Daylight saving time affects European mortality patterns
Reviewers' Comments:

Reviewer #1:
Remarks to the Author:
See attached pdf:
(i) Comments for authors
(ii) EU TRAN Commission report (January 2019)

Reviewer #2:
Remarks to the Author:
This study examined mortality patterns in 16 EU countries according to different days of the week and relative to DST change in both spring and fall. The main findings include a Sunday/Monday effect (low on Sunday and high on Monday) throughout the year, and increases in mortality after DST change in spring and decrease after DST change in fall. Strengths of the paper include its large sample size, diverse and wide geographic coverage and detailed analysis. Limitations of the paper include lack of data on causes of death and the ecological nature of the analysis. Overall I believe this study can make potentially important contribution to the field, but may benefit from several major improvements:
1) A major limitation of the study is lack of data on cause of death, which may provide critical information on how to interpret the results. For example, the Sunday/Monday effect noticed among 35+ age group and the flip pattern noticed in the 10-35 group (men only) could be potentially explained by different main contributors to death in these two groups. In addition, the delayed effect of spring DST change and immediate effect in the fall may also be better explained by different causes of death associated with time change. Lacking such data makes it hard to interpret the findings, and the authors did not provide adequate discussion on this matter. This is a major limitation that needs to be at least acknowledged and the authors should provide more discussion to explore alternative explanations for the results.
2) The authors stated that time change in the spring did not have a significant effect on mortality, which is incorrect. There was an increase in mortality pattern, but occurred 2 weeks after the date when DST took place. More discussions on why this pattern was observed in the dataset is needed. Could it be due to cumulative effect? Again cause of death would be very helpful here.
3) It is unclear to me why ages 35+ were grouped together, as this led to a wide age range. Mortality patterns and causes of death differ between middle and older aged groups. People who are retired may be affected differently by the DST when compared to people who are at working age. The authors should use more refined age groups, and in particular separate according to typical retirement age.

Reviewer #3:
Remarks to the Author:
The authors attempted to present the relationship between daylight saving time transitions and patterns of all-cause mortality in 16 European countries for the period 1988-2012. However, they have only been partially successful in achieving their objective. In fact, I have some comments, all of them major.

1.- The main problem of the manuscript is the lack of control of important confounders. The authors already indicate weather conditions as important confounding (page 10, lines 226 to 228), but indicate that 'they rarely arise around DST transitions'. This would be true if the climatic conditions had not varied in those 24 years (from 1988 to 2012), but it is not like that. Both the variance of these conditions (variability) and the duration (some shorter, others longer) have varied and it is very likely that the beginning of the seasons.

Authors should try to capture this variability, including, for example, random effects indexed by months or seasons.

2.- Another very important confounder is the socioeconomic conditions of each country and of
each country over time. Socio-economic conditions can influence the degree of ‘adaptation’ of your population, among other things.

3. - Related to my comment number 2, there could be other important confounders specific to each country. In fact, figure S1 shows a very important heterogeneity in some of the countries. Thus, for both this and the previous comment, the authors should allow IRRs to vary by country and by year (including random effects, for example).

4. - The authors include the interaction between age and sex. Sounds good to me, but I think you should try other important interactions, all of them with age and gender, for example, gender and month, age and month, gender and country, age and country, etc ...
Point-by-point response to the reviewers’ comments, reproduced verbatim

Reviewer #1:

This study was aimed to assess the relationship between DST and all-cause mortality at a continental level. The authors analyzed more than 59 million deaths from 16 European countries over a 15-year period. The study is very interesting, well written, and is the largest available until today. Contrary to previous findings, the authors did not find any changes after the spring DST transition, whereas a reduction was found after autumn transition. The results are noteworthy, and give substantial contribution to the existing literature. The conclusions are well supported, and strengths and limitations clearly stated into the appropriate section. Minor points have been highlighted, as well some concern (for a not expert in statistics) for easy reproducibility of methods.

A1.0 Thank you.

Minor observations:

R1.1 Line 46 et al The European Union collected also the opinion of international experts, that have been presented and discussed at the TRAN committee audition (Jan 21, 2019) (pdf enclosed).
https://www.europarl.europa.eu/legislative-train/theme-a-europe-fit-for-the-digital-age/filediscontinuing-seasonal-changes-of-time/02-2021
Meira E Cruz M, Miyazawa M, Manfredini R, Cardinals D, Madrid JA, Reiter R, Araujo JF, Agostinho R, Acuña-Castroviejo D. Impact of Daylight Saving Time on circadian timing system: An expert statement. Eur J Intern Med.2019 Feb;60:1-3. doi: 10.1016/j.ejim.2019.01.001. Epub 2019 Jan 5.

A1.1 The above mentioned paper is now cited in the introduction of the revised manuscript and the following sentence has been added: “According to the consensus view of a recent international panel of experts, a sufficient amount of sensible evidence exist today to support the discontinuation of DST.”

R1.2 Line 77 The ‘Monday peak’ for occurrence of acute cardiovascular and cerebrovascular events has been reported by several authors, and even for fatal cases.
Manfredini R, Manfredini F, Boari B, Bergami E, Mari E, Gamberini S, Salmi R, Gallerani M. Seasonal and weekly patterns of hospital admissions for nonfatal and fatal myocardial infarction. Am J Emerg Med. 2009 Nov;27(9):1097-103. doi: 10.1016/j.ajem.2008.08.009.

A1.2 Thank you, we amended our manuscript accordingly. However, we would like to add two additional remarks.
Firstly, to the best of our knowledge, no previous study has precisely described this ‘Monday mortality peak’ on a population level, independently from healthcare system activity variations. It is therefore quite difficult to estimate to what extent acute cardiovascular and cerebrovascular events account for these high mortality rates, particularly in our study, where causes and time of death could simply not be obtained at such a scale.

Secondly, a recent study examining the circadian and septadian variations of sudden cardiac arrests (https://doi.org/10.1016/j.hrthm.2018.08.034) neither observed a morning peak nor an altered incidence on Mondays, but they also observed a nadir on Sundays. Further research is needed to 1) examine its presence in large populations today, where psychosocial stressors - that represent potent triggers of acute cardiovascular and cerebrovascular deaths - are more evenly distributed across the entire week and 2) refine the methodology used for reporting more accurately the time and cause of death.

R1.3 Moreover, in addition to the reported papers by Willich 1994 (ref 30), Peckova 1999 (ref 31), and Arntz 2000 (ref 32), and prior than Jakovljevic 2004 (ref 33), I would remember the first observation of a Monday peak of stroke by our group.
Manfredini R, Casetta I, Paolino E, la Cecilia O, Boari B, Fallica E, Granieri E. Monday preference in onset of ischemic stroke. Am J Med. 2001 Oct 1;111(5):401-3. doi: 10.1016/s0002-9343(01)00836-1.

Line 94
A1.3 This paper is now cited on page 8 of the revised manuscript.

R1.4 ‘it is worth mentioning that the mortality of women [0-10] is higher than that of women [10-35] (but the opposite is true for men).

A1.4 Figure 2 now displays 10 years age groups to address reviewer’ 2 remarks. As this sentence could give rise to confusion, it has been therefore corrected as follows: “The mortality curves tend to be higher for men than for women in all age groups (Figure 2) but it is worth mentioning that the mortality of women aged [0-10) is higher than that of women aged [10-30].”

R1.5 Line 144…DST and Monday Non univocal data are available on the circaseptan variation, although a preference for a Monday preference seems to exist. Among the available studies on DST and myocardial infarction, some studies reported an increase in the first days of the week (attached a summarizing table by our group). In particular, Culic reported a highest peak on Tuesday /spring DST) and Monday (Autumn); Sandhu et al (ref 9) reported a highest peak on Monday (spring); Kirchberger et al (ref 10) reported maximum incidence during the first three days, with highest on Monday (spring), Sipila et al (ref 11) found a highest peak on Wednesday (spring).

Čulić V. Daylight saving time transitions and acute myocardial infarction. Chronobiol Int. 2013 Jun;30(5):662-8. doi:10.3109/07420528.2013.775144. Epub 2013 May 20.

Source:
Manfredini R, Fabbian F, De Giorgi A, Zucchi B, Cappadona R, Signani F, Katsiki N, Mikhailidis DP.
Daylight saving time and myocardial infarction: should we be worried? A review of the evidence. Eur Rev Med Pharmacol Sci. 2018 Feb;22(3):750-755. doi: 10.26355/eurrev_201802_14306.

Line 167 …..Weekend

A1.5 This paper is now cited in the revised manuscript.

R1.6 As for the weekend effect (in addition to Bell 2001, and Walker 2017, refs 38-39), the Authors reported four plausible hypotheses: (i) deaths occurred during the weekend but noticed on next Monday; (ii) limited number of doctors responsible for issuing certificates; (iii) elevated pollution lower on weekends; and (iv) social and domestic activities. To address these issues, our group extensively investigated a series of acute diseases, requesting immediate access to hospitals EDs, such as aneurysm dissection or rupture for example. The existence of a weekend effect on outcome is really impressive. Moreover, the hypothesis put forward by US and UK authors, regarding the presence of less skilled doctors on weekends, it is not present in Italy (and especially in our region Emilia Romagna), where senior doctors and associate professors are called at weekend and night duties exactly as junior doctors.

Gallerani M, Imberti D, Ageno W, Dentali F, Manfredini R. Higher mortality rate in patients hospitalised for acute pulmonary embolism during weekends. Thromb Haemost. 2011 Jul;106(1):83-9. doi: 10.1160/TH11-02-0068. Epub 2011 May 5. Gallerani M, Imberti D, Bossone E, Eagle KA, Manfredini R. Higher mortality in patients hospitalized for acute aortic rupture or dissection during weekends. J Vasc Surg. 2012 May;55(5):1247-54. doi: 10.1016/j.jvs.2011.11.133. Gallerani M, Volpato S, Boari B, Pala M, De Giorgi A, Fabbian F, Gabbasso V, Bossone E, Eagle KA, Carle F, Manfredini R. Outcomes of weekend versus weekday admission for acute aortic dissection or rupture: a retrospective study on the Italian National Hospital Database. Int J Cardiol. 2013 Oct 3;168(3):3117-9. doi: 10.1016/j.ijcard.2013.04.065. Epub 2013 Apr 30. Gallerani M, Fedeli U, Pala M, De Giorgi A, Fabbian F, Manfredini R. Weekend Versus Weekday Admission and In- Hospital Mortality for Pulmonary Embolism: A 14-Year Retrospective Study on the National Hospital Database of Italy. Angiology. 2018 Mar;69(3):236-241. doi: 10.1177/000331971771718706. Epub 2017 Jul 7.
Fabbian F, De Giorgi A, Di Simone E, Cappadona R, Lamberti N, Manfredini F, Boari B, Storari A, Manfredini R. Weekend Effect and in-Hospital Mortality in Elderly Patients with Acute Kidney Injury: A Retrospective Analysis of a National Hospital Database in Italy. J Clin Med. 2020 Jun 11;9(6):1815. doi: 10.3390/jcm9061815.

A1.6 To the best of our knowledge, no consensus view can be drawn from the studies investigating the association between weekday/weekend admission and outcomes/morbidity-mortality. However, the weekend/off-hour effect might be plausible in particular hospital settings, regions, seasons and subgroups of patients. It is still unclear how clinically significant this effect is in practice, as we note a lack of multicentric,
multinational studies with extended definitions of ‘weekend effect’, a wide range of diseases tested and standardized methodologies applied. For example, the metrics used to define ‘weekend effect’ vary greatly among studies: 30-day morbidity/mortality, in-hospital mortality, rate of complications, length of hospital stay, rate of readmissions, quality of recovery, etc. Identified cause – such as systematic workflow disruptions, staffing issues, etc. – do not necessarily translate into higher mortality rates. Finally, we couldn’t find any clear and specific reference to a ‘Monday peak’ in the recent ‘weekend effect’ literature. Please refer to the pdf document entitled “A1.6 Table - Rapid review on weekend effect.pdf”

Hence, we modified the related paragraph in the discussion section as follows: “The greater incidence of mortality on Mondays could also be explained by a possible weekend effect, that is, an altered patient outcome – namely an increased mortality risk – if hospital admissions or interventions occur during the weekend 48-51. Although causal pathways have always proved particularly difficult to determine, it has long been attributed to suboptimal senior staffing, systematic workflow disruptions, and characteristics of patients admitted on weekends (i.e. sicker) compared to weekdays 52-54. Yet some authors have merely failed to identify such effect, emphasizing that it may only be clinically relevant in certain geographic locations, hospital settings, periods of the year, subgroups of patients, etc. In the context of a weekend effect, it is worth mentioning that the frequency of death has not been associated with any specific day of the week50,55.”

Minor points (methods) (as a general reader, not a statistician)

R1.7 As a general reader (not a statistician), I would like to read how authors obtained daily death count written in an easier way. They stated “We obtained daily death counts and annual population numbers (collected by sex, one-year age group, country and NUTS2 - Nomenclature of Territorial Units for Statistics) from national statistical offices of 16 European countries (see above) for the period 1998 to 2012 28,46”. In my opinion the possibility to check and replicate other data by using this method could be useful for other investigators.

A1.7 We rephrased the sentence as follows: “We wrote emails to each national statistical offices ((listed in Supplementary Table 1) to obtain daily death counts and annual population numbers (collected by sex, one-year age group, country and NUTS2 regions - Nomenclature of Territorial Units for Statistics) of 16 European countries (see above) for the period 1998 to 2012 33,68.”

R1.8 Looking at Figure 1 reporting the temporal data of daily death rate/100000 it seems to understand that mortality decreases after spring DST and increases after fall DST. On the other hand, calculation of incidence rate ratios suggests a decrease in mortality after fall DST. Why that? Moreover, how authors calculated incidence rate ratios? I would suggest to explain.

A1.8 The figure 1 is described as follows: “Daily mortality rates are obviously subject to seasonal variations with a downward trend in spring and an upward trend in fall (cf. splines in Figure 1b and 1c). However, when compared to these expected seasonal trends, mortality shows an apparent increase after the DST transition in spring (1b) and an apparent decrease in fall (1c).”

In the method section, we explain in details that IRR are computed with multiple negative binomial regression models. “Daily death counts were analyzed using multiple negative binomial regression models to take into account their over-dispersion. Results are presented as incidence rate ratios (IRR) with 95% confidence interval and were adjusted for year, season, month, day of the week, country, latitude and longitude of the NUTS2 centroid (NUTS2 being clustered into countries), a sine-cosine function that considers daylight seasonality, the weeks following DST transitions, yearly regional GDP, daily mean temperature (Kelvin), daily mean humidity (%) and daily mean wind speed (m/s).”

To make it more obvious for the reader, we also edited Table 1’s caption as follows: “Multiple negative binomial regression model predicting daily mortality rate expressed as incidence rate ratios (IRR) with 95% confidence interval (95% CI).”

After adjusting for 5 additional variables, the result section states: “An adjusted multiple binomial negative regression model (Table 1) shows a significant decrease in death counts in the spring DST (IRRweek1 .965; 95% CI: .951-0.979, p< 0.001; IRRweek2 .972; 95% CI: 0.958-0.986, p< 0.001), and a significant increase in the fall DST (IRRweek1 1.018 95% CI: 1.003-1.033, p= 0.016; IRRweek2 1.023 95% CI: 1.008-1.039, p=0.002). Significant variations
of mortality are mainly observed during the first two weeks following each DST transition. Nevertheless, we note from week 4 onwards after the fall DST a significant, quasi constant decrease in daily death rates.”

R1.9 Finally, I did not found calculations on the observed/expected deaths ratio

A1.9 In the method section, the following sentence was added: “Unadjusted average daily death rate observed in the 16 European countries (1998-2012) was computed as the sum of Death[day] for all NUTS2 regions divided by the sum of Population[day] for all NUTS2 regions, averaged by year and day of the year and displayed in Figure 1 (all sex and all ages) and Figure 2 (by age and 10 years age groups).”

We also slightly changed the caption of figure 1: “Unadjusted average daily death rate/100’000 observed in 16 European countries (1998-2012).” and Figure 2: “Unadjusted average daily death rate/100’000 observed in 16 European countries by sex and 10 years age groups (1998-2012).”

Predicted mortality rates were already explained in the previous version of the manuscript but the figure reference’s number was incorrect: “Third- and second-degree polynomial regression models were used to predict mortality rates arising on Sundays (weekly minimum) and Mondays (weekly maximum) from time before the transition date to 9 weeks after the DST (cf. Figures 1). Time is the number of days away from the DST transition. The mortality rates observed during the 9 weeks consecutive to both DST transition dates were not used in the regression models and thus interpolated in order to search for a deviation in mortality (that would manifest after DST). All statistics were performed with Stata release 17.0.”

Reviewer #2:

This study examined mortality patterns in 16 EU countries according to different days of the week and relative to DST change in both spring and fall. The main findings include a Sunday/Monday effect (low on Sunday and high on Monday) throughout the year, and increases in mortality after DST change in spring and decrease after DST change in fall. Strengths of the paper include its large sample size, diverse and wide geographic coverage and detailed analysis. Limitations of the paper include lack of data on causes of death and the ecological nature of the analysis. Overall I believe this study can make potentially important contribution to the field, but may benefit from several major improvements.

A2.0 Thank you very much.

R2.1 A major limitation of the study is lack of data on cause of death, which may provide critical information on how to interpret the results. For example, the Sunday/Monday effect noticed among 35+ age group and the flip pattern noticed in the 10-35 group (men only) could be potentially explained by different main contributors to death in these two groups. In addition, the delayed effect of spring DST change and immediate effect in the fall may also be better explained by different causes of death associated with time change. Lacking such data makes it hard to interpret the findings, and the authors did not provide adequate discussion on this matter. This is a major limitation that needs to be at least acknowledged and the authors should provide more discussion to explore alternative explanations for the results.

A2.1 Thank you for this comment.

We contacted 16 national statistical offices in order to obtain the corresponding daily causes of deaths and are, to this date, still awaiting definitive answers.

However, statistical offices confirmed what we long anticipated. These data are not publicly available and definitely complicated to obtain, especially when presented by narrow age groups, sex and region, as they can serve as keys (in correlation with other demographics) to identify a given individual. Hence, the rights to privacy may be critically at risk. This process would take several more months and we cannot guarantee its successful completion.

Without understating the importance of these data, the question of their usual quality should not be overlooked. In fact, it depends almost entirely on death certification by physicians and coding according to the International Classification of Diseases, two practices whose accuracy has been largely debated and questioned in the literature:
In summary, we now acknowledged this limitation in the discussion section as follows:

"The most critical limitation of our study is the absence of data with regard to the daily causes of death by age, sex, and NUTS2 region. In fact, these data are not commonly available at the European level and are extremely difficult to obtain from national statistical offices, given that they can serve as key clues to the identification of deaths and pose problems of confidentiality. Yet, many studies suggest that death certificates remain largely inaccurate, particularly in the context of a diminishing number of yearly autopsies."

Please note: Thanks to one of our co-authors, we were able to obtain causes of death for Spain, by NUTS2 region, day, sex, 15 years age groups (0-14, 15-29, 30-44, 45-59, 60-74, 75+) for the period 1999-2012 (1998 was not available) and according to the International Classification of Diseases 10th Revision (ICD10), thereby preserving confidentiality. Raw data cannot be shared.

| 1 | A00-B99 Infectious diseases |
| 2 | C00-D48 Neoplasms |
| 3 | I00-I99 Diseases of the circulatory system |
| 4 | J00-J99 Diseases of the respiratory system |
| 5 | V00-Y99 External causes of morbidity and mortality |
| 6 | other |

We renounced to include these results in the paper and (partially) address reviewer’s 2 remarks, as we fear it would considerably alter the overall message of our study. Total deaths for Spain only represent less than 10% of the total European death numbers and Spain’s all-cause mortality is associated with none of the DST transitions.

Data sources: Death counts according to six causes of death were obtained for Spain, by NUTS2 region, day, sex, 15 years age groups (0-14, 15-29, 30-44, 45-59, 60-74, 75+) for the period 1999-2012 (1998 was not available). To preserve confidentiality, the cause of death was categorized according to the International Classification of Diseases 10th Revision (ICD10), as follows: (A00-B99 Infectious diseases; C00-D48 Neoplasms; I00-I99 Diseases of the circulatory system; J00-J99 Diseases of the respiratory system; V00-Y99 External causes of morbidity and mortality; all remaining ICD10 codes Other.

Statistical analysis: Spain daily death counts for 6 different causes of death were analyzed using multiple Poisson regression models adjusted for the same variables as above, without country’s adjustment.

Results: Cause of death in Spain
Reviewer’s Table 2 shows the distribution of the cause of mortality in Spain according to age and sex. Men are more likely to die from cancer and external causes (accidents, injuries, suicides, crimes) than women. External causes are the most frequent cause of death between 15 and 44 years in men.
Reviewer’s Table 3 reveals, after adjustment for all the listed variables, that all-cause mortality is not associated with any of the DST transitions. The mortality is lower on Sunday. Infectious diseases, neoplasms, external causes and other causes of death are not associated with DST. Diseases of the circulatory systems are significantly more frequent during the two weeks after the spring DST and less frequent during the seven weeks after the fall DST. Diseases of the respiratory systems are not associated with the Spring DST and less frequent during the second, third and four week after the fall DST. Regarding the association of mortality with the day of the week, none was found for infectious and respiratory systems’ diseases. There are 2% more deaths (IRR 1.02) on week-ends for external causes. They are between 4% and 6% more deaths of cancer from Tuesday to Saturday. There are 3% less deaths (IRR 0.97) on week-ends for disease s of the circulatory system, with a Monday peak. For other causes, the mortality is also lower on week-ends and Wednesdays.

Reviewer’s Tables 2 and 3 are provided for the reviewer as “A2.1 Tables 2 -3 Spain causes of death for reviewer.xlsx”.

R2.2 The authors stated that time change in the spring did not have a significant effect on mortality, which is incorrect. There was an increase in mortality pattern, but occurred 2 weeks after the date when DST took place. More discussions on why this pattern was observed in the dataset is needed. Could it be due to cumulative effect? Again cause of death would be very helpful here.

A2.2 We would like to bring to your attention that, after taking into account all the reviewers’ comments and suggestions, we adjusted our results for temporal (year, season, month, day of the week), meteorological (daily mean temperature, humidity and wind speed), geographic (latitude and longitude of the region’s centroid, a sine-cosine function that considers daylight seasonality, yearly country and regional GDP) and population variables (sex and 10 years age group). Adjustment has resulted in the strengthening of all reported IRRs. In this revised version, the week-end effect is confirmed. However, contrary to our previous results, we now observe a significant decrease in mortality during the first two weeks after the Spring DST and a significant increase in mortality during the first two weeks after the fall DST. In addition, we note from week 4 onwards after the fall DST, a significant and quasi constant decrease in daily death rates.

The manuscript has been edited accordingly

Results section:

The figure 1 is described as follows: “Daily mortality rates are obviously subject to seasonal variations with a downward trend in spring and an upward trend in fall (cf. splines in Figure 1b and 1c). However, when compared to these expected seasonal trends, mortality shows an apparent increase after the DST transition in spring (1b) and an apparent decrease in fall (1c).”

“An adjusted multiple binomial negative regression model (Table 1) shows a significant decrease in death counts in the spring DST (IRRweek1 .965; 95% CI: .951-0.979, p< 0.001; IRRweek2 .972; 95% CI: 0.958-0.986, p< 0.001), and a significant increase in the fall DST (IRRweek1 1.018 95% CI: 1.003-1.033, p= 0.016; IRRweek2 1.023 95% CI: 1.008-1.039, p=0.002). Significant variations of mortality are mainly observed during the first two weeks following each DST transition. Nevertheless, we note from week 4 onwards after the fall DST a significant, quasi constant decrease in daily death rates. General mortality in the 16 countries examined shows a continuous and significant downward trend between 1998 and 2012. It also exhibits a clear seasonality: mortality is highest in winter and lowest in spring (when summer is taken as a reference). The values gradually diminish from January to September and then increase again. Mortality rates are higher in men than in women for all the age groups. The older the age group, however, the highest the death rates, irrespective of sex. Regional longitude and latitude are also modest determinants of mortality, as easternmost and northernmost NUTS2 centroids, respectively, are associated with a higher risk of death. In our dataset, Switzerland and Italy have the lowest mortality rates, while Croatia and Poland have the highest. Higher annual and regional (i.e. by NUTS2) gross domestic product (GDP) is significantly associated with a lower risk of death. Finally, as to meteorological variables, we find that an increase in temperature and wind speed, but a decrease in relative humidity were significantly leading to a higher risk of mortality.”

Discussion section:
We kept our four hypothesis and added: We cannot account for the significant decrease in daily mortality that occurs after week 4 of the fall DST, as it occurs independently of the monthly and seasonal effect. Indeed, one would normally expect an increase in mortality at this time of year (cf. Figure S1) 33,34.

R2.3 It is unclear to me why ages 35+ were grouped together, as this led to a wide age range. Mortality patterns and causes of death differ between middle and older aged groups. People who are retired may be affected differently by the DST when compared to people who are at working age. The authors should use more refined age groups, and in particular separate according to typical retirement age.

A2.3 We originally computed the graphs by 5-years age groups and then regrouped the ages according to the observed patterns to simplify the message of our study. We agree with the reviewer and now present 10 years age groups (from 0.0-9.9 years to 80+) both in figure 2 and in the binomial negative regression models.

Reviewer #3:

“The authors attempted to present the relationship between daylight saving time transitions and patterns of all-cause mortality in 16 European countries for the period 1988-2012. However, they have only been partially successful in achieving their objective. In fact, I have some comments, all of them major.

R3.1 The main problem of the manuscript is the lack of control of important confounders. The authors already indicate weather conditions as important confounding (page 10, lines 226 to 228), but indicate that ‘they rarely arise around DST transitions’. This would be true if the climatic conditions had not varied in those 24 years (from 1988 to 2012), but it is not like that. Both the variance of these conditions (variability) and the duration (some shorter, others longer) have varied and it is very likely that the beginning of the seasons. Authors should try to capture this variability, including, for example, random effects indexed by months or seasons.”

A3.1 Thank you very much. First of all, we would like to point out that our study period runs from 1998 (not 1988) to 2012. We fully agree with the reviewer’s comment. Thanks to our co-authors, we obtained daily average values of 3 key meteorological variables (by NUTS-2 region and for the whole study period): temperature, relative humidity and wind speed. We now adjust the binomial negative regression models for these 3 measured continuous variables. The methods, results and discussion sections have been modified accordingly.

R3.2 Another very important confounder is the socioeconomic conditions of each country and of each country over time. Socio-economic conditions can influence the degree of ‘adaptation’ of your population, among other things.

A3. We obtained the gross domestic product (GDP) - as a proxy of socioeconomic conditions - by year, NUTS2 regions and expressed in 2015 USD. These data were not available for several countries before the year 2000 and for Switzerland before the year 2008. In these cases, we imputed the yearly regional GDP among Nuts regions according to the trend in proportion observed during the available years up to 2019 using a regression imputation method. The GDP was then added as an adjusting continuous variable to the binomial negative regression model. The methods, results and discussion sections have been modified accordingly. “The gross domestic product (GDP) is a proxy variable of socioeconomic conditions. The GDP values were downloaded from the Organisation for Economic Co-operation and Development (OECD) web site (https://stats.oecd.org/index.aspx?queryid=67051). GDP is expressed in millions of US dollars, at constant prices and constant purchasing power parities (PPP is the “rate of currency conversion that equalise the purchasing power of different currencies by eliminating the differences in price levels between countries”) with 2015 as the reference year. These data were not available by NUTS2 regions for several countries before the year 2000 and for Switzerland before the year 2008. Thus, we imputed the yearly regional GDP according to the trend observed during the available years 2000-2019, respectively 2008-2019 using a linear regression imputation method.”

R3.3 Related to my comment number 2, there could be other important confounders specific to each country. In fact, figure S1 shows a very important heterogeneity in some of the countries. Thus, for both this and the previous comment, the authors should allow IRRs to vary by country and by year (including random effects, for example).
A3.3 As proposed, we tried to add the “country” variable as a random effect in a “multilevel mixed-effects negative binomial regression”. Unfortunately, after many hours of computing time, this model failed to converge. Instead, we successfully added “country” as a fixed effect, nominal variable in the binomial negative regression model. The methods, results and discussion sections were been modified accordingly.

R3.4 The authors include the interaction between age and sex. Sounds good to me, but I think you should try other important interactions, all of them with age and gender, for example, gender and month, age and month, gender and country, age and country, etc ...

A3.4 As suggested, we included additional interactions in the binomial negative regression model. However, one must remain cautious when taking into account so many interactions, as they can lead to challenging interpretations and blur the main effects.

For the guidance of reviewer 3, we propose a “A3.4 Model with interactions.pdf; page 14-16” which considers all the requested interactions. The following sentences were also added to the method and results section:

Method

“The same model was also run with different sex and age interactions - month, day of the week, spring DST, fall DST and country.”

Results

“The same model with different sex and age interactions - month, day of the week, spring DST, fall DST and country - shows that most are statistically significant with the notable exception of the following ones: sex * DSTs; 10-year age group * DST spring (results not shown).”

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Reviewers' Comments:

Reviewer #1:
Remarks to the Author:
The Authors made great and substantial effort to answer the detailed questions raised by the reviewers, and the manuscript has significantly improved. Although, at a comprehensive evaluation, the crucial point remains to define the precise causes of death (since DST of course may play a role, for example, on some cardiovascular diseases but not on cancer), the Authors again made great effort, and they clearly explained all the difficulties to obtain this information by the different Countries. I now believe that all the points raised have been appropriately answered.

Reviewer #2:
Remarks to the Author:
The authors have addressed my previous comments adequately. I have no more to add.

Reviewer #3:
Remarks to the Author:
The authors responded well not only to my comments but also to the rest of the reviewers. They also included most of them in the new version of the manuscript. I have no further comments.
Point-by-point response to the reviewers’ comments, reproduced verbatim

Reviewer #1 (Remarks to the Author):

The Authors made great and substantial effort to answer the detailed questions raised by the reviewers, and the manuscript has significantly improved. Although, at a comprehensive evaluation, the crucial point remains to define the precise causes of death (since DST of course may play a role, for example, on some cardiovascular diseases but not on cancer), the Authors again made great effort, and they clearly explained all the difficulties to obtain this information by the different Countries. I now believe that all the points raised have been appropriately answered.

Reviewer #2 (Remarks to the Author):

The authors have addressed my previous comments adequately. I have no more to add.

Reviewer #3 (Remarks to the Author):

The authors responded well not only to my comments but also to the rest of the reviewers. They also included most of them in the new version of the manuscript. I have no further comments.

We thank all three reviewers for their thoughtful comments which helped us improve the manuscript.

Prof. François HERRMANN
Geneva, October 27, 2022