay.

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Conflict of interest IB and BD are employed by Cemka-Eval, a contract research organisation that was contracted by MSD France for this study. BD has also received honoraria for consultancy from MSD, Novo-Nordisk, Sanofi. LLB and SD are employed by MSD France. BC, DS and JD have received honoraria from MSD France for participating on the scientific board for this study. BC has also received honoraria for consultancy from AstraZeneca, Boehringer-Ingelheim, Janssen Pharmaceuticals, Eli Lilly, MSD, Novartis, Novo-Nordisk and Sanofi. DS has served as an expert for Sanofi Aventis and Takeda and has been a member of a board for Astellas, MSD and Novartis, and received fees for all these activities. JG has no conflicts of interest.

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