General comment

The thesis is a valuable and original contribution to the literature but shows some weaknesses in epidemiological methods and in biological interpretation.

I thank the examiners for their insightful comments. The changes you have proposed give the thesis a more rounded epidemiological and biological narrative. I have made the changes that you have specified, with some comments justifying the changes.

The main aim of my thesis was to create a statistical framework for examining the dynamics of seasonal mortality, and how monthly anomalous temperature might be associated with (interannual variations in) monthly death rates, by sex and age group. My thesis shows that monthly temperature anomaly is a predictor of mortality, which may be partly causal and partly due to other factors that are correlated with monthly anomalous temperature.

Chapter 4 (published in a paper in eLife) is a statistical analysis of the dynamics of seasonality, while Chapters 5-7 seek to explain the extra-seasonal variations in monthly death rates at comparable times of the year (e.g., does temperature predict how death rates in January in one year differ from January in the next year). I have related the statistical model to common epidemiological frameworks and to the extent possible provided further detailed biological interpretation.

I have detailed the changes I have made below, with appropriate references to the text in the tracked version of the thesis.

Amendments that need to be made

1. There is some confusion in the introduction to the main chapters and in the discussion about the meaning of basic epidemiological terms:

(a) the candidate should propose a formal definition of confounder for example at the end of Chapter 2. Then in substantive chapters (4 to 7) he should specify, based on his formal definition, what confounders might be at work for each analysis. He should identify potential confounders (measured and unmeasured) and note where the models control for these. His current tendency is to define confounders computationally (a posteriori), which is at odds with consensus epidemiological theory.

(b) in the same places he should define effect modifiers formally and then list potential ones of possible importance and note (if measured), if he has investigated that modification and if not why not.

(c) in the same places he should discuss briefly whether or not potential variables are in the causal pathways from temperature to outcomes and the implications of this

(d) these concepts should be finally considered in the Discussion of each substantive chapter in the context of a causal appraisal of the associations

As an example, when he states

"It has also been argued that pollution should not be a confounder of temperature mortality association, as adjusting for pollution excludes the interaction between temperature and pollution" he should be more analytical and discuss the potential role of air pollution as a confounder, as an intermediate variable in the causal pathway and as an effect modifier.

I have added these definitions in the new Section 5.5 on pgs. 152-155. There, I have also listed potential confounding factors, implications of these on my study and potential future work. In doing so, I have both identified potential confounding factors for the association of anomalous monthly temperature and mortality, and explained how my statistical model, with its random intercepts and slopes, at least partially controlled for these, in Section 5.4.4. on pg. 137.

Chapter 4 presents a *descriptive* analysis of seasonality using wavelet methods and no "effect size" is presented. Therefore, I have not included a description of potential confounders in Chapter 4's discussion.

2. There is no discussion of the role of cohort studies (e.g. ACS, ESCAPE) in the study of temperature and seasonality. Perhaps none has been published, but the issue should be discussed, with merits and limitations of such studies.

I have elaborated with the new Section 2.5.4 on pgs. 56-57, with a short discussion of potential future work in Section 8.4 on pg. 224.

3. Season is mainly interpreted in the thesis as a proxy for temperature. It is not made clear what is in season that goes beyond temperature and that could confound the association between temperature and outcomes. For example, seasonal behaviours dictated by social norms (holidays) and not temperature, viral infections not caused driven temperature etc.

This should be discussed when introducing seasonality in Chapter 2 and then briefly in each of the substantive chapters where season is used, and in the general Discussion.

In my thesis, I presented an analysis of patterns of seasonal mortality (Chapter 4). I then presented a framework for analysing how anomalous monthly temperature is associated with interannual variations in monthly death rates. Therefore, my thesis did not use seasonality as a proxy for temperature. Rather, I aimed to explain interannual monthly death rate variation by temperature deviation from the long-term norm.

I clarify, in particular in Section 5.4.4 on pg. 137, how my state-, month- or state-month-specific terms implicitly adjusted for any determinant of mortality specific to each state in each month. This would remove the confounding effect of a holiday in a particular state, for example, Christmas, as it always takes place within the month of December.

4. In addition to the epidemiological methods, there are weaknesses in the biological interpretation of associations, both when appraising the literature and in the interpretation of his findings. For example, on page 35: acritical review of evidence of associations such as suicides. In Chapter 6: "Regarding suicide, higher temperature has been hypothesised as associated with higher levels of distress in younger people." This is a very superficial explanation. The candidate should show awareness of his limitations in pathophysiological interpretations and the speculative nature of such discussions.

I have further examined the available literature on pathways and mechanisms between temperature and injuries. I have appropriately added to the discussion of injuries and anomalous temperature in Section 6.6, emphasising the speculative nature of these pathways on pgs. 182-183. I have also added the potential of future work investigating pathways between anomalous temperature and injuries to the discussion in Section 8.4 on pg. 224.

Regarding biological pathways for other causes of death, such as from cardiorespiratory diseases, I have given detailed descriptions of potential causal pathways in Section 2.4.4 on pgs. 46-48 and in Section 7.6 on pgs. 212-214.

5. There is no mention of internal migration, permanent and temporary (e.g., holidays) in the US, e.g. of elderly people moving from cold to warm States (typically Florida) after retirement. Are deaths attributed to the State in which the death occurred, that of their current main residence, or by some other criterion such as where resident in the last census. e.g. would deaths in retired "snow birds" from Vermont wintering in Florida be recorded as in Florida or Vermont? How would this affect misclassification and consequently your results?

The assignment of place of death is an administrative protocol based on official place of residence which may or may not be the same as where actual exposure death took place. If different, the death in my model structure will be assigned a different exposure. I have added a discussion about the potential impact of migration and 'snow birds' to the discussion in Section 8.2 on pg. 221-222.

Minor

1. **Introduction: 6.6 degree increase by 2100? Level of confidence according to IPCC?**

I have adapted previous wording to give an indication according to IPCC conventions in Section 2.2 on pg. 39.

2. **Note 130: "previous studies"? - this inference like others based on citing the literature is a little weak. We are not requesting a systematic review of the literature, but the candidate should be much more critical in his assessment of previous evidence and alleged causal inferences**

I have elaborated with further sentences in Section 2.4.4 on pg. 47, and in general throughout the thesis.

3. **On displacement, PAGE 37**

"Some speculate that this occurs when increased mortality occurs during elevated temperatures. The implication is that the increase in deaths would not necessarily be of public health significance, since the deaths were only slightly brought forward in time. A study of suicides found no mortality displacement when associating mortality with temperature."

I am not persuaded: (a) displacement does have personal and familial implications (e.g. legacies, psychological preparedness, etc). Second, it is not only an empirical (data-driven) issue, but it needs to be also dealt with theoretically, i.e. as depletion of the most susceptible, before concluding that it is irrelevant.

I have added further discussion sentences in Section 2.4.7 on pgs. 52-53.

4. **There is a very rapid description of the different Bayesian methods, but what are the respective advantages? (e.g., JAGS vs Gibbs etc)? Why certain methods have been used and not others? This is not clear to the non-statistical reader**

I have elaborated with further discussion in Section 2.5.5 on pgs. 57-58.

5. **"Cancer death outcomes are not generally considered as sensitive to temperature changes, and so are all grouped as 'cancers' here." In fact, one could consider death anticipation in terminally ill patients (many) and in certain types of cancer that are likely to increase susceptibility to temperature (e.g. leukaemia)**

I have elaborated with further discussion in Section 3.2.5 on pg. 68.

6. **"A limitation of my results in Chapters 4, 6 and 7 is that I did not investigate seasonality of mortality by socioeconomic characteristics which may help with understanding its determinants and planning responses". This is an interesting comment and the candidate could explain how the impact of temperature on health outcomes might vary by SES based on other data.**

I have added further discussion in Section 8.2 on pgs. 220-221.

7. **The thesis does not consider infectious diseases (too few deaths?). This should be discussed.**

It is correct to point out that there are too few deaths for infectious diseases (beyond respiratory infections which are included in my analyses). I have added a sentence to make that explicit in Section 3.2.5 on pg. 68.