## PEER REVIEW HISTORY



## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | Trends in the Diagnosis of Diseases of Despair in the United States, 2009 – 2018: A Retrospective Cohort Study |
| **AUTHORS** | Brignone, Emily; George, Daniel; Sinoway, Lawrence; Katz, Curren; Sauder, Charity; Murray, Andrea; Gladden, Robert; Kraschnewski, Jennifer |

## VERSION 1 – REVIEW

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| **REVIEWER** | Louise Brådvik<br>Lund University, Faculty of Medicine, Department of Clinical Sciences Lund, Psychiatry, Lund, Sweden |
| **REVIEW RETURNED** | 06-Mar-2020 |

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| **GENERAL COMMENTS** | Review bmjopen-2020-037679<br>Trends in the diagnosis of diseases of despair, 2009-2018<br>This is an interesting study on trends in diseases of despair, which are assumed to be one cause of the increasing mortality (deaths of despair) in the U.S. However, some amendment is needed before it could be accepted for publication.<br>Abstract: Objective includes background, suggest' Background and objective' instead??<br>Aims: there three aims, out which two are related to data analysis of the present sample and the third a general discussion of the possible implication of the findings. The third one is not mentioned in the results but in the discussion. I recommend two aims with an additional sentence on what will be discussed.<br><br>M&M:<br>Age groups c´should be mentioned, as the investigation is made by age. In the discussion, the authors state that they include neonatals, as the mothers may have used substances. This reason for inclusion should be mentioned in the description of the sample.<br><br>Result<br>(line 242) ..'increased by 0.5% percentage points..' Could the authors explain, how ½ % corresponds to 59% relative risk?<br><br>Discussion<br>The discussion section should be improved.<br>Apart from a summary of findings, there are only two references related to the findings (Gaydosh et al and Case & Deaton), and there are probably more (or a statement that there is a lack of studies). The following discussion on the concept of despair includes more references but is not directly related to the actual findings rather limitations to research not only the present one. |

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| | Neonatal abstinence should be mentioned in the M&M section, as the decision to include was taken before the results were achieved.<br>309-315 would suit under a new heading implications and directions for future research and moved after 'limitation and strength'. These are important questions and need emphasized by a heading in the context of future inquiries under the same heading. |

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| **REVIEWER** | Prof David Perkins<br>University of Newcastle<br>Australia |
| **REVIEW RETURNED** | 27-Mar-2020 |

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| **GENERAL COMMENTS** | Thank you for asking me to review this important if depressing paper.<br><br>I think the paper makes an important contribution and has a range of key implications for policy makers, public health and clinical stakeholders. Perhaps, a key is recognition that deaths of despair are increasing in the world's richest nation. I will point to one or two parts of the paper where a little explanation might be important for an international readership who may not be as aware of the US health system as the authors. I am not a professional statistician and will assume that the statistical analysis is reviewed by others.<br><br>The authors realise that simply enumerating deaths of despair is important but not very helpful for those who want to reduce their incidence. The analysis performed in this paper is a vital step to informing interventions to change the pattern for the better.<br><br>As an overseas reviewer I was particularly interested in the types of services that are covered by Highmark. I am not clear if members receive managed care, normal care – whatever that may be, or a combination of a wide range of primary and secondary care. It would also be helpful to make a comment about the characteristics of employer coverage, ACA and Medicare patients since the is assumed knowledge for Americans but may not be so for others (lines 182FF).<br><br>I am also interested in the issue of serious physical comorbidities which are not diseases of despair but may be co-morbid with one of the diseases of despair such as schizophrenia, life-threatening conditions etc, |

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| | The authors made helpful comments explaining the partially overlapping test (line 204ff). The results are presented clearly although my printout seemed to be missing a title for Figure 1.<br><br>The discussion of the results is interesting and the analysis by age and sex is a traditional way of ordering the discussion. I think the most interesting questions are those of inequity, forms of insurance enrolment and the social and cultural location issues.<br><br>It would be worth a note to say that access to care or the presence of a claim in the database does not necessarily imply that the person received adequate, continuing care for that problem or for their health in general. The authors are well aware of addressing the practical significance of their findings which must go beyond but also include the continuing analysis of big data.<br><br>The identification of vulnerable populations, which may include rural and remote residents, and geographical hotspots is important and suggest the need for co-designed primary secondary and tertiary interventions aimed to prevent deaths of despair. These are also likely to require a much wider range of partners than is usually included in conventional health services. It will be interesting to see whether these large programs such as Thrive New York City etc. will have any impact on deaths of despair, perhaps at a district level.<br><br>The authors are clear about the strengths and limitations of the study<br><br>Minor points include the use of split infinitives is a little jarring, places of worship could probably include churches, a reference to secondary prevention might be helpful in the introduction.<br><br>In short, this paper is important and warrants publication. My comments are about emphasis, clarity for international readers, and practical implications and I hope they are useful. |

**VERSION 1 – AUTHOR RESPONSE**

Reviewer(s)' Comments to Author:

Reviewer: 1
Reviewer Name: Louise Brådvik
Institution and Country: Lund University, Faculty of Medicine, Department of Clinical Sciences Lund, Psychiatry, Lund, Sweden Please state any competing interests or state 'None declared': None declared.

Please leave your comments for the authors below Review bmjopen-2020-037679 Trends in the diagnosis of diseases of despair, 2009-2018 This is an interesting study on trends in diseases of despair, which are assumed to be one cause of the increasing mortality (deaths of despair) in the U.S. However, some amendment is needed before it could be accepted for publication.

*AR*: Thank you for your review.

Abstract: Objective includes background, suggest' Background and objective' instead??

*AR*: The abstract section header has been updated as suggested.

Aims: there three aims, out which two are related to data analysis of the present sample and the third a general discussion of the possible implication of the findings. The third one is not mentioned in the results but in the discussion. I recommend two aims with an additional sentence on what will be discussed.

*AR*: We have made the suggested change to the introduction of the aims, please see lines 153 - 155. Please note that these changes also include suggested updates from reviewer 2.

M&M:
Age groups should be mentioned, as the investigation is made by age. In the discussion, the authors state that they include neonatals, as the mothers may have used substances. This reason for inclusion should be mentioned in the description of the sample.

*AR*: Description of the age groups, including the rational for including an infant group, have been added to the methods section. Please see lines 187 - 192.

Result
(line 242) ..'increased by 0.5% percentage points..' Could the authors explain, how ½ % corresponds to 59% relative risk?

*AR*: Because percentage point increases and relative rate increases are presented concurrently throughout the results, a brief description of the relationship between these measures was added to an earlier section – please see lines 248 - 250.

Discussion
The discussion section should be improved.
Apart from a summary of findings, there are only two references related to the findings (Gaydosh et al and Case & Deaton), and there are probably more (or a statement that there is a lack of studies). The following discussion on the concept of despair includes more references but is not directly related to the actual findings rather limitations to research not only the present one.

*AR*: Thank you for this feedback. We have added additional references to recent work in this domain to the discussion section, along with expanded coverage of the linkages between our findings and extant work throughout the discussion.

Neonatal abstinence should be mentioned in the M&M section, as the decision to include was taken before the results were achieved.

*AR*: Please see lines 189 - 191.

309-315 would suit under a new heading implications and directions for future research and moved after 'limitation and strength'. These are important questions and need emphasized by a heading in the context of future inquiries under the same heading.

*AR*: Thank you for the suggestion. We have added section headings for “strengths and limitations” and “directions for future research”, and have expanded upon the discussion of insurance status as a potential barrier to care. Please see lines 379 – 392.

Reviewer: 2
Reviewer Name: Prof David Perkins
Institution and Country:
University of Newcastle
Australia
Please state any competing interests or state ‘None declared’: None declared

Thank you for asking me to review this important if depressing paper.
I think the paper makes an important contribution and has a range of key implications for policy makers, public health and clinical stakeholders. Perhaps, a key is recognition that deaths of despair are increasing in the world’s richest nation. I will point to one or two parts of the paper where a little explanation might be important for an international readership who may not be as aware of the US health system as the authors. I am not a professional statistician and will assume that the statistical analysis is reviewed by others. The authors realise that simply enumerating deaths of despair is important but not very helpful for those who want to reduce their incidence. The analysis performed in this paper is a vital step to informing interventions to change the pattern for the better.

*AR*: We appreciate your supportive comments, and feedback for improving the relevance and accessibility of our work to a broader audience.

As an overseas reviewer I was particularly interested in the types of services that are covered by Highmark. I am not clear if members receive managed care, normal care – whatever that may be, or a combination of a wide range of primary and secondary care. It would also be helpful to make a comment about the characteristics of employer coverage, ACA and Medicare patients since the is assumed knowledge for Americans but may not be so for others (lines 182FF).

*AR*: Thank you for this feedback. We have additional explanation and discussion of insurance coverage (see lines 376 - 389).

I am also interested in the issue of serious physical comorbidities which are not diseases of despair but may be co-morbid with one of the diseases of despair such as schizophrenia, life-threatening conditions etc,

*AR*: We agree that comorbid conditions are an interesting and understudied aspect of this issue. We have added additional analyses describing the prevalence of several types of physical and mental health conditions among individuals with and without diseases of despair diagnoses, and discussed potential avenues for future research that explore this further. Please see lines 182 - 186, 290 - 307, Table 5, 316 – 320, and 398 – 401.

The authors made helpful comments explaining the partially overlapping test (line 204ff).
The results are presented clearly although my printout seemed to be missing a title for Figure 1.

*AR*: Our apologies for the missing title. It appears that the upload process separates the title from the Figure, and we will work with the editors to address this. The figure title is: Age and Gender-Specific Diagnostic Prevalence Rates of Diseases of Despair, 2009 – 2018. The title appears in the main document as well.

The discussion of the results is interesting and the analysis by age and sex is a traditional way of ordering the discussion. I think the most interesting questions are those of inequity,

forms of insurance enrolment and the social and cultural location issues. It would be worth a note to say that access to care or the presence of a claim in the database does not necessarily imply that the person received adequate, continuing care for that problem or for their health in general. The authors are well aware of addressing the practical significance of their findings which must go beyond but also include the continuing analysis of big data.

*AR*: Thank you for this feedback. We have noted that diagnosis does not necessarily suggest the provision of appropriate care, and point to future directions for measuring and assessing the impacts of adequate treatment. Please see lines 391 – 395.

The identification of vulnerable populations, which may include rural and remote residents, and geographical hotspots is important and suggest the need for co-designed primary secondary and tertiary interventions aimed to prevent deaths of despair. These are also likely to require a much wider range of partners than is usually included in conventional health services. It will be interesting to see whether these large programs such as Thrive New York City etc. will have any impact on deaths of despair, perhaps at a district level.

*AR:* Thank you for these insightful comments, which we have woven into the discussion on lines 401 - 407.

The authors are clear about the strengths and limitations of the study
Minor points include the use of split infinitives is a little jarring, places of worship could probably include churches, a reference to secondary prevention might be helpful in the introduction. In short, this paper is important and warrants publication. My comments are about emphasis, clarity for international readers, and practical implications and I hope they are useful.

**VERSION 2 – REVIEW**

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| **REVIEWER** | Louise Brådvik<br>Lund University, Faculty of Medicine, Department of Clinical Sciences<br>Lund, Psychiatry, Lund, Sweden |
| **REVIEW RETURNED** | 25-May-2020 |

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| **GENERAL COMMENTS** | This article has now been thoroughly revised. It is an important and well-written paper, and I now recommend publication. |