PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The health and financial burden of Adverse Childhood Experiences in England and Wales: a combined primary data study of five surveys
AUTHORS	Hughes, Karen; Ford, Kat; Kadel, Rajendra; Sharp, Catherine; Bellis, Mark

VERSION 1 - REVIEW

REVIEWER	Brecht Devleesschauwer Sciensano, Belgium
REVIEW RETURNED	21-Dec-2019

GENERAL COMMENTS	The manuscript is of interest and well written, however I have some questions about the methodology. METHODS 1. How was the complex survey design taken into account in the analyses? 2. What was the rationale for the specific categorization in 0/1/2-3/4+ ? How could this have affected the results? 3. P6: when introducing the formula, you could make it more explicit that you a) calculate three PAF values (for 1 vs 0, 2-3 vs 0, and 4+ vs 0), and b) that you will add these up to the overall PAF for ACE. This would then also make it easier to see the link with the classical, categorical definition of the PAF (see eg https://doi.org/10.1136/jech.2009.090274). 4. P7L29: for the calculation of total costs/burden, I would recommend to only combine the "causes of ill health", and exclude the "risk factors"; first, because combining risk factors and outcomes will lead to double counting, second because you cannot simply add the contributions of different risk factors (ie, PAFs are not added, but combined with a multiplicative model, and taking into account mediation). 5. I have some issues with the definitions in Supplementary Table 4: * "Alcohol use" in GBD is not the same as binge drinking * "Drug use" in GBD is not just cannabis used, but also includes opioid, cocaine, amphetamin and other drug use disorders; furthermore, cannabis use in the past 12 months is not the same as the GBD "cannabis use disorder" cause.

	* "Heart disease" was defined in the survey as "coronary heart disease or heart attack", which would correspond to "ischemic heart disease" in the GBD. * "Respiratory disease" was defined in the survey as "Chronic bronchitis/ Emphysema/ Chronic Obstructive Pulmonary Disease", which would correspond to "chronic obstructive pulmonary diseases" in the GBD. 6. P7L27: "DALYs lost" > "DALYs" (because DALYs are healthy life years lost) DISCUSSION 7. P9L38: Are these studies really comparable? The current study only looked at monetized intangible costs; it is not clear what the other studies looked at. 8. Table 1 shows that several RR were non-significant, yet were still used in the calculations. What was the rationale for this choice? And the implications? 9. What would be the potential for "survival bias"? The survey asked living individuals about episodes of ill health (eg, heart attack, cancer, .., which are also important causes of death). How would this have affected the results?

REVIEWER	Chen Wanqing National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, China
REVIEW RETURNED	07-Jan-2020

GENERAL COMMENTS	This study, by Hughes et al, well descripted the DALY-converted financial burden from detailed attributable factors and diseases in England and Wales, which presents a nice example practice in this area and provides sought for further evaluations in other diseases. Uniform data sources from previous studies from local is also one of the strengths. Below are some minor comments: 1. Wording of Human capital approach: the authors applied a GVA, which is not exactly the standard approach based on per-capita GDP, would it be fairer to say a modified human capital approach? 2. Checking the sources of RR values: RR is critical for PAF calculation, the previous 5 studies are all cross-sectional studies, are they the sources of the RRs or ORs? Or any others (Please ignore this question if the authors have indicated somewhere but I missed). 3. All the main tables and figures are presented by category of ACE, but the details are not well presented in the current Abstract.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

1. How was the complex survey design taken into account in the analyses?

The sampling frameworks within studies utilised stratification at a regional level with lower super output areas (LSOAs) sampled within regions in order to generate samples proportionate to deprivation. We had originally included ‘study’ within multivariate analysis. However, to include the regional element of study design, whilst rerunning the analyses to address later comments we have now included ‘sampling region’. This resulted in only very minor adjustments to the original risk ratios but allowed us to include an additional element of the study design in the modelling.

2. What was the rationale for the specific categorization in 0/1/2-3/4+ ? How could this have affected the results?

This categorisation of ACE count has consistently been used in articles based on these studies as it provides suitable sample sizes within each category for analysis. Similar categorisations are used in ACE studies elsewhere to show how risks of outcomes vary through single, moderate and high levels of ACE exposure, with 4+ ACEs consistently used as a measure of high exposure and consistently associated with an escalation in risk of poor health. In many cases the combination of 2 and 3 ACEs into a single category has been the result of smaller proportions of the sample in each category and similar risks associated with each count. Consequently, we felt we should conform to previous papers published with these data and publications emanating from other studies. We have added a note to this in the methods:

“For the purpose of analysis, and in line with previous studies,1,19-23 positive responses to ACE questions were summed and participants were allocated to an ACE count category: 0 ACEs, 1 ACE, 2-3 ACEs, ≥4 ACEs.”

3. P6: when introducing the formula, you could make it more explicit that you a) calculate three PAF values (for 1 vs 0, 2-3 vs 0, and 4+ vs 0), and b) that you will add these up to the overall PAF for ACE. This would then also make it easier to see the link with the classical, categorical definition of the PAF (see eg https://doi.org/10.1136/jech.2009.090274).
OK

“In line with cost estimates for global regions,12 we calculated PAF values at each ACE count level (1 ACE v 0 ACEs; 2-3 ACEs v 0 ACEs; ≥4 ACEs v 0 ACEs) according to:
where □ is the category of ACE count for the PAF in question, RRACE is the pooled RR associated with each ACE count and PACE is the proportion of the sample exposed to each ACE count. Overall PAFs for ACEs were generated by summing the three PAF values.27”

3. P7L29: for the calculation of total costs/burden, I would recommend to only combine the "causes of ill health", and exclude the "risk factors"; first, because combining risk factors and outcomes will lead to double counting, second because you cannot simply add the contributions of different risk factors (ie, PAFs are not added, but combined with a multiplicative model, and taking into account mediation).

In line with previous estimates (e.g. Fang et al, 2015), we excluded risk factor DALYs related to the nine included causes of ill-health before combining these and consequently double counting was removed. However we have now also included the total cost for causes of ill-health separately (i.e. excluding risk factor DALYs) in the text for comparison with the overall combined cost.

“Across all nine causes of ill-health, total ACE-attributable costs were £33.9 billion (£1.7 billion for Wales and £32.1 billion for England).”

We have also raised this as an issue in the limitations section.

“Further, while we excluded risk factor DALYs linked to included causes of ill-health in calculating overall costs, it is not beyond the ability of this study to calculate the actual burden of ACEs due to multiplicative relationships that may lead to over or under estimates.”

5. I have some issues with the definitions in Supplementary Table 4:

* "Alcohol use" in GBD is not the same as binge drinking

We are grateful to the reviewer for raising this issue. We had used binge drinking as a proxy of more harmful drinking patterns. However, in light of the reviewer’s concern we have now calculated an alternative measure of average daily alcohol use that we feel is a better fit to the GBD definition. The measure combines data from two questions on participants’ 1) usual frequency of alcohol use and 2) typical number of standard drinks per drinking day, to calculate the exposure level of average daily alcohol use at 12g+ per day, which is the lower level of risk identified in the GBD documentation. We thank the reviewer for their observation and feel the new estimates provide a measure of the ACE-related population attributable fractions for alcohol use which is more consistent with the use of GDB data.

* "Drug use" in GBD is not just cannabis used, but also includes opioid, cocaine, amphetamin and other drug use disorders; furthermore, cannabis use in the past 12 months is not the same as the GBD "cannabis use disorder" cause.

Again, we thank the reviewer for this advice. All five surveys also collected data on heroin and crack cocaine use, which is more indicative of drug dependence and injecting drug use as used in the GBD. Consequently, we have now used this measure instead of cannabis use.

* "Heart disease" was defined in the survey as "coronary heart disease or heart attack", which would correspond to "ischemic heart disease" in the GBD.

We have now restricted the cardiovascular disease DALYs included within our analyses to those for ischaemic heart disease (IHD) and hypertensive heart disease (HHD). We understand that HHD and IHD are classified separately in the GDB data. However, even though hypertensive heart failure is included in the GDB classification of HHD our impression is that the general public will tend to include HHD when answering a general question on coronary heart disease and heart attacks. Restricting DALYs to these two categories has reduced the number of DALYs included in the analysis but we feel that this is a better representation of the data.

* "Respiratory disease" was defined in the survey as "Chronic bronchitis/ Emphysema/ Chronic Obstructive Pulmonary Disease", which would correspond to "chronic obstructive pulmonary diseases" in the GBD.

Unlike the heart disease question discussed above, this question asked participants if they had ‘respiratory disease’ and provided the specific conditions mentioned as examples rather than an exhaustive list. Consequently, we would prefer to retain this categorisation as we think it better reflects the understanding of those undertaking the survey, although would be happy to restrict it if the editor felt it important.

6. P7L27: "DALYs lost" > "DALYs" (because DALYs are healthy life years lost)

We have changed this as suggested.

DISCUSSION

7. P9L38: Are these studies really comparable? The current study only looked at monetized intangible costs; it is not clear what the other studies looked at.

A number of the comparisons we have included also used human capital approaches. We have made this clear in the text so that the reader can see costs generated through human capital models and using other methodologies. The current study used a similar approach to that used to produce the regional estimates for Europe and North America, but with PAFs generated using primary data rather than risk estimates from published literature. While this was detailed in the next section, we have now restructured the text slightly to bring it into this section and clarify.

“There are no previous studies estimating the costs of ACEs in England and Wales. However, a study that generated PAFs for ACEs through meta-analyses of risk estimates in published literature estimated the annual costs of ACEs to be equivalent to 2.7% of GDP in Europe and 3.6% of GDP in North America.12 Other studies have measured the costs of specific ACEs, particularly violence against children using similar human capital approaches.”

8. Table 1 shows that several RR were non-significant, yet were still used in the calculations. What was the rationale for this choice? And the implications?

For each health measure there was a significant overall relationship with the ACE count variable (these overall significances can be added if required). Although in some cases each category of ACE count did not significantly differ from the reference category, they all showed a consistent ordinal relationship with risk of each health condition and therefore we considered the relationship plausible across ACE categories. Given these consistent relationships we also felt that excluding certain ACE categories for selected conditions risked type II errors. We have now identified this in the limitations.

Conversely, while ACEs made an overall significant contribution to GLMs for all outcomes, for some, RRs were not significant at all ACE levels.

9. What would be the potential for "survival bias"? The survey asked living individuals about episodes of ill health (e.g. heart attack, cancer, .., which are also important causes of death). How would this have affected the results?

We had raised the issue of missing populations but agree that premature death should also be raised and consequently we have now incorporated this into the limitations section:

Further, some population groups who may be at increased exposure to ACEs (e.g. those incarcerated36 or homeless37) will have been underrepresented. Others likely to have higher ACEs may have died prematurely as a result of conditions related to childhood adversity and so will also be underrepresented in the data. These biases may contribute to reduced relative risks.

Reviewer: 2

1. Wording of Human capital approach: the authors applied a GVA, which is not exactly the standard approach based on per-capita GDP, would it be fairer to say a modified human capital approach?

We have now referred to our approach as a modified human capital approach as suggested.

2. Checking the sources of RR values: RR is critical for PAF calculation, the previous 5 studies are all cross-sectional studies, are they the sources of the RRs or ORs? Or any others (Please ignore this question if the authors have indicated somewhere but I missed).

Yes, we calculated the risk ratios using primary data from the five cross-sectional studies. We identify this in the 'Calculating PAFs' section of the methods:

"Binomial generalized linear modelling was used to calculate risk ratios (RRs) and 95% confidence intervals (CIs) associated with ACE count level for each health outcome, controlling for study location, gender, ethnicity (white or non-white) and deprivation quintile of residence."

3. All the main tables and figures are presented by category of ACE, but the details are not well presented in the current Abstract.

We thank the reviewer for pointing this out and we have now added the categorisations used into the abstract:

"Outcome measures: PAFs for single (1 ACE) and multiple (2-3, ≥4 ACEs) ACE exposure categories for four risk factors"

VERSION 2 – REVIEW

REVIEWER	Brecht Devleesschauwer Sciensano, Belgium
REVIEW RETURNED	01-Mar-2020

GENERAL COMMENTS	Thanks for addressing my comments.

REVIEWER	Chen Wanqing National Cancer Center / National Clinical Research Center for Cancer /Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College China
REVIEW RETURNED	28-Feb-2020

GENERAL COMMENTS	All my questions or concerns have been addressed properly by the authors, I have no further comments.