

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Utilization of primary care before a childhood cancer diagnosis: Do socioeconomic factors matter? A Danish nationwide population-based matched cohort study
AUTHORS	Friis Abrahamsen, Christina; Ahrensberg, Jette Møller; Vedsted, Peter

VERSION 1 – REVIEW

REVIEWER	Claire Vajdic University of New South Wales, Australia
REVIEW RETURNED	25-Apr-2018

GENERAL COMMENTS	<p>RE: Utilization of primary care before a childhood cancer diagnosis: Do socioeconomic factors matter? A nationwide population-based matched cohort study</p> <p>Abrahamsen and colleagues have used linked administrative health data to examine the relationship between parental socioeconomic factors and excess primary care presentations and primary care tests prior to childhood cancer diagnosis. The key variables available for analysis are date of cancer diagnosis, cancer topography, invoiced general practitioner (GP) consultation, invoiced test performed by GP, sociodemographic information and demographic information, at the level of the individual. The study populations were all children (0-15yrs) diagnosed with incident cancer (index case) and randomly selected children living in Denmark and alive at the date of diagnosis of the index case.</p> <p>The manuscript is well written. However, I think that the findings are over-interpreted with respect to delayed diagnosis for childhood cancer, and the role of the GP, parents and GP-parent interaction. This is a very challenging issue to study without comprehensive data showing the complete route to diagnosis, and especially so without knowing the date of first presentation to a health service with signs/symptoms diagnostic for cancer.</p> <p>I offer the following comments:</p>
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	<ol style="list-style-type: none"> 1. Abstract results. "Frequent use of consultations" needs to be defined in the abstract as it is not clear what this means. 2. Abstract conclusions. I'm not convinced that there is enough information from this study to draw conclusions about the handling of patients in general practice. We do not know the reason for the consultation(s), whether the GP referred the patient for specialist consultation, or whether the patient attended the specialist consultation. As noted above, we don't know the routes to diagnosis including whether the child presented to an emergency department, or was hospitalised in the days and weeks prior to the cancer registry-defined date of diagnosis. If I have understood the GP consultation measure correctly, the study has not ascertained GP consultations during hospitalisation? 3. Introduction. Excess healthcare use is also a measure of (other, non-cancer) illness in a child. Children from families of lower socioeconomic means may be more likely to acquire infectious diseases and illnesses related to poor nutrition and other harmful exposures, such as industrial pollution and road pollution. This probably needs to be acknowledged. 4. Methods: date of cancer diagnosis/index date. Did the authors know the full date of diagnosis (ie day, month and year)? And, is the best basis of diagnosis (i.e. histopathology, clinical) also known? I think it is important to acknowledge that the date of clinical diagnosis may vary from the date of diagnosis recorded by cancer registries, and to note the business rules followed by the Danish Cancer Registry. For example, the date of diagnosis may be the date of the biopsy or tissue resection recorded on the diagnostic histopathology report. In some cases, the cancer may have been diagnosed clinically a number of days or weeks prior to histopathological confirmation, depending on the age of the patient, and clinical, health-service and access related factors, and this may not be adequately dealt with by including age, sex and only 5 categories of cancer type in the model. Other cases (e.g. inoperable brain cancer) may only have a clinical diagnosis. 5. Methods: diagnostic procedures. I wonder if the list of diagnostic procedures could be more accurately described as invoiced diagnostic tests? The NHR does not record diagnostic procedures like palpation, visual acuity, temperature, full body physical examination etc. This has implications later in the text when it is stated that "During the three months before the diagnosis, 29% of children with cancer had at least one diagnostic procedure performed in primary care". Is there a typographic error in line 37/38, as blood samples are listed as a type of blood test? 6. Methods: reference group. Were children with cancer eligible to be selected in the reference group? 7. Methods. Are you able to adjust for access to
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	<p>hospital/specialist care, such as urban/metropolitan/rural location or distance to nearest paediatric hospital or specialist services? I appreciate that Denmark has universal health care, but how might this influence GP attendance, and the observed association with family income?</p> <p>8. Methods: number of children in household. In addition to being a socioeconomic factor, the presence of other children in the household can also influence comorbidity, in particular infectious diseases.</p> <p>9. Results: consultations two years before diagnosis. I'm not sure that this finding should be headlined in the abstract because of the marked contribution by the excess in the 1-3 month period, which is likely related to the diagnostic workup, and as noted above, the date of histological vs clinical diagnosis may vary for valid clinical reasons. It may be helpful to see the activity in each of the months in the 1-3 month window. Of potentially greater interest is the excess rate of consultations 4-18 months, especially 4-9 months, prior to diagnosis. Whilst I agree that this is a minor statistically significant excess, it is a fascinating finding and worthy of exploration.</p> <p>10. Results: page 8 line 12+. "During the three months before the diagnosis, 29% of children with cancer had at least one diagnostic procedure performed in primary care". Does the denominator for this calculation only include children who attended primary care in that time period? Is this information reported in a table or figure and are 95% confidence intervals available?</p> <p>11. Discussion: page 8 line 49/50. As noted above, I don't believe that this study does not have the data to show a prolonged "diagnostic interval" in childhood cancer. It does show increased presentations to primary care in the period prior to the cancer-registry defined date of diagnosis.</p> <p>12. Discussion: page 8 line 49/50+. "Our findings indicate that some or several of these factors may be at play in parents with low education". I believe that this claim is difficult to defend without data on the reason for the consultation(s), specialist referrals, specialist visits, ED visits and distance from specialist services.</p> <p>13. Discussion: page 10 3rd paragraph. I do not agree that the potential bias from "the lack of information on the reasons for the requested consultations and performed tests" was reduced by the use of a large dataset and the matching of cases (age and sex alone). I also disagree that the restriction to children lessened the impact of residual confounding by other factors (e.g. comorbidity, geographic access to specialist care).</p> <p>Minor issues</p>
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	<ol style="list-style-type: none"> 1. Methods, reason for visit. Did the findings hold when preventive child health examinations were included? Presumably signs and symptoms ascertained at such visits would also generate tests and/or referrals? I think this would be a sensible sensitivity analysis, from my understanding of preventative child health examinations, and the findings from Sondergaard G et al Scand J Prim Health Care 2008;26:5-11? 2. Methods, statistical analyses. Are any of the SEP variables highly correlated? If so, does this have any implications for including them all in the second model? 3. Results, page 8 line 5/6. The IRR is 1.71, not 1.7 4. Discussion, page 8 line 27/28. I don't think it is correct to talk about the likelihood of "receiving extra" consultations, when patients are <i>attending</i> consultations and we are not presented with any information to conclude that they are <i>extra</i>. 5. Discussion, page 9 line 43/44. Safety-netting requires a brief explanation.
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REVIEWER	Philip McLoone Institute of Health & Well-Being, University of Glasgow, Scotland
REVIEW RETURNED	27-Apr-2018

GENERAL COMMENTS	<p>This paper looks at primary care consultations two years prior to a diagnosis of childhood cancer. The authors also included an age and sex matched sample who did not have a diagnosis of cancer. The analysis employed 4 nationwide registers matched by civil registration number.</p> <p>Unsurprisingly the authors found that among patients diagnosed with cancer consultation rates were substantially higher in the 1- 3 months before diagnosis, compared to matched patients without cancer. They found excess consultations among low/middle income groups at 1-3 months compared to high income groups.</p> <p>The authors explored differences in frequent consultation (4 consultations in 3 months before diagnosis) among cancer cases by parental socio-economic indicators. They found higher consultation rates among children of parents with low income or those who were unemployed</p> <p>The authors conclude that children who are later diagnosed with cancer use primary care more often in the months before the diagnosis. The study also shows that children of parents with low income have more contacts with the GP than children of parents with high income.</p> <p>Analysis The authors do not define the units of consultation or procedure rates – i.e. is it X consultations per 100 patients or X consultations per patient. Individuals can have more than 1 consultation or procedure - it would have been informative to describe the distribution of the number of consultations and procedures within each time period.</p> <p>The authors describe the study as a matched cohort study. I am wondering if this is the correct term. It could be described as a case-control study, as it involves cases (cancer patients) and matched</p>
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	<p>controls and looking at previous consultation rates.</p> <p>The authors repeatedly use the term likelihood. I would prefer that they did not use this term as it has a specific statistical meaning. Here is it used as a general term, but could be confusing especially when used in conjunction with logistic regression and odds ratios</p> <p>Overall This is a straight forward and well-presented study. However, I feel that the authors do not explicitly state what it adds to the existing literature.</p>
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VERSION 1 – AUTHOR RESPONSE

II) Comments from reviewer 1

1. Abstract results. “Frequent use of consultations” needs to be defined in the abstract as it is not clear what this means.

Response: The text in the abstract has been revised as follows:

“Furthermore, we estimated the association between socioeconomic factors and odds of frequent use of consultations, defined as at least four consultations, and the odds of receiving a diagnostic test within three months of diagnosis.”

2. Abstract conclusions. I’m not convinced that there is enough information from

this study to draw conclusions about the handling of patients in general practice. We do not know the reason for the consultation(s), whether the GP referred the patient for specialist consultation, or whether the patient attended the specialist consultation. As noted above, we don’t know the routes to diagnosis including whether the child presented to an emergency department, or was hospitalised in the days and weeks prior to the cancer registry-defined date of diagnosis. If I have understood the GP consultation measure correctly, the study has not ascertained GP consultations during hospitalisation?

Response: We agree that we do not have the full knowledge about the routes to diagnosis for the study population. Furthermore, it is correctly understood that the study does not ascertain GP consultations during hospitalisation. The sentence regarding the handling of patients have been removed from the abstract conclusion.

3. Introduction. Excess healthcare use is also a measure of (other, non-cancer) illness in a child. Children from families of lower socioeconomic means may be more likely to acquire infectious diseases and illnesses related to poor nutrition and other

harmful exposures, such as industrial pollution and road pollution. This probably needs to be acknowledged.

Response: The text have been revised in the introduction and now reads as follows:

Several studies have documented inequalities in the healthcare use between patients with low and high socioeconomic position (SEP) ⁸⁻¹¹. Children from families with lower SEP are more frequent in contact with the health care system. They more often suffer from chronic diseases, are more likely to acquire infectious diseases and have increased risk of injuries ¹²⁻¹⁴. However, the utilization of preventive child health examinations is lower in the deprived part of the population ⁸.

4. Methods: date of cancer diagnosis/index date.

Did the authors know the full date of diagnosis (ie day, month and year)?

And, is the best basis of diagnosis (i.e. histopathology, clinical) also known? I think it is important to acknowledge that the date of clinical diagnosis may vary from the date of diagnosis recorded by cancer registries, and to note the business rules followed by the Danish Cancer Registry. For example, the date of diagnosis may be the date of the biopsy or tissue resection recorded on the diagnostic histopathology report. In some cases, the cancer may have been diagnosed clinically a number of days or weeks prior to histopathological confirmation, depending on the age of the patient, and clinical, health-service and access related factors, and this may not be adequately dealt with by including age, sex and only 5 categories of cancer type in the model. Other cases (e.g. inoperable brain cancer) may only have a clinical diagnosis.

Response:

Thank you, we agree it is an important aspect to consider in cancer studies. We have the exact date of diagnosis (day, month and year). The date of diagnosis in the Danish Cancer registry is based on the international hierarchy, that uses the dates of histological confirmation, admission to hospital and date of death. The histology date always takes precedence over any other date obtained (e.g. admission date). We have added this clarification to the method section in the manuscript. It is of course important to keep in mind that cancer may have been diagnosed clinically prior to histopathological confirmation. This could impact the diagnostic interval. However, we do not expect it to affect the number of consultations/diagnostic tests as we expect it to be only a couple of days difference. We do not expect a systematic difference in the registration according to socioeconomic position and the effect, if any, is therefore

likely to be small. We have also added these considerations in the discussion section (under limitations and strengths).

5. Methods: diagnostic procedures. I wonder if the list of diagnostic procedures could be more accurately described as invoiced diagnostic tests? The NHR does not record diagnostic procedures like palpation, visual acuity, temperature, full body physical examination etc. This has implications later in the text when it is

stated that “During the three months before the diagnosis, 29% of children with cancer had at least one diagnostic procedure performed in primary care”. Is there a typographic error in line 37/38, as blood samples are listed as a type of blood test?

Response:

- a) The text has been revised and the wording “diagnostic procedure” has been changed with “invoiced diagnostic tests” throughout the manuscript
- b) Correct, it was a typographic error. It has been corrected. We apologize for the confusion it may have caused.

6. Methods: reference group. Were children with cancer eligible to be selected in the reference group?

Response: References were only eligible if they had no history of cancer on the day the case was diagnosed with cancer. This has been added in the manuscript under study population, which now read as follows:

“The references had to be alive, without a history of cancer, and resident in Denmark at the index date (i.e. date of diagnosis) and two years before the index date.”

7. Methods. Are you able to adjust for access to hospital/specialist care, such as urban/metropolitan/rural location or distance to nearest paediatric hospital or specialist services? I appreciate that Denmark has universal health care, but how might this influence GP attendance, and the observed association with family income?

Response: We agree that this would be an interesting adjustment in the analysis. Unfortunately, we did not have the appropriate data to make the suggested adjustments in the present study.

8. Methods: number of children in household. In addition to being a socioeconomic factor, the presence of other children in the household can also influence comorbidity, in particular infectious diseases.

Response: We agree, that is something to consider. In the logistic regression we adjusted for the presence of other children in the household in order to address this concern.

9. Results: consultations two years before diagnosis. I'm not sure that this finding

should be headlined in the abstract because of the marked contribution by the excess in the 1-3 month period, which is likely related to the diagnostic workup, and as noted above, the date of histological vs clinical diagnosis may vary for valid clinical reasons. It may be helpful to see the activity in each of the months in the 1-3 month window. Of potentially greater interest is the excess rate of consultations 4-18 months, especially 4-9 months, prior to diagnosis. Whilst I agree that this is a minor statistically significant excess, it is a fascinating finding and worthy of exploration.

Response: The abstract has been revised accordingly to the comment. The sentence regarding consultations two years before diagnosis has been removed from the abstract. We agree with the reviewer, that we risk to lose some information because we chose 3-months periods. After the reviewer's suggestion we took an extra glance at our data to see if any new information could be found by looking at each of the months, but we did not find any new significant details.

10. Results: page 8 line 12+. "During the three months before the diagnosis, 29%

of children with cancer had at least one diagnostic procedure performed in primary care". Does the denominator for this calculation only include children who attended primary care in that time period? Is this information reported in a table or figure and are 95% confidence intervals available?

Response: We apologize that this was not clear. The denominator for the calculation is all the cases (1386 children with cancer). The information has now been added in table 1.

11. Discussion: page 8 line 49/50. As noted above, I don't believe that this study does not have the data to show a prolonged "diagnostic interval" in childhood

cancer. It does show increased presentations to primary care in the period prior to the cancer registry defined date of diagnosis.

Response: We have revised the text and removed the word “also” in order to avoid the reader to think our study shows a prolonged diagnostic interval. We acknowledge it is difficult to draw any conclusion about diagnostic intervals without comprehensive data showing the complete route to diagnosis.

12. Discussion: page 8 line 49/50+. “Our findings indicate that some or several of these factors may be at play in parents with low education”. I believe that this claim is difficult to defend without data on the reason for the consultation(s), specialist referrals, specialist visits, ED visits and distance from specialist services.

Response:

We agree that we cannot claim that these factors are at play. However, we do find that it is a possible explanation for some of the increased presentations in primary care for the children from families with fewer resources. We have added a “could” in order to emphasize that we do not claim this is the case, but more of a possible explanation. The line now read as follows:

“Our findings could indicate that some or several of these factors may be at play in parents with low education”

13. Discussion: page 10 3rd paragraph. I do not agree that the potential bias from

“the lack of information on the reasons for the requested consultations and performed tests” was reduced by the use of a large dataset and the matching of cases (age and sex alone). I also disagree that the restriction to children lessened the impact of residual confounding by other factors (e.g. comorbidity, geographic access to specialist care)

Response: These lines have been removed from the revised manuscript.

III) Minor issues from reviewer 1

1. Methods, reason for visit. Did the findings hold when preventive child health examinations were included? Presumably signs and symptoms ascertained at such visits would also generate tests and/or referrals? I think this would be a sensible sensitivity analysis, from my understanding of preventative child health examinations, and the findings from Sondergaard G et al Scand J Prim Health Care 2008;26:5-11?

Response: It is something we have considered. However, we expect the benefit of such an analysis would be very limited. We agree with the reviewer that it is possible that a preventative child health care examination could generate diagnostic tests or a new consultation. This would be the case for both the references and cases in the study. These preventive health examinations are offered systematic to all children. We are aware that children from families with low SEP are more likely not to use these preventive health examinations. We therefore expect that if we include these examinations in the analysis, we would underestimate the numbers of consultations prior to the diagnosis for the children from families with low SEP.

2. Methods, statistical analyses. Are any of the SEP variables highly correlated? If so, does this have any implications for including them all in the second model?

Response: We agree that this is important and something to be aware of in studies using multiple socioeconomic variables. We examined the SEP variables for correlations, but none of the correlations were high enough to justify removing them in the second model. E.g. income-education correlation was less than 0.50, so not strong enough to justify using income and education as proxies for each other.

3. Results, page 8 line 5/6. The IRR is 1.71, not 1.7

Response: This has been corrected so the IRR now reads 1.71

4. Discussion, page 8 line 27/28. I don't think it is correct to talk about the likelihood of "receiving extra" consultations, when patients are attending

consultations and we are not presented with any information to conclude that they are extra.

Response: We agree that the word "extra" can be misunderstood. The wording has been changed according to the reviewer's comments. The text now reads as follows:

"However, the odds of receiving more consultations and diagnostic tests was modified by parental socioeconomic position."

5. Discussion, page 9 line 43/44. Safety-netting requires a brief explanation.

Response: We have added following explanation about the term safety-netting:

The use of 'safety-netting' as a strategy to manage diagnostic uncertainty is increasingly recognised as important in adult cancer diagnostics and may be even more pertinent in children³⁴. The term 'safety-netting' was introduced to general practice by Roger Neighbour who considered it a core component of the consultation. He defined safety-netting as encompassing three questions GPs might ask themselves when they make a working diagnosis; If I'm right what do I expect to happen? How will I know if I'm wrong? What would I do then? The aim is to ensure patients are monitored until their symptoms are explained³⁵.

IV) Comments from reviewer 2

1. The authors do not define the units of consultation or procedure rates – i.e. is it X consultations per 100 patients or X consultations per patient. Individuals can have more than 1 consultation or procedure - it would have been informative to describe the distribution of the number of consultations and procedures within each time period.

Response:

We have now added a definition for the units in the methods section. It now read as follows:

“The main outcomes were rates of consultations and diagnostic tests per patient performed in general practice; these data were obtained from the NHR”

2. The authors describe the study as a matched cohort study. I am wondering if this is the correct term. It could be described as a case-control study, as it involves cases (cancer patients) and matched controls and looking at previous consultation rates.

Response: We agree that most frequently matching is used in case-control studies but it can also be used in cohort studies. Had the studied outcome been cancer, then I would agree it should be defined as a case—control study (as case-control studies identify subjects by outcome status at the outset of the investigation). However, the outcome of interest in this current study is not cancer but the use of primary care health services.

3.The authors repeatedly use the term likelihood. I would prefer that they did not use this term as it has a specific statistical meaning. Here is it used as a general term, but could be confusing especially when used in conjunction with logistic regression and odds ratios

Response:

The term has been changed according to the reviewer's comments. The term likelihood has been replaced throughout the manuscript with the term "odds".

4.This is a straight forward and well-presented study. However, I feel that the authors do not explicitly state what it adds to the existing literature

Response:

Thank you. We appreciate the positive feedback.

We have revised the text in the conclusion in order to make it a bit more explicit.

We have added the sentence:

"We were able to demonstrate that children from families with lower SEP tended to see the GP more often before cancer diagnosis.

This study shows that despite the direct and free access to GPs and primary care, some social inequalities are seen in the healthcare utilization and handling of these patients in general practice. "

VERSION 2 – REVIEW

REVIEWER	Claire Vajdic University of New South Wales, Australia
REVIEW RETURNED	14-Jun-2018

GENERAL COMMENTS	The authors have addressed my concerns, with one exception. Consideration should be given to acknowledging the lack of adjustment for access to hospital/specialist case as a limitation.
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REVIEWER	Philip McLoone Institute of Health and Wellbeing, University of Glasgow, UK
REVIEW RETURNED	26-Jun-2018

GENERAL COMMENTS	The authors have addressed my previous comments.
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VERSION 2 – AUTHOR RESPONSE

Comment from reviewer 1

Consideration should be given to acknowledging the lack of adjustment for access to hospital/specialist case as a limitation.

Response:

Under the subheading “*Strengths and limitations of the study*” (page 10) we have added the following sentence:

However, we cannot exclude residual confounding by other factors. For example, comorbidity or geographic factors such as distance to GP or nearest hospital, could have influenced our results. It could be argued that geographic factors may influence the use of GP services, as there is a shortage of GPs in the more remote parts of Denmark. This might affect the accessibility and waiting time in the remote parts of Denmark, where a higher proportion of the population have lower SEP. This could potentially influence GP attendance and underestimates the effect of socioeconomic factors on utilization of primary care.