Please resolve all issues in the manuscript based on the peer review report and make a point-by-point response to each of the issues raised in the peer review report. Note, authors must resolve all issues in the manuscript that are raised in the peer-review report(s) and provide point-by-point responses to each of the issues raised in the peer-review report(s); these are listed below for your convenience:

Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: After reviewing manuscript NO: 69371, titled Associated Mortality Risk of Atypical Antipsychotic Medication in individuals with dementia. I recommend the following changes: 1. The authors must restructure and rewrite the results section in the abstract since the presented results are not the main results according to the objective described. Additionally, there are errors in the presentation of the standard deviation values of the age results of the groups described in this section.

Response: Thank you for your feedback and comments. We have amended and restructured the results section to reflect the main study findings in accordance to the study objectives as shown below:

Results

A total of 1,692 patients were identified using natural language processing of which, 587 were prescribed Olanzapine, Quetiapine or Risperidone (common group) whilst 893 (control group) were not prescribed any antipsychotics. Patients prescribed Olanzapine showed an increased risk of death (HR = 1.32; 95% Confidence Interval (CI) = [1.08 - 1.60]; $p < 0.01$), as did those with Risperidone (HR = 1.35; CI = [1.18 - 1.54]; $p < 0.001$). Patients prescribed Quetiapine showed no significant association (HR = 1.09; CI = [0.90 - 1.34]; $p = 0.38$). Factors associated with a lower risk of death were: high MMSE score at diagnosis (HR = 0.72; CI = [0.62 - 0.83]; $p < 0.001$),

identifying as female (HR = 0.73; CI = [0.64 - 0.82]; $p < 0.001$), and being of a White – British ethnic group (HR = 0.82 [0.72 - 0.94]; $p < 0.01$).

2. The authors should carefully review the abbreviations used in the manuscript so that the reader understands from the first time they have mentioned what authors refer to without searching throughout the text.

Response: thank you for your comments. We have now amended all the abbreviations used in the manuscript accordingly.

3. The authors must enrich the discussion of results, according to the paper's objective. The most important result is the impact of antipsychotics on mortality in patients with dementia; this point requires further discussion, including the possible biological effects of these drugs, mainly olanzapine and risperidone, causing higher mortality results in the study. A possible mechanism, imbalance, or adverse metabolic effects that trigger the consumption of these drugs and that in adults with dementia may aggravate the patient's health. It is also suggested to investigate further the effect of biological differences between male and female sex that may intervene and explain the results obtained in this paper.

Response: Thank you for your comments, we have now enhanced the discussion section and aligned this to the study objectives.

The results show a significantly higher mortality risk for those prescribed Olanzapine and Risperidone. This supports previous findings of Gerhard and colleagues, who showed that Quetiapine had a lower mortality risk than Risperidone, while Olanzapine had a similar mortality rate to Risperidone within the elderly population [19]. Gerhard and colleagues argued that their findings could be due to less variance in dosing of Quetiapine. In addition, higher doses of both Olanzapine and Risperidone linked were thought to have been linked to a higher risk of mortality.

Aside from dosing, the differences in mortality rate could be due to the risk of cerebrovascular events. Risperidone and Olanzapine have been associated with greater risks of cerebrovascular events [20-24]. The mechanism by which Risperidone and Olanzapine may increase the risk of cerebrovascular adverse events (CVAEs) could be related to high levels of prolactin. Olanzapine and Risperidone have been associated with high levels of prolactin [25-26]. High levels of prolactin

have been associated with cerebrovascular events [27]. Furthermore, hyperprolactinaemia has been reported to frequently complicate antipsychotic treatments [28].

It is worth noting that Risperidone has not been reported to cause anticholinergic side effects in older adults unlike other atypicals [29]. Within this population, antipsychotics are used to treat *agitation* and *psychotic phenomenon* often presented in dementia. Olanzapine and Risperidone as atypical antipsychotics are commonly prescribed due to their favourable side-effect and safer metabolic profiles [5, 30] age related changes in pharmacokinetics and pharmacodynamics can lead to increased sensitivity to drugs and their side effects [31] consequently impacting on mortality rates.

Polypharmacy is another facet observed within this population of patients that could attribute to the findings of our study. A recent scoping review on the sex and gender differences in polypharmacy in this population could support this theory [32] notably for women with dementia, in comparison to men [32]. Similarly, dementia is implicated in the increased risk of polypharmacy within the elderly population with rates varying from over 65years taking from 6 medications to more than 10 medications in those older than 85years across the world.

This study results contradict the previous findings of Sultana et al. [9], who found no increase in risk hazard across Olanzapine, Quetiapine and Risperidone, there are several differences in our study design that may account for the differing outcomes.

The cohort in the present study covers five different International Classification of Diseases (ICD-10) diagnosis sub-groups (G30, F01, G31.0, F03, F02), rather than vascular dementia (F01) exclusively. As such, the present results are representative of the shared patterns observed across differing dementias. Patients with Alzheimer's Disease (G30) are known to show an increased mortality risk associated with long-term antipsychotic use [33]. This is a plausible finding observed across dementia diagnoses, in particular among vascular dementia patients. A direct comparison of the individual dementia diagnosis sub-groups could assist establish the homogeneity or heterogeneity of the mortality risk effect in future studies.

The geographical differences between the Southampton and South London population also play a vital role in our findings, given the variations in ethnicities and races. The non-medication results are comparable across both studies with women demonstrating a lower risk in comparison to men. In addition, the Caucasian group demonstrated a relatively lower risk compared to most other groups. Consistent with other studies [34], patients with high MMSE scores were also associated with lower risk of mortality. This may either mean the MMSE test is not used in patients with advanced dementias, or that there are systematic patterns due to missing data issues within electronic healthcare records in primary and secondary care organisations. These possible theories could be substantiated with prospective research studies.

Reviewer #2:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: Antipsychotic medication is widely prescribed to patients with dementia displaying neuropsychiatric symptoms, but wider consensus to evaluate clinical epidemiological outcomes is limited.This study was developed to evaluate the impact of atypical antipsychotics associated with mortality in a dementia cohort. It was found that treatment with Olanzapine and Risperidone was associated with an increased mortality risk. Comprehensive research should be needed to better assess clinical epidemiological outcomes associated with diagnosis and therapies to improve clinical management of these patients.

Thank you for your comments, much appreciated

4 LANGUAGE POLISHING REQUIREMENTS FOR REVISED MANUSCRIPTS SUBMITTED BY AUTHORS WHO ARE NON-NATIVE SPEAKERS OF ENGLISH

As the revision process results in changes to the content of the manuscript, language problems may exist in the revised manuscript. Thus, it is necessary to perform further language polishing that will ensure all grammatical, syntactical, formatting and other related errors be resolved, so that the revised manuscript will meet the publication requirement (Grade A).

Authors are requested to send their revised manuscript to a professional English language editing company or a native English-speaking expert to polish the manuscript further. When the authors submit the subsequent polished manuscript to us, they must provide a new language certificate along with the manuscript.

Once this step is completed, the manuscript will be quickly accepted and published online. Please visit the following website for the professional English language editing companies we recommend: https://www.wjgnet.com/bpg/gerinfo/240.

5 ABBREVIATIONS

In general, do not use non-standard abbreviations, unless they appear at least two times in the text preceding the first usage/definition. Certain commonly used abbreviations, such as DNA, RNA, HIV, LD50, PCR, HBV, ECG, WBC, RBC, CT, ESR, CSF, IgG, ELISA, PBS, ATP, EDTA, and mAb, do not need to be defined and can be used directly.

The basic rules on abbreviations are provided here:

(1) Title: Abbreviations are not permitted. Please spell out any abbreviation in the title.

Response: The title abbreviation is clearly spelt out as below:

Associated Mortality Risk of Atypical Antipsychotic Medication in individuals with Dementia (AMRAAD): A Clinical Cohort Study

(2) Running title: Abbreviations are permitted. Also, please shorten the running title to no more than 6 words.

(3) Abstract: Abbreviations must be defined upon first appearance in the Abstract. Example 1: Hepatocellular carcinoma (HCC). Example 2: *Helicobacter pylori* (*H. pylori*).

Response: thank you for your comments, we have amended the abbreviations accordingly.

(1) Science editor:

This manuscript intended to evaluate the impact of atypical antipsychotics on mortality of a dementia cohort. The reviewers raised some major issues, which the scientific editor agrees. Besides, the following issues should be considered. 1. Please organize the manuscript following the requirements of the WJP. For instance, the formats of abstract and references are wrong. Besides, a mandatory section of "Core tips" is missing. 2. Results section, for analysis of multivariate Cox proportional hazards model, please consider combine the categories with very few frequencies to improve statistical power. Like ethnicity. 3. In table 2, there is no need to put asterisk above the HRs to mark the p value, for you have provided the confidence intervals. 4. The resolution of figure 1 should be improved.
Language Quality: Grade B (Minor language polishing)
Scientific Quality: Grade C (Good)

- The abstract format and the referencing style has been amended to journal requirements.
- Core Tips section has been included
- Asterisk highlight significant p values.

7 STEPS FOR SUBMITTING THE REVISED MANUSCRIPT

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References edited using the reference auto-analyser

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Once again thank you to the reviewers for your comments. Hopefully the incorporated amendments improve the quality of the manuscript.

Kind regards

Dr Peter Phiri, PhD

Corresponding author