epidemiology biostatistics and public health formerly ITALIAN JOURNAL OF PUBLIC HEALTH

EBPH – 2024, Volume 19, Issue 2

https://riviste.unimi.it/index.php/ebph/index

Volume 19
Issue 2
December 2024

Milano University Press

epidemiology biostatistics and public health formerly ITALIAN JOURNAL OF PUBLIC HEALTH

PUBLISHER

Milano University Press
Via Festa del Perdono 7
20122 Milano, Italy
riviste@unimi.it

CONTACT

ebph@unimi.it

Milano University Press

epidemiology biostatistics and public health formerly ITALIAN JOURNAL OF PUBLIC HEALTH
Volume 19, Issue 2 | December 2024

CONTENTS

ORIGINAL ARTICLES

SYSTEMATIC REVIEWS AND META- AND POOLED ANALYSES

STATISTICAL METHODS

BOOK REVIEWS

Milano University Press

ISSN 2282-0930 • Epidemiology Biostatistics and Public Health - 2024, Volume 19, Issue 2

Small Area Estimation using Multilevel Regression and Poststratification to Estimate Cannabis Use in the State of Montana

Chase Walker[(1)], *Kristal Jones*[(1)], *Brandn Green*[(1)], *Frances L. Kim*[(1)]

(1) JG Research and Evaluation; Bozeman, Montana, United States.

CORRESPONDING AUTHOR: Chase Walker, JG Research and Evaluation, Bozeman, Montana, United States.
E-mail: chase@jgresearch.org. Tel: +1.406.360.5044

SUMMARY

Background: Small area substance use prevalence estimates at the county, city, or congressional district level are generally unavailable. In this study, we design a cannabis use survey for the state of Montana and use multilevel regression and poststratification (MRP) to generate county-level population prevalence estimates for past year cannabis use.
Methods: We developed a survey that asks questions about cannabis perceptions and use patterns. We analyzed the survey data specifically for the outcome variable of past year cannabis use using MRP to generate population level prevalence estimates at the county level for the state of Montana.
Results: We received 1,958 responses from our survey. We generated county level estimates by age group for cannabis use over the past year and found that MRP estimates were consistent with prior estimations of cannabis use at the state level and provided the ability to use additional data and validated assumptions to refine and downscale estimations of cannabis use, particularly in counties with low response rates.
Conclusion: Multi-modal survey dissemination was cost effective, but future surveys should intend to recruit a larger and more representative sample to minimize selection bias and improve estimation for demographic sub-groups. Overall, MRP provided a promising methodology for generating small-area cannabis use prevalence estimates, adjusting as much as possible for non-representativeness and non-response.

Keywords: MRP; multilevel regression; poststratification; surveillance; estimates; social media; substance use; cannabis; public health.

INTRODUCTION

Changes in the legal status of cannabis in the United States have created unknowns for public health practitioners seeking to understand trends in use patterns and the possible need for expanded educational or prevention interventions. National and state-level public health surveillance methods (National Survey on Drug Use and Health (NSDUH), Youth Risk Behavior Survey (YRBS)) have a necessary time lag between data collection and reporting, and they often do not estimate substance use at local levels due to small sample sizes, which can create a gap in understanding for local policymakers and agencies. To address these limitations, a broad set of efforts have been underway to use innovative survey recruitment methods for rapid surveillance in combination with new statistical methods for small-area estimation and analysis of non-representative surveys [1-4].

This study applies Bayesian multilevel regression and poststratification (MRP) to generate small area estimates for past year cannabis use from a non-randomized survey distributed through social media in Montana. The application of MRP within the context of drug use surveillance is distinctive. Gelman and Little [5], along with other political scientists [6; 7; 8; 9; 10; 11], have established the use of MRP with data from US pre-election polls to estimate election outcomes for a variety of subnational demographic-geographic groups. Consistently these studies find that MRP adjustments yield estimates consistent to other leading election poll analyses, thus demonstrating that non-representative polling can be used for measuring

DOI: 10.54103/2282-0930/26905
Accepted: 24th October 2024

public opinion. A similar application of MRP generate "dynamic" estimates of changing public opinion over time through its analysis of same sex marriage [12]. Most of these applications focus on state-level estimates from national surveys. However, there are examples of using MRP to generate smaller area estimates of political characteristics [13].

The majority of the use of MRP is centered on political science and forecasting election outcomes. However, other studies have demonstrated that MRP can be used more broadly across disciplines, including public health and epidemiology. Zhang et al [14] used MRP to generate small area estimates for chronic obstructive pulmonary disease; Eke et al [15] used it to predict periodontitis at state and local levels; Christofoletti et al [16] used it to estimate population-level leisure time compared to physical activity levels from large-scale health surveys in Brazil; and Downes et al [17] applied MRP to a large national health study to address analytical biases related to non-participation. Most recently, MRP was used to generate estimates of the proportion of people who identify as transgender for youth and adults in the United States [18]. The broad application to data across disciplines, particularly in public health studies examining socially critiqued health behaviors, suggests that MRP is a potentially useful methodology for generating prevalence estimates of substance use.

Surveillance surveys for producing prevalence estimates of marijuana use are primarily conducted at national and state levels. These surveys (e.g., NSDUH) are often conducted face-to-face or via the telephone, and the time intensity often leads to a number of individual responses that are too small to provide sufficient samples to generate small area estimates, especially in largely rural states like Montana with low population density. Web surveys, by contrast, are less expensive and resource intensive but can lead to lower response rates and other issues [19]. These barriers result in a general lack of reliable and accurate information about substance use patterns within many counties. It is also important to consider how willing survey respondents are to report on personal, private, or sensitive matters, as a substantial amount of prior research has found the mode of survey administration can impact the data quality for this type of information [20-25]. Several comparative studies suggest that having a web-based survey for asking respondents about topics like cannabis use, which is potentially sensitive given the ambiguous legal status within the United States, may improve reporting accuracy as compared to in-person or phone-based surveys [25, 26].

This research was originally completed for the state of Montana, which legalized marijuana for recreational use with the passage of ballot initiative 190 (I-190) in the 2020 Montana general election. Public health concerns about legalizing cannabis have included a focus on how use patterns for both adults and youth will change with increased access. County-specific information is especially important in the case of cannabis licensing within Montana, where the state implemented a licensing approach that allowed each county to determine whether or not they would allow for retail sales based on whether the percentage of yes votes on I-190 was greater than 50% or not. With between-county variation (28 of the 56 Montana counties voted in favor of I-190), it became essential to understand how use patterns within counties may be impacted by the new policy environment.

METHODS

MRP provides opportunities for generating small area prevalence estimates from survey data that can address sample bias from online survey sampling without some of the limitations associated with traditional weighting approaches. We developed and administered a cannabis use survey with multi-modal survey distribution and the use of MRP for generating population level small area prevalence estimates to address non-response and selection bias, and non-representativeness within survey samples.

Survey Design and Dissemination

The survey was designed using previously validated survey questions from YRBS, Behavioral Health Risk Factor Surveillance System (BRFSS), and the Canadian Cannabis Survey [27-29]. Survey items included questions on demographics (e.g. age, gender, race, county of residence, education, etc.), cannabis use characteristics for those who used cannabis, and knowledge and perceptions of cannabis and retail use in Montana. A total of 57 questions were asked, with 34 questions only being applicable for those who ever tried cannabis.

The survey was advertised on social media using ads targeted as specific geographies and age groups, providing a cost-effective approach to survey dissemination [30-34], as well as through posters and postcards in public health and social services offices. All modes of recruitment led to a web-based survey on the Alchemer platform. Survey consent questions were asked to ensure participants were at least 15 years old and if they were Montana residents. An IRB was submitted to Western IRB for this project under study number 1319497, however Western IRB found the project to be exempt because it was not collecting personal or identifiable information from subjects.

Multilevel regression

As this research is primarily focused on the potential of MRP methodology for producing SME for substance use behaviors, we present methods and results focused on one outcome, which is past year cannabis use.

We began by developing a multilevel regression model to predict the outcome measure, based on the demographic information from survey respondents, as well as county level predictors. We applied a multilevel logistic regression model to obtain estimates from the individual level survey responses, which allowed for poststratification, or weighting, using these estimates in the second stage of MRP. We started with the model below, generally following the notation of Lopez-Martin et al. [35] and Gelman and Hill [36]:

$$Y_i \sim Bernoulli(\pi_i) \qquad \pi_i = \Pr(past\_year\_use_i = 1)$$

$$logit(\pi_i) = \alpha^{age}_{a[i]} + \beta^{female}Female_i + \beta^{tried}Tried_i + \alpha^{female:age}_{g[i],a[i]} + \alpha^{county}_{c[i]}$$

Where:

$$\alpha^{county}_{c(i)} \sim normal(\mu^{county}_c, \sigma^{county}) \quad \text{for c = 1,…,56}$$

And where:

$$\alpha^{county}_{c(i)} = \delta^0 + \delta^{NW}NW_c + \delta^{W}W_c + \delta^{SW}SW_c + \delta^{SC}SC_c + \delta^{NC}NC_c + \delta^{E}E_c + \delta^{I190}I190_c$$

The model is reparametrized for analysis as:

$$logit(\pi_i) = \mu^0 + \mu^{county}_{c[i]} + \alpha^{age}_{a[i]} + \beta^{female}Female_i + \beta^{tried}Tried_i + \alpha^{female:age}_{g[i],a[i]} + \delta^{NW}NW_{c(i)} + \delta^{W}W_{c(i)} + \delta^{SW}SW_{c(i)} + \delta^{SC}SC_{c(i)} + \delta^{NC}NC_{c(i)} + \delta^{E}E_{c(i)} + \delta^{I190}I190_{c(i)}$$

Where:

$$\alpha^{age}_{a(i,c)} \sim normal(0, \sigma^{age}) \text{ for a = 1,…,4}$$

$$\alpha^{gen.age}_{a(i,c),g(i,c)} \sim normal(0, \sigma^{gen.age}) \text{ for g = 1,2 and a = 1,…,4}$$

$$Female_i = \begin{cases} 1 \text{ if individual i is female} \\ 0 \text{ if individual i is male} \end{cases}$$

$$Tried_i = \begin{cases} 1 \text{ if individual i has tried cannabis at least once in their life} \\ 0 \text{ if individual i has never tried cannabis before} \end{cases}$$

$$NW_{c(i)} = \begin{cases} 1 \text{ if individual i and county c is in the NW region} \\ 0 \text{ otherwise} \end{cases}$$

$$W_{c(i)} = \begin{cases} 1 \text{ if individual i and county c is in the W region} \\ 0 \text{ otherwise} \end{cases}$$

$$SW_{c(i)} = \begin{cases} 1 \text{ if individual i and county c is in the SW region} \\ 0 \text{ otherwise} \end{cases}$$

$$SC_{c(i)} = \begin{cases} 1 \text{ if individual i and county c is in the SC region} \\ 0 \text{ otherwise} \end{cases}$$

$$NC_{c(i)} = \begin{cases} 1 \text{ if individual i and county c is in the NC region} \\ 0 \text{ otherwise} \end{cases}$$

$$E_{c(i)} = \begin{cases} 1 \text{ if individual i and county c is in the E region} \\ 0 \text{ otherwise} \end{cases}$$

$$I190_{c(i)} = \begin{cases} 1 \text{ I190 vote was yes in county c where individual i lives} \\ 0 \text{ I190 vote was no in county c where individual i lives} \end{cases}$$

$$Model\ Priors = normal(0,1)$$

The intercept term represents the individual-level intercept now instead of the county-level intercept, and the term $\mu^{county}_{c(i)}$ represents the county-level adjustments after accounting for differences in regions and I190 votes. The model includes varying intercepts for age, and the interaction term of gender x age can be defined as the adjustments of individual *i's* age or gender x age on the probability of having used cannabis in the past year. $Female_i$ is an indicator variable that takes on a value of 1 if the individual is female and a value of 0 if the individual is male. $Tried_i$ is an indicator variable for if the respondent has tried marijuana at least once in their life, and it takes on a value of 1 if they have and a value of 0 if they have not.

The regional variables are indicator variables, accounting for unexplained variation among regions of the state that may be unaccounted for elsewhere. The county-level predictors represent group variables that account for structural differences among counties, so as to reduce unexplained county level variation. I-190 vote is a variable that represents if a county had a majority vote yes on ballot initiative 190. Including information on I-190 vote accounts for additional county-level variation that can be attributed to general perceptions of marijuana that are not captured by the demographic variables or broad regions.

Although it is more common to use indicator variables or fixed effects for demographic information such as age, representing this information as varying intercepts allows information to essentially be shared or to co-vary between levels of each of these variables, therefore preventing groups with less data from being overly sensitive to having fewer observed values, which is frequently an occurrence in some of our survey groups from lower population areas of the state [35].

We perform a Bayesian analysis using the stan_glmer function from the rstanarm [37] package in R to obtain a vector of 1,000 draws from joint posterior distribution of the model parameters. The MRP estimate for the given outcome in a Bayesian setting is a posterior distribution, and the estimate is displayed as the mean of that distribution. In the Bayesian specification, priors are a necessary part of the model to account for existing knowledge and information about relationships in the model. The rstanarm package by default provides weakly informative priors, but more information can be added to the priors if there is a known prior distribution for a variable, if the default priors make the posterior distribution difficult to explore, or if the default priors lead to computational issues, which is often times the case in modeling applications. To avoid issues, following Lopez-Martin et al. [35], we introduced stronger priors on the scaled coefficients at normal distribution (0, 1) and adjusted the adapt_delta to equal 0.95.

Poststratification

The second step in the MRP modeling process is poststratification: weighting the model estimates for subgroups with more representative population data to correct for some of the known differences between the sample and population of interest. The poststratification table was created by generating a cell with every possible combination of demographic and descriptive attributes and then weighting each corresponding model estimate for each cell by the relative proportion in the population estimates. The demographic subgroups specifically were used for every possible combination of the demographic and geographic variables in the multilevel model. For example, one poststratification cell may include the total number of females, aged 21 to 30, in a given county, meaning there will be a cell with the total count of individuals for every other combination of gender, age, and county.

Once again following the notation of Lopez-Martin et al. [35], the poststratification estimate can be defined as:

$$\theta^{MRP} = \frac{\sum N_j \theta_j}{\sum N_j}$$

Where θ^{MRP} is the final MRP estimate, θ_j is the estimate generated from the multilevel model (using the survey data) for demographic subgroup j in the poststratification table, with corresponding entry of N_j representing the number of people in that subgroup from the population.

In most applications of MRP, population level data come from comprehensive population level surveys, ACS 5-year estimates conducted by the U.S. Census Bureau or the Decennial Census; however, these data are not publicly available at the county level. To address this limitation, we used an alternative source of demographic county-level data (the Survey, Epidemiology, and End Results (SEER) data from the U.S. National Cancer Institute) for the post-stratification table [38]. SEER receives individual response data from the U.S. Census Bureau bridged population estimates and reports county and census tract estimates that include several demographic characteristics (sex, age, race).

The county data included demographic information (proportions) for gender and age by county, as well as the group predictors included in the modeling that vary by county only: the percentage of people by county who voted yes on I-190 and region of the state. Additionally, we needed information on the percentage of people who had ever tried cannabis in the poststratification table. Similar to the group predictors (region and I-190 vote), the poststratification data for ever having tried cannabis would not add new cells to the poststratification table, but rather than varying by county, the ever-tried variable would vary by the age groups. The data for ever tried was gathered from multiple sources, including NSDUH [28], Montana YRBS [27], and Gallup [39]. The county-level poststratification variables were defined as follows:

Gender: Female, Male (G = 2 categories)

Age Group: 15–20, 21–30, 31–40, and 41+ (A = 4 categories)

County: (C = 56)

The poststratification table has a cell for every possible combination of these levels, which in this case was 2 x 4 x 56 = 448 rows.

RESULTS

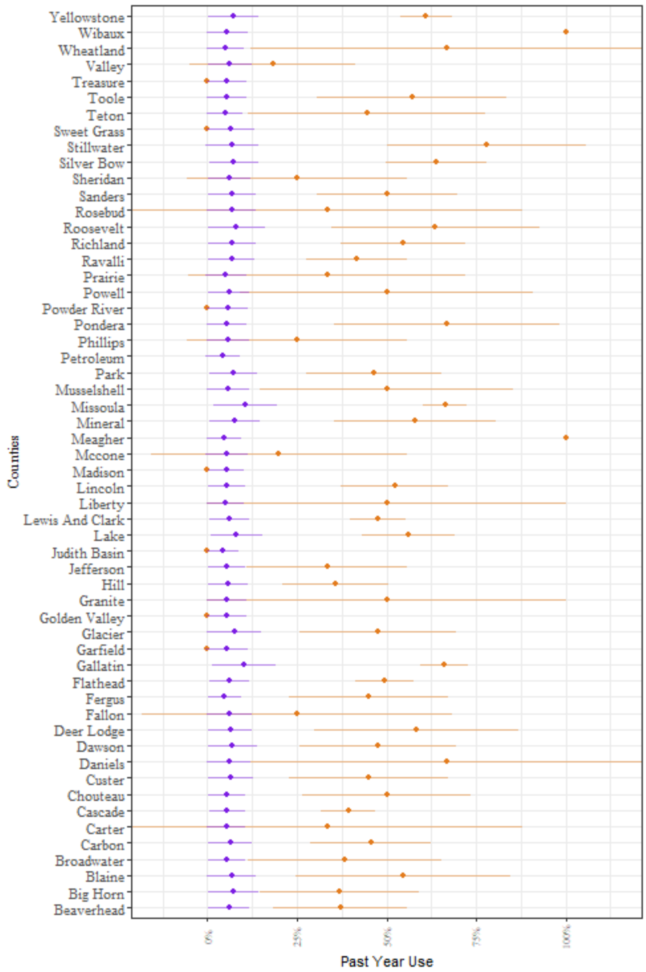
While this survey covered a wide range of cannabis related questions, this paper focuses only on prevalence of cannabis use in the last year and the methodology used to generate these estimates. The survey relied on self-selected responses; therefore, we do not expect the sample to be representative of the Montana population. Overall, the cannabis survey contained a slightly larger proportion of responses from females than males compared to the population. The largest proportion of responses came from the oldest age group, which is also the highest population age group in Montana. Most significantly, the survey was not representative of overall historical cannabis use. This is likely due to non-response or selection bias, evidenced by a substantial skew within the survey data towards individuals who have used cannabis responding to the survey at a much higher rate than non-users, as displayed in Table 1 below. In addition, there are low response rates for many counties across the state, particularly rural counties with already low populations. These biases are a primary motivation for utilizing MRP to generate estimates.

Table 1. Survey respondents who have ever used marijuana

Response	N	%
Tried Marijuana	1,569	*80.46*
Never Tried Marijuana	381	*19.54*

Estimates for past-year cannabis use, measured as the mean of the vector of posterior distributions from MRP by county are displayed below. We find that, in general, counties with a higher population in the state have slightly higher estimated cannabis use patterns than more rural counties. Missoula and Gallatin counties have the largest estimated percentages of cannabis use within the state. These results are unsurprising, as we found that the age group from 21 to 30 exhibit the highest cannabis use of any age group, and this age group is found in higher density in the higher population areas. Additionally, Missoula and Gallatin counties contain the two large universities in the state, which concentrate a large portion of young adults, who are consequently more likely to use cannabis according to our results. Figure 1 displays MRP estimates (purple), and 95% confidence intervals compared to the raw and unadjusted survey responses (orange). As can be seen from the figure, the higher-than-expected use rates across all counties are evident in the raw data, consistent with a greater response rate for users than non-users. The use of MRP provides a clear advantage over using the survey results as the only source of information and not attempting to correct for bias. Centered around a much lower range of use across counties, the MRP estimates match expectations that marijuana use is not likely to display such a wide range of use across counties.

Figure 1. Cannabis use by county: MRP vs. raw survey results



DISCUSSION

One of the primary and well-documented advantages to using MRP is the ability to adjust for highly non-representative data to generate reliable population estimates at national and state levels [11]. In this study, we found that there are key differences and potential barriers between national and state-level applications compared to smaller area applications such as ours that are important for researchers to consider.

One of the advantages of the Bayesian specification and multilevel model is that estimates for demographic or geographic groups with relatively sparse information can be improved through "borrowing strength" from demographically similar cells [35, 11]. Having few survey responses from a demographic or geographic group is likely to be a common issue in surveys that target small areas such as counties, congressional districts, or small towns, where the number of responses may be substantially lower than larger population areas. If, for instance, all of the individuals responding to the survey within a certain age group indicate they were marijuana users, then under a traditional point estimate approach the model would predict that all people within that age group are marijuana users. In the approach used in this study, following Lopez-Martin et. al [35], the model partially pulls the varying intercept for the age group in our example towards the average across all of the other age groups.

However, the varying intercepts approach, which assumes that each group shares a common distribution, does not always generate model predictions that are useful or accurate when there is little information available for certain groups. The use of varying intercepts for demographic variables partially pools information from each level of a variable towards the average across all levels of that variable. For example, while we found that we were able to effectively generate estimates for demographic subgroups such as age and gender, we found that estimates for race were more challenging. Although survey responses were proportionally similar to the racial distribution in Montana, all minority races except for Native American had responses in the single digits. Estimates that would have been generated from the models, particularly in the small area estimation from the county-level model, for any given minority racial group would be very close to the average across all races, which is primarily white in Montana (92% of the survey respondents were white, which is very similar to the percentage of the population in Montana that is white). Therefore, the average across all races is heavily weighted by responses from white individuals, meaning the estimates for minorities would be pulled closer to the estimated rates of use for white individuals and therefore likely not provide accurate estimations of use for other races.

Another key consideration in the use of MRP to quantify responses from a multi-modal survey as used in this study is the need to account for non-response and selection bias in the results. MRP is capable of adjusting for these biases and is a key reason that it is used in forecasting election outcomes, where researchers include variables to control for political factors such as prior votes in the respondent's geographic area, respondents party affiliation, respondents' religious ideology, and respondents' income [6, 10, 11]. This potential informed our selection of MRP for the project, and the research team included controls that we believed to influence whether someone had used marijuana in the past year such as whether a person had ever tried marijuana previously in their life, and the I-190 vote in their county.

A key aspect of MRP is that all control variables in the first-stage model must also be present in the poststratification data at the population level in order to generate estimates. These control factors do not add any rows to the poststratification but are typically expanded to match with geographic factors such as state or region. In our case, when our estimates are by county, the gaps in public health surveillance data on cannabis use made it challenging for our team to identify reliable estimates of some control variables, (i.e., the proportion of individuals who have ever tried marijuana) at the county level. Specifically, our control variable accounting for whether someone had ever tried marijuana in their life did not have population-level estimates by county for Montana, thus introducing a substantial and unanticipated challenge in our modeling that had not appeared to be a previous issue based on our reading of the literature.

To address this challenge, we utilized estimates from other surveys that had attempted to generate estimates at the state and national levels on marijuana use, which included the NSDUH [29], the Montana YRBS [28], and Gallup polls [39]. Each of these surveys contains estimates by age group for the percentage of the population who had ever tried marijuana, so we utilized a combination of these data to incorporate the information into the poststratification table as an alternate work-around to not having county data on lifetime cannabis use available.

Future researchers seeking to utilize MRP will need to consider data availability at the population level for poststratification during the research design phase, and plan survey design and questions for control factors they intend to include with this in mind to ensure that estimation is possible and limit modeling setbacks.

ABBREVIATIONS

I-190: Initiative 190
MRP: Multilevel regression and poststratification
NSDUH: National Survey on Drug Use and Health
YRBS: Youth Risky Behavior Survey

DISCLAIMERS

The results presented here are the work of the authors alone and do not reflect the views of the Department of Public Health and Human Services of the State of Montana.

FUNDING

The original data collection for this work was supported by a contract from the Department of Public Health and Human Services of the State of Montana.

ACKNOWLEDGEMENTS

We would like to thank Megan Higgs of Critical Inference, LLC for providing a review of our statistical methodology. This report results from work originally done for the Montana Public Health Institute (MPHI) and Montana Department of Health and Human Services (DPHHS). MPHI and DPHSS played no role in the writing of this report, the methodology used, or the decision to submit this paper for publication.

CONFLICTS OF INTEREST

None declared.

REFERENCES

1. Fazzino TL, Rose G, Pollack S, Helzer J. Recruiting U.S. and Canadian College Students via Social Media for Participation in a Web-Based Brief Intervention Study. Journal of Studies on Alcohol and Drugs. 2015;76(1):127-132. doi:10.15288/jsad.76.1.127
2. Park DK, Gelman A, Bafumi J. Bayesian Multilevel Estimation with Poststratification: State-Level Estimates from National Polls. Polit anal. 2004;12(4):375-385. doi:10.1093/pan/mph024
3. Rait MA, Prochaska JJ, Rubinstein ML. Recruitment of adolescents for a smoking study: use of traditional strategies and social media. Behav Med Pract Policy Res. 2015;5(3):254-259. doi:10.1007/s13142-015-0312-5
4. Topolovec-Vranic J, Natarajan K. The Use of Social Media in Recruitment for Medical Research Studies: A Scoping Review. J Med Internet Res. 2016;18(11):e286. doi:10.2196/jmir.5698
5. Gelman A, Little TC. Poststratification Into Many Categories Using Hierarchical Logistic Regression. Survey Methodology. Published online 1997:1-17.
6. Ghitza Y, Gelman A. Deep Interactions with MRP: Election Turnout and Voting Patterns Among Small Electoral Subgroups: DEEP INTERACTIONS WITH MRP. American Journal of Political Science. 2013;57(3):762-776. doi:10.1111/ajps.12004
7. Lauderdale BE, Bailey D, Blumenau J, Rivers D. Model-based pre-election polling for national and sub-national outcomes in the US and UK. International Journal of Forecasting. 2020;36(2):399-413. doi:10.1016/j.ijforecast.2019.05.012
8. Trangucci R, Ali I, Gelman A, Rivers D. Voting Patterns in 2016: Exploration Using Multilevel Regression and Poststratification (MRP) on Pre-Election Polls.; 2018.
9. Lax JR, Phillips JH. Gay Rights in the States: Public Opinion and Policy Responsiveness. Am Polit Sci Rev. 2009;103(3):367-386. doi:10.1017/S0003055409990050
10. Park DK, Gelman A, Bafumi J. Bayesian Multilevel Estimation with Poststratification: State-Level Estimates from National Polls. Polit anal. 2004;12(4):375-385. doi:10.1093/pan/mph024
11. Wang W, Rothschild D, Goel S, Gelman A. Forecasting elections with non-representative polls. International Journal of Forecasting. 2015;31(3):980-991.

doi:10.1016/j.ijforecast.2014.06.001
12. Gelman A, Lax J, Phillips J, Gabry J, Trangucci R. Using Multilevel Regression and Poststratification to Estimate Dynamic Public Opinion.; 2018.
13. Tausanovitch C, Warshaw C. Representation in Municipal Government. Am Polit Sci Rev. 2014;108(3):605-641. doi:10.1017/S0003055414000318
14. Zhang X, Holt JB, Lu H, et al. Multilevel Regression and Poststratification for Small-Area Estimation of Population Health Outcomes: A Case Study of Chronic Obstructive Pulmonary Disease Prevalence Using the Behavioral Risk Factor Surveillance System. American Journal of Epidemiology. 2014;179(8):1025-1033. doi:10.1093/aje/kwu018
15. Eke PI, Zhang X, Lu H, et al. Predicting Periodontitis at State and Local Levels in the United States. J Dent Res. 2016;95(5):515-522. doi:10.1177/0022034516629112
16. Christofoletti M, Benedetti TRB, Mendes FG, Carvalho HM. Using Multilevel Regression and Poststratification to Estimate Physical Activity Levels from Health Surveys. IJERPH. 2021;18(14):7477. doi:10.3390/ijerph18147477
17. Downes M, Gurrin LC, English DR, et al. Multilevel Regression and Poststratification: A Modeling Approach to Estimating Population Quantities From Highly Selected Survey Samples. American Journal of Epidemiology. 2018;187(8):1780-1790. doi:10.1093/aje/kwy070
18. Herman JL, Flores AR, O'Neill KK. How Many Adults and Youth Identify As Transgender In The United States? UCLA Williams Institute School of Law; 2022.
19. Jones MK, Calzavara L, Allman D, Worthington CA, Tyndall M, Iveniuk J. A Comparison of Web and Telephone Responses From a National HIV and AIDS Survey. JMIR Public Health Surveill. 2016;2(2):e37. doi:10.2196/publichealth.5184
20. Chang L, Krosnick JA. National Surveys Via Rdd Telephone Interviewing Versus the Internet. Public Opinion Quarterly. 2009;73(4):641-678. doi:10.1093/poq/nfp075
21. Fricker S, Galesic M, Tourangeau R, Yan T. An Experimental Comparison of Web and Telephone Surveys. Public Opinion Quarterly. 2005;69(3):370-392. doi:10.1093/poq/nfi027
22. Greene J, Speizer H, Wiitala W. Telephone and Web: Mixed-Mode Challenge: Mixed Mode Surveys. Health Services Research. 2007;43(1p1):230-248. doi:10.1111/j.1475-6773.2007.00747.x
23. Link M, Mokdad A. Effects of survey mode on self-reports of adult alcohol consumption: A comparison of mail, web and telephone approaches. Journal of Studies on Alcohol. 2005;66(2):239-245. doi:10.15288/jsa.2005.66.239
24. Plante C, Jacques L, Chevalier S, Fournier M. Comparability of Internet and Telephone Data in a Survey on the Respiratory Health of Children. Canadian Respiratory Journal. 2012;19(1):13-18. doi:10.1155/2012/318941
25. Tourangeau R. Measurement Properties of Web Surveys. In: Beyond traditional survey taking: adapting to a changing world. In: Proceedings of Statistics Canada Symposium. ; 2014.
26. Burkill S, Copas A, Couper MP, et al. Using the Web to Collect Data on Sensitive Behaviours: A Study Looking at Mode Effects on the British National Survey of Sexual Attitudes and Lifestyles. Cardoso MA, ed. PLoS ONE. 2016;11(2):e0147983. doi:10.1371/journal.pone.0147983
27. Fischer B, Lee A, Robinson T, Hall W. An overview of select cannabis use and supply indicators pre- and post-legalization in Canada. Subst Abuse Treat Prev Policy. 2021;16(1):77. doi:10.1186/s13011-021-00405-7
28. Montana Office of Public Instruction. 2021 Montana Youth Risky Behavior Survey - High School Results.; 2021. https://opi.mt.gov/Portals/182/Page%20Files/YRBS/2021YRBS/2021_MT_YRBS_FullReport_Sept30.pdf?ver=2021-10-01-082901-390
29. SAMHSA. National Survey on Drug Use and Health: Model-Based Prevalence Estimates (50 States and the District of Columbia).; 2018. https://www.samhsa.gov/data/sites/default/files/reports/rpt32805/2019NSDUHsaeExcelPercents/2019NSDUHsaeExcelPercents/2019NSDUHsaePercents.pdf
30. Fazzino TL, Rose G, Pollack S, Helzer J. Recruiting U.S. and Canadian College Students via Social Media for Participation in a Web-Based Brief Intervention Study. Journal of Studies on Alcohol and Drugs. 2015;76(1):127-132. doi:10.15288/jsad.76.1.127
31. Ford KL, Albritton T, Dunn TA, Crawford K, Neuwirth J, Bull S. Youth Study Recruitment Using Paid Advertising on Instagram, Snapchat, and Facebook: Cross-Sectional Survey Study. JMIR Public Health Surveill. 2019;5(4):e14080. doi:10.2196/14080
32. Park B, Calamaro C. A systematic review of social networking sites: innovative platforms for health research targeting adolescents and young adults. Journal of Nursing Scholarship. 2013;45(3). doi:10.1111/jnu.12032
33. Rait MA, Prochaska JJ, Rubinstein ML. Recruitment of adolescents for a smoking study: use of traditional strategies and social media. Behav Med Pract Policy Res. 2015;5(3):254-259. doi:10.1007/s13142-015-0312-5
34. Topolovec-Vranic J, Natarajan K. The Use of Social Media in Recruitment for Medical Research Studies: A Scoping Review. J Med Internet Res. 2016;18(11):e286. doi:10.2196/jmir.5698
35. Lopez-Martin J, Phillips J, Gelman A. Multilevel Regression and Poststratification Case Studies. Published 2021. https://bookdown.org/jl5522/MRP-case-studies/
36. Gelman A, Hill J. Data Analysis Using Regression and Multilevel/Hierarchical Models. Cambridge University Press; 2007.
37. Goodrich B, Gabry J, Ali I, Brilleman S. rstanarm: Bayesian applied regression modeling via Stan. Published online 2020. https://mc-stan.org/rstanarm

38. National Cancer Institute. Surveillance, Epidemiology, and End Results (SEER) Program Populations (1969-2020). National Cancer Institute, DCCPS, Surveillance Research Program www.seer.cancer.gov/popdata

39. Jones J. Nearly Half of U.S. Adults Have Tried Marijuana. Gallup. https://news.gallup.com/poll/353645/nearly-half-adults-tried-marijuana.aspx. Published 2021.

ISSN 2282-0930 • Epidemiology Biostatistics and Public Health - 2024, Volume 19, Issue 2

Occasional and Continuous Ketamine Users: Consumption Rules and Harm Reduction Strategies

Raimondo Maria Pavarin[(1)]

(1) University of Bologna, Italy.

CORRESPONDING AUTHOR: Dr. Raimondo Maria Pavarin, Research & Innovation on Addiction, Open Group Impresa Sociale Bologna, Italy, Via Milazzo, 30 40121 Bologna – Italy. Tel. 0039 3203343054. Email: r.pavarin2@outlook.it

SUMMARY

Objectives: To describe the phenomenology of ketamine use; to identify feared/unwanted consequences due to the use of ketamine; to identify any common ketamine consumption rules.
Methods: A semi-structured questionnaire was administered to a sample of 48 (31.3% female) substance users living in Italy with recent use of ketamine (last 12 months) and who have never referred to an Addiction Service.
Results: From the results aspects emerge related to particular strategies implemented by interviewees to reduce the impact of ketamine consumption on their health, in everyday life and within social relationships: 1) ketamine consumption and purchase were primarily based on friendship networks and trusted relationships; 2) techniques of camouflage were adopted to keep the consumer status secret; 3) artisan controls to verify the quality of the substances were common; 4) general consumption rules were implemented to avoid unwanted consequences due to the use of ketamine.
Conclusions: The control of ketamine consumption is a complex practice that includes various aspects related not only to the knowledge of the substance, to the dosing-related harm reduction strategies, to the consumption setting, and to the consumer's psycho-physical state, but also to the choice of people to buy from and consume with.

Keywords: substance use; ketamine; consumption rules; harm reduction strategies.

INTRODUCTION

Ketamine was developed in the 1960s and introduced into medical use as a new dissociative anesthetic, and today it remains an alternative choice in pediatric and veterinary medicine [1]. As an anesthetic agent, ketamine can produce both anesthetic and analgesic effects, and has a relatively stable cardiovascular profile [2]. The drug does not depress respiration or the cardiovascular system, it can be used without electricity, oxygen, ventilators, and all the support systems required for other anesthetics. In high-income countries, ketamine is increasingly used to treat depression and chronic pain [3].

Recreational use of ketamine was first documented in the United States in the 1970s, and then it spread internationally in association with the rave dance subculture of the 1980/90s. More recently, it has become part of the current post-rave clubbing and youth dance culture as a mainstream club drug [4], and its use is significantly higher in those frequenting the night-time economy (e.g. discotheques, nightclubs, dance/music events) and is commonly part of poly-substance use [5].

Ketamine is primarily obtained in a powder form and administered by sniffing or inhaling. Other forms of ingestion include intramuscular injection, or occasionally intravenous injection, and oral intake in tablet form [6]. Illicit manufacturing, trafficking, and use of ketamine appears to have started on a large scale in several Asian nations because of its relatively low price compared to other psychotomimetic drugs, and it has subsequently spread to other regions [7, 8].

Psychologically, the acute use of ketamine causes

DOI: 10.54103/2282-0930/26983
Accepted: 11th November 2024

hallucination, symptoms of psychosis, delusion, agitation, confusion, and memory impairment. In addition, many side effects, such as nausea and vomiting, and bizarre dreams, have been reported. These side effects have been documented in a dose-dependent fashion and some of them persisted for several days after administration. Following heavy ketamine use, abusers have experienced a near death feeling, known as a "K hole" [9].

Users are aware of the potency of the drug, but do not pay attention to long-term negative effects [10]. Regular ketamine use is associated with vague abdominal pains of unknown etiology, colloquially termed 'K Cramps', and there is evidence of gastro-intestinal toxicity and urological disorders, particularly hemorrhagic cystitis [11]. Furthermore, long-term recreational use can be associated with the development of dependence and tolerance [12].

Ketamine is generally the last substance a user experiments with in their lifetime, and its effects are perceived differently depending on the dosage, the route of administration, whether intake occurs alone or in a group, and whether it takes place after having eaten or not [13]. The principal physical dangers of most cases of non-medical use are believed to arise mainly from an interaction between the user and the setting of use, as ketamine can leave the user in a confused state (i.e., burns, falls, drowning, traffic accidents, and sexual assault) [14].

The effects that limit the clinical use of ketamine make the drug appealing to recreational drug users [15]. From a user's point of view, the best effects of ketamine consumption seem to be altered senses, an out of body experience, escaping reality, feelings of well-being, and creativity [14]. Unappealing effects are memory loss and decreased sociability [4].

While ketamine is generally associated with the dance and rave scene, the main settings of use are at home or at a friend's house. When taken in club settings, ketamine is often part of a poly-drug repertoire. When used in private settings, it is often taken alone to explore its hallucinogenic effects [10].

As reported above, in the literature there are many studies that describe the experience with ketamine, targeted in particular on the effects considered positive and on the consumers' health consequences. Contrary to studies targeted on other substances [16-24], from which specific precautions emerge in order to control consumption, reduce negative effects, avoid stigma, and keep the consumer's identity separate from that of the drug addict, there is little research on the practices implemented by ketamine consumers to avoid negative problems, or on the rules adopted for safe consumption.

For Moore and Measham [25], the control strategies implemented by ketamine users (dose, context of consumption, management of K hole) serve both to maximize the pleasure and to minimize the harm. In this case, the notion of pleasure is structured around preferences for more or less intense and more or less sociable states of intoxication, which ketamine users attempt to control through drug dose and consumption context.

The most frequent strategies of harm reduction implemented by ketamine users were related to dose and consumption frequency, particularly spacing out sessions, spacing out doses within a session, and limiting the amount and not going over it [26].

This study, which addresses a theoretical sample of substance users living in Italy with recent use of ketamine (last 12 months) and who have never referred to an Addiction Service (AS), has the main aims: 1) to describe differences between occasional and continuous users; 2) to identify any common ketamine consumption rules (practices set out by communities of people who use ketamine) or harm reduction strategies.

MATERIALS AND METHODS

The participants had used ketamine over the last 12 months and had never been referred to AS for substance use problems or had never sought help from AS themselves. As regards the users' selection process, the interviewers resorted to their own personal networks (e.g. friends of friends, acquaintances, work colleagues) and contacts suggested by the interviewees themselves (snowball sampling) or by 'word of mouth'. These interviewees took part on a voluntary basis and were not paid, consent was collected in oral form. Everyone was explained the aims and goals of the study and anonymity was guaranteed along with the possibility to be excluded in the case of second thoughts.

A semi-structured questionnaire was specifically created for the study, partly modifying a tool used in previous works [24]. Twenty subjects were successively interviewed by two different interviewers, and the Kappa test was used to verify their understanding of the questions and the congruency of the responses [27].

The questionnaire collected socio-demographic data (gender, age, birthplace, living situation, educational background, and employment status), information regarding monthly income, relationship with illegal substances and alcohol, integrated with information regarding drug dealing, and risk behaviours.

Regarding alcohol, we collected data related to number of episodes of alcoholic alteration in the last year. The consumption of at least 6 units of alcohol on any occasion in the previous 30 days was defined as binge-drinking [28; 29].

For each illegal substance used we collected data regarding number of consumption days per month, average quantity per episode, average cost per gram/dose. Using these variables, the monthly expenditure for illegal substances was estimated.

Regarding ketamine, we collected further information regarding quality checks, secrecy (i.e. keeping consumption hidden from family, friends, work colleagues; using a code to communicate in regard to the substances), most feared/unwanted consequences of ketamine's use and most common protective behaviours.

In relation to the frequency of ketamine use in the last year, two typologies of consumers have been distinguished: occasional (1/3 episodes of ketamine consumption per month) and continuous > 3 episodes of ketamine consumption per month). The differences between the two groups, as compared with the continuous and categoric variables, were analyzed with Student's t-test and the chi-square test, respectively. The data analyses were performed using the statistical software program STATA 15.0.

In keeping with Italian privacy regulations, the study design was approved by the local research ethics committee (Cod. CE: 19035).

RESULTS

In the period from October to December 2019, 48 subjects, 31% females, 4% non-natives, mean age 23.6 years, were interviewed. The average monthly income was 746€. All of them had a stable home, and most had a medium-high level of education, studied and worked, although there were a considerable number of subjects who neither studied nor worked. During the past year, 85% had engaged in risky behaviours, but none had exchanged syringes (Table 1).

Table 1. General characteristics of the study patients

	Total (48)		Occasional* (22)		Continuous** (26)		P
	N	%	N	%	N	%	
Females	15	31.3	7	31.8	8	30.8	0.938
Not natives	2	4.2	1	4.5	1	3.8	0.904
Secondary school exam certificate	39	81.3	18	81.8	21	80.8	0.980
Living with his family	19	39.6	6	27.3	13	50.0	0.226
18/24 years	30	62.5	13	59.1	17	65.4	0.654
25/34 years	18	37.5	9	40.9	9	34.6	
Studies	18	37.5	8	36.4	6	23.0	0.624
Works	21	43.5	11	50.0	10	38.5	
Neither studies nor works	9	18.8	3	13.6	10	38.5	
Net monthly income <1000 Euro	35	72.9	16	72.7	19	73.1	0.993
Dangerous driving	21	43.8	9	40.9	12	46.2	0.715
Unprotected sex	35	72.9	15	68.2	20	76.9	0.497
Drug dealing	32	66.7	14	63.6	18	69.2	0.682

** 1/3 episodes per month ** >3 episodes per month*

In total, 22 subjects declared they had from 1 to 3 episodes of ketamine consumption per month in the last year (occasional) and 26 at least one episode per week (continuous).

Substance use - Over the last year, all the interviewees had used several drugs, mostly cocaine (94%), MDMA (88%), cannabis (85%), benzodiazepines (75%), speed (75%), LSD (56%), opium (35%), heroin (25%), and hallucinogenic mushrooms (13%). Only one subject injected (heroin).

We observed a more intense pattern of use among the continuous group, evidenced by the higher weekly use of at least two substances other than cannabis. In addition, the continuous group were distinguished by the hgher consumption of cocaine, speed, and MDMA, and the occasional group by the higher consumption of hallucinogenic mushrooms (Table 2).

Table 2. Patterns of substance use

Ketamine in the last year	**Total (48)**	**Occasional* (22)**	**Continuous** (26)**	**P**
Mean age at first use	18.67	19.18	18.23	0.276
Duration of consumption in years	4.96	4.90	5.0	0.932
Average episodes per month	6.4	2.0	10.2	<0.0001
Average Dose gram	0.42	0.34	0.48	0.0993
Average cost per gram (Euro)	42	46	38	0.1481
% Use exclusively at weekends	43.8	63.6	26.9	0.011
Other substances in the last year				
Mean age at first use	13.79	14.14	13.50	0.203
Duration of consumption in years	9.85	10.0	9.73	0.831
% Use exclusively at weekends	12.5	13.6	11.5	0.827
% Cannabis >=4 episodes per week	60.4	59.1	61.5	0.573
% At least 2 substances other than cannabis>=1con-sumption episode per week	37.5	18.2	53.9	0.011
% Cocaine >=1 episodes per week	54.2	31.8	73.1	0.004
% Speed >=1 episode per week	37.5	22.7	50.0	0.052
% Opium >=1 episode per week	14.6	9.1	19.2	0.321
% Heroin >=1 episode per week	4.2	4.6	3.9	0.904
% MDMA >=1 episode per week	22.9	9.1	34.6	0.036
% LSD >=1 episode per month	31.3	36.4	26.9	0.482
% Hallucinogenic mushrooms >=1 episode per month	6.3	13.6	-	0.052
Alcohol in the past year				
% >=3 episodes of alcoholic alteration per week	21.7	28.6	16.0	0.303
% Binge drinking during last 30 days	75.0	81.8	69.2	0.316

** 1/3 episodes per month ** >3 episodes per month*

Regarding alcohol use, all the interviewees reported having been drunk at least once over the past year (22% at least 3 episodes per week) and 75% were identified as 'positive' for binge-drinking over the last month. Alcohol intoxication was more elevated among occasional.

Patterns of ketamine use – The mean age of the first ketamine use was around 18-19 years and lasted for 5 years. On average, there were 6.4 episodes of consumption per month, the average dose was 0.42 g, the average cost per gram was 42€, and the average monthly expenditure per capita was estimated at 150€, higher for the continuous group (continuous 256€, occasional 28€, P=0.0004). Forty-four percent of consumers used ketamine exclusively at weekends, particularly in the occasional group (Table 2). All participants reported inhaling ketamine in a powdered form as the main route of ingestion, and two reported the occasional smoking of the drug.

Concerning quality checks, the majority trusted their dealers (total 33%; occasional 41%, continuous 27%) or used onsite drug safety testing services at party events or at concerts (19%), but we observed a high percentage of people who used sensory controls, particularly using their eyesight (total 31%; occasional 27%, continuous 35%) and their sense of smell (19%).

Regarding secrecy, the majority of occasional tried to keep their substance use hidden, especially from their family (total 69%; occasional 64%, continuous 73%), from their colleagues (Total 50%; occasional 55%, continuous 46%), and from their friends (Total 31%; occasional 46%, continuous 19% P 0.05); just under half paid particular attention to their contacts and resorted to a private code to communicate (total 46%; occasional 50%, continuous 42%).

Unwanted consequences of ketamine use - Another interesting aspect is the fear of having problems related

ISSN 2282-0930 • Epidemiology Biostatistics and Public Health - 2024, Volume 19, Issue 2

to ketamine use. From the interviews, many feared damages were identified as a consequence of the use of ketamine, the most common concerning the justice sphere (69% problems with the law, 50% being unable to hide the effects, 35% being caught in possession of the substance), the health sphere (29% road accidents, 27% long-term physical complications, 25% memory disorders, 23% loss of consumption control), and the condition that being a drug consumer will be made public (21% labelling/stigma). Other fears worth highlighting include the fear of psychic problems (19% hallucinations, 13% depression), psychiatric problems (19%), relational problems (17% loss of important relationships, 15% isolation from others), and complications related to the economic sphere (15% overspending, 10% being ripped off, 8% going into debt). It is worth noting that only one interviewee out of twelve feared developing any form of ketamine addiction. Statistically significant differences were not observed between the two typologies being studied, but we highlight that occasional pay more attention not being ripped off (occasional 18%, continuous 4%), and continuous are most scared of being unable to hide the effects (occasional 41%, continuous 58%), and have reported a higher percentage of memory disorders (occasional 14%, continuous 35%), loss of consumption control (occasional 18%, continuous 27%), hallucinations (occasional 9%, continuous 27%), isolation from others (occasional 9%, continuous 19%), overspending (occasional 9%, continuous 19%), going into debt (occasional 5%, continuous 12%).

Consumption rules – As for protective behaviours individually adopted, we identified fourteen general ketamine consumption rules of thumb shared by all interviewees (regarding where, when, with whom and what doing before consuming; behaviours to avoid, and warnings) (Table 3).

Table 3. Consumption rules

		Total (48)	Occasional* (22)	Continuous** (26)	P
Where	Consuming only during social and recreational activities	50.0	63.6	38.5	0.082
	Consuming only in safe and comfortable setting	27.1	31.8	23.1	0.497
When	Consuming only in positive emotional states	25.0	27.3	23.1	0.738
	Not consuming before activities requiring physical/mental engagement	70.8	68.2	73.1	0.710
With whom	Consuming in company	64.6	72.7	57.7	0.278
	Not consuming with strangers	31.3	31.8	30.8	0.938
	Do not consume with people who are not regular users	27.1	22.7	30.8	0.532
What doing before	Doing sensorial tests before consuming	56.3	45.5	65.4	0.165
	Observing the effects on others before consuming	41.7	54.5	30.8	0.096
	Pre-set budget for purchases	37.5	45.5	30.8	0.295
Behaviours to avoid	Avoiding specific methods of consumption	72.9	72.7	73.1	0.978
	Avoiding the exchange of drug-taking implements	29.2	27.3	30.8	0.791
Warnings	Limiting the quantity taken	43.8	50.0	38.5	0.422
	To take specific precautions to avoid physical harm	37.5	45.5	30.8	0.295

**1/3 episodes per month ** >3 episodes per month*

In order to spare harmful side effects, most ketamine users consumed only in company, used sensory testing to check ketamine before consuming it, avoided specific methods of consumption (e.g. injecting), and did not consume ketamine before activities requiring physical or mental engagement. A percentage ranging from 40% to 50% used ketamine only during social and recreational activities, limiting the quantity and observing the effects on other ketamine users before consuming it. One subject in three took specific precautions to avoid physical harm, pre-set a budget for ketamine purchase, and did not consume it with strangers. One in four avoided the exchange of ketamine-taking implements, consumed only with regular ketamine users, consumed only when in a positive emotional state, and only in safe and comfortable settings.

Moreover, it should be highlighted that 23% of our sample avoided ketamine consumption in public spaces (occasional 36.4%, continuous 12.0%, P=0.041), 13% used ketamine only with experienced users, and 8% did not use different substances in the same period.

Despite statistically significant differences were not observed, more attention was observed among continuous doing sensorial tests before consuming and not to consume with not regular users. On the contrary, occasional pay more attention consuming in company, only during social activities and in safe and comfortable settings, to observe the effects on other before consuming ketamine and to pre-set a budget for ketamine purchase, to limit the quantity taken and to take precautions to avoid physical harms.

DISCUSSION

This study is based on a sample of ketamine consumers who had never been referred to AS for substance use problems: young people, working or attending university, with medium-low income, from a stable home and with a medium-high standard of education. They were well integrated into friendship networks and regularly carried out social and recreational activities, although there was a high propensity for risky behaviours (particularly unsafe sex), and illegal activities (particularly drug dealing).

These were poly-drug users, with an average of eight different substances used in their lifetime, high alcohol abuse, and heavy use of cocaine, MDMA, cannabis, benzodiazepines, and amphetamines. Half used ketamine exclusively on the weekend, and only a minority declared they feared developing ketamine addiction.

Unlike other studies, in which ketamine is one of the last substances used, in our study it should be noted that in 10% of cases ketamine is one of the first 3 substances ever used, and in 42% of cases it is among the top 5 substances.

While most of the interviewees feared having problems related to ketamine use, mostly regarding the justice sphere, long-term physical or psychic complications, and stigma, only a minority reported specific disorders, particularly memory disorders and paranoia.

From the results, other aspects emerge related to particular strategies implemented by interviewees to reduce the impact of ketamine consumption on their health, in everyday life and within social relationships: 1) ketamine consumption and purchase were primarily based on friendship networks and trusted relationships; 2) techniques of camouflage were adopted to keep the consumer status secret; 3) artisan controls to verify the quality of the substances were common; 4) general consumption rules were implemented to avoid unwanted consequences due to the use of ketamine.

As regards ketamine purchase, transactions based on trust, with well-known people, preferably at the seller's home prevailed. Even for consumption, subjects preferred to be at home or in fun contexts, and trusted relationships with friends and well-known people prevailed. In fact, the most appropriate consumption settings were recreational contexts and own home, while the least suitable were work and family.

While ketamine seems to be becoming a mainstream drug of common use among young people frequenting the amusement contexts, its consumption remains associated with a strong fear of being publicly discredited or labelled. Indeed, although purchase and consumption are based on trust, most consumers tried to keep ketamine use secret and adopted coded messages to communicate. The secret was kept not only from family and colleagues, but from friends too. From the interviews it emerged that most of the enrolled subjects feared problems with the law, being unable to hide the ketamine effects, being caught in possession of ketamine, and that the condition of being a ketamine consumer would be made public.

Regarding checking of the drug, while most interviewees trusted their dealers, and only a minority used onsite drug safety testing services at party events or at concerts, unsophisticated drug-checking practices based on habit and tradition have been observed, such as the use of touch and smell, and the preventive observation of what happens to others.

Most of the respondents examined the quality of ketamine by testing it and using their senses. For the checks, some referred to previous experiences, while others trusted the seller, who was considered to be more experienced. In fact, both for consumption and quality assessment, learning derived from trial and error, from suggestions by more experienced consumers, and by observing others. The different purchasing practices evoked an intimate and sensual relationship with ketamine, which had to be observed, touched, smelled and weighed, within a relationship with the seller that presupposed confidence and complicity.

Regarding consumption rules, previous studies have reported that ketamine users try to control dose, consumption frequency, and context of use to maximize the pleasure and to minimize the harm [25]. Dosing-related harm reduction strategies are common among cocaine [17, 19], heroin [20], and ecstasy users [30], and this practice appears to be associated with less drug-related harm in a study conducted among poly-substance users [31].

In our study, we identified many general ketamine consumption rules of thumb shared by all interviewees, mostly related to harm reduction practices and oriented to control the quantity of ketamine taken (pre-set a budget, to limit the quantity), to take specific precautions to limit physical harms (i.e., drinking water), and to avoid particular methods of consumption (not injecting) and the exchange of drug-taking implements. Moreover, we observed behaviours related to the "set" (consuming only in positive emotional states and not before activities requiring physical/mental engagement) and to the setting (consuming only during social and recreational activities, in safe and comfortable setting). In all cases, it was important to carefully select people with whom to consume (only with regular ketamine users) or not to consume (never with strangers or non-regular users) ketamine.

Finally, from our study it emerged that ketamine use is particularly associated with the fun-time world and that the differences resulting from the greater or lesser use of ketamine had levelled over time. Indeed, looking at the two typologies related to ketamine use frequency, we did not observe any difference related to general characteristics, alcohol misuse, main motives for ketamine consumption, and ketamine consumption rules. On the contrary, subjects with a higher frequency of ketamine consumption showed a more intense pattern of use of any illegal drug, particularly cocaine, speed, and MDMA, and experienced a higher prevalence of problems related to ketamine consumption. On the other hand, occasional consumers used ketamine mainly on weekends and were more concerned about secrecy, avoiding ketamine consumption in public spaces.

ROLE OF FUNDING SOURCE

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

I confirm that neither the manuscript nor any parts of its content are currently under consideration or published in another journal.

CONFLICT OF INTEREST

Raimondo Maria Pavarin declare that he has no conflicts of interest.

REFERENCES

1. Zou, J., & Tan, S. (2016). Emerging trends in the abuse of ketamine and its side effects on health: toxicology and addiction potential. Advances in Clinical Toxicology (ACT) - Medwin Publishers, 1(1): 000105 Doi: http://d.researchbib.com/f/3joJIx-q2yhpUIvoTymnTIlpl5wo20iDHAHY0SQIQR2ZQN-jZGN2YaOxMt.pdf
2. Ng, S. H., Tse, M. L., Ng, H. W., & Lau, F. L. (2010). Emergency department presentation of ketamine abusers in Hong Kong: a review of 233 cases. Hong Kong medical journal = Xianggang yi xue za zhi, 16(1), 6–11.
3. Taylor, M., & Potter, G. R. (2013). From "Social Supply" to "Real Dealing" drift, friendship, and trust in drug-dealing careers. Journal of Drug Issues, 43(4), 392-406. https://doi.org/10.1177/0022042612474974
4. Muetzelfeldt, L., Kamboj, S. K., Rees, H., Taylor, J., Morgan, C. J., & Curran, H. V. (2008). Journey through the K-hole: phenomenological aspects of ketamine use. Drug and alcohol dependence, 95(3), 219–229. https://doi.org/10.1016/j.drugalcdep.2008.01.024
5. Kalsi, S. S., Wood, D. M., & Dargan, P. I. (2011). The epidemiology and patterns of acute and chronic toxicity associated with recreational ketamine use. Emerging health threats journal, 4, 7107. https://doi.org/10.3402/ehtj.v4i0.7107
6. Jansen K. L. (2000). A review of the nonmedical use of ketamine: use, users and consequences. Journal of psychoactive drugs, 32(4), 419–433.https://doi.org/10.1080/02791072.2000.10400244
7. UNODC. United Nations office on drugs & crime, 2010. World drug report 2010. United Nations Publications.
8. Liao, Y., Tang, Y. L., & Hao, W. (2017). Ketamine and international regulations. The American journal of drug and alcohol abuse, 43(5), 495–504. https://doi.org/10.1080/00952990.2016.1278449
9. Jansen, K. L., & Darracot-Cankovic, R. (2001). The nonmedical use of ketamine, part two: A review of problem use and dependence. Journal of psychoactive drugs, 33(2), 151–158. https://doi.org/10.1080/02791072.2001.10400480
10. Ravn, S., & Demant, J. (2012). Prevalence and perceptions of ketamine use among Danish clubbers: a mixed-method study. Nordic studies on alcohol and drugs, 29(4), 397-412. https://doi.org/10.2478/v10199-012-0035-6
11. Shahani, R., Streutker, C., Dickson, B., & Stewart, R. J. (2007). Ketamine-associated ulcerative cystitis: a new clinical entity. Urology, 69(5), 810–812. https://doi.org/10.1016/j.urology.2007.01.038
12. EMCDDA. European Monitoring Centre for Drugs, & Drug Addiction. (2002). Report on the risk assessment of ketamine in the framework of the joint action on new synthetic drugs. Office for Official Publication of the European Communities.
13. Reynaud-Maurupt, C., Bello, P. Y., Akoka, S., &

Toufik, A. (2007). Characteristics and behaviors of ketamine users in France in 2003. Journal of psychoactive drugs, 39(1), 1–11. https://doi.org/10.1080/02791072.2007.10399859
14. Dillon, P., Copeland, J., & Jansen, K. (2003). Patterns of use and harms associated with non-medical ketamine use. Drug and alcohol dependence, 69(1), 23–28. https://doi.org/10.1016/s0376-8716(02)00243-0
15. 15 Morgan, C. J., Curran, H. V., & Independent Scientific Committee on Drugs. (2012). Ketamine use: a review. Addiction 107(1): 27–38.
16. Zinberg, N. E. (1984). Drug, set, and setting: The basis for controlled intoxicant use. Yale University Press.
17. Cohen, P., & Sas, A. (1994). Cocaine use in Amsterdam in non deviant subcultures. Addiction Research, 2(1), 71-94. https://doi.org/10.3109/16066359409005547
18. Grund, J. P. C. 1993. Drug use as a social ritual: Functionality, symbolism and determinants of self-regulation. Erasmus Universiteits Drukkerij.
19. Decorte T. (2001). Quality control by cocaine users: underdeveloped harm reduction strategies. European addiction research, 7(4), 161–175. https://doi.org/10.1159/000050737
20. Warburton, H., Turnbull, P. J., & Hough, M. (2005). Occasional and controlled heroin use: Not a problem? Joseph Rowntree Foundation.
21. Paul, K. I., & Moser, K. (2009). Unemployment impairs mental health: Meta-analyses. Journal of Vocational behavior, 74(3), 264-282. https://doi.org/10.1016/j.jvb.2009.01.001
22. Eisenbach-Stangl, I., Moskalewicz, J., & Thom, B. (2009). Two worlds of drug consumption in late modern societies. Ashgate Publishing, Ltd.
23. Cruz, O. S. (2015). Nonproblematic illegal drug use: Drug use management strategies in a Portuguese sample. Journal of Drug Issues, 45(2), 133-150. https://doi.org/10.1177/0022042614559842.
24. Pavarin R. M. (2016). First Consumers, Then Socially Integrated: Results of a Study on 100 Italian Drug Users Who Had Never Turned to Public or Private Addiction Services. Substance use & misuse, 51(7), 892–901. https://doi.org/10.3109/10826084.2016.1155620
25. Moore, K., & Measham, F. (2008). "It's the most fun you can have for twenty quid": Motivations, consequences and meanings of British ketamine use. Addiction Research & Theory, 16(3), 231-244. https://doi.org/10.1080/16066350801983681
26. Vidal Giné, C., Fernández Calderón, F., & López Guerrero, J. (2016). Patterns of use, harm reduction strategies, and their relation to risk behavior and harm in recreational ketamine users. The American journal of drug and alcohol abuse, 42(3), 358–369. https://doi.org/10.3109/00952990.2016.1141211
27. Armstrong, B.K., White, E. & Saracci, R. (1992). Principles of exposure measurement in epidemiology. Oxford: Oxford University Press.
28. Valencia-Martín, J. L., Galán, I., & Rodríguez-Artalejo, F. (2008). The joint association of average volume of alcohol and binge drinking with hazardous driving behaviour and traffic crashes. Addiction (Abingdon, England), 103(5), 749–757. https://doi.org/10.1111/j.1360-0443.2008.02165.x
29. World Health Organization. International Guide for Monitoring Alcohol Consumption and Related Harm. (2000). Available online:http://apps.who.int/iris/bitstream/handle/10665/66529/WHO_MSD_MSB_00.4.pdf?sequence=1 (accessed on 11 August 2022).
30. Jacinto, C., Duterte, M., Sales, P., and Murphy, S. (2008). Maximising the highs and minimising the lows: harm reduction guidance within ecstasy distribution networks. The International journal on drug policy 19(5): 393–400. https://doi.org/10.1016/j.drugpo.2007.09.003
31. Fernández-Calderón, F., Díaz-Batanero, C., Barratt, M. J., and Palamar, J. J. (2019). Harm reduction strategies related to dosing and their relation to harms among festival attendees who use multiple drugs. Drug and alcohol review 38(1): 57–67. https://doi.org/10.1111/dar.12868

ISSN 2282-0930 • Epidemiology Biostatistics and Public Health - 2024, Volume 19, Issue 2

Pollution in the Port Area and Respiratory Events in Santos, Sao Paulo, Brazil

Gerson Bauer[1], Elizabeth Barbosa de Oliveira-Sales[1], Paula Andrea de Santis Bastos[1]

(1) Postgraduation Program in Health and Environment, Universidade Metropolitana de Santos, Santos, SP, Brazil.

CORRESPONDING AUTHOR: Paula Andrea de Santis Bastos, Francisco Glicério Avenue, 8 - Encruzilhada, Santos - SP, ZIP code: 11045-002. Phone: +55 13 32283400. E-mail: paulaasbastos@gmail.com.

SUMMARY

Background: Port activities can cause negative socio-environmental impacts, with air quality degradation being one of them.
Objective: This study aimed to analyze a potential relationship between environmental air pollutants detected by the Environmental Company of the State of Sao Paulo (CETESB) air quality analysis station, located in Ponta da Praia, Santos and the occurrence of health events related to respiratory diseases.
Methods: At the CETESB "Santos – Ponta da Praia" station, from January 2021 to December 2022, monthly cumulative measurement of $PM_{2.5}$ and PM_{10}, SO_2, NO, NO_x and NO_2 inhalable particles were collected. Additionally, respiratory health events were verified through data from Unified Health System (SUS) database in the State of São Paulo from January 2021 to December 2022.
Results: The monthly averages SO_2 and NO_2 levels did not exceed the limits, but $PM_{2.5}$ levels exceed twice in July 2021 and 2022, and PM_{10} levels exceeded four times in May, June and July 2021 and July 2022. Although air quality measured by CETESB station was classified as good, a moderate correlation was identified between NO_2 emission and events of pneumonia, bronchitis, and chronic obstructive pulmonary disease events, especially among vulnerable population, up to 19 years old.
Conclusions: The results are significant for understanding the relationship between respiratory diseases and air pollution in the Port of Santos area.

Keywords: Port of Santos; Air quality; Inhalable gases and particles; Respiratory system diseases; Public health.

INTRODUCTION

The Port of Santos is the busiest in Latin America, the most significant in the Southern Hemisphere, serving as a gateway to South America. Given this, it is essential to note that port activities can lead to negative socio-environmental impacts, one of which is air quality deterioration [1,2,3], particularly from the atmospheric emissions of ships entering and leaving the Port of Santos [4,5].

Over the past few decades, increased international trade has resulted in higher tonnages of goods transported by ships, making maritime emissions a significant source of pollution. More than 80% of global trade is transported by sea in terms of tonnage, according to The International Council on Clean Transportation (ICCT) [6]. For more than 20 years, there have been indications that international maritime transport emits more environmentally impactful pollutants than estimated [7].

The effects of emissions from maritime traffic and cargo handling can affect and contaminate beaches, narrow channels, gulfs, sensitive ecosystems, and port workers, as well as the surrounding population, especially vulnerable groups such as elderly and children. A study conducted at the Port of Leixões, encompassing a resident population of 374,144 within the municipalities of Matosinhos, Leça da Palmeira, and Porto, revealed key findings regarding pollutant dispersion. Prevailing meteorological conditions, characterized by westerly-southwesterly winds (ocean to land) during the day and northeasterly winds (land to ocean) at night, suggest higher pollutant concentrations in the urban area near the port during daytime hours. Dispersion modeling algorithms confirmed that the dominant wind direction is responsible for transporting

DOI: 10.54103/2282-0930/26785
Accepted: 21th November 2024

pollutants over the surrounding area, particularly PM10 and NO_x. Berthed ships constitute the primary source of NO_x emissions, contributing over 50% to the measured concentrations [8]. This finding is corroborated by another study of four Portuguese ports, which attributed 73% of total NOx concentrations to berthed ships [9].

However, in the port environment, it is crucial to consider atmospheric pollutants from other sources, such as trucks, railroads and cargo-handling equipment, all powered by fossil fuels [10,11].

High concentrations of pollutants such as SO_x (Sulfur Oxides), NO_x (Nitrogen Oxides), and particulate matter (PM) have gained global attention due to their potential to exacerbate respiratory diseases, heart problems, hypertension -relates conditions, and even cancer, leading to premature death of affected populations [8,12].

A study investigating the associations between prenatal exposure to $PM_{2.5}$ and neonatal respiratory distress identified a strong link between $PM_{2.5}$ exposure and the need for assisted ventilation, multiple clinical interventions, and systemic antibiotic use in newborns [13].

A study in Turkey found a correlation between between air pollutants and respiratory diseases, where asthma symptoms in children were linked to SO_2 (sulfur dioxide) and PM10 concentrations, which were also associated with chronic obstructive pulmonary disease (COPD) in the elderly population [14].

Air quality standards (PQAr) represent the concentration of a specific pollutant in the atmosphere over a given time period and one of the tools for air quality management. The PQAR are defined by National Environment Council of Brazil - CONAMA Resolution No. 491/2018 [15] and CONSEMA Resolution No. 4/2021 [16]. Air quality, as established by State Decree No. 59,113/2013, can be classified as NI (good), N2 (moderate), N3 (Poor), N4 (very poor) and N5 (awful) [17].

Santos, with a population of 433,991 inhabitants (Brazilian Institute of Geography and Statistics -IBGE/2021), is home to a large port located in close proximity to residential areas, including vulnerable populations of elderly people, children and a large number of tourists, especially weekend and holiday [18].

Considering that the "Santos – Ponta da Praia" station is the CETESB station in Santos closest to the Port of Santos and can indicate the air quality of the port region and its surroundings, the objective of this work is to analyze a possible relationship between the environmental atmospheric pollutants detected by the CETESB air quality analysis station and the occurrence of respiratory diseases.

MATERIAL AND METHODS

This is a cross-sectional study and followed the reporting recommendations from the STROBE (Strengthening the reporting of observational studies in epidemiology) roadmap for observational studies [19].

Data was collected from the air quality monitoring station of CETESB and the SUS (Unified Health System) Department of Informatics database for the State of São Paulo. A total of 3,688 patients were included in the study.

The pollutants detected by the CETESB air quality analysis station located in Ponta da Praia in Santos from January 2021 to December 2022 were analyzed. The air quality monitoring (QUALAR) was carried out by the CETESB station called "Santos – Ponta da Praia". This mobile station is located at the Rebouças Sports Complex, Praça Eng. José Rebouças s/n, Ponta da Praia [19,20]. The station is configured to monitor the following pollutants relevant to this study: inhalable particles (PM_{10} and $PM_{2.5}$), SO_2 and nitrogen oxides (NO, NO_x and NO_2) [20, 21].

To verify the occurrence of respiratory diseases in the city of Santos, an observational and analytical study was carried out using the SUS database in the State of São Paulo through the TabNet DATASUS system (DATASUS, 2022). The data for respiratory diseases were collected according to the International Classification of Diseases and Related Health Problems, 10th Revision (ICD-10). Morbidity data for respiratory diseases (Chapter X of ICD-10), including pneumonia, bronchitis, and COPD, were examined by age group (children, adults, and elderly).

Subsequent statistical analysis was carried out using TIBCO Statistica™ version 14.0.0.15. The Kolmogorov-Smirnov test was used to assess data normality, and Pearson correlation was applied to examine the linear relationship between continuous variables. Statistical significance was set at p<0,05. Correlation magnitudes were classified as weak, moderate, or strong according to Cohen's scale [22].

RESULTS

Table 1 presents the monthly values of $PM_{2.5}$, PM_{10}, SO_2, NO, NO_x and NO_2 monitored by the CETESB station "Santos – Ponta da Praia" from January 2021 to December 2022.

According to CETESB's air quality classification, most measurements were within the "good" category (N1). Only $MP_{2.5}$ and MP_{10} presented some measurements with moderate air quality (N2): July and August 2021 and May to September 2022 for $MP_{2.5}$, and May to September 2021 and 2022 for MP_{10}. As of September 2021, MP_{10} has been rated as poor (N3).

As mentioned, the measurements of NO_2, NO, NO_x and SO_2 in the analyzed period remained at N1.

Table 1. Monthly average values (µg/m³) of pollutants monitored at the CETESB Station "Santos – Ponta da Praia" in the period from January 2021 to December 2022

	Jan 21	FeB 21	Mar 21	APr 21	May 21	Jun 21	Jul 21	AUg 21	SeP 21	OCt 21	Nov 21	DeC 21
MP_{10}	16	21	24	23	**37**	**34**	**37**	28	28	21	21	19
NO_2	19	25	23	24	31	27	36	29	26	20	20	22
NO	12	22	21	23	32	29	40	24	14	10	11	17
NO_x	20	31	29	31	43	38	52	35	25	19	19	26
$MP_{2,5}$	12	11	11	9	14	12	**18**	14	13	8	9	9
SO_2	1	2	2	2	3	2	3	2	1	1	2	2
	Jan 22	**FeB 22**	**Mar 22**	**APr 22**	**MaY 22**	**Jun 22**	**Jul 22**	**AUg 22**	**SeP 22**	**OCt 22**	**Nov 22**	**DeC 22**
MP_{10}	22	19	22	23	28	25	**36**	26	28	21	19	19
NO_2	25	26	27	26	34	34	41	38	35	27	24	23
NO	21	28	23	28	40	36	42	32	29	13	18	18
NO_x	31	37	33	37	51	47	56	46	43	25	28	27
$MP_{2,5}$	11	11	11	10	14	12	**17**	11	12	9	8	10
SO_2	3	3	2	2	3	2	3	3	2	2	3	2

Source: CETESB; Air quality information system – QUALAR.
Note: overtaking according to the current targets are indicated in bold

Figure 1. Pearson correlation (r) between monthly NO_2 values (µg/m³) monitored at the CETESB "Santos – Ponta da Praia" Station and hospital health events of (A) respiratory system diseases, (B) pneumonia and (C) bronchitis, emphysema, and other chronic pulmonary diseases according to the ICD-10 classification in the city of Santos\s.

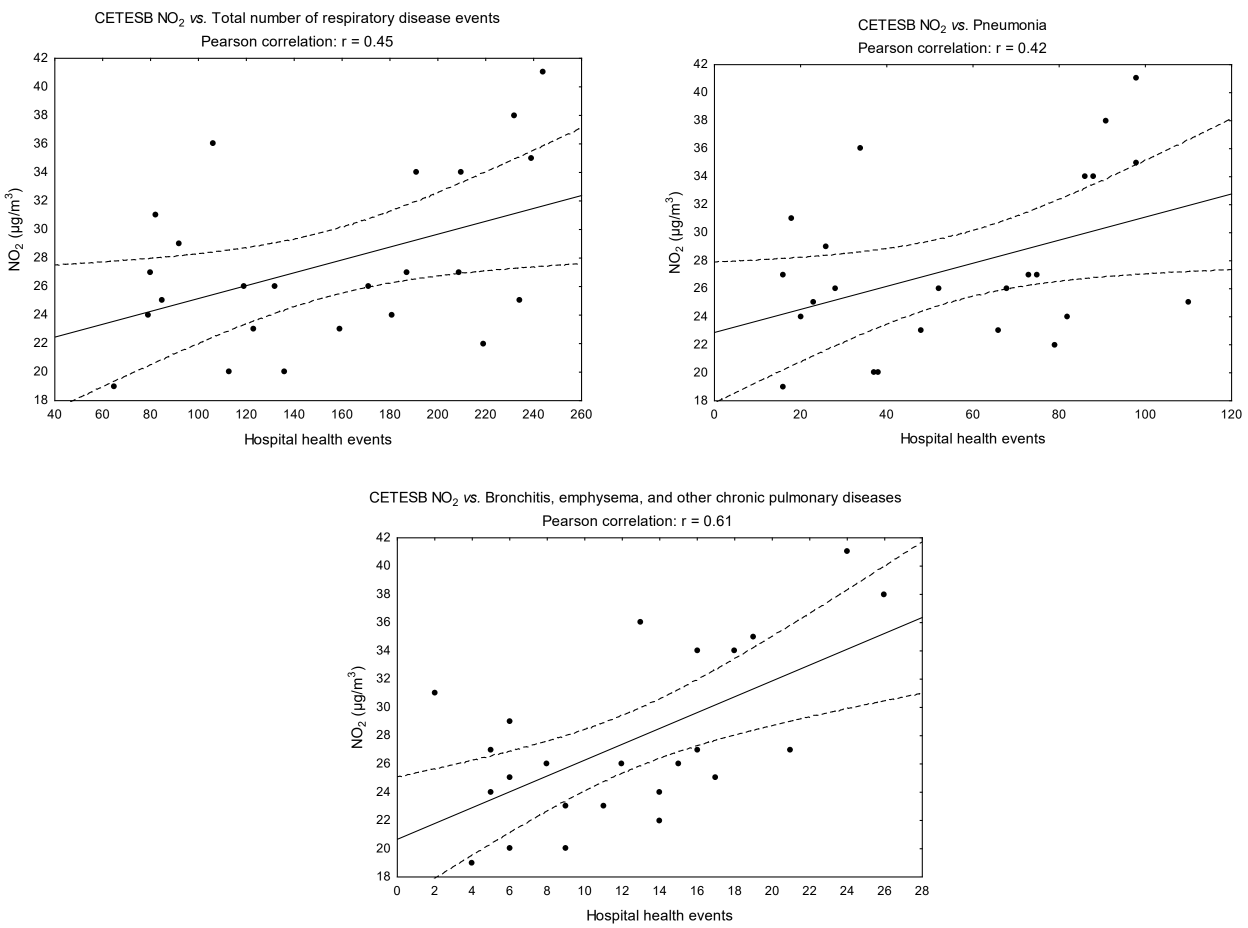


Table 2. Number of Respiratory System Disease Events (ICD-10 Chapter X) Registered in the SUS Database for the Municipality of Santos (SP), Brazil, from January 2021 to December 2022

ICD-10 List	**2021 Jan**	**2021 Feb**	**2021 Mar**	**2021 Apr**	**2021 May**	**2021 Jun**	**2021 Jul**	**2021 Aug**	**2021 Sep**	**2021 Oct**	**2021 Nov**	**2021 Dec**	**TOTAL**
Other diseases of the respiratory system	34	44	46	47	46	43	48	41	55	59	74	96	633
Pneumonia	16	23	48	20	18	16	34	26	28	38	37	79	383
Bronchitis, emphysema and other COPD	4	6	9	5	2	5	13	6	12	6	9	14	91
Acute bronchitis and acute bronchiolitis	3	10	15	3	6	6	8	12	5	1	6	17	92
Asthma	-	-	4	2	5	7	1	4	14	5	10	7	59
Other acute upper respiratory infections	-	-	1	-	1	-	-	-	1	1	-	1	5
Other diseases of the nose and paranasal sinuses	3	1	-	-	1	1	1	2	-	1	-	-	10
Other diseases of the upper respiratory tract	3	1	-	-	2	2	-	-	1	-	-	3	12
Bronchiectasis	-	-	-	2	1	-	-	-	-	1	-	-	4
Acute laryngitis and tracheitis	-	-	-	-	-	-	1	-	1	1	-	-	3
Chronic diseases of the tonsils and adenoids	2	-	-	-	-	-	-	1	-	-	-	1	4
Acute pharyngitis and acute tonsillitis	-	-	-	-	-	-	-	-	1	-	-	1	2
Pneumoconiosis	-	-	-	-	-	-	-	-	1	-	-	-	1
Respiratory system diseases (CID: J00-99)	65	85	123	79	82	80	106	92	119	113	136	**219**	1.299

ICD-10 List	**2022 Jan**	**2022 Feb**	**2022 Mar**	**2022 Abr**	**2022 May**	**2022 Jun**	**2022 Jul**	**2022 Aug**	**2022 Sep**	**2022 Oct**	**2022 Nov**	**2022 Dec**	**TOTAL**
Other diseases of the respiratory system	86	58	79	74	69	66	87	77	103	85	63	66	913
Pneumonia	110	52	73	68	86	88	98	91	98	75	82	66	987
Bronchitis, emphysema and other COPD	17	8	16	15	18	16	24	26	19	21	14	11	205
Acute bronchitis and acute bronchiolitis	14	12	12	11	27	9	20	10	3	7	12	10	147
Asthma	1	-	5	2	9	9	7	17	10	15	9	4	88
Other acute upper respiratory infections	1	1	-	-	-	1	5	5	4	2	-	2	21
Other diseases of the nose and paranasal sinuses	1	-	-	-	-	-	1	-	-	2	-	-	4
Other diseases of the upper respiratory tract	1	-	-	-	-	1	-	2	1	-	-	-	5
Bronchiectasis	1	-	-	-	-	-	-	-	-	1	-	-	2
Acute laryngitis and tracheitis	1	-	-	-	1	-	1	1	1	-	-	-	5
Chronic diseases of the tonsils and adenoids	-	1	1	1	-	1	1	-	-	1	1	-	7
Acute pharyngitis and acute tonsillitis	1	-	1	-	-	-	-	3	-	-	-	-	5
Pneumoconiosis	-	-	-	-	-	-	-	-	-	-	-	-	0
Respiratory system diseases (CID: J00-99)	**234**	132	187	171	**210**	191	**244**	**232**	**239**	**209**	181	159	2.389

Note: overtaking according to the current targets are indicated in bold

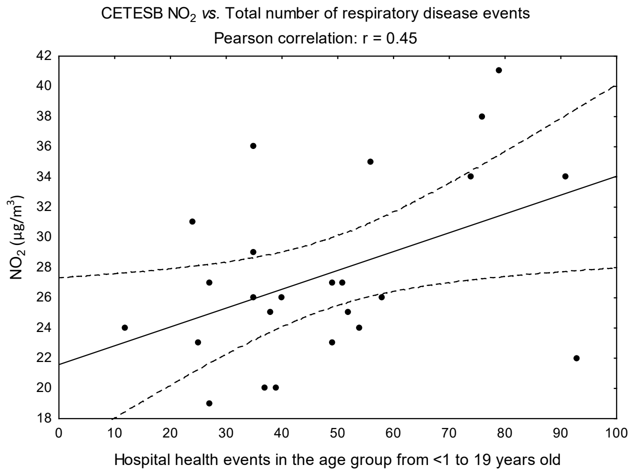
It is worth mentioning that the highest monthly average NO_2 values (n = 712) were observed between May and September 2021 and 2022.

Based on data from DATASUS, 3,688 respiratory health events were recorded in Santos from January 2021 to December 2022, excluding influenza and COVID-19. The data are presented in Table 2. The highest number of events occurred in December 2021 (>200/month, n = 219), January (n = 234), May (n = 210), July (n = 244), August (n = 232), September (n = 239) and October 2022 (n = 209). Most of these events affected children and adolescents (<1-19 years, n = 1156), followed by the elderly population (+60 years; n = 1549) compared to the adult population (20-59 years; n = 925).

The variables of health events classified in Chapter X of ICD-10 (1) pneumonia and bronchitis; (2) emphysema and other chronic lung diseases; and (3) total number of respiratory system diseases showed a significant association with NO_2 emissions ($p<0.05$; Figure 1A, Figure 1B and Figure 1C). The results reveal that the values of the air pollutant NO_2 and the number of bronchitis, emphysema and other chronic pulmonary diseases have a strong ($r = 0.61$) and statistically significant association ($p<0,05$).

Pearson's correlation analysis showed a moderate and statistically significant association ($p<0.05$) between NO_2 emission in the air and the total number of respiratory events from January 2021 to December 2022 in the population up to 19 years old ($r = 0.45$) (Figure 2). No significant differences were obtained between the NO_2 emission in the air and the total number of respiratory events in the adult and elderly populations (data not shown).

Figure 2. Pearson correlation (r) between monthly NO_2 values (µg/m³) monitored at the CETESB Station "Santos – Ponta da Praia" with hospital health events in the age group from <1 to 19 years old



DISCUSSION

Data from DATASUS (January 2021–December 2022) reveal a higher incidence of respiratory diseases (excluding influenza and COVID-19, based on ICD-10 classifications) in specific months: December 2021, and January, May, July, August, September, and October 2022. Children, adolescents, and the elderly experienced a disproportionately higher number of these events compared to adults, highlighting their increased vulnerability and the need for targeted health interventions. This aligns with research from Turkey linking air pollutants to respiratory problems, particularly asthma in children and COPD in the elderly, correlating with SO_2 and PM_{10} concentrations [14,23]. Similarly, a study in the ports of Copenhagen and Elsinore found that PM_{10} accumulation caused health issues, prompting recommendations for reducing NO_x and PM_{10} emissions from ships and monitoring pollutant levels near ports [24].

Our findings show that monthly average $PM_{2.5}$ and PM_{10} levels in Santos frequently exceeded national and state air quality standards (CONSEMA Resolution No. 4/2021, IT-3) during the study period, especially in July—coi ncidentally the month with the highest number of ship dockings in 2022. While overall air quality was generally good, $PM_{2.5}$ and PM_{10} levels reached moderate and even poor classifications (September 2022 for PM_{10}) during several months. It's crucial to consider both ship-based and land-based sources (trucks, railroads, cargo handling, storage) as contributors to PM_{10} emissions in port environments [10,11]. A study by Sarra and Mülfarth (2021) specifically linked PM_{10} emissions in the Ponta da Praia area to grain handling and transportation [5].

The CETESB "Santos – Ponta da Praia" station monitors pollutants relevant to vehicular and overall public health concerns, including $PM_{2.5}$, PM_{10} , SO_2, NO, NO_x, and NO_2 [25,26]. Our analysis revealed a moderate, statistically significant correlation between NO_2 emissions and respiratory events in the susceptible population under 19 years old, and between NO monitored by CETESB and acute bronchitis/bronchiolitis. This underscores the importance of addressing port-related pollution, given the potential exposure of both port workers and nearby residents. Studies from Ambarli port in Turkey [27] and by Sarra and Mülfarth [5] further emphasize the contribution of bulk solid handling to air pollution and increased respiratory health risks. Previous research in Santos [28] found no association between calculated NO_x and respiratory diseases but did observe a correlation between CETESB-monitored NO_x and conditions like acute bronchitis/bronchiolitis and chronic pulmonary diseases.

The Port of Santos's proximity to urban areas, including vulnerable populations (elderly, children) and a substantial tourist influx, amplifies its socio-environmental responsibilities [18]. Globally, ship emissions contribute significantly to premature deaths from cardiorespiratory issues and lung cancer [29]. A study in China's Pearl River Delta highlighted the negative health impacts of marine emissions, particularly near ports, and suggested that adhering to MARPOL standards could mitigate these effects [29]. Therefore, stringent regulation and supervision of the Port of Santos are essential to protect both port workers and the surrounding community [30].

CONCLUSION

While overall air quality in Santos was generally good, $PM_{2.5}$ and PM_{10} levels frequently exceeded air quality targets, particularly during periods of high ship activity. Although no statistically significant correlation was found between PM emissions and overall respiratory events, a moderate correlation was observed between NO_2 emissions and respiratory events in the vulnerable under-19 population. Furthermore, a moderate correlation was found between monitored NO and specific respiratory illnesses like acute bronchitis and bronchiolitis. These findings highlight the complex relationship between respiratory health and air pollution in the Port of Santos region, emphasizing the need for continued monitoring, targeted interventions for vulnerable populations, and strategies to mitigate emissions from both ship and land-based sources.

REFERENCES

1. Gonçalvez A, Nunes LAP. O Grande Porto – A modernização no Porto de Santos. 1st ed. Santos: Realejo, 2008.
2. Zempulski TL. Direito Marítimo e Portuário. 1st ed. Curitiba: Intersaberes, 2022.
3. Santos Port Authority. Fatos e Dados. Santos. 2023 [internet]. Available at: https://www.portodesantos.com.br/fatos-e-dados/.
4. Pimenta MV, Martins MM. Combustíveis marítimos alternativos: relevância e viabilidade. Rev Direito Neg Int Marit Law 2021;1(2):32-53.
5. Sarra SR, Mülfarth RCK. A poluição atmosférica na cidade de santos (Estado de São Paulo - Brasil) e suas repercussões para a saúde / Atmospheric pollution in the city of santos (State of São Paulo - Brasil) and its impacts on health. Braz J Develop 2021 Nov 4;7(11):101963-101981.
6. The International Council on Clean Transportation, Air Pollution and Greenhouse Gas Emissions from Oceangoing Ships: Impacts, Mitigation Options and Opportunities for Managing Growth (2007). Available at: https://theicct.org/sites/default/files/publications/oceangoing_ships_2007.pdf.
7. Corbett JJ, Fischbeck PS, Pandis SN. Global nitrogen and sulfur inventories for oceangoing ships. J Geophys Res Atmos 1999;104(D3):3457–3470.
8. Sorte S, Arunachalam S, Naess B, Seppanen C, Rodrigues V, Valencia A et al. Assessment of source contribution to air quality in an urban area close to a harbor: Case-study in Porto, Portugal. Sci Total Environ 2019; Apr 20;662:347–360.
9. Nunes R, Alvim-Ferraz MCM, Martins F, Sousa S. Assessment of shipping emissions on four ports of Portugal. EP 2017:1-17.
10. HuiHuang T, Wang YM. Influence of vessel upsizing on pollution emissions along Far East-Europe trunk routes. Environ Sci Poll Res 2022; 29:65322–65333.
11. Corbett, J.J. and Koehler, H.W. Updated Emissions from Ocean Shipping. J. Geophys. Res 2003; 108(D20):4650.
12. Mattos AM. Os novos limites dos espaços marítimos nos trinta anos da convenção das nações unidas sobre o direito do mar. In: Beirão AP, Pereira ACA, editors. Reflexões sobre a Convenção do Direito do Mar. Brasília: FUNAG, 2014.
13. Johnson M, Mazur L, Fisher M, Fraser WD, Sun L, Hystad P, Gandhi CK. Prenatal Exposure to Air Pollution and Respiratory Distress in Term Newborns: Results from the MIREC Prospective Pregnancy Cohort. Environ Health Perspect. 2024;132(1):17007. doi: 10.1289/EHP12880. Epub 2024 Jan 25. PMID: 38271058; PMCID: PMC10810300.
14. Arslan H, Baltaci H, Sahin UA, Onat B. The relationship between air pollutants and respiratory diseases for the western Turkey. Atmos Pollut Res 2022;13(2):101322.
15. Brasil. Ministério do Meio Ambiente. Conselho Nacional do Meio Ambiente: Resolução CONAMA nº 491, de 19 de novembro de 2018. Available at: http://conama.mma.gov.br/atos-normativos-sistema.
16. São Paulo. Secretaria de Estrutura e Meio Ambiente. Conselho Estadual do Meio Ambiente: Deliberação CONSEMA nº 04, de 19 de maio de 2021. São Paulo: Conselho Estadual do Meio Ambiente (2021).
17. São Paulo. Decreto nº 59.113, de 23 de abril de 2013. São Paulo: Assembleia Legislativa do Estado de São Paulo (2013).
18. Santos Port Authority. Relatório anual de 2022. Santos. 2023. Available at: https://www.portodesantos.com.br/informacoes-financeiras/relatorios-anuais/.
19. von Elm, E, Altman, DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke, JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. Ann Intern Med 2007;147(8), 573-577. PMID: 17938396
20. Companhia Ambiental do Estado de São Paulo. Qualidade do ar no estado de São Paulo 2022. São Paulo: CETESB. 2023. Available at: https://cetesb.sp.gov.br/ar/.
21. Companhia Ambiental do Estado de São Paulo. Qualidade do ar: redes de monitoramento. Available at: https://cetesb.sp.gov.br/ar/redes-de-monitoramento/.
22. Cohen J. Statistical power analysis for the behavioral sciences. 2nd rev ed. New York: Routledge, 1988.
23. Deniz C, Durmuşoğlu Y. Estimating shipping emissions in the region of the Sea of Marmara, Turkey. Sci Total Environ 2008 Feb 1;390(1):255–261, 2008.
24. Saxe H, Larsen T. Air pollution from ships in three Danish ports. Atmos Environ 2004;38(24):4057–4067.
25. World Health Organization Regional Office for Europe. Air Quality Guidelines – Global Update 2005. Particulate Matter Ozone Nitrogen Dioxide and Sulphur Dioxide. Copenhagen: World Health Organization Europe. 2008.
26. Deniz C, Kilic A. Estimation and assessment of shipping emissions in the region of Ambarlı Port, Turkey. Environ Prog Sustain Energy 2010 Mar 8;29(1):107–115.
27. World Health Organization. WHO global air quality guidelines: particulate matter ($PM_{2.5}$ and PM_{10}), ozone, nitrogen dioxide, sulfur dioxide and carbon monoxide. Geneve: World Health Organization. 2021.
28. Bauer, G.; Oliveira-Sales, E. B. De; Ramires, R. H. De P.; Maquigussa, E.; Bastos, P. A. de S. The emission of NO_x generated by ships in the Port of Santos and the occurrence of health events related to respiratory diseases in Santos's Municipality. Res Soc Dev 2024; 13(7): e6713746311 DOI: 10.33448/rsd-v13i7.46311.
29. Lai HK, Tsang H, Chau J, Lee CH, McGhee SM, Hedley AJ et al. Health impact assessment of marine emissions in Pearl River Delta region. Mar Pollut Bull 2013 Jan 15;66(1-2):158-163.
30. Santos THD. Relação porto-cidade: sustentabilidade Porto de Santos. Santos, SP [Dissertation]. Santos: Universidade Católica de Santos, 2020.

Unveiling the Underlying Severity of Multiple Pandemic Indicators

Manuela Alcañiz[(1)], *Marc Estevez*[(1)], *Miguel Santolino*[(1)]

(1) RISKcenter – Research Institute in Applied Economics (IREA), Dept. Econometrics, Statistics and Applied Economy, Universitat de Barcelona (UB), Spain.

CORRESPONDING AUTHOR: Manuela Alcañiz, Address: Av. Diagonal, 690, 08034 Barcelona, Spain. e-mail: malcaniz@ub.edu. Tlf.: +34934021983.

SUMMARY

Background: Multiple interconnected key metrics are frequently available to track the pandemic progression. One of the difficulties health planners face is determining which provides the best description of the status of the health challenge.
Methods: The aim of this study is to capture the information provided by multiple pandemic magnitudes in a single metric. Drawing on official Spanish data, we apply techniques of dimension reduction of time series to construct a synthetic pandemic indicator that, based on the multivariate information, captures the evolution of disease severity over time. Three metrics of the evolution of the COVID-19 pandemic are used to construct the composite severity indicator: the daily hospitalizations, ICU admissions and deaths attributable to the coronavirus. The time-varying relationship between the severity indicator and the number of positive cases is investigated.
Results: A single indicator adequately explained the variability of the three time series during the analyzed period (May 2020–March 2022). The severity indicator was stable until mid-March 2021, then fell sharply until October 2021, before stabilizing again. The period of decline coincided with mass vaccination. By age group, the association between underlying severity and positive cases in those aged 80+ was almost 20 times higher than in those aged 20-49.
Conclusion: Our methodology can be applied to other infectious diseases to monitor their severity evolution with a single metric. The synthetic indicator may be useful in assessing the impact of public health interventions on reducing disease severity.

Keywords: Factor analysis; Principal component analysis; Pandemics; Vaccination.

INTRODUCTION

One of the difficulties for health planners in monitoring an ongoing disease over time is deciding which metric best describes its status when several interrelated measures are available [1]. In this context, methods for dimension reduction of multiple time series can be very important to find lower-dimensional representations of multiple (correlated) measures. One of the most popular techniques for dimension reduction of time series was proposed by Brillinger, who defined dynamic principal components (DPC) based on the criterion of optimal reconstruction of the original time series [2]. Peña et al generalised the concept of dynamic principal components by relaxing the assumption that the components are linear combinations of the data [3]. They called this method one-sided dynamic principal components (ODPC).

In this study, we illustrate the application of the ODPC methodology to construct a synthetic pandemic indicator that, based on multivariate information, captures the evolution of disease severity over time in a single magnitude. We focus on the coronavirus (COVID-19) pandemic declared by the World Health Organization in 2020. Most people infected with the SARS-CoV-2 virus experienced mild to moderate respiratory illness and recovered without needing hospitalization; however, a significant number fell seriously ill and required regular hospitalization or admission to an intensive care unit (ICU). Some failed to survive the disease.

DOI: 10.54103/2282-0930/27157
Accepted: 10th December 2024

Previous research has mainly attempted to assess the evolution of disease severity based on single COVID-19 indicators, addressing, for example, the number of hospital admissions [4-6], hospital bed occupancy [7,8], the number of ICU admissions [9-11], ICU bed occupancy [12-14], or the number of deaths [15-17]. Other studies have used multivariate principal component techniques, but again focusing on a single COVID-19 indicator, albeit for multiple countries, to cluster countries according to their similarities in the evolution of the pandemic [18-20].

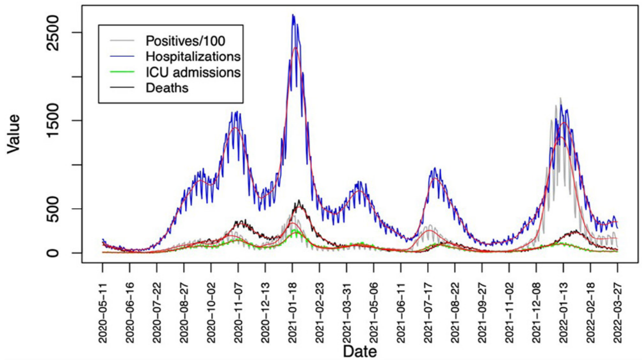
Here, we undertake a joint analysis of three COVID-19 severity indicators: namely, the number of hospitalizations, the number of ICU admissions and the number of deaths. We aim to explore whether applying the ODPC methodology to official Spanish data from May 2020 to March 2022 results in a single component capable of explaining the joint evolution of the three disease-severity time series. This would, first, provide us with a component that reveals the underlying severity of COVID-19 and, second, enable us to analyze in a straightforward fashion the relationship between the synthetic indicator proposed and the number of COVID-19 positive cases detected at each point in time, considering the Spanish population as a whole and by age groups. To analyze how the underlying severity indicator and the number of positive cases are related, a time-varying coefficient linear model (TVLM) is applied [21].

METHODS

Data

In conducting this study, free-access datasets have been used. The daily number of COVID-19 detected cases, hospital admissions, ICU admissions and deaths were obtained from the Spain's National Centre of Epidemiology [22]. Data for each time series is disaggregated by province, age, and gender from May 11, 2020 to March 27, 2022. Multiplicative weekly seasonality was observed, with lower values during weekends. Seasonal effects were adjusted using the LOESS method for seasonal-trend decomposition (STL) [23]. Additionally, the Nadaraya–Watson kernel smoother was applied to remove the noise of the resulting time series [24,25]. Figure 1 displays the original and smoothed COVID-19 time series for the observation period. Stationarity of the time series was investigated to avoid spurious results when analysing the association between time series [26]. After removing weekly seasonality and noise from the original COVID-19 indicators, the stationarity of the resulting time series was confirmed using the augmented Dickey-Fuller (ADF) test.

Figure 1. Original COVID-19 time series with smoothed values (red lines) for Spain. Period from May 11, 2020 to March 27, 2022



One-sided dynamic principal components

Dimension reduction is critical in multivariate vector time series for finding simplifying structures or factors. The application of ODPC is useful when the variability of different time series can be explained with a small number of components. This occurs when time series are highly correlated. Consider the vectors of stationary time series $\boldsymbol{z}_1,\ldots,\boldsymbol{z}_T$, with $\boldsymbol{z}_T=(z_{t,1},\ldots,z_{t,m})'$, t=1,…,*T*. The ODPC can be defined as linear combinations of present and previous values of the series that minimize the mean squared error of the reconstruction. We define the first one-sided dynamic principal component as:

$$f_t(\boldsymbol{a}) = \sum_{h=0}^{k_1} \boldsymbol{z}'_{t-h}\boldsymbol{a}_h, \quad t = k_1+1,\ldots,T \qquad (1)$$

where $\boldsymbol{a}'=(\boldsymbol{a}'_0, \ldots, \boldsymbol{a}'_{k1})$ being $\boldsymbol{a}'_h=(\boldsymbol{a}'_{h,1}, \ldots, \boldsymbol{a}'_{h,m})$, h = 0,…, k_1, the coefficients associated with the lagged values of the time series, and $k_1 \geq 0$ an integer denoting the number of lags used to compute the dynamic principal component. Only the first component is shown, given that it is the only one computed in this study [3].

Then, defining a matrix $\boldsymbol{B}'=[\boldsymbol{b}_0, \ldots, \boldsymbol{b}_{k2}]$, $\boldsymbol{b}_h \in \mathbb{R}^m$, h = 0,…, k_2, the lagged values of the dynamic principal component can be used to reconstruct the original time series $\boldsymbol{z}_T$ as

$$\boldsymbol{z}_t^R(\boldsymbol{a},\boldsymbol{B}) = \sum_{h=0}^{k_2} \boldsymbol{b}_h f_{t-h}(\boldsymbol{a}), \quad t = k_1+k_2+1,\ldots,T \qquad (2)$$

where $k_2 \geq 0$ is an integer indicating the number of lags of the principal component to be used in the reconstruction. Note that if $k_1 = k_2 = 0$, the first ODPC is simply the first ordinary principal component of the data.

The mean squared error (MSE) in the reconstruction of the data is defined as

$$MSE(\boldsymbol{a},\boldsymbol{B}) = \frac{1}{T'm}\sum_{t=(k_1+k_2)+1}^{T} ||\boldsymbol{z}_t - \boldsymbol{z}_t^R(\boldsymbol{a},\boldsymbol{B})||^2$$

where $T' = T - (k_1 + k_2)$ and $\|\cdot\|$ is the Euclidean norm. The optimal values $(\hat{a}, \hat{B})$ of $\boldsymbol{a}$ and $\boldsymbol{B}$ satisfy

$$(\hat{\boldsymbol{a}}, \hat{\boldsymbol{B}}) = \min_{\|\boldsymbol{a}\|=1, \boldsymbol{B}} MSE(\boldsymbol{a}, \boldsymbol{B})$$

An alternating least-squares algorithm defined in Peña et al. [27] can be used to estimate the parameters. In practice, the number of lags (k_1,k_2) need to be chosen. One possible approach to selecting them is to minimize the cross-validated forecast error in a stepwise manner. Consider the *h*-steps ahead forecasts and specify a maximum number of lags and the size of the rolling window used to estimate the forecast error *w*. Then, the first component is computed for each combination of lags up to the maximum number considered, using periods $1,\dots,T-h-t+1$ for $t = 1,\dots,w$. The mean squared prediction error of the *h*-steps ahead forecasts is then calculated for each combination of lags. The number of lags chosen is the one that minimizes the mean squared prediction error. If more than one component is considered, the procedure would be repeated, including the additional component(s) progressively, in order to select the optimal lags and the optimal number of components. The previous stepwise approach could be used to minimize an information criterion instead of the cross-validated prediction error [3].

RESULTS

The analysis was conducted using the R software [28].

Synthetic indicator of underlying severity

High pairwise correlation coefficients were obtained between the number of hospital admissions, ICU admissions and number of deaths, with values between 0.87 and 0.95. Thus, we performed an ODPC analysis to construct a single severity indicator capable of capturing the information from these three COVID-19 series. After rescaling the three time series, the number of lags has to be selected and the parameters estimated. A maximum of 10 lags was considered for the selection of the optimal number of lags. The *h*-steps ahead forecast and the window size chosen were one and ten, respectively.

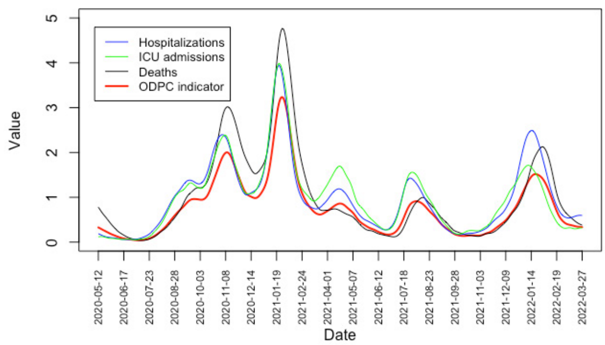
The number of lags that minimized the mean squared error of prediction was one. The estimated coefficients of vector $\boldsymbol{a}$ were:

$$\hat{\boldsymbol{a}}' = (0.03 \quad -0.4 \quad -0.21 \quad 0.22 \quad 0.65 \quad 0.52)$$

This vector $\hat{\boldsymbol{a}}$ contains the estimated weights in the linear combination to construct the dynamic principal component in (1), which captures the underlying severity of COVID-19. Its first three values are the coefficients associated, respectively, with the number of hospitalizations, ICU admissions and deaths in period *t*, while the following three coefficients are those associated with the one-lagged values of the same series.

The MSE of the optimal ODPC was 0.031. This value is considerably lower than the MSE associated with one component in non-dynamic principal components analysis (0.051). The optimal model explained 95.83% of the variability in the three corrected severity time series. Figure 2 shows the three standardized series used to capture the severity of COVID-19, along with the component obtained from the ODPC analysis, which captures this evolution in a synthetic indicator.

Figure 2. Standardized smoothed COVID-19 time series and ODCP indicator for underlying severity. Period from May 11, 2020 to March 27, 2022



The number of positive cases diagnosed showed a moderate correlation with hospital admissions (0.56), ICU admissions (0.36), and deaths (0.30), suggesting that disease severity varies over time. This moderate correlation between positive cases and other indicators is also evident in Figure 1.

Reconstruction and prediction of severity indicators

The underlying severity indicator can be used with matrix $\hat{\boldsymbol{B}}$ to reconstruct the standardized corrected COVID-19 time series, as shown in (2). The resulting estimation of matrix $\boldsymbol{B}$ was the following:

$$\hat{\boldsymbol{B}} = \begin{pmatrix} 7.94 & -6.77 \\ 6.80 & -5.66 \\ -1.81 & 3.31 \end{pmatrix}$$

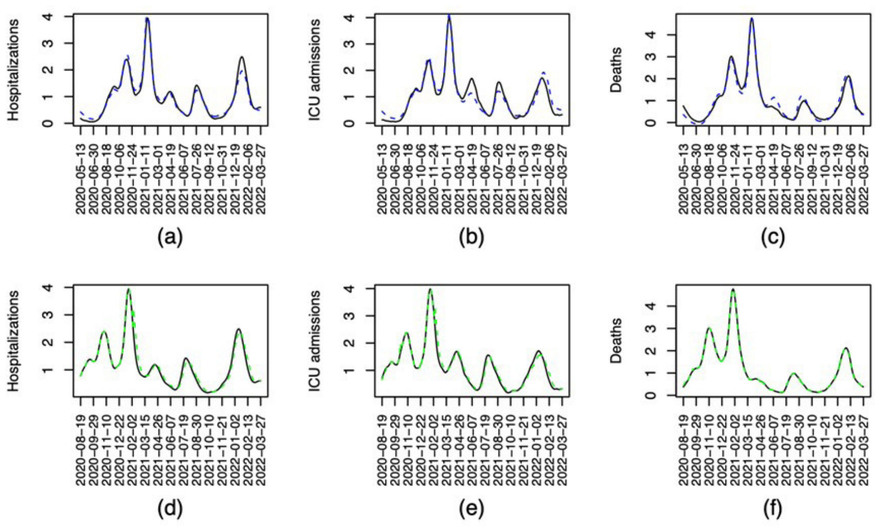
Thus, to reconstruct the hospitalization and ICU admissions time series, the underlying severity indicator has to be multiplied by a positive scalar (7.94 and 6.80, respectively) and the one-lagged indicator by a negative scalar (-6.77 and -5.66, respectively). The series of deaths, on the other hand, is reconstructed by multiplying the underlying severity indicator by a negative scalar (-1.81) and the one-lagged indicator by a positive scalar (3.31). The differing signs of the coefficients for reconstructing these original time series indicate that deaths follow hospital and ICU admissions. Unlike non-dynamic principal components, the flexibility of ODPC captures this sequentiality between the time series.

The reconstructed standardized time series of the number of hospitalizations, ICU admissions and deaths are shown in Figure 3 (upper panel). Note that an accurate reconstruction of these three COVID-19 time series is achieved, particularly for hospitalizations and deaths. The MSE was 0.022 for the number of hospital admissions, 0.038 for the number of ICU admissions and 0.033 for the number of deaths. The underlying severity indicator can then be used to predict the number of hospitalizations, ICU admissions, and deaths. Alternative prediction models for pandemic values have been used in the literature [4,29]. Here, time series forecasting of the future behaviour of the severity indicator is conducted using a SARIMA model, as recommended by Peña et al [27].The predicted severity indicator is multiplied by $\hat{B}$ to reconstruct the forecasted COVID-19 time series. SARIMA-based forecast residuals are included in the predictions of the COVID-19 time series. Based on the first one hundred observations made in the period of study, one-step-ahead predictions of the number of hospitalizations, ICU admissions and deaths were performed from August 19, 2020 to March 27, 2022. These results are shown in Figure 3 (lower panel). A good forecasting performance is observed. When comparing actual observations with the predicted values, the mean squared prediction error was 0.028 for the number of hospital admissions, 0.019 for the number of ICU admissions and 0.001 for the number of deaths.

Association between positive cases and underlying severity

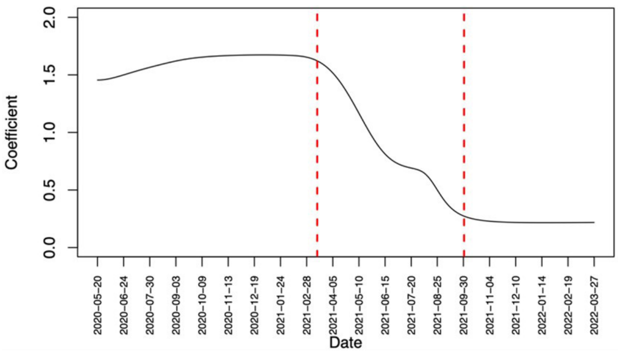
A TVLM is used to analyze the relationship between the underlying severity indicator and the daily number of coronavirus cases detected. Compared to the classical linear model, the TVLM is characterised by allowing the coefficient associated with the independent variable to vary over time [21,30]. As symptoms of severity usually appear later than the onset of the disease [4], we examine the correlation between the underlying severity indicator and the lagged series of positive cases. The highest correlation with the underlying severity indicator was observed for the number of positive cases with eight lags. Therefore, the explanatory variable included in the TVLM is the eight-lagged number of positive cases, as follows, $\mathbf{y}_t=\mathbf{x}_{t-8}\beta_t+\varepsilon_t, t=9,\ldots,T$, where $\mathbf{y}_t$ corresponds to the estimated underlying severity indicator at time t, the regressor $\mathbf{x}_{t-8}$ is the rescaled (to be centred in one) number of diagnosed cases at time t-8 and ε_t is the error term. This model is best estimated using a combination of ordinary least squares and the local polynomial kernel estimator [31]. A bandwidth must be selected to indicate the size of the window in which weighted local regressions are estimated [32]. The chosen bandwidth (0.25) prevented the particular phase of the pandemic wave from affecting the estimation of the time-varying coefficient.

Figure 3. Reconstructed and predicted COVID-19 smoothed time series for Spain. Figures (a), (b) and (c) show the rescaled smooth original time series (black) and reconstructed time series (dashed blue) of COVID-19 for the period May 13, 2020 to March 27, 2022. Figures (d), (e) and (f) show the rescaled smooth original time series (black) and the predicted time series (dashed green) of COVID-19 for the period from August 19, 2020 to March 27, 2022



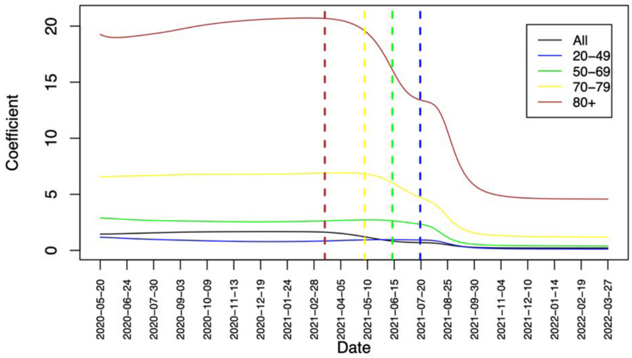
The estimated model has a good explanatory capacity (pseudo-R^2=0.93). The estimated vector of coefficients β_t contains values from 0.22 (minimum) to 1.67 (maximum), with a mean value of 1.04 and a median of 1.37. Figure 4 shows this evolution over the study period. It can be observed that the relationship between the underlying severity and the number of positive cases is quite stable until around mid-March 2021. Up to that point, the estimated coefficient is almost constant around 1.5, before it falls sharply. The drop in value of the coefficient and, therefore, in the expected underlying severity of COVID-19, continues until the beginning of October 2021. After this date, the coefficient value stabilizes at around 0.22 until the end of the period.

Figure 4. Estimated time-varying coefficient of the regression model in which the underlying COVID-19 severity is regressed on the rescaled series of positive cases. Red dashed lines are set at March 15, 2021 and October 1, 2021



To conclude, the underlying severity indicator and its relationship with the number of positives is estimated for the following age groups: 20–49, 50–69, 70–79 and 80 years or more (80+). To obtain comparable results, COVID-19 time series by age group were rescaled by the expected value of the time series for the whole population. Figure 5 shows the estimated coefficients of the TVLM between underlying severity and the number of positive cases in each age group. First, time varying coefficients seem clearly associated with age. Note that the estimated coefficients are higher for the older age groups at any point in time, particularly for the 80+ age group. In addition, all age group coefficients present the same 'constant-drop-constant' pattern, albeit at different moments in time: the younger the age group, the later the drop in the coefficient value begins. In Figure 5, the approximate date when the time-varying coefficient associated with each age group starts to decrease is indicated with a dashed vertical line – March 15, 2021 for the 80+ population (vaccination rate of 23.8%, brown dashed line); May 7, 2021 for 70-79 age interval (37.22%, yellow); June 13, 2021 for the 50–69 age interval (32.8%, green); and July 17, 2021 for the 20–49 age group (37.79%; blue).

Figure 5. Estimated time-varying coefficients for age-group based regression models in which the underlying COVID-19 severity is regressed on the rescaled series of positive cases. Brown, yellow, green and blue dashed lines are set at March 15, 2021; May 7, 2021; June 13, 2021 and July 20, 2021, respectively



DISCUSSION

Policy decisions by public health authorities during a pandemic are based, at least in part, on the evolution of disease severity indicators. Traditionally, these indicators are analyzed individually [10,13,33]. However, here, dynamic principal component techniques were used to synthesize the information from a set of highly correlated indicators, aiming to monitor their evolution with a single metric that can capture the underlying severity of the pandemic.

In this research, we demonstrate that one-sided dynamic principal components, when used to reduce the dimensionality of COVID-19 metrics, accurately capture serial dependence of time series. Moreover, this methodology performs well in forecasting, helping to anticipate future epidemic outcomes [34,35]. Previous studies reporting the dimensional reduction of a set of COVID-19 indicators are scarce. One exception is Swallow et al [1], who conducted their static principal component analysis to a set of COVID-19 indicators in the United Kingdom. We believe our approach may facilitate the interpretation of results when there is sequentiality in the time series data, as observed here with deaths following hospitalizations and ICU admissions.

We found that the relationship between the number of positives and the underlying severity indicator was almost constant until March 2021, showing a high linear correlation between these indicators during that period. However, as of March 2021, the relationship steadily decreased until October 2021, reflecting a decline in the consequences for the population with a positive diagnosis. From October 2021 onwards, the relationship between these metrics was once again constant over time, albeit at a much lower intensity. The period marked by a fall in the estimated association broadly coincided with the mass vaccination of the Spanish population [36]. Many studies have highlighted the effectiveness of vaccination against the serious health consequences associated with COVID-19 [37,38].

Age is a well-known risk factor for serious illness or death after SARS-CoV-2 infection [39]. In our study, we detected three relevant features associated with age. First, older age groups presented higher values of the underlying severity indicator for the same number of people diagnosed with COVID-19, with this ratio being especially high for those over eighty. Second, the same pattern – a decrease in the severity of COVID-19 depending on the number of positive cases after a period of stable association – was observed in all age groups; however, the older the group, the earlier the onset of the fall in the coefficients of the relationship between positives and underlying severity. This could be at least partially attributable to the fact that Spain's vaccination program was initiated among the oldest age groups, with vaccines being made progressively available to younger groups once a high percentage of older people had been vaccinated. Third, the reduction in underlying severity associated with positive diagnoses was more intense (in absolute numbers) with increasing age. However, if we analyze the reduction in relative terms, we find that this association fell by 84% among those aged 20 to 49, by almost 83% among those aged 50 to 69, by almost 80% among those aged 70 to 79, and by 75% in those aged over eighty, indicating that the relative reduction was lower among the older age groups [40,41].

This study is not free of limitations. In constructing the composite index of underlying severity, it would be useful for health decision-making in pandemic settings if the single metric could include more information. We use publicly available Spanish data from the National Centre of Epidemiology [22] from 2020 to 2022. The selection of only three time series in the construction of the single metric was due to the availability of reliable information from the Spanish surveillance system. However, we do not include potentially important variables in the analysis such as excess of mortality, vaccination rate [5], or socio-economic factors [42] of the population under study. In addition, all three time series are considered equally important, but hospitalizations, ICU admissions, and deaths reflect different levels of coronavirus severity. This limitation could be overcome by using time series dimensional reduction techniques that weight the different severities according to health decision-maker criteria. Finally, the underlying severity index is certainly useful for analysing the evolution of the indicators during the observation period, although its value is not easily and directly interpretable, as the reconstruction of the coronavirus time series involves the underlying severity indicator and its one period lagged value.

The methodology used in this research to create a synthetic metric of pandemic severity can be applied to other areas of public health. Multiple interconnected metrics are frequently available in relation to public health issues, and one difficulty health planners face is determining which best describes the health challenge status. This study shows how these alternative metrics can be unified while retaining most of their information, thus providing policymakers with a single metric that describes the health issue's severity and enables them to monitor disease evolution. Analysis of this synthetic indicator can be useful, for example, in assessing the impact of health interventions such as vaccination in reducing disease severity. Health policymakers will be interested in monitoring the evolution of the severity indicator and its relationship with the vaccination coverage of the population in order to evaluate the effectiveness of vaccination policies. Another relevant application for health policymakers is to examine the relationship between the synthetic severity indicator of a disease and alternative socio-economic factors when analyzing the evolution of the disease in different regions and/or population groups.

FUNDING

This study was supported by the Spanish Ministry of Science and Innovation under grant PID2019-369 105986GB-C21, and by the Catalan Government under grants 2020-PANDE-00074 and 2023-CLIMA-00012.

ACKNOWLEDGEMENTS

The authors wish to express their gratitude to Dr. Montserrat Guillen, Director of RISKcenter at the University of Barcelona, for her assistance in the development of this project. The authors are grateful to the editor and the anonymous referees for their helpful comments.

COMPETING INTERESTS

The authors declare no competing interests.

REFERENCES

1. Swallow B, Xiang W, Panovska-Griffiths J. Tracking the national and regional COVID-19 epidemic status in the UK using weighted principal component analysis. Phil Trans R Soc A. 2022;380(2233). doi: 10.1098/rsta.2021.0302.
2. Brillinger DR. Time series: data analysis and theory. San Francisco: Holden-Day, 1981.
3. Peña D, Smucler E, Yohai VJ. Forecasting multiple time series with one-sided dynamic principal compo-

nents. J Am Stat Assoc. 2019;114(528):1683-94. doi: 10.1080/01621459.2018.1520117.
4. Santolino M, Alcañiz M, Bolancé C. Hospitalizations from COVID-19: a health planning tool. Rev Saude Publica 2022;56(51). doi: 10.11606/s1518-8787.2022056004315.
5. Alcañiz M, Estevez M, Santolino M. Risk of hospitalization of diagnosed COVID-19 cases during the pandemic: A time-series analysis to unveil short- and long-run dynamics. J Health Soc Sci. 2024;9(1):144-54. doi: 10.19204/2024/RSKF7
6. Vasileiou E, Simpson CR, Shi T, Kerr S, Agrawal U, Akbari A, et al. Interim findings from first-dose mass COVID-19 vaccination roll-out and COVID-19 hospital admissions in Scotland: a national prospective cohort study. Lancet 2021;397(10285):1646-57. doi: 10.1016/S0140-6736(21)00677-2.
7. Nguyen HM, Turk PJ, McWilliams AD. Forecasting COVID-19 hospital census: A multivariate time-series model based on local infection incidence. JMIR Public Health Surveill. 2021;7(8):e28195. doi: 10.2196/28195.
8. Leclerc QJ, Fuller NM, Keogh RH, Diaz-Ordaz K, Sekula R, Semple MG, et al. Importance of patient bed pathways and length of stay differences in predicting COVID-19 hospital bed occupancy in England. BMC Health Serv Res. 2021;21(566). doi: 10.1186/s12913-021-06509-x.
9. Hatami H, Soleimantabar H, Ghasemian M, Delbari N, Aryannezhad S. Predictors of intensive care unit admission among hospitalized COVID-19 patients in a large university hospital in Tehran, Iran. J Res Health Sci. 2021;21(1): e00510. doi: 10.34172/jrhs.2021.44.
10. Jain V, Yuan JM. Predictive symptoms and comorbidities for severe COVID-19 and intensive care unit admission: a systematic review and meta-analysis. Int J Public Health 2020;65:533–46. doi: 10.1007/s00038-020-01390-7.
11. Karagiannidis C, Windisch W, McAuley DF, Welte T, Busse R. Major differences in ICU admissions during the first and second COVID-19 wave in Germany. Lancet Respir Med. 2021;9(5):e47-e48. doi: 10.1016/S2213-2600(21)00101-6.
12. Zhao C, Tepekule B, Criscuolo NG, Wendel Garcia PD, Hilty MP, Fumeaux T, et al. icumonitoring.ch: a platform for short-term forecasting of intensive care unit occupancy during the COVID-19 epidemic in Switzerland. Swiss Med Wkly. 2020;150:w20277. doi: 10.4414/smw.2020.20277.
13. Hametner C, Böhler L, Kozek M, Bartlechner J, Ecker O, Du ZP, et al. Intensive care unit occupancy predictions in the COVID-19 pandemic based on age-structured modelling and differential flatness. Nonlinear Dyn. 2022;109:57–75. doi: 10.1007/s11071-022-07267-z.
14. Runge M, Richardson RAK, Clay PA, Bell A, Holden TM, Singam M, et al. Modeling robust COVID-19 intensive care unit occupancy thresholds for imposing mitigation to prevent exceeding capacities. PLOS Glob Public Health 2022;2(5):e0000308. doi: 10.1371/journal.pgph.0000308.
15. Yanez ND, Weiss NS, Romand JA, Treggiari MM. COVID-19 mortality risk for older men and women. BMC Public Health 2020;20(1742). doi: 10.1186/s12889-020-09826-8.
16. Abdi Tazeh A, Mohammadpoorasl A, Sarbakhsh P, Abbasi M, Dorosti A, Khayatzadeh S, et al. Investigation of the factors related to mortality and length of hospitalization among COVID-19 patients in East Azerbaijan hospitals, Iran. J Res Health Sci. 2022;22(3):e00557. doi: 10.34172/jrhs.2022.92.
17. Weinberger DM, Chen J, Cohen T, Crawford FW, Mostashari F, Olson D, et al. Estimation of excess deaths associated with the COVID-19 pandemic in the United States, March to May 2020. JAMA Intern Med. 2020;180(10):1336–44. doi: 10.1001/jamainternmed.2020.3391.
18. Duarte P, Riveros-Perez E. Understanding the cycles of COVID-19 incidence: principal component analysis and interaction of biological and socio-economic factors. Ann Med Surg. 2021;66(102437). doi: 10.1016/j.amsu.2021.102437.
19. Nobi A, Tuhin KH, Lee JW. Application of principal component analysis on temporal evolution of COVID-19. PLOS ONE 2021;16(12):e0260899. doi: 10.1371/journal.pone.0260899.
20. Carroll C, Bhattacharjee S, Chen Y, Dubey P, Fan J, Gajardo A, et al. Time dynamics of COVID-19. Sci Rep. 2020;10(21040). doi: 10.1038/s41598-020-77709-4.
21. Casas I, Fernandez-Casal R. tvReg: Time-varying coefficient linear regression for single and multi-equations in R. SSRN 2019;14(1):79-100. doi: 10.2139/ssrn.3363526.
22. Web page National Centre of Epidemiology, Spanish Government. COVID-19 in Spain. 2024. Available from: https://cnecovid.isciii.es/ [Accessed November 4, 2024].
23. Cleveland R, Cleveland W, McRae J, Terpenning I. STL: A seasonal-trend decomposition procedure based on Loess. J Off Stat. 1990;6:3-73.
24. Nadaraya, EA. On estimating regression. Teoriya Veroyatnostei i ee Primeneniya. 1964;9(1):157–9. doi: 10.1137/1109020.
25. Watson, GS. Smooth Regression Analysis. Sankhyā: The Indian Journal of Statistics, Series A (1961-2002). 1964;26(4):359–72. Available from: https://www.jstor.org/stable/25049340 [Accessed July 18, 2024].
26. Said SE, Dickey DA. Testing for unit roots in autoregressive-moving average models of unknown order. Biometrika 1984;71(3):599-607. doi: 10.2307/2336570.
27. Peña D, Smucler E, Yohai VJ. odpc: Fitting of one-sided dynamic principal components. R package version 2.0.5. 2024. Available from: https://www.rdocumentation.org/packages/odpc/versions/2.0.5/topics/odpc [Accessed September 6, 2024].
28. R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. 2024. Available from: https://www.R-project.org/
29. Gerli AG, Miozzo M, Centanni S, Fontana L, Chi-

umello D, Sotgiu G, et al. Forecasting the burden of COVID-19 hospitalized patients during the SARS-CoV-2 second wave in Lombardy, Italy. Panminerva Med. 2021 March;63(1):86-7. doi: 10.23736/S0031-0808.20.04212-3.
30. Peiris M, Perera B. On prediction with fractionally differenced ARIMA models. J Time Ser Anal. 1988;9(3):215-20. doi: 10.1111/j.1467-9892.1988.tb00465.x.
31. Fan J, Gijbels I. Local polynomial modeling and its applications. London: Chapman and Hall; 1996.
32. Fan J, Zhang W. Statistical methods with varying coefficient models. Stat Interface 2008;1:179–95. doi: 10.4310/SII.2008.V1.N1.A15.
33. Guha P, Guha A, Bandyopadhyay T. Application of pooled testing in estimating the prevalence of COVID-19. Health Serv Outcomes Res Method. 2022; 22:163–91. doi: 10.1007/s10742-021-00258-4.
34. James LP, Salomon JA, Buckee CO, Menzies NA. The use and misuse of mathematical modeling for infectious disease policymaking: lessons for the COVID-19 pandemic. Med Decis Making 2021;41:379-85. doi: 10.1177/0272989X21990391.
35. Nixon K, Jindal S, Parker F, Marshall M, Reich NG, Ghobadi K, et al. Real-time COVID-19 forecasting: challenges and opportunities of model performance and translation. Lancet Digit Health 2022;4(10):E699-E701. doi: 10.1016/S2589-7500(22)00167-4.
36. Web page European Centre for Disease Prevention and Control (ECDC). COVID-19 Vaccine tracker. 2024. Available from: https://opendata.ecdc.europa.eu/ [Accessed February 2, 2024].
37. Chemaitelly H, Ayoub HH, Tang P, Coyle P, Yassine HM, Al Thani AA, et al. Long-term COVID-19 booster effectiveness by infection history and clinical vulnerability and immune imprinting: a retrospective population-based cohort study. Lancet Infect Dis. 2023;23(7):816-27. doi: 10.1016/S1473-3099(23)00058-0.
38. Haas EJ, Angulo FJ, McLaughlin JM, Anis E, Singer SR, Khan F, et al. Impact and effectiveness of mRNA BNT162b2 vaccine against SARS-CoV-2 infections and COVID-19 cases, hospitalisations, and deaths following a nationwide vaccination campaign in Israel: an observational study using national surveillance data. Lancet 2021;397(10287):1819-29. doi: 10.1016/S0140-6736(21)00947-8.
39. Web page World Health Organization (WHO). Overview of coronavirus disease (COVID-19). 2024. Available at: https://www.who.int/health-topics/coronavirus [Accessed October 11, 2024].
40. Grannis SJ, Rowley EA, Ong TC, Stenehjem E, Klein NP, DeSilva MB, et al. Interim estimates of COVID-19 vaccine effectiveness against COVID-19-associated Emergency Department or Urgent Care Clinic encounters and hospitalizations among adults during SARS-CoV-2 B.1.617.2 (Delta) Variant predominance - Nine States, June-August 2021. MMWR Morb Mortal Wkly Rep. 2021;70(37):1291-3. doi: 10.15585/mmwr.mm7037e2.
41. Lin DY, Gu Y, Wheeler B, Young H, Holloway S, Sunny SK, et al. Effectiveness of Covid-19 vaccines over a 9-month period in North Carolina. N Engl J Med. 2022;386(10):933-41. doi: 10.1056/NEJMoa2117128.
42. Pizzato M, Gerli AG, La Vecchia C, Alicandro G. Impact of COVID-19 on total excess mortality and geographic disparities in Europe, 2020–2023: a spatio-temporal analysis. Lancet Reg Health Eur. 2024;44(100996). doi: 10.1016/j.lanepe.2024.100996.

ISSN 2282-0930 • Epidemiology Biostatistics and Public Health - 2024, Volume 19, Issue 2

Influenza Vaccination Coverage in Patients with Chronic Diseases: A Descriptive Analysis

Fabio Contarino[(1)], Francesca Bella[(1)], Concetta Randazzo[(1)], Claudio Fiorilla[(3)], Maria Lia Contrino[(4)]

(1) Department of Public Health, Siracusa Local Health Authority, Siracusa, Italy.
(2) Siracusa Cancer Registry, Siracusa Local Health Authority, Siracusa, Italy.
(3) Department of Public Health, University of Naples "Federico II", Naples, Italy.
(4) Head of Department of Public Health, Siracusa Local Health Authority, Siracusa, Italy.

CORRESPONDING AUTHOR: Fabio Contarino, Department of Public Health, Epidemiology Unit, Siracusa Local Health Authority, Traversa la Pizzuta, Siracusa 96100, Italy. Email: fabio.contarino@asp.sr.it.

SUMMARY

Background: Influenza is a major cause of morbidity and mortality worldwide. Individuals with chronic diseases are at greater risk of severe disease or complications. Annual influenza vaccination is fundamental to reduce the burden of disease. Patients with chronic diseases often remain hard to reach and vaccination coverage data are poorly available. The aim of this study is to evaluate the influenza vaccination coverage in subjects from 6 months to 64 years of age with chronic diseases during the 2023/2024 season in Siracusa Local Health Authority, Italy.
Methods: Records of influenza vaccination during 2023/2024 vaccination campaign were matched with the information on chronic diseases. The dataset included information on sex, age, influenza vaccine, chronic diseases, other vaccines administered.
Results: During 2023/24 influenza season, vaccination coverage among the study population was 16.3% and it significantly differed, depending on the underlying disease. The higher VCs were reached in patients with chronic lung diseases (2627/5596; 46.9%), cardiovascular diseases (3250/7009; 46.4%) and chronic liver diseases (105/250; 42.0%), while the lower values were reached in patients with cancers (652/5630; 11.6%) and in patients with chronic inflammatory diseases and bowel malabsorption syndromes (159/1260; 12.6%).
Conclusions: Although influenza vaccination is a safe, effective, and cost-effective method of preventing influenza infection and its complications, VC rates are not satisfactory, and coverage target indicated by Health Authorities remained very far. Reversing this is likely to require a broad range of interventions on patients, caregivers, parents, healthcare providers and health communication.

Keywords: influenza; influenza seasonal vaccination; vaccination coverage; prevention; chronic diseases; high-risk patients; health communication.

INTRODUCTION

With its annual recurrence, influenza is a major cause of morbidity and mortality worldwide, causing 1 billion cases, 3–5 million cases of severe illness and 290,000–650,000 deaths on average each year due to complications (1,2). Some populations, such as older adults, children younger than 5 years, pregnant people, and people with underlying diseases, are at increased risk of complications (2). The burden from seasonal influenza is two-fold. Firstly, there is the direct health impact caused by severe disease and deaths due to influenza. Secondly, there is the economic impact of the large number of mild-to-moderate cases resulting in time off work, losses to production and pressure and costs on health and social care services (3,4).

All population groups can be affected but people with chronic diseases are at more risk of developing severe influenza and influenza-related complications (1,2), because of their frailty, multimorbidity and immunesenescence (5,6).

Annual influenza vaccination is the most effective measure for preventing both influenza and its complications (1,7). Moreover, administering annual influenza vaccines has been shown to be cost-effective

DOI: 10.54103/2282-0930/24148
Accepted: 24th October 2024

and imparts substantial health and economic benefits, including an important reduction in lost days of work (8). Therefore, the World Health Organization (WHO) and National Immunization Technical Advisory Groups (NITAGs) recommend annual seasonal influenza vaccination for these at-risk groups (2,9,10), suggesting a flu vaccination coverage (VC) of at least 75% among older adults and individuals with chronic diseases (11). Although the flu vaccine can be less effective in elderly adults and in people with chronic diseases because of their weaker immune systems, and therefore a weaker immune response to the vaccine (6) , older, vulnerable and high-risk individuals exhibit the greatest benefit from vaccination (12–17).

Despite several high-income countries have included flu vaccination recommendations for subjects with chronic diseases in their national immunization schedules, these population groups remain hard to reach for different reasons and vaccination rates remain below target (18,19). This topic is poor investigated in the literature and vaccination coverage data are poorly available. The Regional Office for Europe of the WHO reported a vaccination coverage of 33.8% in Italian residents with chronic diseases (20). A 2019 Italian study investigated the knowledge and attitudes concerning influenza vaccination in a little sample of adults with chronic diseases, in which less than half (42.1%) received influenza vaccine (21).

There is a large population of chronic disease patients in Italy (22), Chronic diseases affected nearly 40% percent of the Italian population, that is, 24 million Italians of whom 12.5 million have multi-chronicity and risk factors often overlap (23). Chronic diseases are more frequent in the older age groups, reaching 85.4% among people over 75 years old (24), but a significant proportion of those patients are relatively young and active (25–27). In terms of geographic area, the regions of South Italy have a significantly higher prevalence of chronic diseases (28). Specifically, in Sicily there is about one million of people with chronic diseases. Despite the large number of patients with chronic diseases, there are no standardized nor systemic data available on the vaccine coverage of these patients. More information is needed about who gets vaccinated.

Thus, the rationale of this study is to evaluate influenza vaccination coverage in subjects with chronic diseases that increase the risk of complications from influenza. Our study was carried out in Siracusa Local Health Authority (LHA), corresponding to the Province of Siracusa, in Sicily, South Italy, with around 383.604 inhabitants, according to ISTAT data, Italian National Statistics Institute (29), where 59,787 inhabitants were vaccinated during the 2023–2024 influenza season, with a general vaccination coverage of 15.6%; of these, 40,889 were 65 years old or older (VC: 46.5%).

METHODS

This is a descriptive analysis to evaluate flu vaccination coverage in subjects from 6 months to 64 years with higher risk of complications from influenza (study population). The reference study period was the last 2023/2024 influenza vaccination campaign (from October 2023 to February 2024).

Vaccination data were extracted from the provincial immunization database of the local Health Department, that routinely collects data on all administered vaccines. It is a computerized vaccination registry containing information on the vaccination history of every inhabitant of Siracusa Local Health Authority; it can also be used to generate an immunization schedule. Records of influenza vaccination during the reference period were matched with the information on chronic diseases, extracted from a platform of Local Health Authority Health Information System, that allows to know the prevalence of several chronic disease among the population.

In the study period, the following vaccines were recommended and offered in active and free of charge in Sicily (30): live attenuated quadrivalent influenza vaccine (LAIV), indicated for subjects aged from 2 to 17 years old; cell culture based inactivated quadrivalent influenza vaccine (QIV-cc), indicated to subjects aged 2 years and older; inactivated quadrivalent influenza vaccine standard dose (QIV-sd), indicated to subjects aged 6 months and older; high dose inactivated quadrivalent influenza vaccine (QIV-hd), indicated to subjects aged 60 years and older; adjuvanted inactivated quadrivalent influenza vaccine (QIV-a), indicated to subjects aged 65 years and older (Table 1).

In Italy, the vaccination of subjects affected by chronic disease is mainly managed by general practitioners or by family pediatricians for children.

The dataset was decoded in order to identify patients with at least one chronic disease, and according to the Italian Ministry of Health (10) the following major risk categories of diseases were identified: chronic lung diseases, cardiovascular diseases, diabetes mellitus, and other metabolic diseases, chronic renal failure/adrenal insufficiency, hematopathies and hemoglobinopathies, cancer, chronic inflammatory diseases and bowel malabsorption syndromes, chronic liver diseases.

Considering that there was a high overlap between the individuals with chronic diseases and older adults and to avoid duplicate statistics of the sample, we only included the individuals with chronic diseases as one of the study populations in this study. In case of comorbidities, we classified the patient according to the disease uploaded in the computerized vaccination registry by the physician at the time of vaccination.

The final dataset was created, including information on sex, age, influenza vaccine, chronic diseases, other vaccines administered.

Table 1. Influenza vaccines used during the study period

Vaccine's type	Abbreviation	Recommendation of Ministry of Health
Live attenuated quadrivalent influenza vaccine	LAIV	subjects aged from 2 to 17 years old
Cell Culture based inactivated quadrivalent influenza vaccine	QIV-cc	subjects aged 2 years and older
Inactivated quadrivalent influenza vaccine standard dose	QIV-sd	subjects aged 6 months and older
High dose inactivated quadrivalent influenza vaccine	QIV-hd	subjects aged 60 years and older
Adjuvanted with MF59 Inactivated quadrivalent influenza vaccine	QIV-a	subjects aged 65 years and older

RESULTS

From the platform of Local Health Authority Health Information System, 76,331 on 294,371 (25.9%) residents up to 64 years of age reported at least one chronic disease. Of those, 55,439 (72.6%) subjects reported one chronic disease, 12,073 (15.8%) reported two comorbidities, 4,009 (5.3%) three comorbidities and 4,810 (6.3%) more than three comorbidities.

During 2023/24 influenza season, 12,428 (16.3%, the study population) of 76,331 subjects from 6 months to 64 years old with at least one chronic disease received the influenza vaccine. Socio-demographic characteristics, comorbidities, types of influenza vaccine administered, and co-administration of other vaccines are shown in Table 2.

Female were 6,506 (52.2%) and the mean age was 50.6 years. The most frequent diseases identified were cardiovascular diseases (n.3,250; 26,2%); chronic lung diseases (2,627; 21.1%); diabetes mellitus and other metabolic diseases (1,968; 15.8%). Overall, these three categories of diseases affect 63.1% of the study population.

Chronic lung diseases, cancer, chronic inflammatory diseases and bowel malabsorption syndromes, hematopathies and hemoglobinopathies are more frequent among females, while cardiovascular diseases, diabetes mellitus/other metabolic diseases, chronic liver diseases and chronic renal failure/ adrenal insufficiency are more frequent among males in the study population.

Regarding the distribution of the different vaccines in the study population, about 95% received the

Table 2. Demographic characteristics, chronic diseases (stratify by sex), and co-administration of other vaccines of the study population (12,428 subjects)

	n	%
Gender		
Female	6,488	52,2%
Male	5,940	47,8%
Chronic diseases		
Cardiovascular diseases	3,250	26,2%
female	*1589*	*48,9%*
male	*1661*	*51,1%*
Chronic lung diseases	2,627	21,1%
female	*1437*	*54,7%*
male	*1190*	*45,3%*
Diabetes mellitus and other metabolic diseases	1,968	15,8%
female	*973*	*49,4%*
male	*995*	*50,6%*
Cancer	652	5,2%
female	*453*	*69,5%*
male	*199*	*30,5%*

Chronic inflammatory diseases and bowel malabsorption syndromes	159	1,3%
female	*98*	*61,6%*
male	*61*	*38,4%*
Hematopathies and hemoglobinopathies	119	1,0%
female	*72*	*60,5%*
male	*47*	*39,5%*
Chronic liver diseases	105	0,8%
female	*42*	*40,0%*
male	*63*	*60,0%*
Chronic renal failure/adrenal insufficiency	84	0,7%
female	*35*	*41,7%*
male	*49*	*58,3%*
Other diseases	2,034	16,4%
Other vaccines in addition to the flu vaccine		
COVID-19 vaccines	324	2,6%
Pneumococcal vaccines	523	4,2%
Shingles (herpes zoster) vaccines	126	1,0%

inactivated quadrivalent influenza vaccine standard dose (QIV-sd) (not reported in the table).

During the vaccination campaign 2023/2024, 973 (7.8%) subjects received other vaccines in addition to the flu vaccine: 523 (4.2%) received pneumococcal vaccines, 324 (2.6%) COVID-19 vaccine and 126 (1.0%) shingles (herpes zoster) vaccine (Table 2).

Regarding the vaccination setting, more than 99% of study population were vaccinated by the general practitioner or family doctor (data non reported).

Overall, VC among the study was 16.3% and it differed depending on the underlying disease. The higher VCs were reached in patients with chronic lung diseases (2627/5596; 46.9%), cardiovascular diseases (3250/7009; 46.4%) and chronic liver diseases (105/250; 42.0%). The lower VCs were reached in patients with cancers (652/5630; 11.6%) and in patients with chronic inflammatory diseases and bowel malabsorption syndromes (159/1260; 12.6%). The VCs reached per chronic disease are described in Table 3.

Table 3 - Frequency of chronic disease, number of vaccinated and influenza vaccination coverage (%) of subjects aged between 6 months and 64 years and suffering from at least one chronic disease, per comorbidity.

Chronic disease	n. of people from 6 months to 64 years with chronic disease	n. of vaccinated	Vaccination coverage (%)
Chronic lung diseases	5596	2627	46,9
Cardiovascular diseases	7009	3250	46,4
Chronic liver diseases	250	105	42,0
Diabetes mellitus and other metabolic diseases	5620	1968	35,0
Chronic renal failure/adrenal insufficiency	332	84	25,3
Hematopathies and hemoglobinopathies	517	119	23,0
Chronic inflammatory diseases and bowel malabsorption syndromes	1260	159	12,6
Cancers	5630	652	11,6

DISCUSSION

The present study described influenza vaccination coverage in subjects from 6 months to 64 years of age with at least one chronic disease during the 2023/2024 season in Siracusa LHA.

Our study showed a VC value of 16.3% in the study population, ranging from 46.9% to 11.6% depending on the underlying disease. These values are very far from the minimum achievable goal [15]. Higher coverage was reached in patients with cardiovascular diseases, chronic respiratory diseases, metabolic disorders (including diabetes mellitus) and chronic liver diseases, while lower VC have been achieved in patients with cancer, chronic inflammatory diseases and bowel malabsorption syndromes and kidney disease. Primary care physicians play a key role in the vaccination of their patients and their presence in the management of those patients could be associated with a higher frequency of vaccination advice in comparison with other chronic medical diseases that are more likely to be followed by different specialist physician rather than a primary care provider (31–34).

In Italy, influenza VC is far from the goal, although it increased in the last years, peaking the highest recorded in the 2020-2021 season with the outbreak of COVID-19 (35). According to the PASSI survey, flu VC in the season 2021/2022 was 28.7% among subjects 18-64 years old with at least one chronic disease, ranging from 20.1% in subjects with chronic liver diseases to 37.5% in subjects with diabetes (36).

In Europe, although all countries recommend flu vaccination in people with chronic diseases, VCR still far from desirable rate (37), despite the trend increased compared to the past. Moreover, VCR data in those subjects are very scarce, with only four countries reported and the coverage level was greater than or equal to 75% in only three countries (37).

During the study period, 30 subjects reporting a history of drugs or alcohol abuse were vaccinated (data not reported in the Table 2). Addicted people experience high rates of communicable disease and a high prevalence of chronic health diseases (38). The European Monitoring Centre for Drugs and Drug Addiction additionally recommends influenza vaccination for those patients (39). Despite these recommendations, addicted people experience barriers to vaccination and there is evidence that flu vaccine uptake among those people is suboptimal (40). There are very few and often self-reported data on VC among addicted people, precluding synthesis of coverage estimates and comparison to general population (41).

Coverage data are critical to understand vaccine uptake and population immunity, enabling Public Health Authorities to assess coverage gaps and to measure trends over time, both of which are key components of every surveillance program. The number of people with chronic diseases has increased (42,43), it is therefore not surprising that the need has also grown for better data on when, where and who received which vaccine. Despite this and the efforts to promote immunization of high-risk subjects are specific objectives of most national immunization plans, many countries report difficulties in estimating VC data regarding the individuals with chronic medical diseases (44). The limited available evidence suggest that those patients are often under-vaccinated, in general less than the elderly, even in countries with well-functioning healthcare systems (20,31). Those impediments may reflect a lack of information systems or other standardized methodologies for making these data available (45). Even if it is more complex to implement a targeted risk-group strategy than an age-based approach, we think it could be very useful to establish homogeneous and standardized methods to quantify VC in other categories in addition to the older ones, such as chronic patients, pregnant women, HCWs, prisoners, drug addicts and others.

Influenza VCR is sometimes characterized by changes triggered by unpredictable events (46). For example, the COVID-19 pandemic has influenced increased acceptance of influenza vaccination in 2020-2021 in people who were previously eligible for the vaccine but routinely unvaccinated, determining the highest VC recorded in the past 15 years (36,47). Conversely, the report of four deaths allegedly caused by administration of an influenza vaccine (the so-called "Fluad case"), dramatically reduced the influenza vaccine uptake, contributing to the failure of the 2014/2015 vaccination campaign (48,49).

Suboptimal coverage is a complex issue influenced by socio-demographic, programmatic and psychological factors (46,50,51). The fact that vaccination rates among at-risk populations remain low despite recommendations indicates a continuing failure to provide appropriate standards of care (52,53). Reversing this is likely to require a broad range of interventions and a multifactorial approach. A review from countries with high influenza VCRs, identified different key factors for a successful influenza vaccination programme and clustered them into five main pillars: health authority accountability and strengths of the influenza programme, facilitated access to vaccination, healthcare professional accountability and engagement, awareness of the burden and severity of disease and belief in influenza vaccination benefit (46).

In our opinion, the most important encouraging factors for reaching higher coverage rates are a proactive behaviour of healthcare workers. High coverage reached in different countries may have been due to the fact that general practitioners were encouraged to proactively recommend the vaccine to their at-risk patients (34). Patients in high-risk clinical groups are more likely to receive an influenza vaccine after they receive information on the benefits of vaccination to their own health compared with social benefits to others. This correlation is even stronger when the patient perceives themselves as personally at higher risk (32). The role of health communication in delivering correct information exclusively based on facts and scientific evidence (48,49,54), is also crucial.

Our study had several strengths. The first was represented by the large sample and wide range of diseases included in our analysis. Another strength was the use of comprehensive information systems as data sources, and the large number of individuals in the chronic disease management system. This system was opt-in for individuals with certain chronic diseases and an estimated at least 80% of individuals with chronic disease participate in it. Even with poorly available, we reported data on VC among persons with drug or alcohol abuse, a topic little investigated in the literature, although this is a population at elevated risk.

Our study also had some potential limitations, that include the use of only one data source to identify chronic subjects and the lack of data on multiple comorbidities as drivers of flu vaccination. Furthermore, while the dataset offered comprehensive health-related information about the patients' health diseases, certain variables relevant to influenza vaccination behaviour, such as attitudes and beliefs, were not measured, limiting the depth of this study's analysis. However, in our opinion, our study provided useful information about VC among patients at a high-risk of severe influenza.

In conclusion, we think that patients with chronic diseases should be targeted for attaining high VC compared to the remaining population, for whom, annual flu vaccination (and in general every vaccination) should be considered as a critical part of medical care and may be a life-saving act (31,55,56). To effectively address vaccination gaps, it is necessary to understand the key barriers to vaccination in individual with chronic diseases at different levels of the health care delivery systems including the individual, health care provider, and policy level (57).

Any intervention to increase vaccine uptake among patients with chronic diseases should be monitored and evaluated systematically, starting from the quantification and evaluation of VC, to guide development and wider implementation. Coverage data are essential for any surveillance programmes, to understand whether it is sufficient to prevent transmission of disease, to identify gaps in coverage, and to efficiently direct interventions where gaps exist.

AUTHORS' CONTRIBUTIONS

Conceptualization, FC; methodology, FC; acquisition of data, FC, CR; formal analysis and interpretation of data, FC, FB; writing - original draft preparation, FC; writing - review and editing, FC, FB, CF; statistical analysis, FC; supervision and project administration, FC, MLC.

All authors have read and agreed to the submitted version of the manuscript.

INFORMED CONSENT STATEMENT

As this study constituted public health surveillance, ethical approval from the institutional review board was not required. All data were provided and analyzed anonymously.

ABBREVIATIONS

VC: vaccination coverage; VCR: vaccination coverage rates; LHA: Local Health Authority; HCW: health care worker

LAIV: live attenuated quadrivalent influenza vaccine; QIV-cc: cell culture based inactivated quadrivalent influenza vaccine; QIV-sd: inactivated quadrivalent influenza vaccine standard dose; QIV-hd: high dose inactivated quadrivalent influenza vaccine; QIV-a: adjuvanted inactivated quadrivalent influenza vaccine.

REFERENCES

1. World Health Organization. Influenza Fact-Sheets. [cited 2024 Mar 21]; Available from: https://www.who.int/news-room/fact-sheets/detail/influenza-(seasonal)
2. World Health Organization position papers on Influenza. [cited 2024 Apr 10]; Available from: https://iris.who.int/bitstream/handle/10665/354264/WER9719-eng-fre.pdf?sequence=1
3. European Centre for Disease Prevention and Control. Factsheet about seasonal influenza. [cited 2024 Jun 4]; Available from: https://www.ecdc.europa.eu/en/seasonal-influenza/facts/factsheet
4. de Courville C, Cadarette SM, Wissinger E, Alvarez FP. The economic burden of influenza among adults aged 18 to 64: A systematic literature review. Influenza Other Respir Viruses. 2022 May 5;16(3):376–85.
5. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. The Lancet. 2013 Mar;381(9868):752–62.
6. Vetrano DL, Triolo F, Maggi S, Malley R, Jackson TA, Poscia A, et al. Fostering healthy aging: The interdependency of infections, immunity and frailty. Ageing Res Rev [Internet]. 2021 Aug;69:101351. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1568163721000982.
7. CDC. Estimated Influenza Illnesses, Medical Visits, Hospitalizations, and Deaths Prevented by Vaccination in the United States – 2022-2023 Influen-

za Season. [cited 2024 Apr 10]; Available from: https://www.cdc.gov/flu/about/burden-prevented/2022-2023.htm#:~:text=Preliminary%20estimates%20of%20the%20burden,21%2C000%20flu%20deaths%20(9).
8. Smith KJ, Lee BY, Nowalk MP, Raymund M, Zimmerman RK. Cost-effectiveness of dual influenza and pneumococcal vaccination in 50-year-olds. Vaccine. 2010 Nov;28(48):7620–5.
9. Grohskopf LA, Blanton LH, Ferdinands JM, Chung JR, Broder KR, Talbot HK. Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices — United States, 2023–24 Influenza Season. MMWR Recommendations and Reports. 2023 Aug 25;72(2):1–25.
10. Italian Ministry of Health. Influenza prevention and control: recommendations for the 2023-2024 season. [cited 2024 Apr 10]; Available from: https://www.trovanorme.salute.gov.it/norme/renderNormsanPdf?anno=2023&codLeg=93294&parte=1%20&serie=null
11. World Health Assembly, 56. (2003). Prevention and control of influenza pandemics and annual epidemics. [cited 2024 Apr 11]; Available from: https://iris.who.int/bitstream/handle/10665/78320/ea56r19.pdf?sequence=1&isAllowed=y
12. Battistoni A, Volpe M. Flu Vaccination as a Key Prevention Recommendation for Patients at High Cardiovascular Risk: The Next Season's Scenario. High Blood Pressure & Cardiovascular Prevention. 2022 Sep 2;29(5):405–7.
13. Behrouzi B, Bhatt DL, Cannon CP, Vardeny O, Lee DS, Solomon SD, et al. Association of Influenza Vaccination With Cardiovascular Risk. JAMA Netw Open. 2022 Apr 29;5(4):e228873.
14. Modin D, Claggett B, Køber L, Schou M, Jensen JUS, Solomon SD, et al. Influenza Vaccination Is Associated With Reduced Cardiovascular Mortality in Adults With Diabetes: A Nationwide Cohort Study. Diabetes Care. 2020 Sep 1;43(9):2226–33.
15. Bechini A, Ninci A, Del Riccio M, Biondi I, Bianchi J, Bonanni P, et al. Impact of Influenza Vaccination on All-Cause Mortality and Hospitalization for Pneumonia in Adults and the Elderly with Diabetes: A Meta-Analysis of Observational Studies. Vaccines (Basel). 2020 May 30;8(2):263.
16. Lee WJ, Chen LK, Tang GJ, Lan TY. The Impact of Influenza Vaccination on Hospitalizations and Mortality Among Frail Older People. J Am Med Dir Assoc. 2014 Apr;15(4):256–60.
17. Nichol KL. Relation between Influenza Vaccination and Outpatient Visits, Hospitalization, and Mortality in Elderly Persons with Chronic Lung Disease. Ann Intern Med. 1999 Mar 2;130(5):397.
18. Centre for Disease Control and Prevention (CDC). Recommended Immunization Schedules for Adults. (Addendum updated February 29, 2024). [cited 2024 Apr 10]; Available from: https://www.cdc.gov/vaccines/schedules/hcp/imz/adult.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fvaccines%2Fschedules%2Fhcp%2Fadult.html
19. Public Health England (PHE). UK Immunisation Schedule: The Green Book. (Chap. 11). (Last updated 17 March 2022). [cited 2024 Apr 10]; Available from: https://www.gov.uk/government/publications/immunisation-schedule-the-green-book-chapter-11
20. WHO regional office for Europe. Influenza vaccination coverage, chronic diseases. [cited 2024 Apr 10]; Available from: https://gateway.euro.who.int/en/indicators/infl_14-influenza-vaccination-coverage-chronic-diseases/#id=31634
21. Bertoldo G, Pesce A, Pepe A, Pelullo CP, Di Giuseppe G. Seasonal influenza: Knowledge, attitude and vaccine uptake among adults with chronic conditions in Italy. PLoS One. 2019 May 1;14(5):e0215978.
22. Istituto Nazionale di Statistica. Salute e Sanità. . [cited 2024 Apr 11]; Available from: https://www.istat.it/storage/ASI/2022/capitoli/C04.pdf
23. Osservatorio Nazionale sulla Salute nelle Regioni Italiane. Rapporto Osservasalute 2022. [cited 2024 Apr 11]; Available from: https://osservatoriosullasalute.it/osservasalute/rapporto-osservasalute-2022
24. Istituto Superiore di Sanità. La sorveglianza Passi d'Argento. [cited 2024 Apr 11]; Available from: https://www.epicentro.iss.it/passi-argento/
25. Hajat C, Stein E. The global burden of multiple chronic conditions: A narrative review. Prev Med Rep. 2018 Dec;12:284–93.
26. Wijlaars LPMM, Gilbert R, Hardelid P. Chronic conditions in children and young people: learning from administrative data. Arch Dis Child. 2016 Oct;101(10):881–5.
27. Watson KB, Carlson SA, Loustalot F, Town M, Eke PI, Thomas CW, et al. Chronic Conditions Among Adults Aged 18-34 Years — United States, 2019. MMWR Morb Mortal Wkly Rep. 2022 Jul 29;71(30):964–70.
28. ISTAT. The elderly: health conditions in Italy and in the European Union. 2017. [cited 2024 Jun 4]; Available from: https://www.istat.it/it/files//2017/09/Elderly_Health-conditions_2015.pdf
29. Istituto Nazionale di Statistica (ISTAT). Demografia in cifre. Popolazione residente. . [cited 2024 Aug 27]; Available from: https://demo.istat.it/app/?i=POS&l=it
30. Regione Sicilia. Influenza vaccination campaign in Sicily for the 2023-2023 season. [cited 2024 Jul 17]; Available from: http://www.gurs.regione.sicilia.it/Gazzette/g23-38/g23-38.pdf
31. Doherty M, Schmidt-Ott R, Santos JI, Stanberry LR, Hofstetter AM, Rosenthal SL, et al. Vaccination of special populations: Protecting the vulnerable. Vaccine. 2016 Dec;34(52):6681–90.
32. Oakley S, Bouchet J, Costello P, Parker J. Influenza vaccine uptake among at-risk adults (aged 16–64 years) in the UK: a retrospective database analysis. BMC Public Health. 2021 Dec 24;21(1):1734.
33. Collange F, Verger P, Launay O, Pulcini C. Knowledge, attitudes, beliefs and behaviors of general practitioners/family physicians toward their own vaccination: A systematic review. Hum Vaccin Immunother. 2016 May 3;12(5):1282–92.
34. Poon PKM, Zhou W, Chan DCC, Kwok KO, Wong SYS. Recommending COVID-19 Vaccines to Patients: Practice and Concerns of Frontline Family Doctors.

Vaccines (Basel). 2021 Nov 13;9(11):1319.
35. Ministero della Salute. Vaccinazione antinfluenzale - Coperture vaccinali medie. [cited 2024 May 23]; Available from: https://www.salute.gov.it/portale/documentazione/p6_2_8_1_1.jsp?lingua=italiano&id=37
36. Istituto Superiore di Sanità. Progressi delle Aziende Sanitarie per la Salute in Italia: la sorveglianza Passi. Vaccinazione per l'influenza stagionale. [cited 2024 May 20]; Available from: https://www.epicentro.iss.it/passi/dati/VaccinazioneAntinfluenzale?tab-container-1=tab1
37. European Centre for Disease Prevention and Control. Seasonal influenza vaccines. Influenza vaccination. [cited 2024 May 15]; Available from: https://www.ecdc.europa.eu/en/seasonal-influenza/prevention-and-control#vaccinationstrategies
38. Degenhardt L, Webb P, Colledge-Frisby S, Ireland J, Wheeler A, Ottaviano S, et al. Epidemiology of injecting drug use, prevalence of injecting-related harm, and exposure to behavioural and environmental risks among people who inject drugs: a systematic review. Lancet Glob Health. 2023 May;11(5):e659–72.
39. European Centre for Disease Prevention and Control (ECDC) and European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). Prevention and control of infectious diseases among people who inject drugs: 2023 update. Stockholm: ECDC; 2023.
40. Price O, Dietze P, Sullivan SG, Salom C, Peacock A. Uptake, barriers and correlates of influenza vaccination among people who inject drugs in Australia. Drug Alcohol Depend. 2021 Sep;226:108882.
41. Price O, Swanton R, Grebely J, Hajarizadeh B, Webb P, Peacock A, et al. Vaccination coverage among people who inject drugs: A systematic review. International Journal of Drug Policy. 2024 May;127:104382.
42. Miller MA, Rathore MH. Immunization in Special Populations. Adv Pediatr. 2012 Jan;59(1):95–136.
43. Sawyer SM, Drew S, Yeo MS, Britto MT. Adolescents with a chronic condition: challenges living, challenges treating. The Lancet. 2007 Apr;369(9571):1481–9.
44. Martinelli D, Fortunato F, Iannazzo S, Cappelli MG, Prato R. Using Routine Data Sources to Feed an Immunization Information System for High-Risk Patients—A Pilot Study. Front Public Health. 2018 Feb 16;6.
45. Gini R, Francesconi P, Mazzaglia G, Cricelli I, Pasqua A, Gallina P, et al. Chronic disease prevalence from Italian administrative databases in the VALORE project: a validation through comparison of population estimates with general practice databases and national survey. BMC Public Health. 2013 Dec 9;13(1):15.
46. Kassianos G, Banerjee A, Baron-Papillon F, Hampson AW, McElhaney JE, McGeer A, et al. Key policy and programmatic factors to improve influenza vaccination rates based on the experience from four high-performing countries. Drugs Context. 2021 Jan 5;9:1–13.
47. Bachtiger P, Adamson A, Chow JJ, Sisodia R, Quint JK, Peters NS. The Impact of the COVID-19 Pandemic on the Uptake of Influenza Vaccine: UK-Wide Observational Study. JMIR Public Health Surveill. 2021 Apr 14;7(4):e26734.
48. Mahroum N, Watad A, Rosselli R, Brigo F, Chiesa V, Siri A, et al. An infodemiological investigation of the so-called "Fluad effect" during the 2014/2015 influenza vaccination campaign in Italy: Ethical and historical implications. Hum Vaccin Immunother. 2018 Mar 4;14(3):712–8.
49. Rosselli R, Martini M, Bragazzi NL, Watad A. The Public Health Impact of the So-Called "Fluad Effect" on the 2014/2015 Influenza Vaccination Campaign in Italy: Ethical Implications for Health-Care Workers and Health Communication Practitioners. In 2017. p. 125–34.
50. Welch VL, Metcalf T, Macey R, Markus K, Sears AJ, Enstone A, et al. Understanding the Barriers and Attitudes toward Influenza Vaccine Uptake in the Adult General Population: A Rapid Review. Vaccines (Basel). 2023 Jan 13;11(1):180.
51. European Centre for Disease Prevention and Control. Review of scientific literature on drivers and barriers of seasonal influenza vaccination coverage in the EU/EEA. Stockholm: ECDC; 2013.
52. Thomas RE, Demicheli V, Jefferson T. Interventions to increase influenza vaccination rates of those 60 years and older in the community and in institutions. In: Thomas RE, editor. Cochrane Database of Systematic Reviews. Chichester, UK: John Wiley & Sons, Ltd; 2005.
53. Jacobson Vann JC, Szilagyi P. Patient reminder and recall systems to improve immunization rates. Cochrane Database of Systematic Reviews. 2005 Jul 20.
54. Levi M, Sinisgalli E, Lorini C, Santomauro F, Chellini M, Bonanni P. The "Fluad Case" in Italy: Could it have been dealt differently? Hum Vaccin Immunother. 2017 Feb 7;13(2):379–84.
55. Andreoni M, Sticchi L, Nozza S, Sarmati L, Gori A, Tavio M. Recommendations of the Italian society for infectious and tropical diseases (SIMIT) for adult vaccinations. Hum Vaccin Immunother. 2021 Nov 2;17(11):4265–82.
56. Antonelli Incalzi R, Consoli A, Lopalco P, Maggi S, Sesti G, Veronese N, et al. Influenza vaccination for elderly, vulnerable and high-risk subjects: a narrative review and expert opinion. Intern Emerg Med. 2024 Apr 27;19(3):619–40.
57. Jorgensen P, Mereckiene J, Cotter S, Johansen K, Tsolova S, Brown C. How close are countries of the WHO European Region to achieving the goal of vaccinating 75% of key risk groups against influenza? Results from national surveys on seasonal influenza vaccination programmes, 2008/2009 to 2014/2015. Vaccine. 2018 Jan;36(4):442–52.

Determinants of COVID-19 Severity: A Retrospective Analysis of Clinical and Epidemiological Factors in Durango, Mexico

Cynthia Mora Muñoz[(1)], *Hugo Payan Gándara*[(1)], *Jesús Alonso Gándara Mireles*[(2)], *Leslie Patrón Romero*[(3)], *Horacio Almanza- Reyes*[(3)]

(1) Epidemiology Service, State Center of Cancerology, CECAN Durango, Mexico.
(2) Genomics Academy, National Polytechnic Institute, CIIDIR-Durango Unit, México.
(3) Faculty of Medicine and Psychology, Autonomous University of Baja California, Tijuana, Baja California, Mexico.
The authors contributed equally to this work.

CORRESPONDING AUTHOR: Jesús Alonso Gándara Mireles, Genomics Academy, National Polytechnic Institute, CIIDIR-Durango Unit, México. Email: alonso_930@hotmail.com

SUMMARY

Background: The COVID-19 pandemic, caused by SARS-CoV-2, has had a devastating global impact, with millions of confirmed cases and deaths. This study focused on analyzing 63,252 patient records from the state of Durango, Mexico, to identify clinical and epidemiological factors associated with disease severity. Methods: The study employed a descriptive, observational, and retrospective approach, based on open data from the SISVER platform. A descriptive analysis was conducted to summarize demographic and clinical characteristics. A multivariate analysis was performed using the graph of relative inertias to assess how the covariates (comorbidities) were associated with hospitalization, intubation, and death in the patients. Subsequently, odds ratios tests were calculated to evaluate the associations between specific clinical variables, such as pneumonia, obesity, and other comorbidities, and intubation.
Results: We were found that the majority of cases (93.8%) were treated on an outpatient basis, while 6.2% required hospitalization. Hypertension, diabetes, and obesity were the most prevalent comorbidities. The mortality rate in the population was 2.1%, particularly in Jurisdiction I, corresponding to the capital city. Pneumonia was strongly associated with intubation (OR = 9.03, 95% CI = 1.0232 – 44.3230, p = 0.03), and obesity also showed an increased risk (OR = 2.64, 95% CI = 1.0021 – 22.4210, p = 0.02). These findings underscore the importance of identifying and managing comorbidities in patients infected with SARS-CoV-2.
Conclusion: The results highlight the relevance of social determinants of health and the need for public policies that address inequalities in the context of appropriately managing risk factors to reduce morbidity and mortality associated with COVID-19 in Mexico.

Keywords: COVID-19; comorbidities; morbidity and mortality.

INTRODUCTION

The disease caused by the novel coronavirus of 2019 (COVID-19), identified in December 2019, is considered a global public health emergency, reaching pandemic status as declared by the World Health Organization [1]. As of January 2023, a total of 367 million confirmed cases of COVID-19 and 4.4 million deaths due to this disease were recorded worldwide [2]. The spread of the virus and its variants has affected nearly all countries, with a sustained increase in cases across all impacted regions. In Mexico, the first case was reported on February 28, 2020, and since then, the number of infected individuals has increased exponentially, reaching a total of 7,633,355 confirmed cases and 334,336 deaths as of October 25, 2024 [3]. In the state of Durango, Mexico, this emerging viral phenomenon resulted in a cumulative total of 82,201 confirmed cases and 3,704 deaths by

DOI: 10.54103/2282-0930/27374
Accepted: 19th December 2024

the same period, with the current dominant variant in Mexico being Omicron, B.1.1.529 [3,4].

The effects of SARS-CoV-2 on the human body can be classified as mild, moderate, severe, and critical. In the latter two categories, significant clinical manifestations have been identified, including severe respiratory distress, the need for mechanical ventilation, and, in many cases, patient death [5,6]. The severity of this disease has been linked to the presence of pre-existing comorbidities such as hypertension, diabetes, obesity, and cardiovascular diseases, which significantly increase the risk of developing severe complications. This may be due to SARS-CoV-2's ability to exacerbate underlying inflammatory and metabolic processes in these patients [7-9]. However, in addition to pre-existing comorbidities, the social determinants of health—defined as the conditions in which people are born, grow, live, work, and age, including the healthcare system—can influence the population's response to SARS-CoV-2 infection [10,11]. These circumstances result from the distribution of money, power, and resources globally, nationally, and locally, which are in turn shaped by the policies adopted by each country [12,13].

In this regard, Abrams EM & Szefler SJ [14], in their work, highlight that factor such as race/ethnicity, poverty, median income level, housing density, housing insecurity, access to healthcare, occupation, transportation/mobility patterns, education, air quality, food insecurity, old age, among others, could increase SARS-CoV-2 morbidity [14]. Similarly, Salgado de Snyder, V. N., et al. [15], pointed out in their study that the social determinants identified as risk factors for developing severe illness from a SARS-CoV-2 infection include working in an essential job, living in a geographic area with a high population density of Latinos and Blacks, overcrowded living conditions at home, and being unable to consistently practice preventive behaviors to avoid infection—conditions commonly exacerbated by inequalities and poverty [15]. In this context, Mexico is one of the countries with the greatest social and economic diversity, based on its cultural and ecological wealth [16]. In Durango, Mexico, healthcare services are divided into four regions known as Health Jurisdictions (Figure 1), which differ in population size and access to healthcare services. Difficult access or lower educational levels are the main factors that may act as social determinants predisposing individuals to severe outcomes from a SARS-CoV-2 infection.

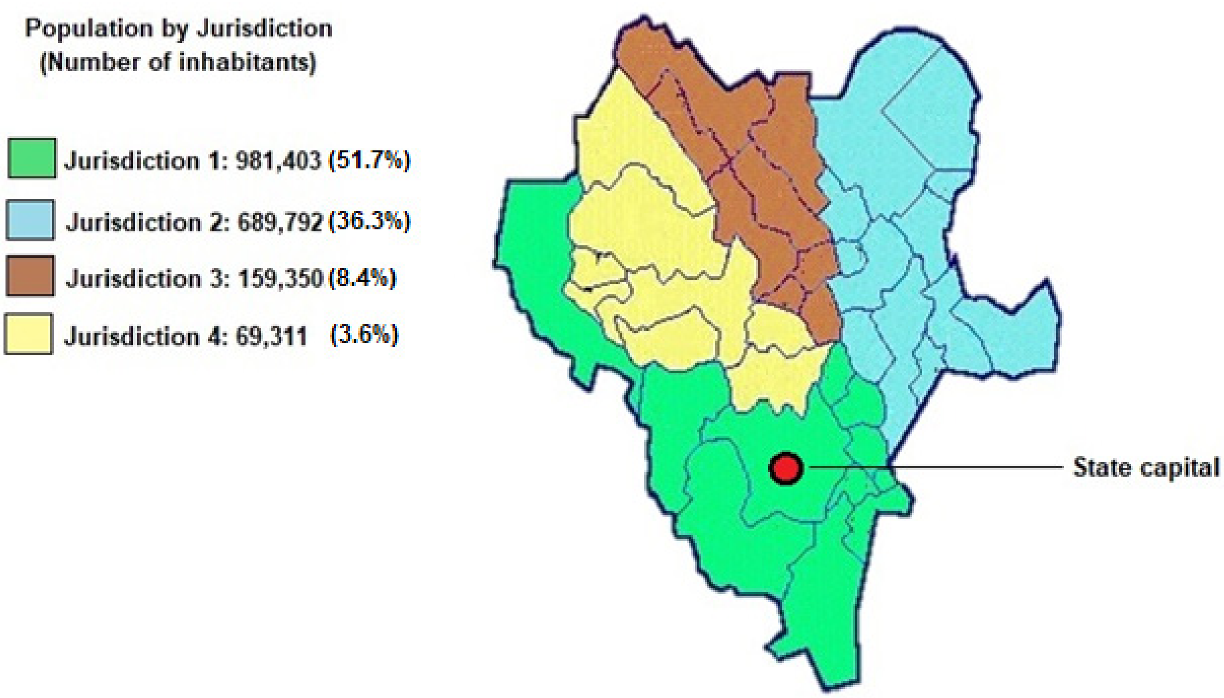
The objective of our study was to describe the clinical and epidemiological profile of patients infected with SARS-CoV-2 in the Health Jurisdictions of the Ministry of Health of Durango, Mexico, and to associate it with an increased risk of developing severe clinical manifestations due to SARS-CoV-2.

MATERIALS AND METHODS

Study Design

This is a descriptive, observational, and retrospective study based on the review of open data from the SISVER platform of patients treated in the four health jurisdictions of the state of Durango, Mexico.

Figure 1. Distribution of the population by health jurisdictions in Durango, Mexico.



ISSN 2282-0930 • Epidemiology Biostatistics and Public Health - 2024, Volume 19, Issue 2

Study Population

The population included all patients treated for symptoms consistent with COVID-19, excluding patients who were repeated in the SISVER platform database between April 5, 2020, and January 21, 2022.

Ethical Declarations

The study was conducted in accordance with the guidelines established in the Declaration of Helsinki and following the Guidelines for Good Clinical Practices of the International Conference on Harmonization, as well as the requirements of the Mexican regulatory body. According to the regulations of the General Health Law on Health Research, under Title II, which addresses ethical aspects of human research, Article 17 defines the risk of research as the probability that the research subject may suffer harm as an immediate or delayed consequence of the study. This research is considered risk-free as it employs retrospective documentary research techniques and methods, with no intentional intervention or modification of the physiological, psychological, or social variables of the individuals participating in the study. Therefore, we did not deem it necessary to implement informed consent.

Clinical Evaluation

To assess the clinical and epidemiological data, we included cases that were admitted with symptoms consistent with the operational definition of COVID-19 disease, confirmed by real-time RT-PCR and positive antigen testing.

Inclusion Criteria

Individuals infected with SARS-CoV-2 with a positive RT-PCR and antigen test from the four health jurisdictions of the Durango Health Services, recorded on the SINAVE platform between April 5, 2020, and January 21, 2022, were included.

Exclusion Criteria

Patients without clinical symptoms of SARS-CoV-2 infection and those with no positive RT-PCR or antigen test were excluded.

Elimination Criteria

Files with illegible or incomplete data were excluded.

Inclusion of Variables

For the epidemiological characteristics, we used variables such as age, sex, comorbidities, symptoms, and nationality.

Differences Between Jurisdictions

To conduct a comparative analysis of the data collected from the four Health Jurisdictions of the state of Durango, given that each jurisdiction presents distinct demographic and socioeconomic characteristics, an analysis was performed to elucidate how these patterns influence the transmission and clinical outcomes of patients.

Data Collection

Open data were obtained from the General Directorate of Epidemiology with the approval of Dr. Christian Zaragoza, General Director. Participant confidentiality was ensured by omitting identifying information from related materials. The researcher affirms and upholds the principle of the participant's right to privacy and will comply with applicable privacy laws. Participant anonymity was guaranteed by using numerical codes corresponding to the treatment data in the digital records.

Definition of Conditions

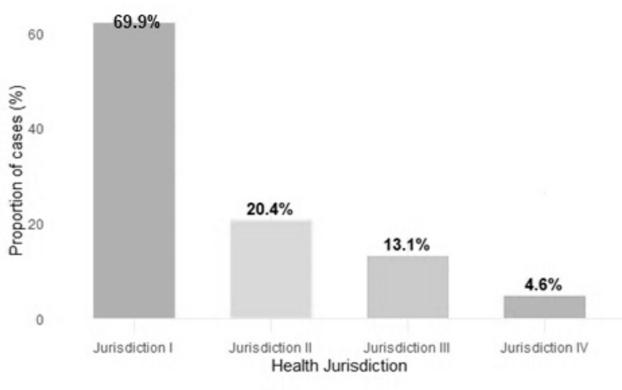
The conditions analyzed as comorbidities in this study, including smoking, were defined based on the clinical records available on the SISVER platform. Smoking was classified as "active smoker" and included patients who reported current tobacco use during medical consultations or whose medical history indicated active smoking at the time of evaluation. The remaining conditions, due to the retrospective nature of the study, were defined according to the diagnoses recorded in the clinical files by healthcare professionals, following standard diagnostic criteria used in routine medical practice.

Statistical Analysis

A descriptive statistical analysis was conducted to summarize the demographic and clinical characteristics of patients. Categorical variables included sex, type of care received (outpatient or hospitalized), deaths, and comorbidities such as hypertension, diabetes, obesity, cardiovascular disease, chronic kidney disease, chronic obstructive pulmonary disease, asthma, immunosuppression, and tobacco use. Continuous variables, such as age, were summarized using the mean and standard deviation.

To evaluate the relationship between specific covariates and severe outcomes, such as hospitalization, intubation, or death, a multivariate analysis of relative inertia was performed. Subsequently, risks were calculated using the odds ratio test for the outcome "intubation" (which was identified in the multivariate analysis as the outcome most strongly associated with the covariates) and the covariates: pneumonia, hypertension, diabetes, obesity, cardiovascular diseases, chronic kidney disease, chronic obstructive pulmonary disease, asthma, immunosuppression, and tobacco use. These results were reported with their corresponding 95% confidence intervals. A p-value < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS version 25 (IBM Corp., Armonk, NY, USA) and RStudio version 4.0.5.

Figure 2. Distribution of COVID-19 cases by jurisdiction



RESULTS

A total of 63,252 valid records were analyzed, corresponding to patients distributed across the four health jurisdictions. The majority of cases (61.9%) were from Jurisdiction I, followed by Jurisdiction II with 20.4%, Jurisdiction III with 13.1%, and Jurisdiction IV with 4.6% (Figure 2).

Of the cases, 54.7% were female patients (34,595), while 45.3% were male (28,657). The mean age for female patients was 38.8 years, with a standard deviation of 12.7 years. For male patients, the mean age was similar at 36.9 years, with a standard deviation of 17.9 years. The overall age range was 10 to 81 years, with the most frequent age group being 30 to 39 years (22.1%), followed by the 20 to 29 years group (21.8%) (Table 1).

Table 2 presents the distribution of patients according to the type of care received (outpatient or inpatient) and the number of recorded deaths, broken down by jurisdiction. Of the 63,252 patients analyzed, most (93.8%) received outpatient care, while only 6.2% required hospitalization. This pattern was consistent across the four jurisdictions, although Jurisdiction IV had a slightly higher percentage of hospitalizations (8.6%) compared to the others (Figure 3).

Table 1. Demographic Distribution of Patients Analyzed by Jurisdiction

Category	Jurisdiction I	Jurisdiction II	Jurisdiction III	Jurisdiction IV	Total
Number of Patients	39,143 (61.9%)	12,927 (20.4%)	8,302 (13.1%)	2,880 (4.6%)	63,252 (100%)
Female Sex (%)	21,347 (61.7%)	7,146 (20.7%)	4,452 (12.9%)	1,650 (4.8%)	34,595 (54.7%)
Mean Age (Female)	-	-	-	-	38.8 (12.7)*
Mean Age (Male)	-	-	-	-	36.9 (11.9)*
Age Range (General)	-	-	-	-	10 – 81 years
Most Frequent Age	-	-	-	-	30-39 years (22.1%) 20-29 years (21.0%)

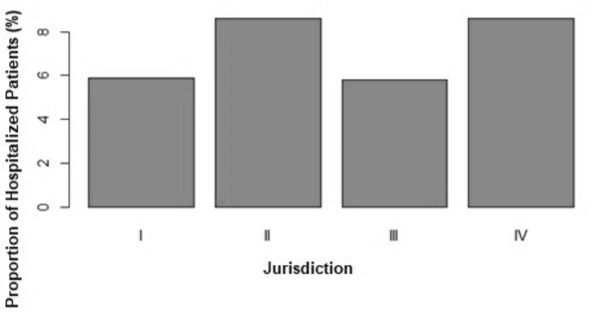
**SD*

ISSN 2282-0930 • Epidemiology Biostatistics and Public Health - 2024, Volume 19, Issue 2

Table 2. Distribution of Patients According to Type of Care and Deaths by Jurisdiction

Category	Jurisdiction I	Jurisdiction II	Jurisdiction III	Jurisdiction IV	Total
Total of Patients	39,143 (61.9%)	12,927 (20.4%)	8,302 (13.1%)	2,880 (4.6%)	63,252 (100%)
Outpatient (%)	36,845 (94.1%)	11,905 (92.1%)	7,820 (94.2%)	2,631 (91.4%)	59,201 (93.8%)
Hospitalized (%)	2,298 (5.9%)	1,022 (7.9%)	482 (5.8%)	249 (8.6%)	4,051 (6.2%)
Total Deaths (%)	464 (1.2%)	107 (0.8%)	84 (1.0%)	45 (1.6%)	1,326 (2.1%)

Figure 3. Proportion of hospitalized patients by jurisdiction



Regarding deaths, 1,326 fatalities were recorded, representing 2.1% of the total patients. Jurisdiction I reported the highest number of deaths, with 464 cases (1.2%), followed by Jurisdiction II with 107 deaths (0.8%). Jurisdictions III and IV reported 84 (1.0%) and 45 (1.6%) deaths, respectively. These results underscore that, while most patients did not require hospitalization, the absolute number of deaths is notable in Jurisdiction I due to its larger volume of cases, while the proportion of deaths in Jurisdiction IV underscores a higher relative risk within a smaller population.

Table 3 shows the distribution of the main comorbidities among patients in the different jurisdictions. The most prevalent comorbidities were hypertension, obesity, and diabetes, while respiratory diseases such as COPD and asthma affected a smaller percentage of the population. Diabetes was present in 7.4% of total cases, with the highest prevalence in Jurisdiction II, where it reached 8.6%. Hypertension affected 11.6% of patients overall, with the highest prevalence in Jurisdiction I (11.8%) and the lowest in Jurisdiction IV (9.7%). Obesity was observed in 9.7% of patients, with variable distribution across the jurisdictions. Jurisdiction II had the highest prevalence (11.4%), while Jurisdiction IV had the lowest (5.2%).

Regarding respiratory diseases, COPD was reported in 0.6% of cases, being more common in Jurisdiction IV (1.1%). Similarly, asthma affected 2.4% of patients, with Jurisdiction I reporting the highest percentage (2.8%), and in total, 1,174 patients had pneumonia (1.8%). Other comorbidities, such as cardiovascular diseases and chronic kidney disease, affected a relatively low percentage of patients, with prevalences below 1.5% in all jurisdictions. Immunosuppression was reported uniformly across all jurisdictions, affecting approximately 0.6% of patients. Lastly, smoking was an important comorbidity, present in 6.3% of total cases, with the highest prevalence in Jurisdiction I (8.4%).

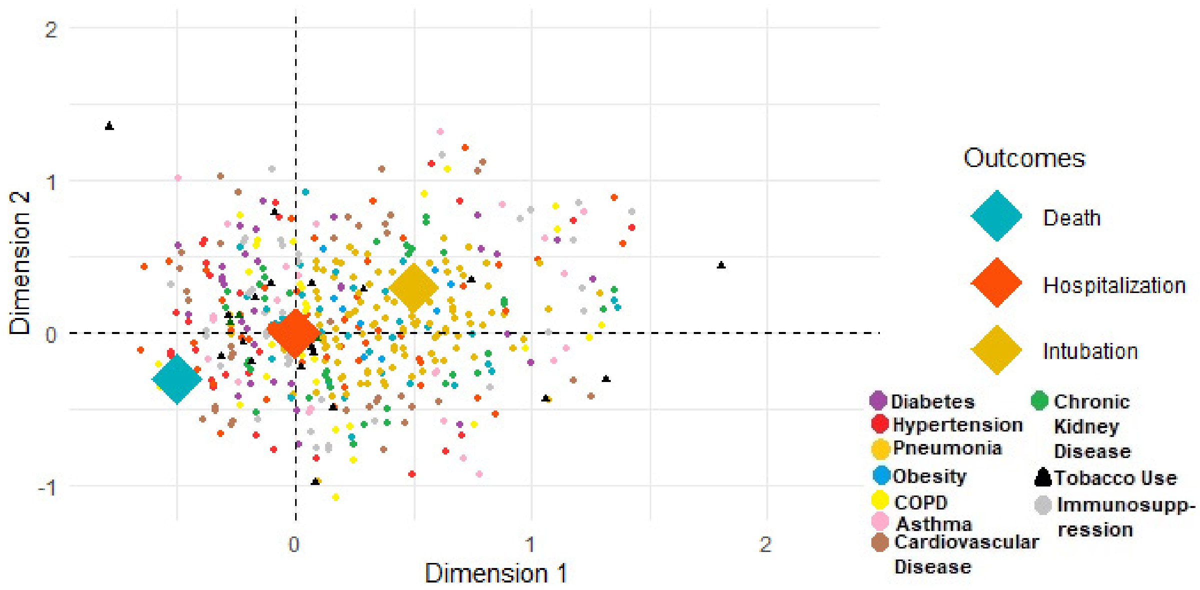
A multivariate analysis was conducted to evaluate the relationship between various covariates and the three severe outcomes included in the study (hospitalization, intubation, and death), using the graph of relative inertias. Relative inertia is a measure that identifies the individual contribution of each covariate to the total variability of the model, providing information about the specific weight of each variable in predicting the outcome. This measure is particularly useful for highlighting the variables with the greatest influence on clinical outcomes.

The results of the analysis generally show a greater tendency of the covariates toward intubation ($r = 0.7362$, $p = 0.02$). Furthermore, the covariates pneumonia and obesity exhibited the highest relative inertias toward intubation. Pneumonia had a relative inertia of $r = 0.6754$, $p = 0.03$, while obesity showed a value of $r = 0.6259$, $p = 0.04$ (Figure 4).

Table 3. Comorbidity Distribution by Jurisdiction

Comorbidity	Jurisdiction I	Jurisdiction II	Jurisdiction III	Jurisdiction IV	Total
Diabetes (%)	2,914 (7.4%)	1,115 (8.6%)	675 (8.1%)	195 (6.8%)	4,899 (7.4%)
Hypertension (%)	4,622 (11.8%)	1,503 (11.6%)	924 (11.1%)	279 (9.7%)	7,328 (11.6%)
Pneumonia (%)	554 (0.8%)	332 (0.5%)	189 (0.3%)	99 (0.15%)	1,174 (1.8%)
Obesity (%)	3,815 (9.7%)	1,468 (11.4%)	813 (9.8%)	151 (5.2%)	6,247 (9.7%)
COPD (%)	253 (0.6%)	116 (0.9%)	92 (1.1%)	33 (1.1%)	494 (0.6%)
Asthma (%)	1,092 (2.8%)	238 (1.8%)	190 (2.3%)	26 (0.9%)	1,546 (2.4%)
Cardiovascular Disease (%)	402 (1.0%)	161 (1.2%)	113 (1.4%)	23 (0.8%)	699 (1.1%)
Chronic Kidney Disease (%)	286 (0.7%)	90 (0.7%)	87 (1.0%)	11 (0.4%)	474 (0.7%)
Tobacco Use (%)	3,290 (8.4%)	498 (4.5%)	190 (2.3%)	26 (0.9%)	4,004 (6.3%)
Immunosuppression (%)	238 (0.6%)	83 (0.6%)	46 (0.6%)	20 (0.7%)	387 (0.6%)

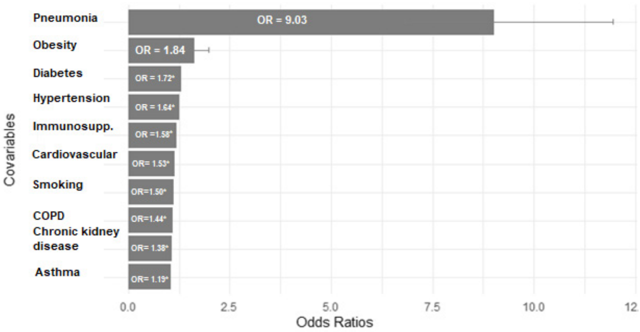
Figure 4. Multivariate analysis using the graph of relative inertias between specific covariates and severe outcomes, such as hospitalization, intubation, or death



ISSN 2282-0930 • Epidemiology Biostatistics and Public Health - 2024, Volume 19, Issue 2

Once it was observed that most covariates were more strongly associated with intubation, the association between each covariate (comorbidities) and intubation was evaluated using the Odds Ratio test (Figure 5). The odds ratios reflect the strength of the association between each covariate and the risk of a patient requiring intubation. Significant associations were found between intubation and pneumonia, with an OR of 9.03 (95% CI: 6.82 - 11.96, p = 0.03). Similarly, a strong association was identified between obesity and intubation, with an OR of 1.84 (95% CI: 1.35 - 1.98, p = 0.001).

Figure 5. Risk association between different covariables and intubation by COVID



**No statistical significance*

DISCUSSION

The findings of this study, which analyzed 63,252 valid records of COVID-19 patients, offer a comprehensive epidemiological and clinical profile of the disease across distinct health jurisdictions in Durango, Mexico. Jurisdiction I, representing the most densely populated region, accounted for 61.9% of total cases, with a notable mortality rate of 2.1%. This highlights the severity of the pandemic in this area, likely influenced by multiple factors, including access to healthcare, the capacity of health infrastructure, and the demographic composition of the population, given that a significant portion of Durango's inhabitants reside there.

A critical insight from the analysis is that 93.8% of the patients received outpatient care, indicating that most cases were mild and did not necessitate hospitalization. However, the 6.2% of patients requiring hospitalization and the 2.1% mortality rate point to the vulnerability of certain subgroups that may not be receiving timely or adequate medical intervention. The predominance of outpatient management mirrors trends reported in other studies, where a significant proportion of COVID-19 patients exhibit mild symptoms manageable at home, while those admitted to hospitals typically face more severe disease courses [17-20].

The pattern of comorbidities observed in this population aligns with existing literature, with hypertension, obesity, and diabetes identified as major contributors to the severity of COVID-19 [21,22]. As noted by Gallo et al. [23], hypertension is often linked with advanced age and other cardiovascular risk factors that may predispose individuals to infection [23]. However, in this study, the median age was relatively young at 38 years, yet 11.6% of patients were hypertensive, suggesting that factors beyond advanced age are at play. Yamazaki O et al. [24], have also demonstrated that the association between pre-existing hypertension and hospital mortality in COVID-19 patients may be largely explained by the concurrent presence of other risk factors such as obesity, diabetes, cardiovascular disease, and chronic kidney disease [24]. Further investigation into the role of hypertension, independent of these co-factors, in the progression of COVID-19 is warranted.

Obesity, present in 9.7% of patients, emerged as a significant risk factor, consistent with findings that obese individuals are more likely to require intubation and face severe complications [25,26]. Michalakis et al. [27], have highlighted the specific inflammatory and immunological challenges posed by obesity, which increase susceptibility to severe respiratory infections and exacerbate the morbidity and mortality of SARS-CoV-2 infections [27]. Our study corroborates these findings, demonstrating a strong association between obesity and the need for intubation, underscoring the necessity of addressing obesity as a modifiable risk factor in both the prevention and management of COVID-19.

The significant association between pneumonia and intubation emphasizes the need for proactive clinical vigilance in managing respiratory complications in COVID-19 patients. This is in line with existing research, which identifies pneumonia as a critical factor that escalates the need for mechanical ventilation and increases mortality risk [28,29]. With 92.9% of intubated patients in this study also diagnosed with pneumonia, healthcare providers must prioritize the early detection and treatment of this condition, particularly in high-risk patients.

Variations in the prevalence of comorbidities across jurisdictions may reflect disparities in healthcare access, socioeconomic status, and lifestyle factors. For instance, Jurisdiction II exhibited the highest prevalence of obesity (11.4%), indicating the need for region-specific interventions. The results underscore the importance of a comprehensive, multidisciplinary public health approach, not only addressing the infectious disease itself but also the underlying risk factors that predispose individuals to severe COVID-19. This approach should include health promotion, education on chronic disease management, and the enhancement of primary healthcare systems to ensure that individuals with comorbidities receive appropriate care and follow-up.

By addressing these multifaceted factors, healthcare systems can better manage the pandemic's impacts and improve outcomes for vulnerable populations, particularly in regions with high comorbidity prevalence and healthcare disparities.

CONCLUSION

This study underscores the substantial burden of comorbidities in COVID-19 patients and their profound impact on disease outcomes, particularly in relation to severity. The strong association between pneumonia and the need for intubation highlights the critical importance of early identification and management of respiratory complications. Furthermore, the recognition of key modifiable risk factors, such as obesity and hypertension, should inform targeted public health strategies aimed at reducing the risk of severe COVID-19 manifestations. The findings reinforce the necessity of a multidisciplinary, patient-centered approach to the management of COVID-19, which integrates early clinical intervention, tailored comorbidity management, and public health initiatives focused on prevention and health promotion in at-risk populations. This holistic approach will be vital in mitigating the long-term impacts of COVID-19, especially in vulnerable demographic groups.

ACKNOWLEDGMENTS

The authors thank the National Council of Humanities Science and Technology [CONAHCYT, Estancias Posdoctorales por México 2022(3)], for the financial support to carry out the project.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article further inquiries can be directed to the corresponding autor.

REFERENCES

1. WHO. Coronavirus disease (COVID-19) pandemic. [Internet]. [citado 2024 Oct 25]. Disponible en: https://www.who.int/europe/emergencies/situations/covid-19
2. UNICEF. [Internet]. [citado 2024 Oct 25]. Disponible en: https://data.unicef.org/resources/covid-19-confirmed-cases-and-deaths-dashboard
3. COVID-19 tablero México. [Internet]. [citado 2024 Oct 25]. Disponible en: https://datos.covid-19.conacyt.mx
4. Taboada BI, Zárate S, García-López R, Muñoz-Medina JE, Gómez-Gil B, Herrera-Estrella A, et al. SARS-CoV-2 Omicron variants BA.4 and BA.5 dominated the fifth COVID-19 epidemiological wave in Mexico. Microb Genom. 2023;9(12):001120. doi:10.1099/mgen.0.001120
5. Pfortmueller CA, Spinetti T, Urman RD, Luedi MM, Schefold JC. COVID-19-associated acute respiratory distress syndrome (CARDS): Current knowledge on pathophysiology and ICU treatment - A narrative review. Best Pract Res Clin Anaesthesiol. 2021;35(3):351-68. doi:10.1016/j.bpa.2020.12.011
6. Li CX, Noreen S, Zhang LX, Saeed M, Wu PF, Ijaz M, et al. A critical analysis of SARS-CoV-2 (COVID-19) complexities, emerging variants, and therapeutic interventions and vaccination strategies. Biomed Pharmacother. 2022;146:112550. doi:10.1016/j.biopha.2021.112550
7. Marušić J, Hasković E, Mujezinović A, Đido V. Correlation of pre-existing comorbidities with disease severity in individuals infected with SARS-COV-2 virus. BMC Public Health. 2024;24(1):1053. doi:10.1186/s12889-024-18457-2
8. Zhang JJ, Dong X, Liu GH, Gao YD. Risk and protective factors for COVID-19 morbidity, severity, and mortality. Clin Rev Allergy Immunol. 2023;64(1):90-107. doi:10.1007/s12016-022-08921-5
9. Vergara P, Rossi L, Biagi A, Falasconi G, Pannone L, Zanni A, et al. Role of comorbidities on the mortality in patients with SARS-CoV-2 infection: an Italian cohort study. Minerva Med. 2023;114(2):185-90. doi:10.23736/S0026-4806.21.07187-1
10. Rollston R, Galea S. COVID-19 and the social determinants of health. Am J Health Promot. 2020;34(6):687-9. doi:10.1177/0890117120930536
11. Mosnaim G, Carrasquel M, Wolfson AR, Peters J, Lang D, Rathkopf M. Social determinants of health and COVID-19. J Allergy Clin Immunol Pract. 2023;11(11):3347-55. doi:10.1016/j.jaip.2023.07.027
12. Green-Laughlin D. COVID-19: A closer lens. Issues Ment Health Nurs. 2020;41(8):662-4. doi:10.1080/01612840.2020.1773736
13. Yi SS, Ali SH, Chin M, Russo RG, Đoàn LN, Rummo P. Contrasting the experiences for high- and low-income Asian Americans during COVID-19. Prev Med Rep. 2021;24:101519. doi:10.1016/j.pmedr.2021.101519
14. Abrams EM, Szefler SJ. COVID-19 and the im-

pact of social determinants of health. Lancet Respir Med. 2020;8(7):659-61. doi:10.1016/S2213-2600(20)30234-4
15. Salgado de Snyder VN, McDaniel M, Padilla AM, Parra-Medina D. Impact of COVID-19 on Latinos: A social determinants of health model and scoping review of the literature. Hisp J Behav Sci. 2021;43(3):174-203
16. CONABIO. México megadiverso. [Internet]. [citado 2024 Oct 25]. Disponible en: https://www.biodiversidad.gob.mx/pais/quees
17. Liapikou A, Tzortzaki E, Hillas G, Markatos M, Papanikolaou IC, Kostikas K. Outpatient management of COVID-19 disease: A holistic patient-centered proposal based on the Greek experience. J Pers Med. 2021;11(8):709. doi:10.3390/jpm11080709
18. Lane A, Hunter K, Lee EL, Hyman D, Bross P, Alabd A, et al. Clinical characteristics and symptom duration among outpatients with COVID-19. Am J Infect Control. 2022;50(4):383-9. doi:10.1016/j.ajic.2021.10.039
19. Li BW, Fan X, Cao WJ, Tian H, Wang SY, Zhang JY, et al. Systematic discovery and pathway analyses of metabolic disturbance in COVID-19. Infect Dis Immun. 2021;1(2):74-85. doi:10.1097/ID9.0000000000000010
20. Guan W, Ni Z, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382(18):1708-20. doi:10.1056/nejmoa2002032
21. Gao YD, Ding M, Dong X, Zhang JJ, Kursat Azkur A, Azkur D, et al. Risk factors for severe and critically ill COVID-19 patients: A review. Allergy. 2021;76(2):428-55. doi:10.1111/all.14657
22. Asselah T, Durantel D, Pasmant E, Lau G, Schinazi RF. COVID-19: Discovery, diagnostics and drug development. J Hepatol. 2021;74(1):168-84. doi:10.1016/j.jhep.2020.09.031
23. Gallo G, Calvez V, Savoia C. Hypertension and COVID-19: Current evidence and perspectives. High Blood Press Cardiovasc Prev. 2022;29(2):115-23. doi:10.1007/s40292-022-00506-9
24. Yamazaki O, Shibata S. Severe COVID-19 and preexisting hypertension: A matter of age?. Hypertens Res. 2022;45(9):1523-5. doi:10.1038/s41440-022-00978-1
25. De Jong A, Molinari N, Pouzeratte Y, Verzilli D, Chanques G, Jung B, et al. Difficult intubation in obese patients: incidence, risk factors, and complications in the operating theatre and in intensive care units. Br J Anaesth. 2015;114(2):297-306. doi:10.1093/bja/aeu373
26. de Leeuw AJM, Oude Luttikhuis MAM, Wellen AC, Müller C, Calkhoven CF. Obesity and its impact on COVID-19. J Mol Med (Berl). 2021;99(7):899-915. doi:10.1007/s00109-021-02072-4
27. Michalakis K, Panagiotou G, Ilias I, Pazaitou-Panayiotou K. Obesity and COVID-19: A jigsaw puzzle with still missing pieces. Clin Obes. 2021;11(1):e12420. doi:10.1111/cob.12420
28. Wicky PH, Dupuis C, Cerf C, Siami S, Cohen Y, Laurent V, et al. Ventilator-associated pneumonia in COVID-19 patients admitted in intensive care units: relapse, therapeutic failure and attributable mortality-a multicentric observational study from the OutcomeRea Network. J Clin Med. 2023;12(4):1298. doi:10.3390/jcm12041298
29. Manrique S, Claverias L, Magret M, Masclans JR, Bodi M, Trefler S, et al. Timing of intubation and ICU mortality in COVID-19 patients: A retrospective analysis of 4198 critically ill patients during the first and second waves. BMC Anesthesiol. 2023;23(1):140. doi:10.1186/s12871-023-02081-5

ISSN 2282-0930 • Epidemiology Biostatistics and Public Health - 2024, Volume 19, Issue 2

Association Between Overweight and Central Obesity in Women of Reproductive Age and Overweight in Children Under Five Years of Age

Jaimini Sarkar[(1)], *Chiradeep Sarkar*[(2)]

(1) Mumbai Metropolitan Region (MMR), Maharashtra, India.
(2) Department of Biotechnology, G. N. Khalsa College (Autonomous), University of Mumbai, Matunga, Mumbai-19, India.

CORRESPONDING AUTHOR: Chiradeep Sarkar, Department of Biotechnology, G. N. Khalsa College (Autonomous), University of Mumbai, Matunga, Mumbai-19, India. e-mail: chiradeep.sarkar@gnkhalsa.edu.in

SUMMARY

Objective: Childhood obesity is becoming an emerging public health issue as it is associated with increased morbidity and premature deaths. Determinants like the child's household characteristics, maternal weight before the preconception stage, and maternal weight in childhood are studied. This study aims to understand the relationship between overweight women of reproductive age and overweight children under the age of five to inform future intervention strategies.
Methods: The data for the study were collected from the India's National Family Health Survey- 5 (NFHS-5). This study is based on publicly available, anonymized secondary data. It has been sub-grouped into urban and rural categories. The percentage of women with high-risk Waist-Hip-Ratio (WHR) and the percentage of overweight women were independent variables whereas the percentage of overweight under-five children was the dependent variable. Spearman rank correlation coefficient, simple linear regression, and multiple linear regression analysis were used to analyze the collected data. Descriptive analysis was done for mean, median, and mode.
Results: Study shows the percentage of overweight women has increased by 4.1%, and the percentage of overweight children has increased by 2% during the NFHS5 (2019-21) compared to NFHS4 (2015-16). The Spearman's rank correlation coefficient (rs) values are 0.4032 for urban, 0.6867 for rural, and 0.5835 for the total population of women with high-risk WHR and overweight children under five years of age whereas the analysis for the percentage of overweight women and percentage of overweight children under five years of age has shown rs=0.389 for rural and rs=0.03893 for total population. Multiple linear regression analysis was done for the total population at a significance level of 0.05 for the independent variables percentage of overweight women, the percentage of women with high risk WHR, and the dependent variable, the percentage of overweight children under five years of age. The results indicated (b0=-3.0448, b1=-0.0202, and b2=0.1397). Simple linear regression of the total population for the independent variable overweight women and dependent variable overweight children under five years of age shows (R=0.0344, Rsquare=0.0012, p-value=0.8421, and b=0.0099) and for the overweight children under five years of age and high-risk WHR women (R=0.5662, Rsquare=0.3205, p-value=0.0003, and b=0.1366).
Conclusions: Central obesity or high-risk WHR in women is more common than being overweight. The number of overweight women as well as children under five years is increasing. Central obesity in women shows a moderate positive relation with overweight in children under five years. It shows when the number of women with high-risk WHR increases, there will be an increase in the number of overweight children under five years of age.

Keywords: Child health; overweight; WHO; obesity; NFHS5; waist-hip ratio.

DOI: 10.54103/2282-0930/26847
Accepted: 3rd December 2024

INTRODUCTION

According to the World Health Organization (WHO), 37 million children under five were overweight in 2022. The data further says the share of children under five years who are defined as obese is increasing from 4.9% in 1995, 5.3% in 2000, and 5.6% in 2022. Overweight is the condition of excessive fat deposits. It is weight for height greater than 2 standard deviations above WHO child growth standards median [1]. Childhood obesity affects physical and psychological health with consequences like non-insulin-dependent diabetes, hypertension, Gastroesophageal Reflux Disease (GERD), cardiovascular problems, hepatic steatosis, bronchial asthma, Obstructive Sleep Apnea (OSA), etc [2].

The studies show family size, maternal health, unhealthy food practices, poor diet, poverty, and physical inactivity are some of the determinants of being overweight in children under five [3]. A study shows that the determining factors are household wealth, a child's dietary diversity, maternal Body Mass Index (BMI), and education [4]. Earlier studies are mainly based on the household characteristics of the child and their association with being overweight.

Studies are also available where the positive association of overweight children with maternal weight in the preconception stage and maternal weight during childhood is observed [5]. There is no study available to understand the association between overweight women of reproductive age and children under five years of age. This study has been designed to find out overweight and central obesity in women of reproductive age (15-49 years) and overweight in children under five years of age.

Among the obesity anthropometric indices, the waist-hip ratio (WHR) is considered superior to BMI in predicting obesity-related diseases [6]. Abdominal obesity showing high WHR has been proven to predict diseases such as hypertension, coronary heart disease, non-insulin-dependent diabetes, and stroke [7]. Hence the WHR is considered a parameter for this study.

The aim of this study is to investigate the association between overweight women of reproductive age, including those with a high-risk WHR, and overweight children under the age of five.

METHODS

Type of the study

Secondary data analysis

Study population

This study covered a population of 724,115 women in the 15-49 age group and children under five. Women and children under five were divided into two sub-samples, urban and rural.

Database used for study

The study data was obtained from the National Family Health Survey-5 (NFHS-5) from the Ministry of Health and Family Welfare (MoHFW), Government of India. The NFHS data for rounds 1-5 are openly available with (MoHFW), India [8].

The NFHS-5 is the fifth in the NFHS series which provides state-wise information on population, health, and nutrition for India. The contents of NFHS-5 are similar to NFHS-4 to allow comparisons over time. But NFHS-5 has included some new topics like preschool education, disability, access to a toilet facility, death registration, bathing practices during menstruation, and methods and reasons for abortion. The anthropometric parameters like the measurement of waist and hip circumferences are included in NFHS5 which were not there in NFHS4.

This national-level survey was carried out in two phases- the first phase was for 17 states and 5 Union territories from 17 June 2019 to 30 January 2020, and the second phase has been completed in 11 States and 3 UTs from 2 January 2020 to 30 April 2021.

Study approval

This study is based on the publicly available data of NFHS5 on the Ministry of Health and Family Welfare website, in India. No identifiable information on the participants is given. As per the data provided, the ethical approval for the NFHS-5 surveys is obtained from the ethics review board of the International Institute for Population Sciences, Mumbai, India. These surveys are reviewed and approved by the ICF Institutional Review Board, USA. Informed written consent for participation in this survey is obtained from the respondents during the survey. Each individual's approval is sought before the patient interview, as per the consistent methodology followed in these national surveys.

Study variables

The primary outcome variable or dependent variable in this study is the percentage of under-five overweight children. Whereas the independent variables or explanatory variables are the percentage of overweight women and the percentage of women with high-risk WHR. The waist and hip circumference measurements were taken using Gulick tapes to measure abdominal obesity. The WHO set cut-offs for women with high-risk WHR (≥0.85 cm) have been used for this study.

ISSN 2282-0930 • Epidemiology Biostatistics and Public Health - 2024, Volume 19, Issue 2

Statistical analysis

The collected data on overweight children under five years of age, overweight women, and high-risk WHR women were provided in percentage (%). Descriptive statistical analysis, mean, median, and mode were calculated for the collected data. The mean, median, and mode are calculated for these percentages reported for each state and Union territory of the country, as well as for urban and rural areas of these states and Union Territories. The mean, median, and mode represent the central or typical values in a distribution hence to understand measures of central tendency in such a large sample size these descriptive tests were done.

Spearman rank correlation coefficient, Simple linear regression, and Multiple linear regression were done to understand the relation between the dependent variable (Y)- the percentage of overweight children under five years of age, and independent variables (X)- the percentage of overweight women and percentage of women with high-risk WHR. Linear regression analysis was done to predict and understand the nature of the relationship between the study variables whereas the Spearman rank correlation coefficient is used to measure the strength of an association and direction of the relationship between these variables. Online statistical software Stats.Blue (https://stats.blue/) was used for all the above-said statistical analysis.

RESULTS

Descriptive analysis shows, that compared to NFHS4 (23.6%), the percentage of women who are overweight has increased in NFHS5 (27.7%). Similarly, the percentage of overweight children has increased from 2.9% to 4.9% in NFHS4 to NFHS5 (Table 1).

Table 1. State & Union Territories wise data on study parameters

	Overweight Women (%)				**Women with high risk WHR (%)**				**Overweight children (%)**			
State	**U***	**Rƚ**	**T5ɸ**	**T4¥**	**U***	**Rƚ**	**T5ɸ**	**T4¥**	**U***	**R‡**	**T5‡**	**T4¥**
Jammu & Kashmir	33.4	27.9	29.3	29.3	89.2	87.3	87.8	–	10.8	9.3	9.6	5.7
Himachal Pradesh	38.3	29.2	30.4	28.6	60.3	62.1	61.9	–	5.4	5.7	5.7	1.9
Punjab	44.3	38.8	40.8	31.3	73.0	72.6	72.8	–	4.4	4.0	4.1	2.3
Uttarakhand	39.1	25.4	29.7	20.4	62.8	63.0	62.9	–	4.4	3.9	4.1	3.5
Haryana	37.5	30.9	33.1	21.0	64.6	61.7	62.6	–	3.3	3.3	3.3	3.1
Delhi	41.2	44.6	41.3	33.5	67.6	69.0	67.7	–	4.0	4.5	4.0	1.2
Uttar Pradesh	30.6	18.3	21.3	16.5	61.7	55.2	56.8	–	3.6	2.9	3.1	1.5
Chandigarh	43.9	–	44.0	41.5	60.4	–	60.7	–	1.9	–	1.9	1.1
Ladakh	28.5	28.2	28.3	16.3	88.6	85.8	86.3	–	17.0	12.4	13.4	4.0
Andhra Pradesh	44.4	32.6	36.3	33.2	52.7	47.2	48.9	–	3.0	2.6	2.7	1.2
Karnataka	37.1	25.6	30.1	23.3	46.8	43.9	45.1	–	3.8	2.9	3.2	2.6
Kerala	40.4	36.0	38.1	32.4	71.1	70.2	70.7	–	3.8	4.2	4.0	3.4
Tamil Nadu	46.1	35.4	40.4	30.9	58.3	53.8	55.9	–	5.1	3.7	4.3	5.0
Telangana	41.7	23.8	30.1	28.6	47.5	42.3	44.1	–	4.2	3.0	3.4	0.7
Puducherry	47.6	43.2	46.2	36.7	55.4	52.0	54.3	–	2.7	6.5	3.8	2.2
Andaman & Nicobar	41.7	35.7	38.1	31.8	72.2	80.7	77.3	–	5.7	5.2	5.4	3.0
Lakshwadeep	34.2	31.0	33.5	40.6	69.1	66.2	68.4	–	10.0	11.8	10.5	1.6
Bihar	25.2	14.2	15.9	11.7	68.4	58.8	60.3	–	2.2	2.4	2.4	1.2
Jharkhand	21.6	8.6	11.9	10.3	66.4	56.2	58.7	–	2.8	2.8	2.8	1.5
Odisha	40.1	19.2	23.0	16.5	70.7	61.3	63.0	–	5.5	3.2	3.5	2.6
West Bengal	27.9	20.3	22.7	19.9	80.1	72.1	74.7	–	6.0	3.6	4.3	2.1
Rajasthan	20.6	10.5	12.9	14.1	62.1	58.1	59.0	–	3.9	3.1	3.3	2.1
Maharashtra	29.6	18.3	23.4	23.4	51.5	38.6	44.5	–	5.2	3.4	4.1	1.9

Gujrat	30.4	17.0	22.6	23.7	47.2	41.2	43.7	–	4.6	3.5	3.9	1.9
Goa	38.1	33.1	36.1	33.5	51.1	51.0	51.1	–	2.2	3.6	2.8	3.7
Dadara, Nagar Haveli, Diu & Daman	34.0	20.3	26.8	23.3	46.2	44.7	45.4	–	1.2	2.5	1.9	3.9
Chattisgarh	23.1	11.3	14.1	11.9	64.5	52.5	55.4	–	5.7	3.6	4.0	2.9
Madhya Pradesh	26.0	13.0	16.6	13.6	42.0	39.9	40.5	–	1.8	2.1	2.0	1.7
Arunachal Pradesh	28.9	22.9	23.9	18.8	66.6	69.4	68.9	–	9.6	9.7	9.7	4.9
Assam	23.8	13.6	15.2	13.2	66.6	67.3	67.2	–	8.0	4.5	4.9	2.3
Manipur	39.0	31.0	34.1	26.0	69.7	63.1	65.7	–	2.9	3.6	3.4	3.1
Meghalaya	17.9	9.7	11.5	12.2	55.7	61.9	60.6	–	4.2	4.0	4.0	3.9
Mizoram	29.7	16.9	24.2	21.0	47.8	47.3	47.6	–	12.1	8.1	10.0	4.2
Nagaland	17.1	13.0	14.4	16.2	59.6	63.4	62.0	–	4.8	4.9	4.9	3.8
Sikkim	41.0	30.8	34.7	26.7	71.9	78.0	75.6	–	3.5	12.2	9.6	8.6
Tripura	29.2	18.4	21.5	16.0	67.7	60.4	62.5	–	9.3	7.8	8.2	3.0
Mean	**33.7**	**23.6**	**27.7**	**23.6**	**62.7**	**58.3**	**60.9**	**--**	**5.2**	**4.8**	**4.9**	**2.9**
Median	**34.1**	**23.4**	**28.8**	**23.3**	**63.7**	**60.9**	**61.3**	**--**	**4.3**	**3.7**	**4.0**	**2.6**
Mode	**41.7**	**18.3**	**30.1**	**28.6**	**66.6**	**87.3**	**87.8**	**--**	**4.4**	**3.6**	**4.0**	**1.9**

**U-Urban; ǂR-Rural; ɸT5-Total NFHS5 (2019-21); ¥T4-Total NFHS4 (2015-16)*

When the mean values are compared for urban-rural difference for percentage of overweight women, percentage of women with central obesity, and percentage of overweight children; all the variables had higher values in urban areas compared to rural ones (Fig 1).

The Spearman rank correlation coefficient analysis shows a significant large positive correlation between the percentage of women with high-risk WHR and the percentage of overweight children under five years of age (Table 2).

The Spearman's rank correlation coefficient (rs) values are 0.4032 for urban, 0.6867 for rural, and 0.5835 for total population. It shows when the number of women with high-risk WHR increases there will be an increase in the number of overweight children

Figure 1. Average of national-level values for overweight women and children

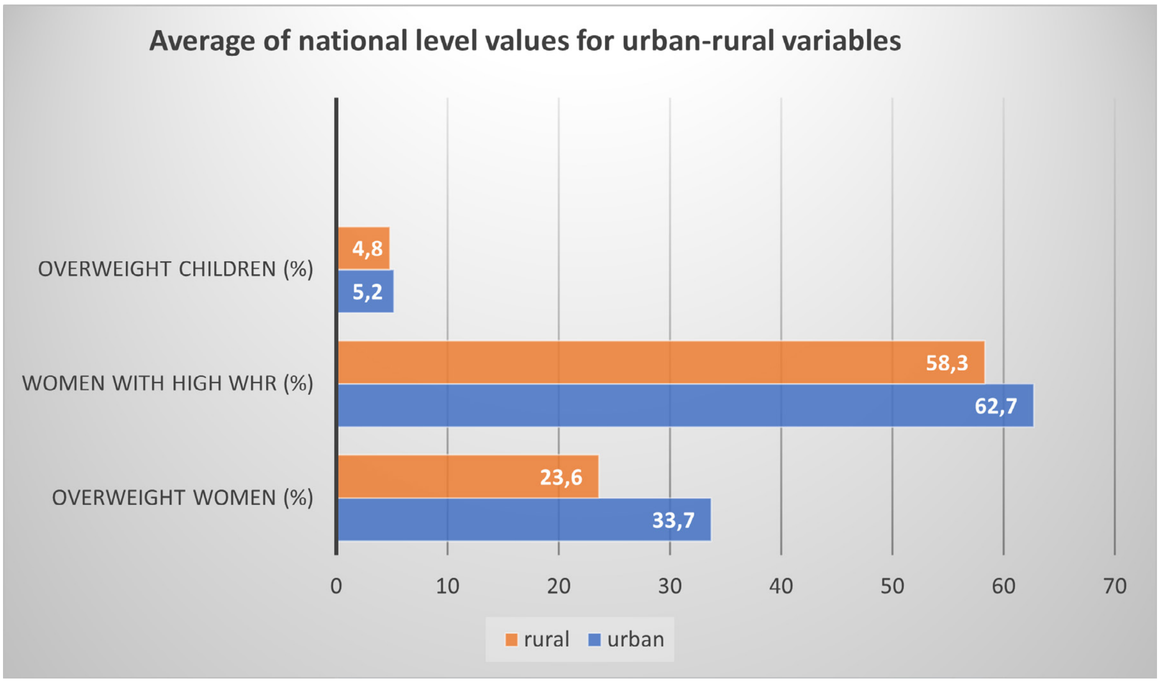


Table 2. Inference table for Spearman's rank correlation coefficient Analysis

Independent variable (X)	Dependent Variable (Y)	Population	Spearman's rank correlation coefficient (r_s)	p-value	Co-variance	Statistic	Results
Overweight women	Overweight children	Urban	-0.2225	0.1922	-24.6857	-1.3306	Non-significant, small, negative relationship
		Rural	0.389	0.01902	43.1357	2.4624	Significant, medium, positive relationship
		Total	0.03893	0.8217	4.3143	0.2271	Non-significant, very small, positive relationship
Women with High-risk WHR	Overweight children	Urban	0.4032	0.01474	44.7429	2.5695	Significant, medium, positive relationship
		Rural	0.6867	0.000003	76.1571	5.5078	Significant, large, positive relationship
		Total	0.5835	0.00018	64.6857	4.19	Significant, large, positive relationship

under five years of age. When the analysis was carried out for the relationship between the percentage of overweight women and the percentage of overweight children under five years of age, it showed a very small positive relationship in rural (rs= 0.389) and total population (rs= 0.03893) whereas a non-significant small negative relationship was observed for urban population (rs= - 0.2225).

Multiple linear regression analysis was done for the total population at a significance level of 0.05 (Table 3).

The independent variables were the percentage of overweight women (X1) and the percentage of women with high-risk WHR (X2) and the dependent variable (Y)-the percentage of overweight children under five years of age. The results indicated that there was a moderate collective significant effect between the percentage of overweight women (X1), the percentage of women with high-risk WHR (X2), and the dependent variable (Y)- the percentage of overweight children under five years of age.

Table 3. Inference table of multiple linear regression analysis for total population

Independent variables (X)	Dependent variable (Y)	Coefficient	α	p-value	Results
Overweight women (X1)	Overweight children	b/b0=-3.0448	0.05	0.1896	Moderate collective significant effect between variables
Women with High-risk WHR (X2)		X1/b1=-0.0202	0.05	0.6331	
		X2/b2=0.1397	0.05	0.0004	
Summary of overall regression-R-square=0.3253 p-value=0.0015					
Regression equation- percentage of overweight children = -3.0448-0.0202. percentage of overweight women + 0.1397. percentage of women with central obesity.					

Simple linear regression of the total population for the independent variable overweight women and dependent variable overweight children under five years of age shows (R= 0.0344, Rsquare= 0.0012, p-value= 0.8421, and b= 0.0099) very weak direct relationship (Table 4).

Simple linear regression for the dependent variable overweight children under five years of age and independent variable central obesity in women (R= 0.5662, Rsquare= 0.3205, p-value= 0.0003, and b= 0.1366) shows a moderate direct relationship. This means when the percentage of women with high-risk WHR will increase by 1 percentage then the percentage of overweight children under five years of age will increase by 0.1366. It shows High-risk WHR in women has more effect than obesity or overweight in children under five years of age.

DISCUSSION

This study shows a significant moderate positive correlation between women with high-risk WHR and overweight children under five years of age. If compared, the WHR in women has a significant relationship with the obesity of the children under five years of age more than the overweight of the women.

Factors like maternal employment [9], family structure [10], childhood daycare and education centres [11], and their effect on the weight of children are studied earlier. At the same time, the earlier studies on the relationship between a parent's obesity and a child's overweight show a positive relation [12]. This study is different as the percentage of women with overweight and high-risk WHR, along with the rate of overweight children is studied. Our findings suggest that with an increasing percentage of women with high-risk WHR, the percentage of overweight children below five will increase.

Our study shows that more urban women are overweight than rural ones, similar to earlier works [13]. A survey of the Nigerian women population shows 35.5% overweight women in urban areas, compared to 21.1% in rural areas. This study shows characteristics of women like household wealth, employment, old age, higher education, marital status, number of children, and contraceptive use are the determinants behind the urban-rural divide of overweight women in reproductive age [14,15].

A similar study was conducted on Bangladeshi women to know the urban-rural obesity trend. This study highlighted the increasing obesity trend in cities is due to rapid urbanization, modern transport, fast and processed food, and a sedentary lifestyle [16].

Urbanization is the most important contributor to being overweight due to access to unhealthy food and less physical activity [17]. The study carried out in Indian urban women of reproductive age for the period 2005-2021 also states the prevalence of obesity has increased in urban India from 23% in 2005-06 to 33% in 2019-21 [18].

As per our study, compared to NFHS4, the percentage of overweight women is increasing at the country level. Similar observations were seen in analyses conducted in Tanzania [19], Kenya [20], and Sub-Saharan African countries like Eswatini, Mauritania, South Africa, Gabon, Lesotho, and Ghana [21].

Overweight children under five years of age are not an urban phenomenon, it is seen in rural also. Maternal factors like age at the time of marriage, BMI, education, and media exposure are considered factors associated with under-five overweight children. Along with these factors, dietary diversity score, sex, age, birth weight, birth rank, and number of children are also the determining factors of childhood overweight [22].

Compared to NFHS4 data, the percentage of overweight children is increasing. A study was carried out on Chinese children to understand the urban-rural trend of childhood overweight for 29 years. It shows childhood obesity has been increasing continuously over the years in the country and though the percentage of overweight children is more in urban than rural, the gap between urban and rural is getting narrower [23]. Our study is important from a future point of view. Policies and interventions should be designed considering the rural children too.

This study shows high-risk waist-to-hip ratio in women is a mixed phenomenon observed in urban and rural women. The overall prevalence of central obesity was observed at 55% when five Indian cities were studied for central obesity in the urban women population [24]. The data analysis of our study shows an increasing trend of central obesity where 62.7% of urban women have high-risk WHR whereas 58.3% of rural women have high-risk WHR. A study carried out

Table 4. Inference table of simple linear regression analysis for total population

Independent variable (X)	Dependent variable (Y)	p-value	α	R	R^2	b	Results
Overweight women	Overweight children	0.8421	0.05	0.0344	0.0012	0.0099	Very weak direct relationship
Women with High-risk WHR	Overweight children	0.0003	0.05	0.5662	0.3205	0.1366	Moderate direct relationship

in the rural population of Meerut, India, has supportive evidence for our finding that high-risk WHR is also a rural phenomenon [25].

Our study shows the percentage of overweight women and overweight children is growing over the period. An analysis carried out to study the prevalence of overweight in adults and children between 1990 to 2015 for 195 countries shows a rising trend of obesity. In more than 70 countries, this trend has doubled [26].

The analysis of our data shows the percentage of women with central obesity is far higher compared to the percentage of overweight women. This is seen in urban as well as rural women population. Overweight or obesity is an important determinant of cardiovascular disease (CVD) and cardiometabolic disease (CMD). High-risk WHR has a positive correlation with the risk of infertility [27] and CVD risk [28]. Our findings highlight the importance of maintaining abdominal fat to maintain healthy WHR levels in women mainly of younger age.

Limitations of study

The strength of this study is a large sample size covering geographically and socio-culturally diverse areas. However, there are some limitations of the study. No data are available for NFHS4 for high-risk WHR, so we could not compare it with the values of NFHS5. This study is based on secondary data, so all the limitations of secondary data apply to it.

Research highlights

a. This study shows a moderate positive correlation between central obesity in women and overweight in under-five children.
b. More urban women are overweight as compared to rural ones. Overweight in children is a mixed phenomenon.
c. Compared to NFHS4, the percentage of overweight women and the percentage of overweight under-five children is increasing.
d. High-risk Waist-Hip-Ratio is seen in urban as well as in rural women.

CONCLUSION

In the present study, we examined the percentage of increase in the overweight of children under five years of age and women in the reproductive age of 15-49 years. Overweight is showing an increasing trend. There is a moderate positive correlation between central obesity in women and overweight in children under five years of age. The study found that the WHR but not overweight in women is an independent risk factor for overweight children under five years of age. However, no significant association was observed in women with overweight and overweight children under five years of age. Further research will help to understand the environmental and biological factors which are responsible for this association.

Overweight in women and children is becoming a public health issue. The study highlights the importance of managing abdominal fat. To prevent overweight, women should focus on healthy diets and physical activity. Curbing the high-risk WHR not only demands changes in diet and lifestyle at an individual level but also changes in policy, physical, and social environment, and cultural norms. Strategically designed awareness programs preferably in regional languages may help to reduce the risk. Policymakers should consider gender-specific risk factors related to women while developing preventive and therapeutic interventions for reducing high-risk WHR.

AUTHOR CONTRIBUTIONS

Both authors contributed to the paper's conception and writing. The first draft of the manuscript was mostly written by JS and CS commented and extended the argument in all versions of the draft. Both authors read and approved the final manuscript.

FUNDING

The authors declare that this study has no funding.

ETHIC APPROVAL

This article does not contain any studies involving animals performed by any authors. This article does not contain any studies involving human participants performed by any author. This study is based on publicly available, anonymized secondary data of NFHS-5, so ethical approval is not applicable.

DATA AVAILABILITY

NFHS-5 data is freely available on the Ministry of Health and Family Welfare, India website.

CONFLICT OF INTEREST

The authors have no relevant financial or non-financial interests to disclose.

INFORMED CONSENT

Informed written consent is not applicable.

REFERENCES

1. https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight
2. Balasundaram P, Krishna S. Obesity Effects on Child Health [Internet]. PubMed. Treasure Island (FL): StatPearls Publishing; 2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK570613/
3. Ayele BA, Tiruneh SA, Ayele AA, Zemene MA, Chanie ES, Hailemeskel HS. Prevalence and determinants of overweight/obesity among under-five children in sub-Saharan Africa: a multilevel analysis. BMC Pediatrics. 2022 Oct 8;22(1).
4. Bishwajit G, Yaya S. Overweight and obesity among under-five children in South Asia. Child and Adolescent Obesity. 2020 Jan 1;3(1):105–21.
5. Mannino A, Sarapis K, Moschonis G. The Effect of Maternal Overweight and Obesity Pre-Pregnancy and During Childhood in the Development of Obesity in Children and Adolescents: A Systematic Literature Review. Nutrients. 2022 Dec 2;14(23):5125.
6. Srikanthan P, Seeman TE, Karlamangla AS. Waist-Hip-Ratio as a Predictor of All-Cause Mortality in High-Functioning Older Adults. Annals of Epidemiology. 2009 Oct;19(10):724–31.
7. Molarius A, Seidell J, Sans S, Tuomilehto J, Kuulasmaa K. Waist and hip circumferences, and waist-hip ratio in 19 populations of the WHO MONICA Project. International Journal of Obesity. 1999 Feb;23(2):116–25.
8. https://main.mohfw.gov.in/sites/default/files/NFHS-5_Phase-I.pdf https://main.mohfw.gov.in/sites/default/files/NFHS-5_Phase-II_0.pdf
9. Fitzsimons E, Pongiglione B. The impact of maternal employment on children's weight: Evidence from the UK. SSM Popul Health. 2018 Nov 30;7:100333. doi: 10.1016/j.ssmph.2018.100333. PMID: 30581966.
10. Stahlmann K, Lissner L, Bogl LH, Mehlig K, Kaprio J, Klosowska JC, Moreno LA, Veidebaum T, Solea A, Molnár D, Lauria F, Börnhorst C, Wolters M, Hebestreit A, Hunsberger M; IDEFICS/I.Family consortia. Family structure in relation to body mass index and metabolic score in European children and adolescents. Pediatr Obes. 2022 Dec;17(12):e12963. doi: 10.1111/ijpo.12963. PMID: 35950257.
11. Herr RM, De Bock F, Diehl K, Wiedemann E, Sterdt E, Blume M, Hoffmann S, Herke M, Reuter M, Iashchenko I, Schneider S. Associations of individual factors and early childhood education and care (ECEC) centres characteristics with preschoolers' BMI in Germany. BMC Public Health. 2022 Jul 26;22(1):1415. doi: 10.1186/s12889-022-13814-5. PMID: 35883054.
12. Tchicaya A, Lorentz N. Relationship between children's body mass index and parents' obesity and socioeconomic status: A multilevel analysis applied with Luxembourg Data. Health. 2014;06(17):2322–32. doi:10.4236/health.2014.617267
13. Reddy KS, Prabhakaran D, Shah P, Shah B. Differences in body mass index and waist : hip ratios in North Indian rural and urban populations. Obesity Reviews. 2002 Aug;3(3):197–202.
14. Ololade Julius Baruwa, Babatunde Makinde Gbadebo, Adeleye O, Hanani Tabana, Adeniyi Francis Fagbamigbe. Decomposing the rural-urban disparities in overweight and obesity among women of reproductive age in Nigeria. BMC Women's Health. 2023 Dec 21;23(1).
15. Kumar P, Mangla S, Kundu S. Inequalities in overweight and obesity among reproductive age group women in India: evidence from National Family Health Survey (2015–16). BMC Women's Health. 2022 Jun 2;22(1).
16. Islam F, Kathak RR, Sumon AH, Molla NH. Prevalence and associated risk factors of general and abdominal obesity in rural and urban women in Bangladesh. Sartorius B, editor. PLOS ONE. 2020 May 29;15(5):e0233754.
17. Thapa R, Dahl C, Aung WP, Bjertness E. Urban–rural differences in overweight and obesity among 25–64 years old Myanmar residents: a cross-sectional, nationwide survey. BMJ Open. 2021 Mar;11(3):e042561.
18. Singh A, Let S, Tiwari S, Chakrabarty M. Spatiotemporal variations and determinants of overweight/obesity among women of reproductive age in urban India during 2005-2021. BMC Public Health. 2023 Oct 5;23(1).
19. Amani Kikula, Semaan A, Balandya B, Makoko NK, Pembe AB, JL Peñalvo, et al. Increasing prevalence of overweight and obesity among Tanzanian women of reproductive age intending to conceive: evidence from three Demographic Health Surveys, 2004-2016. Journal of global health reports. 2023 Oct 4;7.
20. Mkuu RS, Epnere K, Chowdhury MAB. Prevalence and predictors of overweight and obesity among Kenyan women. Preventing Chronic Disease. 2018 Apr 19;15. Available from: https://doi.org/10.5888/pcd15.170401
21. Owobi O, Okonji O, Nzoputam C, Ekholuenetale M. Country-Level Variations in Overweight and Obesity among Reproductive-Aged Women in Sub-Saharan Countries. Women. 2022 Sep 26;2(4):313–25. Available from: https://doi.org/10.3390/women2040029
22. Saha J, Chouhan P, Ahmed F, Ghosh T, Mondal S, Shahid M, Fatima S, Tang K. Overweight/Obesity Prevalence among Under-Five Children and Risk Factors in India: A Cross-Sectional Study Using the National Family Health Survey (2015–2016). Nutrients. 2022 Sep 1;14(17):3621. Available from: https://doi.org/10.3390/nu14173621
23. Zhang YX, Wang ZX, Zhao JS, Chu ZH. Prevalence of Overweight and Obesity among Children and Adolescents in Shandong, China: Urban–Rural

ISSN 2282-0930 • Epidemiology Biostatistics and Public Health - 2024, Volume 19, Issue 2

Disparity. Journal of Tropical Pediatrics. 2016 Mar 10;62(4):293–300. Available from: https://doi.org/10.1093/tropej/fmw011
24. Singh RB, Ghosh S, Beegom R, Mehta AS, De AK, Haque M, Dube GK, Wander GS, Kundu S, Roy S, Krishnan A, Simhadri H, Paranjpe NB, Agarwal N, Kalikar RH, Rastogi SS, Thakur AS. Prevalence and determinants of Central Obesity and Age-Specific Waist: HIP ratio of people in five cities: The Indian Women's Health Study. European Journal of Cardiovascular Prevention & Rehabilitation [Internet]. 1998 Apr 1;5(2):73–7. Available from: https://doi.org/10.1177/174182679800500201
25. Garg M, Bansal R, Gupta M, Gupta CK. Prevalence of hypertension and its association with stress, Indian diabetes risk score and obesity in rural population of Meerut. Indian J Community Health [Internet]. 2020 Mar. 31 [cited 2024 Jul. 12];32(1):62-6. Available from: https://www.iapsmupuk.org/journal/index.php/IJCH/article/view/1272
26. GBD 2015 Obesity Collaborators; Afshin A, Forouzanfar MH, Reitsma MB, Sur P, Estep K, Lee A et al. Health Effects of Overweight and Obesity in 195 Countries over 25 Years. N Engl J Med. 2017 Jul 6;377(1):13-27. doi: 10.1056/NEJMoa1614362. Epub 2017 Jun 12. PMID: 28604169
27. Lai J, Li X, Liu Z, Liao Y, Xiao Z, Wei Y, Cao Y. Association between waist-hip ratio and Female Infertility in the United States: Data from National Health and Nutrition Examination Survey 2017–2020. Obesity Facts. 2024 May 2; Available from: https://doi.org/10.1159/000538974
28. Darbandi M, Pasdar Y, Moradi S, Mohamed HJJ, Hamzeh B, Salimi Y. Discriminatory Capacity of Anthropometric Indices for Cardiovascular Disease in Adults: A Systematic Review and Meta-Analysis. Prev Chronic Dis. 2020 Oct 22;17:E131. doi: 10.5888/pcd17.200112.

ISSN 2282-0930 • Epidemiology Biostatistics and Public Health - 2024, Volume 19, Issue 2

Use of Disinfectants and Cleaning Products Associated with Respiratory Disease: A Scoping Review

Paula Andrea García Quinto[(1)], Erwin Hernando Hernández Rincón[(2)], Juan Miguel Pérez Flórez[(1)], Diana Marcela Díaz Quijano[(3)], Claudia Liliana Jaimes Peñuela[(2)]

(1) Universidad de La Sabana, Colombia.
(2) Department of Family Medicine and Public Health, Universidad de La Sabana, Colombia.
(3) Department of Epidemiology, Universidad de La Sabana, Colombia.

CORRESPONDING AUTHOR: Erwin Hernando Hernández Rincón. Correo: erwin.hernandez1@unisabana.edu.co, Department of Family Medicine and Public Health, Universidad de La Sabana, Campus Universitario Puente del Común, Km 7 Autopista Norte de Chía, Colombia.

SUMMARY

Introduction: there is extensive evidence on the harmful respiratory effects of exposure to disinfectants and cleaning products. Methodology: an exploratory systematic review was carried out in five databases: LILACS, PubMed, MEDLINE and BIREME. Twenty articles from 2013 to 2024 were selected for the present review. Results: chemical compounds present in some disinfectants and cleaning products such as Poly-hexamethylene guanidine (PHMG) and Chloromethylisothiazolinone/Methylisothiazolinone (CMIT/MIT) influence the development of Humidifier Respiratory Distress Syndrome (HDRS) and increased incidence of asthma and Chronic Obstructive Pulmonary Disease (COPD) in adults. Conclusions: There is a relationship between exposure to chemical compounds in certain disinfectants and lung health impairment. It is imperative to increase the general population's awareness of the effects of these substances will lead to improved self-care in those who are in daily contact with these elements.

Keywords: Respiratory Tract Diseases; Disinfectants; Asthma; Chronic Obstructive Pulmonary Disease.

INTRODUCTION

Asepsis measures have transformed the history of mankind forever. Over the years, the way in which human habitations and food are disinfected has evolved in parallel with the development of industrial chemistry and its technification. There is ample evidence on the consequences of the use of antiseptics and disinfectants on human health, as well as the impact of their decomposition products in the water we use for our daily needs and in the cleaning of hospital institutions [1]. On the other hand, interference in the efficacy and functioning of medications has been observed in patients with chronic diseases, and cases of metabolic alterations have even been documented [2–5].

The arrival of the COVID-19 pandemic represented a change in asepsis measures not only in healthcare settings, but even more so in domestic environments, which leads to questioning the impact on health of exposure to new products in addition to considering the harmful effects that the disposal of these can produce on other living beings [4].

It has been documented that the effects of frequent use of cleaning products are largely conditioned by the type of exposure, its frequency and cumulative exposure to them [6, 7]. Therefore, it is important to distinguish between frequent and persistent contact in people depending on their work environment, compared to those exposed to these compounds in domestic environments [7]. In fact, significant harmful effects have been evidenced after relatively short exposures, even with minimal cumulative exposure, especially in children under 5 years, even after years of cessation of the use of these cleaning products [8].

Likewise, the effects produced by contaminants on human beings have called the attention of the scientific community to explore the consequences of their contact with other species that may be exposed, demonstrating the affectation produced by the derivatives of the

DOI: 10.54103/2282-0930/26825
Accepted: 31th October 2024

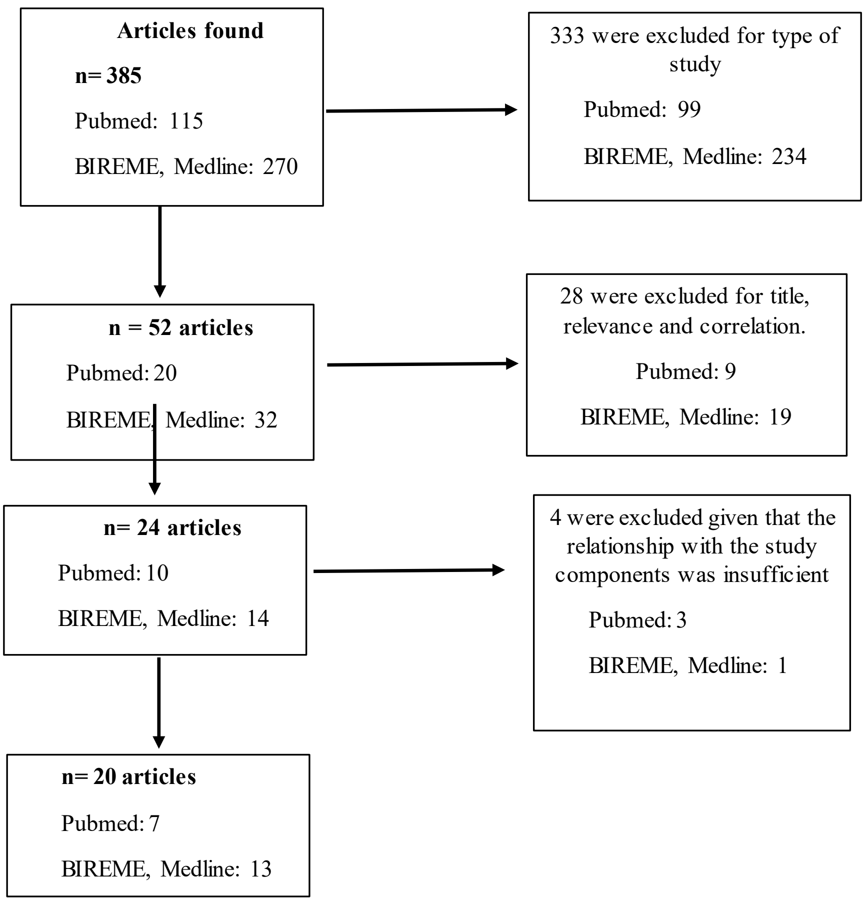
components used in the cleaning products that remain suspended in the air or are expelled in different water sources and that despite the treatment of these persist as residues and can cause harmful effects of which their scope is unknown [9, 10]. In this sense, harmful effects have also been documented that can affect animal species that are in contact with these water sources and that present pathologies that diminish their quality of life and the prolongation of their existence [11].

This investigation was carried out with the objective of analyzing the available evidence on the respiratory consequences derived from the persistent use of disinfectants and antiseptics in the general population.

METHODOLOGY

A scoping review was conducted. The following databases were used for the search: LILACS, MEDLINE, PubMed and BIREME, using the following MeSH terms: "Disinfectants [MeSH]" AND "Lung diseases (MeSH]" in combination with DeCS terms: "Disinfectants" AND "respiratory diseases". In addition, databases such as Embase and Scopus were consulted, and free-reading documents that can be found in Google Scholar, reports from the Panamerican Health Organization (PAHO) and the World Health Organization (WHO) were reviewed to complement with gray literature through snowball method to expand the results for the research.

Figure 1. PRISMA diagram of the selection of articles included in the review.



Source: own elaboration based on the results of the research.

Literature published from January 2013 to February 2024 was collected, retrieving a total of 385 documents, including cohort studies, cross-sectional analyses, case reports, epidemiological investigations, case-control studies, systematic reviews, scoping reviews and narrative reviews.

A filtering of the literature found was carried out taking as inclusion criteria observational studies, randomized clinical studies, systematic reviews and literature reviews that included participants of all ages, studies conducted with human subjects, thus systematic reviews that depicted effects described in animals were also taken into account, with focus on the respiratory effects of exposure to disinfectants or cleaning products, in English and Spanish, that evaluated outcomes such as asthma and COPD, especially if related with the exposure to Olyhexamethylene Guanidine (PHMG) and Chloromethylisothiazolinone/Methylisothiazolinone (CMIT/MIT), and an special focus in studies performed in the context of the COVID-19 pandemic. Articles

ISSN 2282-0930 • Epidemiology Biostatistics and Public Health - 2024, Volume 19, Issue 2

that did not show a direct relationship between the compounds and the development of respiratory diseases such as asthma, Chronic Obstructive Pulmonary Disease (COPD) and Humidifier Respiratory Distress Syndrome (HDRS), effects on other body systems (cardiovascular, gastrointestinal, skin), not published on English or Spanish, not available from open access or access throughout institution. Subsequently, duplicate, non-relevant articles were eliminated. To ensure the reliability of the data extracted, the articles were evaluated and selected according to the quality criteria of the Joanna Briggs Institute [12] and classified according to their methodological rigor and relevance to the research.

A total of 334 articles were obtained from which 52 articles were extracted. A second filtering process was carried out to classify the evidence in two groups: relationship between disinfectants or cleaning products and development of lung lesions or respiratory diseases. Twenty articles were used for the present review. The first two authors classified and read the articles found and a third author resolved discrepancies in the information retrieved. The article selection process is schematized in Figure 1.

The PRISMA statement [13] was implemented to synthesize the results found in exploratory systematic reviews (PRISMA-ScR), PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) and subsequently the steps proposed by Arksey and O'Malley [14] and revised by Levac were followed [15], which are based on a) identification of the research question; b) identification of relevant studies; c) selection of studies; d) data extraction; e) synthesis and reporting of results. The research question was answered: What are the respiratory health consequences of prolonged exposure to disinfectants, antiseptics or cleaning products in the general population?

RESULTS

A total of 20 articles were included in this review. Of which 5 were narrative reviews, 5 systematic reviews, 2 cohort studies, 2 randomized clinical trials, 2 cross-sectional studies, 1 epidemiological investigation, 1 clinical description and 2 case reports. Of the included studies, 60% were conducted in South Korea, 30% in China, and the remaining 10% in the United States. The main characteristics of the studies included are described in Table 1.

Table 1. Characteristics of the studies included in the exploratory review

Title	Year	Authors	Summary	Ref
Exposures to humidifier disinfectant and various health conditions in Korean based on personal exposure assessment data from compensation claimants.	2023	Hong, M, et al	The use of disinfectants is associated with bronchitis, allergic rhinitis and asthma in children. Toxic hepatitis and preterm delivery in pregnant women.	[16]
Health effects associated with the use of humidifying disinfectants: a systematic review for exploration.	2022	Song, J, et al	The pulmonary effects of disinfectants to humidifiers are dose responsive. Compounds such as CMIT/MIT can cause of illness.	[17]
Characteristics of a new respiratory syndrome associated with the use of a disinfectant humidifier: disinfectant humidifier-related respiratory syndrome (HDRS).	2020	Leem, J, et al	Description of humidifier-associated respiratory syndrome as responsible for lung disease associated with the use of fragrances and humidification systems.	[18]
Association of occupational exposure to disinfectants with incidence of chronic obstructive pulmonary disease among U.S. nurses.	2019	Dumas, O, et al	Healthcare workers in contact with cleaning products have a higher risk factor for developing COPD.	[19]
Association between occupational exposure to disinfectants and asthma in young adults working in cleaning or health care services: results of a cross-sectional analysis in Germany.	2019	Weinmann, T, et al	Major risk factor in cleaning-related professions or occupations for contracting occupational asthma.	[20]

Occupation and task as risk factors for asthma related outcomes among healthcare workers in New York City..	2019	Caridi, M, et al	Higher incidence of occupational asthma in surgical-related professions due to significant exposure to cleaning products.	[21]
Two cases of toxic lung injury associated with chloromethylisothiazolinone and methylisothiazolinone.	2018	Lee, E, et al	Description of a case of twin girls with respiratory syndrome associated with humidifier disinfectants, radiological follow-up until the age of 5.	[22]
Humidifier disinfectants are a cause of lung injury among adults in South Korea: a community-based case-control study.	2016	Park, J-H, et al	Description of the main findings in radiography that can confirm HDRS in suspected patients.	[23]
Work-related respiratory symptoms among healthcare facility cleaners: a cross-sectional study.	2014	Lipinska-Ojrzanowska, A, et al	There is a documented correlation between respiratory distress symptoms and bronchial irritation among cleaning staff.	[24]
A cluster of lung injury cases associated with the use of household humidifiers: an epidemiological investigation.	2014	Kim, H, et al	Radiographic timeline of respiratory illness related to humidifier disinfectants.	[25]
A cluster of lung injuries associated with the use of household humidifiers: clinical, radiological, and pathological description of a new syndrome.	2014	Hong, S, et al	Clinical and radiological description of HDRS.	[8]
Humidifier Disinfectant–associated Children's Interstitial Lung Disease	2014	Kim, K, et al	Clinical description of respiratory syndrome associated with humidifier disinfectants.	[26]
Inhalation toxicity from humidifier disinfectants as a risk factor for infant interstitial lung disease in Korea: a case-control study.	2013	Yang, H, et al	Pulmonary repercussions of infant exposure to humidifier disinfectant components.	[27]
Frequency, intensity, and duration of exposure: what we know about work-related asthma risks for healthcare workers due to cleaning and disinfection.	2023	Wilson, A, et al	Relationship between the frequency, intensity, and concentration of exposure to cleaning products and the incidence of chronic respiratory diseases.	[28]
Review of health risks from inhalation of chloromethylisothiazolinone (CMIT) and methylisothiazolinone (MIT) used as disinfectants in household humidifiers.	2022	Kim, J, et al	New pathological link found between the use of CMIT/MIT as components in humidifier disinfectants.	[11]
A general overview of health risks and occupational injuries and diseases attributed to cleaning agents in Sweden.	2022	Kathare, M, et al	Relationship between the incidence of chronic respiratory diseases and occupational cleaning tasks.	[7]
Are healthcare workers at a higher risk of developing obstructive respiratory diseases due to cleaning and disinfection agents? A systematic review and meta-analysis.	2021	Starke, K, et al	There is an increased risk of contracting obstructive lung disease among healthcare workers exposed to disinfectants and cleaning products.	[6]

Source: own elaboration based on the results of the review

The studies reviewed in this investigation focused mainly on the adverse effects of the components of humidifier disinfectants used both in homes and health institutions, which were associated with pulmonary diseases in pregnant women, children and young adults [11, 25, 27]. HDRS was observed to represent the leading cause of lung disease, with an incidence of 47.3 (95% CI 6.1 - 369.7 in 2014) and 116.1 (95%

CI 6.5 - 206.3 in 2016) [23]. Despite the existence of policies prohibiting the use of harmful components [17, 18, 22] and occupational measures aimed at mitigating the toxic effects of cleaning product components [17, 19–23].

In addition, a relationship was found between cleaning products used both in homes and in occupational work of health personnel and the development of respiratory symptoms, de novo asthma and asthma exacerbation in countries such as China, Switzerland and the United States [7, 19, 24]. The characteristics of the articles used in this review are summarized in Table 1.

Humidifier disinfectants and its relationship with HDRS

Humidifier disinfectants are widely used in South Korea to prevent bacterial growth in the water tanks, the occurrence of respiratory symptoms of unknown etiology has been suggested, with a challenging therapeutic response to corticosteroids and bronchodilators, starting in 2011 [8, 25–27].

At a hospital in South Korea, an outbreak of respiratory symptoms was reported in 30 patients, including pregnant women, that were neither associated with an infectious agent nor attributed to autoimmune pathology [23, 25]. During their hospitalization, radiological and tomographic imaging was performed, revealing ground-glass opacities in all patients. In these patients a common factor was revealed: the use of humidifier disinfectants containing PHMG as the main ingredient [24].

It has been evidenced in the literature that humidifier disinfectant components contain not only PHMG, but (CMIT/MIT) [11, 17], compounds that are related to HDRS.

In addition, the incidence of HDRS has been shown to have a positive correlation with the estimated exposure concentration to the compound and the distance at which the person has contact with these compounds [17]. This generates a wide diversity of pathologies ranging from otorhinolaryngological disease to neoplasms of pulmonary origin [16]. Case reports have even been described of exposure to these compounds for only months and the presence of pulmonary pathology in twin girls of 6 months of age, with pathological radiological findings that persisted after 5 years of presenting symptoms and the subsequent suspension of exposure to the compounds [22].

Other effects that have been described at the pulmonary level, described as non-HDRS diseases, are idiopathic interstitial pneumonia, bronchitis, allergic rhinitis and asthma. Extrapulmonary cases of toxic hepatitis, ocular irritation and increased development of COPD have been reported in patients not exposed to tobacco smoke or any other additional predisposing factor [8, 22, 23].

Currently, the mechanism of action of these components for the development of pulmonary disease is unknown; however, it is presumed that its etiology may be due to reactive oxygen species that cause inflammation, which can lead to cell death and genomic alterations [16].

Cleaning products and development of asthma and COPD

Currently, disinfectants used in the health care field contain multiple chemical compounds to ensure the cleaning and disinfecting action of fixed areas and different medical devices [19]. There is sufficient evidence that suggests the relationship between exposure to household and occupational cleaning products and the development of chronic lung diseases such as asthma and COPD [6, 16, 17, 19–21, 24, 26, 28].

The cleaning products most found in studies include formaldehyde, glutaraldehyde, sodium hypochlorite, hydrogen peroxide, alcohol, quaternary ammonium compounds and enzymatic cleaners [20]. A significant dose-dependent association has been observed between the use of any disinfectant and the frequency with which these products are used, with the development of the pathologies [19, 21, 28].

In addition, several variables that could be related to the development of pulmonary diseases were evaluated, such as active use or history of tobacco use, occupational exposure within health care institutions, and whether the participants had a previous diagnosis of asthma. No statistically significant association was found between tobacco exposure and the development of asthma or COPD compared with exposure to other products for the same outcome. However, a positive association was found between work tasks performed within health care institutions and the development or exacerbation of the pulmonary pathologies [19].

Analysis of the literature revealed that cleaning personnel in health care institutions face a significantly higher risk of developing COPD and asthma due to their greater exposure and frequency of contact with chemical components. Similarly, health personnel who work in surgical rooms and perform cleaning or disinfection tasks, both in fixed areas and on medical equipment, such as operating room nurses and surgical instrument technicians, show a higher incidence of pathologies such as asthma, COPD and its exacerbations. On the contrary, administrative activities, hospital care and outpatients, despite involving contact with chemical components of cleaning products, show a lower association with the development or exacerbation of these diseases [19–21, 28, 29]. A summary of the most relevant components of disinfectants and cleaning products related to lung diseases is presented in Table 2.

Table 2. Most relevant components of disinfectants and cleaning products related to lung disease

Compound	Respiratory disease associated	Non respiratory effects
PHMG CMIT/MIT	Lung disease associated with disinfectants Pulmonary fibrosis COPD Asthma Upper and lower respiratory tract diseases Allergic asthma and rhinitis	Psychiatric effects Toxic hepatitis Eye irritation Premature birth
Glutaraldehyde Peracetic Acid Chloramines Quaternary Ammonium	Occupational asthma COPD	Eye irritation Contact dermatitis
Sodium Hypochlorite Hydrogen Peroxide	COPD	Eye irritation Contact dermatitis

Source: Own elaboration based on references [6–8, 11].

DISCUSSION

Furthermore, most of the studies reviewed have focused on the clinical and radiological manifestations observed in patients during their consultation in emergency departments, which suggests the relationship these products may have as one of the main causes of pulmonary disease. However, so far, no conclusive evidence has been found to establish a direct relationship between the distance at which contact with these substances occurs, nor the duration or cumulative concentration of exposure, and the development of respiratory diseases. These findings underscore the need for future research that delves deeper into the underlying mechanisms and risk factors associated with the use of disinfectants in humidifiers, with the goal of developing more effective prevention strategies [4, 10].

One of the studies mentions a direct relationship between the exposure to Humidifier Disinfectants and the development of lung injury [23], nonetheless, the conclusion drawn by this study must be taken with caution, though it has high ICs and ORs that may be distorted by the small sample size. Yet, the inclusion of this study is considered important as it can provide a theoretical and empirical foundation for a much larger experimental design to mitigate the limitations of this one.

In conducting this scoping review a wide array of study types was included, ranging from observational studies and systematic reviews to case reports. This inherent heterogeneity can pose challenges to the validity and quality of the results. To mitigate this effect, a comprehensive strategy for categorizing the included studies based on their design, quality, and relevance was performed. A subgroup analysis to separately evaluate the outcomes of different study types allowed for a more nuanced interpretation of the data. Additionally, using robust criteria for assessing the quality of each study type helped to ensure that only high-quality evidence was given significant weight in the analysis.

Despite these measures, several limitations may arise from this approach. Firstly, the variability in study design and quality can lead to inconsistent findings that complicate the synthesis of results. Secondly, case reports and narrative reviews, though informative, often lack the rigorous methodology of experimental studies, potentially introducing biases. Finally, the inclusion of diverse study types may limit the ability to draw definitive conclusions, necessitating cautious interpretation of the findings. By acknowledging and addressing these limitations, we can enhance the robustness and reliability of our scoping review.

Since 2011, the sale of humidifier disinfectants containing PHMGs among their components was banned in South Korea. However, cases of respiratory diseases associated with the use of cleaning products persist in this country despite the measures adopted. It is relevant to mention that the incidence of cases has decreased and that the evidence that has been collected so far comes from retrospective studies. In the literature consulted, no recent cases of HDRS were documented. However, there is also limited availability of the effects of these compounds for the development of mild pulmonary alterations [16–18].

In addition, the factors that may be associated with mortality in patients who develop HDRS are not yet known in depth, since no relationship was found between parenchymal involvement at the radiological level on admission to the emergency department and the incidence of complications and fatal outcomes in patients who presented the syndrome [16, 17].

Regarding the pathogenesis of respiratory disease associated with humidifier disinfectants, there is information about the mechanism of action, such as

ISSN 2282-0930 • Epidemiology Biostatistics and Public Health - 2024, Volume 19, Issue 2

inhibition of sulfhydryl group (SH) enzyme activity and other proteins leading to cell death by CMIT/MIT compounds and inhibition of B-lactamase and destruction of cell structure by PHMG [16]. The exposition to these substances has been related to fibroinflammatory processes in bronchioles and pulmonary parenchyma that led to bronchiolitis obliterans [30]. Vaporized particles of the substance used in cleaning products are extremely small and can present radiological findings such as subpleural sparring and diffuse alveolar damage[31]. However, there is still not a complete understanding of the relationship of the chemical compounds and the organic molecular reactions that lead to the development of the disease, so therapeutic strategies in these cases are limited.

On the other hand, regarding the cleaning products currently used, there is growing evidence about the pathogenesis of the compounds and the effects they have at the respiratory level, yet it is still very limited [5, 32]. It has been suggested that lung damage produces a severe inflammatory reaction by irritation leading to tissue destruction, which is not only dependent on concentration but also the sensitivity of the cells to produce this damage is proportional to exposure [33]. Some studies have suggested that exposition to these substances could cause an activation of immune system that would facilitate allergic sensitization by compromising the function of epithelial barriers [34]. Chronical inflammation in low degree could even lead to a destruction in the pulmonary parenchyma that could mimic and obstructive disease like COPD [35].

The chemical compounds found in household cleaning products and the cleaning and disinfection of fixed surfaces in places such as hospitals, orthodontic centers and medical equipment surfaces that are most found are: Formaldehyde, Glutaraldehyde, Sodium Hypochlorite, Hydrogen Peroxide, alcohol, quaternary ammonium compounds and enzymatic cleaners [19]. This opens the door to a discussion of replacement of current cleaning agents with less toxic alternatives, with the same efficacy and effectiveness of the current ones, but without the consequences that have a negative impact on both human and environmental health.

CONCLUSION

Research reveals an association between exposure to certain disinfectants and lung health. It is crucial that governments prioritize measures to reduce the presence of these compounds in everyday products. In addition, increasing public awareness of their effects can improve self-care, especially among those with ongoing exposure. These actions are essential to mitigate the negative impact on respiratory health and promote safer environments.

The risk of bias and the heterogeneity that emerges from the article challenges the generalization of conclusions observed in this review. However, they provide theoretical support to continue deepening and increasing the knowledge of the natural history of the disease as well as the harmful effects that products so common in household use can have, compromising people's quality of life.

Although occupational safety policies exist, none of the articles reviewed document the adherence of professionals and workers exposed to chemicals to processes and elements designed to minimize these effects on their health. Likewise, adherence to institutional policies designed to mitigate the harmful effects of cleaning components on workers' health is not reported.

AUTHORSHIP CONTRIBUTION

The conceptualization and planning of the research was carried out by all the authors. Data collection, processing, and analysis were performed by the first 3 authors. The writing, organization, and approval of the final manuscript were carried out by all authors.

DECLARATION

Research derived from project MED-342-2023 of Universidad de La Sabana, Colombia.

FUNDING

None.

CONFLICT OF INTEREST

None.

REFERENCES

1. Xue B, Guo X, Cao J, et al. The occurrence, ecological risk, and control of disinfection by-products from intensified wastewater disinfection during the COVID-19 pandemic. Science of The Total Environment 2023; 900: 165602.
2. Eslamy HK, Newman B. Pneumonia in Normal and Immunocompromised Children: An Overview and Update. Radiol Clin North Am 2011; 49: 895–920.
3. Truong K, Thai K. Cushing's syndrome induced by enhanced systemic absorption of topical corticosteroids when co-administered with hand sanitiser in a patient with COVID-19-induced chronic plaque psoriasis. Skin Research and Technology; 29. Epub ahead of print 13 June 2023. DOI: 10.1111/srt.13375.
4. Hashemi F, Hoepner L, Hamidinejad FS, et al. A

comprehensive health effects assessment of the use of sanitizers and disinfectants during COVID-19 pandemic: a global survey. Environmental Science and Pollution Research 2023; 30: 72368–72388.
5. Marques AC, Mariana M, Cairrao E. Triclosan and Its Consequences on the Reproductive, Cardiovascular and Thyroid Levels. Int J Mol Sci 2022; 23: 11427.
6. Romero Starke K, Friedrich S, Schubert M, et al. Are Healthcare Workers at an Increased Risk for Obstructive Respiratory Diseases Due to Cleaning and Disinfection Agents? A Systematic Review and Meta-Analysis. Int J Environ Res Public Health 2021; 18: 5159.
7. [Kathare M, Julander A, Erfani B, et al. An Overview of Cleaning Agents' Health Hazards and Occupational Injuries and Diseases Attributed to Them in Sweden. Ann Work Expo Health 2022; 66: 741–753.
8. Hong S-B, Kim HJ, Huh JW, et al. A cluster of lung injury associated with home humidifier use: clinical, radiological and pathological description of a new syndrome. Thorax 2014; 69: 694–702.
9. [9] Dang C, Zhang Y, Zheng M, et al. Effect of chlorine disinfectant influx on biological sewage treatment process under the COVID-19 pandemic: Performance, mechanisms and implications. Water Res 2023; 244: 120453.
10. Benedusi M, Tamburini E, Sicurella M, et al. The Lesson Learned from the COVID-19 Pandemic: Can an Active Chemical Be Effective, Safe, Harmless-for-Humans and Low-Cost at a Time? Evidence on Aerosolized Hypochlorous Acid. Int J Environ Res Public Health 2022; 19: 13163.
11. Kim J, Park S, Zoh KE, et al. Review of Inhalation Health Risks Involving Chloromethylisothiazolinone (CMIT) and Methylisothiazolinone (MIT) Used as Disinfectants in Household Humidifiers. J Korean Med Sci; 37. Epub ahead of print 2022. DOI: 10.3346/jkms.2022.37.e101.
12. Peters MD, Godfrey C, McInerney P, et al. Scoping reviews. In: JBI Manual for Evidence Synthesis. JBI, 2024. Epub ahead of print 2024. DOI: 10.46658/JBIMES-24-09.
13. Tricco AC, Lillie E, Zarin W, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. Ann Intern Med 2018; 169: 467–473.
14. Arksey H, O'Malley L. Scoping studies: towards a methodological framework. Int J Soc Res Methodol 2005; 8: 19–32.
15. Levac D, Colquhoun H, O'Brien KK. Scoping studies: advancing the methodology. Implementation Science 2010; 5: 69.
16. Hong M, Ju MJ, Yoon J, et al. Exposures to humidifier disinfectant and various health conditions in Korean based on personal exposure assessment data of claimants for compensation. BMC Public Health 2023; 23: 1800.
17. Song J-H, Ahn J, Park MY, et al. Health Effects Associated With Humidifier Disinfectant Use: A Systematic Review for Exploration. J Korean Med Sci; 37. Epub ahead of print 2022. DOI: 10.3346/jkms.2022.37.e257.
18. Leem JH, Joh J-S, Hong Y-S, et al. Characteristics of a new respiratory syndrome associated with the use of a humidifier disinfectant: humidifier disinfectant-related respiratory syndrome (HDRS). Int J Occup Med Environ Health 2020; 33: 829–839.
19. Dumas O, Varraso R, Boggs KM, et al. Association of Occupational Exposure to Disinfectants With Incidence of Chronic Obstructive Pulmonary Disease Among US Female Nurses. JAMA Netw Open 2019; 2: e1913563.
20. Weinmann T, Forster F, von Mutius E, et al. Association Between Occupational Exposure to Disinfectants and Asthma in Young Adults Working in Cleaning or Health Services. J Occup Environ Med 2019; 61: 754–759.
21. Caridi MN, Humann MJ, Liang X, et al. Occupation and task as risk factors for asthma-related outcomes among healthcare workers in New York City. Int J Hyg Environ Health 2019; 222: 211–220.
22. Lee E, Son SK, Yoon J, et al. Two Cases of Chloromethylisothiazolinone and Methylisothiazolinone-associated Toxic Lung Injury. J Korean Med Sci 2018; 33: e119.
23. Park J-H, Kim HJ, Kwon G-Y, et al. Humidifier Disinfectants Are a Cause of Lung Injury among Adults in South Korea: A Community-Based Case-Control Study. PLoS One 2016; 11: e0151849.
24. Lipińska-Ojrzanowska A, Wiszniewska M, Świerczyńska-Machura D, et al. Work-related respiratory symptoms among health centres cleaners: A cross-sectional study. Int J Occup Med Environ Health; 27. Epub ahead of print 1 January 2014. DOI: 10.2478/s13382-014-0272-x.
25. Kim HJ, Lee M-S, Hong S-B, et al. A cluster of lung injury cases associated with home humidifier use: an epidemiological investigation. Thorax 2014; 69: 703–708.
26. Kim KW, Ahn K, Yang HJ, et al. Humidifier Disinfectant–associated Children's Interstitial Lung Disease. Am J Respir Crit Care Med 2014; 189: 48–56.
27. Yang H-J, Kim H-J, Yu J, et al. Inhalation toxicity of humidifier disinfectants as a risk factor of children's interstitial lung disease in Korea: a case-control study. PLoS One 2013; 8: e64430.
28. Wilson AM, O. Ogunseye O, Fingesi T, et al. Exposure frequency, intensity, and duration: What we know about work-related asthma risks for healthcare workers from cleaning and disinfection. J Occup Environ Hyg 2023; 20: 350–363.
29. Lam J, Koustas E, Sutton P, et al. Exposure to formaldehyde and asthma outcomes: A systematic review, meta-analysis, and economic assessment. PLoS One 2021; 16: e0248258.
30. Huh J-W, Hong S-B, Do K-H, et al. Inhalation Lung Injury Associated with Humidifier Disinfectants in Adults. J Korean Med Sci 2016; 31: 1857.
31. Koo HJ, Do K-H, Chae EJ, et al. Humidifier disinfectant-associated lung injury in adults: Prognostic factors in predicting short-term outcome. Eur Radiol 2017; 27: 203–211.
32. Kim J, Konkel K, Mentari E, et al. Adverse events in the U.S. following ocular exposure to alcohol-based hand sanitizers. Clin Toxicol (Phila) 2023; 61: 86–88.

ISSN 2282-0930 • Epidemiology Biostatistics and Public Health - 2024, Volume 19, Issue 2

33. Clausen PA, Frederiksen M, Sejbæk CS, et al. Chemicals inhaled from spray cleaning and disinfection products and their respiratory effects. A comprehensive review. Int J Hyg Environ Health 2020; 229: 113592.
34. Siracusa A, De Blay F, Folletti I, et al. Asthma and exposure to cleaning products - a European Academy of Allergy and Clinical Immunology task force consensus statement. Allergy 2013; 68: 1532–1545.
35. Svanes Ø, Bertelsen RJ, Lygre SHL, et al. Cleaning at Home and at Work in Relation to Lung Function Decline and Airway Obstruction. Am J Respir Crit Care Med 2018; 197: 1157–1163.

ISSN 2282-0930 • Epidemiology Biostatistics and Public Health - 2024, Volume 19, Issue 2

Excess Mortality (2020-2023) as Proxy of COVID-19 Deaths?

Emmanuel Obi Okoro(1), Nehemiah Arhoesere Ikoba(2)

(1) Department of Medicine, University of Ilorin, Nigeria.
(2) Department of Statistics, University of Ilorin, Nigeria.

CORRESPONDING AUTHOR: Dr. E. O. Okoro, Department of Medicine University of Ilorin, PMB 1515, Ilorin, Nigeria. Telephone: +2348037301311. Email: eookoro2003@gmail.com, eookoro@unilorin.edu.ng

SUMMARY

Importance: Concerns regarding excess mortality estimates and the subjective nature of diverse models utilized have emerged. We examined its theoretical underpinning by exploring two popular excess mortality models based on regression and time series analyses that highlight their weaknesses in forecasting excess deaths during COVID-19 emergency.
Observations: Excess mortality estimates are errors/residuals of prediction models increasingly used to determine the number of unreported deaths from COVID-19. That several prediction models are used to model baseline excess deaths underscores the lack of a definitive choice thereby signposting its subjective nature. A general lack of assessment of the assumptions governing such models was another drawback in relying on estimates of excess mortality derived from them.
Conclusions and Relevance: In assessing the impact of COVID-19 (or any public health emergency), reported death counts and other mortality statistics, when combined with relevant auxiliary information, can offer a better view of the pandemic impact rather than reliance on a subjective metric such as excess death which can be misleading. More importantly, mathematical modeling though useful in an unfolding pandemic, once data become available, this should supersede forecasted estimates in decision-making or impact assessment.

Keywords: Excess mortality; COVID-19; modeling.

INTRODUCTION

The outbreak of the corona virus (COVID-19) pandemic in 2020 resulted in an unprecedented global impact in public health policy formulation and implementation. The ramifications of the pandemic are still being felt across the globe even after World Health Organization (WHO) declared the pandemic over in May 2023 [1]. Excess mortality is a prominent and widely used metric in assessing the human toll of the COVID-19 pandemic. However, this measure has been the subject of extensive misinterpretation and it is even promoted over and above the reported death statistics from the pandemic itself.

Excess mortality is claimed to be a more objective and comparable measure of the mortality impact of COVID-19 across countries than the reported death counts [2,3]. It is generally believed that understanding excess mortality not only provides a more comprehensive view of the pandemic's impact, it can also help in the development and implementation of effective public health initiatives [3].

The emphasis placed on excess mortality extends beyond the public health community and appears to have informed views of politicians and media [4]. Surprisingly, there seem little to no critical appraisal of this projection-based approach [4]. In this contribution, we investigate the excess mortality statistic and examine whether its widespread use is justified theoretically. The excess mortality estimates based on linear regression [5] and time series analysis [6] are examined to highlight the serious limitations of the formulation that has been at the heart of public policy response to the COVID-19 pandemic globally.

Theoretical Basis

Excess mortality is a term used frequently in epidemiology and public health that refers to the number of deaths from all- causes during a crisis

DOI: 10.54103/2282-0930/27538
Accepted: 19th December 2024

above and beyond what we would have expected under normal conditions [3,7]. It is claimed in several studies that, excess mortality is a more comprehensive measure of the total impact of the pandemic on deaths than the confirmed COVID-19 death count alone. It was also claimed that it captures not only the confirmed deaths, but also COVID-19 deaths that were not correctly diagnosed and reported [3,7], in addition to deaths from other causes that could be attributable to the overall crisis conditions [7].

The use of excess mortality as a metric for gauging the impact of public health emergencies has been documented since 1665 [5]. Under-reporting of the number of deaths is a very critical factor and the possibility increases with countries at the lower rung of the economic spectrum (low and middle-income countries).

Excess Mortality Estimation based on Linear Regression

The excess mortality measure utilized in [5] uses a linear regression model to project all-cause mortality for 2020 and 2021 with historical data (2015-2019).

The specified regression model for all-cause mortality was given as [5]:

$$D_{t,Y}=\alpha_t+\beta\cdot Y+\varepsilon$$

where, $D_{t,Y}$ is the number of deaths observed on week (or month, or quarter) t in year Y, β is a linear slope across years, α_t is the time-varying intercept (fixed effects), and $\varepsilon\sim N(0,\sigma^2)$ is Gaussian noise.

We note that the residual or error variable , is assumed to be normally distributed with zero mean and constant variance σ^2. However, the assumption of a constant error variance (homoscedasticity) for time series count data is very tenuous, as such data are inherently heteroscedastic (time-varying error variance) [9]. It was indeed conceded in [5] that the residual may be temporally or spatially autocorrelated but no remedial measures were taken by the investigators to mitigate this serious drawback that limits the quality of estimates obtained .

The excess mortality projection for New Zealand has been highlighted to be flawed because it ignored the changes in the population growth rate [4]. There was no discussion in the report [5] of why this model should accurately forecast expected deaths, with a claim that there is a '*yearly trend over recent years due to changing population structure or socio-economic factors*", which is rather vague [4]. The model lacks a population variable, so whatever the population growth rate was from 2015 to 2019 is implicitly projected forward at the same linear rate into the future [4]. This is poorly suited to capture migration-induced changes in population growth, which was the case with New Zealand during the early years of the pandemic with lockdowns and border closure [4].

Excess death estimates that do not incorporate statistical uncertainty cannot be used for inference. The excess mortality estimates presented in [5] importantly overlooks confidence intervals.

It has been suggested [4] that peer review in public health tends to be more collegial than adversarial, with less critical reviews which are faster and author teams larger (internalizing different views). Specifically, the claimed negative cumulative excess mortality in the case of New Zealand was just an artifact of an inappropriate way to predict expected deaths in a country with a fluctuating population growth rate [4] and this highlights a visible inadequacy of the excess death conceptualization.

There is an evident dissonance in the excess mortality arguments presented in [5]. For one, France and Belgium were mentioned to have accurate COVID-19 reporting and the excess mortality estimates for these countries were underestimated by the model. It was adduced that the likely reason for negative excess mortality was that the non-COVID mortality has decreased, mostly due to the influenza suppression, leading to the excess mortality underestimating the true number of COVID deaths [5]. A counter position to this argument is that if negative excess mortality translates to an underestimation of the true COVID-19 deaths, why does positive excess mortality not equally translate to an overestimation of the true COVID-19 deaths?

Evaluation of Excess Mortality Model based on Seasonal Time Series

The Seasonal Autoregressive Integrated Moving Average (SARIMA) model was used in [6] as the baseline model to predict expected deaths from all-causes mortality. The training data covered from January 2015 to February 2020, utilizing estimated monthly populations as covariates. Spearman correlation coefficients between all-cause excess mortality and reported COVID-19 deaths were computed for the different demographic groupings in the dataset. It was reported that, based on the analysis, COVID-19 comprised >99.992% of deaths. The 95% confidence intervals for all relative risks (RR) were determined via the geometric means of monthly RRs within specific periods (yearly, pre-pandemic, and pandemic).

Further, the index case of COVID-19 in the US was reported on February 2, 2020 while vaccination commenced on December 14, 2020. It is therefore unclear why data of deaths from February 2020 were not incorporated into the analysis as reported [6]. The report also lumped part of the post-vaccination era (December 2020 to February 2021) into the pre-vaccination period. The correct pre-vaccination period for the US was February 2020 to December 12, 2020.

Excess mortality as a measure for highlighting the impact of COVID-19 deaths can provide misleading results. For example, the total cumulative observed deaths in the US between 2020 and 2023 during the

ISSN 2282-0930 • Epidemiology Biostatistics and Public Health - 2024, Volume 19, Issue 2

COVID-19 global health crisis were under-estimated by 1,382,480 deaths based on the SARIMA model deployed by the investigators [6,8]. While this error in prediction seem large (Table 1), the report did not contain *goodness–of-fit* metrics to allow for assessment of the predictive capacity of the model used to forecast the all-cause deaths up to 2023 when the pandemic emergency was declared over.

***Excess Mortality are Residuals*:** Residuals measure the departure of fitted values from observed values of the dependent variable [9]. They can be used to detect model *mis-specification, outliers, or observations* with poor fit; and to detect influential observations, or observations with a big impact on the fitted model [9]. For count data, the simple residual (excess mortality in this case) is heteroscedastic and asymmetric, even in large samples [9]. The residuals in count data modeling do not have zero mean, constant variance, and symmetric distribution, unlike what obtains using ordinary least squares regression [9].

Model adequacy procedures such as the examination of the residuals, goodness-of-fit, and tangential measures are important procedures in a model assessment and these were lacking in both models[5,6]. In establishing a strong relationship between excess mortality and COVID-19 deaths, the Spearman rank correlation coefficient was used with the assumption of non-normality in [6]. However, if the authors have assumed non-normality of the time series data of death counts, then the utilization of the SARIMA model is not justified.

A model should be judged based on its performance in comparison with the observed data. The linear regression model itself [5] uses estimates of the population sizes (from the United Nations World Population Prospects [10] which distorts the true situation, as alluded to by [4]. Population growth, especially during the pandemic period is not expected to be a linear trend, but this was the basis of the formulation. The analysis as reported incorrectly used point estimates as the basis for establishing excess deaths, without providing any computed confidence intervals for the estimates.

Excess mortality as defined in the literature is in reality, the error of prediction. A POSER IS: *what will excess mortality be called if there was no pandemic or what would the excess deaths be attributable to?* Recent studies in the US [11,12] have clearly shown that COVID-19 and its related deaths were not the leading causes of death in the United States all through the pandemic period. The excess death formulation is highly correlated with reported COVID-19 deaths as highlighted in [5] (Figure 4) and [6] (Figure 2), respectively. Therefore its trajectory is actually based on the reported COVID-19 mortality that is *a priori* termed to be poorly collected.

Excess Mortality Assessment In Europe

One large-scale data-driven assessment of the impact of COVID-19 in Europe was presented by [13]. This spatio-temporal analysis of excess mortality correctly leveraged on quasi-Poisson regression models using the pre-pandemic data as baseline. The study in [13] incorporated population dynamics and control for potential cofounders in the method. While the modeling approach in [13] ticks several boxes, as this critical review points out, the field often takes model assumptions at face value without stringent residual diagnostics, thorough sensitivity analysis, and rigorous verification of the underpinning distributional assumptions.

A rich mix of socioeconomic indicators based on World Bank 2020 estimates (and in some instances 2018 and 2019 estimates) were integrated into the modeling framework by [13] to reflect possible country-level disparities in excess deaths. It is noted that the investigators [13] validated the baseline data with other data sources and this was consistent with other sources. Population data were obtained from the United Nations' regularly-updated database although as earlier pointed out in [4], this may distort the reality especially during the early stages of the pandemic. It is also worth stating that these population numbers are based on modeling and are not the observed population numbers for the countries surveyed. Sensitivity analysis was, however, carried out by the investigators in [13] to establish consistency of the model estimates in 2018-2019 (a year before the pandemic began).

Table 1: Predicted and Reported COVID-19 Death Statistics of SARIMA model*

S/N	<25 years (%)	25-64 years (%)	≥ 65 years (%)	TOTAL
Expected/Predicted Mortality/ Deaths (SARIMA model)	190,950 (2.06%)	2,174,407 (23.58%)	6,815,746 (74.46%)	9,261,003
Observed Mortality/Deaths	208,556 (1.96%)	2,610,917 (24.53%)	7,823,960 (73.51%)	10,643,433
Observed-Expected Ratio (Disparity)	1.09	1.20	1.13	1.15

**Constructed with data in [6]*

Summary and Synthesis

These observations make a case for using multiple metrics (such as cause-specific mortality, hospitalization rates, and long-term COVID-19 sequelae) in assessing the pandemic mortality impact. Such triangulation of findings from various indicators can lead researchers beyond a one-dimensional and potentially misleading proxy such as excess mortality. In particular, systematic integration of confidence intervals, scenario analyses, and comparison to alternative modeling approaches with well-established assumptions would enhance the robustness and interpretability of results.

The current availability of comprehensive death registries, COVID-19-specific mortality data, and cause-of-death statistics should take precedence over purely model-based excess mortality estimates. Observed data should guide adjustments or recalibrations of models to deliver the best results rather than an over-reliance on forecasts. Future analyses should routinely involve goodness-of-fit, heteroscedasticity, and temporal dependence and more flexible model structures.

CONCLUSION

Emerging data when a new pandemic breaks should be the basis for decision making rather than a recourse to predictive models whose utility are high only when new data are yet to be available. Such predictive models may be inappropriate in capturing the uncertainties and dynamics of an evolving pandemic as COVID-19 clearly show when it was predicted as catastrophic in Sub–Saharan Africa despite early pre-vaccine data showing otherwise. Additionally, a lack of establishing distributional assumptions underpinning any model casts aspersions on the quality of inference that could be extracted from such analysis.

Predictive models serve as a guide and their projections can be helpful when an epidemic is unfolding. However, where data become available, the observed results must take greater precedence over forecasted values, as the issue of under-reporting (in the case of COVID-19 deaths) may be less debilitating than basing policy response on a *one-cap-fits-all* predictive model, which in itself suffers several deficiencies. In assessing the impact of COVID-19 (or any public health emergency), other metrics in addition to the death counts should be utilized. These statistics, when combined with relevant auxiliary information, offer a better view of the pandemic impact rather than reliance on a subjective and potentially misleading metric such as the *excess death*.

AUTHORS CONTRIBUTION

EOO and NAI are joint first authors.

ACKNOWLEDGEMENT

This work was self–funded; and we have no conflict of interest to declare.

DEDICATION

This work is dedicated to the memory of Dr. Patrick I Okoro (1940-2024).

REFERENCES

1. World Health Organization (2023) "Statement on the fifteenth meeting of the IHR (2005) Emergency Committee on the COVID-19 PANDEMIC " AVAILABLE AT: https://www.who.int/news/item/05-05-2023-statement
2. Leon DA, Shkolnikov VM, Smeeth L, Magnus P, Pechholdova M, and Jarvis CI (2020). Covid-19: a need for real-time monitoring of weekly excess deaths. *The Lancet*, 395, e81
3. Excess mortality during the Coronavirus pandemic (COVID-19). World Health Organization (WHO, 2023). Methods for estimating the excess mortality associated with the COVID-19 pandemic. Published August 4, 2023. Accessible online via https://www.who.int/publications/m/item/methods-for-estimating-the-excess-mortality-associated-with-the-covid-19-pandemic
4. Gibson J (2024), Cumulative excess deaths in New Zealand in the COVID-19 era: biases from ignoring changes in population growth rates , New Zealand Economic Papers ,58:1,95-106, DOI :10.1080/00779954-2024.2314770
5. Karlinsky A and Kobak D (2021). Tracking excess mortality across countries during the COVID-19 pandemic with the World Mortality Dataset. *Elife,* 10: e69336
6. Faust JS, Renton B, Bongiovanni T, et al. (2024) Racial and ethnic disparities in age-specific all-cause mortality during the COVID-19 pandemic. *JAMA Network Open.* 2024; 7(10):e2438918. doi:10.1001/jamanetworkopen.2024.38918
7. Mathieu E, Ritchie H, Rodes-Guirao L, Appel C, Giattino C, Hasell J, Macdonald B, Dattani S, Beltekian D, Ortiz-Ospina E, and Roser M (2020). Coronavirus Pandemic (COVID-19). Published online at ourWorldinData.org. Retrieved from: https://ourworldindata.org/coronavirus
8. Okoro EO and Ikoba NA (2024) "Error in data interpretation in the Table of Article " Leading Causes of Death in the US, 2019-2023" Correction on:

ISSN 2282-0930 • Epidemiology Biostatistics and Public Health - 2024, Volume 19, Issue 2

Ahmad et al JAMA 2024, 332 (12),957-958 submitted on October 22, 2024, Posted online October 29, 2024. Accessed via https://www.jamanetwork.com/journals/jamaarticle-abstract/282207

9. Cameron AC, Trivedi PK (1998). Regression Analysis for Count Data. Cambridge University Press, Cambridge, United Kingdom.
10. United Nations, Department of Economic and Social Affairs, Population Division (2022). World Population Prospects 2022, Online Edition.
11. Ahmad FB, Cisewski JA, Anderson RN (2024), Leading Causes of Death in the US, 2019-2023, JAMA 332 (12): 957-958.doi.10.1001/jama.2024.15563
12. Curtin SC, Tejada-Vera B, Bastian BA (2024). Deaths: Leading causes for 2021. *National Vital Statistics Reports;* vol 73 no 4. Hyattsville, MD: National Center for Health Statistics. DOI: https://dx.doi.org/10.15620/cdc/147882.
13. Pizzato M, Gerli AG, La Vecchia C, Alicandro G (2024). Impact of COVID-19 on total excess mortality and geographic disparities in Europe, 2020-2023: a spatio-temporal analysis. *The Lancet Regional Health - Europe,*44: 100996; DOI: https://doi.org/10.1016/j.lanepe.2024.100996

ISSN 2282-0930 • Epidemiology Biostatistics and Public Health - 2024, Volume 19, Issue 2

Public Health Nutrition: Rural, Urban, and Global Community-Based Practice. Margaret Barth, Ronny Bell, Karen Grimmer, Karen Kyle, Adam Hege, New York, NY: Springer, 2020, 502 pp, $83.36. ISBN: 978-0826146847

Nikolaos O. Nikitidis[1]

(1) Department of Dietetics and Nutrition, University of Thessaly, Trikala, Greece

CORRESPONDING AUTHOR: Nikolaos O. Nikitidis, 26 K Karamanli street, 54639 Thessaloniki, Greece. Tel: +302310831833. E-mail: nikitidis@yahoo.com

Although this book originally intended as an introductory text for the education of future public health nutrition practitioners, it has evolved to forge and aspire public health nutrition leaders. Throughout the text, information, models, processes, examples, and practice activities, readers are acquiring the necessary knowledge and skills for successful engagement in the public health nutrition discipline.

The book consists of 17 chapters and is structured into four main parts: Part I: *Foundations of Public Health Nutrition* covers history and principles, nutritional epidemiology, behavioral aspects, and food policy. Part II: *The Cultural Aspects of Public Health Nutrition* explores nutrition, health promotion, and interprofessional practice in various public health nutrition settings. Part III: *Community Assessment, Planning, Implementing, and Evaluation* involves community nutrition assessment, program planning, and public health nutrition intervention evaluation. Part IV: *Current and Future Challenges in Public Health Nutrition and Sustainability* covers nutrition-related health issues, professional development needs, sustainability concerns, food systems, and environmental health trends.

As expected, it discusses a broad spectrum of themes concerning public health nutrition, and the knowledge provided can help tackle issues in various communities, rural, urban, or global. Also, covers significant contemporary trends like telehealth, mHealth, collaborative grantsmanship, and creative communication tactics. The utilization of interprofessional and evidence-based approaches is considered a favorable element. Even though the examples used focused on the United States, they remain relevant in diverse contexts.

The variety of educational resources that can be accessed is quite remarkable. Every chapter offers learning objectives, key concepts, a glossary, case studies, questions, activities, and study resources. There are even supplementary materials specifically designed for instructors including the Instructor's Manual, Test Bank, PowerPoints, Image Bank, and Syllabus. The extensive educational material not only provides knowledge but also fosters skills and builds competencies, including health needs assessment, problem-solving and critical thinking, evidence based public health practice, and leadership.

For maximum versatility, apart from the printed book, the contents are available online for easy access, portability, and searchability and in an e-book form for use on most mobile devices and computers. This textbook can serve as a valuable resource for students and professionals specializing in nutrition, public policy, social work, and other health science-related areas.

The editors and contributors consist of academics, researchers, mentors, and experts in public health nutrition, guaranteeing the quality of the information presented. We firmly believe that the book effectively fulfills the authors' goal as "*an effective tool for training and inspiring future public health nutrition professionals to engage in transformative practice everywhere in the world to nourish the physical, emotional, and spiritual dimensions of all human beings.*"

FUNDING: The work was not financially supported by any organization.

DOI: 10.54103/2282-0930/27055
Accepted: 31th October 2024