Article details: 2013-0034	
Title	Secular trends in end-stage renal disease requiring dialysis in Manitoba, Canada: a population-based study
Authors	Paul Komenda, Nancy Yu, Stella Leung, Keevin Bernstein, James Blanchard, Manish Sood, Claudio Rigatto, Navdeep Tangri
Reviewer 1	Sabrina Pit
Institution	University Centre for Rural Health, University of Sydney, New South Wales, Australia
General comments	Comments: General comments: The paper is relevant and the idea is well thought out. However, I believe the execution of the methods and content needs a lot more attention to detail. The paper has errors in terms of referencing figures/ tables. Data described in the text does not match up with the figures and tables. There are also spelling and grammar errors that need to be fixed up. More importantly, I had real trouble understanding the validation methods section and its results. Because the validation method appears to determine the rest of the paper, I think it is critical that the reader can easily understands this section. Introduction: • P3 line 20, can you please give the incidence rates numbers (that have slowed down) • P4, line 45, reference not formatted properly Methods: • P5, line 5, can you please explain why you choose 90 days and 21 days apart. This is not clear. Results: • P6,line 30: table 2 in text is currently Appendix Table. This needs to be fixed up • Line 32-36: I cannot find any of these numbers in the table/Appendix, so I am unclear where these numbers come from? • Line 44 to 45: The data is not shown for yearly increments. What is this based on? It looks like your sensitivity is lowest when you use 3 year data retrieval periods not one year periods? • Line 50-56: so you base your best case definition on kappa and accuracy, so why do you display this very large table? • What are the implications of this section on the rest of your paper? • Do the numbers change dramatically in the rest of your analyses (trends etc) if you select another case definition and time period? Maybe a sensitivity analyses is required here, as I am not convinced or clear how you determined your final case definition? • Do sensitivity and specificity change over a particular time period (eg does it get better overtime)? • Page 7, line 35 – 38: there is no peak in Figure 2 for the group 65-74 in the line '1989' which I assume represents the eighties? • Page 7, line 49: 10/100,000 looks more like 25/100,000 for the rural remote north group, and 120 was reached in 2009, in 2010 it declined according to figure 3a???? • What's the rational for the time periods you used; why did not you do: 2010 (1 yr) , 2008-2010 (3yr), 2006-2010 (5 yr), 2003-2010 (7 yr). Discussion: • P8: ESRD is ESKD • P10, line 1: Would providers wait years to submit claims? That seems unlikely to me, don't they submit claims to get paid?
Reviewer 2	Alice Dragomir
Institution	Surgery/Urology, McGill University, Montréal, Quebec
General comments	General comments: The manuscript 'Secular trends in ESKD incidence and prevalence in Canada over 27 years: and emerging epidemic in the North" is a descriptive study of a cohort of 9,489 individuals identified in the Manitoba Health Physician Claims (MHPC) database with at least one record for dialysis from April 1, 1984 through March 31, 2011. The primary objective of this study was to examine the incidence, prevalence and geographic trends of ESKD over 27 years using validated administrative case definitions. The ESKD cases identified in the MHPC database according to four case definitions were compared to the records of the Manitoba Renal Program (MRP) Dialysis Registry.

The main finding of this paper is that over a 27 years period, there is a disproportionate increase in the rate of ESKD in the remote, rural North of Manitoba. In addition, while the incidence of ESKD doubled from 1984 to 2010, in the same period the prevalence of ESKD increased 8 times.
My specific comments about this manuscript include the following:
Major concerns
1. I suggest the authors to reformulate the title and the objectives to better reflect the 2 distinguished parts of this study: first, the validation of ESKD case definitions, and second, the trends in ESKD incidence and prevalence.
2. The assumption of Poisson distribution to calculate the 95% confidence intervals needs to be explained (Page 6, lines 30-31).
3. In Page 6, lines 31-33 it was mentioned ''Temporal trends were examined in the age-adjusted incidence and prevalence using a linear regression model.'' Yet, no results were given for this analysis. I suggest removing all statistical analyses from the Methods section which are not presented in the Results section.
4. The results presented in page 7 paragraph 4 are not matching with the data presented in Table 2. The accuracy and agreement scores: values 0.84 and 0.63 with 0.87 and 0.67 from table, and 0.93 and 0.82 with 0.96 and 0.85, respectively; please verify which one are the valid values. In addition, in line 52, the interval 2004-2009 seems to be 2004-2010 in the table.
5. In the Methods section (page 6, lines 20-23) it was specified that the incidence rate of ESKD was calculated starting with 1989, with a washout period from 1984-1988. Yet, in the Results section (page 8, paragraph 1) the value of 16.88/100,000 was reported as age adjusted incidence of ESKD in 1984. Please explain.
6. Results (page 8, lines 33-35): ''Prevalence rates of ESKD appear again to be increasing with age with rates of 8% in the 75-84 age deciles in comparison with rates of < 1% in the same age group 27 years ago.'' This sentence needs to be revised: '' … increasing with time …'' instead of '' … increasing with age …''.
7. Results (page 8, lines 33-38): ''Finally, the peak prevalence of ESKD by age has also shifted over the last two decades, with the peak now being 75-84, as compared with 65-74 in the 1980s''. This text is not matching with the figure 2. First, in the figure there is no data shown for the 1980 to 1989 period. Second, over the entire period from 1989 to 2010, the peak prevalence of ESKD was observed in the group of age 75-84. I suggest to authors to reformulate the sentence accordingly.
8. Results (page 8, lines 47-49). As there is a washout period from 1984-1988, how the incidence rate of 10-20/100,000 in early 1980's in the urban and southern/mid rural region of Manitoba was calculated? Or, the incidence of 10/100,000 in 1984 in the rural remote north of Manitoba? See also the 5th comment. Furthermore, there is no data shown in Figure 3b for the period before 1989.
9. Whereas the authors provided discussion in relation with potential explanations of the increase of ESKD incidence (on page 9, lines 43-50), the paper lacks discussion related to the discrepancy between the trends of ESKD prevalence and incidence rates. It is well known that the prevalence rate is proportional with the incidence rate as well as with the duration of the disease. If the incidence rate has doubled, how the authors explain this excessive increase of the prevalence rate? (please see Figure 1 and page 8, paragraph 1)
Minor comments
1. CKD abbreviation was used for the first time in page 4, line 43, but was not previously defined.
2. Because of the washout period from 1984-1988, the trend of ESKD incidence was over a 22 years period and not over a 27 years period. Please make the appropriate modification on the manuscript text and title.
3. Page 9, line 57. There is a missing coma after ''the highest incidence''.
Reviewed by:
Alice Dragomir, MSc, PhD
Assistant Professor, McGill University
Scientist, The Research Institute of the McGill University Health Center

Please note that I have no conflict of interest in reviewing this manuscript.

General comments:
The authors submitted a revised version of the manuscript ''Secular trends in ESRD incidence and prevalence in Canada over 27 years: and emerging epidemic in the North". The main objective of this study was to describe the long-term secular and geographic trends in ESRD over 22 years in a single provider Canadian healthcare system. In addition, a separate manuscript (" Determining the optimal administrative case definition for End Stage Renal Disease'') has been submitted by the authors to address the objective of developing and validating administrative case definitions for

	ESRD in the province of Manitoba. The authors have not provided a cover letter describing the point by point raised by the reviewer. Major concerns: 1. The authors have based the ESRD case definition of the first manuscript, on the findings obtained in the second manuscript. This has been mentioned in page 6 paragraph 3: ''The detailed methods of validating administrative case definitions for chronic dialysis are described in a separate manuscript''. I suggest that a reference should be mentioned, or the authors should declare the ESRD case definition as considered in this manuscript. This paragraph should be reformulated. 2. Page 6, paragraph 3, the values (47.6% sensitive and 99.8% specific) are still inconsistent with the Table. These have been changed in the abstract but not in the manuscript text. 3. Last phrase of the paragraph 3, page 6 is incomplete. 4. The results section of the abstract should not include findings from the second manuscript. The phrase ''The most specific and least sensitive case definition was any two dialysis treatment claims > 90 days apart with no gaps in treatment greater that 21 days (97.5% specific, 52.7% sensitive).'' should be removed. 5. Page 4, paragraph 3, and page 6, paragraph 2, the selection period (April 1, 1984 through March 31, 2011) is different from the one specified in the abstract. Reviewed by Alice Dragomir, MSc, PhD Assistant Professor, McGill University Scientist, The Research Institute of the McGill University Health Center Please note that I have no conflict of interest in reviewing this manuscript.
Author response	Reviewer: Sabrina Pit, University of Sydney Comments to the Author General comments: The paper is relevant and the idea is well thought out. However, I believe the execution of the methods and content needs a lot more attention to detail. The paper has errors in terms of referencing figures/ tables. Data described in the text does not match up with the figures and tables. There are also spelling and grammar errors that need to be fixed up. More importantly, I had real trouble understanding the validation methods section and its results. Because the validation method appears to determine the rest of the paper, I think it is critical that the reader can easily understands this section. This comment was brought up by the editors as well. We have now split the paper into two separate manuscripts: one describing the validation of the case definition and one describing the interesting secular trends in epidemiology for Manitoba. Introduction: 1. P3 line 20, can you please give the incidence rates numbers (that have slowed down) 2. P4, line 45, reference not formatted properly References have been thoroughly checked and reformatted. Methods: 3. P5, line 5, can you please explain why you choose 90 days and 21 days apart. This is not clear. The case definitions chosen were derived from conventional definitions for chronic ESRD typically reported by large registries such as the United States Renal Data System and Canadian Organ Replacement Registry. These case definitions have been employed in other validation studies (Clement et al.). The rationale behind these will be described in detail in the now separate VALIDATION manuscript. Results: 4. P6,line 30: table 2 in text is currently Appendix Table. This needs to be fixed up. As the papers are now split into two, all Tables are renumbered and checked for accuracy in referencing. Thank-you for catching this.

	5. Line 32-36: I cannot find any of these numbers in the table/Appendix, so I am unclear where these numbers come from? These numbers are now in the VALIDATION manuscript and have been removed. 6. Line 44 to 45: The data is not shown for yearly increments. What is this based on? It looks like your sensitivity is lowest when you use 3 year data retrieval periods not one year periods? These are now discussed in the VALIDATION manuscript. 7. Line 50-56: so you base your best case definition on kappa and accuracy, so why do you display this very large table? These are now discussed in the VALIDATION manuscript. 8. What are the implications of this section on the rest of your paper? These are now discussed in the VALIDATION manuscript. 9. Do the numbers change dramatically in the rest of your analyses (trends etc) if you select another case definition and time period? Maybe a sensitivity analyses is required here, as I am not convinced or clear how you determined your final case definition? These are now discussed in the VALIDATION manuscript. 10. Do sensitivity and specificity change over a particular time period (eg does it get better overtime)? These are now discussed in the VALIDATION manuscript. 11. Page 7, line 35 – 38: there is no peak in Figure 2 for the group 65-74 in the line '1989' which I assume represents the eighties? That is correct. 12. Page 7, line 49: 10/100,000 looks more like 25/100,000 for the rural remote north group, and 120 was reached in 2009, in 2010 it declined according to figure 3a???? There is some cyclic variation as in previous years. As the denominator population in this group is smaller, it is subject to more dramatic variability in incidence. 13. What's the rational for the time periods you used; why did not you do: 2010 (1 yr) , 2008-2010 (3yr), 2006-2010 (5 yr), 2003-2010 (7 yr). These are now discussed in the VALIDATION manuscript. Discussion: 14. P8: ESRD is ESKD All terms are now changed to ESRD to keep standard. 15. P10, line 1: Would providers wait years to submit claims? That seems unlikely to me, don't they submit claims to get paid? These are now discussed in the VALIDATION manuscript. Reviewer: Alice Dragomir, McGill University Comments to the Author General comments: The manuscript 'Secular trends in ESKD incidence and prevalence in Canada over 27 years: and emerging epidemic in the North" is a descriptive study of a cohort of 9,489 individuals identified in the Manitoba Health Physician Claims (MHPC) database with at least one record for dialysis from April 1, 1984 through March 31, 2011. The primary objective of this study was to examine the incidence, prevalence and

	geographic trends of ESKD over 27 years using validated administrative case definitions. The ESKD cases identified in the MHPC database according to four case definitions were compared to the records of the Manitoba Renal Program (MRP) Dialysis Registry. The main finding of this paper is that over a 27 years period, there is a disproportionate increase in the rate of ESKD in the remote, rural North of Manitoba. In addition, while the incidence of ESKD doubled from 1984 to 2010, in the same period the prevalence of ESKD increased 8 times. My specific comments about this manuscript include the following: Major concerns 1. I suggest the authors to reformulate the title and the objectives to better reflect the 2 distinguished parts of this study: first, the validation of ESKD case definitions, and second, the trends in ESKD incidence and prevalence. [Editors' note: We would prefer two separate submissions if the definition has not been validated, as described previously.] As suggested by the editors and other reviewers, we have now split this into two separate manuscripts. 2. The assumption of Poisson distribution to calculate the 95% confidence intervals needs to be explained (Page 6, lines 30-31). We have added the following to the methods: "Ninety-five percent confidence intervals were calculated assuming a Poisson distribution as new ESRD cases per year occur with some irregularity." 3. In Page 6, lines 31-33 it was mentioned ''Temporal trends were examined in the age-adjusted incidence and prevalence using a linear regression model.'' Yet, no results were given for this analysis. I suggest removing all statistical analyses from the Methods section which are not presented in the Results section. We have deleted this line. 4. The results presented in page 7 paragraph 4 are not matching with the data presented in Table 2. The accuracy and agreement scores: values 0.84 and 0.63 with 0.87 and 0.67 from table, and 0.93 and 0.82 with 0.96 and 0.85, respectively; please verify which one are the valid values. In addition, in line 52, the interval 2004-2009 seems to be 2004-2010 in the table. This has been updated and moved to the VALIDATION paper. 5. In the Methods section (page 6, lines 20-23) it was specified that the incidence rate of ESKD was calculated starting with 1989, with a washout period from 1984-1988. Yet, in the Results section (page 8, paragraph 1) the value of 16.88/100,000 was reported as age adjusted incidence of ESKD in 1984. Please explain. The washout period was employed and all rates reported should start in 1989. The manuscript has been amended to reflect this and the data presented in the figures. Thank-you for pointing out this error. 6. Results (page 8, lines 33-35): ''Prevalence rates of ESKD appear again to be increasing with age with rates of 8% in the 75-84 age deciles in comparison with rates of < 1% in the same age group 27 years ago.'' This sentence needs to be revised: '' … increasing with time …'' instead of '' … increasing with age …''. "age" has been replaced with "time". Thank-you for pointing out this error. 7. Results (page 8, lines 33-38): ''Finally, the peak prevalence of ESKD by age has also shifted over the last two decades, with the peak now being 75-84, as compared with 65-74 in the 1980s''. This text is not matching with the figure 2. First, in the figure there is no data shown for the 1980 to 1989 period. Second, over the entire period from 1989 to 2010, the peak prevalence of ESKD was observed in the group of age 75-84. I suggest to authors to reformulate the sentence accordingly. The manuscript has been amended to reflect the time period actually reported. The sentence pertaining to peak of age categories has been deleted.

	8. Results (page 8, lines 47-49). As there is a washout period from 1984-1988, how the incidence rate of 10-20/100,000 in early 1980's in the urban and southern/mid rural region of Manitoba was calculated? Or, the incidence of 10/100,000 in 1984 in the rural remote north of Manitoba? See also the 5th comment. Furthermore, there is no data shown in Figure 3b for the period before 1989. "1984" and "early 1980's" have been changed to "1989" to correctly reflect the data presented. 9. Whereas the authors provided discussion in relation with potential explanations of the increase of ESKD incidence (on page 9, lines 43-50), the paper lacks discussion related to the discrepancy between the trends of ESKD prevalence and incidence rates. It is well known that the prevalence rate is proportional with the incidence rate as well as with the duration of the disease. If the incidence rate has doubled, how the authors explain this excessive increase of the prevalence rate? (please see Figure 1 and page 8, paragraph 1) The first paragraph of the discussion now has the additional sentence: "The increase in prevalence rate of ESRD is dramatically outpacing the increase in incidence indicating that at least some patients are experiencing improved survival." Minor comments 1. CKD abbreviation was used for the first time in page 4, line 43, but was not previously defined. Thank-you. This has been corrected. 2. Because of the washout period from 1984-1988, the trend of ESKD incidence was over a 22 years period and not over a 27 years period. Please make the appropriate modification on the manuscript text and title. As above. The text has been amended. 3. Page 9, line 57. There is a missing comma after ''the highest incidence''. The comma has been added.
	Reviewer 1: Alice Dragomir, MSc, PhD Assistant Professor, McGill University Scientist, The Research Institute of the McGill University Health Center Comments to the Author General comments: The authors submitted a revised version of the manuscript ''Secular trends in ESRD incidence and prevalence in Canada over 27 years: and emerging epidemic in the North". The main objective of this study was to describe the long-term secular and geographic trends in ESRD over 22 years in a single provider Canadian healthcare system. In addition, a separate manuscript (" Determining the optimal administrative case definition for End Stage Renal Disease'') has been submitted by the authors to address the objective of developing and validating administrative case definitions for ESRD in the province of Manitoba. Major concerns: 1. The authors have based the ESRD case definition of the first manuscript, on the findings obtained in the second manuscript. This has been mentioned in page 6 paragraph 3: ''The detailed methods of validating administrative case definitions for chronic dialysis are described in a separate manuscript''. I suggest that a reference should be mentioned, or the authors should declare the ESRD case definition as considered in this manuscript. This paragraph should be reformulated. This concern was also noted by the editor and the paragraph referenced here (p.6 paragraph 3) has been moved to the Methods section as suggested.

	2. Page 6, paragraph 3, the values (47.6% sensitive and 99.8% specific) are still inconsistent with the Table. These have been changed in the abstract but not in the manuscript text. We have corrected this discrepancy in the abstract 3. Last phrase of the paragraph 3, page 6 is incomplete. This has been corrected and the paragraph moved to Methods section as above. 4. The results section of the abstract should not include findings from the second manuscript. The phrase ''The most specific and least sensitive case definition was any two dialysis treatment claims > 90 days apart with no gaps in treatment greater that 21 days (97.5% specific, 52.7% sensitive).'' should be removed. This has been corrected. 5. Page 4, paragraph 3, and page 6, paragraph 2, the selection period (April 1, 1984 through March 31, 2011) is different from the one specified in the abstract. This has been corrected.