Changes in antidepressant dispensation rates during the COVID-19 pandemic in Europe.

A retrospective observational study using register data from Austria, Latvia, Slovenia and Sweden.

Author: Astrid Syvertsen

Supervisor: Pär Flodin, Research Specialist, Department of Global Public Health, Karolinska Institutet.
Co-Supervisor: Anna-Clara Hollander, Principal Researcher, Department of Global Public Health, Karolinska Institutet

The Master program in Public Health Sciences at KI is carried out in collaboration between mainly three departments: The Department of Global Public Health, the Institute of Environmental Medicine and the Department of Medicine, Solna.

The master program has two specialisations; Public Health Epidemiology and Health Promotion and Intervention. The master thesis of 30 credits is written within the selected specialization.

Jette Möller
Program Director

Declaration

I hereby affirm that this Master thesis was composed by myself, that the work herein is my own except where explicitly stated otherwise in the text. This work has not been submitted for any other degree or professional qualification except as specified; nor has it been published. Where other people’s work has been used (either from a printed source, internet, or any other source), this has been carefully acknowledged and referenced.

Stockholm, May 7th

Author: Astrid Syvertsen

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Astrid Syvertsen

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Abstract

Introduction: The coronavirus pandemic is widely believed to have worsened the general population's mental health. Understanding the consequences of the pandemic is a widely recognised research priority to inform decision-makers in future epidemics and pandemics. Antidepressant dispensations are available in medical registers, which constitute a suitable data source when studying the changes in the population`s mental health. However, few studies have related the change in antidepressants with the implementation of containment policies.

Aim: The aim of this study was to assess changes in dispensation rates of antidepressant drugs during the pandemic, and relate these to containment measures in Europe.

Methods: Pre-pandemic data were used to train Autoregressive Integrated Moving Average models to forecast expected rates in antidepressant dispensations. Change was measured as the deviation in observed dispensation rates from the expected. COVID-19 index was used to assess the associations between changes in dispensation rates and the monthly intensity score of containment measures.

Results: Spiked and isolated peaks in the initial months of the pandemic were observed in Austria, Slovenia, and Sweden, which likely could be attributed to stockpiling behaviours. After excluding these initial peaks, the change in antidepressant dispensations returned to near-expected. On the contrary, increased antidepressant dispensations were sustained throughout 2020 in Latvia. Most associations between dispensation rates and containment measures were non-significant, although a few weak negative associations were found.

Conclusion: The decreasing and near-normal rates in antidepressant dispensations during the pandemic do not support the commonly held belief of deteriorated population mental health during the coronavirus pandemic.

Keywords: coronavirus, pandemic, depression, antidepressant drugs, mental health

Table of Contents

Abstract **5**

1 Introduction **8**

1.1 COVID-19 and its recent precursors 8
1.2 The COVID-19 pandemic and Mental Health 8
1.3 Problem description 9
1.4 Antidepressant dispensations from pharmacies 10
1.5 Aim of the study 11
1.6 Research Questions 11

2 Methods **11**

2.1 Study design 11
2.1.1 Retrospective observational study using forecasting models 11
2.1.2 ARIMA forecasting models 11
2.1.3 Akaike Information Criterion 12
2.1.4 Time points selected to compare observed with expected rates 12

2.2 Study setting 13
2.2.1 Austria 13
2.2.2 Latvia 13
2.2.3 Slovenia 14
2.2.4 Sweden 14
2.3.1 Outcome and outcome variable 14
2.3.2 Containment measure indices 15
2.3.2 Age and sex variables 15

2.4 Data analysis 16

3 Results **19**

3.1 Baseline dispensation rates 19

3.2 Changes in drug dispensation rates 19
3.2.1 Austria 19
3.2.2 Latvia 21
3.2.3 Slovenia 22
2.3.4 Sweden. 23

3.3 Impact of country-specific Containment Measures 25

4 Discussion **26**

4.1 Summary of main findings 26

4.2 Generalisability and future directions 29

4.3 Strengths and limitations 30

5 Conclusion **32**

6 Funding and Final Acknowledgements **32**

References **33**

Appendices **37**

Supplementary Tables 37

Glossary/List of abbreviations

AD	Antidepressant Dispensation
AIC	Akaike Information Criterion
ARIMA	Autoregressive, Integrative, Moving Average models
BM	Bootstrap Method
C19 pandemic	Short for the COVID-19 pandemic
CIOMS	Council for International Organization of Medical Sciences
CMD	Common Mental Disorder
COVID	Coronavirus
DDD	Daily Defined Dose
EU	European Union
EPiCSS	Epidemiology of Psychiatric Conditions, Substance use and Social Environment (research group at Karolinska Institutet)
IPV	Intimate Partner Violence
KI	Karolinska Institutet
MERS-COVID	Middle East Respiratory Virus
PERISCOPE	Pan-European Response to the Impact of COVID-19 and Future Pandemic and Epidemics
DRR	Dispensation Rate Ratio
PTSD	Posttraumatic Stress Disorder
SD	Social Distancing
SARS	Severe Acute Respiratory Syndrome
SR	School Restrictions
WHO	World Health Organization

1 Introduction

1.1 COVID-19 and its recent precursors

Signs of Coronavirus (COVID) infection generally span a wide spectrum from an asymptomatic state to death, with the risk of fatality making infection control a vital public and global health priority (1–3). Since the start of the millennium, there has been several COVID outbreaks globally (2,4). For example, in 2003, at least 8000 were infected by the Severe Acute Respiratory Syndrome (SARS-COVID) in mainly Asian countries(4), followed by another multi-country outbreak of the Middle East Respiratory Coronavirus (MERS-COVID) in 2012 (5). These outbreaks foreshadowed the possibility of a future pandemic involving the COVID virus and triggered alarm amongst researchers and global health institutions worldwide (4). These fears were realised when the full impact of the COVID-19 variant was revealed in the number of confirmed cases and countries affected, which lead the World Health Organization (WHO) to declare COVID-19 as a `pandemic´ on March 11th 2020 (6)

The implementation of national-level policies to respond to any viral health emergency involves a delicate balance between the need to combat the spread of the virus whilst at the same time, ensuring that mitigation policies do not undermine other important health priorities (7). In the case of the COVID-19 pandemic (hereby referred to as `C19 pandemic´ for short), the various intensities of infection control unleashed a series of natural experiments, reflecting different epidemiological approaches from one country to another (3,7). These policy differences offer opportunities to compare varying national responses to the C19 pandemic on population health outcomes. Epidemiology provides a framework for comparing the change in these outcomes and, ultimately, informing decision-makers who may be required to respond to future epidemics and pandemics (3).

1.2 The COVID-19 pandemic and Mental Health

Concerns regarding the effects of the C19 pandemic on the mental health of the general population were raised at an early stage in the pandemic (8–10). In broad terms, the C19 pandemic may impact the mental health of the population, either *directly* due to actual infection or *indirectly* as a result of the implementation of various constraints on everyday life to respond to the outbreak(11). For example, research from the SARS-COVID outbreak in 2003 revealed that COVID survivors were at higher risk, than the non-infected control group, of developing psychological distress and prolonged elevated stress levels (12). Similarly, in a 12- year follow-up cohort study from Taiwan after the SARS-COVID outbreak, survivors were found to have increased risk of psychiatric diagnoses such as anxiety, depression, posttraumatic stress disorder (PTSD), and suicide compared to the non-infected control group(13).

Containment measures that may *indirectly* affect the mental health of populations include school restrictions, social distancing, and work-from-home policies(11,14,15). The implementation of social restrictions heightened well-established risk factors associated with depression and other common mental disorders (CMD) (10,16,17). Examples of such risk factors are isolation, economic stress, and unsatisfactory occupational engagement (16). For example, an Australian study compared survey responses collected before and during the C19 pandemic, finding that difficulties with school restrictions were associated with increased mental health issues in adolescents(18). However, older age groups might have been the most affected. In Europe, approximately 95% of the fatal COVID cases are among the elderly population, leading to stringent social distancing measures in communities and institutions catering them(19,20). In a Scottish mixed-methods study on the elderly population, the majority of the respondents reported that the isolation due to social distancing measures exacerbated the feeling of loneliness compared to before the C19 pandemic (21).

Other studies suggest that enforcing similar policies may have protected certain groups. For example, stay-at-home policies may have contributed to more flexibility in occupational schedules and a greater work-life balance(11). Similarly, it may be possible that students who habitually experienced heightened stress levels due to bullying or peer-group pressure found relief from the school restrictions (22,23)

1.3 Problem description

Most studies from the early waves of the C19 pandemic report an immediate deterioration of the mental health of the general population (9,17,24,25). For example, in a meta-analysis including 204 countries, Santomauro et al(26) identified 53.2 million additional cases of clinical depression worldwide during the C19 pandemic. However, the quality of this evidence can be questioned. A number of the studies use self-reported measures and commonly lack comparison groups or reference to pre-pandemic trends (9,17). Furthermore, heterogeneity in sampling methods raises questions regarding the applicability to the general population (24,27). Finally, inconsistency in diagnostic cut-offs makes it difficult to compare mental health changes across national borders. Complementing the current evidence base with high-quality data and stronger study designs is broadly acknowledged as a research priority within global and public health (8).

Against this backdrop, medical register data provides valuable complements when studying changes in population mental health. Medical register data may be described as any recorded information about a person`s mental diagnosis or treatment based on standardised diagnostic criteria.

1.4 Antidepressant dispensations from pharmacies

Depression is a common and relatively prevalent disorder in the population, and is arguably a suitable indicator for the mental health in a population(28). To study the change in depression, this thesis utilises data provided by national registers on drug dispensations from pharmacies to study the change in antidepressant (AD) dispens’ations during the C19 pandemic. AD drugs are considered one of the first-line treatments for moderate to severe depression and are commonly prescribed concurrently with psychological treatment to patients diagnosed with clinical depression (29,30). Hence, AD dispensations rates may serve as a proxy for the prevalence of multiple depressive symptoms in the European population with (near) universal access to health care(22,31).

Studies examining changes in AD dispensation rates during the C19 pandemic disclose mixed findings. A Scandinavian study found general increases in AD rates by the end of 2020 in Denmark, Norway and Sweden (31). Similar trends were also identified in Israel (32). In contrast, a declining trend in AD dispensation were identified in Portugal (22), and no significant changes in AD dispensation rates were found in Poland(33). In Canada, an immediate increase was displayed in the first month of the C19 pandemic, which in turn reverted to close-to-expected levels by the end of 2020(34). Few studies have, however, attempted to relate the change in AD dispensation rates during the C19 pandemic to the implementation of country-specific containment measures. Information about the potential relationship between containment measures and depression is valuable for decision-makers in responding to future epidemics and pandemics(8). This study aims to address this knowledge gap.

1.5 Aim of the study

This study aims to analyse the changes in AD dispensation rates during the C19 pandemic in European countries and relate these changes to different country-specific containment measures.

1.6 Research Questions

Primary research question. How have the dispensation rates in AD changed during the C19 pandemic in the studied European countries?

Secondary research questions.

[A] Which age groups and sex are most affected?

[B] Are changes in antidepressant dispensation rates associated with implementing country-specific containment measures?

2 Methods

2.1 Study design

2.1.1 Retrospective observational study using forecasting models

This retrospective observational study uses drug registry data to assess the change in AD dispensation rates and its association with containment measures during the C19 pandemic. Forecasting models based on pre-pandemic data are used to predict a counterfactual scenario assuming that the C19 pandemic did not actually happen. The change is subsequently derived from comparing the observed and expected rates. Forecasting models are commonly considered advantageous because of their ability to adjust for underlying trends and seasonality when predicting the expected rate(35)

Training forecasting models rely on the availability of routinely collected data on the outcome variable. For example, in Europe, information about AD dispensation is routinely recorded in official registries with near universal coverage. This makes AD dispensation rates a suitable outcome for studying the change in mental health of the general population in Europe (36).

2.1.2 ARIMA forecasting models

In this thesis, Autoregressive (*AR*), Integrated (*I*), Moving Average (*MA*) forecasting models are used to predict the expected rates in AD dispensation rates. ARIMA models are commonly employed in epidemiological studies, and adjust for seasonality and trends in predicting the counterfactual scenario (37). *AR* in the ARIMA acronym refers to the underlying assumption that lagged and past values of the variable can be used to predict the future(38). ARIMA models are linear regression models that rely on stationarity to predict expected rates. Therefore, *I* refer to converting non-stationary data, such as seasonality, to stationary data. Finally, *MA* refers to calculating how the average in the underlying trend changes over time by considering the number of lagged forecast errors(38,39). When building ARIMA models, it is common to obtain multiple models. The model that best align with the historical data are chosen based on model selection estimators. This departs from the philosophical assumption that there is a single "best" model that represents the most probable counterfactual scenario(40).

2.1.3 Akaike Information Criterion

This study uses the Akaike Information Criterion (AIC) to determine which prediction model that best explains the historical data (40,41). The AIC is among the most frequently used criteria for evaluating prediction models, and is commonly employed in epidemiology (41). Each prediction model is given a score based on the goodness-of-fit criteria, and the ARIMA model with the lowest AIC score is selected.

2.1.4 Time points selected to compare observed with expected rates

To allow for examination of the change in AD dispensation rates at various time points during the intra-pandemic period, I have chosen to study the *immediate-*, *intermediate* and *long-term changes* in AD dispensations.

The *immediate change* is defined as the deviation from expected rates in March 2020, which coincides with the onset of the C19 pandemic. This time point may be justified by findings from similar studies attributing isolated peaks in March 2020 to stockpiling tendencies among individuals with valid prescriptions (31,34,42)

The *intermediate change* is defined as the deviation from expected rates in April 2020. The selection of this time point departs from the assumption that the onset of the C19 pandemic in March 2020 may have had an immediate effect on depression. Following this assumption, the change in AD dispensations would only be observable at least one month later. The change in AD dispensations will likely lag because of the time taken to develop depressive symptoms, seek treatment, and finally dispense the AD drug.

The *long-term change* is defined as the average deviation from expected rates in the entire intra-pandemic period; from March 2020 through December 2020.

2.2 Study setting

The study setting is a number of European countries. This project is part of a larger European Union (EU) funded research initiative called: Pan-European Response to the Impact of COVID-19 and Future Pandemic and Epidemics (PERISCOPE). The EPiCSS research group at Karolinska Institutet (KI) leads this specific project. The research group requested data showing the aggregated number of unique individuals dispensing prescribed AD drugs per month from 2015 through 2020, stratified by age group and sex to European countries. The national registries in Austria, Latvia, Slovenia and Sweden replied to the inquiry and met the eligibility criteria,

2.2.1 Austria

Data on AD dispensation was provided by the *Federation of Social Insurances (Dachverband der Österreichischen Sozialversicherung)* and prepared by the Institute for Advanced Sciences (HIS)(43). The data was structured in monthly counts from January 2015 through July 2021, compromising a total of 8,548,000 AD dispensations, or a monthly average of 127,582 AD dispensations. The age groups were structured in spans of ten years, starting at age group 10-19 and ending at the 80+ year group. The database covered the entire Austrian population, estimated to be 8,900,000 inhabitants (December 2020).

2.2.2 Latvia

Data was received from the Latvian Center for Disease Control and Prevention (*Slimību Profilakses un Kontroles Centrs*) (44), covering the entire Latvian population of 1,900,000 inhabitants (December 2020). The data on AD dispensation was structured in monthly counts from January 2015 through December 2020. The age groups were structured in spans of four years, starting at age group 0-4 and ending at the 95+ year group. The dataset includes 219,497 AD dispensations, yielding a monthly average of 3,658 AD dispensations.

2.2.3 Slovenia

The Slovenian National Institute of Public Health (*Nacionalni Inštitut za Javno Zdravje*) (45) provided data covering the entire Slovenian population of 2,100,000 (December 2020). The data was structured in monthly totals from January 2015 through December 2020, with age intervals of four years, starting at 0-4 years and ending at the 95+ age group. The dataset compromised 3,029,634 AD dispensations, rendering a monthly average of 50,493 AD dispensations.

2.2.4 Sweden

The dataset covering the entire Swedish population of 10,300,00 million (December 2020) was provided by the National Prescribed Drug Register (*Läkemedelsregisteret*)(46). The data was structured as monthly totals from January 2015 through July 2021, starting with the age group 0-14 years and ending at 90+ years. The dataset includes a total of 27,262,295 AD dispensations, or a monthly average of 406,990 dispensations.

2.3 Data collection

2.3.1 Outcome and outcome variable

The outcome is monthly total counts of unique individuals dispensing AD drugs at pharmacies. Only drugs with the Anatomical Therapeutic Chemical (ATC) classification code N06A, i.e. “Antidepressants” are included in this study(47). If an individual purchased AD drugs two or more times within the same month, such person was only counted once. The population denominator is the covered population corresponding to the same month. Hence, the observed and predicted time series display the monthly number of unique individuals dispensing AD prescription drugs per 100,000 persons.

The outcome variable is thus the ratio between the observed and the predicted monthly number of unique individuals purchasing prescribed AD per 100,000 persons, subsequently referred to as Dispensing Rate Ratios (DRR).

2.3.2 Containment measure indices

To ease quantifiable comparisons between countries, assessments have been made using the validated intensity-score-based index provided by Kubinec et al.(14). The index includes the following six indices representing different domains in which containment measures were implemented to reduce the likelihood of transmission: “general social distancing, school restrictions, business restrictions, face masks, health monitoring, and health resources”(14). The index was created by combining two large datasets on different governmental policy responses, namely the “CoronaNet COVID-19 Government Response Event” and “the Oxford COVID-19 Government response tracker” (14). The initiative to pool these comprehensive datasets arose from the objective of studying the effects of countermeasures employed to mitigate the spread of COVID. The data are quantified as an intensity score between 0-100 in the six indices, where 100 corresponds to the maximum value observed among the studied countries. The cooccurrence of several containment-specific characteristics determines the intensity score (14). The factors used to determine the intensity score in each indice are described thoroughly in detail by Kubinec et al (14).

Periods of heightened infection control during the C19 pandemic involved the simultaneous implementation of multiple containment measures, resulting in strong correlations between the indices (14). To avoid multiple comparisons using all six indices, I have chosen the following two indices; “general social distancing” (SD) and “school restrictions” (SR). These indices can plausibly be considered invasive on the population`s mental health. Existing survey-based studies conducted in the early waves of the C19 pandemic suggest a positive relationship between the implementation of these containment measures and increased mental distress (24,48)

2.3.2 Age and sex variables

To facilitate cross-country comparisons categorising relevant age groups to study the impact of the C19 pandemic on the mental health of the general population, the following age groups were selected: 0-29 years, 30-59 years and 60+ years. The terms “school age” and “parents” are particularly relevant to studying school restrictions on AD dispensation rates, and refer to the 0-29 and 30-59 age groups years respectively. Sex is defined as either females ♀ or males ♂.

2.4 Data analysis

2.4.1 Research Question 1

Observed data from January 2015 to December 2020 was sequenced in a time series format with monthly counts of AD dispensation. AD dispensation rates were created by normalising the number of unique individuals AD dispensation drug with the population denominator in the same month (expressed as per 100,000 persons).

Subsequently, the time series of monthly dispensation rates between January 2015 to February 2020 was used to train auto ARIMA models (with 12 months periodicity), using auto ARIMA functions implemented in the Python library *pmdarima 2.0.1*. ARIMA models were evaluated by the goodness-of-fit criteria using AIC, and the best model was used to predict C19 pandemic dispensation rates.

The ARIMA predictions were compared to the actual observed intra-pandemic rates. First, the change in AD dispensation rates during the pandemic was expressed as Dispensation Rate Ratio (DRR), calculated by dividing the observed with ARIMA expected dispensation rates. Thereafter, 95% confidence intervals were calculated using the bootstrap method (BM) with resampling replacement of 500 iterations. Briefly, this was accomplished by simulating new time series where each data point was drawn from a normal distribution with similar mean and standard deviation as the predicted time series. From each simulated time series, I calculated a new DRR, and the original DRR were subsequently compared to the distribution of simulated DRR, yielding an estimated 95% CI of the DRR.

2.4.2 Research Question 2

COVID-19 indices provided by Kubinec et al.(14) were retrieved to test for associations between changes in AD dispensation and containment measures (retrieved from: https://github.com/coronanetDataScience/corona_index). To enable pandemic-induced comparison between countries, all indices were converted to the intensity score of 0 at the start of the C19 pandemic. Thereafter, all indices were scaled accordingly to the intensity score from minimum to maximum, displayed as 0-100, where 100 corresponded to the maximum value observed among the studied countries. For each country and each age group, separate models were specified to correspond to the SD and SR indices. Specifically, the average intensity score was calculated in the indices SR and SD per month and a comparison was then made to the immediate change in AD dispensation in the same month. In addition, a *dummy variable* was included to control for the effects of the C19 pandemic unrelated to the implementation of containment measures. Examples of such effects unrelated to the implementation of containment measures are grief due to fatal COVID-19 cases in friends and family, or a general fear of transmission and contracting the infection. The dummy variable was coded as 0`s in the pre-pandemic period and 1`s in the intra-pandemic period. Then, the dummy variable and intensity indice scores were tested in the ARIMA model, yielding βeta values reflecting the strength and directionality of the association. The significance level was set to α 0.05. All statistical analyses were carried out using the statistical software Python 3.11.

2.5 Ethical Considerations

The use of medical register databases for research purposes presents potential opportunities to the researcher, but also raises fundamental ethical concern (49–52). Medical registers are primary administrative, electronic databases, often including entire populations, and are neither created nor maintained for the sole purpose of research (51). However, register-based research provides a genuine opportunity to study population samples with limited selection bias. In the context of the C19 pandemic and AD dispensation, registry-based studies allow a gateway to study changes in entire populations.

The social value of public health research is one of the core principles in both the World Medical Association Declaration of Helsinki (1964)(53) and International Ethical Guidelines for Biomedical Research Involving Human Subjects (CIOMS 2016) supported by the WHO (54). This study can be justified as being in alignment with the principle of social value, as it provides valuable insights into the impact of the pandemic that may help to mitigate the burden of depression in future epidemics and pandemics.

The social value of such register-based studies may come into conflicts with other ethical principles of the Declaration of Helsinki and CIOMS 2016, namely the requirements of voluntarism and informed consent(55). These principles stress that no individual shall be used for the sole benefit of another party and is particularly important in clinical studies involving the risk of harm to research participants. Registry based studies differ from most other epidemiological study designs because an ethical committee waives the requirement for informed consent on behalf of the population (51). The argument against seeking individual consent is based in part on the disproportionately high level of resources that would be required to enable the inclusion of the large sample which may run to millions of participants. Furthermore, allowing participants to opt out would likely introduce selection bias, threaten the internal validity of the study and reduce the statistical power of the sample (49,51)

Consequently, a requirement to obtain informed consent would restrict the potential of social value from population-based registry studies. However, despite the lack of individual consent, ethical committees oversee the confidentiality of sensitive data and respect for individuals included in the study(55). Furthermore, legal safeguards exist to prohibit the circulation of individual-level microdata across country borders(56). To address these ethical concerns in this thesis, all data included was aggregated and stratified by age and sex. Due to the study`s inability to stratify by covariates other than sex and age group, no vulnerable groups are threatened by potential stigmatisation. According to the Swedish Ethical Review Authority, this this study does not require ethical approval as it reports using aggregated data (reference 2021-01501). No competing interests were disclosed.

3 Results

3.1 Baseline dispensation rates

Baseline dispensation rates in AD during the 12 months before the onset of the C19 pandemic varied greatly by country. The rates were calculated as the average monthly count of AD dispensations in all ages and sexes from March 2019 through February 2020 (12 months before the start of the pandemic in March 2020). The highest baseline rate was found in Sweden (3530 per 100,000 person) followed by Slovenia (2091 per 100,000 person), Austria (1361 per 100,000 person) and Latvia (132 per 100,000). Thus, Sweden had 27 times higher rates than in Latvia.

3.2 Changes in drug dispensation rates

3.2.1 Austria

Immediate change: The Austrian population at large displayed a statistically significant immediate increase of 10% (♀♂, DRR= 1.10; 95% CI 1.05-1.16) in March 2020 (Figure 1). The 0-29 age group showed the highest increase, within which females displayed the highest immediate increase of 18% through March 2020 (♀, DRR = 1.18; 95%CI 1.06-1.31) (Table 1).

Intermediate change: AD dispensation rates in the general population decreased by 6% (♀♂, DRR= 0.94; 95% CI 0.88-0.98) in April 2020. The steepest decline was seen in the 60 year and above age groups, in which males decreased by 12% compared to expected rates (♀♂, DRR = 0.88; 95%CI 0.81-0.97).

Long-term change: No deviation from expected rates were identified in the general population. However, the age-stratified analysis displayed both increasing and decreasing change (Table 3). The 0-29 and 30-59 age groups displayed increased rates, yielding an increase of 11% and 6% (0-29 years, ♀♂, DRR= 1.11; 95% CI 1.08-1.16 | 20-59 years, ♀♂, DRR= 1.06; 95%CI 1.04-1.09) respectively. In contrast, women aged 60 and above displayed an average decrease of 2% (♀, DRR= 0.98; 95% CI 0.95-0.99).

TABLE 1 ***Immediate change.*** **The immediate change in AD dispensations in March expressed as Dispensation Rate Ratio (DRR) [Observed / Expected] including 95% confidence intervals in Austria, Latvia, Slovenia, and Sweden.**

Immediate change	**DRR (95%CI)**	**Austria**	**Latvia**	**Slovenia**	**Sweden**
Both sexes	All ages	1.10 (1.05-1.16) *	1.20 (0.82-2.13)	1.06 (1.01-1.11) *	1.10 (1.06-1.13) *
	0-29	1.18 (1.06-1.32) *	1.52 (1.25-1.96) *	1.02 (0.94-1.12)	1.05 (0.98-1.13)
	30-59	1.15 (1.07-1.26) *	1.12 (0.79-1.84)	1.07 (1.01-1.13) *	1.12 (1.07-1.17) *
	60+	1.06 (1.00-1.13) *	1.18 (0.89-2.44)	1.04 (0.98-1.11)	1.07 (1.05-1.11) *
Females (♀)	All Ages	1.09 (1.02-1.17) *	1.18 (0.86-1.95)	1.06 (1.00-1.12) *	1.10 (1.07-1.14) *
	0-29	1.18 (1.06-1.31) *	1.34 (1.11-1.68) *	1.02 (0.95-1.20)	1.05 (0.98-1.13)
	30-59	1.15 (1.07-1.25) *	1.13 (0.77-2.28)	1.03 (0.96-1.11) *	1.13 (1.08-1.18) *
	60+	1.06 (1.00-1.14) *	1.22 (0.82-2.46)	1.08 (1.02-1.13) *	1.06 (1.04-1.10) *
Males (♂)	All ages	1.11 (1.05-1.17) *	1.18 (0.85-1.85)	1.07 (1.01-1.13) *	1.07 (1.03-1.12) *
	0-29	1.09 (1.01-1.17) *	1.51 (1.15-2.19) *	0.92 (0.83-1.03)	1.03 (0.96-1.10)
	30-59	1.09 (1.01-1.21) *	1.09 (0.77-1.84)	1.02 (0.96-1.09)	1.09 (1.04-1.15) *
	60+	1.07 (0.99-1.07)	1.19 (0.84-1.91)	1.02 (0.96-1.10)	1.07 (1.04-1.10) *

** Indicates that the DRR significantly deviates from the expected rate accordingly to age group, sex, and calendar month.*

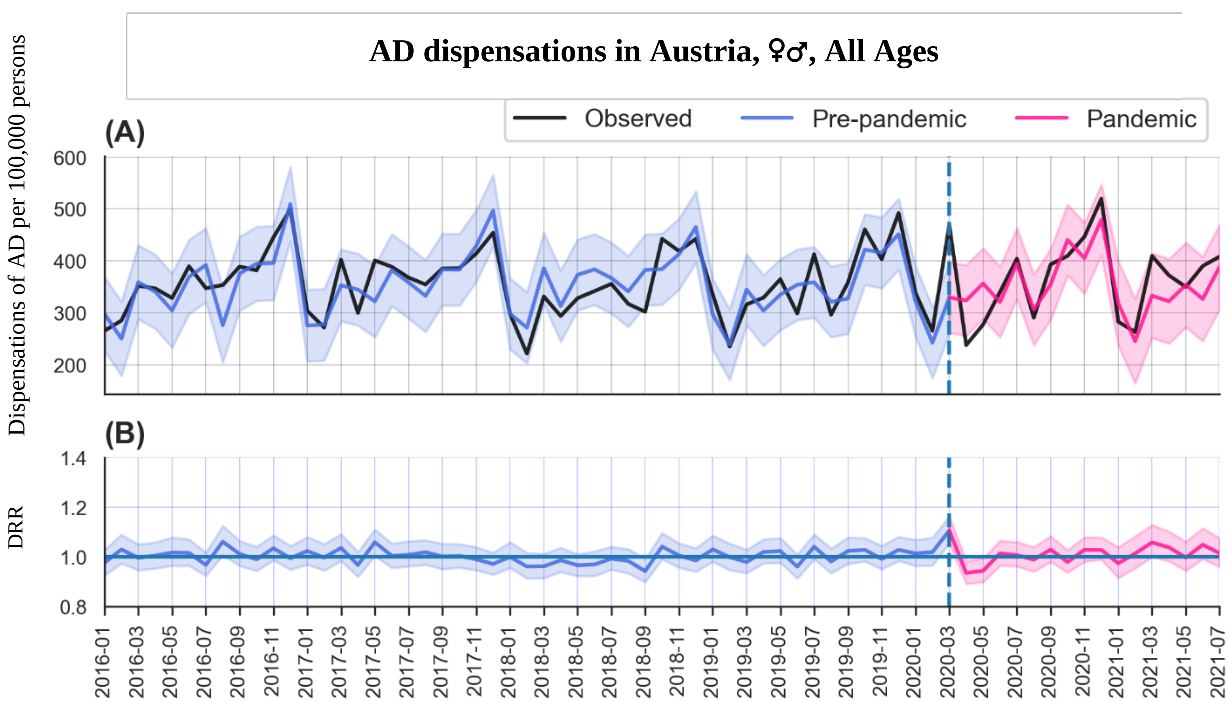

FIGURE 1 AD dispensations, both sexes (♀♂), All Ages. (A) Monthly dispensing rate per 100,000 individuals. (B) Dispensation Rate Ratios[observed/expected].

3.2.2 Latvia

The Latvian population at large (both sexes and all age groups) displayed no statistically significant changes in any selected time points measured. However, further investigations into sex- and age-stratified analysis illuminated pronounced differences in the 0-29 age group at all three measurements (Table 1 | Figure 2).

Immediate change: in March 2020, the 0-29 age group displayed increased dispensations in both sexes, yielding 34% (♀, DRR= 1.34; 95% CI 1.11-1.68) and 51% (♂, DRR= 1.51; 95%CI 1.15-2.19) respectively.

Intermediate change: The increased rates displayed in the 0-29 age group in March 2020 were sustained in April 2020 in both females and males, yielding an increase of 35% (♀♂, DRR = 1.35; 95% CI 1.08-1.77).

Long-term change: The increased levels in the 0-29 age group displayed in the early months of the C19 pandemic sustained more or less throughout 2020. The highest increase was shown in November 2020, yielding an increase of 83% (♀♂, DRR =1.83; 95% CI 1.40-2.65) (Supplementary Table 1 | Appendix A). The average change in DRR from March through December 2020 displayed an increase of 52% in the 0-29 age group (♀♂, DRR=1.52; 95%CI 1.40-1.68) (Table 3).

TABLE 2 *Intermediate change.* AD dispensations in April 2020 expressed as Dispensation Rate Ratio (DRR) [Observed / Expected] and 95% confidence intervals in Austria, Latvia, Slovenia, and Sweden.

Intermediate change | DRR (95%CI)		**Austria**	**Latvia**	**Slovenia**	**Sweden**
Both sexes	All ages	0.94 (0.88-0.98)*	1.018 (0.71-1.86)	1.10 (1.05-1.15)*	0.96 (0.93-1.00)
	0-29	0.95 (0.87-1.05)	1.35 (1.08-1.77)*	0.93 (0.85-1.01)	0.93 (0.86-1.01)
	30-59	0.96 (0.88-1.06)	1.04 (0.70-1.96)	1.04 (0.98-1.11)	0.95 (0.91-0.99)*
	60+	0.92 (0.87-0.98)*	0.96 (0.63-2.13)	1.17 (1.10-1.26)*	0.97 (0.94-1.00)
Females (♀)	All Ages	0.93 (0.87-1.00)	1.02 (0.69-1.87)	1.12 (1.06-1.17)*	0.96 (0.92-0.99)*
	0-29	0.98 (0.80-1.10)	1.12 (0.90-1.48)	0.92 (0.86-1.00)	0.93 (0.87-1.02)
	30-59	0.94 (0.87-1.03)	1.05 (0.66-2.53)	1.04 (0.97-1.12)	0.94 (0.91-0.99)*
	60+	0.92 (0.86-0.99)*	0.94 (0.60-2.19)	1.17 (1.10-1.24)*	0.97 (0.95-1.00)
Males (♂)	All ages	0.93 (0.88-0.98)*	1.05 (0.76-1.73)	1.06 (1.01-1.12)	0.97 (0.93-1.00)
	0-29	0.92 (0.86-0.98)*	1.27 (0.95-1.89)	0.96 (0.85-1.08)	0.93 (0.86-1.00)
	30-59	0.97 (0.88-1.07)	0.98 (0.68-1.76)	1.04 (0.981.11)	0.96 (0.91-1.02)
	60+	0.88 (0.81-0.97)*	1.02 (0.72-1.87)	1.14 (1.06-1.24)*	0.97 (0.94-1.00)

** Indicates that the DRR significantly deviates from the expected rate estimation accordingly to age group, sex, and calendar month.*

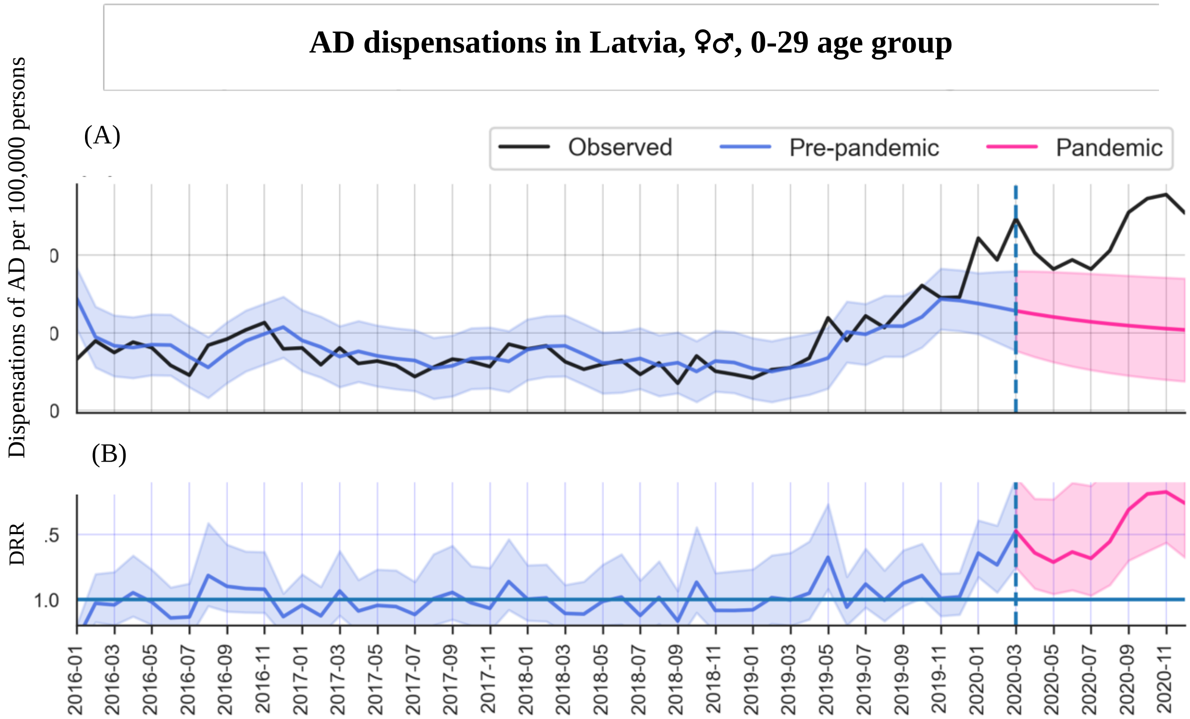

FIGURE 2 AD dispensations, both sexes (♀♂), and 0-29 age group in Latvia (A) Monthly dispensing rate per 100,000 individuals. (B) Dispensation Rate Ratios[observed/expected].

3.2.3 Slovenia.

Immediate change: The Slovenian population displayed a statistically significant increase of 6% (♀♂, DRR= 1.06 95%CI 1.01-1.11) in March 2020 (Table 1 | Figure 3).

Intermediate change: Contrary to Austria and Sweden but similar to Latvia, the dispensation rates in AD in the entire Slovenian population continued to increase to 10% compared to expected rates in April 2020 (♀♂, DRR= 1.10; 95%CI 1.05-1.15) (Table 2). The dispensation rates peaked in May 2020, displaying an increase of 38% in the entire population compared to expected rates in the same month (♀♂, DRR=1.38 95%CI 1.32-1.45) (Supplementary Figure 2 | Appendix). The 60 year and above age group displayed the highest relative increase of 43% (♀♂, DRR = 1.43; 95% CI 1.35-1.53).

Long-term change: The increased rates displayed in March, April, and May 2020 were not sustained in either sex or age group throughout 2020 and dropped rapidly to close-to-expected rates. The Slovenian population at large (all ages and sexes) (Table 3 | Figure 3) displayed an average increase of 5% from March through December 2020 (♀♂, DRR= 1.05; 95%CI 1.03-1.06).

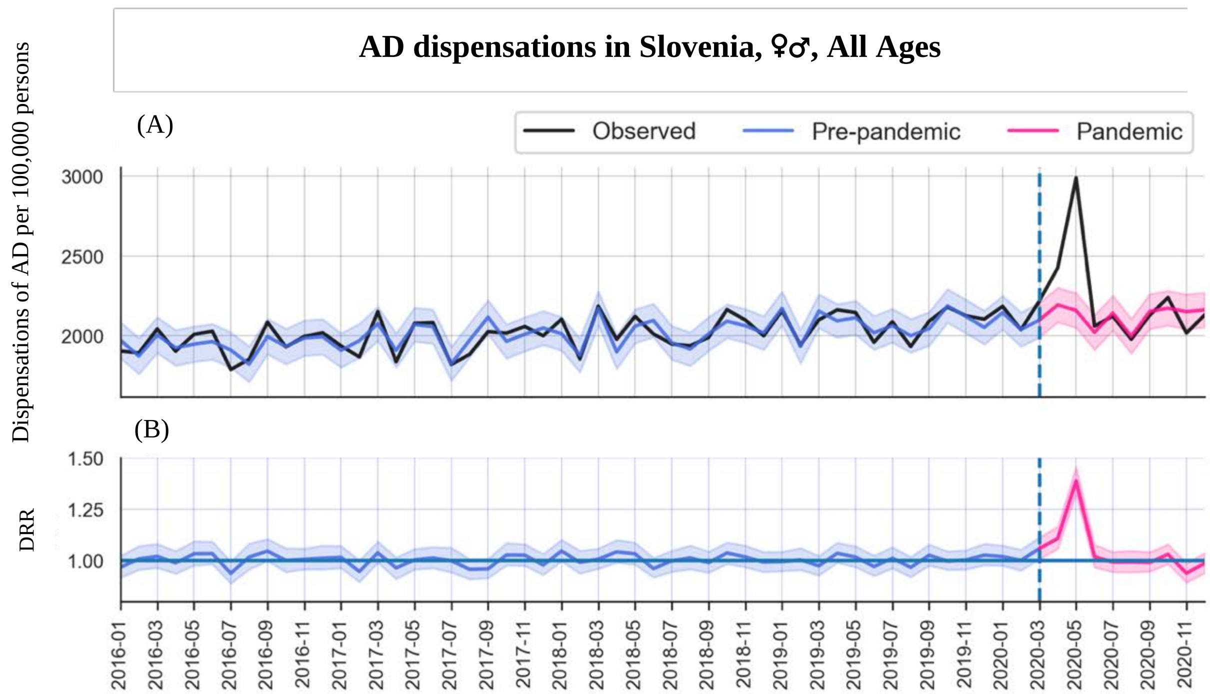

FIGURE 3 AD dispensations, both sexes (♀♂), all ages in Slovenia. (A) Monthly dispensing rate per 100,000 individuals. (B) Dispensation Rate Ratios[observed/expected].

2.3.4 Sweden.

Immediate change: An immediate increase of 10% (♀♂, DRR=1.10; 95%CI 1.06-1.13) in AD dispensation was displayed in March 2020 in Sweden's general population. The highest increase was displayed in the 30-59 age group (♀♂, DRR = 1.07; 95%CI 1.01-1.13), in which women displayed a more significant burden than males.

Intermediate change: All age groups and sexes displayed decreasing rates in the first month (April 2020) following the onset of the C19 pandemic (Table 2). Similar to the benchmark in March 2020, the 30-59 age group displayed the most significant change of -5% (♀♂, DRR = 0.95, 95%CI 0.91-0.99).

Long-term change*:* Neither the increasing nor decreasing rates displayed in March and April were sustained throughout 2020. By the end of 2020, rates had returned to close-to-expected levels in the general population.

TABLE 3 ***Long-term change*****. The average change in AD dispensation rates during the C19 pandemic (March 2020 – through December 2020) expressed as Dispensation Rate Ratios (DRR) and 95% confidence intervals in Austria, Latvia, Slovenia, and Sweden.**

Long-term change	**DRR (95%CI)**	**Austria**	**Latvia**	**Slovenia**	**Sweden**
Both sexes	All ages	1.00 (0.99-1.02)	1.04 (0.88-1.26)	1.05 (1.03-1.06)*	0.99 (0.98-1.01)
	0-29	1.11 (1.08-1.15)*	1.52 (1.40-1.68)*	1.02 (0.99-1.04)	1.00 (0.97-1.03)
	30-59	1.06 (1.04-1.09)*	0.97 (0.80-1.20	1.03 (0.98-1.08)	1.00 (0.98-1.01)
	60+	0.98 (0.96-1.00)	1.03 (0.84-1.35)	1.06 (1.03-1.08)*	0.98 (0.97-0.99)*
Females (♀)	All Ages	1.00 (0.98-1.02)	1.04 (0.88-1.27)	1.05 (1.04-1.07)*	0.99 (0.98-1.00)
	0-29	1.11 (1.08-1.16)*	1.33 (1.22-1.47)*	1.03 (1.00-1.06)*	0.99 (0.97-1.02)
	30-59	1.07 (1.04-1.10)*	1.01 (0.81-1.35)	1.02 (0.99-1.05)	1.00 (0.98-1.02)
	60+	0.98 (0.95-0.99)*	1.02 (0.82-1.33)	1.06 (1.04-1.08)*	0.98 (0.97-0.99)*
Males (♂)	All ages	1.01 (0.99-1.03)	1.01 (0.86-1.21)	1.03 (1.01-1.05)*	0.99 (0.98-1.007)
	0-29	1.02 (0.99-1.04)	1.34 (1.17-1.53)*	0.98 (0.93-1.03)	0.97 (0.94-0.99)*
	30-59	1.04 (1.01-1.07)*	0.91 (0.76-1.10)	1.03 (1.01-1.05)*	1.00 (0.98-1.02)
	60+	0.96 (0.93-1.00)	1.02 (0.85-1.27)	1.03 (1.01-1.06)*	0.98 (0.97-0.99)*

** Indicates that the DRR significantly deviates from the expected rate accordingly to age group, sex, and calendar month.*

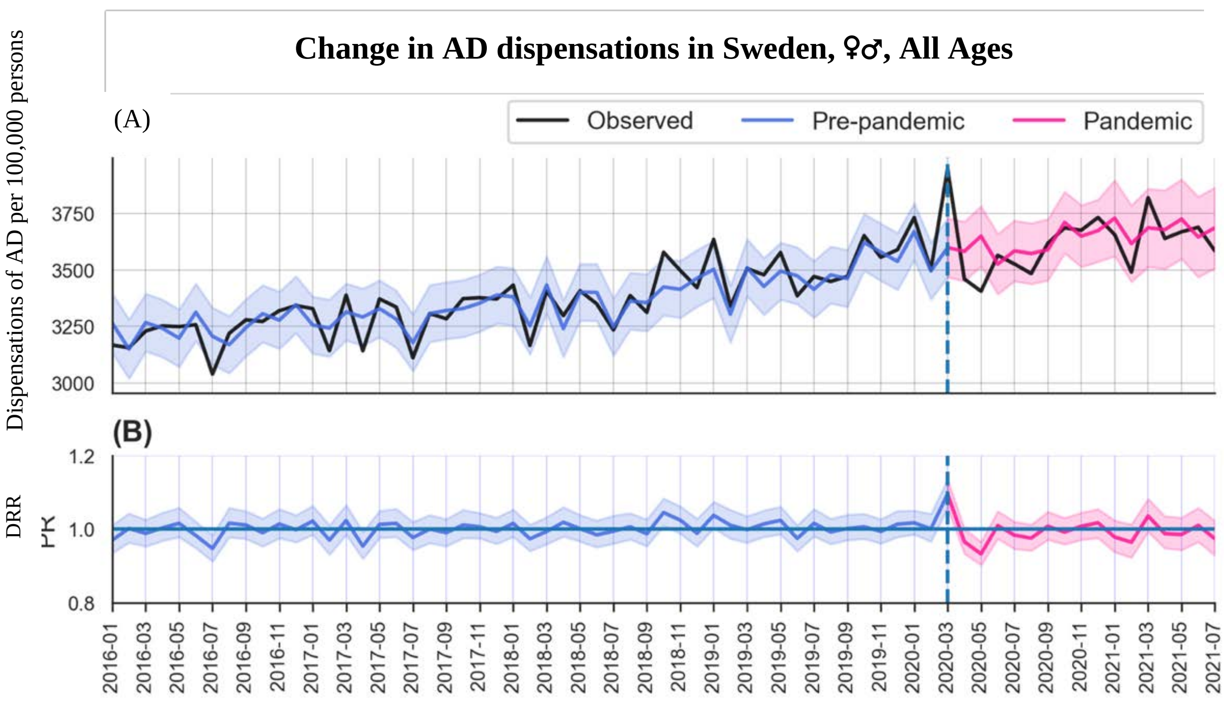

FIGURE 2 AD dispensations, both sexes (♀♂), All Ages in Sweden. (A) Monthly dispensing rate per 100,000 individuals. (B) Dispensation Rate Ratios[observed/expected].

3.3 Impact of country-specific Containment Measures.

The relationships between the investigated containment indices and change in AD dispensation rates were generally weak (Table 4). SR in Austria were associated with slight decreases in AD dispensation (β= 6.5 x 10^{-5}, *P*=0.04). No statistically significant associations between SR and change in AD dispensation were found in the younger "school-age" group (0-29 years) in any of the countries included. In similarity with SR, SD was negatively associated with changes in AD dispensations (β= -0.0003, *P*= 0.00). This corresponds to a reduction of 30 individuals dispensing AD for each unit increase in SR in Sweden. No other countries displayed statistically significant associations between SD and changes in AD dispensations.

TABLE 4 Associations between containment measures and change in AD dispensation by country, indice and age group.

Country	Indice	All ages, βeta	P-value	0-29 years, βeta	*P-value*	30-59 years, βeta	*P-value*	60+ years, βeta	*P-value*
Austria	**SD**	-2.1 x 10^{-6}	0.57	-2.2 x 10^{-6}	0.10	-1.6 x 10^{-6}	0.62	-1.1 x 10^{-5}	0.28
	SR	-6.5 x 10^{-5}	0.04*	-4.6 x 10^{-6}	0.30	-6.9 x 10^{-5}	0.00*	-0.0001	0.00*
Latvia	**SD**	8.25 x 10^{-7}	0.94	5.7 x 10^{-7}	0.56	6.9 x 10^{-7}	0.96	1.79 x 10^{-6}	0.88
	SR	-1.8 x 10^{-6}	0.68	1.69 x 10^{-6}	0.38	-4.3 x 10^{-7}	0.49	8.36 x 10^{-7}	0.90
Slovenia	**SD**	-4.4 x 10^{-5}	0.84	-9 x 10^{-6}	0.62	-7.8 x 10^{-5}	0.72	-5.9 x 10^{-5}	0.90
	SR	-2.8 x 10-5	0.93	-8.5 x 10-6	0.31	-6.5 x 10^{-6}	0.98	-7.5 x 10^{-5}	0.88
Sweden	**SD**	-0.0003	0.00*	-0.0001	0.02*	-0.0004	0.98	-0.0005	0.00*
	SR	6.01 x 10-5	0.81	9.21 x 10-6	0.80	0.0001	0.55	-5.1 x 10^{-5}	0.84

SD = Social Distancing, SR= School Restrictions

* Indicates statistically significant results at p <0.05, uncorrected

4 Discussion

4.1 Summary of main findings

4.1.1 Changes in AD dispensation rates

In this cross-country analysis of change in AD dispensations during the C19 pandemic, several country-specific differences were found, as well as the appearance of certain patterns in the larger European sample. Women generally displayed higher increases in most countries and across age groups compared to their male counterparts. Within the first month of the C19 pandemic, all countries displayed increased rates in AD dispensation. However, in April 2020, Latvia and Slovenia continued to display increased rates, whereas Austria and Sweden decreased to lower-than-expected levels. Overall, the increases were highest in Latvia, in which the increased levels displayed at the start of the C19 pandemic were sustained throughout 2020 within the 0-29 age group.

In contrast, a significant pattern was observed in Austria, Slovenia, and Sweden, where all three countries largely displayed isolated peaks in the early stages of the C19 pandemic, followed by a drop to either close-to or lower-than-expected AD rates that more or less stagnated until the end of 2020.

4.1.2 The relationship between the changes in dispensation rates and containment measures

Despite the substantial increases in AD dispensation rates in the lower age groups in particular Austria and Latvia, no significant association was found between the implementation of SR and the change in AD dispensation rate in this age group in any of the countries included in this study. Contrary to existing literature which has suggested a positive link between containment measures and increased mental health (48,57), a slight negative association between SD change in AD was identified. This suggests that the implementation of containment measures was association with a slight reduction in AD dispensations, and that the overall effect of the C19 pandemic on AD dispensation was not substantially impacted by specific containment measures.

4.2 Interpretation of main findings

The early isolated peaks that were followed by a rapid drop in AD dispensation may be attributable to stockpiling behaviour by individuals who held valid prescriptions before the onset of the C19 pandemic but had yet to receive the psychical dispensation at a pharmacy. Indicators of AD stockpiling in the early months of the C19 pandemic have also been found in other registry-based studies analysing change in psychotropic rates during the C19 pandemic (31,34). It is essential to highlight that the outcome variable utilised in this study does not separate incident cases from all unique individuals dispensing AD per month. This limits what conclusions that can be drawn. However, to aid the interpretation of these indications and attempt to illuminated C19 pandemic -induced change in AD dispensations, a *post-hoc* sensitivity was conducted which excluded the isolated spike months (Supplementary Table 3 | Appendix).

After excluding the assumed stockpiling months from the long-term DRR, Austria and Slovenia, which had previously displayed significant long-term increases (Table 3), generally dropped to close-to-expected and lower-than-expected rates, indicating no change and decreasing rates in AD dispensation in the intra-pandemic period. By comparison, in Latvia, where there were few indications of stockpiling, only minor changes were displayed when March 2020 was excluded from the average DRR. These patterns are consistent with the findings on other healthcare utilisation studies during the C19 pandemic. In general, healthcare utilisation studies provide valuable support to dispensation rate studies, as the ability to obtain an AD prescription depends on the individual`s health-seeking behaviour as well as access to a trained physician. Similarly to the findings of this study, Flodin et al. (11) found decreasing healthcare utilisation rates for all European countries except Latvia during the C19 pandemic. Likewise, an Austrian study on the change in healthcare utilisation of psychotherapy during the C19 pandemic identified that the use of therapy remained on par with pre-pandemic rates (58).

Although the actual AD dispensation rates generally did not differ from the expected rates in Austria, studies using other mental health indicators, such as suicide rates, alcohol consumption, and Intimate Partner Violence (IPV), suggest a different trend (59–61). For example, Pirkis et al. (62) found an increase in suicide in the Austrian population of 10% during the C19 pandemic.

Similarly, another study found an increase of 23% in weekly alcohol consumption during the C19 pandemic among adults in Austria(61). Globally as well as in Austria, reports of IPV suggest increases during the C19 pandemic(60). Similar findings were also displayed in Slovenia(63,64). For example, one study of emergency psychiatric services in Slovenia reported increased rates of attempted suicide among children and adolescents during the C19 pandemic(65). On the flip side, there are few indications of increased alcohol consumption in the Slovene population. Likewise, in Skåne County in Sweden, no significant changes were found in the numbers seeking treatment at addiction facilities (66). Overall, the results obtained from the above studies may suggest that the change observed in AD dispensation in this study may not accurately reflect the true change to the overall levels of depression experienced during the C19 pandemic.

In the Latvian case, the DRR in AD change displayed in this study may be influenced by the recent change in access to mental health care. Until recently, Latvian mental health services were primarily limited to providing in-patient care, leading to a likely underestimation of the prevalence of depression and other CMDs within the population at large(67,68). Consequently, new funds from the EU in 2019 were allocated to improve Latvia's outpatient mental health care by strengthening the current facilities and opening new psychiatric clinics(67). This recent change in access to health care may have influenced the intra-pandemic DRR findings if individuals that had been suffering for a long period of time finally received delayed treatment during the C19 pandemic. Assuming this is accurate, caution should be exercised when interpreting the magnitude of the increases in Latvia during the C19 pandemic.

4.2.1 Interpretation of findings on containment measures

The discrepancy between this study`s findings on containment measures and existing literature on the burden of containment measures on mental health (48,57,69) raise the question if strict containment measures during the C19 pandemic reduced the access to health care services. Studies on the change in using healthcare helplines phones are usually free for the entire population, and may serve as an alternative indicator of mental health because they do not rely on access to health care services. A Swiss study on the change in helpline call volumes found that the number of such calls increased during the C19 pandemic and were associated with periods of more intense containment measures (69). The indication that the Swiss population sought alternative healthcare services during the most restrictive periods may support the proposition that this study`s findings may be influenced by reduced access of mental health care during the most stringent periods. However, it may also be possible that the hindrance for seeking help was higher during the most stringent periods. For example, individuals may have not perceived the significance of their mental health issues when comparing themselves to the severity of the fatalities in the ongoing C19 pandemic. This could be a scenario for some of the health care workers during the C19 pandemic in a Canadian study, finding that seeking formal support for mental health issues were low (70)

On the other side, other studies report resilience during stringent periods and adaptability to the new normal in the population(71). This gives rise to alternative explanations. Populations at large may have adopted to the new normal. Furthermore, the temporal nature of the C19 pandemic and its associated restrictions may have had a less invasive effect on mental health than initially expected. It may also be possible that the increased awareness during the C19 pandemic about mental health counteracted the risk factors associated with the implementation of containment measures. For example, Tomaz et al. (21) identified that Scottish elderly people utilised social media and videocalls as surrogates for physical interactions. Others reported that the slower pace of life had given them an opportunity to reconnect with old friends and neighbours. Hence, paradoxically, social restrictions may have actually united communities(21). Furthermore, the notion that `we are all in the same boat´ may have been comforting and therapeutic for some groups.

4.2 Generalisability and future directions

This study uses national register data on AD dispensations, enabling reliable statistical data about the change in AD dispensation recording during the C19 pandemic. However, careful considerations should be made regarding generalising results on individual- and subgroup level (56, 72). No other subgroup analysis was conducted other than by age group and sex.

Against this backdrop, future research should study the change in the impact of the C19 pandemic on AD dispensation rates across socioeconomic groups. The differential burden of major depressive disorder among individuals with lower socioeconomic positions was well-established before the C19 pandemic (73). Further concerns about the inequitable exposure distribution to the C19 pandemic and the risk factors associated with developing common mental disorders have been raised (74). Illuminating how the impact of mental health burdens during the C19 pandemic differs across socioeconomic groups is important to prevent aggravating mental health burdens and to design equitable mitigation interventions in future epidemics and pandemics (75).

4.3 Strengths and limitations

Strengths. The main strength of this study is its utilisation of population-wide registries on AD dispensation collected both before and during the C19 pandemic. To my knowledge, this is the most extensive cross-country study on the change in AD dispensations during the C19 pandemic. The C19 pandemic poses new methodological challenges in controlling for other effects of the C19 pandemic that may impact the estimate of change in AD dispensations. Hence, the influential impact of the C19 pandemic across multiple domains leaves few, if any, plausible control series or unaffected populations available for comparison. However, by comparing estimates of countries with similar economic, cultural and health system characteristics, we may more robustly attribute changes in desired outcomes to the C19 pandemic (3, 76). With its similarities in universal health coverage and availability of population-wide AD dispensation registries, Europe can be considered a suitable sample for comparison. Another strength of this thesis is the relatively long pre-pandemic time series, allowing for better predictions the counterfactual scenario (38).

Limitations. There are a number of limitations to this study. Firstly, the quality of drug registers may vary from one country to another and also between months and years. This may ultimately impact the prediction of the forecast models of the forecasting model and the validity of the results and comparison. Despite requests asking for age group intervals of 5 years, the research group received mixed age group intervals from the different data providers. In the analysis of the association between SR and change in AD dispensation in “school age” (0-29 years), it may have been more optimal to exclude individuals over high-school age.

Secondly, no other forecasting models were trained in this study and it is not possible to exclude that other forecasting models may have provided a more optimal fit. This is in particular relevant in the Latvian case, where the ARIMA prediction seems to follow a more irregular pattern compared to for example Sweden. The Latvian sample is the smallest of all the included countries. Due to the lower power in the Latvian sample, it is likely that this ARIMA prediction would have benefited from longer pre-pandemic time series to predict a better counterfactual scenario.

Thirdly, the use of a proxy indicator, such as AD dispensations, to study general change in mental health is inevitably subject to limitations. Although AD drugs are primarily designed to treat individuals with depression, they also treat many other conditions, such as chronic pain, insomnia and migraine (77). In this study, I was unable to exclude the use of AD dispensations for other conditions than depression. Since the comparison group in this study is the same population, this limitation does not *per se* introduce bias. However, bias may be introduced if the C19 pandemic influences changes in the utilisation of AD drugs for conditions beyond depression. In this study, it was not possible to adjust the results to reflect potential confounders and mediators such as socioeconomic status, prior depression diagnosis, inpatient COVID-infection and long-COVID diagnosis (25, 78) Lastly, it was not possible to obtain access to Daily Defined Dose (DDD) or incident cases of AD dispensations. These variables may indicate a change in severity among AD users during the C19 pandemic and pandemic-induced change in new AD users.

5 Conclusion

In conclusion, the decreasing and near-normal rates in antidepressant dispensations identified in Austria, Slovenia and Sweden during the C19 pandemic do not support the commonly held belief of deteriorated population mental health during the C19 pandemic. The impact of containment measures on the change in AD dispensations did not substantially differ from other stressors on mental health during the C19 pandemic unrelated to containment measures. With regards to the public health implications of these study findings, this study calls into question whether the change in AD dispensations mirrors the actual change in depression during the C19 pandemic. Due to the acknowledged limitations of this study, this question still needs to be answered fully. However, comparing findings from different study designs and indicators of mental health is valuable to incite speculation about the influence of access to mental health care services and behavioural reluctance to seek mental healthcare during the C19 pandemic. Alternatively, it may be possible that the general population gained resilience to developing depression and that the mitigation interventions during the C19 pandemic counteracted the expected impacts.

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Appendices

Supplementary Tables

SUPPLEMENTARY TABLE 1 – Change in antidepressant dispensations in Latvia in November 2020. Measured as Dispensation Rate Ratio (DRR) and 95% confidence intervals.

DRR (95%CI)		Latvia
Both sexes	All ages	1.05 (0.61-2.88)
	0-29	1.83 (1.40- 2.65) *
	30-59	0.96 (0.57-2.98)
	60+	0.98 (0.48-4.56)
Females[♀]	All ages	1.04 (0.86-1.29)
	0-29	1.33 (1.21-1.47) *
	30-59	1.03 (0.47 – 4.34)
	60+	0.97 (0.49-4.19)
Males [♂]	All ages	0.96 (0.60-2.71)
	0-29	1.34 (0.93- 2.57)
	30-59	0.86 (0.50-2.04)
	60+	0.99 (0.59 – 2.78)

** Indicates that the DRR significantly deviates from the expected rate accordingly to age group, sex, and calendar month.*

SUPPLEMENTARY TABLE 2 – Change in antidepressant dispensations in Slovenia in May 2020. Measured as Dispensation Rate Ratio (DRR)and 95% confidence intervals.

DRR (95%CI)		Slovenia
Both sexes	All ages	1.38 (1.32-1.45) *
	0-29	1.18 (1.09-1.28) *
	30-59	1.31 (1.24-1.39) *
	60+	1.43 (1.35 -1.53) *
Females[♀]	All ages	1.39 (1.32-1.46) *
	0-29	1.18 (1.09-1.28)
	30-59	1.33 (1.24-1.44) *
	60+	1.44 (1.36-1.53) *
Males [♂]	All ages	1.36 (1.29-1.44) *
	0-29	1.17 (1.04 – 1.35) *
	30-59	1.27 (1.20-1.35) *
	60+	1.42 (1.32 -1.53) *

** Indicates that the DRR significantly deviates from the expected rate accordingly to age group, sex, and calendar month.*

SUPPLEMENTARY TABLE 3 – <u>Sensitivity analysis (Stockpiling tendency scenario)</u> The average change in AD dispensation rates during the Pandemix(April 2020 – through December 2020) measured as Dispensation Rate Ratio (DRR) including 95% confidence intervals in Austria, Latvia, Slovenia, and Sweden.

Long-term change | DDR (95%CI)		**Austria (Excluding March)**	**Latvia (Excluding March)**	**Slovenia (Excluding March, April, May)**	**Sweden (Excluding March)**
Both sexes	All ages	0.99 (0.98-1.01)	1.02 (0.85-1.30)	0.99 (0.97-1.01)	0.98 (0.97-1.00)
	0-29	1.01 (0.98-1.03)	1.31 (1.14-1.53) *	0.96 (0.90-1.02)	0.98 (0.94-1.01)
	30-59	0.98 (0.95-1.01)	0.95 (0.78-1.22)	0.99 (0.96-1.01)	0.98 (0.97-1.00)
	60+	0.97 (0.95-0.99) *	0.99 (0.80-1.33)	0.98 (0.96-1.02)	0.97 (0.96-0.98) *
Females[♀]	All ages	0.99 (0.97-1.01)	1.02 (0.85-1.29)	0.99 (0.97-1.02)	0.98 (0.97-0.99) *
	0-29	1.11 (1.07- 1.15)*	1.33 (1.20-1.48) *	1.02 (0.99-1.05)	0.99 (0.95-1.02)
	30-59	0.97 (0.94-1.10)	1.00 (0.79 -1.39)	0.97 (0.94-1.02)	0.98 (0.97-1.00)
	60+	0.96 (0.95-0.98) *	0.99 (0.78-1.31)	0.99 (0.97-1.02)	0.97 (0.96-0.99) *
Males [♂]	All ages	1.00 (0.99-1.03)	0.99 (0.83-1.20)	0.97 (0.95-1.00)	0.98 (0.97-0.99) *
	0-29	1.01 (0.98-1.03)	1.32 (1.15-1.52) *	0.96 (0.90-1.02)	0.96 (0.94-0.99) *
	30-59	0.98 (0.95-1.00)	0.89 (0.74-1.10)	0.99 (0.96-1.01)	0.99 (0.97-1.01)
	60+	0.95 (0.92-0.99) *	1.00 (0.84-1.24)	0.96 (0.94-0.99) *	0.98 (0.96 –0.99)*

** Indicates that the DRR significantly deviates from the expected rate accordingly to age group, sex, and calendar*