RESEARCH PROPOSAL

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Background/Rationale

Non-pharmaceutical interventions (NPI) constitute one of the strongest tools to control the spread of the ongoing SARS-CoV-2 (COVID) pandemic. Understanding their effectiveness is crucial, especially given their adverse socioeconomical impact. A proper study of their combined effect on reducing the incidence of the virus is required to correctly assess the best protocol for future interventions. There are many studies available on some combinations of NPIs in different regions, but none includes the application of a COVID passport measure to control the access to certain social events, which has been in vigour in some European countries only recently. The current analysis intends to determine the effectiveness of this intervention.

Research Aims

As stated, we would like to assess the usefulness of the COVID passport intervention in different countries.

Methods

Data sources

- For DEATH stratified by age and sex: https://dc-covid.site.ined.fr/en/data/pooled-datafiles/ (as of 2021-12-13):
    - *Austria: 0-4yr, 5-14yr, 15-24yr, 25-34yr, 35-44yr, 45-54yr, 55-64yr, 65-74yr, 75-84yr, 85+yr // male/female // 2020-03-12 to 2021-12-03*
    - *Belgium: 0-24yr, 25-44yr, 45-64yr, 65-74yr, 75-84yr, 85+yr // male/female // 2020-03-10 to 2021-12-01*
    - Canada: 0-19yr, 20-29yr, 30-39yr, 40-49yr, 50-59yr, 60-69yr, 70-79yr, 80+yr // male/female // 2020-11-25 to 2021-11-07
    - *Denmark: <70yr, 70-79yr, 80-89yr, 90+yr // male/female // 2020-04-03 to 2021-12-02*
    - *France: 0-24yr, 25-34yr, 35-44yr, 45-54yr, 55-64yr, 65-74yr, 75-84yr, 85-94yr, 95+yr // male/female // 2020-03-20 to 2021-12-02*
    - Germany: 0-9yr, 10-19yr, 20-29yr, 30-39yr, 40-49yr, 50-59yr, 60-69yr, 70-79yr, 80-89yr, 90+yr // male/female // 2020-03-29 to 2021-12-01
    - Italy: 0-9yr, 10-19yr, 20-29yr, 30-39yr, 40-49yr, 50-59yr, 60-69yr, 70-79yr, 80-89yr, 90+yr // male/female // 2020-03-09 to 2021-11-24
    - Japan: 0-9yr, 10-19yr, 20-29yr, 30-39yr, 40-49yr, 50-59yr, 60-69yr, 70-79yr, 80-89yr, 90+yr // male/female // 2020-03-31 to 2021-11-30
    - Moldova: 0-4yr, 5-9yr, 10-14yr, 15-19yr, 20-24yr, 25-29yr, 30-34yr, 35-39yr, 40-44yr, 45-49yr, 50-54yr, 55-59yr, 60-64yr, 65-69yr, 70-74yr, 75-79yr, 80-84yr, 85+yr // male/female// 2020-03-8 to 2021-12-02
    - Netherlands: 0-4yr, 5-9yr, 10-14yr, 15-19yr, 20-24yr, 25-29yr, 30-34yr, 35-39yr, 40-44yr, 45-49yr, 50-54yr, 55-59yr, 60-64yr, 65-69yr, 70-74yr, 75-79yr, 80-84yr, 85+yr // male/female// 2020-03-23 to 2021-11-30
    - *Norway: <40yr, 40-49yr, 50-59yr, 60-69yr, 70-79yr, 80-89yr, 90+yr // male/female // 2020-04-15 to 2021-12-02*
    - Portugal: 0-9yr, 10-19yr, 20-29yr, 30-39yr, 40-49yr, 50-59yr, 60-69yr, 70-79yr, 80+yr // male/female // 2020-03-23 to 2021-12-01
    - Romania: 0-9yr, 10-19yr, 20-29yr, 30-39yr, 40-49yr, 50-59yr, 60-69yr, 70-79yr, 80+yr // male/female // 2020-03-22 to 2021-12-02
    - *Scotland: 1-14yr, 15-44yr, 45-64yr, 65-74yr, 75-84yr, 85+yr // male/female// 2020-03-22 to 2021-11-28*

    - South Korea: 0-9yr, 10-19yr, 20-29yr, 30-39yr, 40-49yr, 50-59yr, 60-69yr, 70-79yr, 80+yr // male/female // 2020-03-04 to 2021-06-04
    - Spain: 0-9yr, 10-19yr, 20-29yr, 30-39yr, 40-49yr, 50-59yr, 60-69yr, 70-79yr, 80+yr // male/female // 2020-02-13 to 2021-12-01
    - *Sweden: 0-49yr, 50-59yr, 60-69yr, 70-74yr, 75-79yr, 80-84yr, 85-89yr, 90+yr // male/female // 2020-05-12 to 2021-12-02*
    - Switzerland: 0-9yr, 10-19yr, 20-29yr, 30-39yr, 40-49yr, 50-59yr, 60-69yr, 70-79yr, 80+yr // male/female // 2020-04-13 to 2021-12-02
    - *USA: 0-4yr, 5-14yr, 15-24yr, 25-34yr, 35-44yr, 45-54yr, 55-64yr, 65-74yr, 75-84yr, 85+yr // male/female // 2020-01-04 to 2021-12-01*
    - Ukraine: 0-9yr, 10-19yr, 20-29yr, 30-39yr, 40-49yr, 50-59yr, 60-69yr, 70-79yr, 80-89yr, 90+yr // male/female // 2020-02-13 to 2021-11-30
    - England and Wales: 0-19yr, 20-39yr, 40-59yr, 60-79yr, 80+yr // male/female // 2020-03-11 to 2021-12-01

Some of the previous datasets are weekly and some daily. Some are repeated, from more than one reporting agency. We will do the following:

- Aggregate age blocks as 0-19yr, 20-39yr, 40-59yr, 60-79yr, 80+yr, therefore using data from the following countries: Canada, Germany, Italy, Japan, Moldova, Netherlands, Portugal, Romania, South Korea, Spain, Switzerland, Ukraine and England and Wales. The previous countries in *italics* are thus not comparable. I have not found any other available data set with comparable age blocks anywhere for any of them.
- If more than one count available, we will use the one reported to be more reliable, or an average of both if the previous is not applicable.
- Aggregate data weekly for comparison between countries, if daily data is available.

- For CASES and VACCINATIONS, not stratified by age nor sex:
    - England: https://coronavirus.data.gov.uk/details/cases?areaType=overview&areaName=United%20Kingdom
    - Wales: https://public.tableau.com/app/profile/public.health.wales.health.protection/viz/RapidCOVID-19virology-Public/Headlinesummary
    - Scotland: https://www.opendata.nhs.scot/dataset/covid-19-in-scotland // https://www.opendata.nhs.scot/dataset/covid-19-vaccination-in-scotland
    - Ireland: https://www.hpsc.ie/a-z/respiratory/coronavirus/novelcoronavirus/casesinireland/
    - Many other EU countries, including Denmark: https://www.ecdc.europa.eu/en/covid-19/data

I could not find stratified data for a sensible number of countries/regions. As COVID passport intervention effects has not been studied in any case, I thought we could analyse it for cases and vaccinations (or hospital admissions as well, if desired) for all age/sex aggregated data. Different UK regions as well as Ireland and Denmark will be selected, and possibly all other European countries in the ECDC dataset: Austria, Belgium, Bulgaria, Croatia, Cyprus, Czechia, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Liechtenstein, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain and Sweden.

- For some European countries and several NPI dates: https://www.ecdc.europa.eu/en/publications-data/download-data-response-measures-covid-19
- For COVID passport dates for some European countries: https://covid-statistics.jrc.ec.europa.eu/RMeasures

COVID passport is a recent measure and I think there will be no other option but to look up the date of its application in some countries individually in Google. The same is true for certain selected non-European countries.

- Australia weekly data of Strokes, Diabetes, Heart conditions, etc. Not by age nor sex: https://www.abs.gov.au/statistics/health/causes-death/provisional-mortality-statistics/latest-release

This data is not stratified by sex nor age, but I believe it will still be useful for checking robustness of the model anyway. I have not found many pages with weekly health data, only annual.

QUESTIONS:
- Is the selection of countries for deaths by age and sex ok? Should we also model the others, for their respective age blocks? Should we exclude non European countries?
- Is the decision of analysing cases and vaccination without accounting for age and sex alright?
- Should we also analyse hospital admissions, given that we have the information?
- Should we also include the other 30 European countries, given that we have the information?

Study population/s and stratification/s
As written in the previous section, depending on the outcome, the study will account for stratification for different countries, sex and/or age blocks. Only comparable datasets will be used for each triplet (country, age range, sex) if applicable.

Intervention/exposure variables
The variables accounted for will include:

- Day of the week (Mon, Tue, Wed, Thu, Fri, Sat, Sun): categorical variable with 7 levels
- COVID passport NPI: categorical variable
    - 0 when the NPI was not into effect
    - 1 for the LAG (see following section) following days after it came into effect, to account for the lag caused by the incubation period of the virus, or any other lags if the NPI status changes again
    - 2 when the NPI was into effect after the lag period only for restricted events (such as only for night clubs, or only for cultural events)
    - 3 when the NPI was into effect after the lag period for a wider range of events (large gatherings, bars, trains, cafés, workplace)
- Face masks: categorical variable
    - 0 when NPI was not into effect
    - 1 LAG
    - 2 recommended
    - 3 required in some specified shared/public spaces outside the home with other people present, or some situations when social distancing not possible
    - 4 required in all shared/public spaces outside the home with other people present or all situations when social distancing not possible
    - 5 required outside the home at all times regardless of location or presence of other people
- Public gathering restriction: categorical variable
    - 0 not into effect
    - 1 LAG
    - 2 restrictions on very large gatherings (the limit is above 1000 people)
    - 3 restrictions on gatherings between 101-1000 people
    - 4 restrictions on gatherings between 11-100 people
    - 5 restrictions on gatherings of 10 people or less
- Stay at home: categorical variable

  - 0 not into effect
  - 1 LAG
  - 2 recommend not leaving house
  - 3 require not leaving house with exceptions for daily exercise, grocery shopping, and 'essential' trips
  - 4 require not leaving house with minimal exceptions (eg allowed to leave once a week, or only one person can leave at a time, etc)
- Closure of schools: categorical variable
  - 0 not into effect
  - 1 LAG
  - 2 recommend closing or all schools open with alterations resulting in significant differences compared to non-Covid-19 operations
  - 3 require closing (only some levels or categories, eg just high school, or just public schools)
  - 4 require closing all levels
- Closure of workplaces: categorical variable
  - 0 not into effect
  - 1 LAG
  - 2 recommend closing (or recommend work from home) or all businesses open with alterations resulting in significant differences compared to non-Covid-19 operations
  - 2 require closing (or work from home) for some sectors or categories of workers
  - 3 require closing (or work from home) for all-but-essential workplaces (eg grocery stores, doctors)

QUESTIONS:
- Should I include less or more NPIs (cancel public events, close public transport, economic policies, travelling restrictions)?
- Should I be less detailed in separating levels? I have followed Oxford Covid-19 Government Response Tracker's indexes (https://github.com/OxCGRT/covid-policy-tracker/blob/master/documentation/codebook.md) but I could keep it simpler.

Outcome/s of interest

The same model will be run to evaluate different COVID incidence measures. For all of them, a certain lag after the application of all NPIs will be accounted for. The values in the specified range will be tested for robustness, and the value for the main model detailed as follows:

- Weekly confirmed cases (LAG 2-7): LAG 5
- Weekly admissions in hospital, if modelled: LAG 7
- Weekly mortality attributed to the pandemic (LAG 17-21): LAG 19
- Weekly values of vaccinated people (LAG 7-14): LAG 11

QUESTIONS:
- For vaccinated people, should we treat them all equally, or only count fully vaccinated people, or count first dose / second dose separately…?
- Are the lags correct? I found these numbers in different articles and by self reasoning, but not sure.

Data analysis

As we will perform all methods on data stratified on country, age and sex (if applicable, if not the stratification is void), from now on we will say CAS data when referring to the data separated into country, age and sex blocks.

Moreover, all analyses will be done for raw data, for the logarithm or hyperbolic sine to minimize the influence of extreme data counts, and for moving average means to increase smoothness. The most well-behaved model will be selected.

Firstly, segmented linear regression (SLR) assessment on CAS data will be performed as an initial inspection of the effect. It will be done for all populations and stratifications mentioned but will only take the COVID passport NPI covariate into account. The procedure will consist in the following:

1. Select a timepoint t* when the intervention was officially formalised by the government for each country, if applicable.
2. Initial visualization of the data to select the timeline of the intervention. We will restrict the regression to the particular wave of the NPI, to minimize the effect of other confounding covariates, for instance weather conditions. Therefore we will select the maximal interval containing t* that is strictly concave or convex.
3. Create a categorical variable quantifying the application of the COVID passport NPI.
4. Select the SLR model with coefficients b0, b1, b2, b3 and b4. We will have two timepoints, t* and t*+LAG. We would expect a change in slope or step on the second one but not on the first.
5. Perform a Durbin-Watson test on the residuals of the model. If negative, go to step 6. If not, do step 4 again transforming the model, for instance, to a Cochranne-Orcutt autocorrelated linear model.
6. Perform a test to see the validity of the hypothesis b3=0.

Then, the main models will be created using ARIMAX methodology. For all CAS data, the procedure is the following:

1. Create categorical variables for all NPIs as specified above.
2. Select a triple (p,d,q) to build the model ARIMAX(p,d,q). This will be done in different ways: both by letting the built function select the most optimal model by itself, and also by looking at the stationarity, ACF and PCF plots of the data ourselves. A sensible criteria should be applied, as for the lag we would expect for different outcomes (ranges written in Outcome/s of interest section). Seasonality should probably be included as well. Stationarity should be checked with Dickey-Fueller test.
3. Check the residuals of the model by looking at their ACF plot and performing normality (Shaphiro-Wilk), heteroskedasticity (Breusch-Pagan) and randomness (Ljung-Box) tests on them. Check also for significance of coefficients. If they do not look like white noise then we should modify the model.
4. Determine the effect of the NPI of the model by looking at its coefficient. This is not exactly accurate but I believe this is how it is usually assessed in other papers.
5. Compare all models for different stratifications. Aggregate the results with inverse-variance weighted average or other Mantel-Haenzel methods.

To check for multicollinearity and for the robustness of the model, we will also do the following, both for the ARIMAX and the SLR when applicable:

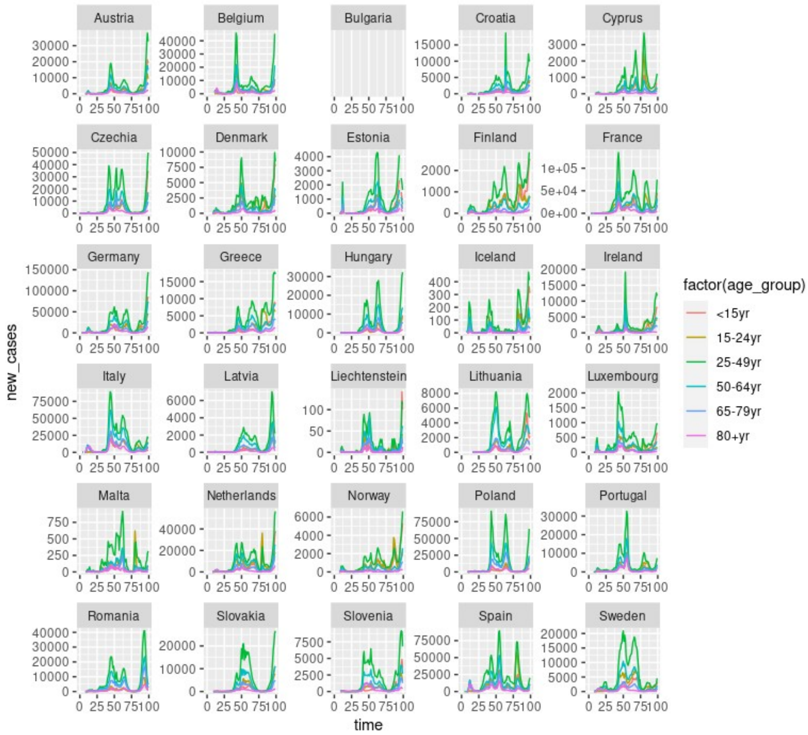
- Run the model dropping all covariates one by one to see which coefficient varies the most in absence or presence of other covariates. This check will enable us to further asses which countries deliver the most reliable effect information.
- Let interventions have a longer impact after they are lifted.
- Let the windows for the moving average take larger or smaller values.
- Perturb the lags slightly. For instance, for cases data, we could allow for 2-7 days of lag instead of 5.

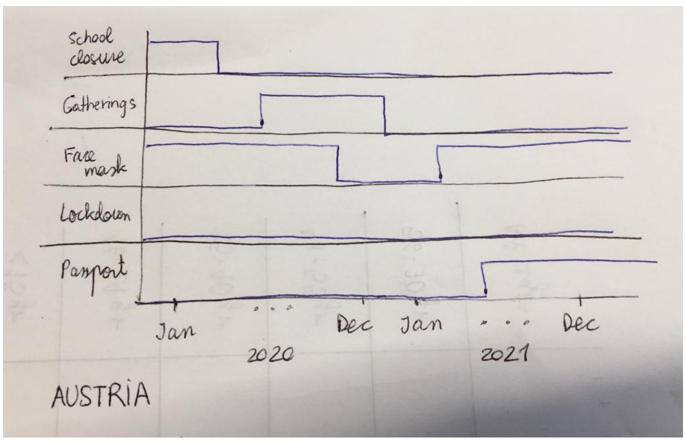
- Change the data slightly, particularly for not very reliable values like cases (allowing for a uniformly at random addition or subtraction of weekly data taken from a Binomial with probability (average new cases)/(population), in the latter situation).
- Run the model with data for a seemingly random outcome, like strokes, for which we would expect no effect whatsoever.
- Permute data within and between countries to ensure the results are not due to spurious effects.
- For the case of daily data available which we have aggregated, we will use the model to compare its performance versus weekly data.

Mock tables and figures

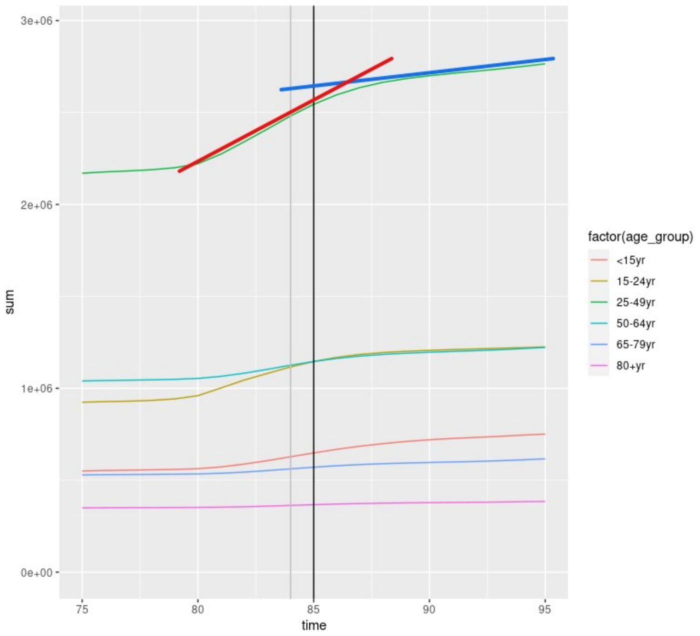
Let N=#countries·#age factors·#sex factors=C·A·S, and O=#outcomes. We expect to produce the following results after our analyses:

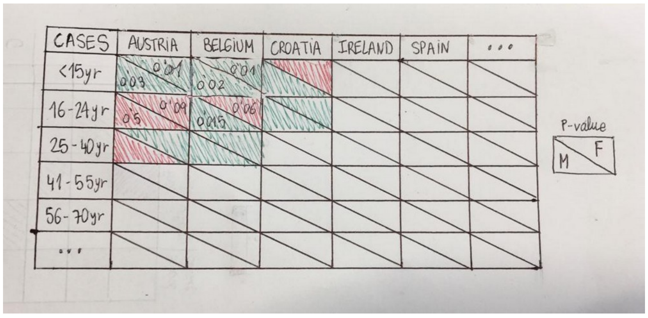
- Initial C·S plots of behaviour for the data of all outcomes factored by A
- Initial C plots of NPI timeline
- Possibly other summary data plots



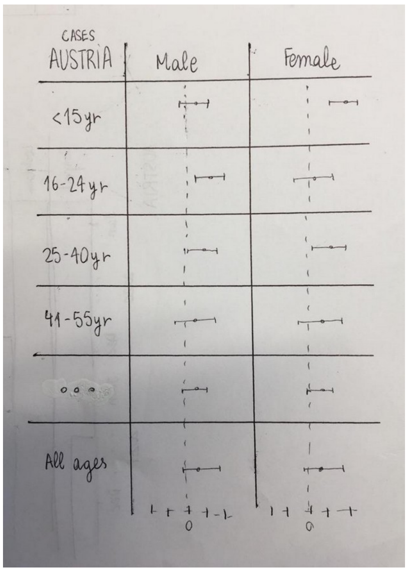


- SLR: N plots for all outcomes with regression lines for the pre-intervention period, lag period and post-lag period.
- SLR: O tables with C columns, A rows and S-divided entries with the results of the b3=0 tests.





- ARIMAX: Plot with the effect computed by the model by A (rows) and S (columns) with its uncertainty.



- ARIMAX: More graphics summarizing information by aggregating the previous plots for C, A, S or a combination of them.

- Double entry tables of effect change when dropping one covariate