PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Prevalence and prescription patterns of oral glucocorticoids in adults: a retrospective cross-sectional and cohort analysis in France
AUTHORS	Bénard-Laribière, Anne; Pariente, Antoine; Pambrun, Elodie; Bégaud, Bernard; Fardet, Laurence; Noize, Pernelle

VERSION 1 - REVIEW

REVIEWER	M Boers VU University Medical Center Dept of Epidemiology & Biostatistics; Amsterdam Rheumatology and immunology Center
REVIEW RETURNED	02-Feb-2017

GENERAL COMMENTS	Benard 2017 This is an interesting manuscript that describes the prevalence and developments in the prescription of glucocorticoids (GC) in the general French population. Due to the unique source (a random sample of a database that contains 90% of the French population) it provides a unique view into the prescription patterns in France. The study is well done and described, and the results match the conclusions. Main concerns 1. A key element that is missing from the results is the dose. These data are essential to interpret the results in full: both for short- and longterm prescriptions: mean dose, cumulative dose, duration (with SDs). For example, the impact of the high prevalence of unique prescriptions is higher if the dose is 30 mg of pred eq/d compared to 5. 2. I wonder about the definition of chronic or 'longterm' as at least 6 prescriptions in a year. In my country (NL) prescriptions can be given for a max of 3 months (and then renewed), so this definition would incorrectly miss all of my patients on prednisolone (max 4 prescriptions/y). This may be different in France, but the definition should be justified. Also, given the fact that some prescriptions may be missed it would be interesting to extend the research for comorbidities and the handling of these (eg osteoporosis) to the 'midterm' group. 3. Analysis: purely descriptive, which makes me wonder whether the reported differences between sexes, age categories, and the increase over time is significant (highly likely so), and whether there is any interaction between these. Eg, is the increase over time different for males and females (looks not to be), etc. 4. Discussion: very wordy, can probably be tightened up. Minor issues 1. Tables: too much detail. Apart from the absolute numbers in the

	column headers, the results can be expressed in % only. Consider a sans-serif font for tables (eg Calibri).Otherwise good layout; Table 1, perhaps insert some horizontal white space between the main row categories. 2. Figure: the changes are exaggerated by the fact that the y-axis does not include zero. Please consider doing this, and if not, indicate the selection by inserting a broken axis symbol on the lower end of the axis. Reduce the number of tick labels by 50%. Delete the legend, and place the series labels close to the respective series lines. Error bars should indicate SD, not 95% CI. As these are highly similar, you can consider only plotting the error bar upwards for the top series, and downwards for the bottom series. Series lines should be made thicker, error bars also (but less) and horizontal whiskers can be deleted. Enlarge font size of titles and tick labels. Delete the y axis title and tick labels of the right panel. 3. Change appendix figures accordingly.

REVIEWER	Ludovic CASANOVA Aix Marseille University, Department of general practice, Marseille, France INSERM, UMR912 "Economics and Social Sciences Applied to Health & Analysis of Medical Information" (SESSTIM), F-13385, Marseille, France
REVIEW RETURNED	13-Mar-2017

GENERAL COMMENTS	This is a topic of interest to practitioners. However, there are too many apparent discrepancies in the methodology for this manuscript to be published in its present state. This work has three distinct aims: to study the changes in the prevalence of patients receiving a corticotherapy, description of the comorbidities and indications in these patients when they undergo a short-term or long-term treatment, and lastly to identify lack of adherence to the prescriptions. The main finding was hence a notable increase in short-term treatments, with an insufficient level of adhesion to the prescription. 1) GENERAL COMMENTS The main difficulty in coming to grips with this manuscript lies with the lack of distinction between the patients treated short-term and long-term by GC. A more clear and regular distinction between these two populations is necessary throughout the manuscript. The indications, the complications, and the progression of these two groups are fundamentally different at the clinical level. The main finding of this study is of interest. Yet in light of the huge differences between the indication for a long-term corticotherapy and a short-term corticotherapy, the presentation of the differences between the groups yields little of value. The findings in regard to the treatment of osteoporosis are of particular relevance to practitioners. Lastly, the co-prescriptions wrongly deemed to be inappropriate (e.g. PPIs and potassium) are probably influenced by unobserved factors and are only of marginal interest. 2) INTRODUCTION Lines 13 to 17: A clear distinction needs to be made between a) the risks of complication generated by the long-term corticotherapy, b) the short-term corticotherapy, and c) the risks inherent to both. In regard to complications from long-term corticotherapy, specifying

	the time period after which the risks become manifest and measurable (by defining them) seems necessary. Providing the various delays will justify the selection of the six reimbursements in the methodology. A more precise specification of the secondary objectives at the end of the Introduction section is also needed. 3) METHOD It is hard to understand the relevance of the cross-sectional analysis before an analysis of the cohort. A subanalysis of the cohort should allow the results of the cross-sectional analysis to be seen. In this regard, specifying the mode of inclusion of the cohort and its nature is needed. Is it fair to assume that it involved a historic open inclusion cohort, with re-engagement of the patients after an event? An exhaustive list of the CIP codes used to generate the list of the oral GCs that were considered should be provided as an appendix. Also, the presence of hydrocortisone, which is a glucocorticoid substitution treatment more commonly used for adrenal insufficiency should also be justified. Could it also be specified whether all dosage forms were considered, such as celestene drops for example? There are several uncertainties regarding the comorbidities. 1) It is stated that “GC initiators were described in terms of age, sex, and concurrent drugs reimbursed at index date.” Were just the drugs reimbursed on the day of the index date taken into account? If yes, is it possible that a large number of co-prescriptions and hence comorbidities were not featured since a short-term treatment with GCs is frequently administered in an emergency and hence involves a prescription that differs from the chronic treatment of a patient. 2/ Diabetes is a pathology that is readily recognized due to its LTA number or by the reimbursement of antidiabetics. Yet did the psychotic disorders concern all of the long-term N°23 afflictions, or were the ICD-10 codes used? Furthermore, as there is no LTA code for osteoporosis, it is hence highly likely that the prevalence is affected by the quality of the algorithm that was used. It would be useful to expand on this issue. Further down, it is stated that “Comorbidities and indications for oral GC treatment were identified using data from diagnoses related to hospital stays or chronic diseases (ALDs), and medication reimbursement data in the 12 month period preceding the patient’s index date.” For the sake of reproducibility of research findings, it is paramount to specify which code and which medication was used. If the algorithms cannot be presented due to lack of space, they can be added as an appendix. The number of patients for whom no initial indication for prescription of GCs was found needs to be specified (in Table 1). While it is stated that “Measures for prevention/monitoring of osteoporosis among these individuals were identified by at least one of the following criteria … ,“ the frequency and the time period with which these criteria were measured are not indicated (it subsequently becomes clear that it is a year). When the performance of bone densitometry in the year following the introduction of a treatment by corticoid is considered, it would be of interest to also look at the year preceding the index date. In clinical practice it is common for bone densitometry to be performed prior to initiating a long-term corticoid treatment. In regard to potassium and PPIs; why was this limited to prescriptions concomitant with those for corticoids? Also, in regard to the prescription of PPIs, it might be better to refer

	to non-indicated prescriptions rather than “inappropriate ulcer prophylaxis.” Lastly, the definition of short, medium, and long-term treatment groups needs to be clarified. In the year that followed the index date, six reimbursements were deemed to correspond with a long-term treatment. Why was the ICP code not used more to determine the number of tablets rather than the number of issuances and/or the time between the reimbursements? If this was not done, it should be specified and expanded on. 4) RESULTS Regarding the increase in the prevalence of patients treated at least once by GC, it is preferable to present the absolute increase in the prevalence, that is to say 2.4%. Presentation of the absolute increase is also preferable for all of the subgroups. The short-term, medium-term, and long-term groups, as well as the number of reimbursements should be specified in Table 1. For Figure 1: the selection of the limits for the Y-axis overstates the data. It would be preferable to start with 0% and to use an upper limit of 25 % for all of the graphs, including those in the Supplementary files which vary from 18%, to 22% and 25%. Lastly, a presentation of the characteristics of co-prescription (potassium/PPI) and presentation as a function of the three groups in Table 2 would be most useful. The Supplementary files are not given due consideration and they are barely referred to in the Results section, which is unfortunate. 5) DISCUSSION The same comment applies here too: it would be preferable to refer to absolute decrease. It is paramount that the sentence “Thus, the increase in prevalent use could mainly be due to more and more prescribing in unjustified situations” is rephrased as it is worded too strongly. For the argumentation in regard to the increase in the prevalence of patients treated by GC for a short duration at the expense of the ENL indication, it would have been interesting to know the change in the co-prescriptions (Antibiotics, Respiratory/otological drugs, Concurrent antibiotics and respiratory/otological drugs) over time. It would be appropriate to alter the following sentence: “This could mainly be due to the growing number of unjustified prescriptions rather than to situations with a favorable benefit/risk ratio.”

VERSION 1 – AUTHOR RESPONSE

Reviewer#1
M Boers
VU University Medical Center; Dept of Epidemiology & Biostatistics; Amsterdam Rheumatology and immunology Center

This is an interesting manuscript that describes the prevalence and developments in the prescription of glucocorticoids (GC) in the general French population. Due to the unique source (a random sample of a database that contains 90% of the French population) it provides a unique view into the prescription patterns in France. The study is well done and described, and the results match the conclusions.

Main concerns
Reviewer#1, Comment 1

A key element that is missing from the results is the dose. These data are essential to interpret the results in full: both for short- and longterm prescriptions: mean dose, cumulative dose, duration (with SDs). For example, the impact of the high prevalence of unique prescriptions is higher if the dose is 30 mg of pred eq/d compared to 5.

Authors
We thank the Reviewer for this valuable comment and agree that assessment of the dose is crucial, as it is undoubtedly true that many GC-related adverse effects depend on dose and duration of treatment. Unfortunately, neither the dose prescribed/duration of treatment, nor the indication for prescribing, are systematically informed in the French health insurance system which main objective is to provide affiliates with reimbursements. Consequently, we cannot describe these parameters accurately from reliable and directly available information using this datasource. In some situations (e.g. antihypertensives, antidiabetics, etc.), this can be overcome by deriving the probable duration and dosage of the prescription using the number and strength of tablets/treatment units per refunded medication pack or the DDD established by the WHO. However, this does not seem to constitute a valid approach for GCs given they could either be prescribed at high- or low-dose for acute or chronic conditions. The DDD determined by the WHO for prednisolone (10mg/d) for instance clearly relates more to long-term therapies than short-term ones during which the dose can be much higher.
This was confirmed in further analysis (not shown in the manuscript). In these, the cumulative dose over the year following GC treatment initiation was estimated using the number of medication packs dispensed and reimbursed per individual. The mean cumulative dose (±SD) of prednisolone equivalent over the year of follow-up was around 400 mg (±140) for individuals with a single reimbursement, around 1,050 mg (±600) for those who had 2 to 5 reimbursements, and around 4,800 mg (±3,500) for those who had ≥6 reimbursements (and up to 55,650 mg). As these results were showing a very important heterogeneity with regards to the amount of DDD within each class of individuals, we concluded such measure would be very unlikely to adequately approach the correct duration of use of treatments and decided not to use it for our analyses.
The Methods section, § Data source, has been amended to define more precisely the data collected in the EGB database and those not captured (page 5 line 5 and line 12): “For all beneficiaries, it consists of the exhaustive recording of drug reimbursements, with identification of medication packs, including the number and dosage strengths of treatment units. The database also contains hospitalization data (diagnoses and dates), and the existence of certain chronic diseases (Affections de Longue Durée, ALD, an administrative status allowing full reimbursement of health care for a given condition; e.g. diabetes, cancer, psychosis). Diagnoses or indications for prescribing are not collected in the EGB database, nor the dose prescribed or the duration of treatment.”

Reviewer#1, Comment 2
I wonder about the definition of chronic or ‘longterm’ as at least 6 prescriptions in a year. In my country (NL) prescriptions can be given for a max of 3 months (and then renewed), so this definition would incorrectly miss all of my patients on prednisolone (max 4 prescriptions/y). This may be different in France, but the definition should be justified.

Authors
We acknowledge the Reviewer for this sensible comment that relates to a point of primary importance. Indeed, we did not justify enough the definition employed for short-, mid- and long-term users.
All recommendations intended for physicians involved in the management of chronic exposure to GC therapy agree on the definition of long-term GC therapy that is at least 3 months, in any dosage and for any reason. Unfortunately, as previously said, the duration of treatment is not collected in the EGB database. In France, GC treatment is issued for a maximum of 30 days and individuals have to renew their treatment each month. According to these rules and given the lack of data concerning the prescribed duration of treatment, we hypothesized that each GC reimbursement corresponded to a

maximum of one month of treatment. As we could not exclude (i) overlap of renewals, and (ii) intermittent courses of oral GC rather than continuous treatment, we considered reasonable to assume that individuals with ≥6 reimbursements/year were quite certainly treated for chronic diseases. Under the same reasoning conversely, a unique dispensing appeared to be a robust indicator of short-term use.
We defined this aspect in the Methods section to provide reader with a clear understanding of the definition we used in this revised version of the manuscript (page 7 line 31): “All parameters were examined overall and according to the duration of therapy. The EGB database does not provide the total duration of treatments but GC treatment is issued for a maximum of 30 days in France and individuals have to renew their treatment each month. We consequently assessed GC treatment duration according to the number of oral GC reimbursements (consecutive or not) identified during the 12-month period following the index date. Users who had a unique reimbursement were arbitrarily defined as short-term users, those who had 2 to 5 reimbursements as mid-term users, and those with ≥6 reimbursements as long-term users. We assumed that individuals with ≥6 reimbursements/year were treated for chronic diseases.”

Reviewer#1, Comment 3
Also, given the fact that some prescriptions may be missed it would be interesting to extend the research for comorbidities and the handling of these (eg osteoporosis) to the ‘midterm’ group.

Authors
We thank the Reviewer for this valuable comment.
In further analysis, potassium supplementation and ulcer prophylaxis were also examined among mid-term users: concurrent reimbursement of oral GCs and potassium supplementation concerned 1.8% of mid-term users (versus 23.7% of long-term users), of whom 71.0% never had any serum potassium assay during the two weeks preceding the prescription. This was quite similar to that observed for short-term users (0.5% with potassium supplementation, of whom 87.0% with no serum potassium assay). Regarding ulcer prophylaxis, 16.7% of mid-term users had at least one concurrent reimbursement of oral GC and PPI without known concurrent NSAID or aspirin use; this was 7.1% for short-term users and 49.8% for long-term users. As this was much similar to what was observed in short-term users, we did not detailed this information in the manuscript, and did not extend this description to that of osteoporosis, which relates to a recommendation even more exclusively considering long-term users.

In agreement with the Reviewer’s comment, we added a Table detailing the characteristics of the different groups of user for these therapeutic associated measures (Table 3 in the revised manuscript) for potassium supplementation/monitoring and PPI use, but not for osteoporosis as previously explained.

Table 3. Measures for kalaemia and gastric protection associated with the prescription of oral glucocorticoids (GC) therapy over the year following treatment start (figures are percentages)
All GC initiators N=206,759 Short-term users* N=139,703 Mid-term users* N=63,267 Long-term users* N=3,789
At least one concurrent reimbursement of GC and potassium supplements 1.3 0.5 1.8 23.7
Without any serum potassium level measurement during the preceding 2-week period 0.8 0.4 1.3 8.8

At least one concurrent reimbursement of GC and PPI without concurrent NSAID or aspirin use 10.8 7.1 16.7 49.8
*Short-term users: 1 reimbursement/year; mid-term users: 2 to 5 reimbursements/year; long-term users: ≥6 reimbursements
NSAID: Non Steroidal Anti-Inflammatory Drug; PPI: Proton Pump Inhibitor

Reviewer#1, Comment 4
Analysis: purely descriptive, which makes me wonder whether the reported differences between sexes, age categories, and the increase over time is significant (highly likely so), and whether there is any interaction between these. Eg, is the increase over time different for males and females (looks not to be), etc.

Authors
We thank the Reviewer for this valuable comment. As the relative change value is a standardized proportion for each group, obtained by bootstrap and corresponding to the median of the values estimated over 500 different samples, no simple testing can be made to compare it between groups. Unfortunately, there is thus no way to test for heterogeneity of this value between group, which can only be appraised by considering the estimates for each group and their corresponding 95% confidence interval. Doing so, one can only observe that differences for relative changes appears weak between groups, with differences being only identifiable in the absence of statistical testing for change in prevalence of use for people aged 18-49y (value of the higher bound of the 95%CI is inferior to the values of the lower bound of 95%CI for changes observed in patients aged 50-59y, 60-69y or 70-79y). Compared to the 50-59 and 60-69y groups, a potentially lower increase in the prevalence of use is also likely for patients aged ≥80y, although there is a limited overlap of 95%CIs. Finally, as strict statistical comparison cannot be performed, we preferred not to comment on these potential differences in the manuscript and leave these evaluations up to the reader.
The same considerations would worth for sex.

Reviewer#1, Comment 5
Discussion: very wordy, can probably be tightened up.

Authors
We shortened the discussion as much as possible and asked for the help of a native speaker to make it less wordy.

Minor issues
Reviewer#1, Comment 6
Tables: too much detail. Apart from the absolute numbers in the column headers, the results can be expressed in % only. Consider a sans-serif font for tables (eg Calibri). Otherwise good layout; Table 1, perhaps insert some horizontal white space between the main row categories.

Authors
As suggested by the Reviewer, the tables have been modified accordingly.

Reviewer#1, Comment 7
• Figure: the changes are exaggerated by the fact that the y-axis does not include zero. Please consider doing this, and if not, indicate the selection by inserting a broken axis symbol on the lower end of the axis.
• Reduce the number of tick labels by 50%.
• Delete the legend, and place the series labels close to the respective series lines.
• Error bars should indicate SD, not 95%CI. As these are highly similar, you can consider only plotting the error bar upwards for the top series, and downwards for the bottom series.
• Series lines should be made thicker, error bars also (but less) and horizontal whiskers can be deleted.
• Enlarge font size of titles and tick labels.
• Delete the y-axis title and tick labels of the right panel.
• Change appendix figures accordingly.

Authors
We thank the Reviewer for this accurate comment. We altered the presentation of the main figure and those inserted in the supplementary files accordingly to the exception of SD for which we preferred to keep the presentation of 95%CI to be consistent with the presentation in the text.

Reviewer#2
L Casanova
Aix Marseille University, Department of general practice, Marseille, France
INSERM, UMR912 "Economics and Social Sciences Applied to Health & Analysis of Medical Information" (SESSTIM), F-13385, Marseille, France

This is a topic of interest to practitioners. However, there are too many apparent discrepancies in the methodology for this manuscript to be published in its present state. This work has three distinct aims: to study the changes in the prevalence of patients receiving a corticotherapy, description of the comorbidities and indications in these patients when they undergo a short-term or long-term treatment, and lastly to identify lack of adherence to the prescriptions. The main finding was hence a notable increase in short-term treatments, with an insufficient level of adhesion to the prescription.

Authors
We thank the Reviewer for his appraisal of the manuscript and the comments and suggestions he made. One aspect of the research (the last presented by the Reviewer) seems nonetheless to have been not fully understood: the goals of the study were actually to estimate the prevalence of use and describe GC users characteristics at baseline and according to the length of use. However, according to the limitations of the database and to the lack of information regarding the duration of the prescribed therapy, we did not study a potential lack of adherence that would have needed such data. Indeed, these can only be done using this database for drugs only used in a chronic continuous way, which does not correspond to the situation of GC. Therefore “an insufficient level of adhesion to the prescription”, as evoked by the Reviewer, could not be a main finding of the study.
We provided extensive answers to the following comments of the Reviewer.

Reviewer#2, Comment 1
General comments: The main difficulty in coming to grips with this manuscript lies with the lack of distinction between the patients treated short-term and long-term by GC. A more clear and regular distinction between these two populations is necessary throughout the manuscript. The indications, the complications, and the progression of these two groups are fundamentally different at the clinical level. The main finding of this study is of interest. Yet in light of the huge differences between the indication for a long-term corticotherapy and a short-term corticotherapy, the presentation of the differences between the groups yields little of value.

Authors
We thank the Reviewer for this valuable comment. We do agree that the populations of GC short-term users and long-term ones are very different owing to, amongst other reasons, the differences in indications for such use. This is indeed the main reason why we differentiated between these two populations all over the manuscript. However, in order to present with an overall picture of GC use and its evolution over the period, both had to be presented in the same manuscript. As underlined by the Reviewer, the added value stands less in the comparison of the characteristics of such users (which indeed only confirm that they are likely to be adequately classified regarding GC use indication) than to the description of each category and of the trends that concern it. The discussion section actually essentially focuses on these points.

Reviewer#2, Comment 2

General comments: The findings in regard to the treatment of osteoporosis are of particular relevance to practitioners. Lastly, the co-prescriptions wrongly deemed to be inappropriate (e.g. PPIs and potassium) are probably influenced by unobserved factors and are only of marginal interest.

Authors
We agree with the Reviewer that the results concerning osteoporosis are of peculiar importance. The other items were discussed with expert clinical practitioners who were willing to examine whether other therapeutics measures were associated with GC prescription, that would relate to historical recommendations, for which there is a lack of an evidence-based grounding (and that are indeed yesterday's news and no more teached). To stick with this objective, we thus adopted definitions for these items that allowed identifying situations in which they were unlikely to be justified by other medical factors. PPI concomitant use for instance, was considered only when observed in individuals without comedications with NSAIDs or aspirin. We acknowledge that this is of lesser value than the information concerning osteoporosis but we believe this corresponds potentially to unjustified use of drugs that always conveys a risk for no demonstrated benefit and that should thus be lowered as much as possible.

Reviewer#2, Comment 3
Introduction: Lines 13 to 17: A clear distinction needs to be made between a) the risks of complication generated by the long-term corticotherapy, b) the short-term corticotherapy, and c) the risks inherent to both. In regard to complications from long-term corticotherapy, specifying the time period after which the risks become manifest and measurable (by defining them) seems necessary. Providing the various delays will justify the selection of the six reimbursements in the methodology.

Authors
We thank the Reviewer for this valuable comment. We did not define our length of treatment by considering the associated risks but only the potential context of use i.e. the indication of it. As explained in our response to Reviewer#1 Comment 2, the threshold of ≥6 reimbursement/year to define long-term users was arbitrarily determined, as the duration of treatment is not collected in the EGB database. As previously stated in the response to this comment, all recommendations intended for physicians involved in the management of chronic exposure to GC therapy agree on the definition of long-term GC therapy that is at least 3 months, in any dosage and for any reason. Unfortunately, the duration of treatment is not collected in the EGB database. In France, GC treatment is issued for a maximum of 30 days and individuals have to renew their treatment each month. According to these rules and given the lack of data concerning the prescribed duration of treatment, we hypothesized that each GC reimbursement corresponded to a maximum of one month of treatment. As we could not exclude (i) overlap of renewals, and (ii) intermittent courses of oral GC rather than continuous treatment, we considered reasonable to assume that individuals with ≥6 reimbursements/year were quite certainly treated for chronic diseases. Under the same reasoning conversely, a unique dispensing appeared to be a robust indicator of short-term use.
We defined this aspect in the Methods section to provide reader with a clear understanding of the definition we used in this revised version of the manuscript (page 7 line 31): "All parameters were examined overall and according to the duration of therapy. The EGB database does not provide the total duration of treatments but GC treatment is issued for a maximum of 30 days in France and individuals have to renew their treatment each month. We consequently assessed GC treatment duration according to the number of oral GC reimbursements (consecutive or not) identified during the 12-month period following the index date. Users who had a unique reimbursement were arbitrarily defined as short-term users, those who had 2 to 5 reimbursements as mid-term users, and those with ≥6 reimbursements as long-term users. We assumed that individuals with ≥6 reimbursements/year were treated for chronic diseases."

Reviewer#2, Comment 4

Introduction: A more precise specification of the secondary objectives at the end of the Introduction section is also needed.

Authors
As suggested by the Reviewer, the last paragraph of the Introduction section has been completed as follows: “This population-based study aimed at describing trends in the use of oral GCs among adults, the characteristics of GC initiators, and the prescriptions for the prevention of potential adverse effects associated with GC therapy.”

Reviewer#2, Comment 5
Method: It is hard to understand the relevance of the cross-sectional analysis before an analysis of the cohort. A subanalysis of the cohort should allow the results of the cross-sectional analysis to be seen.

Authors
Although we agree that a cohort study is quoted with a higher level of evidence than a cross-sectional study, only repeated cross-sectional studies allow studying trends in use in a general population. Cohort would mostly allow studying trends in use in a predefined population of users here. Even with a dynamic design, it would be less adapted to the repeated assessment of prevalence that was performed here and which was the main justification for the repeated cross-sectional design. Of course, as pointed by the Reviewer, this does not present with the longitudinal aspect needed to study the durations of use/number of reimbursements over time and thus needed to be completed by the cohort analysis in the work we present.
For that, we preferred to conduct a separate analysis for the study of prevalence and the study of patterns of use as we thought they were complementary and individually unable to allow achieving all of the study objectives.

Reviewer#2, Comment 6
In this regard, specifying the mode of inclusion of the cohort and its nature is needed. Is it fair to assume that it involved a historic open inclusion cohort, with re-engagement of the patients after an event?

Authors
We thank the Reviewer for his valuable comment. The cohort was constituted of GC initiators, all being considered only once in the cohort (from the first identified GC delivery after start of cohort period constitution to anniversary date of this first delivery date that constituted the index date for individuals). This was not enough detailed in the initially submitted version of the manuscript. We developed this aspect in the methods revised section as follows (page 5 line 46): “Identified individuals could only contribute once to the cohort constitution”.

Reviewer#2, Comment 7
Method: An exhaustive list of the CIP codes used to generate the list of the oral GCs that were considered should be provided as an appendix. Also, the presence of hydrocortisone, which is a glucocorticoid substitution treatment more commonly used for adrenal insufficiency should also be justified. Could it also be specified whether all dosage forms were considered, such as celestene drops for example?

Authors
We are not sure we understand the Reviewer’s comment. As he specifies, oral hydrocortisone is licensed for adrenal insufficiency; for this reason, we did not focus on hydrocortisone in this study that only considered oral GCs used for their anti-inflammatory and immunosuppressant proprieties. This is mentioned in the §Study design page 5 line 23: “All individuals who had at least one reimbursement of

an oral GC (i.e., betamethasone, dexamethasone, methylprednisolone, prednisolone, and prednisone) were identified for each year studied." In accordance with what we explained above, this definition implies that: (i) hydrocortisone was not considered in the study, and (ii) all oral forms of the above-mentioned GC conversely were, including oral drops (and consequently betamethasone drops marketed in France as brand celestene and generics).
CIP nomenclature is a French classification where each presentation of a proprietary medicinal product is identified by a presentation identification code. As these codes are only used in France, we thought that adding the exhaustive list of codes used would uselessly obscure the manuscript and appendix and did not do it currently; we would of course provide it if the Editor believes it could add value to the manuscript.

Reviewer#2, Comment 8
Method: There are several uncertainties regarding the comorbidities. 1) It is stated that "GC initiators were described in terms of age, sex, and concurrent drugs reimbursed at index date." Were just the drugs reimbursed on the day of the index date taken into account? If yes, is it possible that a large number of co-prescriptions and hence comorbidities were not featured since a short-term treatment with GCs is frequently administered in an emergency and hence involves a prescription that differs from the chronic treatment of a patient.

Authors
The reviewer is perfectly right: the value of the measured comorbidities/co-prescriptions depends highly on the procedures used for their assessment.
To avoid being affected by the limitations he pointed, the definitions and modalities of assessment retained for these comorbidities implied a combination of items that were scrutinized over a period of time of 12 months (comorbidities: both medical diagnoses and drugs reimbursed). The question was different for co-prescriptions as we wanted to highlight which were those co-delivered with GCs and potentially reflecting the indication. With regards to this objective, considering drugs reimbursed before or after index date would have been less appropriate as drugs identified would have been less likely to be prescribed for the same indication than the GC identified at index date.
This was stated in the Methods section page 6, line 11 and rephrased as follows for a better understanding: "A description of drugs reimbursed at index date (concurrent drugs) was also performed as these potentially reflect the indication of GC therapy."

Reviewer#2, Comment 9
Method, Comorbidities: 2/ Diabetes is a pathology that is readily recognized due to its LTA number or by the reimbursement of antidiabetics. Yet did the psychotic disorders concern all of the long-term N°23 afflictions, or were the ICD-10 codes used?
Furthermore, as there is no LTA code for osteoporosis, it is hence highly likely that the prevalence is affected by the quality of the algorithm that was used. It would be useful to expand on this issue.
Further down, it is stated that "Comorbidities and indications for oral GC treatment were identified using data from diagnoses related to hospital stays or chronic diseases (ALDs), and medication reimbursement data in the 12-month period preceding the patient's index date." For the sake of reproducibility of research findings, it is paramount to specify which code and which medication was used. If the algorithms cannot be presented due to lack of space, they can be added as an appendix.

Authors
Psychotic disorders and osteoporosis were identified during the 12-month period preceding the index date as follows: psychotic disorders were identified among hospital discharge summary and ALDs registration using ICD-10 codes F20-F29 (Schizophrenia, schizotypal and delusional disorders) and using the reimbursement of antipsychotics (ATC code N05A, with the exclusion of lithium salts N05AN); osteoporosis was identified among hospital discharge summary using ICD-10 codes M80-M81 and M83-M85 (Disorders of bone density and structure), and using the reimbursement of drugs

for osteoporosis management: ATC codes M05BA/M05BB (biphosphonates), M05BX04 (denosumab), M05BX03 (strontium ranelate), G03XC01 (raloxifene), H05BA (calcitonin), and H05AA02 (teriparatide). Calcium and vitamin D were not considered due to the lack of specificity of these drugs to identify osteoporosis.
As suggested by the Reviewer, a complete list of codes used to identify comorbidities and indications of GC therapy is now provided in supplementary file.

Reviewer#2, Comment 10
The number of patients for whom no initial indication for prescription of GCs was found needs to be specified (in Table 1).

Authors
As mentioned page 8 line 38, at least one recognized GC indication was identified in the database in 61.1% of long-term users at treatment initiation; frequencies among all GC initiators, short- and mid-term users are shown in Table 1. The number of individuals for whom no initial indication for prescription of GCs can be easily derived from this and we thus did not present it explicitly. However, if the Editor believes that this should be placed in the Table 1, we will modify the manuscript accordingly.

Reviewer#2, Comment 11
Method: While it is stated that “Measures for prevention/monitoring of osteoporosis among these individuals were identified by at least one of the following criteria… ,“ (page 6 line 34, Authors’ note) the frequency and the time period with which these criteria were measured are not indicated (it subsequently becomes clear that it is a year).

Authors
This was indeed stated in the first sentence of the Method § Therapeutic behaviour associated with the prescription of GCs, “…Over the year following GC treatment initiation, we scrutinized two types of preventive measures:…” (page 6 line 15). In order not to be redundant, we preferred not to repeat this after few lines.

Reviewer#2, Comment 12
When the performance of bone densitometry in the year following the introduction of a treatment by corticoid is considered, it would be of interest to also look at the year preceding the index date. In clinical practice it is common for bone densitometry to be performed prior to initiating a long-term corticoid treatment.

Authors
We thank the Reviewer for this important comment. The definition we made was elaborated to allow measuring to what extent the recommendations of bone densitometry monitoring were respected (one DXA per year over the two first years in the absence of specific treatment for osteoporosis). For this reason, we considered the respect of recommendation during the first year to be either represented by the identification of one DXA over the year, either by the presence of an anti-osteoporotic treatment.
The point raised by the reviewer does not match with this recommendation but could have explained a potential underperforming of DXA if individuals had been closely monitored before treatment start. We thus performed additional analyses to see to which extent this could account. After doing so, it appeared that among the 1,469 individuals at increased risk of GC-induced osteoporosis, only 58 had at least a DXA performed in the 12-month period preceding the index date, of which 50 had another DXA performed during the year following initiation. Consequently, the hypothesis of an apparent low rate of DXA performed during the year following treatment initiation owing to DXA performed prior to treatment initiation does not seem to be confirmed. As this did not add to the manuscript, we did not

add the results of these supplementary analyses in the revised version.

Reviewer#2, Comment 13
Method: In regard to potassium and PPIs, why was this limited to prescriptions concomitant with those for corticoids? Also, in regard to the prescription of PPIs, it might be better to refer to non-indicated prescriptions rather than “inappropriate ulcer prophylaxis.”

Authors
We thank the reviewer for this valuable comment. As indication for prescribing is not collected in the EGB database, we focused on concurrent reimbursement of oral GC and PPI at the same date in order to maximize the hypothesis that PPIs were potentially prescribed to prevent GC-induced peptic ulcer (this being scrutinized for all of the identified GC deliveries for an individual over her/his one-year period of follow-up). The same logical reasoning was applied for the assessment of potentially inappropriate potassium supplementation.
As suggested by the Reviewer, the Methods section has been revised (page 6 line 52): “A priori non-indicated prescription of PPIs was defined as at least one concurrent reimbursement of oral GC and PPI in the absence of NSAID or aspirin at the same date.”

Reviewer#2, Comment 14
Method: Lastly, the definition of short, medium, and long-term treatment groups needs to be clarified. In the year that followed the index date, six reimbursements were deemed to correspond with a long-term treatment. Why was the ICP code not used more to determine the number of tablets rather than the number of issuances and/or the time between the reimbursements? If this was not done, it should be specified and expanded on.

Authors
As specified in response to the Reviewer’s Comment 3, we clarified the definition of short-, mid- and long-term users in the Methods section.
We thank the Reviewer for this comment, which supports Reviewer#1 Comments 1 and 2.
As previously stated in the responses to these comments, neither the dose prescribed/duration of treatment, nor the indication for prescribing, are systematically informed in the French health insurance system which main objective is to provide affiliates with reimbursements. Consequently, we cannot describe these parameters accurately from reliable and directly available information using this datasource. In some situations (e.g. antihypertensives, antidiabetics, etc.), this can be overcome by deriving the probable duration and dosage of the prescription using the number and strength of tablets/treatment units per refunded medication pack or the DDD established by the WHO. However, this does not seem to constitute a valid approach for GCs given they could either be prescribed at high- or low-dose for acute or chronic conditions. The DDD determined by the WHO for prednisolone (10mg/d) for instance clearly relates more to long-term therapies than short-term ones during which the dose can be much higher.
This was confirmed in further analysis (not shown in the manuscript). In these, the cumulative dose over the year following GC treatment initiation was estimated using the number of medication packs dispensed and reimbursed per individual. The mean cumulative dose (±SD) of prednisolone equivalent over the year of follow-up was around 400 mg (±140) for individuals with a single reimbursement, around 1,050 mg (±600) for those who had 2 to 5 reimbursements, and around 4,800 mg (±3,500) for those who had ≥6 reimbursements (and up to 55,650 mg). As these results were showing a very important heterogeneity with regards to the amount of DDD within each class of individuals, we concluded such measure would be very unlikely to adequately approach the correct duration of use of treatments and decided not to use it for our analyses.
The Methods section, § Data source, has been amended to define more precisely the data collected in the EGB database and those not captured (page 5 line 5 and line 12): “For all beneficiaries, it

consists of the exhaustive recording of drug reimbursements, with identification of medication packs, including the number and dosage strengths of treatment units. The database also contains hospitalization data (diagnoses and dates), and the existence of certain chronic diseases (Affections de Longue Durée, ALD, an administrative status allowing full reimbursement of health care for a given condition; e.g. diabetes, cancer, psychosis). Diagnoses or indications for prescribing are not collected in the EGB database, nor the dose prescribed or the duration of treatment."

Reviewer#2, Comment 15
Results: Regarding the increase in the prevalence of patients treated at least once by GC, it is preferable to present the absolute increase in the prevalence, that is to say 2.4%. Presentation of the absolute increase is also preferable for all of the subgroups.

Authors
We thank the Reviewer for his comment. We preferred to use relative changes as the level of use could vary greatly between groups (age categories, etc.). Thus, an apparently similar change of ±2% would have very different meaning depending on the initial value for the group or category and an absolute variation would not allow perceiving this difference. We consequently do believe it is more valuable to present the relative variations together with their 95%CI given that, additionally, absolute changes can be easily derived form the presented data.

Reviewer#2, Comment 16
Results: The short-term, medium-term, and long-term groups, as well as the number of reimbursements should be specified in Table 1.

Authors
As suggested by the Reviewer, the labels "short-, mid- and long-term users" are now mentioned in the head of lines of Table 1. The mean number of reimbursements (SD) was also added and detailed for each group in Table 1.

Reviewer#2, Comment 17
Results: For Figure 1: the selection of the limits for the Y-axis overstates the data. It would be preferable to start with 0% and to use an upper limit of 25 % for all of the graphs, including those in the Supplementary files which vary from 18%, to 22% and 25%.

Authors
We thank the Reviewer for this valuable comment. As suggested by the Reviewer#1 Comment 7, Figure 1 and appendix figures have been deeply revised. Y-axis now included zero, and the upper limit is 26% for all the graphs.

Reviewer#2, Comment 18
Results: Lastly, a presentation of the characteristics of co-prescription (potassium/PPI) and presentation as a function of the three groups in Table 2 would be most useful.

Authors
We thank the Reviewer for this suggestion. Table 2 only refers to GC users considered at increased risk of GC-induced osteoporosis and describes measures for prevention/monitoring of osteoporosis among these individuals and it would be difficult to include the information he asks to this table. To do so (and in line with Reviewer#1 Comment 3), we preferred to add a third Table devoted to this information.

Reviewer#2, Comment 19
Results: The Supplementary files are not given due consideration and they are barely referred to in

the Results section, which is unfortunate.

Authors
We thank the Reviewer for this comment. In order to improve the visibility of all available estimates, we added a reference to the Supplementary files, according to the detailed results in this paragraph page 7 line 58: “It mostly concerned prednisolone (+21.6% [+20.8 to +22.3%]) (online Figure S1); this was the most used GC over the study period, irrespective of age and sex”; page 8 line 5: “The prevalence of use was higher among women whatever their age, the highest value being observed in those aged 50-59 years (21.9% in 2014 [21.4 to 22.3%]) (online Figure S2).”

Reviewer#2, Comment 20
Discussion: The same comment applies here too: it would be preferable to refer to absolute decrease.

Authors
See response to Reviewer’s Comment 15.

Reviewer#2, Comment 21
Discussion: It is paramount that the sentence “Thus, the increase in prevalent use could mainly be due to more and more prescribing in unjustified situations” is rephrased as it is worded too strongly.

Authors
We understand this might be discussed and could be considered as a personal and strong interpretation of the results, despite we used the term “could”. With regards to the Reviewer’s comment and as the reader can easily makes its own opinion regarding this aspect, we decided to remove this sentence from the discussion.

Reviewer#2, Comment 22
Discussion: For the argumentation in regard to the increase in the prevalence of patients treated by GC for a short duration at the expense of the ENL indication, it would have been interesting to know the change in the co-prescriptions (Antibiotics, Respiratory/otological drugs, Concurrent antibiotics and respiratory/otological drugs) over time.

Authors
We thank the Reviewer for this interesting comment. We preferred indeed not to do such evaluation (and did not detailed these aspects in the repeated cross-sectional analysis evaluating trends) as a lot of efforts have been made for long time and especially over the period in France to lower the use of antibiotics. Thus, a decrease in the concomitant use of such drugs could not reflect a true decrease of use of GCs in upper-respiratory tract infections for instance, but only the lesser use of antibiotics in such indications. This unfortunately does not allow drawing proper trends for such indications of use over the period. Of course, it only affects the identification of such unrecognized indications.

Reviewer#2, Comment 23
It would be appropriate to alter the following sentence: “This could mainly be due to the growing number of unjustified prescriptions rather than to situations with a favorable benefit/risk ratio.”

Authors
We do agree with the reviewer this might be partly overstated. However, the incidence of the main indications for GC are all lower-equal to 5-10/100,000 per year making it almost impossible to account for all of the observed increase in use that, on a linear basis, would be close to 2% per year. As data of incidence for these indications are however scarce*, we softened the conclusion sentence to the following “This could partly be due to an increase in the number of unjustified prescriptions that would exceed the number of those performed in situations where the benefit/risk ratio is recognized

favorable", and the abstract conclusion accordingly.

*Currently, we did not add the corresponding references to the text (adding 5-6 references would be needed) as some are ancient and data were only found from reports in French of the Haute Autorité de Santé. If these were however judged to be of interest for the manuscript, we would be happy to do so.

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5. Orphanet. Portail des maladies rares et des médicaments orphelins. Artérite à cellules géantes. http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=FR&Expert=397 (Accessed 24 March 2017)

VERSION 2 – REVIEW

REVIEWER	M. Boers Dept Epidemiology&Biostatistics; Amsterdam Rheumatology and Immunology Center VUmc Amsterdam, NL
REVIEW RETURNED	05-Apr-2017

GENERAL COMMENTS	The authors have addressed my comments well. No further comments.