Author's response to reviews

Title: Predictive Factors of Urinary Tract Infections among the Oldest Old in the General Population. A Population Based Prospective Follow-up Study.

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Author's response to reviews: see over
Dear (deputy) editors of the BMC Medicine,

Herewith we would like to submit our revised manuscript ‘Predictive Factors of Urinary Tract Infections among the Oldest Old in the General Population. A Population Based Prospective Follow-up Study’ to the BMC Medicine.

In this document we reply to the comments of the editors and the reviewers. The changes that were made according to the editors’ and reviewers’ comments were highlighted in the revised manuscript.

Editors comments:

1) We would particularly encourage you to address the point raised by both referees’ 1 and 3 regarding the loss of 7 participants in the study from urinary tract infection with further discussion of the potential reasons behind this finding. We received mortality data from the municipality and data on specific causes of death from Statistics Netherlands, according to the International Classification of Diseases and Related Disorders (ICD-10, code N39.0 (urinary tract infection). Unfortunately we did not have any further information about the underlying factors associated with these deceased participants.

2) We would also strongly encourage you to expand the ‘Introduction’ section of your manuscript in order to provide our readers with greater background and context to the various problems and complications associated with urinary tract infections. As recommended, we expanded the introduction section to report more about the various problems associated with UTI in older populations.

Referee 1: Lindsay Nicolle

1. The authors have used a physician diagnosis together with urinalysis findings for diagnosis. Symptomatic urinary tract infection is over-diagnosed in elderly populations given the high prevalence of asymptomatic bacteriuria and propensity to interpret nonlocalizing clinical deterioration as “urinary infection” in more impaired patients. The authors acknowledge this in the full paragraph on page 14 as a potential limitation of their study, but they should discuss this a little more fully and particularly note that the estimates of urinary infection in this population are likely overestimates. It is indeed well known that asymptomatic bacteriuria is a frequent problem in elderly populations, especially in nursing home residents. We also agree with the reviewer that due to the high percentage of participants with disability in daily living in our study population the ascertainment of symptomatic UTI could have been problematic. However, in our study population, the incidence of UTI was 11.2 per 100 person years at risk for persons aged 86 and over which is comparable with data from the Dutch national GP registration (Reference: http://www.nationaalkompas.nl/gezondheid-en-ziekte/ziekten-en-aandoeningen/urinewegen-en-de-geslachtsorganen/acute-urineweginfecties/incidentie-en-sterfte-naar-leeftijd-en-geslacht/) in which the definition of UTI was based on symptoms of UTI and a positive nitrite test and/or
culture. They found incidences of 11.7 for men and 29.4 for women aged 85 years and over. Based on these data from the national GP registration and the fact participants in our study actively visited their treating physician with UTI like symptoms, we believe that this possible overestimation is limited. We discussed this point in more detail in the discussion section of the manuscript (page 17, paragraph 1).

2. The observed associations with urinary tract infection are consistent with all other studies in older populations. In their discussion, the authors should note that none of these associations appear to be modifiable. We thank the reviewer for this comment and added this suggestion to the discussion (page 17, paragraph 2). They could also be more critical with respect to the practical implications of their observations. The majority of elderly individuals with urinary tract infection experience complicated urinary tract infection, and there is no evidence that any interventions such as oestrogen, cranberry or other probiotics, or prophylactic antimicrobial therapy will prevent complicated urinary infection. We expanded the introduction and discussion and added several sentences concerning the lack of evidence of therapeutic or preventive medications for UTI in older persons.

3. With respect to considering potential interventions, the individuals with frequent recurrent infections which would be of greatest interest. What proportion of these elderly individuals experienced more than two infections a year? In the table below we present the number of participants that experienced 2 of more infections per year of follow-up. 34 of 479 participants had two or more infections between the age of 85 and 86 years (7.1%). On average 6.5 % of all participants experienced more than one infection per year. We added this information to the manuscript (Page 11, last paragraph)

<table>
<thead>
<tr>
<th>Two or more UTI a year</th>
<th>% of total study population</th>
<th>% of participants with UTI during that year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Between 86 and 87</td>
<td>35/479 = 7.3</td>
<td>35/64 = 54.7</td>
</tr>
<tr>
<td>Between 87 and 88</td>
<td>30/420 = 7.1</td>
<td>30/73 = 41.1</td>
</tr>
<tr>
<td>Between 88 and 89</td>
<td>21/362 = 5.8</td>
<td>21/45 = 46.7</td>
</tr>
<tr>
<td>Between 89 and 90</td>
<td>18/315= 5.7</td>
<td>18/45 = 40.0</td>
</tr>
<tr>
<td>Average</td>
<td>6.5</td>
<td>45.6</td>
</tr>
</tbody>
</table>

4. Table 1 could be incorporated as another column with Table 2. Thank you for this suggestion. We incorporated table 1 in table 2.

5. Page 9, the authors note that seven participants died from urinary tract infection. This is 2.8% of all patients who died during follow-up, which is a high mortality attributable to urinary tract infection. Is there specific information with respect to these seven deaths and how they were directly attributable to urinary tract infection? We received mortality data from the municipality and specific data on causes of death were obtained from Statistics Netherlands, according to the International Classification of Diseases and Related Disorders (ICD-10, code N39.0: urinary tract infection). Unfortunately we did not have any information about the underlying factors associated with these deceased participants.
Referee 2: Adrian Wagg:

Introduction:
The authors make no mention, however of the problem with UTI case ascertainment and the influence of asymptomatic bacteriuria in this population leading to mistaken ‘diagnosis of UTI’ and how this might have an impact on identified associated risk factors. We expanded the introduction and discussion section to explore more the underlying problems with the diagnosis of UTI in the elderly. Also see comment 1 of Referee 1.

Materials and methods:

The case ascertainment of UTI is a pragmatic one and presumably arises from retrospective analysis of clinician records? This should be specified.
Information about UTI was registered in patients’ record prospectively. Each year data were gathered about the development of clinical diagnosed UTI during the preceding year from clinician interviews and records. We added this information to the manuscript (page 7, paragraph 1)

Did participants give consent for this study specifically or for the whole project? If the latter, did participants consent to the use of their data for such additional analysis?
Participants gave informed consent for the whole project and the use of their medical records for additional analysis. We added this to the materials and methods of the manuscript (page 6, paragraph 1).

There was no information of catheterization as being a risk factor for both bacteriuria and UTI – was this not included, particularly as the population contained institutionalized older people some of whom might be expected to have a long term catheter in situ.
We agree with the referee that long term catheterization is a strong risk factor for UTI/bacteriuria. Unfortunately, we did not have any information about long-term catheterization in our study population and could not report on the predicting effect. These is a limitation of our study, but we believe that this may not have affected the results of our study much, since in Dutch nursing homes there is a policy to avoid the use of catheters in situ and it has been so for many years (Cools HJ: Twaalf jaar Infectiebeleid in een verpleeghuis [12-year infection policy in a nursing homes] Ned Tijdschr Geneeskd 1994, 138: 184-188). We added the lack of information on catheterization to the discussion section of the manuscript (page 17, paragraph 2).

Were there any data about pad use in those with self reported incontinence of urine as this too has been shown to result in an excess risk of UTI/bacteriuria?
We agree with the referee that pad use would be a very interesting potential predictor of UTI. In our study, information about pad use was obtained from the PRAFAB questionnaire. In total 91 participants reported that they used pads for their self reported incontinence, of which 29 have had UTI. The HR for pads vs non pads was 1.2 (0.6, 2.5) P=0.680. We added this finding to the new table 1 (a combination of the old table 1 and table 2).

Discussion:
There is some editorial work to be done on the English for readability here but the discussion is apt, well referenced and there are no extrapolations beyond the relevance of the results. We thank the referee for this nice comment about the study. We have checked the English for readability and we have made changes that have hopefully improved readability.
Referee 3: Tomas Griebling

Major compulsory revisions

1) Most of the survey instruments used in this study (MMSE, GDS-15, GARS, PRAFAB-Questionnaire, etc.) were developed and validated in English. Were these administrated to subject in English or Dutch? Have Dutch translations for these instruments been validated and back-translation methodology. If available, this information should be included in the references. All the instruments were administrated in Dutch. The GARS and PRAFAB are Dutch instruments. They are constructed and validated in the Netherlands. The MMSE and GDS-15 are frequently used in Dutch research and standardised for older populations. The MMSE is validated by Heeren TJ, Lagaay AM, von BeekWC, Rooymans HG, Hijmans W. Reference values for the Mini-Mental State Examination (MMSE) in octo- and nonagenarians. J Am Geriatr Soc. 1990, 38:1093-6. The sensitivity and specificity of the GDS-15 is validated. (de Craen AJ, Heeren TJ, Gussekloo J Accuracy of the 15-item geriatric depression scale (GDS-15) in a community sample of the oldest old. Int J Geriatr Psychiatry 2003, 18:63-6.) We included these references and added that all questionnaires were validated in Dutch (page 8 first paragraph).

2) For the variable examining disability (loss of independence of at least one ADL), was this examined as a dichotomous variable? Yes, we used a dichotomous variable for ADL. The GARS-items were dichotomized. Participants were grouped into those who had no difficulty with GARS-items (score 1) and those who had difficulty or were not able to perform (score 2, 3, 4). The total GARS score was calculated by adding the total scores of the nine items of the GARS and then dichotomized into score 9 (independently) and scores > 9 (difficulty or unable to perform independently). We added this to the manuscript on page 8, paragraph 1.

It would be very interesting to see which specific ADL limitation(s) are associated with risk of developing UTI. Although small numbers may prevent complete analysis of some of the nine ADLs, a subanalysis by specific ADL would be most interesting. We agree with the referee that it would be very interesting to get more information on specific ADL limitations. In the table below, incidences of UTI and HRs are reported for all 9 ADL items. All single GARS-items were predicting the risk in developing UTI. We added this to the results section of the manuscript (page 12 paragraph 2).
3) The term ‘prostatism’ is outdated and no longer used in clinical or research practice. Does this refer to Lower Urinary Tract symptoms (LUTS) caused by benign prostatic hyperplasia (BPH)? I would encourage the authors to use terminology for voiding dysfunction as outlined by the International Continence Society. This information is updated regularly and is typically published in Neurourology & Urodynamics or available through the ICS. The appropriate reference should be cited for the terminology chosen.

We meant the term LUTS caused by benign prostatic hyperplasia (BPH). We changed the text in the manuscript and tables.

4) C-reactive protein (CRP) was used as a measure of ‘general health status’. Has this laboratory test been validated in any way for this variable? If so, this information should be included in the Methods section with citation of the appropriate reference. Since CRP is increased in acute and chronic disease, we used CRP as a marker of unknown disease. den Elzen WP, Willems JM, Westendorg RG, de Craen AJ, Assendelft WJ, Gussekloo J: Effect of anemia and comorbidity on

<table>
<thead>
<tr>
<th>ADL-item</th>
<th>Incidence in index group, per 100 py (95% CI)</th>
<th>Incidence in reference group*, per 100 py (95% CI)</th>
<th>HR (95%CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disability in daily living †</td>
<td>283 (59.1)</td>
<td>6.3 (4.3, 8.3)</td>
<td>2.4 (1.6, 3.5)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Getting around the house</td>
<td>133 (27.8)</td>
<td>2.8 (2.2, 3.4)</td>
<td>2.4 (1.7, 3.3)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Getting into and out of bed</td>
<td>128 (26.7)</td>
<td>2.7 (2.2, 3.3)</td>
<td>2.6 (1.9, 3.7)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Standing up from a chair</td>
<td>147 (30.7)</td>
<td>2.9 (2.3, 3.5)</td>
<td>2.0 (1.4, 2.8)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Going to the toilet</td>
<td>103 (21.5)</td>
<td>2.6 (2.1, 3.2)</td>
<td>3.8 (2.7, 5.4)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Dressing oneself</td>
<td>183 (38.2)</td>
<td>2.7 (2.1, 3.4)</td>
<td>2.1 (1.5, 3.0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Washing hands and face</td>
<td>65 (13.6)</td>
<td>2.9 (2.4, 3.6)</td>
<td>3.3 (2.2, 4.9)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Washing whole body</td>
<td>204 (42.6)</td>
<td>2.5 (2.0, 3.3)</td>
<td>2.3 (1.7, 3.3)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Preparing breakfast</td>
<td>80 (16.7)</td>
<td>2.9 (2.4, 3.5)</td>
<td>3.1 (2.1, 4.6)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Drinking and feeding oneself</td>
<td>44 (9.2)</td>
<td>3.0 (2.5, 3.6)</td>
<td>3.5 (2.3, 5.6)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

UTI= urinary tract infection; py= person-years; CI= confidence interval; HR= hazard ratio.

* Definition of reference groups: no disability in daily living, no disability in getting around the house, no disability in getting into and out of bed, no disability standing up from chair, no disability going to the toilet, no disability dressing oneself, no disability washing hands and face, no disability washing whole body, no disability preparing breakfast, no disability drinking and feeding oneself.

† Disability in daily living = unable to do any one of the nine basic activities of daily living independently, according to the Groningen Activity Restriction Scale.
5) This study cohort included subject living in the community as well as subjects living in long-term care facilities. These are very different populations, particularly with regard to potential development of UTI. It would be very helpful to include a stratified analysis of these subjects to see if the predictor variables are different in these two groups.

We did a stratified analysis for both groups and found no difference in predictor variables (See table below). No further differences in hazard ratios were observed for the other potentially predictive factors between participants living in the community or living in long-term care facilities. We added this information to page 13, paragraph 1 of the manuscript.

<table>
<thead>
<tr>
<th></th>
<th>Living in community</th>
<th>HR (95%CI)</th>
<th>P value</th>
<th>Living in long-term care facility</th>
<th>HR (95%CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary school only</td>
<td>372</td>
<td>1.2 (0.8,1.9)</td>
<td>0.452</td>
<td>105</td>
<td>2.3 (1.1, 4.9)</td>
<td>0.036</td>
</tr>
<tr>
<td>Severe cognitive impairment (MMSE&lt;19)</td>
<td>371</td>
<td>1.9 (1.1,3.4)</td>
<td>0.030</td>
<td>103</td>
<td>2.3 (1.2, 4.4)</td>
<td>0.009</td>
</tr>
<tr>
<td>Disability in daily living</td>
<td>371</td>
<td>1.9 (1.3, 2.9)</td>
<td>0.002</td>
<td>107</td>
<td>3.6 (1.1, 11.7)</td>
<td>0.033</td>
</tr>
<tr>
<td>UTI between the ages of 85 and 86 years</td>
<td>372</td>
<td>3.3 (2.1, 5.3)</td>
<td>&lt;0.001</td>
<td>107</td>
<td>4.1 (2.2, 7.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Unintentional loss of faeces</td>
<td>367</td>
<td>2.7 (1.6, 4.8)</td>
<td>&lt;0.001</td>
<td>102</td>
<td>2.5 (1.3, 4.6)</td>
<td>0.004</td>
</tr>
<tr>
<td>Self-reported urine incontinence</td>
<td>367</td>
<td>1.7 (1.2, 2.6)</td>
<td>0.007</td>
<td>102</td>
<td>1.9 (0.9, 4.0)</td>
<td>0.071</td>
</tr>
</tbody>
</table>

6) It is noted that 7 subjects died of UTI. How was this determined? Death directly from UTI is unusual, although it may be a contributing factor in some cases. Did these patients develop urosepsis? Were they hospitalized prior to death? Were there other underlying urologic conditions which might contribute (renal obstruction, acute urinary retention, etc.)? Unfortunately, we did not have any information about the underlying factors associated with these deceased participants. We received mortality data from the municipality and specific data on causes of death were obtained from Statistics Netherlands, according to the International Classification of Diseases and Related Disorders (ICD-10, code N39.0).

7) In the Results section, it is noted that stroke and elevated CRP (> 5 mg/L) showed significantly higher rates of UTI in women, but not in men. It states the data are not shown. Why are the data excluded from presentation? I would recommend including this information. We added the results in the manuscript on page 13, paragraph 1.

Moreover, stroke showed significantly higher risk for developing UTI in women (HR 2.0 [95%CI 1.2, 3.4]; \( P = 0.005 \)), but not in men (HR 1.6 [95%CI 0.6, 4.2]; \( P = 0.346 \)). Also higher risk was found for CRP > 5 mg/l in women (HR 1.5 [95%CI 1.0, 2.2]; \( P = 0.049 \)), but not in men (HR 0.8 [95%CI 0.4, 1.8]; \( P = 0.633 \)).

8) Were any subjects in this study receiving any form of preventive therapy for UTI? The authors note that there has been data to support the use of several different therapies (low-dose antibiotics, vaginal estrogens, cranberry supplementation, etc.) for prophylaxis. This would be important information which could significantly alter the observed results. Unfortunately, we do not have any information about the use of preventive therapy for UTI in our study population. However, it is not presumable that in the period 1997-1999, the inclusion
period of the study, these preventive strategies were frequently used. We therefore believe that preventive therapy use may not have affected our results.

9) Depression was eliminated as a potential predictor variable in the multivariate models because the GDS-15 was not administered to subjects with significant cognitive impairment (MMSE<19). It appears that this involved 90 subjects. Of the subjects evaluated with the GDS-15, it appears that 58 had depressive symptoms. It would be helpful to show a subanalysis of these subjects by group to see if depression was linked to UTI in the group without severe cognitive impairment. Thank you for this suggestion. Since the GDS-15 was not administered to those with severe cognitive impairment, the results reported for GDS-15 are based only on those without severe cognitive impairment. The HR 1.0 (95%CI 0.5, 1.7); \( P = 0.897 \) shows that depression is not linked to UTI in those without severe cognitive impairment.

Minor Essential Revisions

10) In Figure 1, please provide a key to differentiate the two lines. Currently it is listed as ‘green line’ and ‘blue line’; however I only had a black & white print available. Some readers may also not have easy access to color in this Figure. This would improve the ability to interpret results. Done

11) Please provide an English translation for Reference number 3 in addition to the Dutch. This would be helpful for non-Dutch speakers reading this article. We added an English translation for this reference.

Discretionary Revisions

12) You might consider also including the Dutch (or original language) titles in addition to the English translation for references 6 and 33. We added the Dutch titles for references 6, 33 and also for reference 27.

We hope you will consider our manuscript for publication in BMC Medicine.

On behalf of all authors,
Yours sincerely,

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