PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Exploring the role of pain as an early predictor of Category 2 pressure ulcers: A prospective Cohort Study.
AUTHORS	Smith, Isabelle; Brown, Sarah; McGinnis, Elizabeth; Briggs, Michelle; Coleman, Susanne; Dealey, Carol; Muir, Delia; Nelson, E. Andrea; Stenvenson, Rebecca; Stubbs, Nikki; Wilson, Lyn; Brown, Julia; Nixon, Jane

VERSION 1 - REVIEW

REVIEWER	Jan Kottner Charité-Universitätsmedizin Berlin, Germany
REVIEW RETURNED	17-Aug-2016

GENERAL COMMENTS	Thank you very much for the invitation to review this manuscript. This is a very important and high quality study about a so far largely unexplored phenomenon. Please find some minor comments below (1) The manuscript is formatted perfectly according to STROBE. However, please delete the "/", choose "Background" or "Rationale", delete the ":" (2) Aims, p. 5, line 39, first objective: Please delete "… after conducting full stepwise…" This is rather technical and does not change the objective. (3) Patients, p. 6, second para: Here you say, that being immobile or having limited mobility according to the respective Braden item was an inclusion criterion. In Table 1 Baseline Characteristics there is a huge proportion of patients having slightly or no mobility problems. That you used all four categories also becomes clear in the quantitative variables section (p. 9). This seems to be inconsistent. (4) Outcomes: From the text it seems clear how the outcomes were defined, but Figure 1 is unfortunately confusing. Above all the relation between the first and second decision tree is not clear. It seems that both decisions are in fact separate, not sure. Either adjust the figure or delete it. (5) Data sources, p. 7, second para: What does a "minimum of 13 pre-specified areas" means. I recommend to list all skin areas of interest that the reader knows exactly where you looked at. (6) Data sources, p. 8: You asked the patients, whether they think that the pain is related to a PU or lying/sitting for a long time. What was the rational for this question? How did you use/analyzed this? (7) Results: I recommend clearly state in the table heading whether the results are on skin area or patient level. (8) Results, log regressions: Please provide some kind of model fit

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	index. (9) Table 6: There is the variable chronic wound. I think it is important to have more information about the type (and maybe locations) when predicting PU occurrence. (9) General comment: It would be extremely interesting to provide more detailed data about the types and frequencies about the variable “skin alterations”. Which skin alterations occurred at which areas, how often? Maybe a subgroup analyses is feasible to explore specific associations with PU development?

REVIEWER	Susan Kennerly East Carolina University, USA
REVIEW RETURNED	07-Sep-2016

GENERAL COMMENTS	Thank you for the opportunity to review this manuscript about pressure area related pain as a potential early predictor of Category > 2 pressure ulcer (PU) development in patients from hospital and community settings. The purpose of the study, which aims to assess a priori variables as potential covariates and identify variables that are independently predictive of Category > 2 PUs, is of general interest to healthcare providers due to the multifactorial nature of the study and is especially relevant to caregivers involved in PU prevention. The manuscript can be strengthened by adding clarity to the labeling of models and ensuring that that numbers and percentages presented are applied consistently in narrative and tables throughout the manuscript. The Aims and Objectives provided on page 5 could also be used to enhance the organization of the manuscript and facilitate the reader’s understanding by introducing and discussing the models of analyses in sections according to study aims. The authors are encouraged to consider these suggestions and the following recommendations in refining the manuscript for publication consideration. Recommendations: Abstract, Results Section, Page 3: Recheck numbers and percentages provided to ensure that they correspond with numbers and percentages presented later in the body and tables of the manuscript. Abstract, Conclusions Section, Page 3: It is stated that all 4 models contained pain as a risk factor, yet the model as presented later in the manuscript (pages 17-20) does not contain “pressure area related pain” as a variable. It is contained in the listing of Table 6. It would be helpful to the reader to expand/clarify this in the subsequent narrative describing Table 6. Introduction, Page 5, Line 24: The term “Grade 1” is used to refer to skin and throughout the remainder of the manuscript the term “Category” is used. Suggest that “Category“ be substituted for “Grade”. Methods, Study Design, Page 5, Line 49: Follow-up is described as twice weekly for 30 days or until patient is no longer at high risk, transferred, or died. Clarify how long the period of observation is for each of these and the number of patients in each general group.

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	Since the overall study period is nearly 2 years, it is important to understanding study implementation to be made aware of the typically observation period and the number of observations made per patient. Later, some information is given in terms of number of skin assessment sites, but none about number of times these assessments were conducted. Methods, Outcomes, Page 6, Lines 31-36: The outcomes paragraph with reference to Figure 1 is misleading to reader regarding primary and secondary outcomes. Figure 1 is structured in two parts with a top and bottom section. The top specifies “outcome” and the bottom “primary outcome”. All of the top portion is bracketed showing that it is included/integrated into the lower portion of the figure. Secondary outcomes are not represented on the diagram. A revision of this figure with inclusion of time to development and clear representation of secondary outcomes versus primary outcomes would be more consistent with the narrative and also calls attention to the importance of time to development, which is also a significant study finding. Number of assessments should be added to the narrative description of the figure. Methods, Statistical Methods, Primary Analysis, Page 8, Line 58: The confidence interval applied to the Logistic regression model is appropriate for the study. However, the use of a p-value less than 0.1 for the associated likelihood ratio test seems less stringent than is typically found in clinical studies. Examination of the four models presented in the manuscript reveals that all p-values reported as significant are 0.0476 or less except for the model with a priori factors which reports pressure area related pain as significant at p=0.0931. The inclusion of this factor in the model and setting the chosen level of significance at less than 0.1 requires further explanation/justification in the manuscript. Results, Descriptive Data and Table 1, Page 11/12: Table 1 contains some quite interesting information about the characteristics of participants. Consider adding a closer examination of the Worst skin status a baseline to the descriptive discussion. While it is true that the reader can review Table 1 and discover that as much as 86% of the sample had some skin or wound problem at baseline, this information is quite pertinent to the subsequent development of PUs and also is directly related to the inclusion of only high risk patients in the sample. Table 4, Page 14: Table 4 was a bit challenging to interpret because of the change from number of new PUs to New PU with the listing of the number of skin assessments. For clarity and ease of reader interpretation, consider expanding the table heading labels to reflect number of assessments. Table 6 Narrative Explanation, page 17/18: Add information about findings specific to pressure area related pain which has previously been reported as present in all four models and is also part of the listing in Table 6.

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REVIEWER	Tracey Yap Duke University USA
REVIEW RETURNED	08-Sep-2016

GENERAL COMMENTS	I appreciate the opportunity to review this manuscript regarding pressure area related pain as a potential early predictor of Category > 2 pressure ulcer (PrU) development in patients from both the hospital and community settings. The purpose of this study, which aims to assess a priori variables as potential covariates and identify variables that are independently predictive of Category > 2 PrUs, is of interest to all healthcare providers. General Comments: The Abstract does not match numbers and percentages presented later in the body and tables of the manuscript; for example, it is confusing to the reader that table 4 is inclusive of all 7260 and not the 1266 eligible because this is in essence people vs skin sites. Consider expanding the table heading labels to reflect number of assessments. All of the models were to contain pain as a risk factor; however, not all models presented within the text contain the "pressure area related pain" construct. On page 18 it is not mentioned, yet is in table 6. Also, it is not clear to the reader (would make it much easier to follow) which tables are which models? Please add information about findings specific to pressure area related pain on page 17 and 18; this information was previously reported as present in all four models and is also part of the listing in Table 6. It needs to be made clear why the models were more stringent about exclusion criteria, and also why they were less stringent about statistical significance (one model set at .1 rather than .05 as are the others). For the study design described on page 5, what % of the people observed in these periods? Page 6, what is the rationale for why > 2 PrUs could not participate? Yet, only high-risk were included…not clear. Regarding primary and secondary outcomes and figure 1; this is confusing—the top of figure 1 is outcomes and the bottom section is primary outcome. Furthermore, where is the time to development depicted? A revision of this figure with inclusion of time to development and clear representation of secondary outcomes versus primary outcomes is needed. This manuscript can be improved by adding clarity to the labeling of the models and ensuring that that numbers and percentages presented are applied consistently in narrative, tables, and abstract. My belief is the most interesting finding is the rate of development was faster for those with pain…

VERSION 1 – AUTHOR RESPONSE

Reviewer 1: Jan Jottner

Comment	Response
The manuscript is formatted perfectly according to STROBE. However, please delete the "/",	"\Rationale" deleted and all ":" removed after every heading.

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choose “Background” or “Rationale”, delete the “:”	
Aims, p. 5, line 39, first objective: Please delete “… after conducting full stepwise…” This is rather technical and does not change the objective.	Deleted
Patients, p. 6, second para: Here you say, that being immobile or having limited mobility according to the respective Braden item was an inclusion criterion. In Table 1 Baseline Characteristics there is a huge proportion of patients having slightly or no mobility problems. That you used all four categories also becomes clear in the quantitative variables section (p. 9). This seems to be inconsistent.	On P.6, second paragraph we state than the inclusion criteria for being at high risk is one or more of the following criteria: a) bedfast/chairfast AND completely immobile/have very limited mobility according to the Braden scale, b) localised skin pain on any pressure area skin site, c) Category 1 PU on any pressure area skin site. Therefore, we would not expect all patients to be immobile or with limited mobility.
Outcomes: From the text it seems clear how the outcomes were defined, but Figure 1 is unfortunately confusing. Above all the relation between the first and second decision tree is not clear. It seems that both decisions are in fact separate, not sure. Either adjust the figure or delete it.	The authors have update the flow chart for clarity in line with the other reviewers comments but we would consider deleting it if it is still considered to be too confusing.
Data sources, p. 7, second para: What does a “minimum of 13 pre-specified areas” means. I recommend to list all skin areas of interest that the reader knows exactly where you looked at.	The authors have added in the 13 pre-specifired skin sites, removed the word “minimum” and added that research nurses could record additional pressure area skin sites if identified.
Data sources, p. 8: You asked the patients, whether they think that the pain is related to a PU or lying/sitting for a long time. What was the rational for this question? How did you use/analyzed this?	We have explained in the manuscript that this question is included to identify pressure related pain. We did not want to collect data on other types of pain such as arthritic pain. The data was collected as a dichotomous variable (pain yes/no) and the authors feel this is clear in the models by describing the variable as “the presence of pressure related pain”.
Results: I recommend clearly state in the table heading whether the results are on skin area or patient level.	The table headers have been updated to ensure they specify whether the data/results are at the patient level or the skin site level.
Results, log regressions: Please provide some kind of model fit index.	The authors are cautious about adding this in. We could add in an analogue to R^2 for the fixed effects models but this would not be consistent

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	across all models. We could also add in information criteria statistics (eg. AIC or BIC) however the models are for difference outcomes and therefore these statistics could not be compared. The authors propose not adding in some model fit index as they believe that the point estimates and corresponding confidence intervals should be sufficient.
Table 6: There is the variable chronic wound. I think it is important to have more information about the type (and maybe locations) when predicting PU occurrence.	The authors have included the presence of a chronic wound in the model as an indicator that there is skin damage. Further research is currently ongoing to explore this data further including type/location of wounds in predicting PU occurrence.
General comment: It would be extremely interesting to provide more detailed data about the types and frequencies about the variable "skin alterations". Which skin alterations occurred at which areas, how often? Maybe a subgroup analyses is feasible to explore specific associations with PU development?	The authors acknowledge that this is of interest and although not conducted for this publication is being explored in further research.

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Reviewer 2: Susan Kennerly

Comment	Response
The Aims and Objectives provided on page 5 could also be used to enhance the organization of the manuscript and facilitate the reader's understanding by introducing and discussing the models of analyses in sections according to study aims.	The authors feel that the methods section clearly outlines the analyses conducted and that the results section follows a similar structure.
Abstract, Results Section, Page 3: Recheck numbers and percentages provided to ensure that they correspond with numbers and percentages presented later in the body and tables of the manuscript.	We have fully cross checked and corrected the manuscript.
Abstract, Conclusions Section, Page 3: It is stated that all 4 models contained pain as a risk factor, yet the model as presented later in the manuscript (pages 17-20) does not contain "pressure area related pain" as a variable. It is contained in the listing of Table 6. It would be helpful to the reader to expand/clarify this in the subsequent narrative describing Table 6.	The text for table 6 is below and we have highlighted where the narrative around the presence of pressure area related pain is included. "The final over-dispersion model retained the variables (category 1 PU, skin alterations and the presence of pressure related pain) from the final primary analysis model and: presence of pre-existing Category 2 PU (OR(95% CI)=2.09(1.35-3.23),p=0.0009), presence of chronic wound (OR(95% CI)=1.66(1.06-2.62),p=0.0277) and Braden Activity subscale (P-value for overall analysis of effects=0.0476). Within this model the estimate of the odds of Category≥2 PU development in the presence of pressure area related pain increased (OR(95%CI)=1.85(1.07-3.20),p=0.0271)(**Error! Reference source not found.**)."
Methods, Study Design, Page 5, Line 49: Follow-up is described as twice weekly for 30 days or until patient is no longer at high risk, transferred, or died. Clarify how long the period of observation is for each of these and the number of patients in each general group. Since the overall study period is nearly 2 years, it is important to understanding study implementation to be made aware of the typically observation period and the number of observations made per patient. Later, some information is given in terms of number of skin assessment sites, but none about number of times these assessments were conducted.	We have added to Study Design that the follow-up period is for a maximum of 30 days. Note that the follow up phase is less than 30 days if the patient completes the study early through death/transfer/no longer at high risk. We have added reasons for completing the study to Figure 2 and included the length of follow up under the patients section within the results (P10).
Methods, Outcomes, Page 6, Lines 31-36: The outcomes paragraph with reference to Figure 1 is misleading to reader regarding primary and secondary outcomes. Figure 1 is structured in two parts with a top and bottom section. The top	The authors have update the flow chart for clarity in line with the other reviewers comments but we would consider deleting it if it is still considered to be too confusing.

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specifies “outcome” and the bottom “primary outcome”. All of the top portion is bracketed showing that it is included/integrated into the lower portion of the figure. Secondary outcomes are not represented on the diagram. A revision of this figure with inclusion of time to development and clear representation of secondary outcomes versus primary outcomes would be more consistent with the narrative and also calls attention to the importance of time to development, which is also a significant study finding. Number of assessments should be added to the narrative description of the figure.	
Methods, Statistical Methods, Primary Analysis, Page 8, Line 58: The confidence interval applied to the Logistic regression model is appropriate for the study. However, the use of a p-value less than 0.1 for the associated likelihood ratio test seems less stringent than is typically found in clinical studies. Examination of the four models presented in the manuscript reveals that all p-values reported as significant are 0.0476 or less except for the model with a priori factors which reports pressure area related pain as significant at p=0.0931. The inclusion of this factor in the model and setting the chosen level of significance at less than 0.1 requires further explanation/justification in the manuscript.	Whilst we had included in the narrative that gender, braden moisture, braden activity, presence of a chronic wound and presence of a pre-exsiting category 2 PU were statistically significantly associated with the odds of a developing a new category 2 or above PU in the univariable analysis for the over-dispersion analysis (table 6) we had not highlighted the corresponding p-values in the table as bold. This has now been done. The point relating to having a p-value of less than 0.1 for the associated LRT is based on recommendations and the reference to this has been added under the methods section.
Results, Descriptive Data and Table 1, Page 11/12: Table 1 contains some quite interesting information about the characteristics of participants. Consider adding a closer examination of the Worst skin status a baseline to the descriptive discussion. While it is true that the reader can review Table 1 and discover that as much as 86% of the sample had some skin or wound problem at baseline, this information is quite pertinent to the subsequent development of PUs and also is directly related to the inclusion of only high risk patients in the sample.	A sentence highlighting the levels of skin damage has been added to the descriptive data section.
Table 4, Page 14: Table 4 was a bit challenging to interpret because of the change from number of new PUs to New PU with the listing of the number of skin assessments. For clarity and ease of reader interpretation, consider expanding the table heading labels to reflect number of assessments.	All table headers have been reviewed and updated to include patient level/skin site level as appropriate for clarity.
Table 6 Narrative Explanation, page 17/18: Add information about findings specific to pressure area related pain which has previously been reported as present in all four models and is also part of the listing in Table 6.	This relates to the above comment and the authors provide the same response: The text for table 6 is below and we have highlighted where the narrative around the presence of pressure area related pain is included. “The final over-dispersion model

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	retained the variables (category 1 PU, skin alterations and the presence of pressure related pain) from the final primary analysis model and: presence of pre-existing Category 2 PU (OR(95% CI)=2.09(1.35-3.23),p=0.0009), presence of chronic wound (OR(95% CI)=1.66(1.06-2.62),p=0.0277) and Braden Activity subscale (P-value for overall analysis of effects=0.0476). Within this model the estimate of the odds of Category≥2 PU development in the presence of pressure area related pain increased (OR(95%CI)=1.85(1.07-3.20),p=0.0271)(**Error! Reference source not found.**).”

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Reviewer 3: Tracey Yap

Comment	Response
The Abstract does not match numbers and percentages presented later in the body and tables of the manuscript; for example, it is confusing to the reader that table 4 is inclusive of all 7260 and not the 1266 eligible because this is in essence people vs skin sites. Consider expanding the table heading labels to reflect number of assessments.	We believe this is a misunderstanding. Figure 2 which indicates that 1266 patients were eligible relates to the patient pathway whereas table 4 relates to the skin site level data. The headers have been updated for clarity throughout the manuscript.
All of the models were to contain pain as a risk factor; however, not all models presented within the text contain the "pressure area related pain" construct. On page 18 it is not mentioned, yet is in table 6. Also, it is not clear to the reader (would make it much easier to follow) which tables are which models? Please add information about findings specific to pressure area related pain on page 17 and 18; this information was previously reported as present in all four models and is also part of the listing in Table 6.	This is in line with the previous reviewer's comment and the authors respond with the same: The text for table 6 is below and we have highlighted where the narrative around the presence of pressure area related pain is included. "The final over-dispersion model retained the variables (category 1 PU, skin alterations and the presence of pressure related pain) from the final primary analysis model and: presence of pre-existing Category 2 PU (OR(95% CI)=2.09(1.35-3.23),p=0.0009), presence of chronic wound (OR(95% CI)=1.66(1.06-2.62),p=0.0277) and Braden Activity subscale (P-value for overall analysis of effects=0.0476). Within this model the estimate of the odds of Category≥2 PU development in the presence of pressure area related pain increased (OR(95%CI)=1.85(1.07-3.20),p=0.0271)(**Error! Reference source not found.**)." We have also updated he headers on each table to make it clear which tables are which models.
Introduction, Page 5, Line 24: The term "Grade 1" is used to refer to skin and throughout the remainder of the manuscript the term "Category" is used. Suggest that "Category" be substituted for "Grade".	The reason we used the term "Grade" here is in line with the referenced papers.
It needs to be made clear why the models were more stringent about exclusion criteria, and also why they were less stringent about statistical significance (one model set at .1 rather than .05 as are the others).	The point relating to having a p-value of less than 0.1 for the associated LRT is based on recommendations and the reference to this has been added under the methods section.
For the study design described on page 5, what % of the people observed in these periods?	The reasons for study completion have been included in Figure 2.
Page 6, what is the rationale for why > 2 PrUs could not participate? Yet, only high-risk were included…not clear.	As the primary outcome was identifying whether pain is a predictor of subsequent cat >2 PU development we did not include patients with more than 1 existing

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	cat 2 PU as this would have reduced the number of skin sites where a new PU could develop and be included in the analysis (existing PU skin sites were excluded from analysis).
Regarding primary and secondary outcomes and figure 1; this is confusing—the top of figure 1 is outcomes and the bottom section is primary outcome. Furthermore, where is the time to development depicted? A revision of this figure with inclusion of time to development and clear representation of secondary outcomes versus primary outcomes is needed.	The authors have update the flow chart for clarity in line with the other reviewers comments but we would consider deleting it if it is still considered to be too confusing.
This manuscript can be improved by adding clarity to the labeling of the models and ensuring that that numbers and percentages presented are applied consistently in narrative, tables, and abstract.	We thank the reviewer for their comment and we have fully cross checked the manuscript and updated the headers where appropriate.

VERSION 2 – REVIEW

REVIEWER	Jan Kottner Charité-Universitätsmedizin Berlin, Germany
REVIEW RETURNED	13-Nov-2016

GENERAL COMMENTS	Thank you very much for adressing the review comments. The manuscript is very clear now.

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