**Author’s response to reviews**

**Title:** Impact of Drug Burden Index on adverse health outcomes in Irish community-dwelling older people: a cohort study

**Authors:**

Catherine Byrne (catherinebyrne@rcsi.com)

Caroline Walsh (carolinewalsh@rcsi.ie)

Caitriona Cahir (caitrionacahir@rcsi.ie)

Kathleen Bennett (kathleenebennett@rcsi.ie)

**Version:** 2  **Date:** 03 Mar 2019

**Author’s response to reviews:**

Reviewer 1:

1. The data base used (GMS) covers only 40% of the Population of the 60-65 years, while for the above > 65 years 96% are expected to be covered. In both cases the coverage is linked to the income. The authors might consider to discuss the potential Impact of the socioeconomic Status of the patients involved in the data and the eventual Impact on the outcomes.

Thank you. To clarify, this study included subjects ≥65 years of age. At the time of this study, ~40% of the Irish population aged 65-70 years were covered by the GMS, and ~96% of the population aged >70 years were covered.

We have added text to the limitations in the discussion on the potential impact of socioeconomic status of those included on outcomes, as follows:

“Socioeconomic bias towards low income individuals aged 65-70 years may have affected the findings since only approximately 40% of the population in this age group were covered by the GMS scheme. Socioeconomically deprived individuals may be more prone to multimorbidity and the use of DBI medications, which may result in an overestimation of the impact of the DBI score on health outcomes. However, socioeconomic bias in those aged >70 years is expected to be considerably lower as approximately 96% of this population were covered by the GMS [7, 8].”
2. As not every Reader is familiar with the drugs included in the DBIs, the publication would gain from the Addition of the DBI drugs considered in this study and their potential dose-ADR consideration.

Thank you. We have previously published a consensus list of DBI medications relevant to Ireland and their corresponding minimum daily dosages in older people in another journal (Byrne CJ et al. Anticholinergic and sedative drug burden in community-dwelling older people: a national database study. BMJ Open. 2018;8:e022500). Therefore, we did not include this DBI list again in this manuscript. We have referenced this publication in the manuscript (reference number 4).

3. In table 3 the educational Level is described as "Primary", "secondary" and "tertiary", without any Explanation what this is referring to. Details should be included in the table legend.

Thank you. We have added details of the educational levels in the Table 3 legend as follows:

“Highest level of education achieved: Primary includes primary school or no formal education; Secondary includes secondary school or high school or equivalent; Tertiary includes university degree or equivalent.”

Reviewer 2:

ABSTRACT:

- Conclusions: Can you be more specific about what kind of risk is being predicted? For example, "…screening tool for predicting risk of poor health outcomes in older people…”

Thank you. We have amended this sentence to be more specific about the kind of risk being predicted as follows:

“The findings validate the use of the DBI tool for predicting risk of functional impairment, falls, frailty and reduced quality of life in older people in Ireland…..”

BACKGROUND:

- Line 20-21: The parent paper (ref 4) that is referenced does not have the aim of developing a DBI screening tool. The primary outcome of that paper was to investigate the prevalence of exposure to DBI medications and patient factors associated with DBI exposure. As part of that, they defined a consensus list of DBI medicines available in Ireland. Unsure of the word 'screening tool' is appropriate in that sense; as it implies a systematic way or electronic tool, that
streamlines the process of determining DBI medicines. A more transparent sentence referring to the subset of the DBI medicine list in the parent paper might be more representative of the analysis conducted.

Thank you. We have updated the wording of these sentences (shown below). In addition, throughout the manuscript, we have changed the term ‘DBI screening tool’ to ‘DBI tool’.

“A consensus list of DBI medications relevant to Ireland, and their corresponding minimum daily dosages in older people, was previously developed and applied to a national pharmacy claims database in Ireland [4]. This involved using the Irish DBI list in conjunction with the original DBI formula [2], referred to as the DBI tool, to determine an individual’s DBI score. The relationship between DBI score and health outcomes in older aged people living in Ireland has not previously been examined……..”

METHODS:

- Medication exposure: Line 14: Related to comment above. Consider revising the use of the term 'DBI screening tool' throughout the entire manuscript.

Thank you. We have changed the term ‘DBI screening tool’ to ‘DBI tool’ throughout the entire manuscript.

- Medication exposure: Line 22: Figure 1 illustrates the two cohorts that were used to investigate the effect of DBI related to a different set of outcomes. Please state the rationale for using different cohorts with different follow up times for clarity.

Thank you. We have added text to explain the rationale for using different cohorts with different follow up times as follows:

“Total DBI exposure for each participant was calculated as the sum of exposure to any DBI medication dispensed in the 12 months before the time-period specified for outcome assessment. Outcomes included in this study were either assessed at the time of interview or over the 12-month period preceding the interview. As GMS eligibility may change over time, 2 cohorts of participants were included in this study – Cohort 1 included eligible participants in the year preceding the interview date, and Cohort 2 included eligible participants in the year preceding one year before the interview date, to account for the varying time windows for outcome assessment. Outcomes relating to an individual’s condition at the time of the interview included functional status, frailty and QoL. For these outcomes, DBI exposure was determined from 0-12 months prior to the interview date (Cohort 1) (Figure 1). Outcomes relating to an individual’s condition over the 12-month period preceding the interview included self-reported falls and
healthcare utilisation. For these outcomes, DBI exposure was determined from 13-24 months prior to the interview data (Cohort 2) (Figure 1).”

- To improve ease of readability, it would be helpful to explicitly state which outcomes were assess for each cohort in the text in addition to that which is currently stated in the Figure.

Thank you. We have amended the text to state which outcomes were assessed for each cohort as follows:

“Outcomes relating to an individual’s condition at the time of the interview included functional status, frailty and QoL. For these outcomes, DBI exposure was determined from 0-12 months prior to the interview date (Cohort 1) (Figure 1). Outcomes relating to an individual’s condition over the 12-month period preceding the interview included self-reported falls and healthcare utilisation. For these outcomes, DBI exposure was determined from 13-24 months prior to the interview data (Cohort 2) (Figure 1).”

- Outcomes: Falls were measured using self-report. This should be included throughout the manuscript (including the tables and footnotes) when describing falls for transparency and accuracy.

Thank you. We have included throughout the manuscript, including tables and footnotes, that falls were measured using self-report and, where appropriate, changed to using the term ‘self-reported falls’ instead of ‘falls’.

- Statistical analyses: It is mentioned that participants with missing data for any outcome, exposure, or covariate were excluded from analysis, but the extent of missingness is not included in the manuscript. This should be clearly stated in the manuscript. Ideally, the authors would compare those participants who were included/excluded from analysis to determine if there are important differences.

Thank you. We have included a sentence in the results stating the extent of missingness for each outcome as follows:

“For these analyses, due to missing data, 55 (2.86%) participants were excluded for both the ADL and IADL outcomes, 703 (36.54%) participants were excluded for the frailty outcome, 678 (35.24%) participants were excluded for the QoL outcome, 55 (3.09%) participants were excluded for both the self-reported falls and hospital admission outcomes, and 56 (3.14%) participants were excluded for the ED visits outcome.”
In the limitations of this manuscript, we have already noted that “missing data for the outcomes of frailty and QoL were relatively high, which may have biased our results.”

We acknowledge the reviewer’s suggestion to do a comparison between included and excluded participants. However, this is not possible as we no longer have access to the data at this time.

RESULTS:

- The results only include the high DBI exposure vs. none, but do not include the low DBI exposure vs. none. Why are these results not reported in the Results section? They are referenced later in the Discussion.

Thank you. In Table 3, we provided results for both low and high DBI exposure vs none. In the text of the results, for simplicity, we decided to only include results for high DBI exposure vs none. However, based on this comment, we have added the results for low DBI vs none to the text in the results section, as follows:

“Low DBI exposure (DBI score >0 and <1) vs none was significantly associated with self-reported falls (adjusted OR 1.40, 95% CI 1.08, 1.81), frailty (adjusted OR 1.39, 95% CI 1.06, 1.83), and reduced QoL (β=-1.55, 95% CI -2.37, -0.73). High DBI exposure (DBI score≥1) vs none was significantly associated with impaired function (ADL impairment adjusted OR 1.89, 95% CI 1.25, 2.88; IADL impairment adjusted OR 2.97, 95% CI 1.91, 4.61), self-reported falls (adjusted OR 1.50, 95% CI 1.03, 2.18), frailty (adjusted OR 1.74, 95% CI 1.14, 2.67), and reduced QoL (β=-1.84, 95% CI -3.14, -0.54). There was no significant association between any DBI exposure and healthcare utilisation (hospital admission or ED visits) (Table 3).”

DISCUSSION:

- "We found that increasing exposure to DBI medications…” Suggest using a different word as "increasing" implies that some sort of intervention was done. Consider "high" exposure.

Thank you. We have changed the word “increasing” to “high” exposure for this sentence as follows:

“We found that high exposure to DBI medications was independently associated with important adverse health outcomes in Irish community-dwelling older people.”

- Para 2, lines 10-11: the word 'approximately' should be inserted before 'two DBI medications', as the 'minimum dose' differs from one medicine to the other, and it would be
incorrect to state that the sum of exposure of any two DBI drugs would be equal to a 1-unit increase in the DBI score.

Thank you. To clarify, an individual’s DBI score is calculated by summing the DBI score for each DBI medication taken. For each DBI medication taken, the score for that medication is equal to the dose taken by the patient (D) divided by the minimum daily dose for that drug (δ) plus the dose taken by the patient (D) (i.e. D/ δ + D). Therefore, if a patient is on the minimum daily dose of a DBI drug, the DBI score for that drug would be 0.5, and if a patient was on two DBI drugs each at the minimum daily dose, the sum DBI score for these two drugs would be exactly equal to 1.

- Para 2, lines 13-14: Insert an example of a positively worded statement to give context to the nature of the statements included in the CASP QoL measure, since there was no pre-text given prior to that sentence.

Thank you. We have included examples of positively worded statements for the CASP-19 QoL measure as follows:

“A 2-point reduction in CASP score is equivalent to answering two positively worded statements ‘Rarely’ instead of ‘Sometimes’ [29]. Examples of positively worded statements in the CASP-19 score include “I can do the things I want to do” and “I feel full of energy these days” [13].”

- Para 5. Please reference other studies that might have had similar or the same conclusions made.

Thank you. We have added references to other studies that have had similar conclusions to ours as follows:

“These findings concur with those of previous studies conducted in other countries [2, 18-22, 24, 25, 27]. Therefore, strategies aimed at reducing the number and/or the dose of DBI medications might lead to improved outcomes.”

- Limitations: The authors point out that the risk of bias is likely to be minimal from medications being purchased OTC. One additional point that could be considered for inclusion is that this bias is likely non-differential across the exposure groups, which is another reason why it is likely not a major concern.

Thank you. We have added this point to limitations, as follows:
“…given that GMS patients can obtain most OTC medicines on prescription for a small co-payment, the risk of bias is likely to be minimal and non-differential across the exposure groups.”

- Limitations: One major limitation that the authors did not mention is their lack of adjusting for severity of co-morbid conditions. This should be included.

Thank you. We have included this limitation as follows:

“Finally, no adjustment was made in terms of the severity of co-morbid conditions, which may have had an impact on the findings.”

Reviewer 3:

No revisions required.