PEER REVIEW HISTORY

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ARTICLE DETAILS

| TITLE (PROVISIONAL) | Association between chronic bladder catheterization and bladder cancer incidence and mortality: A population-based retrospective cohort study in Ontario, Canada |
|---------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| AUTHORS             | Hird, Amanda; Saskin, Refik; Liu, Ying; Lee, Yuna; Ajib, Khaled; Matta, Rano; Kodama, Ronald; Carr, Lesley; Kulkarni, Girish; Herschorn, Sender; Narod, Steven A.; Nam, Robert |

VERSION 1 – REVIEW

| REVIEWER           | Husmann, Douglas A  
|                   | Mayo Clinic Rochester, Urology |
|                   | REVIEW RETURNED      | 22-Apr-2021 |
| GENERAL COMMENTS   | MS ID: bmjopen-2021-050728 |
|                   | Title: Association between chronic urinary catheterization and bladder cancer incidence and mortality: A population-based study |
|                   | Abstract:  
|                   | 1. See comment #1 under Article summary; it was not until I read the article summary that I realized the study population included individuals with indwelling catheters and on CIC. I would suggest the authors somehow have this fact in the title and clarify this point in the abstract; Although I understand the merits of this study, the real question that needs to be answered is to compare patients with an indwelling catheter to patients with similar systemic problems managed differently, e.g., patients with NGB managed with indwelling catheter vs. intermittent catheterization. Several studies have documented that patients with neurogenic bladders have a higher risk of malignancy; one of the critical yet unanswered questions is there a difference in malignancy potential in patients managed with CIC vs. indwelling catheter. This paper cannot address this clinically pertinent question.  

2. The authors will need to define UTI; in our experience, >85% of our bacterial cultures are positive in patients with CIC, >90% with an indwelling catheter. Are we talking about bacterial colonization, symptomatic UTI, or, as I presume, in a study based on diagnostic codes, any pharmacologically treated bacteriuria? This fact should be stated in the abstract.  

3. Since tobacco usage is the primary cause of bladder cancer, is this study controlled for tobacco usage between the two study populations? I do note the authors address this point later in their |
Article Summary:
1. In reviewing this paper, it is at this point that I became aware that the “chronic urinary catheterization group” included patients with an indwelling catheter and intermittent catheterization; the authors need to clarify this point. Please consider mentioning this in the title and abstract. This reader mistook the term “chronic catheterization as a long-term indwelling catheter, either suprapubic tube or urethral. Until I reached this point of the article, please address this earlier in the paper.

Introduction:
1. As mentioned previously, I find it confusing that in the title, abstract, and here in the introduction, the authors consistently say indwelling catheters, yet, in the article summary, they mention the study population includes patients on clean intermittent catheterization (CIC) and indwelling catheters. Since the study population is a mixture of patients with indwelling catheters and CIC, the introduction should also raise this point. The authors need to point out that current literature suggests that intermittent catheterization may also be associated with bladder cancer. Hypothetically, intermittent catheterization could pose less of a risk for cancer development than an indwelling cath.

2. Probably not necessary in the introduction, but certainly needs to be mentioned in the discussion, is the concept that the underlying disease process that could require catheterization, e.g., neurogenic bladder, could also be a primary etiology for bladder cancer. Although the control populations have some patients with primary neurogenic disease, neurologic dysfunction is a spectrum disorder. Individuals with the most progressive neurologic pathology or more severe spinal cord injury (ASIA) require catheterization. Are they at the highest risk for malignancy developing compared to those with less severe damage? Is it the progressive neural pathology, the catheter, or the chronic bacteriuria the cause of the malignancy? Or does the malignancy arise due to a combination of these factors?

3. I do find it somewhat misleading that the authors’ state catheter duration is related to the malignancy. I believe this to be true; however, my major hang-up as a reviewer is that the authors are reviewing patients with indwelling catheters and those using CIC. Could they possibly reword the last paragraph of the introduction, e.g., We examined a population-based cohort of 36,903 patients requiring chronic urinary catheterization as part of the management. This population consisted of patients using either an indwelling catheter or intermittent catheterization.

Materials and Methods
1. Again, I would encourage the authors to be upfront regarding a mixed study population, e.g. among patients with either an indwelling catheter or intermittent catheterization between …
2. Although I do like the design of this study, a significant concern is that this paper will prove that catheterization be it CIC or indwelling (the authors cannot separate the two patient groups from their data), is associated with the development of a bladder tumor; however, cancer could also arise as a consequence of the altered cellular milieu associated with a neurogenic bladder. Alternatively, it could be a two-step process of neural injury causing a cellular disorder aggravated by catheterization, bacteriuria, or bladder stones. Note that neuropathic pathology could cause a spectrum disorder, those with the most abnormal bladder environment also having the worse neurologic symptoms. Although the authors try to have neurologic conditions in the controls, they did not grade the severity of the neurologic disorders in patients not requiring catheterization. The authors will need to bring this point out in the discussion.

3. It would be nice if the authors could better classify UTI; I realize this may be impossible using coding data. These patients are frequently overtreated for a UTI in the emergency departments and or just treated for the presence of asymptomatic bacteriuria by their primary care physician. The authors’ data will be accurate regarding how often they were treated for UTI, not how often they were treated appropriately. That said, the critical point here is that bacteriuria may be associated with malignancy. I have seen several patients with bladder cancers treated for a recurrent UTI for months by their physician before referral to a urologist reveals a bladder tumor as the source for their recurrent symptoms; this would not be apparent in their data. It may be that the chronic bacteriuria masks the irritative symptoms that the malignancy can cause, pt being treated for multiple UTI when they have a malignancy- e.g., misdiagnosis.

Results
1. Again not to belabor the point, but the authors should state "eight fold higher among patients requiring catheter management either CIC or an indwelling catheter page 15 lines 12-16

2. In the results, individuals with bladder stones were at significantly high risk for malignancy. Although this point is well known, this critical point would be good to note in the abstract.

Discussion
1. Line 7-9 page 17, again could the authors please state that 1.1% of patients requiring either intermittent catheterization or an indwelling catheter developed bladder cancer. This is a more accurate clarification of their data.

2. Although I agree with the authors’ conclusions regarding the association of UTI to the development of bladder cancer, I have seen so many of these patients treated with recurrent UTI for months that upon evaluation have a bladder tumor; I am concerned the tumors were causing the symptoms and just misdiagnosed, would the authors feel comfortable addressing this issue in the discussion?
3. I am concerned that the authors allude that regular screening of patients managed with either an indwelling catheter or intermittent catheterization after a certain number of years may be beneficial. It undoubtedly is not fiscally responsible due to the low incidence of malignancy. Rather than screening everyone, suggest the author use their data to come up with screening criteria, e.g., consider cystoscopy in patients with a history of bladder calculi, or patients treated for three or more symptomatic UTI in a year, this would be more consistent with the authors’ findings, rather than stating screen all patients managed by an indwelling catheter or CIC after X years.

4. Again as mentioned previously, neurogenic bladder dysfunction alone could be the etiology of the cellular abnormalities that stimulate cancer development. The cellular alterations noted in a neurogenic bladder are most likely a spectrum disorder. Those with the most advanced or worse neurologic pathology would have the most severe urothelial cellular abnormality and more likely to require catheterization; unless we match the control population to the severity of the neurologic impairment, we would be unable to discern this fact. This concept should be brought up in the discussion.

REVIEWER

Lyrratzopoulos, Georgios
University College London, Department of Epidemiology & Public Health, Health Behaviour Research Centre

REVIEW RETURNED
03-May-2021

GENERAL COMMENTS

This is an interesting paper, it provides an empirical exploration of the oncological safety of long-term bladder catheterisation and finds associations with 3-fold greater risk of bladder cancer. I think the data are interesting, and the design and statistical approach per se are faultless, but I think the paper / interpretation needs to be much more caveat ed. Please address the following points.

1. Why is it the case that long-term bladder catheterisation might induce neoplasia of the bladder? Is there a mechanistic model?
2. Is the average follow-up of 8 years (which was at times as short as 2 years) convincingly long for neoplasia development de novo?
3. Relatedly, what is the role of UTI as a major confounder here? If I understood it well, the way the study describes how UTI was assessed is geared towards really serious UTI leading to ER attendance or hospitalisation – however these patients are likely to have many and recurrent UTIs not necessarily treated in hospital but in community. Therefore, there is a large risk of residual confounding. In table 2 we see that 40% of the long-term catheterised patients had a UTI during the follow-up period: I simply do not think this percentage is believable, in truth it must be nearly 100% (except perhaps for some lucky patients with very short catheterisation. Further, these % does not give an indication about UTI duration. Noting that there is 40-fold greater percentage of ‘UTI’ among catheterised patients compared to the incidence of the outcome (bladder cancer) – so any potential misclassification (of UTI exposure) or residual confounding from number / duration of UTI, may have very large consequences in
the estimation of differences in risk of bladder cancer between cases and controls. I may well have got it wrong but please consider the points and make your paper stronger in its narrative and methodological considerations.

4. How were the patients diagnosed – mode and ‘route’ to diagnosis. Did they develop symptoms such as haematuria prompting cystoscopy? Lack of information here is a major limitation. I wonder if there is large potential for over-diagnosis, e.g. mechanical friction or UTI (not necessarily captured in the administrative data) cause haematuria which prompts cystoscopy which detects abnormalities consistent with bladder carcinoma, but essentially this is an incidental identification. I am not saying that this ‘pathway’ to incidental identification is actually what happens, but postulating the potential for the findings being explainable through over-detection. The lack of stage at diagnosis information is in that respect a big limitation that together with evidence on diagnostic route/model of presentation should be addressed by future research.

5. Taking it all in the round [the lack of clear mechanistic model, the very limited follow-up which is unlikely to be truly inducing oncogenesis, the likely unmeasured confounding by (additional to what was captured in the data) UTI burden, and the potential for over-diagnosis] should be taken very seriously into account, and the abstract-conclusion and discussion / conclusion (main text) need to be in my opinion caveated with these important limitations and pointing to future research. The data should be published, but with appropriate interpretation. I should otherwise congratulate the authors for excellent use of the healthcare data available to them and related linkages and phenotyping of exposures and outcomes of interest.

**VERSION 1 – AUTHOR RESPONSE**

Reviewer: 1

Abstract:

See comment #1 under Article summary; it was not until I read the article summary that I realized the study population included individuals with indwelling catheters and on CIC. I would suggest the authors somehow have this fact in the title and clarify this point in the abstract; Although I understand the merits of this study, the real question that needs to be answered is to compare patients with an indwelling catheter to patients with similar systemic problems managed differently, e.g., patients with NGB managed with indwelling catheter vs. intermittent catheterization. Several studies have documented that patients with neurogenic bladders have a higher risk of malignancy; one of the critical yet unanswered questions is there a difference in malignancy potential in patients managed with CIC vs. indwelling catheter. This paper cannot address this clinically pertinent question.

This was made more explicitly clear that the exposure group includes both indwelling and CIC populations.

For example, Methods: The study population represented a broad cohort of patients with chronic bladder instrumentation. In the absence of individual patient-level data, it was not possible to distinguish clean
intermittent from indwelling catheterization or to identify patients who transitioned from intermittent to indwelling catheterization or vise versa. We have revised the terminology throughout the manuscript to “chronic bladder catheterization”, which is a more all-encompassing term, but also made it more explicitly clear early on in the manuscript the combined nature of the exposure group. The authors will need to define UTI; in our experience, >85% of our bacterial cultures are positive in patients with CIC, >90% with an indwelling catheter. Are we talking about bacterial colonization, symptomatic UTI, or, as I presume, in a study based on diagnostic codes, any pharmacologically treated bacteriuria? This fact should be stated in the abstract. While felt it was important to include a measure of infection in the model as this may be an important confounding factor. We agree that this population will often have “positive” urine cultures. Therefore, we defined UTI as symptomatic infections, specifically: infection related to a catheter in genital tract, pyelonephritis, epididymorchitis, pyelonephritis, urinary tract-related abscesses, prostatitis, etc as listed in Appendix 1. We chose symptomatic episodes as we felt this would be the most accurate way of capturing these events, in the absence of individual level patient data. This is presented in the Methods sectio. Since tobacco usage is the primary cause of bladder cancer, is this study controlled for tobacco usage between the two study populations? I do note the authors address this point later in their paper, article summary. No reply necessary, however, this point should be covered in the discussion, and it is not. This is listed as a limitation in the Discussion as a potential unmeasured confounder.

Article Summary:

In reviewing this paper, it is at this point that I became aware that the “chronic urinary catheterization group” included patients with an indwelling catheter and intermittent catheterization; the authors need to clarify this point. Please consider mentioning this in the title and abstract. This reader mistook the term “chronic catheterization as a long-term indwelling catheter, either suprapubic tube or urethral. Until I reached this point of the article, please address this earlier in the paper. We have made this clearer throughout the paper, for example:

Abstract: Objectives: To compare the risk of bladder cancer and bladder cancer mortality among patients with chronic bladder catheterization (indwelling or intermittent) to patients from the general population. 

Introduction: Thus, we examined a population-based cohort of 36,903 patients requiring chronic bladder catheterization (indwelling suprapubic or urethral catheter or patients preforming clean intermittent catheterization) and examined their risk of bladder cancer and mortality compared to a matched cohort of patients from the general population.

Introduction:

As mentioned previously, I find it confusing that in the title, abstract, and here in the introduction, the authors consistently say indwelling catheters, yet, in the article summary, they mention the study population includes patients on clean intermittent catheterization (CIC) and indwelling catheters. Since the study population is a mixture of patients with indwelling catheters and CIC, the introduction should also raise this point. The authors need to point out that current literature suggests that intermittent catheterization may also be associated with bladder cancer. Hypothetically, intermittent catheterization could pose less of a risk for cancer development than an indwelling cath. This has been clarified throughout the paper and we have elaborated on this limitation in the Discussion: In this study, the definition of chronic catheterization using administrative data is unvalidated and it is impossible to differentiate indwelling catheter versus intermittent catheterization in the absence of individual patient-level data. Hypothetically, intermittent catheterization could pose less of a risk for
cancer development compared to indwelling urethral or suprapubic catheterization. Given the limitations of administrative data, we were unable to explore this in the current study.

Probably not necessary in the introduction, but certainly needs to be mentioned in the discussion, is the concept that the underlying disease process that could require catheterization, e.g., neurogenic bladder, could also be a primary etiology for bladder cancer. Although the control populations have some patients with primary neurogenic disease, neurologic dysfunction is a spectrum disorder. Individuals with the most progressive neurologic pathology or more severe spinal cord injury (ASIA) require catheterization. Are they at the highest risk for malignancy developing compared to those with less severe damage? Is it the progressive neural pathology, the catheter, or the chronic bacteriuria the cause of the malignancy? Or does the malignancy arise due to a combination of these factors?

Added to limitations in the Discussion:
On subgroup analysis among patients with suspected neurological lower urinary tract dysfunction, our study findings were consistent. However, we were unable to explore the association between severity of neurological dysfunction and risk of bladder cancer incidence and mortality in the absence of individual patient data.

I do find it somewhat misleading that the authors' state catheter duration is related to the malignancy. I believe this to be true; however, my major hang-up as a reviewer is that the authors are reviewing patients with indwelling catheters and those using CIC. Could they possibly reword the last paragraph of the introduction, e.g., We examined a population-based cohort of 36,903 patients requiring chronic urinary catheterization as part of the management. This population consisted of patients using either an indwelling catheter or intermittent catheterization.

This has been revised.

Materials and Methods

Again, I would encourage the authors to be upfront regarding a mixed study population, e.g. among patients with either an indwelling catheter or intermittent catheterization.

This has been revised.

Although I do like the design of this study, a significant concern is that this paper will prove that catheterization be it CIC or indwelling (the authors cannot separate the two patient groups from their data), is associated with the development of a bladder tumor; however, cancer could also arise as a consequence of the altered cellular milieu associated with a neurogenic bladder. Alternatively, it could be a two-step process of neural injury causing a cellular disorder aggravated by catheterization, bacteriuria, or bladder stones. Note that neuropathic pathology could cause a spectrum disorder, those with the most abnormal bladder environment also having the worse neurologic symptoms. Although the authors try to have neurologic conditions in the controls, they did not grade the severity of the neurologic disorders in patients not requiring catheterization. The authors will need to bring this point out in the discussion.

This is an interesting point and has been added to the Discussion:

Discussion: It remains uncertain whether this association represents a direct relationship between inflammation and bladder cancer incidence or other cellular-level alterations that occur as a result of neurogenic bladder dysfunction.

Limitations: However, we were unable to explore the association between severity of neurological dysfunction and risk of bladder cancer incidence and mortality in the absence of individual patient data. It would be nice if the authors could better classify UTI; I realize this may be impossible using coding data. These patients are frequently overtreated for a UTI in the emergency departments and or just treated for the presence of asymptomatic bacteriuria by their primary care physician. The authors’ data will be accurate regarding how often they were treated for UTI, not how often they were treated appropriately. That said, the critical point here is that bacteriuria may be associated with malignancy. I have seen several patients with bladder cancers treated for a recurrent UTI for months by their physician
before referral to a urologist reveals a bladder tumor as the source for their recurrent symptoms; this would not be apparent in their data. It may be that the chronic bacteriuria masks the irritative symptoms that the malignancy can cause, pt being treated for multiple UTI when they have a malignancy- e.g., misdiagnosis.

This is also a good point. Even in the presence of individual level patient data, it is very difficult to tease out UTI-related symptomatology or irritative symptomatology from cancer or even underlying neurological lower urinary tract dysfunction. We attempted to more accurately identify “true” UTIs using the coding described above, but we agree, there is potential for misclassification and residual confounding.

Discussion, Limitations: In this patient population, it can be challenging to differentiate true UTIs from irritative symptomatology from the underlying neurological disease or even bladder cancer-induced storage symptoms. Also, this patient population often has chronic bacteriuria which may prompt unnecessary antibiotic treatment in the outpatient setting, thus the use of positive urine cultures or antibiotic prescriptions as a marker of UTI could introduce significant bias. To try to more accurately identify UTIs, we included symptomatic events prompting emergency department assessment, instrumentation, or hospitalization. There may still be an element misclassification bias and residual confounding as a result of the challenges associated with defining this covariate and this should be considered when interpreting our results.

Results

Again not to belabor the point, but the authors should state “eight fold higher among patients requiring catheter management either CIC or an indwelling catheter page 15 lines 12-16

The results section has been revised accordingly.
In the results, individuals with bladder stones were at significantly high risk for malignancy. Although this point is well known, this critical point would be good to note in the abstract.
This has been added to the abstract.

Discussion

Line 7-9 page 17, again could the authors please state that 1.1% of patients requiring either intermittent catheterization or an indwelling catheter developed bladder cancer. This is a more accurate clarification of their data.
This has been revised.
Although I agree with the authors’ conclusions regarding the association of UTI to the development of bladder cancer, I have seen so many of these patients treated with recurrent UTI for months that upon evaluation have a bladder tumor; I am concerned the tumors were causing the symptoms and just misdiagnosed, would the authors feel comfortable addressing this issue In the discussion?
This has been added to the Limitations section of the Discussion.
I am concerned that the authors allude that regular screening of patients managed with either an indwelling catheter or intermittent catheterization after a certain number of years may be beneficial. It undoubtedly is not fiscally responsible due to the low incidence of malignancy. Rather than screening everyone, suggest the author use their data to come up with screening criteria, e.g., consider cystoscopy in patients with a history of bladder calculi, or patients treated for three or more symptomatic UTI in a year, this would be more consistent with the authors’ findings, rather than stating screen all patients managed by an indwelling catheter or CIC after X years.
We have tempered these recommendations, highlighting that this analysis was exploratory.

Discussion: In an exploratory analysis, patients had an increase in the risk of developing bladder cancer with longer catheter duration. The duration cut-offs were arbitrarily based on the quintile distribution. Patients with chronic catherization beyond 2.9 years appeared to be at the highest risk. We also found that patients with bladder calculi and more frequent symptomatic UTIs had an incremental increase in the
risk of bladder cancer incidence and mortality. Future studies are needed to validate these findings. Targeted screening interventions for high-risk populations may be warranted although this was outside the scope of the current study.

Again as mentioned previously, neurogenic bladder dysfunction alone could be the etiology of the cellular abnormalities that stimulate cancer development. The cellular alterations noted in a neurogenic bladder are most likely a spectrum disorder. Those with the most advanced or worse neurologic pathology would have the most severe urothelial cellular abnormality and more likely to require catheterization; unless we match the control population to the severity of the neurologic impairment, we would be unable to discern this fact. This concept should be brought up in the discussion.

This has been added to the Discussion.

Reviewer: 2

This is an interesting paper, it provides an empirical exploration of the oncological safety of long-term bladder catheterisation and finds associations with 3-fold greater risk of bladder cancer. I think the data are interesting, and the design and statistical approach per se are faultless, but I think the paper / interpretation needs to be much more caveated. Please address the following points.

Why is it the case that long-term bladder catheterisation might induce neoplasia of the bladder? Is there a mechanistic model?

This has been added to the Discussion. We postulate this is related to inflammation, but the exact mechanism at a cellular level has not be elucidated.

Is the average follow-up of 8 years (which was at times as short as 2 years) convincingly long for neoplasia development de novo?

Median FU was 8.8 years for the entire cohort (IQR 5-12 years).

We agree that follow-up duration is a limitation to the current study and has been listed as limitation in the Discussion. This was the maximum follow-up possible as we intentionally chose the start-time for the study based on a change in administrative data coding. We did not limit our study population based on follow-up duration in order to minimize the potential for selection bias. We chose a time-to-event analysis model in order to account for this difference in follow-up duration between subjects while still allowing us to keep all patients in the study cohort (for as long as they were able to contribute data).

Relatedly, what is the role of UTI as a major confounder here? If I understood it well, the way the study describes how UTI was assessed is geared towards really serious UTI leading to ER attendance or hospitalisation – however these patients are likely to have many and recurrent UTIs not necessarily treated in hospital but in community. Therefore, there is a large risk of residual confounding. In table 2 we see that 40% of the long-term catheterised patients had a UTI during the follow-up period: I simply do not think this percentage is believable, in truth it must be nearly 100% (except perhaps for some lucky patients with very short catheterisation. Further, these % does not give an indication about UTI duration.

Noting that there is 40-fold greater percentage of ‘UTI’ among catheterised patients compared to the incidence of the outcome (bladder cancer) – so any potential misclassification (of UTI exposure) or residual confounding from number / duration of UTI, may have very large consequences in the estimation of differences in risk of bladder cancer between cases and controls. I may well have got it wrong but please consider the points and make your paper stronger in its narrative and methodological considerations.

In the absence of individualized patient data, it is very difficult to make the distinction between positive urine cultures (which would be present in almost all patients) and symptomatic infections. Even in the presence of individual level patient data, it is very difficult to tease out UTI-related symptomatology or irritative symptomatology from cancer or underlying neurological lower urinary tract dysfunction. We
chose a definition that would almost certainly flag a real urinary tract infection (ER admission, admission, or instrumentation for infection) and we acknowledge that there may be an aspect of residual confounding.

We have expanded on this in the Discussion section and specifically mentioned residual confounding as a limitation.

In this patient population, it can be challenging to differential true UTIs from irritative symptomatology from the underlying neurological disease or even bladder cancer-induced storage symptoms. Also, this patient population often has chronic bacteriuria which may prompt unnecessary antibiotic treatment in the outpatient setting, thus the use of positive urine cultures or antibiotic prescriptions as a marker of UTI could lead to significant bias. To try to more accurately identify UTIs, we included symptomatic events prompting emergency department assessment, instrumentation, or hospitalization. There may still be an element misclassification bias and residual confounding as a result of the challenges associated with defining this covariate and this should be considered when interpreting our results.

How were the patients diagnosed – mode and ‘route’ to diagnosis. Did they develop symptoms such as haematuria prompting cystoscopy? Lack of information here is a major limitation. I wonder if there is large potential for over-diagnosis, e.g. mechanical friction or UTI (not necessarily captured in the administrative data) cause haematuria which prompts cystoscopy which detects abnormalities consistent with bladder carcinoma, but essentially this is an incidental identification. I am not saying that this ‘pathway’ to incidental identification is actually what happens, but postulating the potential for the findings being explainable through over-detection. The lack of stage at diagnosis information is in that respect a big limitation that together with evidence on diagnostic route/model of presentation should be addressed by future research.

The exact sequence of events leading to bladder cancer diagnosis is difficult to assess in the absence of individual level data.

To address the potential for detection bias, a sensitivity analysis with a urology-specific control group (who would have ready access to relevant diagnostic procedures) revealed similar parameter estimates. We have added a comment about the lack of stage data as a limitation.

Taking it all in the round [the lack of clear mechanistic model, the very limited follow-up which is unlikely to be truly inducing oncogenesis, the likely unmeasured confounding by (additional to what was captured in the data) UTI burden, and the potential for over-diagnosis] should be taken very seriously into account, and the abstract-conclusion and discussion / conclusion (main text) need to be in my opinion caveated with these important limitations and pointing to future research. The data should be published, but with appropriate interpretation. I should otherwise congratulate the authors for excellent use of the healthcare data available to them and related linkages and phenotyping of exposures and outcomes of interest.

We agree. The limitations were expanded in the Discussion and the conclusions have been tempered to reflect this.

Conclusion: Study limitations, including the potential for misclassification, residual confounding, and detection bias, highlight the need for validation of our results in future studies. Acknowledging these limitations, the findings highlight the need for physicians to be aware of this risk when managing patients with chronic catheters.

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**VERSION 2 – REVIEW**

| REVIEWER       | Husmann, Douglas A  
|                | Mayo Clinic Rochester, Urology |
|----------------|-------------------------------|
| REVIEW RETURNED | 14-Jun-2021                   |
GENERAL COMMENTS

Introduction:
1) The authors do a better job in defining chronic catheterization, the last paragraph on page 8/80, I would however have liked them to define this term earlier in their discussion say page 7/80 line 30. Defining their definition of chronic catheterization early in the introduction would aid in preventing any confusion regarding the population the authors are evaluating.

Materials and Methods
1. Although the authors define chronic catheterization in the introduction of the paper, they should redefine this term in the methodology e.g. line 11-13 page 9/80

Results and Discussion
I. I remain concerned regarding the findings of bacteriuria with cancer, although I personally believe the authors are correct, Multiple patients with either an indwelling catheter or on clean intermittent catheterization are treated with antibiotics for a UTI when bacteria are found on urinalysis or urine culture and the patients are asymptomatic, I do not believe the authors can adequately separate out these two patient populations base on their methodology. Is it bacteriuria? or symptomatic UTI that are related? Also concerned that numerous patients I have seen with bladder cancer in this patient population were treated for months to years for a "UTI" when cystoscopy revealed a tumor? Questionably the tumor causing the patient symptoms, not the bacteriuria. The authors do discuss this point on page 19.

Overall I congratulate the authors they have made substantial and informative alterations to this manuscript with their revision.

REVIEWER
Lyratzopoulos, Georgios
University College London, Department of Epidemiology & Public Health, Health Behaviour Research Centre

REVIEW RETURNED 29-May-2021

GENERAL COMMENTS
thank you - you have improved the manuscript and reflected/addressed the issues of interpretation and necessary caveating of conclusions.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

1. The authors do a better job in defining chronic catheterization, the last paragraph on page 8/80, I would however have liked them to define this term earlier in their discussion say page 7/80 line 30. Defining their definition of chronic catheterization early in the introduction would aid in preventing any confusion regarding the population the authors are evaluating.

1. This has been revised accordingly.

Materials and Methods
2. Although the authors define chronic catheterization in the introduction of the paper, they should redefine this term in the methodology e.g. line 11-13 page 9/80

1. This statement was made in the last paragraph of the introduction and is discussed again in the Methods/Study Subjects section.

   The study population represented a broad cohort of patients with chronic bladder instrumentation and could include an indwelling suprapubic or urethral catheter or patients preforming clean intermittent catheterization. In the absence of individual patient-level data, it was not possible to distinguish clean intermittent from indwelling catheterization or to identify patients who transitioned from intermittent to indwelling catheterization or vise versa.

Results and Discussion

3. I remain concerned regarding the findings of bacteriuria with cancer, although I personally believe the authors are correct. Multiple patients with either an indwelling catheter or on clean intermittent catheterization are treated with antibiotics for a UTI when bacteria are found on urinalysis or urine culture and the patients are asymptomatic, I do not believe the authors can adequately separate out these two patient populations base on their methodology. Is it bacteriuria? or symptomatic UTI that are related? Also concerned that numerous patients I have seen with bladder cancer in this patient population were treated for months to years for a "UTI" when cystoscopy revealed a tumor? Questionably the tumor causing the patient symptoms, not the bacteriuria. The authors do discuss this point on page 19.

1. We agree. We have discussed this in detail in the paper as a limitation and potential source of bias/residual confounding to make this clear for the reader.

3. Overall I congratulate the authors they have made substantial and informative alterations to this manuscript with their revision.

Thank you.

Reviewer: 2

1. Thank you - you have improved the manuscript and reflected/addressed the issues of interpretation and necessary caveation of conclusions.

1. Thank you.