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Combining the 'medicalized approach' and the 'incremental approach' to a new cost-of-illness method: The economic burden of diabetes to the French national health insurance

--Manuscript Draft--

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Abstract:	A better understanding of the economic burden of diabetes constitutes a major public health challenge in order to design new ways to curb diabetes health care expenditure. The aim of this study was to develop a new cost-of-illness method in order to assess the specific and nonspecific costs of diabetes from a public payer perspective. Using medical and administrative data from the major French national health insurance system covering about 59 million individuals in 2012, we identified people with diabetes and then estimated the economic burden of diabetes. Various methods were used: (a) global cost of patients with diabetes, (b) cost of treatment directly related to diabetes (i.e. 'medicalized approach'), (c) incremental regression-based approach, (d) incremental matched-control approach and (e) a novel combination of the 'medicalized approach' and the 'incremental matched-control' approach.. We identified 3 million individuals with diabetes (5% of the population). The total expenditure of this population amounted to €19 billion, representing 15% of total expenditure reimbursed to the entire population. €10 billion (52%) of this total expenditure were considered to be attributable to diabetes care: €2.3 billion (23% of €10 billion) were directly attributable and €7.7 billion were attributable to additional reimbursed expenditure indirectly related to diabetes (77%). Inpatient care represented the major part of the expenditure attributable to diabetes care (22%) together with drugs (20%) and medical auxiliaries (15%). Antidiabetic drugs represented an expenditure of about €1.1 billion, accounting for 49% of all diabetes-specific expenditure.

	This study shows the economic impact of the assumption concerning definition of costs on evaluation of the economic burden of diabetes. The proposed new cost-of-illness method provides specific insight for policy makers to enhance diabetes management and assess the opportunity costs of diabetes complications' management programs.
Response to Reviewers:	Reviewer #1: The study estimates the healthcare costs of diabetes to the French National Health Insurance using four different methods, including one novel approach. It estimates a substantial cost burden due to diabetes. One of the main advantages of the study is the vast number of observations it uses to provide very precise estimates even for sub groups of people with diabetes. It could also be potentially interesting because it provides a new approach to estimating and disentangling the cost burden. However, there are substantial points the authors need to improve upon before a potential publication. Some general points: The specific contribution of the findings to the existing literature needs to be made clearer. At the moment this is not the case. Also the manuscript is very hard to read. The phrasing needs substantial improvement to make it clearer what the authors want to say. Also the English needs improvement and there are several very obvious spelling mistakes. We made a few changes in the manuscript in order to make the specific findings clearer. A new translation was also carried out. Also there are many claims made in the manuscript not backed up by references. If they are not a direct result of the analysis in the paper they should be supported by references. Overall, the manuscript needs a substantial overhaul. References were added in order to support claims which were not directly related to the results. Major specific points: 1. There is no comparison or context with other studies on the cost burden of diabetes in France or other comparable countries. This makes it difficult to interpret the findings. Several references were added. 2. There is no comparison to other studies in the literature that have compared different costing approaches to estimate the healthcare costs of diabetes. are your findings comparable and do they point into a similar direction? Several references were added. 3. In the introduction it states that the study wants to compare the different costing approaches. However, reading the manuscript I cannot find any true comparison of the estimates nor a discussion about which estimate may provide us with a better idea of the costs of diabetes in France. Table 7 was added. 4. In the Introduction it states that the growth of the population may be a problem due to more people with diabetes, I guess. However, I think if the relative number of people with diabetes stays the same this should not lead to an aggravation of the problem. Please clarify. Several references were added. 5. For a better understanding of the estimated models, especially for the incremental costing approaches, it would be good to provide some formal representation in the form of an equation. A formal representation (equation) was added (p10). 6. Provide references for the used estimation approaches, especially Methods 1 and 2.

Several references were added (see in particular ref 8, 9).

7. What type of matching approach was used? There are many. What variables exactly were used for the matching? Why do you use age groups and not age itself to match on?

A matching approach was used based on 10-year age-groups and gender. We defined a control group of patients without diabetes stratified by 10-year age-groups and gender. The excess reimbursements related to diabetes were therefore estimated for each age-group as the difference between the expenditure of the diabetes population (case) and the expenditure of the population without diabetes (control). In other words, the reimbursed expenditure differential was estimated by gender and by 10-year age-groups. Ten-year age-groups were used rather than exact age groups in order to allow regional analysis of diabetes expenditure by means of the same methodology with a sufficient number of individuals in each group to provide significant and robust results. As the incremental approach is designed to identify costs that are causally related to diabetes (such as the costs related to complications of diabetes), no adjustment can be performed for variables causally related to diabetes.

8. In the discussion, please explain what you refer to with the GMATCH approach. It would be better not to mention the specific function in the discussion but rather discuss the approach that is behind this function. Also it seems that you did not even try to estimate this other matching function. Or did you?
In the new version we do not refer to the GMATCH approach.

8. Why do you use the head and neck cancer study for guidance, for example to inform your use of the log-link function on page 7. Not clear to me. There should be guidance in the econometric literature on what function to use. Just using the most popular one does not convince me and it is also not clear to me how the most popular one is determined.

Reference was changed (ref 10).

9.The approach used in the regression based section using a "nil coefficient" is unknown to me. Please make clearer what is done here. Is this not just a simple regression?

It was a wrong translation (“nil expenditure” instead of “subjects with zero expenditure”).

10. Why do you not also match on some regional dummies and why do you not include such a variable in your regression. Are there really no additional control variables that could be used.

A regional analysis of diabetes expenditure using the same methodology was also performed, but the results are not presented in this paper.

11. The headings in the results section are not appropriate. They should not state any of the results but rather give an idea of what the section is about. Please change these.

Headings in the results sections were modified.

12. To which table do you refer to in section 4.2.?
A new table was added : table 3
+ table 7 + figure 1

13. What does it mean that the Chi test in section 4.3 was not significant? Does it suggest the fit of the model was good or bad?

Results from the GLM regression estimates are shown in Appendix 1. The fit of the model was assessed by using the goodness-of-fit Pearson’s Chi-square test, which was not statistically significant. Which means that the hypothesis of independence

between the observed values and those estimated by the model assessing the fit of the selected model was then rejected.

14. Also present the coefficients for the covariates in Table 3.
See Appendix 1

15. What table are you referring to in section 4.5.2.?
A new table was added : table 5

16. Method 4 to estimate costs is unclear to me. At present I find it hard to understand what is done here exactly. It needs to be made clearer what exactly is done and how this is novel and contributes to a better understanding of the healthcare costs of diabetes. Especially because this is one of the major selling points of the manuscript.
More details were added.

17. In the Discussion section the authors talk about the need to use the "safest, most active and less expensive drugs" to reduce the cost burden of diabetes. Isn't this the same as the most cost-effective drugs? Why do you not use this well known term here? “Cost-effective drugs” was added.

18. What is the Baumal disease effect the authors talk about in the discussion? More explanations were added.

19. What do you mean by "static" and "dynamic approach" on page 14? This is unclear and needs further elaboration. We changed words “static” by ‘transversal” and “dynamic” by “longitudinal” (wrong translation).
Minor points:

At the end of the Introduction the authors state "...will be presented in the last section, followed by the discussion." This does not make sense as the last section is the discussion then. Changed

On page 3, what countries do you refer to when talking about "northern European countries" and what do you intent to say with "the number of observations is less important"? Please also provide references supporting these claims. New references were added (ref 16-19)

What are "invalid pensions" on page 4? disability pensions

On page 4 please provide references about where the deprivation index is used routinely. Two references were added : 17,18

17. Rey, G., Jougla, E., Fouillet, A., Hémon, D.: Ecological association between a deprivation index and mortality in France over the period 1997 - 2001: variations with spatial scale, degree of urbanicity, age, gender and cause of death. BMC Public Health. 9, 33 (2009).
18. Haut Conseil de la Santé Publique: Indicateurs de suivi des inégalités sociales de santé,
http://www.hcsp.fr/Explore.cgi/Telecharger?NomFichier=hcspr20130619_indicateurinegalitesocialesante.pdf.

What does "cost of the inequality of developing..." on page 7 mean. What does inequality refer to? Changed.

Similarly, what does "not fully respected" mean, again on page 7. Unclear to me.
Wrong translation replaced by : “However, this simplifying assumption is not fully met, as factors other than age and gender may also be involved in the comparison between the health care expenditure of patients with or without diabetes”

Both the term "euros" and "€" are used. Please make it consistent. Ok

Provide the full name for NICE. Ok

Reviewer #2: The authors provide a manuscript, where they estimate "The economic burden of diabetes to the French national health insurance". They provide different estimates based on different approaches. At the same time they claim having developed a new method for cost-of-illness studies.

I definitely see some value in this paper. However, if it is a main and novel aspect of this paper that the authors have developed a new cost-of-illness method, this should be obvious from the title and from the abstract. An alternative title could be: "Combining the 'medicalized approach' and the 'incremental approach' to a new cost-of-illness method: The economic burden of diabetes to the French national health insurance" We changed title.

The abstract should be revised accordingly. Developing the new approach should be part of the objective; some more details should be provided in the methods; and this achievement should be stated in the conclusion. We adapted the abstract according to your remarks.

In general, no matter what the main focus/objective of this manuscript would be, I think the different methods applies should be mentioned more specifically in the abstract. Currently it only reads: "We used methods identified in the literature and also a new approach based on the combination of existing methods." This does not mean anything. I don't think it would be necessary to mention that they were identified in the literature, but it should be mentioned that they are (a) the overall costs of subjects with diabetes, (b) costs of treatment directly related to diabetes (i.e. the 'medicalized approach'), (c) the incremental regression approach, (d) the incremental matched-control approach; and (e) a novel method, a combination of the medicalized approach and the incremental approach. Thank you very much. We changed according to your proposal and it is clearer.

However, I think the authors should go a little bit more into detail regarding the method(s) they applied: Regarding Method 4, the new and innovative method, the authors state "the global medicalized and matched control incremental definitions were combined in order to distinguish health care expenditure specific to the management of diabetes from that related to management of complications and/or excess health care consumption induced by a degraded health status due to diabetes". But this to me is not specific enough. More details were added.

Has as a first step the medicalized approach been applied? Have the costs of the incremental approach afterwards been removed from the data (step 2)? Has based on this reduced data set the matched control incremental approach been applied (step 3)? These steps may appear obvious to the authors, but I think they should be mentioned explicitly. More details were added.

Regarding Method 3.2, Lines 29-34 I also was a little bit confused: The authors state that they "defined a control group of patients without diabetes with matching variables that were related to diabetes". I think here the authors also need to elaborate a bit. I thought, one goal of the incremental approach was to identify costs that are causally related to diabetes. This includes the costs of consequences, such as retinopathy etc. Therefore, it should not be adjusted for variables which are causally affected by diabetes, correct? If not, please clarify. In any case, please elaborate.
As the incremental approach is designed to identify costs that are causally related to diabetes (such as the costs related to complications of diabetes), no adjustment can be performed for variables causally related to diabetes.

Here, you could also discuss the aspect, that a joint confounder may affect both, the incidence of diabetes and the incidence of other diseases. If not adjusting for these variables, the costs associated with diabetes would be overestimated. Changed

	Regarding Method 1 and Method 2 I felt that the authors should have provided references. For example they could cite some papers that applied these two methods, or alternatively, reference an overview article which reports about these methods. Several references were added. Regarding the Matching algorithm of Method 3.2 I also would have expected to see the details. Which variables were exactly used for matching? Which matching algorithm has been applied exactly? Nearest neighbor? Perfect match? I assume no propensity score matching. Details of the matching algorithm could also be supplied in an appendix. Alternative matching approaches that could have been applied could also be mentioned within the discussion. More details were added. I also think it would be nice to present an overview table, which compares the results of the alternative cost-of-illness approaches right next to each other. Table 7 was added. Finally, considering that this is a new non-mainstream cost-of-illness method, it would be great if the authors would discuss which further method development has been taken place. In this journal, the European Journal of Health Economics, for example, in April of this year there has been an article about conducting cost-of-illness studies based on massive data. Changed et reference 40 was added.

Title page

Combining the 'medicalized approach' and the 'incremental approach' to a new cost-of-illness method: The economic burden of diabetes to the French national health insurance

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Manuscript

Abstract

A better understanding of the economic burden of diabetes constitutes a major public health challenge in order to design new ways to curb diabetes health care expenditure. The aim of this study was to develop a **new cost-of-illness method** in order to assess the specific and nonspecific costs of diabetes from a public payer perspective.

Using medical and administrative data from the major French national health insurance system covering about 59 million individuals in 2012, we identified people with diabetes and then estimated the economic burden of diabetes. Various methods were used: (a) global cost of patients with diabetes, (b) cost of treatment directly related to diabetes (i.e. 'medicalized approach'), (c) incremental regression-based approach, (d) incremental matched-control approach and (e) a novel combination of the 'medicalized approach' and the 'incremental matched-control' approach..

We identified 3 million individuals with diabetes (5% of the population). The total expenditure of this population amounted to €19 billion, representing 15% of total expenditure reimbursed to the entire population. €10 billion (52%) of this total expenditure were considered to be attributable to diabetes care: €2.3 billion (23% of €10 billion) were directly attributable and €7.7 billion were attributable to additional reimbursed expenditure indirectly related to diabetes (77%). Inpatient care represented the major part of the expenditure attributable to diabetes care (22%) together with drugs (20%) and medical auxiliaries (15%). Antidiabetic drugs represented an expenditure of about €1.1 billion, accounting for 49% of all diabetes-specific expenditure.

This study shows the economic impact of the assumption concerning definition of costs on evaluation of the economic burden of diabetes. The proposed new cost-of-illness method provides specific insight for policy makers to enhance diabetes management and assess the opportunity costs of diabetes complications' management programs.

Key-Words: Diabetes, Cost of illness, Econometrics, Health administrative databases

1. Introduction

A better understanding of the economic burden of diabetes constitutes a major public health challenge for health insurers in order to identify ways to improve diabetes follow-up and control the dynamics of diabetes-related expenditure [1–3]. In France, diabetes is a major public health problem, as about 3 million patients who received care for diabetes in 2012, i.e. 4.6% of the whole population [1]. In view of the growing prevalence of the main risk factors for diabetes (ageing of the population, obesity and sedentary lifestyle), as well as the growing population, this situation is likely to worsen with time [1, 4–7]. The severity of diabetic complications, such as cardiovascular disease, renal failure and amputations ([2]), and the association between diabetes and excess risk of other chronic diseases such as certain cancers ([3]), justify active management of this disease [1].

The scope of costs included to evaluate the economic burden of a disease is the subject of intense discussion in the literature [8–13]. When the definition of costs is restricted to health care expenditure, excluding costs related to impaired quality of life, there is still a persistent debate between supporters of a comprehensive expenditure approach and supporters of a more restrictive approach, targeted to specific expenditure related to management of the disease. Between these two extremes, an intermediate, so-called incremental, definition has also been widely used [12, 13]. This method consists of measuring the excess expenditure related to the disease by comparing the expenditure of individuals with the disease to that of individuals without the disease but presenting similar demographic and socioeconomic characteristics in order to isolate the costs specifically due to the disease.

The three most commonly used expenditure-based approaches [8]address different and complementary economic and epidemiological questions. First, the global comprehensive approach provides an overall picture of all expenditure of a population with a particular disease (type of care, concentration, dispersion), whether or not this expenditure is related to the disease [6] . Second, medicalized approaches can be used to distinguish expenditure that is highly specific to the disease from other types of expenditure, with an *a priori* definition of specific expenditure. These approaches provide insight into the costs of the various types of care used to treat the disease. Third, incremental approaches can be used to distinguish overconsumption of a particular population due to the illness, its complications and the impaired health status related to the disease. These methods can be used to estimate the overall costs of the disease without identifying, ex-ante, the expenditure specifically related to the disease.

The present study was designed to contribute to the international literature by comparing the various approaches recently used in cost-of-illness studies to evaluate the financial burden of diabetes [14]. It also presents a new approach based on a combination of existing methods to distinguish direct costs specifically due to diabetes by means of a medicalized approach from costs related to complications and impaired health status by means of an incremental approach. In particular, we identified reimbursements specific to antidiabetic treatments, as well as reimbursements related to the main complications of diabetes (cardiovascular diseases and chronic renal failure). Reimbursements of diabetes-related health care expenditure were extracted from the *Système National d'Information InterRégimes de l'Assurance Maladie* [National Health Insurance Information System] (SNIIRAM) database in 2012[15].

In the following section, we will describe the data used for this study. We will then describe the methodology used to estimate national health insurance reimbursements effectively related to diabetes. Finally, the results of the study will be presented, followed by a discussion.

2. Data

The *Système National d'Information InterRégimes de l'Assurance Maladie* [National Health Insurance Information System] (SNIIRAM), designed to provide a better understanding and more accurate evaluation of quality of care, health care use and associated expenditure, was set up in France in the early 2000s [15]. While some administrative databases in other countries are only representative of a subpopulation (e.g. in the U.S., Medicare data are representative of individuals 65 years and older), the SNIIRAM database contains data on all reimbursed health care expenditure (inpatient, outpatient and cash payments) for the entire population living in France. It also includes sociodemographic, medical and administrative data concerning these beneficiaries (age, gender, diagnoses of long-term diseases eligible for 100% reimbursement, diagnoses reported during hospitalisations, town of residence, date of death) [15] . The SNIIRAM database is therefore probably one of the largest national health databases in the world, in contrast with databases in northern European countries [16–19], in which data are representative of the entire population, but based on a smaller number of observations.

Reimbursements of diabetes-related health care expenditure were extracted from the SNIIRAM database in 2012 for people insured by the French health insurance general scheme and local schemes (86% of the French population, 59 million individuals), with the approval of the French data protection authority (*Commission Nationale Informatique et Liberté*). The French health insurance general scheme covers salaried workers, retired private sector individuals, and, more generally, all individuals not covered by a specific scheme (farmers, self-

employed, special schemes), and their relatives (76% of the population living in France). Local schemes provide health insurance coverage for civil servants, students, and hospital staff (10% of the population living in France).

The scope of expenditure considered in this study included outpatient care (office visits, drugs, medical devices, nursing care, laboratory tests), and hospital expenditure, including public and private medical, surgical and obstetric (MSO) hospital stays, aftercare and rehabilitation (CR) and psychiatric admissions. Cash payments, such as daily allowances or disability pensions were also taken into account, but only for those paid by the general scheme, as data from local schemes may be incomplete or missing. The expenditure studied in this paper represented a total of €124 billion in 2012 that can be linked to general health scheme and local scheme beneficiaries.

3. Method

3.1. Identification and characteristics of the diabetic population in 2012

An algorithm was used to qualify a patient as diabetic if and only if this patient had received at least three reimbursements for antidiabetic drugs (oral or insulin) in 2012 (at least two reimbursements if at least one large pack size was dispensed), or in 2011 in order to avoid censorship effects, or when this patient had been allocated long-term disease (LTD) status for diabetes in 2012. The list of antidiabetic drugs corresponds to class A10 of the Anatomical Therapeutic Chemical (ATC) classification, with the exception of benfluorex [20]. In addition to age and gender, two variables were used as a proxy to characterize the individual's financial situation: complementary universal health insurance coverage (CMU-C) and an ecological deprivation index [21, 22]. Complementary universal health insurance coverage ("couverture maladie universelle complémentaire" or CMU-C) is provided by national health insurance schemes to people with incomes lower than a defined ceiling (€7,934 for a single person as of July 2012). The deprivation index reflects a major part of spatial socioeconomic heterogeneity based on four indicators (median household income, percentage of high school graduates in the population aged 15 years and older, percentage of blue-collar workers in the active population, and the unemployment rate) homogeneously throughout metropolitan France. This index is routinely used to observe, analyse, and manage spatial health inequalities.

3.2. Definitions of the scope of diabetes-related reimbursed expenditure

Three main methods that have been recently used to estimate the financial burden of a disease [8] were used in this study. In addition, for the first time in the literature to the best of our knowledge, a combination of two of these methods was used in order to propose a new approach (Method 4).

Method 1: Global comprehensive definition

The global comprehensive definition was initially adopted in order to establish an estimate of all expenditure (for diabetes or for any other disease) reimbursed to patients with diabetes and to therefore characterize the burden of reimbursements paid to these patients compared to all reimbursements to all patients [8]. The sum of all expenditure reimbursed to patients with diabetes was calculated. This global comprehensive analysis also allows a description of types of care used and the distribution of annual expenditure reimbursed to patients (mean, dispersion, concentration of expenditure).

Method 2: Medicalized approach

In the context of the medicalized approach, reimbursements paid to the diabetic population for diabetes-specific expenditure were entirely and directly attributed to diabetes [8, 9]. The following types of outpatient expenditure were considered to be diabetes-specific: endocrinologist visits, reimbursements of medical devices on the "*Liste des Produits et des Prestations* remboursables" (LPP) [List of reimbursed medical devices and services] intrinsically related to diabetes (dip-sticks, insulin pens and insulin pump materials), reimbursements of antidiabetic drugs (oral and insulin), reimbursements of blood glucose and glycated haemoglobin (HbA1c) assays and reimbursements of podiatrist fees (fee set up by national health insurance to improve the prevention of diabetic foot lesions for patients at high risk). For inpatient care, reimbursements related to Medicine, Surgery, and Obstetrics (MSO) hospital stays for diabetes (as a principal or related diagnosis, corresponding to codes E10-E14 of the International Classification of Diseases, Tenth edition) were considered to be diabetes-specific and were also entirely attributed to diabetes-related reimbursements. The expenditure observed for patients not identified as having diabetes according to the algorithm, but who were admitted to hospital with a diagnosis of diabetes in 2012 (as a principal or related diagnosis) or who had received at least one reimbursement of podiatrist fees for diabetes in 2012 was also added to the diabetes-specific expenditure (to compensate for incomplete detection by the algorithm of a small number of patients with diabetes).

Method 3: Incremental approach

The incremental approach includes both a regression-based approach and a matched-control approach, in which a control group of patients without the disease is used to estimate the cost of illness.

Method 3.1: Regression-based incremental approach

The regression-based incremental approach is also commonly used in the literature [10, 12, 23]. A large number of papers have been published on modelling of health care expenditure in order to take into account two important characteristics of the distribution of health care expenditure: the large number of subjects with zero expenditure and the highly-skewed distribution (for a formal description of the various challenges involved in health care expenditure estimation models refer to [24–26]). The various models reported in the literature comprise two equations designed to take zero expenditure into account. The first equation models the individual's decision to access health care services, i.e. the probability of having health care expenditure different from zero. The second equation determines the level of health care consumption in the subsample of individuals with health care expenditure different from zero.

These two equations can be estimated according to two models depending on the economic hypothesis adopted to characterize the relationship between the decision to access health care and the level of health care consumption. The Sample Selection Model is based on the hypothesis of a correlation between the two decisions. The second type of model is the Two-Part Model. This model is based on the hypothesis that the decision to access health care and the level of health care consumption are not correlated and that these two equations are independent. The Two-Part Model cannot conclude on a causal inference between exogenous variables and the level of health care expenditure because this model does not take into account individual heterogeneity, which certainly influences the probability of health care consumption and the level of health care consumption. However, the Two-Part Model is sufficient for prediction of health care expenditure, as this calculation does not analyse the effect of a particular variable [26].

The objective of the present study was to simulate the mean level of health care expenditure of the population rather than interpret and analyse coefficients of health care demand. Consequently, we adopted the hypothesis that there is no relationship between the decision to access health care and the level of health care consumption. We therefore exclusively estimated the second part of a Two-Part Model concerning only those people with at least one reimbursement detected in the SNIIRAM database. The level of health care consumption was estimated by the Generalized Linear Model (GLM). We chose the most appropriate link function for our data log-link with

a gamma distribution and tested the goodness of fit of this model [10] (see goodness of fit test results in Appendix 1).

The vector of control variables is composed of age, gender, and diabetes status. In order to calculate the annual spending attributable to diabetes, annual spending was initially predicted by using the coefficients of the GLM estimation

using a GLM specification where D_i is healthcare spending and $X_{1,i}$ are the explanatory variables used in the estimation. Health care consumption is predicted by:

$$\hat{E}(D_i|X_{1,i}) = \exp(X'_{1,i}\hat{\beta})$$

The hypothetical health care expenditure of patients with diabetes if they did not have diabetes was then estimated by applying a coefficient of 0 associated with diabetes in the health care expenditure equation. Diabetes-specific expenditure was estimated by the mean difference between these two predictions [10].

Method 3.2: Matched-control incremental approach

A matched-control incremental approach was then performed for all spending to determine the impact of diabetes on health care expenditure ([27, 28]). According to this method, the excess reimbursements attributable to diabetes were measured by determining the differential between reimbursements paid to patients with diabetes and those without diabetes. To calculate this excess reimbursement, we defined a control group of patients without diabetes stratified by 10-year age-groups. The excess reimbursements related to diabetes were therefore estimated for each age-group as the difference between the expenditure of the diabetes population (case) and the expenditure of the population without diabetes (control). In other words, the reimbursed expenditure differential was estimated by gender and by 10-year age-groups. Ten-year age-groups were used rather than exact age groups in order to allow regional analysis of diabetes expenditure by means of the same methodology with a sufficient number of individuals in each group to provide significant and robust results. As the incremental approach is designed to identify costs that are causally related to diabetes (such as the costs related to complications of diabetes), no adjustment can be performed for variables causally related to diabetes.

Method 4: Combination of medicalized and incremental approaches

Lastly, the global medicalized and matched-control incremental definitions were used in combination (Table 1) to distinguish health care expenditure specific to the management of diabetes (using the global medicalized approach) from that related to management of complications and/or excess health care consumption induced by impaired health status due to diabetes (using the incremental approach). Both of these methods have been used

previously [10], but not necessarily in the same study in order to provide a better understanding of the expenditure attributable to diabetes. Firstly, diabetes-specific expenditure was entirely and directly attributed to diabetes according to the medicalized approach. Secondly, the matched-control incremental approach was then performed on the overall population to determine the impact of diabetes on the rest of health care expenditure (not specific to diabetes), as diabetes is a risk factor for certain chronic diseases. Excess reimbursements for diabetes-related complications, matched for age and gender, represent the cost of developing a specific disease for a patient with diabetes. The implicit hypothesis is that if diabetes complications could be eradicated, excess reimbursements would be zero. However, this simplifying assumption is not fully met, as factors other than age and gender may also be involved in the comparison between the health care expenditure of patients with or without diabetes [20, 29].

INSERT Table 1: allocation of diabetes-related reimbursements

4. Results

4.1. Characteristics of the diabetic population in 2012

According to the algorithm used in this study, 2.9 million people with diabetes were identified among the 59 million general health scheme and local scheme beneficiaries in 2012. The main characteristics of patients with diabetes identified by this algorithm are described in Table 2. As expected, these patients were older than the general population with a mean age of 66 years versus 39 years, as the prevalence of diabetes increases very markedly with age. Diabetes also appears to be related to socioeconomic markers, as an over-representation of people with diabetes was observed in territories with lower socioeconomic status. One quarter of patients with diabetes in 2012 lived in territories with the lowest socioeconomic quintile (versus 20% for the general population) and only 16% lived in territories with the highest socioeconomic quintile.

INSERT Table 2: General descriptive statistics of the SNIIRAM database

4.2. Global comprehensive approach: reimbursements paid to patients with diabetes

The sum of all reimbursements (health care consumption, daily allowances and disability pensions) for patients with diabetes, whether or not the expenditure was related to diabetes, was €19 billion (Table 7), i.e. 15% of all general health scheme and local scheme reimbursements (€124 billion).

In 2012, patients with diabetes (mean age: 66 years) therefore received an average of €6,714 of health insurance reimbursements. Hospital expenditure represented 42% of all reimbursements, pharmacy expenditure represented 21% and other outpatient care (medical fees, nursing care etc.) represented 31%, and cash payments (daily allowances and disability pensions) represented 6% of all reimbursements (Figure 1).

A U-shaped relationship was observed between mean reimbursed expenditure and age, which is likely to be related to insulin therapy for people with type 1 diabetes at a younger age due to progression of the disease over time and the development of complications, as well as other diseases. Patients with diabetes under the age of 16 years received a mean reimbursement of €7,000 (Table 3) versus €5,500 for patients between the ages of 16 and 45 years and €6,000 for patients between the ages of 46 and 65 years. In 2012, people with diabetes 65 years and older received a mean reimbursed expenditure of €7,300. The mean reimbursement of insulin-treated patients was €12,200 versus €5,200 for other people with diabetes. Finally, mean reimbursed expenditure for patients living in areas with the lowest socioeconomic index was €6,845 versus €6,469 for those living in territories with the highest socioeconomic index. This difference cannot be explained by differences in mean age, which was equal to 66 years in these two types of territories.

A very widely dispersed distribution of reimbursements paid to patients with diabetes was observed. Although the mean reimbursement was €6,714/year, the median was only €2,526 in 2012. 10% of patients with diabetes received more than €16,673 and 5% received more than €25,856. The concentration of reimbursements was therefore particularly high, with 10% of patients with diabetes (280,000 people) concentrating 51% of the €19 billion of reimbursements, 5% concentrating 35% of reimbursements and 1% concentrating 14%.

INSERT Figure 1: Breakdown of reimbursements to patients with diabetes

INSERT Table 3- Mean reimbursements to patients with diabetes in 2012

4.3. Regression-based incremental approach: spending attributable to diabetes

Results from the GLM regression estimates are shown in Appendix 1. The fit of the model was assessed by using the goodness-of-fit Pearson's Chi-square test, which was not statistically significant. The hypothesis of independence between the observed values and those estimated by the model assessing the fit of the selected model was then rejected.

The results of the fitted model were used to calculate the per-person spending attributable to diabetes (Table 4). The average spending attributable to diabetes clearly increased with age. For people 80 years and older, this

expenditure was €6,539 versus €3,387 for the 50-59 age-group. Based on the average spending attributable to diabetes, the aggregate healthcare spending related to diabetes was €11.3 billion (all schemes).

INSERT Table 4- Estimated aggregate and mean economic burden of diabetes by age-group using the regression-based approach

4.4. Incremental definition: matched-control approach

The additional expenditure measured by the matched-control approach corresponds to expenditure directly related to the treatment of diabetes, but also expenditure indirectly related to diabetes, for example expenditure related to obesity, a major risk factor for diabetes, or social deprivation, which can make the management of diabetes more complex and which is also linked to obesity and type 2 diabetes. According to this approach, the financial burden of diabetes was €7.7 billion (Table 7) with 58% due to outpatient care, 22% due to hospital care and 20% due to drugs.

4.5. A global medicalized and incremental definition: diabetes-related reimbursed expenditure in France

4.5.1. Estimation of the reimbursed expenditure related to the management of diabetes

According to the medicalized approach, the total diabetes-specific reimbursed expenditure (see Table 1 for a list of diabetes-specific expenditure) was €2.3 billion in 2012 (Table 7). The excess reimbursements paid to patients with diabetes for all non-diabetes-specific expenditure represented €7.7 billion (Table 7). Diabetes-related reimbursed expenditure therefore represented a total of €10 billion (Table 7): 23% for diabetes-specific reimbursed expenditure and 77% for excess reimbursements due to diabetes. Diabetes-related reimbursed expenditure also represented 52% of all expenditure reimbursed to patients with diabetes (€19 billion). The per patient cost of diabetes was €3,387. Non-diabetes-related reimbursed expenditure (€9 billion, the difference between €19 billion, the global reimbursement received by people with diabetes and €10 billion the cost of diabetes among these €19 billion) corresponded to expenditure, which, in the absence of diabetes, would have theoretically been reimbursed to these patients, based on the expenditure of age- and gender-matched patients without diabetes.

Antidiabetic drugs (oral hypoglycaemic agents or insulin) represented an expenditure of about €1.1 billion in 2012, i.e. one half (49%) of all diabetes-specific expenditure (€2.3 billion, see Figure 2). Insulin therapy accounted for €400 million of this total €1.1 billion expenditure. Diabetes-specific medical devices (e.g., dip-sticks, insulin pens, insulin pump necessary materials) represented an expenditure of about €793 million, i.e.

35% of all diabetes-specific expenditure. Hospital stays specifically for diabetes represented a moderate share of diabetes-specific reimbursed expenditure (€270 million, i.e. 12% of diabetes-specific expenditure). Other types of expenditure, such as blood glucose and glycated haemoglobin assays, podiatrist fees or endocrinologist visits (private practice and outpatient visits) represented a marginal share of diabetes-specific expenditure (4%).

INSERT Figure2 – Breakdown of the €2.3 billion diabetes-specific expenditure

4.5.2. Burden of complications, nursing care, and sick leave

Cardiovascular diseases constitute a major complication or comorbidity of diabetes [30]. More than one quarter of patients with diabetes suffer from cardiovascular disease. The high prevalence of this disease in the population with diabetes as well as the more complex management due to the presence of comorbidities can explain a higher mean annual reimbursed expenditure for health care related to cardiovascular diseases for patients with diabetes compared to other patients. For example, for men over the age of 80 years, the mean reimbursed expenditure for drug treatments of hypertension was €114 for men without diabetes and €200 for men with diabetes (Table 5). Overall, by summing the excess reimbursements paid to the overall population with diabetes of all ages, the estimated diabetes-related reimbursed expenditure for antihypertensive drugs was €330 million, i.e. 20% of all reimbursements for these drugs (see Table 6). Using the same methodology as for antihypertensive drugs, the diabetes-related excess reimbursed expenditure for lipid-lowering drugs was €240 million. Finally, the excess expenditure for all drugs used in the management of cardiovascular disease (antihypertensive, antiplatelet and lipid-lowering drugs, treatments for heart failure and peripheral artery disease) represented 7% of the financial burden of diabetes, i.e. €697 million.

Another important diabetes-related complication, renal failure, was associated with high hospital stay expenditure. The diabetes-related excess reimbursements for hospital stays due to end-stage renal disease represented €279 million, i.e. 30% of all reimbursements paid for this disease to hospitals. The expenditure related to nephrologist visits attributed to diabetes (€6.3 million) represented 21% of all nephrologist visit expenditure. The last complication frequently associated with diabetes, diabetic foot ulcers and amputations, induced excess reimbursements of €112 million, i.e. almost one-half of all expenditure reimbursed for these diagnoses.

Nursing care expenditure presented a particularly high proportion of the expenditure due to the excess reimbursements to patients with diabetes that amounted to €1.4 billion, i.e. 30% of all reimbursed nursing care expenditure. For women with diabetes over the age of 80 years, the mean nursing care reimbursement was

€1,938 versus €629 for an age-matched woman without diabetes. Thus, in this age-group, the total reimbursed nursing care expenditure attributable to diabetes, i.e. induced by the excess reimbursements paid to women with diabetes of this age, was €377 million. The great majority of elderly patients treated with insulin, who are not always able to perform their injections by themselves, can partly explain this high use of nursing care in France.

Finally, diabetes and its complications can require intensive treatments that decrease the patient's working capacity, leading to the payment of a cash allowance by national health insurance (daily sick leave allowances or disability pensions), in the smaller proportion of people in working-age groups. For example, a man with diabetes between the ages of 50 and 59 years received an average of €1,861 of sick leave payments versus €916 (less than half) for an age-matched man without diabetes. The global excess payment of daily allowances to patients with diabetes represented a total of €528 million.

INSERT Table 5- Mean reimbursements for patients with and without diabetes and excess reimbursements due to diabetes

INSERT Table 6- Breakdown of the non-diabetes-specific expenditure according to certain types of expenditure

INSERT Table 7- Allocation of diabetes-related reimbursements paid by the general health scheme and local schemes

5. Discussion and conclusion

The four methodologies used in this study provided a range of different economic estimates of the burden of diabetes. Each method provides specific insight for policy makers to enhance diabetes management. Using a new, combined approach, diabetes-related reimbursed expenditure was estimated to be about €10 billion. We calculated that care for diabetes complications (cardiovascular diseases, chronic renal failure, diabetic foot ulcers and amputations) and additional treatments accounted for the majority of the cost of diabetes care (€7.7 billion, 77%). Hospitalization for ischaemic heart disease and heart failure accounted for €510 million. This result highlights the economic impact of cardiovascular risk prevention by monitoring HbA1c, lipids and blood pressure, but also by preventing smoking and obesity among patients with diabetes. Pay for performance programmes targeting general practitioners or disease management programmes for patients with diabetes could include these objectives in order to enhance follow-up of people with diabetes. These programmes may have a

positive impact on the health status of patients with diabetes and, in the long term, should lower the overall health care expenditure by decreasing the number of events related to complications [31, 32].

Drugs (about €1.1 billion) represented one-half of the estimated cost of diabetes according to the medicalized approach. From a decision-maker's point of view, this conclusion highlights the importance of promoting the most cost-effective drugs. The increasing variety of available pharmacological agents requires guidelines comprising therapeutic strategies that take these qualities into account. In France, the *Haute Autorité de Santé* (French Health Authority) released guidelines in 2013 recommending the use of metformin as first-line monotherapy. When dual therapy is required, the recommended first-line treatment is a combination of metformin and sulphonylurea. Insulin is the treatment of choice when oral therapy does not achieve the glycaemic target. In 2015 the National Institute for Health and Care Excellence (NICE) published new guidelines, in which the costs of drugs were explicitly taken into account to choose the therapeutic strategy. These guidelines clearly state that if two drugs in the same class are appropriate, one should choose the option with the lowest acquisition cost. In line with the NICE guidelines, the *Caisse Nationale d'Assurance Maladie des Travailleurs Salariés* (French National Health Insurance, CNAMTS), after consulting the French Health Authority, published comparisons of average treatment costs of various treatment strategies as well as comparisons of the price difference within each strategy between brand-name and generic drugs [33].

The high level of nursing care expenditure due to diabetes provides a different insight into the importance of developing new ways to provide care to insulin-treated patients, particularly elderly patients [34, 35], as, in the context of an ageing population and a high level of fee for services payment of nursing care, the growing number of patients on insulin will have a major impact on nursing care expenditure. Innovations promoting patient autonomy could be of particular interest. In this case, innovations may lead to productivity gains, contrary to the predictions of Baumol's disease effect which explains part of the increase of health care expenditure [36]. According to Baumol, productivity growth through innovation in the health care sector is often thought to be slower than in most other industries, partly because much of this expenditure concerns health care professional services. For this reason, the relative cost of health care tends to increase over time in relation to other consumer products—a phenomenon often referred to as the cost disease effect. A review of the payment system for nurses caring for insulin-treated patients in France could also be initiated. Firstly, bundled payment could replace fee for services payments of nurses when they provide long-term care for people with diabetes. Furthermore, National Health insurance could require evaluation of the rationale of a nurse's intervention after a defined duration of treatment.

From a methodological perspective, the comprehensive approach provides an upper bound for the estimation of cost of illnesses. It provides an accurate picture of the overall expenditure of the population with a given disease. It also provides insight into the importance of top spenders: 1% of patients with diabetes accounted for 14% of the total expenditure of all patients. A particular focus on this population could help to curb the growth of health care expenditure for patients with diabetes.

The use of a medical and administrative database allows precise analysis of expenditure and identifies the types of expenditure providing the greatest contribution to the economic burden of diabetes. However, the limited number of sociodemographic variables may affect the results obtained by incremental approaches, as the estimated coefficient could be biased if variables highly correlated to diabetes are not available. The economic burden of diabetes could then be either underestimated or overestimated. For example, obesity is a strong risk factor for diabetes, and a low socio-economic level is associated with obesity and therefore with diabetes [20]. However, a low socioeconomic level may also be linked with other behaviours - smoking for example - or decreased or increased use of health care. Another example is that of genetic factors, which are also strong determinants of diabetes, and which display marked variability between ethnic groups. People belonging to certain specific ethnic groups may be more likely to develop diabetes, as well as other non-diabetes related diseases. They may also be derived from a lower socioeconomic background. To run a sensitivity test, we added to the control vector, surrogate variables a proxy of the individual's financial situation and the ecological deprivation index [21] only available for metropolitan France after excluding the overseas territories for which it is not available. The economic burden of diabetes in metropolitan France was €10.7 billion when age and sex were introduced as the only control variables, but €10.3 billion when the ecological deprivation index was added. In the absence of control for the economic situation, the coefficient associated with diabetes was therefore probably overestimated. Other variables such as BMI, smoking, ethnicity, etc., were not available to be tested. Nevertheless, joint confounders may affect both the incidence of diabetes and the incidence of other diseases. The cost associated with diabetes could therefore be overestimated by not adjusting for these variables.

The matched-control approach, which compares the health care expenditure of subjects with and without the disease and attributes the differences to the cost of illness, requires the use of a reasonably comparable control group. Sensitivity analysis was conducted in order to test the impact of choosing 10-year age-groups instead of 5-year age-groups. No significant difference was observed, thereby confirming the robustness of our results. In a recent article about the cost of head and neck cancers in the United States [12], the matching variables used were age, sex, race, insurance status, the number of priority medical conditions (proxy for comorbidities) and year of

data collection. We restricted the matching variables to age and sex, as race is not available in our database in which all individuals are insured by the national health insurance scheme. We did not add a proxy for comorbidities, as we considered age to be a good proxy to control for comorbidities for patients with diabetes [37]. A regional analysis of diabetes expenditure using the same methodology was also performed, but the results are not presented in this paper. Our results were compared with those based on the same database (Sniiram), but using a top-down approach [38]. In this study, based on the same population (French population covered by the health insurance general scheme), in 2012, €6.2 billion were attributed to direct management of diabetes and its complications except for cardiovascular complications, end-stage renal diseases or gestational diabetes, which were estimated separately. The results of this study were also broadly consistent with those of earlier studies [6, 39], although it is difficult to perform more detailed comparisons, particularly due to differences in time (1999 or 2007 cost data), but also differences in population definitions and data sources (survey and then extrapolation to the French population). It could also have been interesting to apply the new methodology, a prevalence-based top-down regression approach, developed for cost-of illness studies based on massive recently published data [40]. This method was not available at the time of our study, but it would also required preliminary adaptations and tests in order to assess, in particular, the feasibility for application on a database comprising information about 59 million individuals. This could be the subject of further investigations on cost-of-illness methods.

This study highlights robust methods that can be used to estimate the cost of diabetes. These methods provide policymakers with diverse and accurate information on the components of the cost of diabetes and therefore shed new light on the debate concerning the public policies to be implemented. In this context, a transversal approach (2012) to the financial burden of diabetes adopted in this study could be usefully completed by a longitudinal approach taking into account the growth of expenditure in relation to the increasing prevalence of the disease and particularly the development of diabetic complications. By validating these various methods, this study demonstrates the value of using these methods for other chronic diseases in order to improve the management of chronic diseases.

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Table

Table 1 - Allocation of diabetes-related reimbursements

Method	Scope of health insurance reimbursements	Results
Method 1	**Reimbursements in the population with diabetes**	**Subsection 4.2**
Method 2	**Medicalized approach: reimbursements specific to diabetes** • Endocrinologist visits, dip-sticks, insulin pens and insulin pump materials, reimbursements of antidiabetic drugs (oral and insulin), reimbursements of blood glucose and glycated haemoglobin, Medicine, Surgery, and Obstetrics (MSO) hospital stays for diabetes	**Subsection 4.5**
Method 3.1	**Incremental definition: Regression-based approach** • Estimation of the determinants of the level of health care expenditure as a function of diabetes by controlling for individual characteristics.	**Subsection 4.3**
Method 3.2	**Incremental definition: Matched-control approach** • Comparing all medical expenditure of patients with and patients without diabetes by gender and by 10-year age-groups	**Subsection 4.4**
Method 4	**Combination of medicalized and matched-control incremental approaches**	**Subsection 4.5**

Table 2 - General descriptive statistics of the SNIIRAM database

	Study population: General Health Scheme and Local schemes	Patients with diabetes (type 1 or 2)
Number of patients	59 million	2.9 million
Proportion of women	54%	48%
Age		
Mean age	39 years	66 years
Median age	38 years	66 years
Expenditure		
Total reimbursed expenditure	€124 billion	€19 billion
Mean reimbursement per individual	€2,199	€6,714
Ecological deprivation index		
Q1 (people living in territories with the highest socioeconomic index)	20%	16%
Q2	20%	18%
Q3	20%	19%
Q4	20%	21%
Q5 (people living in territories with the lowest socioeconomic index)	20%	25%
Complementary universal health insurance coverage for the less well off (CMU-C)		
% CMU-C (≤60 years)	11%	14%

Source: CNAMTS\SNIIRAM

Table 3 - Mean reimbursements to patients with diabetes in 2012

	Mean reimbursement paid by general health scheme and local schemes
Age	
Less than 16 years	€6,986
16-45 years	€5,514
46-64 years	€6,015
65 years and older	€7,324
Ecological deprivation index	
Q1 (people living in territories with the highest socioeconomic index)	€6,469
Q2	€6,540
Q3	€6,811
Q4	€6,678
Q5 (people living in territories with the lowest socioeconomic index)	€6,845
Patients with insulin-treated diabetes	
Yes	€12,254
No	€5,234
Concentration of reimbursements	
10% of patients with diabetes	More than €16,673 (51% of total reimbursements paid to patients with diabetes)
	More than €25,856 (35%)

5% of patients with diabetes	More than €59,748 (14%)
1% of patients with diabetes	

Source: CNAMTS\SNIIRAM 2012

Table 4 - Estimated aggregate and mean economic burden of diabetes by age-group using the regression-based approach

	Regression-based approach	
	Total expenditure attributable to diabetes (95% CI)	Mean expenditure attributable to diabetes (95% CI)
Under 40 years	€203 million (€202 – 204 million)	€1,644 (€1,640 – 1,648)
40 to 49 years	€462 million (€461 – 463 million)	€2,312 (€2,306 – 2,318)
50 to 59 years	€1,787 million (€1,782 – 1,791 million)	€3,387 (€3,379 – 3,396)
60 to 69 years	€2,802 million (€2,795 – 2,810 million)	€3,271 (€3,263 – 3,280)
70 to 79 years	€3,087 million (€3,078 – 3,096 million)	€4,466 (€4,454 – 4,479)
Over 80 years	€3,164 million (€3,155 – 3,173 million)	€6,539 (€6,520 – 6,558)
All ages	€11,301 million (€11,072 – 11,332 million)	€3,921 (€3,910 – 3,932)

Source: CNAMTS\SNIIRAM 2012

Table 5- Mean reimbursements for patients with and without diabetes and excess reimbursements due to diabetes

Types of expenditure	Mean reimbursement for patients with diabetes	Mean reimbursement for patients without diabetes	Excess reimbursements due to diabetes
Medical fees			
General practitioner			
Men 80 years and older	€268	€195	€14 million
Women 80 years and older	€310	€223	€25 million
Drugs			
Antihypertensive drugs			
Men 80 years and older	€200	€114	€17 million
Women 80 years and older	€209	€111	€28 million
Lipid-lowering drugs			
Men 80 years and older	€122	€68	€11 million
Women 80 years old and over	€100	€46	€16 million
Auxiliaries			
Nurses			
Men 80 years and older	€1,292	€453	€164 million
Women 80 years and older	€1,938	€629	€377 million
Sick leave payments			
Men 50-59 years old	€1,861	€916	€278 million
Women 50-59 years old	€1,111	€690	€98 million
Hospital			
End-stage renal disease			
Men 80 years and older	€194	€87	€21 million
Women 80 years and older	€124	€32	€27 million
Ischaemic heart disease			
Men 80 years and older	€172	€102	€14 million

Women 80 years and older	€93	€43	€14 million
Stroke			
Men 80 years and older	€106	€77	€6 million
Women 80 years and older	€94	€68	€8 million

Source: CNAMTS\SNIIRAM 2012

Table 6 - Breakdown of the non-diabetes-specific expenditure according to certain types of expenditure

Types of expenditure	Overall expenditure – for patients with diabetes	Excess reimbursements due to diabetes (percentage of all expenditure for patients with diabetes [according to the type of expenditure])	Proportion of the excess reimbursement due to diabetes among the total reimbursed expenditure (overall population)
Medical fees			
General practitioner	€627 million	€279 million (44%)	5.5%
Cardiologist	€37 million	€16 million (43%)	9.4%
Ophthalmologist	€27 million	€10 million (37%)	3.9%
Nephrologist	€ 9 million	€6 million (67%)	21.3%
Drugs			
Antiplatelet drugs	€131 million	€82 million (63%)	20.1%
Antihypertensive drugs	€519 million	€330 million (64%)	19.4%
Lipid-lowering drugs	€371 million	€240 million (65%)	20.3%
Heart disease and Peripheral Artery Disease	€101 million	€45 million (45%)	19.0%
Lucentis® (ranibizumab)	€72 million	€22 million (31%)	6.6%
Medical devices			
Obstructive sleep apnoea devices	€117 million	€82 million (70%)	22.5%
Laboratory tests			
Cholesterol assays and renal function tests	€46 million	€28 million (61%)	13.4%
Auxiliaries			
Nurses	€1,865 million	€1,425 million (76%)	30.3%
Physiotherapists	€367 million	€99 million (27%)	3.5%
Hospital			
Foot ulcer/amputation	€131 million	€112 million (85%)	44.8%
End-stage renal disease	€362 million	€279 million (77%)	29.9%

Chronic renal failure - Acute renal failure	€171 million	€106 million (62%)	16.8%
Ischaemic heart disease	€317 million	€188 million (59%)	17.5%
Heart failure	€196 million	€124 million (63%)	21.3%

Source: CNAMTS\SNIIRAM 2012

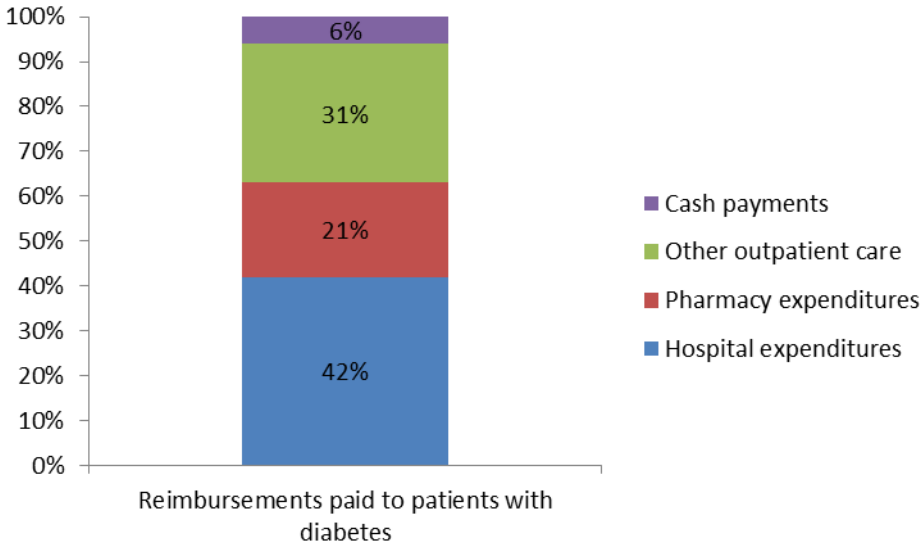
Table 7 - Allocation of diabetes-related reimbursements paid by the general health scheme and local schemes

Method	Scope of health insurance reimbursements	Results
Method 1	**Reimbursements within the population with diabetes**	**€19 billion**
Method 2	**Medicalized approach: reimbursements specific to diabetes**	**€2.3 billion**
Method 3.1	**Incremental definition: Regression-based approach**	**€9.8 billion**
Method 3.2	**Incremental definition: Matched-control approach**	**€7.7 billion**
Method 4	**Combination of medicalized and matched-control incremental approaches**	**€10 billion**

Source: CNAMTS\SNIIRAM 2012

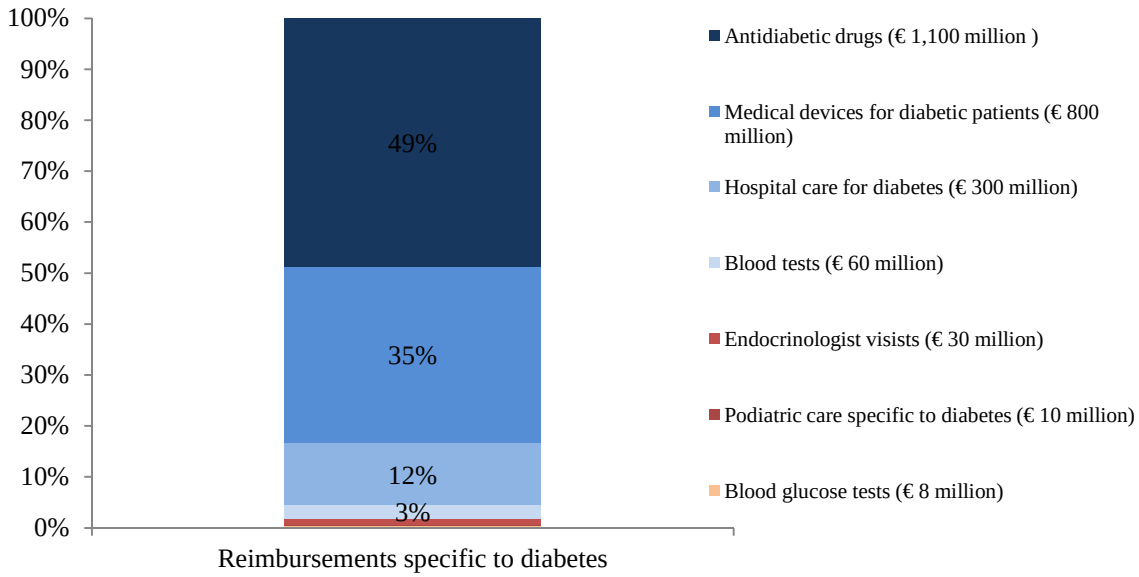
Figure

Figure 1- Breakdown of reimbursements to patients with diabetes



Source: CNAMTS\SNIIRAM 2012

Figure 2 - Breakdown of the €2.3 billion diabetes-specific expenditure



Source: CNAMTS\SNIIRAM 2012

Authors

First of all, we would like to thank both reviewers for their helpful and constructive comments. In this new submission we tried to take into account most of their comments. We also asked for a new translation was carried out by a different person. We hope this new version will be clearer and with a better English.

Reviewer #1: The study estimates the healthcare costs of diabetes to the French National Health Insurance using four different methods, including one novel approach. It estimates a substantial cost burden due to diabetes.
One of the main advantages of the study is the vast number of observations it uses to provide very precise estimates even for sub groups of people with diabetes. It could also be potentially interesting because it provides a new approach to estimating and disentangling the cost burden. However, there are substantial points the authors need to improve upon before a potential publication.

Some general points: The specific contribution of the findings to the existing literature needs to be made clearer. At the moment this is not the case. Also the manuscript is very hard to read. The phrasing needs substantial improvement to make it clearer what the authors want to say. Also the English needs improvement and there are several very obvious spelling mistakes.

We made a few changes in the manuscript in order to make the specific findings clearer. A new translation was also carried out.

Also there are many claims made in the manuscript not backed up by references.
If they are not a direct result of the analysis in the paper they should be supported by references. Overall, the manuscript needs a substantial overhaul.

References were added in order to support claims which were not directly related to the results.

Major specific points:

1. There is no comparison or context with other studies on the cost burden of diabetes in France or other comparable countries. This makes it difficult to interpret the findings.

Several references were added.

2. There is no comparison to other studies in the literature that have compared different costing approaches to estimate the healthcare costs of diabetes. are your findings comparable and do they point into a similar direction?
Several references were added.

3. In the introduction it states that the study wants to compare the different costing approaches. However, reading the manuscript I cannot find any true comparison of the estimates nor a discussion about which estimate may provide us with a better idea of the costs of diabetes in France. Table 7 was added.

4. In the Introduction it states that the growth of the population may be a problem due to more people with diabetes, I guess. However, I think if the relative number of people with diabetes stays the same this should not lead to an aggravation of the problem. Please clarify.

Several references were added.

5. For a better understanding of the estimated models, especially for the incremental costing approaches, it would be good to provide some formal representation in the form of an equation.

A formal representation (equation) was added (p10).

6. Provide references for the used estimation approaches, especially Methods 1 and 2.

Several references were added (see in particular ref 8, 9).

7. What type of matching approach was used? There are many. What variables exactly were used for the matching? Why do you use age groups and not age itself to match on?

A matching approach was used based on 10-year age-groups and gender. We defined a control group of patients without diabetes stratified by 10-year age-groups and gender. The excess reimbursements related to diabetes were therefore estimated for each age-group as the difference between the expenditure of the diabetes population (case) and the expenditure of the population without diabetes (control). In other words, the reimbursed expenditure differential was estimated by gender and by 10-year age-groups. Ten-year age-groups were used rather than exact age groups in order to allow regional analysis of diabetes expenditure by means of the same methodology with a sufficient number of individuals in each group to provide significant and robust results. As the incremental approach is designed to identify costs that are causally related to diabetes (such as the costs related to complications of diabetes), no adjustment can be performed for variables causally related to diabetes.

8. In the discussion, please explain what you refer to with the GMATCH approach. It would be better not to mention the specific function in the discussion but rather discuss the approach that is behind this function. Also it seems that you did not even try to estimate this other matching function. Or did you?
In the new version we do not refer to the GMATCH approach.

8. Why do you use the head and neck cancer study for guidance, for example to inform your use of the log-link function on page 7. Not clear to me. There should be guidance in the econometric literature on what function to use. Just using the most popular one does not convince me and it is also not clear to me how the most popular one is determined.

Reference was changed (ref 10).

9.The approach used in the regression based section using a "nil coefficient" is unknown to me. Please make clearer what is done here. Is this not just a simple regression?

It was a wrong translation (“nil expenditure” instead of “subjects with zero expenditure”).

10. Why do you not also match on some regional dummies and why do you not include such a variable in your regression. Are there really no additional control variables that could be used.

A regional analysis of diabetes expenditure using the same methodology was also performed, but the results are not presented in this paper.

11. The headings in the results section are not appropriate. They should not state any of the results but rather give an idea of what the section is about. Please change these.

Headings in the results sections were modified.

12. To which table do you refer to in section 4.2.?
A new table was added : table 3
+ table 7 + figure 1

13. What does it mean that the Chi test in section 4.3 was not significant? Does it suggest the fit of the model was good or bad?

Results from the GLM regression estimates are shown in Appendix 1. The fit of the model was assessed by using the goodness-of-fit Pearson’s Chi-square test, which was not statistically significant. Which means that the hypothesis of independence between the observed values and those estimated by the model assessing the fit of the selected model was then rejected.

14. Also present the coefficients for the covariates in Table 3.
See Appendix 1

15. What table are you referring to in section 4.5.2.?
A new table was added : table 5

16. Method 4 to estimate costs is unclear to me. At present I find it hard to understand what is done here exactly. It needs to be made clearer what exactly is done and how this is novel and contributes to a better understanding of the healthcare costs of diabetes. Especially because this is one of the major selling points of the manuscript. More details were added.

17. In the Discussion section the authors talk about the need to use the "safest, most active and less expensive drugs" to reduce the cost burden of diabetes. Isn't this the same as the most cost-effective drugs? Why do you not use this well known term here? “Cost-effective drugs” was added.

18. What is the Baumal disease effect the authors talk about in the discussion? More explanations were added.

19. What do you mean by "static" and "dynamic approach" on page 14? This is unclear and needs further elaboration. We changed words “static” by ‘transversal” and “dynamic” by “longitudinal” (wrong translation).

Minor points:

At the end of the Introduction the authors state "...will be presented in the last section, followed by the discussion." This does not make sense as the last section is the discussion then. Changed

On page 3, what countries do you refer to when talking about "northern European countries" and what do you intent to say with "the number of observations is less important"? Please also provide references supporting these claims. New references were added (ref 16-19)

What are "invalid pensions" on page 4? disability pensions

On page 4 please provide references about where the deprivation index is used routinely. Two references were added : 17,18

17. Rey, G., Jougla, E., Fouillet, A., Hémon, D.: Ecological association between a deprivation index and mortality in France over the period 1997 - 2001: variations with spatial scale, degree of urbanicity, age, gender and cause of death. BMC Public Health. 9, 33 (2009).
18. Haut Conseil de la Santé Publique: Indicateurs de suivi des inégalités sociales de santé, http://www.hcsp.fr/Explore.cgi/Telecharger?NomFichier=hcspr20130619_indicateurinegalitesocialesante.pdf.

What does "cost of the inequality of developing..." on page 7 mean. What does inequality refer to? Changed.

Similarly, what does "not fully respected" mean, again on page 7. Unclear to me. Wrong translation replaced by : “However, this simplifying assumption is not fully met, as factors other than age and gender may also be involved in the comparison between the health care expenditure of patients with or without diabetes”

Both the term "euros" and "€" are used. Please make it consistent. Ok

Provide the full name for NICE. Ok

Reviewer #2: The authors provide a manuscript, where they estimate "The economic burden of diabetes to the French national health insurance". They provide different estimates based on different approaches. At the same time they claim having developed a new method for cost-of-illness studies.

I definitely see some value in this paper. However, if it is a main and novel aspect of this paper that the authors have developed a new cost-of-illness method, this should be obvious from the title and from the abstract. An alternative title could be:
"Combining the 'medicalized approach' and the 'incremental approach' to a new cost-of-illness method: The economic burden of diabetes to the French national health insurance" We changed title.

The abstract should be revised accordingly. Developing the new approach should be part of the objective; some more details should be provided in the methods; and this achievement should be stated in the conclusion. We adapted the abstract according to your remarks.

In general, no matter what the main focus/objective of this manuscript would be, I think the different methods applies should be mentioned more specifically in the abstract. Currently it only reads: "We used methods identified in the literature and also a new approach based on the combination of existing methods." This does not mean anything. I don't think it would be necessary to mention that they were identified in the literature, but it should be mentioned that they are (a) the overall costs of subjects with diabetes, (b) costs of treatment directly related to diabetes (i.e. the 'medicalized approach'), (c) the incremental regression approach, (d) the incremental matched-control approach; and (e) a novel method, a combination of the medicalized approach and the incremental approach. Thank you very much. We changed according to your proposal and it is clearer.

However, I think the authors should go a little bit more into detail regarding the method(s) they applied: Regarding Method 4, the new and innovative method, the authors state "the global medicalized and matched control incremental definitions were combined in order to distinguish health care expenditure specific to the management of diabetes from that related to management of complications and/or excess health care consumption induced by a degraded health status due to diabetes". But this to me is not specific enough. More details were added.

Has as a first step the medicalized approach been applied? Have the costs of the incremental approach afterwards been removed from the data (step 2)? Has based on this reduced data set the matched control incremental approach been applied (step 3)? These steps may appear obvious to the authors, but I think they should be mentioned explicitly. More details were added.

Regarding Method 3.2, Lines 29-34 I also was a little bit confused: The authors state that they "defined a control group of patients without diabetes with matching variables that were related to diabetes". I think here the authors also need to elaborate a bit. I thought, one goal of the incremental approach was to identify costs that are causally related to diabetes. This includes the costs of consequences, such as retinopathy etc. Therefore, it should not be adjusted for variables which are causally affected by diabetes, correct? If not, please clarify. In any case, please elaborate.
As the incremental approach is designed to identify costs that are causally related to diabetes (such as the costs related to complications of diabetes), no adjustment can be performed for variables causally related to diabetes.

Here, you could also discuss the aspect, that a joint confounder may affect both, the incidence of diabetes and the incidence of other diseases. If not adjusting for these variables, the costs associated with diabetes would be overestimated. Changed

Regarding Method 1 and Method 2 I felt that the authors should have provided references. For example they could cite some papers that applied these two methods, or alternatively, reference an overview article which reports about these methods. Several references were

added.

Regarding the Matching algorithm of Method 3.2 I also would have expected to see the details. Which variables were exactly used for matching? Which matching algorithm has been applied exactly? Nearest neighbor? Perfect match? I assume no propensity score matching. Details of the matching algorithm could also be supplied in an appendix. Alternative matching approaches that could have been applied could also be mentioned within the discussion. More details were added.

I also think it would be nice to present an overview table, which compares the results of the alternative cost-of-illness approaches right next to each other. Table 7 was added.

Finally, considering that this is a new non-mainstream cost-of-illness method, it would be great if the authors would discuss which further method development has been taken place. In this journal, the European Journal of Health Economics, for example, in April of this year there has been an article about conducting cost-of-illness studies based on massive data. Changed et reference 40 was added.