PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Results of Florida's Amyotrophic Lateral Sclerosis Surveillance Project, 2009-2011
AUTHORS	Cecilia Freer, Tara Hylton, Heather M. Jordan, Wendy E. Kaye, Sabrina Singh, Youjie Huang

VERSION 1 - REVIEW

REVIEWER	Dr. Joachim Wolf Dept. of Neurology Diakonissenkrankenhaus Mannheim Germany
REVIEW RETURNED	20-Jan-2015

GENERAL COMMENTS	This is an interesting manuscript reporting on a retrospective analysis of prevalent and incident ALS patients in Florida. So far there was a lack of population-based data on ALS patients in this state. Thus these results may contribute to improve epidemiology of this serious disease in the USA. Interestingly, but not surprisingly, Hispanics were underrepresented. Several studies showed ethnic differences in ALS incidence, with higher incidence in populations with European ancestry. Though, different access to health systems has to be considered. There are some points that should be addressed by the authors: 1. The number of patients should be mentioned in the results' section of the abstract. 2. It seems, that the search for and enrolment of patients was quite difficult. In this context the report of a patient depended on the memory of the involved neurologist. How could you guarantee that all the treated patients were reported and not only a special selection of patients? How could you ensure that date of diagnosis of suspected incident patients was within the study period 2009-2011? Furthermore it is very important to notice that 109 neurologists didn't take part in the surveillance project although they had diagnosed ALS patients. 3. You wrote: "Persons with ALS that were diagnosed prior to 2009 could have been reported ..." Does it mean that reporting was voluntary? This however would influence analysis of ALS prevalence. 4. How was date of symptom onset determined? 5. Diagnosis of early frontotemporal dementia is difficult. So results on the frequency of dementia should be handled with caution, particularly as the methods of evaluation of dementia were not known. 6. How many samples of cases were selected? This should be mentioned in the methods' section.

	7. You estimated a period prevalence, which resembled prevalence data of several prospective population-based registries. However in these registries point-prevalences were calculated. This should be mentioned. The methodology of your surveillance project is not suitable to calculate prevalence data. So you should decide whether you don't use prevalence data or whether you explain methodical concerns. 8. Please explain how you calculated the expected number of patients (1505) 9. "Immediate family" member should be stated more precisely. 10. I would suggest to present table 2 only with data of incident patients (1021). In the disease course (and in prevalent patients) the criteria definite and probable increase considerably. 11. In the discussion section it is important that you point to the limitations of your study in comparison to population-based prospective registries more thoroughly. Nevertheless your contribution is important for further epidemiological studies in the USA.

REVIEWER	Paul H. Gordon, MD, PhD Indian Health Service Dept Health and Human Services Northern Navajo Medical Center Shiprock, NM USA
REVIEW RETURNED	31-Jan-2015

GENERAL COMMENTS	The investigators describe surveillance data on incidence and prevalence of ALS in Florida during 2009-2011. Data were obtained from neurologists. Not all neurologists, including those at VA hospitals, participated. A proportion of cases were selected for verification. Separately, cases were identified from death certificates and hospital discharge data. The project was supported by a bill signed into law by GW Bush in 2008 that created a National ALS Registry and was made possible when the Toxic Substances and Disease Registry funded this ALS surveillance project in Florida. The findings are in line with other reports: average annual incidence 1.81/100,000 was higher in men and white people. The period prevalence was 3.95/100,000. The Discussion gives, without stating it explicitly, a glimpse of the almost heroic undertaking this study was. The investigators contacted – repeatedly and in person- more than 800 neurologists statewide and collected nearly 2000 case reports. Those physicians who refused to participate did so despite repeated educational efforts on the part of the research team. Some specific comments: The writing is concise and clear. Abstract, Conclusion, 1st sentence: This was a time-consuming and expensive project, but there are no data in the abstract on this point, and so the conclusion seems disjointed. The sentence might be better placed in the Discussion (though there is no mention of cost anywhere) and replaced by a final sentence on future directions.

	What are the next steps in ALS? Page 9, line 7 “Revised” El Escorial criteria. Different than the original. Page 9, last sentence. Why did the investigators determine period prevalence and not point prevalence? Suggest make the reasoning clear, since most studies calculate point prevalence and the two are not strictly comparable. Throughout the article comparison is made to the expected number of cases and expected incidence rate. Suggest state how this value was chosen: ie, the median annual incidence rate of high quality studies reported by Hirtz et al. Along these lines, page 6, line 9, the range of incidence rates reported by Hirtz et al was 0.7-2.5 not 1.6 – 2.5. The reported 4.3% rate of dementia is not backed by any supporting diagnostic evidence and is not especially meaningful. Too many studies on the topic point to a higher rate. This project is a rigorous analysis of the epidemiology of ALS in an entire state, is on par with the quality of reports of ALS registries in Europe and so brings the U.S. in line with other countries in an area of investigation that has lagged too far behind for too long. The investigators successfully completed something that hasn’t been done on this scale in the U.S. until now. A comment aimed at the designers of future studies and not the current study’s investigators. The authors allude to the issue without directly addressing it in two comments in the discussion: 1) page 14, line 12, ‘…there is a concern of [misdiagnosis]’ and 2) page 14, line 9 ‘dementia (another neurodegenerative disease) may go undiagnosed…or physicians do not screen for dementia.’ The concern is that this approach overlooks cases from potentially important groups. The methodology identified 96.7% of cases, an estimate based on other research using the same methodology, ie capturing those patients who appeared at major ALS centers. The problem is not that neurologists made the diagnosis wrong – a neurologist probably makes the diagnosis accurately > 90% of the time (Rowland LP, Mitsumoto H, Przedborski S. Amyotrophic lateral sclerosis... Merritt's Neurology. p. 802-808.) The problem is that large groups of people do not or cannot get to a neurologist when they acquire ALS, ie the design does not screen all segments of society. The methodology ascertains patients from clinic records and death certificates; neither source identifies as many patients as a community-based design. In this study, ALS increased with age, was more common in men than women and more common in whites than minority groups, replicating the pattern seen in other high quality, but not community-based studies. The same pattern is seen in Parkinson disease, a different neurodegenerative disease that, nonetheless, shares many features with ALS. A comparison with community-based approaches shows that register-based studies miss 24-40% of cases (Schoenberg Neurology 1985; Morgante, Neurology 1992; Tison, Acta Neurol Scand 1994; de Rijk J Neurol Neurosurg Psychiatry 1997; among others). In register-based studies, incidence of PD increases until a certain age then declines

and is higher among men; in community-based studies, rates continue to increase in the most elderly, never dropping off, and sex differences vanish. Register –based studies miss women and the elderly, and I will add, miss minorities.

This difference in findings depending on study design has nothing to do with neurologists misdiagnosing patients –it has everything to do with certain groups never seeing a neurologist. Because they are too sick, too poor, too isolated or too undereducated. Whole groups of people don't appear at ALS centers and don't have ALS placed on their death certificate. As an example, people diagnosed with ALS in the Navajo Nation, a 27,000 sq mi area of land that is home to roughly 250,000 Navajo people, never go to the ALS center 250 miles away because they do not possess the myriad resources (financial, cultural) that are necessary to make a journey that is far in both distance and ethos, and they may not be captured by a death record search because some undergo traditional burials outside the standard reporting system. The same can be said for elderly women in nursing homes who are made comfortable instead of being sent to a neurologist. I have evaluated people who moved to a nursing home because of ALS, but I can honestly say, after 20 years of work at ALS centers, I don't think I have seen a single person referred from a nursing home for a first-time diagnosis of ALS.

Many neurologists in the state did not participate in this study or contribute patients. All ALS centers participated and most of the patients were identified through ALS centers, but patients who attend these centers are not the same as the general population of ALS patients. They are younger and more likely to have limb-onset, be men and be white. Women, minorities, the elderly and frail, and those with more severe ALS appear in lower proportion (Sorenson et al, Neurology, 2007, among others).

Does any of this matter? It depends on the goal of the study and what epidemiologists believe they can contribute. If the goal is to contribute to the solutions to important questions about ALS, then it matters a great deal; 150 years of research in clinic –based samples has netted very little. Where do the answers lie? We see that neurodegenerative disorders present in unforeseen ways in some groups of Americans when compared to white people (Gordon et al, JAMA neurology 2013; Movement Disorders 2012, Movement Disorders, In Press.) Perhaps some of the answers are kept by unique populations, the elderly, the poor, and women.

In 1996, Valerie McGuire and colleagues reported one of the first rigorous epidemiological studies on ALS outside Olmsted County. The case capture methods were similar to the current study, canvassing of neurologists. The investigators used the project to examine incidence and prevalence, and in a breakthrough, rates in minority people. They also examined occupational exposures, physical activity, diet, trauma, cigarette use and alcohol consumption as possible etiological factors. It is hard to believe, but this groundbreaking research was done two decades ago. The future bacons.

So what might a future study look like for a disease as rare, disabling and deadly as ALS? Perhaps a combined case ascertainment strategy in which most patients are identified through the registry and specific groups are targeted with community-based canvasing, either through door-to-door visits of every house or

	through some mix of statistical sampling, advertising, and outreach: tribal reservations, poor communities, rural communities, minority communities, nursing homes, and retirement communities as well as their community centers, leaders and health workers must all be identified and screened. If other neurodegenerative diseases are any indication, The incidence of ALS is higher than we think, and the missing 24-42%, of patients are more diverse; older, more likely to be women, more likely to be minority, and sicker than we think. Whether these people hold any secrets to these awful disorders is unknown, but we need to look. And look everywhere. Methodologies that overlooks certain groups miss a rare opportunity to understand how a neurodegenerative disease affects those who are never counted, and in doing so, misses an opportunity to learn about the disease.

REVIEWER	Adriano Chio University of Torino, Italy
REVIEW RETURNED	01-Feb-2015

GENERAL COMMENTS	The findings of a Florida state-wide ALS surveillance project are reported. Epidemiological data (2009-2011) have been collected through neurologists practising in the area, discharge data and death certificates. Data were verified using clinical charts and EMG registrations. Incidence rate was 1.7-1.9/100,000 population. Four% of patients were reported to be demented and some 5% to have a family history for ALS. This study is part of the nationwide effort to establish an US ALS register. The study is methodologically good since it considers all available sources of data to reach a complete case ascertainment. All efforts have been done to verify the correctness of reported ALS diagnoses. I have a few comments 1. Prevalence rate is likely to be underestimated, since cases diagnosed before 2009 and still living are not catch by the study. This aspect should be acknowledged and discussed. 2. To estimate the completeness of case ascertainment a capture-recapture analysis is mandatory.

VERSION 1 – AUTHOR RESPONSE

Reviewer Name Dr. Joachim Wolf
Institution and Country Dept. of Neurology, Diakonissenkrankenhaus, Mannheim, Germany
Please state any competing interests or state ‘None declared’: None declared
Please leave your comments for the authors below
This is an interesting manuscript reporting on a retrospective analysis of prevalent and incident ALS patients in Florida. So far there was a lack of population-based data on ALS patients in this state. Thus these results may contribute to improve epidemiology of this serious disease in the USA. Interestingly, but not surprisingly, Hispanics were underrepresented. Several studies showed ethnic differences in ALS incidence, with higher incidence in populations with European ancestry. Though, different access to health systems has to be considered.
There are some points that should be addressed by the authors:

1. The number of patients should be mentioned in the results' section of the abstract.

Response: The authors appreciate Dr. Wolf's review of our manuscript. The authors agree with this suggested edit and a notation of the 1,450 reported cases has been added to the abstract (Page 2, Line 17).

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2. It seems, that the search for and enrolment of patients was quite difficult. In this context the report of a patient depended on the memory of the involved neurologist. How could you guarantee that all the treated patients were reported and not only a special selection of patients? How could you ensure that date of diagnosis of suspected incident patients was within the study period 2009-2011? Furthermore it is very important to notice that 109 neurologists didn't take part in the surveillance project although they had diagnosed ALS patients.

Reponses: Yes, as noted, collecting eligible case reports was a massive effort and we are confident in the project's case reporting methodology. The methods were designed to capture incident and prevalent ALS cases. Specifically, neurologists and their office staff were asked to report all ALS patients under the neurologist's care starting in January 1, 2009 through December 31, 2011. ALS Surveillance Project staff provided detailed case reporting instructions to the neurologists and staff members. For example, ICD-9 codes were provided to aid in the retrieval of patient lists from electronic medical records and medical billing systems. Therefore, all ALS cases in Florida under a reporting neurologist's care alive at some point during the period January 1, 2009 through December 31, 2011 should have been reported, not only a special selection of patients. It is possible that a small number of cases may have gone unreported; we cannot guarantee that every eligible case was reported. We acknowledge the words "should have been" may have been misleading, therefore we modified the text to read "…before 2009 were reported…" in the methods (Page 8, Line 12).

Patient medical records were reviewed in order to complete the ALS Case Reporting form (reporting form). The reporting form included a question "date of diagnosis". ALS Surveillance Project staff provided detailed case reporting instructions to reporting providers. We are confident this question was completed properly. Patients with dates of diagnosis before January 1, 2009 were excluded to calculate incidence rates. An edit was made to the text to inform the reader that the reporting form was completed after a review of the patient's medical chart (Page 8, Line 15).
We agree it is important to recognize that not all neurologists that did diagnose or care for ALS patients actually reported cases to the project. We did not make any edits to the manuscript because we believe the discussion section already addresses this limitation.

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3. You wrote: "Persons with ALS that were diagnosed before 2009 could have been reported ..." Does it mean that reporting was voluntary? This however would influence analysis of ALS prevalence.

Response: The reporting of ALS cases is not mandated in Florida; therefore participation by all reporting providers was voluntary. ALS Surveillance Project staff provided detailed case reporting instructions to all reporting providers to ensure all eligible prevalent and incident cases were reported. As noted above, we acknowledge the original text could have been misleading; therefore a small edit was made to the text (Page 8, Line 12).

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4. How was date of symptom onset determined?

Response: The date of symptom onset was reported by the neurologist after a review of the patient's medical chart. An edit was made to the text to inform the reader of this process (Page 8, Line 15).

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5. Diagnosis of early frontotemporal dementia is difficult. So results on the frequency of dementia should be handled with caution, particularly as the methods of evaluation of dementia were not known.

Response: We appreciate and concur with the reviewer's comment. We edited the methods section to explain patient medical charts were reviewed to complete the reporting form (Page 8, Line 15) and we edited the discussion section to include the difficulty of diagnosing dementia (Page 15, Lines 6 & 7).

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6. How many samples of cases were selected? This should be mentioned in the methods' section.

Response: There was not case selection for the initial reporting. All cases under the neurologists' care from January 1, 2009 through December 31, 2011 were eligible to be reported. We did select reported cases for the medical record verification process which we described in the methods section. Further, the results section states that 15% of reported cases were selected for medical record verification. We did not make any edits to the manuscript based on this comment. We would be happy to provide further clarification to the reviewer, if warranted.

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7. You estimated a period prevalence, which resembled prevalence data of several prospective population-based registries. However in these registries point-prevalences were calculated. This should be mentioned. The methodology of your surveillance project is not suitable to calculate prevalence data. So you should decide whether you don't use prevalence data or whether you explain methodical concerns.

Response: The authors were not able to determine if reported cases died, therefore it was impossible to report point prevalence. The authors chose to report a period prevalence to add to the current United States-based literature. We concur with the reviewer's comment that reporting a period prevalence and comparing it to a point prevalence might not be appropriate. We have chosen to revise the discussion section to compare the period prevalence in Florida to the reported period prevalence in the recently publishing Morbidity and Mortality Weekly Report (MMWR), "Prevalence of Amyotrophic Lateral Sclerosis – United States, 2010-2011".1 Further, we acknowledge the 12 month period prevalence (3.95 per 100,000 persons) noted in the current manuscript reports a slightly shorter time period compared to the ~14 month period prevalence (3.9 per 100,000 persons) in the MMWR. Edits were made to the discussion section to address these points (Page 13, Lines 20-22; Page 14, Lines 1-13).

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8. Please explain how you calculated the expected number of patients (1505)

Response: To calculate the expected number of ALS cases, the project team used 2010 U.S. Census population data for the state of Florida. A total of 18,801,310 people resided in Florida in 2010.2 According to Hirtz and colleagues (2007), the median annual incidence rate for all studies in their review article was 1.6 per 100,000 people, and in the class I studies it was 2.1 per 100,000 people

(range 0.7-2.5) and the median reported prevalence of all studies was 4.0 per 100,000 people. We used 2.0 as the incidence and 4.0 for the prevalence to calculate the estimated number of ALS cases. An explanation of the calculation has been moved from the discussion section to the methods section (Page 8, Lines 8-10).

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9. "Immediate family" member should be stated more precisely.

Response: The authors agree with this suggested edit. Changes were made to the methods (Page 8, Lines 17 & 18).

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10. I would suggest to present table 2 only with data of incident patients (1021). In the disease course (and in prevalent patients) the criteria definite and probable increase considerably.

Response: The authors agree with this suggested edit and table 2 was modified to include data for incident cases (Page 12). Slight modifications to the text in the results section were also made (Page 12, Line 5).

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11. In the discussion section it is important that you point to the limitations of your study in comparison to population-based prospective registries more thoroughly.

Response: As noted above, the authors acknowledge that reporting a period prevalence and comparing it to a point prevalence might not be appropriate. Rather than compare the period prevalence to international studies reporting period prevalence, we revised the discussion section to compare the period prevalence in Florida to the reported period prevalence in the recently publishing Morbidity and Mortality Weekly Report (MMWR), “Prevalence of Amyotrophic Lateral Sclerosis – United States, 2010-2011”.1 We also incorporated additional edits to acknowledge the limitations of the current study versus population-based prospective registries in the US and abroad. Edits were made to the discussion section to address these points (Page 13, Lines 20-22; Page 14, Lines 1-13).

Nevertheless your contribution is important for further epidemiological studies in the USA.
Joachim Wolf

Reviewer Name Paul H. Gordon, MD, PhD
Institution and Country Indian Health Service, Dept Health and Human Services, Northern Navajo Medical Center
Shiprock, NM, USA
Please state any competing interests or state ‘None declared’: None declared
Please leave your comments for the authors below
The investigators describe surveillance data on incidence and prevalence of ALS in Florida during 2009-2011. Data were obtained from neurologists. Not all neurologists, including those at VA hospitals, participated. A proportion of cases were selected for verification. Separately, cases were identified from death certificates and hospital discharge data. The project was supported by a bill signed into law by GW Bush in 2008 that created a National ALS Registry and was made possible when the Toxic Substances and Disease Registry funded this ALS surveillance project in Florida.

The findings are in line with other reports: average annual incidence 1.81/100,000 was higher in men and white people. The period prevalence was 3.95/100,000.
The Discussion gives, without stating it explicitly, a glimpse of the almost heroic undertaking this study was. The investigators contacted – repeatedly and in person- more than 800 neurologists statewide and collected nearly 2000 case reports. Those physicians who refused to participate did so despite repeated educational efforts on the part of the research team.
Some specific comments:
The writing is concise and clear.

Response: We thank the reviewer for an excellent summary of our work and appreciate his constructive commentary and suggestions as responded to below.

Abstract, Conclusion, 1st sentence: This was a time-consuming and expensive project, but there are no data in the abstract on this point, and so the conclusion seems disjointed. The sentence might be better placed in the Discussion (though there is no mention of cost anywhere) and replaced by a final sentence on future directions. What are the next steps in ALS?

Response: The authors agree with the reviewer and a modification to the abstract has been made (Page 3, Lines 1-7).

Page 9, line 7 “Revised” El Escorial criteria. Different than the original.

Response: Yes, the revised El Escorial criteria were used to classify ALS patients. The word revised was added to the text (Page 6, Line 6; Page 8, Line 17; Page 9, Line 10; Page 12, Line 4).

Page 9, last sentence. Why did the investigators determine period prevalence and not point prevalence? Suggest make the reasoning clear, since most studies calculate point prevalence and the two are not strictly comparable.

Response: As noted in the response to Reviewer 1, the authors were not able to determine if reported cases died, therefore it was impossible to report point prevalence. The authors chose to report a period prevalence to add to the current United States-based literature. We concur with the reviewer’s comment that reporting a period prevalence and comparing it to a point prevalence is not appropriate. We have chosen to revise the discussion section to compare the period prevalence in Florida to the reported period prevalence in the recently publishing Morbidity and Mortality Weekly Report (MMWR), “Prevalence of Amyotrophic Lateral Sclerosis – United States, 2010-2011”.1 Further, we acknowledge the 12 month period prevalence (3.95 per 100,000 persons) noted in the current manuscript reports a slightly shorter time period compared to the ~14 month period prevalence (3.9 per 100,000 persons) in the MMWR. Edits were made to the discussion section to address these points (Page 13, Lines 20-22; Page 14 Lines 1-13).

Throughout the article comparison is made to the expected number of cases and expected incidence rate. Suggest state how this value was chosen: ie, the median annual incidence rate of high quality studies reported by Hirtz et al. Along these lines, page 6, line 9, the range of incidence rates reported

by Hirtz et al was 0.7-2.5 not 1.6 – 2.5.

Response: The authors thank the reviewer for noting the correct range of incidence rates. The manuscript has been edited to reflect the correct range (Page 6, Line 10-12). The authors agree with the reviewer to include how the expected number of incident cases was computed. Edits were made to the methods section to better describe the calculation (Page 8, Lines 8-10).

The reported 4.3% rate of dementia is not backed by any supporting diagnostic evidence and is not especially meaningful. Too many studies on the topic point to a higher rate.

Response: Reviewer #1 also cautioned us about reporting the percentage of cases with dementia. The reporting neurologist performed a chart review while completing the reporting form. If dementia was noted in the chart, it was subsequently noted on the reporting form. We made an edit to methods section to explain patient charts were reviewed to complete the reporting form (Page 8, Line 15). We also made an edit to the discussion section to further describe the limitations collecting dementia data (Page 15, Lines 6 & 7).

This project is a rigorous analysis of the epidemiology of ALS in an entire state, is on par with the quality of reports of ALS registries in Europe and so brings the U.S. in line with other countries in an area of investigation that has lagged too far behind for too long. The investigators successfully completed something that hasn't been done on this scale in the U.S. until now.

A comment aimed at the designers of future studies and not the current study's investigators. The authors allude to the issue without directly addressing it in two comments in the discussion: 1) page 14, line 12, '…there is a concern of [misdiagnosis]' and 2) page 14, line 9 'dementia (another neurodegenerative disease) may go undiagnosed…or physicians do not screen for dementia.'

The concern is that this approach overlooks cases from potentially important groups. The methodology identified 96.7% of cases, an estimate based on other research using the same methodology, ie capturing those patients who appeared at major ALS centers. The problem is not that neurologists made the diagnosis wrong – a neurologist probably makes the diagnosis accurately > 90% of the time (Rowland LP, Mitsumoto H, Przedborski S. Amyotrophic lateral sclerosis... Merritt's Neurology. p. 802-808.) The problem is that large groups of people do not or cannot get to a neurologist when they acquire ALS, ie the design does not screen all segments of society.

The methodology ascertains patients from clinic records and death certificates; neither source identifies as many patients as a community-based design. In this study, ALS increased with age, was more common in men than women and more common in whites than minority groups, replicating the pattern seen in other high quality, but not community-based studies. The same pattern is seen in Parkinson disease, a different neurodegenerative disease that, nonetheless, shares many features with ALS. A comparison with community-based approaches shows that register-based studies miss 24-40% of cases (Schoenberg Neurology 1985; Morgante, Neurology 1992; Tison, Acta Neurol Scand 1994; de Rijk J Neurol Neurosurg Psychiatry 1997; among others). In register-based studies, incidence of PD increases until a certain age then declines and is higher among men; in community-based studies, rates continue to increase in the most elderly, never dropping off, and sex differences vanish. Register –based studies miss women and the elderly, and I will add, miss minorities.

This difference in findings depending on study design has nothing to do with neurologists misdiagnosing patients –it has everything to do with certain groups never seeing a neurologist.

Because they are too sick, too poor, too isolated or too undereducated. Whole groups of people don't appear at ALS centers and don't have ALS placed on their death certificate. As an example, people diagnosed with ALS in the Navajo Nation, a 27,000 sq mi area of land that is home to roughly 250,000 Navajo people, never go to the ALS center 250 miles away because they do not possess the myriad resources (financial, cultural) that are necessary to make a journey that is far in both distance and ethos, and they may not be captured by a death record search because some undergo traditional burials outside the standard reporting system. The same can be said for elderly women in nursing homes who are made comfortable instead of being sent to a neurologist. I have evaluated people who moved to a nursing home because of ALS, but I can honestly say, after 20 years of work at ALS centers, I don't think I have seen a single person referred from a nursing home for a first-time diagnosis of ALS.

Many neurologists in the state did not participate in this study or contribute patients. All ALS centers participated and most of the patients were identified through ALS centers, but patients who attend these centers are not the same as the general population of ALS patients. They are younger and more likely to have limb-onset, be men and be white. Women, minorities, the elderly and frail, and those with more severe ALS appear in lower proportion (Sorenson et al, Neurology, 2007, among others).

Does any of this matter? It depends on the goal of the study and what epidemiologists believe they can contribute. If the goal is to contribute to the solutions to important questions about ALS, then it matters a great deal; 150 years of research in clinic –based samples has netted very little. Where do the answers lie? We see that neurodegenerative disorders present in unforeseen ways in some groups of Americans when compared to white people (Gordon et al, JAMA neurology 2013; Movement Disorders 2012, Movement Disorders, In Press.) Perhaps some of the answers are kept by unique populations, the elderly, the poor, and women.

In 1996, Valerie McGuire and colleagues reported one of the first rigorous epidemiological studies on ALS outside Olmsted County. The case capture methods were similar to the current study, canvassing of neurologists. The investigators used the project to examine incidence and prevalence, and in a breakthrough, rates in minority people. They also examined occupational exposures, physical activity, diet, trauma, cigarette use and alcohol consumption as possible etiological factors. It is hard to believe, but this groundbreaking research was done two decades ago. The future bacons.

So what might a future study look like for a disease as rare, disabling and deadly as ALS? Perhaps a combined case ascertainment strategy in which most patients are identified through the registry and specific groups are targeted with community-based canvasing, either through door-to-door visits of every house or through some mix of statistical sampling, advertising, and outreach: tribal reservations, poor communities, rural communities, minority communities, nursing homes, and retirement communities as well as their community centers, leaders and health workers must all be identified and screened.

If other neurodegenerative diseases are any indication, The incidence of ALS is higher than we think, and the missing 24-42%, of patients are more diverse; older, more likely to be women, more likely to be minority, and sicker than we think. Whether these people hold any secrets to these awful disorders is unknown, but we need to look. And look everywhere. Methodologies that overlooks certain groups miss a rare opportunity to understand how a neurodegenerative disease affects those who are never counted, and in doing so, misses an opportunity to learn about the disease.

Response: As noted by Donaghy and colleagues (2010),4 due to the severity of motor neuron diseases, all patients should be seen by a neurologist at least one time during their disease. To date, few epidemiological studies of ALS incidence have been conducted in the United States using a case

ascertainment methodology designed to collect case reports for all ALS cases from all neurologists diagnosing and/or treating ALS patient in the project's catchment area. Rather, most studies use clinical samples or death certificate data to generate incidence rates. In addition, a paucity of information exists on the proportion of neurologists who diagnose and/or treat ALS patients in a defined period of time, which is helpful information for patient care planning.

After discussing with the project's consulting neurologist, we believe our neurologist recruitment and ALS case data collection methodology is novel and that our approach allowed for unbiased participation and near complete reporting. It is almost inconceivable that a "young" person would not be referred to a neurologist if clinically affected by ALS. It is possible that those with no insurance would have some risk of not being reported, but even these seem unlikely that they would not be seen at least once. Further, our consulting neurologist's group examined elderly subjects in nursing homes. In addition to looking at cognitive function, they screened subjects for a number of neurodegenerative disorders. They examined over 500 subjects and did not detect one case of unrecognized ALS. Unfortunately given the rarity of the disease this does not exclude the possibility of unrecognized ALS it seems likely that any missing cases would be exceedingly low.

According to the Kaiser Family Foundation website http://kff.org/other/state-indicator/number-of-nursing-facility-residents/, in 2011 there were 72,373 people in certified nursing facilities. Even if we did not capture case reports for everyone in a nursing home, the number would be 3-12 cases using a prevalence rate of 4/100,000 and 17/100,000 (MMWR prevalence rate for 70-79 year olds and the highest rate1). It is also likely that some of the people in the nursing homes would be there because of their ALS and would not have developed it there making the 3-12 case on the high side. It is not possible to examine every possible person in the state of Florida. It is always possible that some cases could go undiagnosed. The incidence actually decreases precipitously in the elderly (making their risk to start with low) and the disease is very dramatic in its course making it unlikely that they would not see a neurologist if they are affected. Any missed cases would have to be very low.

In Florida there were 127,432 people who listed being Native American on the 2010 US Census (71,458 NA & 55,974 NA + white). If we missed every Native American and the prevalence is similar to whites, we would have missed 5-7 cases. A recent paper suggests that the incidence of ALS in Native Americans is less than half of whites making the number of potentially missed cases even smaller.5

Although we agree that is it possible that we did not find everyone given most surveillance systems do not get 100% of cases, we do not believe it is valid to compare Parkinson's disease with ALS because the research shows that those who are undiagnosed have milder symptoms that do not interfere with their daily lives. As we have stated before, we may miss someone at the early stages of disease but it is unlikely that he/she has no interaction with the medical profession as the disease progresses.

We did not make any edits to the manuscript based on this comment because we already noted that we may have missed a small number of cases in the discussion section.

eviewer Name Adriano Chio
Institution and Country 'Rita Levi Montalcini' Department of Neuroscience, University of Torino, Italy
Please state any competing interests or state 'None declared': None declared
Please leave your comments for the authors below
The findings of a Florida state-wide ALS surveillance project are reported. Epidemiological data (2009-2011) have been collected through neurologists practising in the area, discharge data and death certificates. Data were verified using clinical charts and EMG registrations. Incidence rate was 1.7-1.9/100,000 population. Four% of patients were reported to be demented and some 5% to have a family history for ALS.
This study is part of the nationwide effort to establish an US ALS register. The study is

methodologically good since it considers all available sources of data to reach a complete case ascertainment. All efforts have been done to verify the correctness of reported ALS diagnoses.

I have a few comments
1. Prevalence rate is likely to be underestimated, since cases diagnosed before 2009 and still living are not catch by the study. This aspect should be acknowledged and discussed.

Response: The authors thank Dr. Chio for his review of our manuscript. The case ascertainment methods were designed to capture incident and prevalent ALS cases. Specifically, neurologists and their office staff were asked to report all ALS patients under the neurologist's care starting in January 1, 2009 through December 31, 2011. ALS Surveillance Project staff provided detailed case reporting instructions to the neurologists and staff members. For example, ICD-9 codes were provided to aid in the retrieval of patient lists from electronic medical records and medical billing systems. Therefore, all ALS cases in Florida under a reporting neurologist's care alive at some point during the period January 1, 2009 through December 31, 2011 should have been reported, not only a special selection of patients. It is possible that a small number of cases may have gone unreported; we cannot guarantee that every eligible case was reported. We acknowledge the words "should have been" may have been misleading, therefore we modified the text to read "…before 2009 were reported…" in the methods (Page 8, Line 12).

Further, the authors were not able to determine if reported cases died, therefore it was impossible to report point prevalence. The authors chose to report a period prevalence to add to the current United States-based literature. We concur with reviewer 1's comment that reporting a period prevalence and comparing it to a point prevalence is not appropriate. We have chosen to revise the discussion section to compare the period prevalence in Florida to the reported period prevalence in the recently publishing Morbidity and Mortality Weekly Report (MMWR), "Prevalence of Amyotrophic Lateral Sclerosis – United States, 2010-2011".1 Further, we acknowledge the 12 month period prevalence (3.95 per 100,000 persons) noted in the current manuscript reports a slightly shorter time period compared to the ~14 month period prevalence (3.9 per 100,000 persons) in the MMWR. Edits were made to the discussion section to address these points (Page 13, Lines 20-22; Page 14, Lines 1-13).

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2. To estimate the completeness of case ascertainment a capture-recapture analysis is mandatory.

Response: It is the authors' understanding that the Agency for Toxic Substances and Disease Registry (ATSDR) will use the data from the ALS Surveillance Projects to validate the completeness of the National ALS Registry, which may include a capture-recapture analysis. In order to do capture-recapture analysis, there has to be multiple data sources. This project had only one data source for case ascertainment, medical records review. Death data and hospital discharge data were only used to identify possible cases and seek a neurologist to report the case. Death data and hospital discharge data were not added to the case count unless a physician case report was received. Therefore, while we agree that capture-recapture analysis can be useful, it is not possible to conduct in this project. No edits were made to the manuscript based on this comment.

VERSION 2 – REVIEW

REVIEWER	Dr. Joachim Wolf Dept. of Neurology Diakonissenkrankenhaus Mannheim Germany
REVIEW RETURNED	13-Feb-2015

GENERAL COMMENTS	All my questions have been answered sufficiently. I have no further comments and would recommend publication of the manuscript.

REVIEWER	Paul H. Gordon, MD, PhD Indian Health Service Dept Health and Human Services Northern Navajo Medical Center Shiprock, NM USA
REVIEW RETURNED	08-Mar-2015

GENERAL COMMENTS	I thank the authors for their responsiveness to the reviewers' suggestions. The article is improved. One minor point: On page 9, the investigators point out that they determined period and not point prevalence because the date of death was unknown. The statisticians in the 5th reference of the 'author's response to decision letter' thought of one approach to circumventing this problem JAMA Neurol 2013… On the final point, I said in the previous review that comments on possibly missing patients in certain groups were for future works and not the paper at hand. Addition of a statement on capture-recapture helps, but, despite the authors' other justifications, we don't have many answers to ALS and don't really know if this type of design misses patients until efforts are expended to examine certain groups. I disagree with the responses, which give the impression that it doesn't matter because there are hardly any cases to be missed anyway. Vulnerable populations are that precisely because they are consistently and repeatedly glossed over. A vulnerable population is 'groups that are not well integrated into the health care system because of ethnic, cultural, economic, geographic, or health characteristics. This isolation puts members of these groups at risk for not obtaining necessary medical care, and thus constitutes a potential threat to their health. It is important enough in a country as diverse as the U.S. that NIH has an entire institute dedicated to the issue; CDC and Florida Dept of Health give resources through programs dedicated to vulnerable populations. Members of these groups must be given attention at all stages of research. Otherwise, we risk propagating the health disparities that

exist in the U.S today and miss a valuable opportunity to learn something new about ALS.

Some census numbers on vulnerable populations in Florida:

American Indians 135,000 people
People in Jail on any given day 55,000
Number uninsured: 3,760,000
Number below the poverty level: 2,350,000
Number homeless: 47,862
Undocumented immigrants: 900,000
Number non-English speakers: 1,980,000
Elders age >65 yrs: 3,259,602

Number in nursing homes: 72,373

The current study identified 1450 cases in a state of 18M. How many cases might be overlooked in the multiple millions of members of vulnerable groups? The point is, we don't know until we look.

Some comments made on specific points in the response:
1. The paper by Donaghy et al: the healthcare system and degree of population diversity in Ireland is far different than those in the U.S. '…should be seen by a neurologist' cannot be equated with 'is seen' especially in vulnerable populations.

2. Re data given by my friend Dr. Sorenson: the number of ALS cases expected in a study of 500 nursing home residents is 0. Separately, more cases are expected in Florida than Olmsted County because of the older age of Florida residents.

3. 'The incidence actually decreases…in the elderly…' This is the crux. We don't know! And is what was found in other diseases: cases in the elderly are missed until specific efforts are made to identify them.

4. The comment on rates in Florida's American Indians is speculative. We don't know until we look.

5. The possible analogy between the distribution of PD and ALS is absolutely valid. There is remarkable clinical and pathological overlap between the disorders. A quick pubmed search yielded more than 1000 articles on the two conditions. In either case, why ALS rates decline in the elderly when they do not in PD and AD has not been explained. One plausible explanation is that we miss elderly with ALS in the same way that was done for PD previously.
I disagree with the comment on why patients with PD were overlooked. The risk for being overlooked in studies of this type is being a member of a vulnerable population, not having mild disease. I also disagree with the comment that patients with ALS would not be missed because it is severe. Elderly in nursing homes, especially women, are not sent for evaluation for neurological conditions of all kinds because, among other reasons, of the notion that many additional tests would create discomfort and not add meaningfully to a limited lifespan.

REVIEWER	Adriano Chio University of Torino, Italy
REVIEW RETURNED	13-Feb-2015

GENERAL COMMENTS	The authors responded satisfactorily to all my concerns

VERSION 2 – AUTHOR RESPONSE

The authors appreciate the reviews of Dr. Wolf, Dr. Chio, and Dr. Gordon and we are pleased with the recommendation for publication. We thank Dr. Gordon for his additional comments. We would specifically like to address the issue of point vs period prevalence. The Florida mortality and hospitalization data were authorized for use to attempt to collect case reports for possible ALS cases that were not yet reported to the project. The Institutional Review Board did not authorize their use for additional analysis purposes, including calculating point prevalence. Current and future research could certainly benefit by including these data sets for both case ascertainment and analysis purposes. For example, using mortality data, the New Jersey ALS Surveillance project followed incident cases and reported a median time from diagnosis to death of 21 months (Jordan H, Fagliano J, Rechtman L, Lefkowitz D, Kaye W. Effects of demographic factors on survival of time after a diagnosis of Amyotrophic Lateral Sclerosis. Neuroepidemiology; manuscript in press).

The authors certainly understand the importance of including all vulnerable populations in public health research and surveillance. Based on information from our consulting neurologist, we still believe that there are few people with ALS that do not interact with the medical system at all regardless of their vulnerability. We agree that the paper from Mayo clinic had a small sample size; however it is encouraging that they found no undiagnosed cases of ALS among the nursing home residents assessed. As we stated in our manuscript, we believe we captured a very large number of eligible cases and acknowledge that it is possible that we missed cases. We believe the previous edits to the paragraph in the discussion section addressed the original comments, particularly in the context of the current surveillance project. There is much work to be completed in this field and there are areas that to be worked on that could lead to improved surveillance of ALS. We are grateful for colleagues pressing forward to better understand and conquer this disease.