PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The epidemiology of knee osteoarthritis in general practice: a registry-based study
AUTHORS	Spitaels, David; Mamouris, Pavlos; Vaes, Bert; Smeets, Miek; Luyten, F; Hermens, Rosella; Vankrunkelsven, Patrik

VERSION 1 - REVIEW

REVIEWER	Wei Wang U S FOOD AND DRUG ADMINISTRATION
REVIEW RETURNED	27-Jun-2019

GENERAL COMMENTS	In this manuscript, the authors investigated the trends in the prevalence and incidence of knee osteoarthritis over a 20-year period, trends in comorbidity, and trends in drug prescriptions using a registry-based study. The presented study results are pretty comprehensive and the presented data analysis is appropriate, and I only have several minor comments that may need to be addressed before the manuscript can be accepted, (1) In the methods section, the authors need to provide some details regarding how to evaluate the incidence; (2) Please keep the table title for Table 1 and Table 3 consistent, specifically, for the fourth column, Table 3 should also be presented as Overall Trend; (3) For the joinpoint regression analysis in Table 1 and Table 3, the authors need to provide the justification in the statistical analysis method section to justify why at most three trends were provided. (4) I did not find the ¥ foot note in the Table 3. Please add it.

REVIEWER	Kristin Gustafsson Department of Physiotherapy, Rehabilitation Centre, Ryhov County Hospital Jönköping, Jönköping, Sweden Division of Physiotherapy, Department of Medical and Health Sciences, Linköping University, Linköping, Sweden
REVIEW RETURNED	27-Aug-2019

GENERAL COMMENTS	Thank you for the opportunity to review this manuscript, entitled “The epidemiology of knee osteoarthritis in general practice: a registry-based study” for BMJ Open. The authors have conducted a register-based study in a primary health-care population in Flanders, Belgium, with trend analyses of prevalence and incidence of knee osteoarthritis over a 20-years period, including

	trends in comorbidity and drug prescriptions. The objectives of the study are interesting for the BMJ Open readers, however there are some major concerns that needs to be adressed. Please see comments below. General comments The population of the study is vaguely described in the manuscript. In the abstract, all of the 440,140 individuals in the Intego database are described as the study participant, but that doesn't seem correct when reading the tables. The manuscript could benefit of a clearer description of the study population, preferably with a flowchart to describe the formations of the groups, including excluded and eventual drop-outs, in the knee OA population and the yearly contact group (YCG) in numbers. This is important as the robustness of the results depends on this description. To be able to determine how representive their studied population is, and to interpret the generalizability of the population that the authors draw their conclusions from, more information and description of their sample and the total population from which they have collected their sample, is needed. How is for example the socioeconomic profile of the included participant, and the included practices in comparison to those that were excluded? If this is not possible, it needs to be addressed as a weakness and the strengths and conclusions need to be humble. In the abstract, the article summary and all through in the manuscript, it would be preferable if more of the focus where on this specific study, instead of on the Intego database. Further, please see comments under the specific paragraphs of the manuscript below. Specific Comments Introduction: It appears to lack a coherent rationale building to a clear research question in the introduction. The authors explore knee OA prevalence and incidence together with comorbidity and drug prescriptions, but needs to more specific in why and how these outcomes are connected to each other. What is the gap of knowledge that this article will fill? Describing and motivating the Intego database in the last sentences, focusing more on the ability to access to data than the research questions that this study aims to answer. The last paragraph in the introduction would suit better earlier in the introduction or in the discussion. Method: The main concern is the description of selection of the population in this study. Focus now is on the 440,140 included in the Intego database (is those induvial of all ages or is this a specific age population?), but not all of those formed the study participants, if I have understood correct. The manuscript could benefit from describing inclusion and exclusion criteria, and by using a flowchart over participants with knee OA prevalence group and the YCGs. Some other thoughts; is it sufficient to include only those practices that had an "optimal data registration", is there not a risk that selection bias will occur? How is the term "optimal registration practices" defined, measured and controlled over time? Is it

	possible to address the coverage and completeness of the Intego database? How many GPs are excluded and why, and are there specific characteristics in those practices that are excluded at this point? Approximately, what proportion of the GPs and practices in Flanders were included in the database? Are they included or excluded on more conditions than only optimal registration? Such information would help the reader to determine if the studied population is representative. And for clarity and generalizability, it is important to take socioeconomic factors into account in the for the interpretation of the results, since there is well-known facts that both knee OA and overall poorer health are more common among socioeconomically more disadvantage individuals. What was the socioeconomic profile of the patients treated at the included compared to the non-included practices? Later in the manuscript the authors states that Intego covers more than 2% of the Flemish population. Do they have information of the socioeconomic profile of those 2 %, in comparison to the total Flemish population? Comorbidity was measured before the patients first was registered with knee OA, is that correct? So for those registered with knee OA the first years of the studied period, e.g. 1997, could this result in that those individuals were registered with fewer diseases than those who had their knee OA diagnose e.g. 2013, and effecting the results of the study? Do you have information about if the drugs were prescribed due to the knee OA or due to for example other painful conditions? Was the drug prescription calculated after the knee OA diagnose or before (unlike comorbidity that was calculated before)? In many countries today both acetaminophen and some oral NSAIDs are sold as over-counter drugs which are not registered. The manuscript could benefit from describing the prescribing procedure in Belgium. Results: It would be preferable to have clearer demographic data on the studied population, both those with knee OA and of those that composed the YCGs. Mean and range of age, proportion of gender, BMI, smokers and socioeconomic status if possible, before presenting the outcomes such as prevalence and incidence. The definition of disease burden is better suited in the method section, with an explanation under table 2. Some further questions; How large proportion of those with knee OA had comorbidities (is that what you mean with incidence in table 2)? Could the authors motivate why those specific comorbidities are presented in the results (compared to Supplement 1)? How about osteoarthritis in other joints than the knee? Did you considered to report trends in comorbidity and prescriptions of drugs among those that did not have a knee OA diagnose in the study, the YCG group, to be able to compare if trends were equal or unequal in those two groups? Equal positive trends could be the effect of a different and increased behavior in coding for example, and the study design could have benefit of having a control group to compare those trends with. Discussion:

	The statistical significant differences detected in this study with positive trends in both prevalence and incidence of OA and comorbidities in the population with knee OA and drug prescriptions, are those differences of clinical significance? Or could they be the effect of other factors such as an increased coding behavior or increased knowledge among GPs about OA and diagnosing the disease. Could it, for example be financial incentives of an increased coding as there is in some countries. Please discuss further. The authors states in line 46, page 8 that pharmacological treatment with acetaminophen should remain the first line treatment for knee OA patients. However, this may lead to a risk of miss-understanding. According to international guidelines, pharmacological treatment for knee OA should be introduced first as a secondary step, if core-treatment (first-line treatment) such as exercise therapy and information and coping strategies has failed to help the patient. If no data exist on the socioeconomic profile of the participants in this study, it should be addressed as a limitation in the discussion due to the known connection between both prevalence of OA, other comorbidity as well as drug consumption and socioeconomic status. Tables and figures: Table 1: Can table 1 and supplement 3 be presented as one table? When reading table 1, it would be preferable to also have frequencies and not only proportions when interpreting the results. And also a description/explanation to the different trend frames under the table. Figure 1 and 3- The figures are a little unclear to interpret regard the design of the different lines, that is not consistent with the explanation box. Other questions/comments: How has informed consent for participation in the study been collected from the involved patients? The authors stated the funding of the Intego database, however no information about who financed the work behind this specific article. The authors state the ethical approval of the Intego database, however do they have ethical approval for these specific research questions? There is a mix of concepts regarding comorbidity, multi-morbidity, multimorbidity (including spelling of keyword). I also have some concerns about some of the references. In the introduction for example, there are references that do not appear to refer to the primary data source, but to an article that itself refers to the primary source. One example of this is in line 49, page, reference 14. Reference 8 includes no information about pharmacological management. Reference 32 reflects a slightly different population, patients on a waiting-list for replacement surgery, which should be addressed.

VERSION 1 – AUTHOR RESPONSE

REVIEWER 1: Kristin Gustafsson		
	Major comments	Response
1	The population of the study is vaguely described in the manuscript. In the abstract, all of the 440,140 individuals in the Intego database are described as the study participant, but that doesn't seem correct when reading the tables. The manuscript could benefit of a clearer description of the study population, preferably with a flowchart to describe the formations of the groups, including excluded and eventual drop-outs, in the knee OA population and the yearly contact group (YCG) in numbers. This is important as the robustness of the results depends on this description. To be able to determine how representive their studied population is, and to interpret the generalizability of the population that the authors draw their conclusions from, more information and description of their sample and the total population from which they have collected their sample, is needed. How is for example the socioeconomic profile of the included participant, and the included practices in comparison to those that were excluded? If this is not possible, it needs to be addressed as a weakness and the strengths and conclusions need to be humble.	It is necessary that the readers have a clear understanding of the study population. Based on this comment, we propose several modifications in the method section to provide a clearer description of the study population: 1/ In the paragraph with the study population we clearly describe the yearly contact group. These patients are used in de denominator for all time trend analyses. 2/ We provide a supplementary file 1 with the exact numbers of the yearly contact group population for every year in the study. 3/ We provide a supplementary file 2 with the exact number of participating GP practices during the study period. This is a registry-based study in which we look at the population that is available each year. This is a significant difference with cohort studies or RCTs. In registry-based studies, inclusion criteria are based on the quality of registration by the participating GP practices, and not on patient level. General practitioners willing to participate in Intego have to pass three general quality criteria: the average number of new diagnoses per patient per year should be higher than one; the percentage of diagnoses recorded without using keywords should be less than five percent; these parameters must remain stable for at least three years. Some registrations on patient level, for example smoking status or body mass index, were excluded in our analyses, because they were suboptimally registered for the population in the yearly contact group. Therefore, it is not common practice to provide patient flowcharts with in- and excluded patients, missing data, and dropouts for registry based studies. Due to privacy, socioeconomic patient profiles are not available on patient level. This information is available on practice level based on the postal code. However, since GP practices in Flanders often take care of patients living in neighboring

		municipalities and people living within a specific postal code can have a different socioeconomic status, we in general do not use this information in our analyses. In the discussion, we added this as a limitation since we were not able to draw conclusions for the included patients on their socioeconomic status.
2	In the abstract, the article summary and all through in the manuscript, it would be preferable if more of the focus where on this specific study, instead of on the Intego database. Further, please see comments under the specific paragraphs of the manuscript below.	We agree. In the revised manuscript we only mentioned the Intego database to describe the recruitment of the patient population. In the method section, we have chosen to provide some information about the registration in Intego, rather than only refer to the protocol of the study. By doing so we can anticipate on questions concerning the validity of the study results. For example, by explaining that the data are historically accumulated for each individual patient. This means that even though the database started in 1994, all patient information that was registered before that time was also incorporated in Intego for the individual patients. In the revised version, we limit the information on the Intego database to the sections on study design and study limitations.
	Minor comments	
INTRO	It appears to lack a coherent rationale building to a clear research question in the introduction. The authors explore knee OA prevalence and incidence together with comorbidity and drug prescriptions, but needs to more specific in why and how these outcomes are connected to each other. What is the gap of knowledge that this article will fill?	We improved the coherence and complex interaction between prevalence, incidence and comorbidity in the second paragraph of the introduction. There are already numerous reports on multimorbidity and disease prevalence, but studies that describe time trends and patterns in GPs' prescription behavior are scare. The Intego database offers the opportunity to look at all these aspects. Adjustments in text: There are numerous reports that the number of people suffering from chronic diseases, multimorbdity and polypharmacy continues to increase, but those studies are mainly based on cross-sectional studies in different populations.[15] Time trends in the prevalence of multimorbdity and polypharmacy are scare.[16 17] The Flemish primary care-based Intego network offers an

		excellent opportunity to evaluate those trends.
INTRO	Describing and motivating the Intego database in the last sentences, focusing more on the ability to access to data than the research questions that this study aims to answer. The last paragraph in the introduction would suit better earlier in the introduction or in the discussion.	In the last sentence of the second paragraph in the introduction, we describe the importance of the Intego database and make a link to the research objectives. Intego provides the opportunity to look at the complexity at the moment of diagnosis and how the profile changes The argumentation for first choice pharmacological treatment has been moved from the introduction to the discussion.
METH	The main concern is the description of selection of the population in this study. Focus now is on the 440,140 included in the Intego database (is those induvial of all ages or is this a specific age population?), but not all of those formed the study participants, if I have understood correct. The manuscript could benefit from describing inclusion and exclusion criteria, and by using a flowchart over participants with knee OA prevalence group and the YCGs.	Based on your first major comment we rewrote the method section to give a clear explanation about the study population. The 440,140 people refer to the number of individual patients that were registered during the study period. Because Intego is an open registry, the amount of individual included patients changes every year. In the revised version, we clearly describe the study population that was used for the time trend analyses and we provide supplementary files with their details. Adjustments in text: Study population For the present study, data over a 20-year time interval from 1 January 1996 to 31 December 2015 were used. In this period, 440,140 unique patients were registered in the Intego database. The yearly contact group (=YCG) is defined as the number of different patients who consulted their GP in a given year.[23] During the study period, the YCG varied between 81,763 and 151,971 people (see supplementary file 1 for the exact number per year). Throughout the study period, 79 GP practices provided their data, with 72% contributing for 15 or more years (see supplementary file 2). Extracted information concerned data on prevalence, incidence, clinical characteristics of patients (e.g. multimorbidity) and pharmacotherapy. This study was reported in accordance with the RECORD checklist specific to observational studies using routinely collected health data.[24]
METH	Some other thoughts; is it sufficient to include only those practices that had an “optimal data registration”, is there not a risk that selection bias will occur? How is	Based on your first major comments we rewrote the paragraph in the method section that explains the data source.

	the term “optimal registration practices” defined, measured and controlled over time? Is it possible to address the coverage and completeness of the Intego database? How many GPs are excluded and why, and are there specific characteristics in those practices that are excluded at this point? Approximately, what proportion of the GPs and practices in Flanders were included in the database? Are they included or excluded on more conditions than only optimal registration? Such information would help the reader to determine if the studied population is representative. And for clarity and generalizability, it is important to take socioeconomic factors into account in the for the interpretation of the results, since there is well-known facts that both knee OA and overall poorer health are more common among socioeconomically more disadvantage individuals. What was the socioeconomic profile of the patients treated at the included compared to the non-included practices? Later in the manuscript the authors states that Intego covers more than 2% of the Flemish population. Do they have information of the socioeconomic profile of those 2 %, in comparison to the total Flemish population?	In registry-based studies, it is important to put high quality data registration as a priority. This will always provide certain selection bias in registry-based studies, but you need to be sure that the quality of the data is valid. Adjustments in text: General practices have to pass three quality criteria before being accepted as participants in Intego, what results in a reliable morbidity database.[19] In the first paragraph of the method section, we describe the data source and Intego registry. For more background on the protocol, selection procedures and representability of the Intego data, we refer to the protocol of Truyers et al. Concerning your remark to consider the social-economic factors. Intego does not provide data on socio-economic profile because it serves as a medical database. We made the comparison with 2% of the population to state that Intego population is representative for the Flemish population. In our answer to the first major comment, we added more explanation concerning the socio-economic patient profiles in Intego. Adjustments in text: Intego covers more than 2% of the Flemish population, highly representative for age and gender.[19] A sufficient sample size in primary care registration networks is advised to be about 1% of the population, which allows the study of common diseases.[46]
	Comorbidity was measured before the patients first was registered with knee OA, is that correct? So for those registered with knee OA the first years of the studied period, e.g. 1997, could this result in that those individuals were registered with fewer diseases than those who had their knee OA diagnose e.g. 2013, and effecting the results of the study?	The historical accumulation of data is indeed one of the strengths of Intego. Systematic registration started from 1994. For all new patients their full history with regard to multimorbidity is registered. This means that all the information, that is already available in the electronic health record, will also be integrated at the time of inclusion in Intego. This is a major difference with a cohort study. In our study, multimorbidity was measured for all incident cases with knee osteoarthritis.

	Do you have information about if the drugs were prescribed due to the knee OA or due to for example other painful conditions? Was the drug prescription calculated after the knee OA diagnose or before (unlike comorbidity that was calculated before)? In many countries today both acetaminophen and some oral NSAIDs are sold as over-counter drugs, which are not registered. The manuscript could benefit from describing the prescribing procedure in Belgium.	In the revised version, we made a clear differentiation between drug prescription and drug use. With the Intego database, we evaluate the behavior of the GP and the way that they prescribe drugs. The primary goal is to look at trends in their prescription patterns. In this perspective, absolute numbers are less important. The medication prescription was registered for all prevalent cases with knee OA. The prescription of a specific medication was considered positive if it was prescribed at least once in a given year. In Belgium, acetaminophen and some low oral NSAID are available over the counter. Over the counter availability, could be considered as part of self-care to reduce the burden on health care systems and increase people's choice to take informed treatment decisions. Adjustments in text: Furthermore, the discrepancy between drug prescription by the professional and drug use by the patient can be accumulated by the over the counter availability of acetaminophen and some low oral NSAID in Belgium. Over the counter availability, could be considered as part of self-care to reduce the burden on health care systems and increase people's choice to take informed treatment decisions, but the medical outcome resulting from therapeutic options bypassing the physician prescription stays a major issue.[43]
RESULT	It would be preferable to have clearer demographic data on the studied population, both those with knee OA and of those that composed the YCGs. Mean and range of age, proportion of gender, BMI, smokers and socioeconomic status if possible, before presenting the outcomes such as prevalence and incidence.	Data on smoking and BMI has indeed been collected in Intego, but there are too many missing values to draw significant conclusions. Information on socioeconomic status is currently not available, because a link with postal code and insurance reimbursement status is currently investigated. We will add this in the study limitations.
	The definition of disease burden is better suited in the method section, with an explanation under table 2. Some further questions; How large proportion of those with knee OA had	In this study, we decided to make trend analyses on the population in the Intego register. We did not define specific cohorts in the register to make comparisons

	comorbidities (is that what you mean with incidence in table 2)? Could the authors motivate why those specific comorbidities are presented in the results (compared to Supplement 1)? How about osteoarthritis in other joints than the knee? Did you considered to report trends in comorbidity and prescriptions of drugs among those that did not have a knee OA diagnose in the study, the YCG group, to be able to compare if trends were equal or unequal in those two groups? Equal positive trends could be the effect of a different and increased behavior in coding for example, and the study design could have benefit of having a control group to compare those trends with.	between patients with or without knee osteoarthritis. Concerning your question about the proportion of patients with knee OA and multimorbidity: multimorbidity was measured for all incident cases with knee OA. We added this information in the legend of Table 2. In table 2 we presented trends in comorbidities that were already described for patients with knee OA (in the introduction) Supplement 1 was added to specify how the mean disease count was calculated. In Intego we were able to look at other joint involvement of osteoarthritis because they all have a specific ICPC-2 codes (knee OA: L90; hip OA: L89, hand and others: L91). These demographic results show that hand OA is most commonly registered, followed by knee and hip AO. This information was already demonstrated in multiple epidemiological studies and therefore not included in our study.
DISC	The statistical significant differences detected in this study with positive trends in both prevalence and incidence of OA and comorbidities in the population with knee OA and drug prescriptions, are those differences of clinical significance? Or could they be the effect of other factors such as an increased coding behavior or increased knowledge among GPs about OA and diagnosing the disease. Could it, for example be financial incentives of an increased coding as there is in some countries. Please discuss further.	New disease insights on knee osteoarthritis and new possibilities with electronic health record systems will certainly influence the coding behavior of GPs. In Belgium, there are incentives for GPs if they use certain features of their electronic health record, but they do not apply on coded diagnoses for disease. It mainly concerns the percentage of electronic prescriptions for medications and reimbursement features. Thus, we think this will not have a major influence on the data registration. You are indeed right that there are many factors that influence doctors' decisions. The Intego database contains routinely collected data and is therefore a reflection of daily practice. The registering doctors do not receive instructions on medical decision making. They are only instructed to register systematically (i.e. by coded diagnoses) in their electronic health record. Nevertheless, it is of course true that many factors can lead to changes or other trends in the observed data. For example, easier registration possibilities, new issued

		guidelines, changes in reimbursement criteria for medicines, can lead to changes in the medical decision making process.Finally, the Hawthorne effect is not appropriate for the Intego database, since Intego handles strict inclusion criteria for participating GPs. Before being accepted as participants in Intego GPs have to pass three quality criteria concerning data registration.
	The authors states in line 46, page 8 that pharmacological treatment with acetaminophen should remain the first line treatment for knee OA patients. However, this may lead to a risk of miss-understanding. According to international guidelines, pharmacological treatment for knee OA should be introduced first as a secondary step, if core-treatment (first-line treatment) such as exercise therapy and information and coping strategies has failed to help the patient.	Thank you for this comment. We indeed need to clarify that acetaminophen should remain the first line pharmacological treatment. It should always be proposed additionally to the conservative treatment options (that we explained in the introduction). We will state that all patients need to be advised on the following core treatments (source NICE guidelines): • Access to appropriate information • Activity and exercise • Interventions to achieve weight loss if the person is overweight or obese
	If no data exist on the socioeconomic profile of the participants in this study, it should be addressed as a limitation in the discussion due to the known connection between both prevalence of OA, other comorbidity as well as drug consumption and socioeconomic status.	To date, we can indeed make no link between disease related information and socioeconomic profile of the patient. We addressed this in the study limitations.
TABLE1	Can table 1 and supplement 3 be presented as one table? When reading table 1, it would be preferable to also have frequencies and not only proportions when interpreting the results. And also a description/explanation to the different trend frames under the table.	In order to provide the reader with a clear overview, we provided a new supplementary file 1. This file provides a clear overview of the numerators and denominators that were used for our time trend analyses.
FIG 1	Figure 1 and 3- The figures are a little unclear to interpret regard the design of the different lines, that is not consistent with the explanation box.	In the revised version, the information In the explanation boxes is clearly described. We adjusted the design.
	Other comments	
	How has informed consent for participation in the study been collected from the involved patients?	In the Intego protocol, participating GP practices have to inform their patients that the practice participates in a morbidity registration network. Patients can choose to opt out for the possibility of their anonymized data extraction. For apparent privacy reasons each patient is assigned a random number at the moment of data extraction. This file is then encrypted and sent to an independent

		trusted third party that recodes the data and subsequently sends it to the department of general practice of the KU Leuven where it is stored into the central database. The trusted third party procedure has been in place since 2012. This procedure was by the Belgian Privacy Commission.
	The authors state the ethical approval of the Intego database, however do they have ethical approval for these specific research questions	We have an approval from the ethics committee for epidemiological research on the Intego database. This permission completely covered the current investigation.
	There is a mix of concepts regarding comorbidity, multi-morbidity, multimorbidity (including spelling of keyword).	Thank you for this remark. In literature, there are many different definitions and interpretations of this phenomenon used. This causes ambiguity. In Intego, we propose to use the term multimorbidity defined as the co-occurrence of medical conditions within one person. In the revised version we uniformly used the term multimorbidity and added definitions and references of van den Akker et al. and van Dijk et al.
	I also have some concerns about some of the references. In the introduction for example, there are references that do not appear to refer to the primary data source, but to an article that itself refers to the primary source. One example of this is in line 49, page, reference 14. Reference 8 includes no information about pharmacological management. Reference 32 reflects a slightly different population, patients on a waiting-list for replacement surgery, which should be addressed	In the revised manuscript version, we made sure that references refer to the primary source. In our earlier version, we sometimes referred to the most recent article. In the revised version: 1/ the reference 14 now refers to the article of Reeuwijk et al., 2010. 2/ in the introduction we added a sentence to describe the core conservative management options for knee OA. We replaced reference 8 to this sentence. 3/ In the first manuscript version we used reference 32 to describe comorbidities. In the revised version, we described common comorbidities in the introduction and referred to Reeuwijk et al. Thus, we removed this citation. In the discussion, we added the systematic review of Podmore et al. that refers to the risks of comorbidity for THR and TKR surgery.

REVIEWER 2: Wei Wang		
	Minor comments	Response
1	In the methods section, the authors need to provide some details regarding how to evaluate the incidence;	We added details concerning the definition and calculation of the incidence in the method section. Adjustments in text:

		The incidence in Intego is calculated as the number of new cases of disease divided by the person-time magnitude. Calculating disease prevalence and incidence requires both a numerator (number of persons with a disease) and a matching denominator (the 'population at risk' being studied). Determining primary care practice denominators is challenging.[25] The yearly contact group (YCG) are the patients, which visit the practice at least once in a given year. The Practice Population consists of the YCG plus the group, which does not visit their general practitioner in a given period.
2	Please keep the table title for Table 1 and Table 3 consistent, specifically, for the fourth column, Table 3 should also be presented as Overall Trend;	In the revised version, all titles in the table mention that it concerns trend analyses. In addition, we changed the terminology in column four of table 3 to 'overall trend'.
3	For the joinpoint regression analysis in Table 1 and Table 3, the authors need to provide the justification in the statistical analysis method section to justify why at most three trends were provided.	The default value for the maximum number of Joinpoints depends on the number of data points; also, a Joinpoint cannot occur within a user-specified number of data points from the beginning or end of a series and there must be at least a user-specified number of data points between two Joinpoints. We added this information in the method section.
4	I did not find the ¥ foot note in the Table 3. Please add it	Thank you. This was added in the last column.

VERSION 2 – REVIEW

REVIEWER	wei wang U S FOOD AND DRUG ADMINISTRATION
REVIEW RETURNED	28-Sep-2019

GENERAL COMMENTS	The revised manuscript addressed all my previous comments.

REVIEWER	Kristin Gustafsson Department of Medical and Health Sciences, Linköping University, Sweden
REVIEW RETURNED	03-Oct-2019

GENERAL COMMENTS	Thank you for the opportunity to once again review the manuscript entitled "The epidemiology of knee osteoarthritis in general practice: a registry-based study". The authors have revised and improved the manuscript according to previous comments, however some specific comments and issues still remain that I would like to address.

	Study population and study design: Register-based studies provide an exciting opportunity to study real-world data from daily clinical practice, and the possibility to use already collected data to follow large samples sizes over long periods. I agree on, that in registry-based studies, it is important to put high quality data registration as a priority. How the Intego database has handled this is well described, and the quality check of the included participants (GPs and practices) is a strength in this set-up. Another strength with registry-based research is the often high external validity compared to RCT-designs. Therefore, in registry-based research, it is also important to know how representative the included patients are for the population you want to draw your conclusions on. Since this study not aiming to study the quality of registration, but trends in prevalence of knee OA and other comorbidity, and the results and the conclusion of the study reflects back to an individual level (that eg. knee OA and multimorbidity has increased) it would be preferable to have more information of the population that the authors draw their conclusion from. At this moment, I find that this is still vaguely described in this study. For example; to only include GPs and practices with optimal registration will of course lead to high quality of the dataset but at the same time you should be humble to the fact that those GPs and practices that do not fulfilling this selection may or may not have patients from a slightly different population with regards to, for example socioeconomic factors. So information not only about quality of data but also how representative the included population is with information such as for example coverage (how many units that are included) would help the reader understanding the selected population. To determine if the included population is representative for 1) general patient in a primary care setting, 2) the Belgium population or 3) the Flemish population, or 4) for the Intego database. I still interpret that the information about the study population is missing in the manuscript and if that remains the authors should be more careful, less generable, with what population they express themselves about in the conclusion, including being more humble the use of strong expressions through-out the manuscript, such as excellent and perfectly, when describing the Intego database. Yearly contact group: By adding the supplementary file 1 and the description in the method section, the yearly contact group, are now more clearly defined. As the authors state, it is challenging to determine “the population at risk” in primary practice care. They have in this study chosen to use the YCG as the denominator. However, with a disease that is so strongly associated to age, it can be argued if also children should be included in the YCG (population at risk). Wouldn’t it be preferable to instead use only, for example the YCG ≤25 years? Then results of this study would be easier to compare to other prevalence studies of knee OA. In addition, several of the comments in the previous review are discussed in the reply-letter without actions in the manuscript, or in the declarations section to the manuscript. For example; changes in coding behavior, lack of socioeconomic data (mentioned but not discussed) informed consent, ethical approval for this specific study.

	And the manuscript also still needs to be reviewed and on detail level. Examples on details discovered during the reading process: Affiliations: No author has been assigned the affiliation number 4. Figures: Both figure 1 and figure 3 are missing axis titles on the y-axis. Tables: Express that disease burden is in mean value in table 2, and please provide some complementary distribution measures to this mean value (eg. SD). Supplementary files: Please provide supplementary file 1 and 5 with proportions (%) as well, and not only report frequencies. Regarding supplementary file 5: for example: the total prevalence of knee OA in 1996 n=1596, however when summarizing the prevalence in the reported age cohorts n=1423. Is the rest <25, that don't seem correct. Definitions: There is still a mix of definitions regarding comorbidity and multi-morbidity in the manuscript, the tables and the supplementary files. References: Regarding reference number 12 "almost all patients with OA suffer from at least one comorbid disease". I find this a central reference in the introduction. It is however important to be aware of that this refers to an elderly population of hip and knee OA patients. Regarding reference 39, referring to the risk of comorbidity for THR and TKR surgery; you may have misunderstood my previos comment. I cannot see that this sentence is nessesary for this manuscript, since a rather small proportion (approximaltely 10-15%) of patients with knee OA will be in need of replacement surgery.

VERSION 2 – AUTHOR RESPONSE

REVIEWER 1: Kristin Gustafsson	
Additional comments	Response
Study population and study design: Register-based studies provide an exciting opportunity to study real-world data from daily clinical practice, and the possibility to use already collected data to follow large samples sizes over long periods. I agree on, that in registry-based studies, it is important to put high quality data registration as a priority. How the Intego database has handled this is well	We thank the reviewer for this very relevant question on the selection of the practices and the study population. The reviewer clearly described the opportunities of registry-based studies and the importance of high quality data registration. Registries can provide externally valid long-term comparative effectiveness data.

described, and the quality check of the included participants (GPs and practices) is a strength in this set-up. Another strength with registry-based research is the often high external validity compared to RCT-designs. Therefore, in registry-based research, it is also important to know how representative the included patients are for the population you want to draw your conclusions on. Since this study not aiming to study the quality of registration, but trends in prevalence of knee OA and other comorbidity, and the results and the conclusion of the study reflects back to an individual level (that e.g. knee OA and multimorbidity has increased) it would be preferable to have more information of the population that the authors draw their conclusion from. At this moment, I find that this is still vaguely described in this study. For example; to only include GPs and practices with optimal registration will of course lead to high quality of the dataset but at the same time you should be humble to the fact that those GPs and practices that do not fulfilling this selection may or may not have patients from a slightly different population with regards to, for example socioeconomic factors. So information not only about quality of data but also how representative the included population is with information such as for example coverage (how many units that are included) would help the reader understanding the selected population. To determine if the included population is representative for 1) general patient in a primary care setting, 2) the Belgium population or 3) the Flemish population, or 4) for the Intego database. I still interpret that the information about the study population is missing in the manuscript and if that remains the authors should be more careful, less generable, with what population they express themselves about in the conclusion, including being more humble the use of strong expressions through-out the manuscript, such as excellent and	The reviewer requested more information on the selection of the GP practices because this is important for the (external) validity and representativeness. Indeed, the GPs who participate in the epidemiological network have been selected based on the quality of their registration and therefore it is not a randomly chosen group. However, it can probably be assumed that those who register only differ from their colleagues in the fact that they are somewhat more convenient in working with medical software, but not in their medical practice and not in the composition (e.g. morbidity) of their patients. In this way, it is possible with this registration network to generate basic epidemiological data of almost all first-line disorders, including incidence and prevalence figures by age and gender and perform trend analyses. In the discussion of our manuscript, we added information on the external validity and representativeness for the Flemish population: Intego covers more than 2% of the Flemish population, representative in terms of age and gender. Deckers et al. (Deckers JG, Paget WJ, Schellevis FG, et al. European primary care surveillance networks: their structure and operation. Fam Pract. 2006;23:151-8) performed an inventory of European surveillance registration networks and formulated minimal standard criteria for these networks. When fulfilling identical minimal criteria they can provide comparable estimates of morbidity, ultimately leading to improved national and European surveillance. For continuous surveillance networks, they advise that the sample size should be around 1% of the population, which will allow the study of common diseases (e.g. knee osteoarthritis). We added this information in the paragraph with strengths and limitations: Intego covers more than 2% of the Flemish population, representative in terms of age and gender. Deckers et al. updated an inventory of primary care surveillance networks in Europa and formulated minimal standard criteria for these networks. When fulfilling identical minimal criteria networks can provide comparable estimates of morbidity, ultimately leading to improved national and European surveillance. For continuous surveillance networks, they advise that a sufficient sample size is approximately 1% of the population, which will allow the study of common diseases. Concerning your question for the representativeness of the Intego data for the Belgium population. In Belgium,

perfectly, when describing the Intego database.	we have a Flemish and French speaking community. Both regions have partial autonomy on their organization of healthcare. Intego is funded by the Flemish government. To date, only Flemish GPs take part in this registration network. Since primary care can be organized differently in both regions, we do not extrapolate conclusions from Intego for the entire country, but only for the Flemish region. External validation of the Intego database has been examined by means of national and international comparisons. Truyers et al. (Truyers C, Goderis G, Dewitte H, et al. The Intego database: background, methods and basic results of a Flemish general practice-based continuous morbidity registration project. BMC Med Inform Decis Mak. 2014;14:48.) described in their methodological paper the comparison with (inter)national networks. The results were comparable for the corresponding research domains. Nationally, overall cancer incidence is compared to the Limburg Cancer Registry (LIKAR). Incidence rates of influenza and acute respiratory illness are compared to the European Influenza Surveillance Scheme, EISN. Data found in Intego are routinely compared to the 'Tweede nationale studie', studying morbidity and care in Dutch general practice (Van der Linden M, Westert G, De Bakker D, et al. [Second national study in diseases and practice in general practice. Complaints and diseases in the population and in general practice] Utrecht / Bilthoven, NIVEL / RIVM. 2004.). Several diseases were compared to the Dutch CMR (Nijmegen) and RNH (Maastricht). (Van de Lisdonk E, van den Bosch W: Ziekten in de huisartspraktijk., 4 edn. Maarssen: Elsevier gezondheidszorg; 2013.) Adjustment in text (method section, first paragraph): The design, selection process, quality control procedures and comparability with other (inter)national registration networks were described in detail previously. The reviewer suggested tempering the use of strong expressions: words like 'excellent' and 'perfectly' could be seen as prejudicial in the method section and were therefore removed or replaced by neutral terminology.
Yearly contact group: By adding the supplementary file 1 and the description in the method section, the yearly contact group, are now more clearly defined. As the authors state, it is challenging to determine "the population	We are pleased to read that the yearly contact group is clearly defined in the method section. As the reviewer suggested, cut-off points at 25 years are highly recommended for primary care based surveillance networks. Supplementary file 1 has been adjusted accordingly.

at risk" in primary practice care. They have in this study chosen to use the YCG as the denominator. However, with a disease that is so strongly associated to age, it can be argued if also children should be included in the YCG (population at risk). Wouldn't it be preferable to instead use only, for example the YCG ≤25 years? Then results of this study would be easier to compare to other prevalence studies of knee OA.	
In addition, several of the comments in the previous review are discussed in the reply-letter without actions in the manuscript, or in the declarations section to the manuscript. For example; changes in coding behavior, lack of socioeconomic data (mentioned but not discussed) informed consent, ethical approval for this specific study.	We thank the reviewer for this remark. Since we thought that the response to reviewers' letters are accessible for the readers, we did not incorporate all previous answers in the main manuscript. Based on your suggestions we made the following adjustments in the main document: 1/ Concerning your question about the changes in coding behavior: In our previous response, we explained that in Belgium, there are incentives for GPs if they use certain features of their electronic health record, but they do not apply on coded diagnoses for disease. 2/ Concerning your questions about the lack of socioeconomic data. In the previous response, we replied that due to privacy, socioeconomic patient profiles are not available on patient level. We propose to add the following clarification in the manuscript. Adjustments in text (paragraph strengths & limitations): This information is available on practice level and based on the postal code. However, since GP practices in Flanders often take care of patients living in neighboring municipalities and people living within a specific postal code can have a different socioeconomic status, we in general do not use this information in our analyses. In the discussion, we added a limitation that we were not able to draw firm conclusions for the included patients on their socioeconomic status. 3/ Concerning your question about the informed consent, we added the following explanation in the manuscript Adjustments in text (footnotes, ethics approval):

	In the Intego protocol, participating GP practices have to inform their patients that the practice participates in a morbidity registration network. Patients can choose to opt out for the possibility of their anonymized data extraction. 4/ Concerning your question about the specific ethical approval, we added the following explanation in the manuscript: Adjustments in text (footnotes, ethics approval): This permission completely covered the current investigation.
And the manuscript also still needs to be reviewed and on detail level. Examples on details discovered during the reading process: Affiliations: No author has been assigned the affiliation number 4.	The affiliation number 4 was added to the corresponding author Rosella Hermens.
Figures: Both figure 1 and figure 3 are missing axis titles on the y-axis.	The axis titles on the y-axis are added in the second revision. For figure 1 it concerns %, for figure 2 it concerns ‰.
Tables: Express that disease burden is in mean value in table 2, and please provide some complementary distribution measures to this mean value (eg. SD).	1/ We added a legend to describe the mean value and provided a reference to supplementary file 3. 2/ The SD values were added in Table 2.
Supplementary files: Please provide supplementary file 1 and 5 with proportions (%) as well, and not only report frequencies.	In supplementary file 1 and 5 the proportions are now prescribed as well. In the legend of supplementary file 1 we clearly state that these proportions describe the data from the Intego registry and are not standardized for the total Flemish population.
Regarding supplementary file 5: for example: the total prevalence of knee OA in 1996 n=1596, however when summarizing the prevalence in the reported age cohorts n=1423. Is the rest <25, that don't seem correct	Indeed, in previous versions we extracted the data from age cohorts < 25 years of age. Closer look at the coding taught us that this age cohort is highly susceptible for misclassification (e.g., juvenile arthritis or traumatic lesions can be classified as knee osteoarthritis). The youngest age cohort was previously not mentioned in the supplementary files. Based on your comment, we propose two modifications: 1/ We already added the possibility of misclassification in the study limitations, but now clearly described that we found higher risk for misclassification in the younger age cohorts. 2/ Based on your suggestions, we added the age cohorts and proportions to supplementary file 5 so the reader will have a clear overview how the total numbers are calculated.

Definitions: There is still a mix of definitions regarding comorbidity and multi-morbidity in the manuscript, the tables and the supplementary files.	In our previous response letter, we explained the different definitions and interpretations between comorbidity and multimorbidity. This causes ambiguity. In Intego, we propose to use the term multimorbidity defined as the co-occurrence of medical conditions within one person. In the first revised manuscript, we proposed to keep three specific references for comorbidity as it references to a specific disease in the corresponding sentence. However, as you suggest, it is better to be consequent and so we uniformly modified the terminology to multimorbidity in all tables and supplementary files.
References: Regarding reference number 12 “almost all patients with OA suffer from at least one comorbid disease”. I find this a central reference in the introduction. It is however important to be aware of that this refers to an elderly population of hip and knee OA patients.	You are indeed correct that it is quite dangerous to make general assumptions concerning multimorbidity. Studies of patient with knee osteoarthritis often use different measuring methods to compare multimorbidity (e.g. they can use different sets of diseases to define multimorbidity) or they look at specific patient groups (e.g. specific age cohorts, preoperative patients, etc…). Therefore, we removed this sentence from our introduction and propose to make the following adjustments in text and references. Adjustment in text (introduction): OA is a disease with one of the highest rates of multimorbidity in patients who are managed in general practice. (van Oostrom SH, Picavet HS, de Bruin SR, et al. Multimorbidity of chronic diseases and health care utilization in general practice. BMC Fam Pract. 2014;15:61; Kadam UT, Jordan K, Croft PR. Clinical comorbidity in patients with osteoarthritis: a case-control study of general practice consulters in England and Wales. Ann Rheum Dis. 2004;63:408-14.)
Regarding reference 39, referring to the risk of comorbidity for THR an d TKR surgery; you may have misunderstood my previous comment. I cannot see that this sentence is necessary for this manuscript, since a rather small proportion (approximately 10-15%) of patients with knee OA will be in need of replacement surgery.	We indeed misunderstood your previous comment. At this location, this sentence is not used in the right context. Thus, we propose do remove this sentence and citation.

VERSION 3 – REVIEW

REVIEWER	Kristin Gustafsson Division of Physiotherapy, Department of Medical and Health Sciences, Linköping University, Linköping, Sweden and Department of Physiotherapy, Rehabilitation Centre, Ryhov County Hospital, Jönköping, Sweden
REVIEW RETURNED	05-Nov-2019

GENERAL COMMENTS	Dear authors, I have send my comments to the editor