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CONTENTS

EDITORIAL

ORIGINAL ARTICLES

NARRATIVE REVIEWS

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PUBLIC HEALTH AND MEDICAL HUMANITIES HISTORY CORNER

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The Italian Society of Medical Statistics and Clinical Epidemiology (SISMEC) Working Group (WG) on "Environment, Climate and Health": topics, aims and perspectives

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In the latest edition of the Conference of the Parties (COP 28, Dubai, 2023), the discussion on air pollution-induced climate change was expanded to include for the first time the health concerns of exposed populations [1]. This fact enshrines the indissolubility of the three themes – Environment, Climate and Health – not only within the scientific community, but also in political, educational and dissemination contexts.

The 12th National Congress of the Italian Society of Medical Statistics and Clinical Epidemiology (SISMEC) held in 2023 and entitled "Environment, Climate and Populations," as well as the pre-congress workshop focusing on the environment and respiratory diseases, highlighted the diverse perspectives that many Society members are dealing with regarding these issues. This experience gave rise to the need to connect the different views, skills and experiences in order to effectively address methodological, statistical, epidemiological and educational challenges, by setting up a new working group (WG) within the Society. Preliminary open meetings have identified several areas where our Society can make meaningful contributions through its vision and methodological expertise, including:

- Fostering the *availability of integrated and interconnected high-quality data* on health outcomes and environmental exposures;
- Pursuing studies on the h*ealth impact assessment* of extreme weather events (e.g. heat waves, droughts, flooding), and contaminants of various matrices (e.g. air, water, soil, noise), including pollution related to specific sources such as existing and planned productive settlements [2];
- Promoting the design and conduction of studies to evaluate the *effectiveness of interventions* for climate change *mitigation and adaptation,* such as urban reforestation projects [3-4];
- Contributing significantly to research areas necessitating advanced statistical and epidemiological methods, including *exposomics* as the assessment of lifestyle and environmental interactions [5-6];
- Assessing the multi-generational impact of environmental exposure on health [7-8];
- Investigating the impact of joint exposure to different factors, such as the interaction between environment, climate and social class, on health. *Environmental justice* [9], a movement born in the eighties in United States, has now become a goal of many national and international agencies, including the Environmental Protection Agency and the World Health Organization. Studying the socio-economic determinants influencing health [10] and their interaction with climate and environment is therefore fundamental in a participatory context that aims to eliminate the unequal distribution of environmental harms in populations [11];
- Examining *other methodological aspects* that are intertwined with the aforementioned themes, such as individual exposure assessment, measurement error, geocoding techniques, maps production, and the assessment of health impacts arising from exposure mixtures [12].

GOALS

With respect to these themes and others that may emerge at a later stage, the WG aims to:

i. engage in collaborative discussions to deepen the methodological and statistical aspects related to the identified issues;
ii. develop and consolidate networking activities both with other WGs and commissions active within the Society, and through interlocution with other Scientific Societies active on the same issues, also fostering the development of joint research projects;
iii. promote training and dissemination/communica-

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tion activities at different levels and for different audiences.

ACTIVITIES

In its first two years of activity, the WG aims to:

- organize an initial educational and dissemination event, and produce a subsequent report for publication in the Society's journal;
- interact with active SISMEC WGs and commissions (C) [indicated between square brackets] on common areas, such as:
  - o use of methods of machine learning techniques for environmental epidemiology, e.g., for exposure assessment [WG: Machine Learning];
  - o causal inference in environmental epidemiology studies [WG: Causal Inference in Epidemiology];
  - o environment and frailty [WG: Observational Studies];
  - o Privacy and data security [C: Privacy];
- organize a series of seminars and workshops, including a workshop for the upcoming 13th Society National Congress in 2025, dedicated to relevant topics in the field of health and climate studies;
- promote dissemination to the general public audience, through media and events.

We are confident that the introduction of this new working group will stimulate the debate within our Society, encouraging other members to join and to be engaged in its initiatives. Environmental issues, climate change and health inequalities represent some of the most pressing challenges of our times; therefore, it is imperative that we seize the opportunity to contribute our expertise as biostatisticians and epidemiologists.

WG (in alphabetical order)

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Analysis of COVID-19 Pandemic Waves in Death Figures of Turkey

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SUMMARY

Introduction: The COVID-19 pandemic has resulted in a substantial number of deaths worldwide, making it crucial to conduct a periodical behavior analysis of the COVID-19 death figures. By understanding the trends and patterns in mortality rates, decision-makers can make informed choices on prioritization of interventions to pandemics.
Method: Death figures due to COVID-19 between 17 March 2020 and 27 November 2022 were taken into account in this study. Mortality data were analyzed using statistical and graphical methods. Von Bertalanffy's growth model parameters were estimated for each wave. Then the model performance measures were calculated.
Discussion: In this study, the course and change of daily mortality data over time were examined. The data reveal that the COVID-19 pandemic occurred in Turkey as four waves. Von Bertalanffy's growth model appears to be an explanatory model for all pandemic waves according to the performance measures.
Conclusion: It was observed that the COVID-19 pandemic spread in Turkey in four waves. Investigating COVID-19 and similar pandemics using versatile and multidisciplinary methods is of great importance in understanding and predicting the behavior of pandemics.

Keywords: COVID-19; pandemic waves; growth models.

INTRODUCTION

COVID-19, also known as Coronavirus Disease 2019, is a highly contagious viral illness caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). First identified in December 2019 in Wuhan, China, it rapidly spread across the globe, resulting in a global pandemic [1]. The COVID-19 pandemic has had a profound impact on global health, society, and economies. To effectively combat this unprecedented crisis, extensive research on various aspects of COVID-19 is of paramount importance.

The COVID-19 pandemic has resulted in a substantial number of deaths worldwide, making it crucial to conduct a periodical behavior analysis of the COVID-19 death figures. By analyzing the trends, patterns, and factors influencing COVID-19 mortality rates, researchers and policymakers can gain valuable insights that contribute to effective response strategies, resource allocation, and public health interventions. Globally, as of 14 June 2023, there have been 767.984.989 confirmed cases of COVID-19, including 6.943.390 deaths, reported to WHO. As of 12 June 2023, a total of 13.397.334.282 vaccine doses have been administered [2]. In Turkey, from 3 January 2020 to 19 June 2023, there have been 17.042.722 confirmed cases of COVID-19 with 101.492 deaths, reported. As of 28 January 2023, a total of 139.694.693 vaccine doses have been administered [3].

A periodic behavior analysis of COVID-19 death figures provides a means to track and monitor the progression of the pandemic's impact on mortality rates. By examining the data over time, researchers can identify fluctuations, spikes, or declining trends in death figures, enabling a better understanding of the disease's trajectory. This analysis allows for the identification of hotspots or regions experiencing a surge in fatalities, facilitating targeted interventions and resource allocation to mitigate further spread and save lives.

A periodical behavior analysis of COVID-19 death figures provides policymakers with essential data-driven insights for evidence-based decision-making. By understanding the trends and patterns in mortality rates, decision-makers can make informed choices regarding resource allocation, healthcare system strengthening, preventive measures, and prioritization of interventions. COVID-19 seems to have lost its feature of being a serious epidemic lately. Although

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there are reports of cases in some countries, its place on the international agenda has declined. It is not on the agenda in Turkey at the moment, but efforts are being made to eliminate the socio-economic effects of the pandemic.

Numerous mathematical models are being produced to forecast the future of COVID-19 pandemic in the US and worldwide [4,5]. Several growth models, time series models, SIR model with their variants are used for forecasting the case and the death figures of COVID-19 in the literature [6-13]. WHO collects scientific studies containing the latest international findings and information about COVID-19 and publishes them in the WHO COVID-19 Research Database by updating them daily [14].

METHODOLOGY

Analyzing the behavior of COVID-19 death figures allows for the evaluation of the effectiveness of intervention measures implemented to control the spread of the virus. This information is valuable for refining public health strategies, modifying interventions, and identifying best practices to minimize mortality rates. For these reasons, analyses were made and interpreted on the time series to determine the increases, decreases and peaks in daily mortality data. It has been determined that the periodic increases and decreases in daily mortality data occur in four waves. In addition, Von Bertalanffy's growth model (VBGM) parameters were estimated for each pandemic wave.

Data Analysis

Turkish authorities had announced COVID-19 figures daily between 17 March 2020 and 30 May 2022. After 31 May 2022, Turkish authorities have announced the figures as weekly, biweekly, and more recently three weekly periods [3].

Mortality data were analyzed using statistical and graphical methods. Cumulative and daily death figures of COVID-19 have been given in Figure 1 and Figure 2 respectively. The waves of the pandemic are illustrated by Figure 3. Summary information and statistics on the waves of the pandemic are given in Table 1.

Figure 1. Cumulative daily death figures of COVID-19 in Turkey

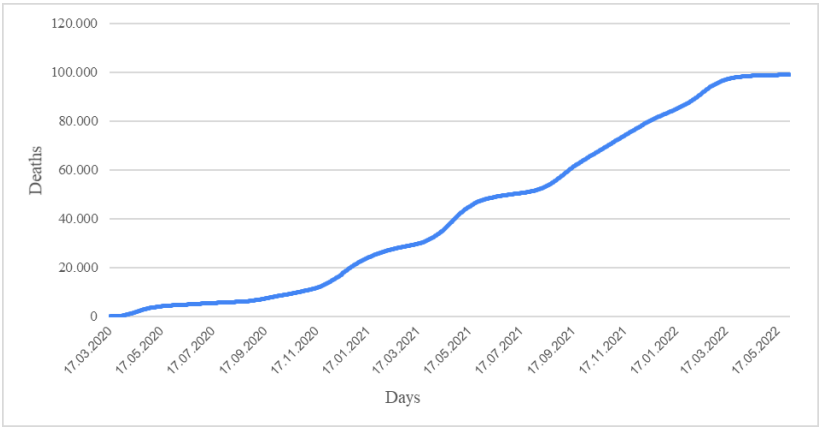

Figure 2. Daily death figures of COVID-19 in Turkey

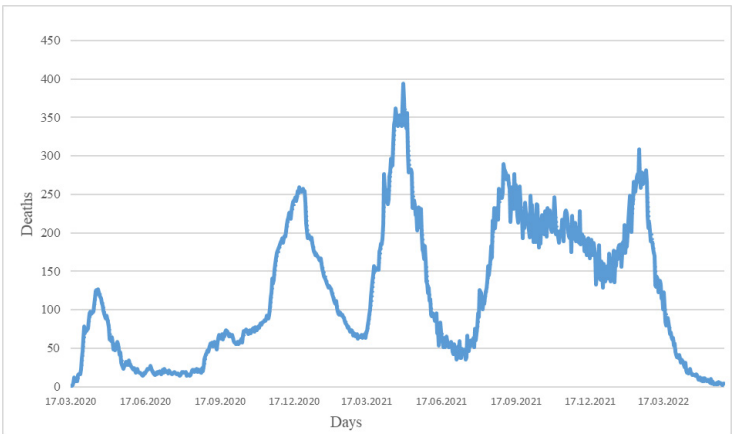

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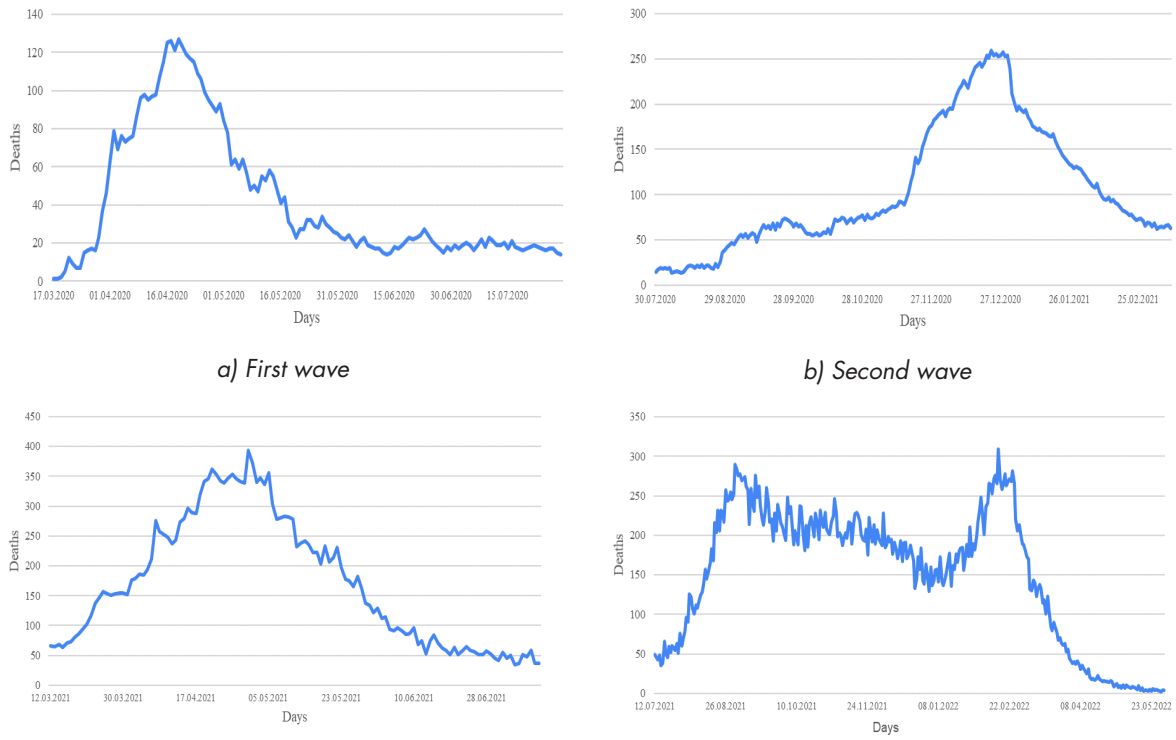
Figure 3. Waves of daily deaths



a) First wave

b) Second wave

c) Third wave

d) Fourth wave

The first wave of the COVID-19 pandemic lasted for 135 days, with the minimum number of deaths 1 and the maximum number of deaths 127 during this period. The average death figures during this period were 42 with a standard deviation of 34.26. The second wave of the pandemic lasted for 225 days, with the minimum number of deaths being 14 and the maximum number of deaths being 259. The third wave of the pandemic which has shortest period lasted for 122 days, with the minimum number of deaths being 35 and the maximum number of deaths being 394. The fourth wave of the pandemic which is the longest wave lasted for 324 days, with the minimum number of deaths being 2 and the maximum number of deaths being 309 in this period. Fourth wave between 12 July 2021 and 31 May 2022 has bimodal behavior which were on 1 September 2021 with 290 deaths and on 15 February 2022 with 309 deaths.

The death figures were reported weekly between 3 May 2022 and 2 October 2022, biweekly between 3 October 2022 and 13 November 2022 and tree weekly after 14 November 2022. The maximum number of deaths being 380 were occurred on the week of 01-07.08.2022. The average number of deaths per day this week is about 54. During this 189-day period, a total of 2527 deaths due to COVID-19 were reported, with a daily average of approximately 14.

Although it is the shortest wave, the third wave has the highest daily death value with 394 deaths among all waves of the pandemic. The highest variation in standard deviations is also seen in the third wave.

Table 1. Descriptive statistics and information by waves

Waves	Begin Date	End Date	Peak Date	Maximum Deaths	Minimum Deaths	Average Deaths	Standard Deviations
First Wave	17.03.2020	29.07.2020	19.04.2020	127	1	42	34,6
Second Wave	30.07.2020	11.03.2021	23.12.2020	259	14	105	68,52
Third Wave	12.03.2021	11.07.2021	30.04.2021	394	35	172	106,39
Fourth Wave	12.07.2021	31.05.2022	15.02.2022	309	2	150	86
Last period	30.05.2022	27.11.2022	01-07.08.2022	380	11	≈ 14	NA

Von Bertalanffy's Growth Model

Growth curve models are often used in the biological sciences to model population size, height, biomass, fungal growth, and other variables, but these methods are also used for modeling and analysis in economics, public health, and other statistical fields. There are many growth curve models in the literature. One of them is Von Bertalanffy's growth model (VBGM). Von Bertalanffy [15] has introduced the growth curve model to model fish weight growth. VBGM is used to model mean length depending on age in animals. A simplified form of the growth model given in (1) is used in this study. Where, α_0, α_1 and α_2 are the model parameters. This model is also used for the pandemic figures in recent years [6]. The parameters of the growth model were estimated by Least Squared Error method in (2) for each pandemic wave and given in Table 2.

$$g(t) = \alpha_0 (1 - \exp(-t/\alpha_1))^{\alpha_2} \quad (1)$$

$$\hat{\boldsymbol{\alpha}} = \arg\min \sum (y(t) - \hat{g}(t))^2 \quad (2)$$

Where, $\hat{\boldsymbol{\alpha}}$ is the estimation of the $\boldsymbol{\alpha}$, y(t) is the observed value at time t, and $\hat{g}(t)$ is the prediction at time t by the considered model g(t).

Mean Square Error (MSE) and R^2 have been used to model performance measures in this study, and they are given in (3), (4) respectively. Where n is the number of observations and $\bar{y}$ is the average value of the observations. Model performance are given in Table 3.

$$MSE = \frac{1}{n}\sum_{i=1}^{n}(y(t) - \hat{g}(t))^2 \quad (3)$$

$$R^2 = 1 - \sum_{i=1}^{n}(y(t) - \hat{g}(t))^2 / \sum_{i=1}^{n}(y(t) - \bar{y})^2 \quad (4)$$

Cumulative death figures for each wave have been log transformed and the parameters given in Table 2 have been obtained.

Table 2. Model parameters by waves

Period	α_0	α_1	α_2
First Wave	8,536	15,947	0,907
Second Wave	14,091	728,767	0,239
Third Wave	10,281	48,868	0,249
Fourth Wave	10,957	104,229	0,24

According to the performance measures in Table 3, the model represents successfully the cumulative death figures of Turkey. Model performance values were recalculated for the original values and are given in Table 3. According to the results, the VBGM appears to be an explanatory model for all pandemic waves.

Table 3. Model performances by waves

Waves	Transformed data		Original data	
	MSE	R^2	MSE	R^2
First Wave	0.012	0.996	43756	0.988
Second Wave	0.009	0.997	1714336	0.975
Third Wave	0.008	0.995	1182078	0.979
Fourth Wave	0.005	0.997	1175434	0.996

DISCUSSION

This article highlights the significance of a periodical behavior analysis of COVID-19 death figures in understanding the impact of the pandemic and shaping evidence-based decision-making. In this study, the course and change of daily mortality data over time were examined. The data reveal that the COVID-19 pandemic occurred in Turkey as four waves. VBGM parameters were estimated for each wave, and it is seen that the model parameters of each wave differ. According to the results, the VBGM appears to be an explanatory model for all pandemic waves. This analysis helps optimize public health responses, minimize the loss of life, and reduce the burden on healthcare systems.

There are limited studies in the literature from statistical analyzing perspective of pandemic waves using the death figures. However, some related example studies exist as following. Wei et al. [16] studied to classify the epidemic patterns of countries and territories worldwide. They evaluated the pandemic situation over the first year in countries and territories across the world and identified their similarities in terms of situation and trend. Kunno et al. [17] compared the characteristics of three waves during the COVID-19 pandemic in Thailand. Significant differences between the pandemic waves were concluded. Seong et al. [18] compared demographics, transmission chains, case fatality rates, social activity levels and public health responses between the second and third waves in South Korea. Significant differences in transmission chains between the second and third waves were concluded.

CONCLUSION

A periodical behavior analysis of COVID-19 death figures is of paramount importance in understanding

the impact of the pandemic, identifying high-risk groups, assessing intervention effectiveness, and guiding evidence-based decision-making. By continually monitoring and analyzing these figures, researchers and policymakers can develop targeted strategies that effectively address the challenges posed by COVID-19 and mitigate its impact on global health and well-being.

During the past 3.5 years, the COVID-19 pandemic has had significant effects in many areas, from public health to tourism, education, food and industrial production supply chain. Investigating COVID-19 and similar pandemics using versatile and multidisciplinary methods is of great importance in understanding and predicting both the behavior of pandemics and their spread and death rates.

With this study, it was observed that the COVID-19 pandemic spread in Turkey in four waves, causing deaths. Considering the performance criteria, it has been shown that the pandemic behavior can be explained for each wave with VBGM, and it has been observed that the pandemic preventive measures should continue until the results are obtained.

In future studies, the effects of preventive measures on the spread of the pandemic and changes in the death rate will be investigated with some stochastic models.

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2022: Are We Back to the pre-COVID-19 Pandemic Period in the Management of out-of-Hospital Cardiac Arrest?

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SUMMARY

Introduction: The COVID-19 pandemic caused a significant strain on the Emergency system, particularly for time-dependent diseases like Out of Hospital Cardiac Arrest (OHCA). Studies have shown an increase in the incidence of OHCA during different waves of the pandemic, but there is limited evidence on how survival rates and rescue efforts have been affected in the post-pandemic period.
Methods: We performed a retrospective observational cohort study of all OHCA rescues by AREU (Agenzia Regionale Emergenza Urgenza), in the Lombardy region in March in three different years (2019, 2021 and 2022). We used rescue mission data collected in AREU's database, where logistic information of patient rescue missions managed by the Lombardy Region's 112 system is recorded.
Results: This study was an epidemiology analysis of OHCA after the pandemic. The results showed no significant changes in the probability of receiving bystander cardiopulmonary resuscitation (22.5% vs 24.0%; p=0.41) and public access defibrillation (3.6 vs 3.2; p=0.50) compared to pre-pandemic period. However, there was a decrease in the probability of ROSC (11.5% vs 6.2%; p<0.01).
Conclusion: According to our analysis, there appears to be a return to the pre-pandemic phase with regard to the OHCA network. However, it remains to be pointed out that a careful study of disease networks is essential to understand the resilience of our health system and to understand whether we have returned to a system similar to the pre-pandemic phase after the COVID-19 pandemic.

Keywords: COVID-19; Resuscitation; Out-of-Hospital cardiac arrest; Emergency Medical Service.

INTRODUCTION

The COVID-19 pandemic had a significant impact on the Emergency Medical Services (EMS), with Italy being the first country to be involved [1-2]. Several changes were observed in the EMS, including the frequency and nature of hospital patients' access [3-4] as well as the epidemiological modification of diagnosed diseases. Additionally, many changes were recorded in the single European Emergency Number (NUE) 112 [5], particularly regarding time-dependent pathologies [6]. All the aforementioned factors resulted in a need for the reorganization of the Italy's EMS system, which included among others the telemedicine protocols, the restructuring of the hospital network and the adoption of remote work practices [7]. The Out of Hospital Cardiac Arrest (OHCA) network was influenced by two factors during the COVID-19 pandemic. Firstly, the social distancing, and then the spread of the virus [8]. Social distancing reduced the likelihood of early bystander cardiopulmonary resuscitation (CPR), while COVID-19 led to a decrease in basic life support training [9], which affected the ability of bystanders to recognize and manage OHCA. Additionally, the fear of contracting the virus made bystanders less eager to perform CPR. In 2020, there was a higher frequency of OHCA at home compared to 2019 (82.2% vs 87.3%) where access to defibrillators is limited. Our research [10] indicates a decrease in bystanders CPR during

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the first pandemic wave in March 2020 compared to March 2019 (0.73 [0.60–0.88]; p =0.0008); an increase in OHCA cases at home and a reduced use of public access defibrillators (PAD) (0.44 [0.27–0.72]; p = 0.0009) [10].

The objective of this study was to assess the state of pre-hospital management of OHCA in the Lombardy region, with the aim of determining whether conditions are currently similar to those experienced prior to the onset of the COVID-19 pandemic. The EMS missions in Lombardy region are coordinated by AREU (Regional Emergency and Urgency Agency) [11] and all data from the mission are recorded in the EmMa (Emergency Management) regional portal by rescue team.

METHODS

A retrospective observational cohort study was conducted in the Lombardy region following the principles outlined by the Declaration of Helsinki. The study analysed EMS rescue data of the Lombardy region recorded on EmMa (Emergency Management system). EmMa is a software that collects all the logistical information of the rescue, necessary to analyse the timing of the rescue and where to reach the patient. Information about the event's location and the patient's emergency is needed to decide which vehicle to send to the scene (helicopter, basic medical vehicle or advanced medical vehicle). All vehicles are linked to a GPS system for logistical reasons and all information is collected during the mission and made available anonymously and aggregated for analysis on the EMS system. The aim was to explore the impact of the pandemic across three distinct periods - March 2019 (pre-COVID-19), March 2020 (first peak of the pandemic) and March 2022 (post pandemic) in alignment with the Italian COVID-19 timeline [12]. The categorical variables are presented as number and percentage and Z test for proportion was applied. Continuous variables are presented as mean and standard deviation (SD). Continuous variables were tested for normality by Kolmogorov–Smirnov test and Z test for means was applied. Differences were considered significant with $p < 0.05$, otherwise, they were considered non-significant (NS). The Prism 8.0.1 statistical software (GraphPad Software LLC, San Diego, CA, USA) was used to this aim.

RESULTS

In March 2019, a total of 1,097 cases of out-of-hospital cardiac arrest (OHCA) were reported, with (57,3%) cases occurring in males. The following year, in March 2020, the number of OHCA cases increased to 1,767, with 1020 (57,8%) cases in males. However, in March of 2022, the total number of OHCA cases decreased to 995, with 570 (57,3%) cases in males (data not shown). These data indicate that males had a higher incidence of OHCA cases compared to females in all three years. Furthermore, unknown sex cases were an insignificant proportion of the total OHCA cases examined. Regarding the place where OHCA occurred during the three examined periods, In March 2019, 856 out of the total cases took place at home, representing 78% of the total. In March 2020, the number of OHCA at home increased to 1644, accounting for 93% of the total. By March 2022, the number of OHCA at home decreased to 855, representing 86% of the total. The remaining number of OHCA cases occurred in other places (data not shown).

As shown in Table 1, results suggest that the mean age of OHCA cases has increased over time, but the standard deviation has fluctuated. It is important to note that these results are limited to the month of March and may not be representative of OHCA cases throughout the entire year. On March 2022 a total of 995 OHCA was recorded on Emergency Management (EmMa), accounting for 10,3% of total OHCA registered in 2022. There was a statistically significant rise in the percentage of diagnoses as compared to March 2019, which saw 1097 cases (9,0%) (p<0.01). However, there was a decrease as compared to March 2020, which recorded 1767 cases (13.2%) (p<0.01), coinciding with the first wave.

Table 1: Mean age, standard deviation (SD) and p value of OHCA cases for three different years, March of 2019, March of 2020, and March of 2022

Year	Mean age	SD	*p* value
mar-19	73,9	16,6	
mar-20	75,7	13,8	*p*<0,05*
mar-22	75,2	15,9	*p*<0,05*

**Z test for means; compared to March 2019*

As shown in Table 2, there was no significant difference in the likelihood of receiving bystander CPR performed by lay individuals in March 2019 (22.5%) and March 2022 (24.0%) (p=0.41). Additionally, there was no significant change in the probability of being rescued using a PAD (3.6% vs 3.2%; p=0.50). However, the chances of achieving ROSC were considerably lower in 2022 compared to 2019 (11,5% vs 6,2%; p<0.01).

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Table 2: Characteristics of OHCA rescue in March of three different periods

	2019 N (%)	**2020 N (%)**	**2022 N (%)**
OHCA in March	1097	1767	995
bystander CPR	247 (22.5)	308 (17.4)	239 (24.0)
PAD	40 (3.6)	29 (1.6)	31 (3.2)
ROSC	126 (11.5)	40 (2.3)	61 (6.2)*

*OHCA= out-of-hospital cardiac arrest; CPR= cardiopulmonary resuscitation; PAD= public access defibrillation; ROSC= Return of spontaneous circulation. *Z test for proportion<0.01; compared to March 2019*

DISCUSSION

Based on data emerging from a simple analysis of one variable, it has become clear that the epidemiology of OHCA has undergone some changes. Firstly, the majority of cases occurred at home during the inter-pandemic period, due to restriction policies, and the percentage of cases in the post-pandemic period only slightly decreased, compared to pre-pandemic period. Males had a higher incidence of OHCA cases in all three years analysed. Furthermore, while percentage of bystander CPR and PAD access have returned to 2019 levels, ROSC remained approximately 5% lower than pre-pandemic period. Many factors could have contributed, but it is worth noting that lay rescuers' response during arrests is now in line with the pre-pandemic period. The COVID-19 pandemic has heavily impacted EMS organization, and continuous analysis of rescue efforts and the development of an epidemiological observatory are essential to ensuring a return to pre-pandemic effectiveness. Moreover, the EMS was among the first to register changes in its organization during the pandemic's first wave. Finally, networks analysis could be helpful, even during inter-pandemic periods, as it will aid in predicting new pandemic waves identifying potential alerts.

The analysis of COVID-19 impact, through data collected by the EMS system, is necessary. In fact, in addition to time-dependent pathologies, the EMS system has recorded other relevant changes, in no time depend pathologies [13-15]. For this reason, carrying out retrospective observational studies is relevant, also to plan the new pandemic preparedness statement [16].

The data highlight some differences from the research published by Marijon et al. [8], which showed an increase in OHCA at home similar to our data (90.2 *vs* 93.0%) and a reduction in ROSC of 10%, whereas in our study it was 5.3%. Unfortunately, this last data is difficult to compare because all cardiac arrests were included in our analysis, and we considered ROSC only if achieved on the scene by the rescue crew. Whereas, Marijon et al. analysed the mortality in the Emergency Department. But previous research highlights ROSC reduction linked by a reduction of bystander Resuscitation [17].

However, data are collected by the EMS dispatched centres [18], thus one possible limitation of our study is a reduced occurrence of data entry during an emergency call, especially during COVID-19 pandemic [19]. Moreover, as a retrospective study, the changes recorded could be linked to other phenomena, which emerged in the post-pandemic phase, and should not be linked to COVID-19 only. As shown in previous studies, March is a month in which a variation in ROSC achievement is observed, this phenomenon is unclear, but could be related to the flu season and the beginning of spring [20] or other meteorogical factor [21-23]. Finally, analysing all type of cardiac arrests might lead to different bias. Indeed, the epidemiology of trauma events has changed during the pandemic [4,7,24], and the rate of ROSC may be influenced [25].

In conclusion in the post-pandemic phase, the use of the Public Access Defibrillator and by standard cardiopulmonary resuscitation was in alignment with the pre-pandemic phase. However, we highlight a slight reduction in the return on spontaneous circulation compared to the pre-pandemic phase.

AUTHORS' CONTRIBUTIONS

GS conceived and designed the study; GS and GR collected and analysed the data; GS, GMS and AA interpreted the results of the experiments; GS drafted the first version of the manuscript; all authors edited, revised the manuscript, and approved the final version before submission.

ETHICS

Ethical approval for this study was not required because we used aggregated data collected for administrative purpose.

CONFLICTS OF INTEREST

None declared.

INFORMED CONSENT STATEMENT

Patient consent was waived by the IRB due to the retrospective nature of the study.

DATA AVAILABILITY STATEMENT

The data presented in this study are available on request from the corresponding author.

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Study Design and Research Protocol for diagnostic or prognostic studies in the Age of Artificial Intelligence: A Biostatistician's Perspective

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SUMMARY

Introduction: As the integration of Artificial Intelligence (AI) in healthcare continues to advance, the need for rigorous study design and research protocols tailored to diagnostic and prognostic studies becomes paramount.
Aim: The primary objective of this work is to highlight the biostatistician's point of view about the key points of the research protocol involving AI.
Methods: Assessing the current state-of-the-art guidelines, we outline the methodological challenges faced by biostatisticians when collaborating on research protocols in the era of AI-driven medical research.
Results: The proposed overview on research protocol involving AI elucidates key considerations in study design, encompassing evaluations of data quality, analysis of biases, methodological approaches, determination of sample size, and validation strategies tailored specifically to AI applications. This position paper underscores the pivotal role of strong statistical frameworks in ensuring the reliability, validity, and applicability of findings derived from AI-based diagnostic and prognostic models. Moreover, the paper seeks to highlight the critical importance of incorporating transparent reporting standards to enhance the reproducibility and clarity of AI-driven studies.
Conclusions: By offering a comprehensive biostatistician's viewpoint, this paper strives to significantly contribute to the methodological progression of diagnostic and prognostic studies in the era of Artificial Intelligence.

Keywords: Artificial Intelligence; Diagnostic and Prognostic studies; Research Protocol; Biostatistics.

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INTRODUCTION

In July 2023, the European Medicine Agency (EMA) reported that "Artificial intelligence (AI) refers to systems that display intelligent behavior by analyzing their environment and taking actions – with some degree of autonomy – to achieve specific goals" (https://www.ema.europa.eu/en/use-artificial-intelligence-ai-medicinal-product-lifecycle). As an application of AI, Machine Learning (ML) enables systems to learn from data without being explicitly programmed [1]. In the following, for the sake of brevity we will refer to "AI" approaches including also ML and DL (Deep Learning, a type of ML based on artificial neural networks).

The increasing availability of digitalized healthcare data and the rapid development of big data analytic methods has made possible the recent exponential increase of applications of AI in healthcare. Three key questions derived: 1) Are AI based studies producing *more accurate* evidence with respect to the "standard" statistical methods? 2) Can we *successfully* use AI approaches to diagnose diseases and predict the prognosis? 3) Will AI *take the place* of a physician in the future even?

With respect to the first point, there is no general answer, since it is strictly related to the specific context of application, the aim of the study and the type of data. As an example, when the performance of neural networks (NN) with respect to logistic regression has been explored using tabular data, with the aim of predicting readmission for all causes in hospital one month after discharge for heart failure [2], authors concluded that the performance of NN and logistic regression models implemented with the LASSO method was the same. Interestingly, in a paper published in 1996 (3] in which the advantages and disadvantages of the application of NN and logistic regression were compared (always referring to tabular data), the author concluded that logistic regression is the best choice if the goal is to explore a possible causal relationship between a dependent variable and independent variables. Otherwise, "neural networks can be particularly useful when the primary objective is the prediction of results and important interactions or complex non-linearities exist in the data set, although these preferences are less clear if a regression modeler can model them using appropriate regression splines and interaction terms". On the other hand, nowadays with the increasing availability of multi-modal sources of data, AI approaches could be the preferred choice with respect to standard statistical approaches, being able to handle heterogeneous data sources [4].

About the second question, where the main aim is to predict a probability of diagnosis or prognosis, the evidence currently available is probably affected by publication bias. There is a high risk that works using AI with non-positive conclusions may not have been published and therefore what is found is always in favor of successful performances. In addition, in studies where AI is used with the goal of diagnosing disease, the weak element is often represented by the gold standard or the reference used such as diagnostic guidelines. If there are no established guidelines for the investigated diseases, how accurate the diagnosis from AI can be? This is a relevant issue, as it has been pointed out in an editorial in Lancet Digital Health in 2019: "how can an AI model be trained when experts themselves disagree on the correct answer to a question?": in other words, what is the "ground truth" for AI if physicians did not agree on a diagnosis? [5].

For the third and final question, according to Jiang and coworkers' reflection on the past, present and future of AI in medicine [6], AI will not take the place of the physicians in the future, although AI could support their decision and in some specific areas replace the clinical evaluations. The same conclusion emerges in an editorial published in the Radiology Artificial Intelligence magazine in 2019 [7], where the author concludes that the right question should be whether «radiologists will one day be replaced by those *who use* AI». In an older review, the conclusion was similar: «There is compelling evidence that medical AI can play a vital role in assisting the clinician to deliver health care efficiently in the 21st century. There is little doubt that these techniques will serve to enhance and complement the 'medical intelligence' of the future clinician» [8]. Nowadays the rise of "generative AI" (broadly speaking AI systems that have the ability to generate new content or data that is similar to, but not identical to, existing data) poses additional challenges about the "human role" in the process [9]. Large language models (LLMs) have demonstrated intriguing capabilities in the medical field, but they also exhibit certain limitations [10,11].

As can be seen from the above, the widespread use of AI in medicine has certainly opened a great debate in the medical community. The exponential rise of these new approaches underlines the urgent need to have both guidelines to improve the quality of research involving AI and to better report the evidence from clinical research using AI.

Therefore, the starting point for AI-based studies should be the research protocol as it is when classical statistical methods are employed. A good research protocol must meet some requirements that represent the cornerstones of the research methodology, well beyond the mere estimation of the sample size, which often seems to be the only issue in which the biostatistician should be involved. As also underlined in the EMA draft: "all requirements in the ICH E6 guideline for good clinical practice (GCP) or VICH GL9 Good Clinical Practices (veterinary) would be expected to apply to the use of AI within the context of clinical trials".

This position paper aims to specifically highlight the biostatistician's point of view about the key points of the protocol involving AI from the study aim to the sample size and methodological aspects. Starting from reviewing the state of the art for guidelines

currently available, the main points required in a research protocol when AI methods are involved will be discussed.

Guidelines for the use of AI in medical research: state of the art

As it is well known, the most popular and utilized guidelines for reporting the main study types are gathered in the "EQUATOR network", a website aimed at "Enhancing the QUAlity and Transparency Of health Research" (https://www.equator-network.org/). Considering the scope of this paper, we focused our attention on the most known and applied guidelines, namely CONSORT (CONsolidated Standards of Reporting Trials) for clinical trials, STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) for observational studies, STARD (who deals with STAndards for the Reporting of Diagnostic accuracy studies) and TRIPOD (Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis) for diagnostic/prognostic studies, looking for whether and how the corresponding expert boards have taken into account the issue of AI in their activity and in the delivered documents.

Starting with STROBE, the initiative developed and published several extensions after the main issue, some concerning methodological aspects (for respondent-driven sampling: STROBE-RDS, using mendelian randomization: STROBE-MR), others focusing on specific observational studies (Molecular Epidemiology: STROBE-ME; Nutritional Epidemiology: STROBE-nut), still others dedicated to a given pathology (newborn infection: STROBE-NI). Until today, the STROBE group have not published any extension concerning the role and methods of AI in observational studies.

The STARD working group produced a methodological extension to the core guideline in order to assist researchers in the design and reporting of accuracy studies that use Bayesian Latent Class Models (STARD-BLCM) as well as to guide diagnostic research in dementia (STARDdem). Differently from STROBE, the STARD group is promoting the development of STARD-AI extension, with the aim of providing recommendations for reporting "artificial intelligence-centered diagnostic test". Such initiative resulted in a paper published in BMJ Open where they described "the methods that will be used to develop STARD-AI" [12]. Up to now (2023, dec) STARD-AI has not been published.

TRIPOD is becoming the main reference for clinical researchers aiming at developing and validating multivariable diagnostic or prognostic models. At present there is only an extension devoted to clustered data (TRIPOD-Cluster, https://www.tripod-statement.org/). Similarly to STARD, a working group started to reflect about specificities of models based on AI and the protocol for developing TRIPOD-AI has been published [13]. To be noted that such protocol embraces both TRIPOD and PROBAST, the latter dealing more closely with risk of bias in observational studies. Also in this case, up to now (2023, dec) TRIPOD-AI has not been published.

Among initiatives aiming at enhance the quality of clinical studies, CONSORT is the first in order of time and, after the first seminal guideline for reporting parallel group randomized trials, about twenty extensions were delivered addressing specific designs (non-inferiority trials, cluster trials,…) or non-pharmacological interventions (herbal, acupuncture, socio-psychological,…), or others. In this case, CONSORT-AI extension was fully delivered and published on BMJ [14]. This guideline, however, deals with "interventions with an AI component" and does not face methodological and statistical issues. In other terms, as trials of social or psychological interventions need to be described with some crucial peculiarities, also interventions which use AI "need to undergo rigorous, prospective evaluation to demonstrate impact on health outcomes". Accordingly, CONSORT-AI (in parallel with its companion statement for clinical trial protocols the well-known SPIRIT-AI or Standard Protocol Items: Recommendations for Interventional Trials - Artificial Intelligence extension) includes 14 new items which should be taken into consideration when the intervention is AI-based. The CONSORT-AI extension was developed through a staged consensus process, involving a literature review and expert consultation to generate 29 candidate items, which were assessed by an international multi-stakeholder group in a multiple-stage Delphi survey, finally producing the 14 new selected items. It has to be noted that CONSORT-AI does not affect the traditional statistical approach in clinical trials at all and it is focused mainly on specific points: the distinction between inclusion/exclusion criteria at the level of participants and at the level of input data, the onsite and offsite requirements to use AI in the intervention, the management of missing data which present relevant specificities in this context, the human-AI interaction which, if not standardized, could affect the generalizability of the findings.

RESEARCH PROTOCOL SECTIONS

Objectives/Endpoints

As for any kind of study, it is essential firstly to clearly define the objective of the study since it guides all subsequent phases of protocol development from the selection of the study sample to the definition of the data to be collected and the event of interest. Regarding diagnostic/prognostic studies, to define the aim of the study, the following points must be clearly specified: the source population, the predictors and the outcome of interest.

To correctly define the source population, it must be kept in mind which subjects will take advantage of the results of the diagnostic/prognostic model and therefore indicate the characteristics of the selected population (e.g. elderly, patients affected by a specific disease, general population). The identification of the source population is particularly helpful in the definition of inclusion and exclusion criteria (further details are given in the next section). Moreover, the candidate predictors or diagnostic methods that will be evaluated should be listed, for example salivary antibody biomarkers [15], genetic phenotypes [16], cerebrospinal fluid biomarkers, magnetic resonance imaging, functional imaging data [17]. Finally, the outcome should be mentioned as for example the patients' classification based on disease stage (e.g. patients with mild cognitive impairment or Alzheimer's disease) or types (e.g. heart failure subtypes) or patients' prediction of a clinical outcome (e.g. death or recurrence).

Of note, using AI methods to predict the occurrence of clinical outcomes is a methodological issue, therefore, considering the development of AI models as the main objective of the study is misleading as the aim must be of a clinical nature.

Study Design

The study protocol of AI-based studies in addition to the classical description of study settings and list of countries where data will be collected, should include the description of "the onsite and offsite requirements needed to integrate the AI intervention into the trial setting" [18]. This level of detail is requested since AI algorithms are strictly dependent on the environment in which they are developed, which significantly affects their generalizability. It is therefore essential to define the requirements to support both onsite and offsite integration of AI algorithms. The onsite and offsite requirements integrate the information needed i) to ensure the AI system application works within the environment *in which* the AI algorithm has been developed (and here we can talk about reproducibility); and ii) to ensure the AI system application work in a *different* environment than the one in which it has been developed (and here we can talk about replicability).

In a classical research protocol setting, the inclusion and exclusion criteria at the level of participants must be well detailed. In AI research protocol setting, the inclusion/exclusion criteria must be doubled to encompass the input data too. Therefore, the inclusion (or exclusion) criteria regarding data collected on the participants and analyzed through AI approaches should be reported in the protocol. If input data characteristics drive the pre-randomization eligibility, then the inclusion/exclusion criteria for input data should be specified in the protocol. In other words, the minimum requirements for input data must be detailed. For example, the resolution level for imaging data could be a requirement of data input. It is not enough to report the inclusion/exclusion criteria but also how, when and whom will be evaluated. The risk of selection bias and loss of power is related to inclusion/exclusion criteria in pre-randomization steps or in pre-enrolment. In fact, subjects could meet the inclusion criteria at participant level, but not meet one of the inclusion criteria at input data level so that if the data is unsuitable for the use of the AI system, the participant will be excluded by enrollment. Possibly differential access to the study population is then introduced and the size of the eligible population is reduced, leading to the risk of not having a sufficiently large population from which to select the trial participants.

As concerns the general choice of the study design, conventional experimental or observational designs can be used with AI methodologies. The choice of the appropriate study design usually depends on the main study purpose. For example, if the purpose is diagnostic accuracy, designs include cross-sectional studies, case-control studies, as well as non-randomized or randomized comparative studies. Among the latter, AI techniques may be used for making diagnosis of a specific disease of interest, as compared to the standard diagnostic test. Otherwise, if the study purpose is to develop or validate a prediction model, cohort designs, ideally with prospectively collected longitudinal data, should be employed.

Type and quality of data

In the landscape of applying AI in healthcare, understanding the nuances of data types is paramount to ensuring the reliability and accuracy of outcomes. In a research protocol involving AI it is expected to have a variety of data sources higher than with classical statistical approaches. Data can be broadly categorized into structured, unstructured, and semi-structured formats. Structured data, characterized by a predefined format, includes tabular information commonly found in electronic health records (EHRs). Unstructured data, on the other hand, lacks a predetermined structure and encompasses diverse forms such as narrative clinical notes, medical images, and free-text entries. Semi-structured data falls in between, combining elements of both structured and unstructured data, often seen in documents with defined tags or fields. These various types of health data originate from a multitude of sources, each offering unique insights into patient health. EHRs stand out as a primary source of structured clinical data, capturing essential information from patient demographics to clinical measurements. Biomedical databases collect data from clinical studies and disease registries, forming a foundation for large-scale analytics. Medical imaging platforms store diagnostic images, facilitating collaboration among healthcare professionals. Genomic registries aggregate genetic information, empowering AI applications for personalized

medicine. Wearable devices and sensors provide real-time continuous monitoring data, contributing to a dynamic understanding of patient health over time. However, the accuracy of AI-driven insights hinges on the quality of the underlying data.

Quality control of data is a fundamental step that determines the precision and reliability of the results. This involves rigorous processes such as data cleaning, normalization, and validation to identify and rectify inconsistencies or errors and all these processes should be clearly described in the research protocol.

Data quality parameters can be classified according to whether they concern the outcome or the features (candidate predictors/variables). The first category includes classes overlap, label purity, and class's parity, which can cause an AI classifier to assign an observation to the wrong class. In classification/diagnostic problems, class overlap occurs if subjects from different classes are in close proximity to each other or class boundaries are overlapping with each other. Similarly, label errors or inconsistencies in labels affect the classification task and the decision made during the modelling of the data set. Noise in label assignment can originate from insufficient information, subjectivity, and coding issues. Regarding classes parity, a recent systematic review on data quality in AI models for head and neck cancer [19] suggested that models with good balance in the outcome classes had significantly higher median discrimination than those that did not adjust for classes imbalance.

The second category of data quality parameters include feature relevance, collinearity, data completeness, outlier detection and representativeness. Elimination of features that are either redundant or highly related or irrelevant is highly recommended during training and can be handled through dimensionality reduction techniques. Incomplete, inconsistent, duplicated, or missing data can cause a drastic deterioration in the predictive capacity of the AI model. It is advisable using missing data imputation techniques, choosing between a very simple approach consisting of estimating a value for a feature from observed values (like mean, median, mode or a suitable constant) and then replacing all missing values with the calculated statistic, or more robust missing data imputation techniques based on the maximum-likelihood (frequentist setting) or on the maximum posterior distribution (Bayesian setting) [20].

Finally, to ensure the validity of AI inference, it is crucial that the data accurately represents the characteristics of the target population. Evaluating representativeness involves understanding if the dataset contains all possible instances or if it is a sample of instances extracted from a larger set. In case the dataset is indeed a sample, it is important to ascertain the population size compared to the observed sample and to articulate the degree of representativeness of the sample with respect to the source population. A recent study analyzed the representativeness of U.S. cohorts utilized in training AI models, revealing a systematic bias in the patient cohorts employed for clinical applications. In fact, seven out of ten of the examined studies relied on cohorts from only three states, while 34 states were not considered at all [21]. The effect of training on cohorts from specific geographical locations and subsequently making inferences on data from different locations could be the worsening of performance and fairness, especially in the presence of unequal geographical distribution [22].

Bias

Systematic biases may occur in every phase of the conduction of diagnostic/prognostic studies from the formulation of the research question to the AI model implementation. It is therefore important to be aware of these biases in the study protocol, to implement adequate strategies to avoid them or mitigate their effects (https://catalogofbias.org/). As mentioned before, it is crucial to clearly specify in the protocol inclusion and exclusion criteria of enrollment in the study. Once the source population is defined, it is also extremely important to avoid *sampling bias* that may result in an unrepresentative sample of the initial population. The solution should involve collecting data from randomly selected subjects of all the categories of interest in the reference population, emphasizing the need to precisely define these categories in the protocol. A further issue is in the subsequent data collection and pre-processing phases, where *measurement bias* may be encountered, involving poor precision/accuracy in measuring candidate predictors of outcomes (misclassification), and *exclusion bias*, where features deemed irrelevant are excluded, potentially due to extreme values or missing data. Another concern may be *label bias*, where not all modes of a variable (label) are represented in the collected data, as mentioned in the previous section on data quality.

These biases may lead to the implementation of inaccurate models since relevant predictors may not be included due to the lack of valid information or irrelevant variables selected due to erroneous measurement. Antidotes to these problems include the use of validated tools for defining outcomes and predictors and minimizing missing data. In the protocol definition, the methods used to identify outcomes and features/predictors should be accurately reported as well as the description of any pre-planned stratified analyses, if necessary.

During model development and validation, biases can also emerge from disparities between training and test sets, a crucial point for creating a robust model, and furthermore *confirmation bias* and overfitting, which are both possible and plausible in AI models. Solutions include random allocation of subjects between training and test sets and subsequent internal and external validation of the obtained algorithm. The research protocol should then detail the procedures

for defining training and test sets and describe the algorithm internal or external validation.

In model implementation, the change over time of variables' distribution in the population (covariate shift) or of the strength of the relationship between predictors and outcome (concept drift) may limit the model's predictive ability. Therefore, although no strategies are available to mitigate these biases, monitoring the model's utility over time is crucial to understand whether its use is still appropriate [23].

Methodological approaches

Adopting AI methods does not avoid establishing robust methodological approaches to ensure the reproducibility and validity of findings. To develop and implement AI techniques, a structured approach involving key steps must be used to train and select the final model. In the following, we summarize the steps that should be included in the research protocol in the "Methods" section.

Training Various Models/Algorithms: The initial step involves training multiple models/algorithms on the dataset. Commonly used algorithms (especially on tabular data) include linear discriminant analysis, logistic regression, flexible discriminant analysis, and decision trees. These models are applied to the training dataset, and their performance should be systematically compared on a test set using discrimination measures such as the Receiver Operating Characteristics (ROC) curve with the corresponding Area Under the Curve (AUC) that serves as a summary metric, indicating the classifier's ability to differentiate between positive and negative classes/targets. A higher AUC means superior model performance. In addition to discrimination measures for model evaluation, calibration measures, including Calibration Plots and indices such as the Integrated Calibration Index [24], focus on the reliability of predicted probabilities ensuring that the model's probability estimates reflect the true likelihood of outcomes. These complementary evaluations contribute to a comprehensive assessment of the models/algorithms' performance.

Model Validation Techniques. To evaluate the model's performance variability, k-fold cross-validation is commonly employed. The dataset is divided into K sections or folds, with each fold serving as the testing set at different points. For instance, in 5-fold cross-validation (K=5), the dataset is divided into five folds. During each iteration, one fold is designated as the testing set, and the remaining folds are used for training. This process is iterated until each of the five folds has been used as the testing set. This approach enables an estimation of the model's performance or accuracy, ensuring robustness. Following the initial validation using k-fold cross-validation on the training dataset, the models/algorithms' performance is further assessed using an independent testing dataset.

Selection of Final Model/Algorithm. Post-validation, i.e. the selection of the final model/algorithm is automated, considering the best cross-validated performance metrics both in terms of discrimination and calibration. The selection process emphasizes also a balance between computational efficiency, robust performance, and the model's transferability. Ultimately, a single model is retained based on its superior performance across these criteria. To enhance reproducibility, transparency is paramount. It is necessary in the study protocol and in the successive study report to fully document the algorithms, model architectures, hyperparameters, and preprocessing steps, in order to facilitate the replication of the process by other researchers.

Validity: whenever possible, the study protocol should provide some details about the evaluation of both internal and external validity, indispensable in ascertaining the relevance and generalizability of findings. Internal validity as detailed above addresses the accuracy and consistency of predictions within a specific dataset, while external validity assesses the applicability of the model's outcomes to diverse patient populations or healthcare settings. To enhance internal validity, as described above, researchers must employ rigorous cross-validation techniques, ensuring that models are not overfitting to peculiarities within the training dataset. Furthermore, incorporating diverse datasets representative of various demographic groups helps minimize bias, enhancing the generalizability of the developed models. External validity, on the other hand, is bolstered by collaboration and data-sharing initiatives across institutions. Multi-center studies and collaborative efforts contribute to a more comprehensive understanding of the diverse factors influencing health outcomes. It is crucial to validate AI models across different healthcare environments to ascertain their utility in varied clinical scenarios.

Sample size

Regarding sample size calculation, we focus on the development of diagnostic and prognostic models, which are the primary applications of AI in healthcare. Regardless of the chosen AI approach, the essential prerequisite for constructing and validating such models is the availability of data with an appropriate sample size. This is crucial to ensure the models' robustness and accuracy in predicting various types of outcomes, whether binary, continuous, or time-to-event, both in terms of calibration and discrimination. Hence, sample size justification is an indispensable section of the research protocols to support reliable and accurate predictive models. Determining an appropriate sample size for a prognostic or diagnostic model typically involves considering the number of predictor variables and the incidence/prevalence of the outcome, with an old rule of the thumb of having at least ten events per predictor [25]. However, this simplistic approach overlooks factors such as the type, magnitude, and

potential values of the predictors, often resulting in poorly fitted models that struggle to generalize to new data. Recent simulation studies suggest that additional considerations are necessary, including the choice of modeling strategy and expected performance on out-of-sample data. Riley and colleagues [26] proposed a more comprehensive approach, incorporating expected model performance, the number of candidate predictors, and the prevalence of the outcome in the target population when calculating the sample size. This kind of approach could be a basis also when an AI algorithm is used instead of a traditional one on tabular data, and work is in progress to generalize the idea to AI tools through simulation approaches (https://github.com/ewancarr/pmsims-iscb). Of note, in a recent paper focused on survival prediction models, using real and simulated data, it has been shown that deep neural networks and random forests need at least from 2 to 3 times the sample size calculated according to Riley's method to achieve the performance of the reference [27]. Things become considerably more intricate when non-tabular data, such as unstructured sources like signals, images, or text, are employed in model development, often necessitating the use of Deep Learning algorithms. In this domain, essentially two approaches can be employed. The first is an "a priori" approach, which involves specifying the number of hidden layers in the neural network, the number of neurons within these hidden layers, and determining the minimum number of observations based on the activation function used [28]. This approach, however, has been specifically developed by the authors within a very particular context (discrete choice analysis), utilizing simulations and real data. On the other hand, the second approach relies on post-hoc evaluation, meaning it is applied when (at least part) of the data are already available to the researcher. This method involves empirically evaluating the performance at "small" sample sizes, allowing the extrapolation of performance as a function of the training set size. This is achieved by estimating the learning curve of the algorithm through fitting an inverse power-law function [29,30]. Some extensions are in progress in order to leverage information from publicly available data from related studies to inform the estimation process, to obtain robust estimates of the learning curve at the study planning stage [31].

DISCUSSION AND CONCLUSIONS

When the objective of the study is to predict a probability of diagnosis/prognosis the role of AI approaches is very promising, considering the increasing heterogeneity and complexity of the health data sources. In this context, our recommendations are tailored specifically to cases involving diagnostic and prognostic studies, aligning with the forthcoming TRIPOD-AI guidelines.

When instead the research question is explanatory in nature, we are just now at the very beginning of the potential AI applications in causal discovery and more research in this field is needed [32,33]. This aspect was not addressed in the current paper and is not covered by any other guidelines to our knowledge.

To summarize, we suggest that in research protocol using AI approaches as a first point the data quality control is particularly crucial since therapeutic decisions based on AI analyses can directly affect patient lives. A meticulous approach to ensuring data accuracy not only enhances the credibility of AI applications but also promotes trust among healthcare practitioners and patients. As AI continues to revolutionize healthcare, an unwavering commitment to data quality will be essential in harnessing the full potential of these transformative technologies.

Secondly, addressing biases in AI studies requires meticulous attention at every stage: protocols should transparently report the strategies used to mitigate biases, contributing to the validity and reliability of study results. Finally, open-source code sharing, and comprehensive documentation play pivotal roles in AI applications, enabling the scientific community to validate and build upon existing work. Moreover, the importance of reproducibility extends to clinical settings. Clinicians and healthcare professionals need confidence in the reliability of AI-generated insights for informed decision-making. Transparent methodologies contribute to scientific rigor and foster trust, promoting the responsible adoption of these technologies in real-world healthcare scenarios.

By offering a comprehensive biostatistician's viewpoint, this paper strives to significantly contribute to the methodological progression of diagnostic and prognostic studies in the era of Artificial Intelligence. It underscores scenarios where these methods could provide benefits over conventional approaches and identifies situations in which these approaches might yield biased results. This highlights the importance of a collaborative effort in fostering the development of trustworthy and clinically applicable AI models, with the ultimate goal of bringing substantial improvements in patient outcomes.

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Analysis of High Levels of Urine Proteins as a Sign of Impaired Kidney Function in Communities Around a Nickel Mining Industry in Morosi District, Southeast Sulawesi

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SUMMARY

The study is proposed to analyse the influence of individual and environmental factors on urine proteins levels as a parameter for impaired kidney function in the community around Nickel mining industry in Morosi Sub-District, Southeast Sulawesi Indonesia. This quantitative study used a cross sectional study design. The population was people in 3 villages around the nickel mining industry aged 20-59 years. The sample size was 61 people using simple random sampling technique. Independent variable was age as representation of individual factor and environmental factors including housing condition, water quality, waste management and household liquid waste. Urine proteins as a parameter for impaired kidney function was the dependent variable. Data were collected by questionnaire and taking urine samples. Data were analysed using the multinomial logistic regression test with a significance level of 95%. The results show that age, water source quality, solid waste management and waste water management can be associated with proteinuria in communities around the Morosi nickel mining industry.

Keywords: Kidney disease; age; water; environment; waste; liquid.

SUMMARY

The existence of the nickel mining industry in Morosi District, Southeast Sulawesi, has had both positive and negative impacts on the surrounding community [1,2]. The positive impacts of the existence of the mining industry include opening up opportunities for small and micro businesses in the community and agricultural products such as vegetables which are also marketed to the mining industry environment. In this way, the income of people around the industry increases by around 20.5% [1]. Furthermore, there are job opportunities for people living around the mining industry [3]. Meanwhile, the negative impact of the presence of the nickel mining industry is its contribution to the low quality of the environment, including the quality of water, land and air sources for the surrounding community [4,5]. The Pollution Index at locations closed to the mining industry was identified to be in the range of 7.20 PI. The nickel mining industry has carried out nickel and nickel ore (smelter) processing and refining activities. Emissions from nickel mine management include dust or ash and also gases such as CO, SO_x and NO_x [6].

The air pollution which contains dangerous toxins, especially fine particles, can stay in the air longer. People living in this environment will inhale these toxic fine particles (directly without realizing it. These fine particles disrupt and damage the blood circulation system and the first organ affected is the kidneys. Disorders of the circulatory system become very vital for the continued function of other body organs, including the condition of the kidneys. Therefore, hypertension is often suggested to be the main cause in

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chronic kidney sufferers [7]. Furthermore, people who use contaminated water sources for their daily needs can also infect body organs, including the kidneys. If the human kidney organ damage, the glomerulus cannot filter and reabsorb food substances, including. As a result, food substances cannot become energy or repair cells in the human body. The substances which cannot be absorbed will be excreted in the urine, resulting in high urine proteins levels. Therefore, high urine protein reflects impaired kidney function [8].

The seriousness of kidney disease can also be seen from changes in the frequency of urination in a day, blood in the urine, nausea and vomiting and swelling, especially in the feet and ankles [8]. Several previous studies stated that high levels of urine proteins could be caused by exposure to cadmium (Cd) originating from various sources including food or inhalation of small doses of Cd over a long period of time [9]. Cadmium can accumulate in the body, especially the liver and kidneys [9]. Cadmium is a type of heavy metal that is dangerous because this element can cause vascular and kidney damage. High levels of cadmium in human blood may result in high levels of urine proteins [10]. Through disruption in the balance of calcium and phosphate in the kidneys among other pathogenetic mechanisms. The existence of the nickel mining industry in Morosi has contributed to increasing levels of heavy metals, including cadmium.

The degree of exposure to hazardous materials of people around the industry is of course related to several factors. For example, the longer people live around the mining industry, the higher the level of exposure to these dangerous substances will be. The amount of time a person has lived around the mining industry is proportional to an individual's age. However, it can also be said that if someone moves to an area near the industry at some point in their life, the amount of time spent will be shorter compared to someone of the same age who has always lived in that area.

Previous studies stated that the worse the home conditions and environmental sanitation of individuals around the mining industry, the higher their serum creatinine levels compared to those with good home conditions and environmental sanitation [11]. High serum creatinine levels are also an indicator of the level of kidney damage. However, is the effect the same when using urine protein chemical parameters to see the influence of age and environmental conditions on the level of kidney damage in the community around the Morosi nickel mining industry? Therefore, the aim of this research is to analyze the effect of age and environmental conditions on urine protein in communities around the Morosi Nickel mine, Southeast Sulawesi Province, Indonesia. Environmental conditions include housing conditions, water quality, solid waste and liquid waste management. Meanwhile, the age shows how long the individual has lived in that environment.

METHODS

Research Design

This research uses quantitative methods with an analytical observational approach with a cross sectional study design. This research was conducted in 3 villages around the nickel mining industry, namely Tanggobu, Porara and Morosi Villages, Morosi District, Konawe Regency, Southeast Sulawesi Province from July to August 2022.

Population and samples

The population of this study is formed by adults in Tanggobu Village, Morosi, Porara, Morosi District aged 20-59 years. The sample size was 61 subjects selected using simple random sampling technique. The sample inclusion criteria were adults aged 20-59 years who were willing to be respondents, could communicate well, and had lived in the research location for at least 1 year.

Research variables

In our research the dependent variable is represented by urine protein levels. This variable (y) is divided into 4 categories, namely undetectable (0-0.1 g/L), low (0.1 g/L $\leq$ y < 1 g/L), moderate (1 g/L $\leq$ y < 3 g/L), and high (y $\geq$ 3 g/L) [12]. The independent variables are age and, among environmental factors, house condition, water sources, waste management and household waste management. Age is divided into 2 categories, namely early adulthood (20-39 years) and advanced adulthood (40-59 years) [13]. All environmental factor variables are divided into 2 categories, namely good and bad, according to whether or not the environmental conditions meet the health standards set by the Ministry of Health of the Republic of Indonesia [14].

Data collection and analysis

There were 61 respondents interviewed with a questionnaire and their urine samples taken. We collected spot urine samples and used the dipstick urinalysis method to determine urine protein levels using urine Reagent Strips (URIT 13G Brand). Then, the data were processed with SPSS version 25 using the multinomial logistic regression test with a significance level of 0.05.

Research Ethics

This research was conducted after obtaining approval from the Mandala Waluya University research ethics committee no. 039/KEP/UMW/V/2022 dated 16 May 2022. Respondents' participation in this research was based on their informed consent and was voluntary.

ISSN 2282-0930 • Epidemiology Biostatistics and Public Health - 2023, Volume 18, Issue 2

Table 1. Characteristics of respondents in three villages in the Morosi Nickel Mine Industrial area

Respondent's Characteristics		Frequency	Percent (%)
Sex	Female	43	70.5
	Male	18	29.5
Marital status	Single	5	8.2
	Married	51	83.6
	Widow widower	5	8.2
Education	No school	2	3.3
	Elementary school	28	45.9
	Junior high school	11	18.0
	Seniour high school	15	24.6
	Diploma	1	1.6
	Bachelor	4	6.6
	Total	61	100.0

RESULTS

Respondent Characteristics

This research recruited 61 respondents, most of whom were female (43 people, 70.5%). There were only 18 male respondents (29.5%) (Table 1). The majority of respondents were married (83.6%). However, there were few single people and widows/widowers, namely 5 people each (8.2%). The education level of respondents was mostly elementary school (45.9%). There were also quite a lot of respondents with a high school education, namely 24.6%. However, there were a small number of respondents who had a diploma (1.6%) and bachelor's degree (6.6%). There were also some respondents who participated in this research who had never been to school, namely 3.3%.

Urine proteins Levels

There were only 8.2% respondents whose urine protein levels was low. However, there were 88.5% respondents whose urine protein levels were undetectable (0-0.1 g/L). Respondents whose protein levels were medium and high, there were only 1.6% (Table 2).

Table 2. Urine Proteins Levels, Individual and Environmental Factors in three Villages in the Morosi Nickel Mine Industrial Area

Factors	Variables	Frequency	Percent
Urine proteins Levels	Undetectable (0 – 0.1 g/L)	54	88.5
	Low (from >0.1 g/L to ≤ 1 g/L)	5	8.2
	Moderate (from >1 g/L to < 3 g/L)	1	1.6
	High (≥ 3 g/L)	1	1.6
Individual	**Age group: Years old**		
	Early adulthood (20-39)	26	42.6
	Advanced adulthood (40-59)	35	57.4
Environment	**Quality of Water sources:**		
	Good	49	80.3
	Bad	12	19.7
	Housing condition:		
	Good	31	50.8
	Bad	30	49.2
	Household Solid waste management:		
	Good	24	39.3
	Bad	37	60.7
	Household WaterWaste Management:		
	Good	39	63.9
	Bad	22	36.1

Table 3. Parameter Estimates of low urine proteins vs undetectable urine proteins for individual and environmental factors

Urine Proteins	B	Std. Error	Wald	df	Sig.	Exp(B)	95% C.I. for Exp(B)	
							Lower Bound	Upper Bound
Intercept	24.449	3.802	41.343	1	0.000			
Age	0.053	0.069	0.586	1	0.444	1.054	0.921	1.206
Water Source	-29.158	1.192	598.179	1	0.000	2.171	2.099	2.247
Housing condition	-0.130	1.086	0.014	1	0.905	0.878	0.104	7.381
Solid Waste Management	-28.149	0.000	.	1	.	5.957	5.957	5.957
Waste Water Management	-0.532	1.098	0.235	1	0.628	0.587	0.068	5.053

The reference category of urine proteins is: Undetectable

The reference category of environmental factors (water source, housing condition, solid and water waste management) are: Bad

Individual and Environmental Factors

Individual factors related to age show that the older adult group is the most dominant (57.4%) compared to the early adult group (42.6%) (Table 2). Environmental factors include the quality of water sources used daily, condition of the house, management of solid waste and liquid waste from the house. It was identified that the majority of respondents had a good water source (80.3%), adequate housing conditions (50.8%), and good household wastewater management (63.9%). However, there is still a lot of solid waste management that is not good (60.7%).

Multivariate analysis

Table 3 explains that individual factors (age) and environmental factors have a significant effect on low urine protein levels (>0.1 g/L to <1 g/L). The coefficient value of multinomial logistic regression (B) is 24,449, where this value is positive and significant at p<0.0001. This means that the younger the age and the better the quality of the individual's environment, the probability of having an undetectable urine protein level (0-0.1 g/L) is very high with a standard error of 3,802. Of the several variables, there was only water source which has a very significant effect on low urine protein levels (>0.1 g/L to <1 g/L) compared to age and other environmental factors such as house condition (p=0.905), solid waste management and liquid (p<0.628). The water source coefficient value is -29.158, where this value is negative and significant at p<0.0001. This means that if an individual uses a poor water source, the probability of having undetectable protein levels (0-0.1 g/L) is very low compared to low protein levels (>0.1 g/L to <1 g/L). The Odds Ratio of the water source is 2.171, which means that individuals with a water source which is 1 time worse are estimated to have a low urine protein level (> 0.1 g/L to > 1 g/L) 2.171 times more likely, compared to individuals with the quality of the water source is 1 time better.

Table 4 explains that age and environmental variables do not have a significant effect on medium urine protein levels (>1 g/L to <3 g/L) (p=0.996). However, the coefficient value of the multinomial logistic regression (B) is 191.854, which is positive, but not significant. This means that the younger the age and the better the environmental quality, the probability that an individual will have undetectable urine protein levels (0-0.1 g/L) is very high, with a standard error of 36.551. Of the several variables, there were only house conditions which effected significantly for moderate protein levels (>1 g/L to <3 g/L) with p<0.000, compared to age (p=0.996), water source (p=0.998), solid waste management (p=0.998) and liquid waste management (p=0.997). The coefficient value of house condition is -18,968, where this value is negative and significant at p<0.0001. This means that if an individual lives in poor housing conditions, the probability of having undetectable protein levels (0-0.1 g/L) is very low compared to moderate urine protein levels (>1 g/L to <3 g/L). The odds ratio of the house condition is 5.787. This means that individuals with housing conditions which are 1 time worse are estimated to have medium urine protein levels (>1 g/L to <3 g/L) 5,787 times more likely, compared to individuals with housing conditions that are 1 time better.

Moreover, table 5 also shows that age and environmental variables do not have a significant effect on high urine protein levels (≥3 g/L) (p=0.995). However, the multinomial logistic regression coefficient (B) value is -484,966, which is positive, but not significant. This means that if age gets older and environmental quality gets worse, the probability of

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Table 4. Parameter Estimates of medium urine proteins vs undetectable urine proteins for individual and environmental factors

Urine Proteins	B	Std. Error	Wald	df	Sig.	Exp(B)	95% C.I. for Exp(B)	
							Lower Bound	Upper Bound
Intercept	191.854	36551.557	0.000	1	0.996			
Age	-5.592	1045.359	0.000	1	0.996	0.004	0.000	.[c]
Water Source	-59.833	20158.490	0.000	1	0.998	1.035	0.000	.[c]
Housing condition	-18.968	0.000	.	1	.	5.787	5.787	5.787
Solid Waste Management	43.236	15621.065	0.000	1	0.998	.[c]	0.000	.[c]
Waste Water Management	-81.956	22511.427	0.000	1	0.997	2.552	0.000	.[c]

The reference category of urine proteins is: Undetectable

The reference category of environmental factors (water source, housing condition, solid and water waste management) are: Bad

.[c]: Constant

an individual having an undetectable urine protein level (0-0.1 g/L) is very low, with a standard error of 84.241. Of the several variables, there was only house condition which effects significantly for high protein levels (≥3 g/L) with p<0.000, compared to the variables age (p=0.996), water source (p=0.997), solid waste management (p= 0.999) and liquid waste management (p=0.998). The coefficient value of house condition is 19,632, where this value is positive and significant at p<0.0001. This means that if an individual lives in good housing conditions, the probability of having undetectable protein levels (0-0.1 g/L) is very high compared to high urine protein levels (≥3 g/L). Meanwhile, the Odds Ratio of housing conditions to high urine protein levels (≥3 g/L) is not readable.

DISCUSSION

This study has shown that the quality of water source and housing condition are determinants of the high levels of urine proteins in the community around the Morosi mining industry. The water sources used by the community there may have been contaminated by heavy metals and waste from both industry and households. There are around 19.7% of households

Table 5. Parameter Estimates of high urine proteins vs undetectable urine proteins for individual and environmental factors

Urine Proteins	B	Std. Error	Wald	df	Sig.	Exp(B)	95% C.I. for Exp(B)	
							Lower Bound	Upper Bound
Intercept	-484.966	84241.777	0.000	1	0.995			
Age	6.783	1343.953	0.000	1	0.996	883.050	0.000	.[c]
Water Source	62.910	19890.903	0.000	1	0.997	0.000	0.000	.[c]
Housing condition	19.632	0.000	.	1	.	.[c]	.[c]	.[c]
Solid Waste Management	9.506	13840.769	0.000	1	0.999	13446.440	0.000	.[c]
Waste water management	36.159	14686.078	0.000	1	0.998	5056116588 144295.000	0.000	.[c]

The reference category of urine proteins is: Undetectable

The reference category of environmental factors (water source, housing condition, solid and water waste management) are: Bad

.[c]: Constant

who use dug wells for their daily needs. Dug wells that are exposed to heavy metals such as arsenic, lead and cadmium when someone drinks them will circulate in the blood which is then bound by low-molecular-weight (LMW) proteins. LMW proteins that have bound these heavy metals will be absorbed by the tubules [15]. An increase in the load of such proteins in the tubular lumen leads to saturation of the reabsorption mechanisms by tubular cells, and, in the most severe or chronic conditions, causes toxic damage, which favors increased excretion of all proteins in the urine, including low protein [16,17].

Dug wells are also said to be more susceptible to contamination from various sources, including latrines [18]. The dug wells with polluted water is a source of infection, including Helicobacter pylori infection [19]. Helicobacter pylori disrupts the upper digestive system, especially stomach ulcers, duodenum and certain stomach cancers. In the excavated water from nickel mining fields, it has been identified that there are several indigenous bacteria that are resistant to heavy metal stress. These resistant bacteria include *Escherichia, enterococcus, Bacillus sp., staphylococcus, Klebsiella* and *Pseudomonas* species of bacteria [20].

Individuals who used contaminated water sources may become infected with the urinary tract. This condition also concerns a person's personal hygiene behaviours. The worse a person's personal hygiene behaviours are, the more likely it is that urinary tract infections will occur. If the urinary tract is infected, it will cause excessive excretion of small proteins. An infected urinary tract can damage the tubules and glomeruli, resulting in impaired proximal tubular reabsorption [21]. An abnormal increase in protein production will exceed the reabsorption capacity of the proximal tubule. Finally, protein levels in the urine will be high and postinfectious glomerulonephritis occurs. Post-infectious glomerulonephritis is caused by an immune response to pathogens [22,23]. These manifestations can be acute or chronic because they depend on the type of microorganisms present in the polluted water. Immune system disorders in chronic kidney disease also increase the individual's susceptibility to virus-related to reduce the body's response to vaccines [23].

This study also shows that poor housing conditions are also a cause of high proteinurine levels. The mechanism of influence of poor housing conditions on proteinurine levels and kidney health is through a complex mechanism involving individual and structural factors. Firstly, there is exposure to fine particles in the house. These fine particles can affect kidney health [24, 25, 26]. Individuals living in homes with poor conditions are also more susceptible to heat, lower water availability, and poor water quality, resulting in acute kidney injury, chronic kidney disease, and nephrolithiasis [27, 28,29, 30].

Furthermore, inadequate housing conditions can also affect health through neurohormonal mechanisms, including stress. Acute stress is thought to cause kidney disease through increased blood pressure, heart rate, and decreased vascular reactivity, mediated by the autonomic nervous system, hypothalamic-pituitary-adrenal axis, inflammatory cytokines, and endothelinA [31,32,33,34,35]. Moreover, poor housing conditions also have an impact on social aspects, such as social exclusion which ultimately triggers psychological stress and results in hypertension, sodium and water retention. Stress contributes to increased sympathetic nervous system activity, secretion of glucocorticoids, and inflammatory cytokines, which contribute to higher rates of vascular disease, including risk factors for chronic kidney disease [24].

Finally, it can be said that the mechanism of influence of environmental factors on proteinuria levels is complex and involves factors such as glomerular hemodynamic, tubular absorption, and diffusion gradients. Alterations in multiple pathways and different molecular interactions may lead to the same clinical endpoints of proteinuria and chronic kidney disease. Glomerular diseases encompass a variety of immune and nonimmune disorders that can attack and damage multiple components of the glomerular filtration barrier. In many of these conditions, renal visceral epithelial cells respond to injury along defined pathways, which may explain the resulting clinical and histological changes.

CONCLUSIONS

The quality of water sources and house conditions determine the high levels of protein urine in communities around the Morosi nickel mining industry. The quality of water sources is associated with the inclusion of pollutant sources in the form of heavy metals and solid waste and waste. These two pollutants have a negative impact on a person's body condition, allowing urine protein levels to become high through a complex mechanism. House conditions that do not meet the requirements also have an impact on air circulation and affect aspects of the physical, social and psychological health of the occupants. This condition tends to increase proteinurine levels. The higher levels of urine proteins indicate the level of kidney damage. Therefore, poor water source and housing conditions influenced to the kidney health conditions in people around the nickel mining industry.

Finally, this study can give information for health policy makers and programs to increase community health around the Morosi nickel mining industry. For example, providing piped clean water facilities and improving housing condition and environment can become priority programs in Morosi Sub district.

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CONFLICTING INTEREST

All authors declare no conflicts of interest in this paper.

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The Dimensionality Reduction Problem: A Comprehensive Exploration of Disjoint Principal Component Analysis (DPCA) and Disjoint Multiple Correspondence Analysis (DMCA)

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SUMMARY

This paper delves into the realm of advanced data analysis, focusing on two powerful dimensionality reduction methods: Disjoint Principal Component Analysis (DPCA) and Disjoint Multiple Correspondence Analysis (DMCA). Methodological marvels in their own right, these approaches are scrutinized for their unique properties and applications across diverse domains. We navigate through the intricacies of their algorithms and explore how they unveil patterns within complex datasets. The comparative analysis highlights the strengths and weaknesses of DPCA and DMCA, shedding light on their distinct contributions to the analytical landscape. This paper serves as a comprehensive guide for researchers and analysts seeking deeper insights into these cutting-edge techniques for dimensional reduction.

Keywords: dimensionality reduction model; multivariate analysis; principal component analysis; multiple corrispondence analysis.

INTRODUCTION

In the era of big data, large and massive data sets are increasingly common that often include a progressive increase of the measurements and the number of variables used is always bigger. For this reason, the research of new statistical approaches to reduce the number of variables considerably while still retaining much of the information in the original data set is always under way. We know that in the field of dimensionality reduction methods, a variety of very known techniques have been proposed [1]. The most used and cited methods are surely principal component analysis [2] and factorial analysis [3] for quantitative data, and multiple correspondence analysis [4] for categorical data. Nevertheless, one of the most crucial topics related to these methods is the interpretation of components (i.e., factors) that define the latent subspace.

For example, in the case of PCA and FA, the main issue is related to the fact that each principal component (PC) typically is a linear combination of all manifest (i.e., observed) variables (MVs). In particular, for each PC all loadings are typically nonzero, even though only few MVs are relevant for the corresponding PC. This makes it often difficult to interpret the derived PCs, i.e., to understand what are the variables that really define each factor. In the specialized literature, several extensions of PCA have been proposed to specify subsets of MVs that most explain PCs. A very known approach consists to proceed is to artificially set the loadings with absolute values smaller than a threshold to zero, although Cadima and Jolliffe [5] consider this thresholding approach potentially misleading and subjective. Alternative and more statistically rigorous procedures for enhancing the interpretation are based on postprocessing methods such as rotations [6]. Nevertheless, the rotation procedures do not generate loadings exactly or

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close to zero and, then, thresholding is still required. Although, we note that in the context of FA, standard errors of rotated loadings are available, and thus, the evaluation of small loadings can be facilitated by using this inferential information. In Tibshirani et al. [7], a regularization of PCA is proposed to solve the sparsity problem. This approach consists in shrinking loadings toward zero by maximizing the explained variance of PCs penalized to shrink and select nonzero loadings. Also, Jolliffe et al. [8], propose an example of sparse principal component analysis (SPCA), in which the sparse loading matrix (i.e., namely with very few nonzero loadings) is obtained by using a simple least absolute shrinkage and selection operator (LASSO)-based approach. A probabilistic formulation of the SPCA approach is proposed by Guan and Dy [9]. Moreover, Shen and Huang [10] propose a SPCA via a regularized singular value decomposition (SVD) approach. Conversely, d'Aspremont et al. [11] propose another extension of SPCA: the direct sparse PCA (DSPCA), which reformulates the problem directly incorporating a sparsity criterion in the PCA.

However, even though several extensions of PCA have been proposed, they do not necessarily provide a simpler PC interpretation, since some MVs may still load on several PCs leaving the problem unresolved.

On the other hand, approaches similar to those used in PCA framework have been used in the FA. An example is confirmatory factor analysis (CFA) proposed by Jöreskog [12], where all the relationships between MVs and factors are studied and only few relationships between MVs and factors are specified by associating each MV to a single factor inducing disjoint classes of MVs. Obviously, in this way, the interpretation is greatly simplified since factors are exactly explained by a subset of MVs only. However, a drawback of CFA is that the assignment of a MV to a factor is based on the a priori knowledge of the researcher, which is not often guaranteed in the empirical cases.

An important method to solve the interpretability problem is the disjoint principal component analysis (DPCA) model introduced by Ferrara et al. [13] which is a particular case of the clustering and disjoint principal component analysis (CDPCA) model proposed by Vichi and Saporta [14], focusing only on the classification of MVs. Note that here, components/factors are formed by disjoint classes of MVs automatically identified instead that a priori fixed. In the last work, Ferrara et al. [15] propose a probabilistic approach of DPCA, named probabilistic disjoint principal component analysis (PDPCA).

This work aims to explore from a methodological point of view how key factors emerge during the process of dimensionality reduction for categorical data in the medical field, influencing the final representation of crucial information for clinical research. By closely examining the selection and combination of categorical variables in our specific medical context, we aim to identify determining factors that can significantly impact the understanding of relationships between different medical conditions, treatments, or responses to therapies. This approach not only provides valuable support for scholars and data analysts but also contributes to enhancing confidence in the insights extracted from the data, fostering a clear and transparent understanding of information. In summary, our research aims to improve interpretability in the dimensionality reduction of categorical data in the field of clinical research, offering an analytical and methodological framework that can be applied in medical contexts to achieve clearer and more meaningful results.

BACKGROUND

Let $X = [x_{ij}]$ ($i = 1, \ldots, n$; $j = 1, \ldots, J$) be a $n \times J$ data matrix containing the measurements of J variables on n objects. Without loss of generality, after a location and scale transformation, we assume that all the variables are centred. For better understanding the algebraic proofs of the manuscript, the reader can refer Trefethen, L. N. and Bau, D. [16].

Principal component analysis

Principal component analysis [2] is generally seen as the orthogonal linear transformation of a set of J correlated variables, in matrix X, into a set of H (where $1 \leq H \leq J$ and $n > J$) principal components (PCs). Given a $J \times H$ loadings matrix A (i.e., factorial weights matrix), the $n \times H$ scores matrix Y can be written as

$$Y = XA \tag{1}$$

such that $\max_A \{tr(\Sigma_Y)\}$ subject to the constraint $A'A = I_H$ that implies $\Sigma_Y = diag(\sigma^2_{y_1}, \ldots, \sigma^2_{y_H})$. With standardized data PCs are such that $\Sigma_Y = I_H$.

Another formalization of PCA is the reconstruction of data matrix. In particular, the PCA model for reconstructing data is

$$X = YA' + E \tag{2}$$

where E is the $n \times J$ error matrix. Substituting Equation (1) in Equation (2) we obtain

$$X = XAA' + E \tag{3}$$

Proof 1

It is proved that the LSE problem of model (3), i.e., $\min_A \|X - XAA'\|^2$ is equivalent to maximize $tr(\Sigma_Y)$, i.e.,

$$tr(\Sigma_Y) = tr\left(n^{-1}Y'Y\right) = n^{-1}\|Y^2\| = n^{-1}\|XA\|^2 \tag{4}$$

therefore, it corresponds to compute PCs. Moreover, let us recall that the following decomposition holds for any orthogonal matrix A:

$$\|X\|^2 = \|X - XAA'\|^2 + \|XAA'\|^2 \quad (5)$$

in fact, let start from $\|X\|^2$ then add and subtract XAA', we obtain

$$\begin{aligned}\|X\|^2 &= \|X - XAA' + XAA'\|^2 \\ &= tr\begin{pmatrix}((X - XAA') + XAA')' \\ ((X - XAA') + XAA')\end{pmatrix} \\ &= \|X - XAA'\|^2 + \|XAA'\|^2 \\ &+2tr\left(X - XAA'\right)'(XAA'))\end{aligned} \quad (6)$$

where the double product is null since $tr(X'XAA') - tr(AA'X'XAA') = 0$, because A is orthogonal. Therefore, minimising $\|X - XAA'\|^2$ corresponds to maximise $\|XAA'\|^2$ since $\|X\|^2$ is constant as the orthogonal matrix A varies. Now, it is easy to show that

$$\begin{aligned}\|XAA'\|^2 &= tr(AA'X'XAA') = tr(A'X'XAA'A) \\ &= tr(A'X'XA) = \|XA\|^2 = ntr(\Sigma_Y)\end{aligned} \quad (7)$$

and therefore if $\|XAA'\|^2$ is maximised also $ntr(\Sigma_Y)$ is maximised. In other words, minimize the error resulting in Equation 3 corresponds to maximize the variance of the principal components matrix Y. This is the objective function of the PCA algorithm.

Probabilistic principal component analysis

Probabilistic principal component analysis (PPCA) [17], is a probabilistic formulation of PCA. In particular, just recall the model formalization of PCA shown in Equation (2) and assume the following hypothesis:

i. $y_i \sim N_H(0, \Sigma_Y)$, where $\Sigma_Y = I_H$;
ii. $e_i \sim N_J(0, \Sigma_E)$, where $\Sigma_E = \sigma^2 I_J$;
iii. $Cov(e_i, y_i) = \Sigma_{EY} = 0$

Thus, like factorial analysis (FA), PCs are defined independent, standardized, Gaussian, and a mutual independence between Y and E is assumed. Statistically, these hypotheses imply the following covariance matrix structure of X:

$$\begin{aligned}\Sigma_X &= n^{-1}X'X = n^{-1}AY'YA' + E'E \\ &= A\Sigma_Y A' + \Sigma_E = AA' + \sigma^2 I_J\end{aligned} \quad (8)$$

and, consequently, the Gaussian distribution of data $x_i \sim N_J(0, AA' + \sigma^2 I_J)$. A similar form of the covariance matrix is specified in FA, which differs from PPCA only in the more general specification of $\Sigma_E = diag(\sigma_1^2, \ldots, \sigma_J^2)$, which is not necessarily based on a isotropic error covariance as in PPCA. This modification leads to significant differences in the behavior of the two methods [18].

The ML estimate of Σ_X (i.e., the estimation of A and σ^2 can be obtained by the standard EM algorithm [19]. We can define the log-likelihood function as follows:

$$l(A, \sigma^2 \mid X) = -\frac{n}{2}\begin{Bmatrix} Jln(2\pi) + \ln(AA' + \sigma^2 I_J) \\ +tr\left[(AA' + \sigma^2 I_J)^{-1} S\right] \end{Bmatrix} \quad (9)$$

where $S = n^{-1}\sum_{i=1}^{n}(x_i - \mu)(x_i - \mu)'$ is the observed sample covariance matrix with μ supposed known and estimated by the sample mean.

Proof 2

It is proved that the ML estimators of A and σ^2 for the isotropic error model correspond to the PCA solution. A formal, short and easy proof depends on the two following results:

a) $AA' + \sigma^2 I_J = AA' + \sigma^2 I_H \sigma^{2(J-H)} = (1 + \sigma^2)^H \sigma^{(J-H)}$

b) $(AA' + \sigma^2 I_J)^{-1} = \sigma^{-2} I_J - A\left[\sigma^2(\sigma^2 I_H + AA')\right]^{-1}$
$A' = \sigma^{-2} I_J - (\sigma^2(\sigma^2 + 1)AA')^{-1}$

thus substituting a) and b) in Equation (9), the log-likelihood function can be written as:

$$l(A, \sigma^2 \mid X) = -\frac{n}{2}\begin{Bmatrix}\left[\ln(1 + \sigma^2)^H \sigma^{(J-H)}\right] + tr\left[\frac{S}{\sigma^2}\right] \\ -(\sigma^2(\sigma^2 + 1))^{-1} tr(AA'S)\end{Bmatrix} + C \quad (10)$$

where C is a constant not depending on both A and σ^2. In this way, it can be directly observed that the ML estimate of A (i.e., $\hat{A}$) is equal to the LS estimate. In particular, to maximize (10), we need to maximize

$$tr(AA'S) = tr(A'SA) \quad (11)$$

and considering the spectral decomposition of S show below:

$$S = ULU' \quad (12)$$

where U is orthogonal matrix which columns are eigenvectors of S and L is diagonal matrix which elements are the corresponding eigenvalues.

The solution is given by the H eigenvectors $U_{(H)}$ corresponding to the largest H eigenvalues (reported in the diagonal matrix $L_{(H)}$) of the covariance matrix S, i.e., $\hat{A} = U_{(H)}$. However, since $\Sigma_Y = I_H$, to reconstruct the matrix X according model (2), PCs have to be scaled for their variance and the variance of the error term. Then,

$$\hat{A} = U_{(H)}\left(L_{(H)} - \sigma^2 I_H\right)^{1/2} \quad (13)$$

For estimating σ^2 we need to set the derivative of the log-likelihood function with respect to σ^2 equal to zero as shown in Equation (14)

$$\frac{\partial l}{\partial \sigma^2} = K\sigma^4\left(\sigma^2+1\right) + (J-H)\sigma^2\left(\sigma^2+1\right)^2 - tr(S)\left(\sigma^2+1\right)^2 + \left(2\sigma^2+1\right)tr(AA'S) = 0 \quad (14)$$

Thus, the solution is given by

$$\hat{\sigma}^2 = \frac{tr(S) - tr(A'SA)}{(J-H)} \quad (15)$$

Disjoint principal component analysis

The disjoint principal component analysis (DPCA) model can be formally written as the PCA model (2) where some constraints on the loading matrix A are imposed [14], following the idea of SEM, which allows researchers to model LVs through disjoint classes of correlated MVs [20]. In particular, the following constraints are defined:

iv. $\sum_{j=1}^{J} a_{jh}^2 = 1, \quad h = 1,\ldots, H$

v. $\sum_{j=1}^{J}\left(a_{jh}a_{jr}\right)^2 = 0, \quad h = 1,\ldots, H-1;\ r = h+1,\ldots, H;$

vi. $\sum_{h=1}^{H} a_{jh}^2 > 0, \quad j = 1,\ldots, J.$

The constraints iv-vi imply:

c) A is column-orthonormal, i.e. A'A = I;
d) each row of A has at most a single loading for a LV, i.e. a MV can contribute only to a single LV;
e) from (d) a partition of MVs is induced and each LV is represented as a linear combination of a single class of variables.

Moreover, the loading matrix A can be re-parameterized as the product of two matrices as follows:

$$A = BV \quad (16)$$

where $V = [v_{jh}]$ is a $J \times H$ binary and row stochastic matrix defining a partition of variables into H classes identifying H PCs, with $v_{jh} = 1$, if the j^{th} variable belong to h^{th} class, $v_{jh} = 0$, otherwise; B is a $J \times J$ diagonal matrix weighting MVs. In this way, constraints iv-vi become $\sum_{j=1}^{i} v_{jh}b_j^2 = 1$; $\sum_{h=1}^{H}\sum_{j=1}^{J} v_{jh}b_j^2 = H$, and the DPCA is can be specified as follows:

$$X = YV'B + E \quad (17)$$

where Y is a linear combination defined as Y = XBV. Thus, model (14) can be expressed as

$$X = XBVV'B + E \quad (18)$$

such that

1) $V = \left[v_{jk} : \forall v_{jk} \in \{0,1\}\right]$ (binary);
2) $V1_k = 1_J$ (row stochastic);
3) $B = diag(b_1, \ldots b_J)$ (diagonal);
4) $V'BBV = I_k$ (orthonormal);

Proof 3

Note that in FA framework the Bartlett's weighted LS score, which takes the following form

$$Y = X\Sigma_E^{-1}BV\left(V'B\Sigma_E^{-1}BV\right)^{-1} \quad (19)$$

it is reduced to Y=XBV when an isotropic error is specified. In fact

$$\begin{aligned} Y &= X(\sigma^2 I_J)^{-1}BV\left(V'B(\sigma^2 I_J)^{-1}BV\right)^{-1} = \\ &= X\sigma^2 BV\sigma^2\left(V'BBV\right)^{-1} = \\ &= XBV\left(V'BBV\right)^{-1} = \\ &= XBV \end{aligned} \quad (20)$$

The LS estimators of the models (17) and (18) are the optimal solutions of the following quadratic problem with respect to unknown parameters B and V:

$$\min_{B,V} \|X - XBVV'B\|^2 \quad (21)$$

such that constraints 1) - 4) are satisfied.

Proof 4

It is interesting to note the following decomposition:

$$\|X\|^2 = \|X - XBVV'B\|^2 + \|XBVV'B\|^2 \quad (22)$$

The proof of the decomposition is given by

$$\|X\|^2 = \|X - XBVV'B\|^2 + \|XBVV'B\|^2 + 2\,tr\left[\left(X - XBVV'B\right)'\left(XBVV'B\right)\right] \quad (23)$$

thus,

$$tr\left[\left(X - XBVV'B\right)'\left(XBVV'B\right)\right] = 0 \quad (24)$$

In fact,

$$tr\left[\left(X-XBVV'B\right)'\left(XBVV'B\right)\right]=$$
$$=tr\left(X'XBVV'B\right)-tr\left(BVV'BX'XBVV'B\right)=$$
$$=tr\left(V'BX'XBV\right)-\ tr\left(V'BX'XBVV'BBV\right)=0 \quad (25)$$

since in the second member of the previous equation $V'BBV = I_k$. From decomposition (22), by minimizing equation (21), the second term of the right-hand side of (22) is maximized.

Moreover, the second term of the (22) can be written as

$$\begin{aligned}\left\|XBVV'B\right\|^2 &= tr\left(BVV'BX'XBVV'B\right)\\ &= tr\left(V'BX'XBV(V'BBV)\right)=\\ &= tr\left(V'BX'XBV\right)=XBV^2\\ &= n\ tr\left(\Sigma_Y\right)=tr\left(Y'Y\right)=\\ &= tr\left(V'B\Sigma_XBV\right)=\sum_{k=1}^{K}v_k'\,B\Sigma_XBv_k\end{aligned} \quad (26)$$

therefore, the minimization problem shown in Equation (21) corresponds to maximize the total variance of the PCs (26). Then, DPCA model is a constrained formulation of the PCA model, where the loading matrix has the form A=BV, with B and V satisfying constraints 1) - 4), and the solution of Equations (21) and (26) can be find through a constrained Alternating Least Squares (ALS) algorithm.

Probabilistic disjoint principal component analysis

The probabilistic disjoint principal component analysis (PDPCA) is an isotropic error model that joins the features of PPCA and DPCA [15]. PDPCA model is defined by the DPCA model in shown in Equations (17) and (18), subject to the constraints defined in 1) - 4), in which we consider the PPCA assumptions i-iii. For these properties, the PDPCA model produces the following covariance matrix structure of X:

$$\Sigma_X=\frac{1}{n}X'X=\frac{1}{n}BV(Y'Y)V'B+\Sigma_E=BV\Sigma_YV'B+\sigma^2I_J \quad (27)$$

with the related Gaussian distribution $x_i \sim N_J(0, BVV'B+\sigma^2I_J$, since $\Sigma_Y = I_H$. Let $(x_1, \ldots x_n)$ be a sample of i.i.d. J dimensional observations, where $x_i \sim N_J\left(0, BVV'B+\sigma^2I_J\right)$, the corresponding log-likelihood function can be formulated as

$$l\left(V,B,\sigma^2\,|X\right)=-\frac{n}{2}\begin{Bmatrix}\ln\left|BV\Sigma_YV'B+\sigma^2I_J\right|\\ +tr\left(\left(BV\Sigma_YV'B+\sigma^2I_J\right)^{-1}S\right)\\ +Jln\left(2\pi\right)\end{Bmatrix} \quad (28)$$

By the maximizing the log-likelihood function shown in Equation (28) through an expectation-maximization (EM) algorithm [21], subject to the constraints defined in 1) - 4) and under PPCA assumptions i-iii, we obtain the following ML estimator:

the ML estimator of b_h is

$$\hat{b}_k={}_hU_{(1)}\left({}_hL_{(1)}-\sigma^2I_H\right)^{1/2} \quad (29)$$

where ${}_hU_{(1)}$ and ${}_hL_{(1)}$ respectively are the eigenvector and the corresponding largest eigenvalue of matrix Σ_{X_h}. The estimates of V is obtained by assigning each variable to the class that most increases the log-likelihood, i.e.,

$$\begin{aligned}\hat{v}_{jh}=1 \text{ if } & l\left(V,B_h,\sigma^2\right)\\ &= max\left\{l\left(V,B_m,\sigma^2\right):m=1,\ldots,H\right\}\end{aligned} \quad (30)$$

$\hat{v}_{jh} = 0$ otherwise.

Finally, the ML estimator of σ^2 is

$$\hat{\sigma}^2=\frac{1}{J-H}\sum_{h=1}^{H}\left(tr(\Sigma_{X_h})-\frac{1}{n}y_h'\,y_h\right) \quad (31)$$

that is the average of the loss corresponding to the H classes.

Disjoint multiple correspondence analysis

The disjoint multiple correspondence analysis (DMCA) model is a particular case of the disjoint principal component analysis (DPCA) introduced in the subsection 2.3. In fact, the DMCA model can be considered as the DPCA applied to a categorical data matrix appropriately centred as $X = J^{1/2}J\Psi L^{1/2}$. Where J is the number of qualitative variables; $\Psi=\left[\Psi_1,\ldots,\Psi_J\right]$ is the binary block matrix formed by J indicator binary matrices Ψ_J with elements Ψ_{i,i_m}=1 if the i^{th} observation has assumed category m for variable J, $\psi_{i,i_m}=0$ otherwise; $L=diag\left(\Psi'1_N\right)$; $J=I_N-N^{-1}1_N1_N'$ is the idempotent centring matrix with.

Therefore, to introduce the DMCA model we can consider PCA model shown in Equation (3) and the re-parameterization of the loading matrix given by A = BV:

$$J^{1/2}J\Psi L^{1/2}=J^{1/2}J\Psi L^{1/2}BVV'B+E \quad (32)$$

such that

1) $V=\left[v_{jk}:\forall v_{jk}\in\{0,1\}\right]$ (binary);
2) $V1_K=1_J$ (row stochastic);
3) $B=diag\left(b_1,\ldots,b_J\right)$ (diagonal);
4) $V'BBV=I_K$ (orthonormal).

The LS estimators of the models (32) are the optimal solutions of the following quadratic problem with respect to unknown parameters B and V:

$$\min_{B,V} \left\| J^{1/2}\Psi L^{1/2} - J^{1/2}\Psi L^{1/2}BVV'B \right\|^2 \qquad (33)$$

such that constraints 1) - 4) are satisfied. Then, fixed the number of factor *H*, the maximization of (33) can be solved by using ALS algorithm.

DISCUSSION

In this work we analysed the methodological properties of the dimensionality reduction approaches in the case of continuous and categorical data. The two approaches discussed in this work are Disjoint Principal Component Analysis (DPCA) and Disjoint Multiple Correspondence Analysis (DMCA), two statistical methods that could find interesting applications in the clinical field.

In clinical genetics, DPCA could be a valuable tool for delving into complex genetic data. It enables the identification of specific variance patterns within subsets of genes or genetic markers. This application is particularly beneficial for uncovering genetic associations related to specific clinical conditions or responses to various treatments. Similarly, in biomarker research, DPCA offers a means to separate the variance linked to different categories of biomarkers. This capability aids in identifying patterns that hold clinical significance, providing valuable insights for diagnostic and prognostic purposes. Medical imaging, such as data obtained from magnetic resonance or computed tomography scans, stands to benefit from DPCA. This method can assist in pinpointing specific patterns within different regions of medical images, contributing significantly to the early diagnosis of various pathologies.

Turning our attention to DMCA, its application in epidemiological analysis is noteworthy. When dealing with categorical clinical data, such as classifying diseases into distinct categories, DMCA proves useful. It helps in identifying specific risk factors associated with particular health conditions, aiding in the development of targeted preventive measures. Moreover, in lifestyle habits studies, DMCA serves as a valuable analytical tool. By examining the relationships between various categorical variables, such as tobacco consumption, physical activity, and diet, DMCA contributes to a more nuanced understanding of their impacts on health, providing crucial information for personalized interventions. In the assessment of patients' quality of life, DMCA plays a significant role. Analysing data related to categorical variables like symptoms, emotional impact, and overall satisfaction, DMCA provides a comprehensive view of health status. This holistic understanding can guide healthcare professionals in tailoring treatment plans and interventions to improve patients' overall well-being.

In conclusion, both DPCA and DMCA offer valuable insights for clinical research and analysis. Their applications in clinical genetics, biomarker research, medical imaging, epidemiological analysis, lifestyle habits studies, and quality of life assessment showcase their versatility in addressing diverse aspects of healthcare and medical research. The choice between these approaches depends on the specific characteristics of the data and the research goals in the clinical context.

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Correlation between Physical Activity Time Reported by the IPAQ and Accelerometer in Syrian Adults

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SUMMARY

Background: The accelerometer and self-report questionnaires have been recommended as efficient methods to measure physical activity (PA). The aim of this work is to investigate issues associated with PA assessment using the ActiGraph WGT3X-BT (AG) accelerometer and the Syrian version of the International Physical Activity Questionnaire-short form (IPAQ-SF-SY) in adults living in Damascus city.
Methods: A sample of 52 (age 18- 60 years) Syrian men (17) and women (35) in a cross-sectional study wore the AG accelerometer for seven days and completed the IPAQ-SF-SY on the seventh day. Total PA, time spends in standing and sitting assessed by IPAQ-SF-SY and AG accelerometer were compared.
Results: The IPAQ-SF-SY overestimates PA time among Syrian adults. IPAQ-SF-SY reported more time of total PA [763(660) vs 607(149) min, p=0.003], vigorous PA [29(1) vs 1(0.2) min, p=0.524], moderate PA [94(76) vs 42(22) min, p=0.032], MVPA [122(106) vs 43(22) min, p=0.019], and significantly less sedentary time than AG accelerometer [447(180) vs 643(93) min, p=0.728], mean (SD) respectively. Some differences were noticed in the correlations by gender, age, BMI, education statues, and smoking for PA and sedentary behavior (SB). For all correlations, there were no significant differences between sub groups.
Conclusions: Data suggest that it is important to improve the specificity and sensitivity of the IPAQ-SF-SY with Arabic-speaking subjects and further study is needed to approve the utilization of PA self-report in Arabic.

Keywords: Questionnaire; Self-report; Acigraph; Sitting time; Measurements; MVPA.

INTRODUCTION

Regular physical activity (PA) is well documented as a critical component of a healthy lifestyle and disease prevention [1]. However, public health care organizations, and others involved in an intervention project should have valid and reliable methods for measuring PA [2]. Accurate PA assessment is essential to determine baseline PA degrees and to set up goals for increasing PA [3]. Measurement of PA behavior can be performed in many ways, including the implementation of direct, (subjective) based on accelerometer usage, and indirect (objective) based on self-report questionnaires [4]. The validity of the accelerometer as a direct and quantitative measurement of PA has been confirmed [4,5]. Questionnaires as an indirect tool are the preferred method for determining large-scale monitoring and observational studies [6]. Limitations of indirect assessment of PA behavior have been well documented including desirability bias [7].

Scientific groups have worked toward standardizing self-report assessments of PA and thus the International Physical Activity Questionnaire (IPAQ) [3,8] has been widely implemented. IPAQ can provide both researchers and physicians with estimate of PA behavior for adults aged [9]. The validation and reliabilities of the IPAQ as a population indicator tool was examined and reported in an international study of several countries [10]. In general, epidemiological studies usually use questionnaires to measure PA

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levels, because it is easy, inexpensive and a useful tool in determining high and low levels of PA [11]. The validity and reliability of IPAQ has been determined in several countries; however, most of the studies that have validated the IPAQ by comparing its results with those of accelerometer tools were performed in developed countries [10, 12]. Therefore, it needs to be examined in other regions and with various target groups [13].

In light of the beneficial effects of PA on health, more insight into the PA behavior of populations is needed. The IPAQ might be a successful method towards providing this information. However, no studies has used the direct based on using accelerometer, or indirect based on self-report questionnaires to detect intervention related changes in Syria. Also, there has been no research conducted to quantify the PA of youth or adult Syrian population. Therefore, this study aimed to investigate the time spent in standing and sitting postures to measure the PA behavior to the sensitivity and specificity of the IPAQ-SF-SY compared with AG accelerometer for detecting intervention related to PA in Syrian adults.

MATERIAL AND METHODS

Participants and study design

A random population sample of 61 adults (41 females; 20 males) aged between 18 and 60 years was selected from various workplaces within the Syrian Atomic Energy Commission (SAEC) in Damascus, Syria. The study protocol was approved by the Atomic Energy Human Ethics Committee. The research was conducted in compliance with the guidelines outlined in the Helsinki Declaration of the World Medical Association. Prior to participation, each participant provided informed consent following a comprehensive explanation of the study protocol.

Participant characteristics

Participants who met the study's criteria were those willing to wear an AG accelerometer for seven consecutive days and complete the IPAQ-SF-SY in Arabic. To be included in the analysis, participants needed a minimum of 600 minutes of valid daily monitor wear on at least four days. Nine individuals (6 females, 3 males) were excluded from the analysis for not meeting the required accelerometer wear time. The final sample comprised 52 participants (17 men, 35 women) who successfully completed the physical activity log and recorded steps for seven days. The participants had a mean (SD) age of 40.6 (9.1) years and a mean Body Mass Index (BMI) of 28.5 (4.6) kg/m2. The majority were overweight or obese (39 subjects, 75%). Most participants were married and cohabiting with their partners (42 subjects, 80.8%), while a few were single and living alone (10 subjects, 19.2%). The majority had completed secondary school or higher education (47 subjects, 90.4%), with a small number having lower levels of education (5 subjects, 9.6%) [4].

Measurements

All participants with comprehensive data on objectively measured physical activity (PA), height, and weight were incorporated in the present analysis. Height measurements were taken to the nearest 0.5 cm using a wall-mounted stadiometer (Seca, Model: 225 1721009; Germany). Body weight was recorded to the nearest 0.1 kg utilizing a portable battery-operated digital scale with a maximum capacity of 130 kg (Seca, Model: 7671321004; Germany), regularly calibrated. Participants were weighed barefoot and lightly dressed. The collected weight and height measurements were utilized to calculate Body Mass Index (BMI, kg/m2)

Accelerometer processing

Participants were eligible for the study if they agreed to wear an AG accelerometer for at least seven consecutive days. The study employed a triaxial accelerometer (ActiGraph GT3X +, ActiGraph, Pensacola, FL. 32502 USA) to assess physical activity (PA). The device was configured to record data on PA, including activity counts, energy expenditure (kcal), steps, and activity intensity (as metabolic equivalents (METs))[14]. Participants were advised to wear the accelerometer on their left hip for seven consecutive days during waking hours, excluding contact, washing, bathing, swimming, or sleeping activities[15]. Subjects were asked to remove the device before aquatic activities like showering, swimming, or bathing. The AG accelerometer data was processed using ActiLife 6 software and exported to Microsoft Excel format. Within Microsoft Excel, minutes of PA, including light, moderate, vigorous, and sitting time, were calculated as mean minutes per day. ActiLife 6 software was used to initialize the accelerometer and download results, and raw data was converted with Freedson cut points (i.e., Sedentary <100 counts/minute, Light: 100–1951, Moderate: 1952–5724, Vigorous: >5724 counts/minute)[16]. Average daily time in moderate-to-vigorous physical activity (MVPA) (min/day) and sitting time (min/day) were calculated[17]. The daily average was multiplied by seven to create a weekly total [18].

The International Physical Activity Questionnaire (IPAQ)

Participants meeting the study's criteria were those willing to complete surveys in Arabic. The

Syrian version of the International Physical Activity Questionnaire Short Form (IPAQ-SF-SY) was selected to evaluate physical activity (PA) behaviors in the study population. This questionnaire is structured to facilitate comparisons with national and international PA guidelines. A 7-item IPAQ-SF-SY was employed to record self-reported PA over the preceding seven days, a widely used tool for assessing PA levels[8]. After wearing AG accelerometers for a week, participants completed the IPAQ-SF-SY survey, providing information on demographic details (age, gender, relationship status, anthropometric data, education level, and smoking habits). Following the IPAQ-SF-SY scoring guidelines, data from the questionnaire were aggregated for each item over the past week (light, moderate, vigorous intensity, moderate-to-vigorous intensity PA, and sitting time)[8]. Total activity minutes were calculated by summing the reported weekly PA minutes from the IPAQ-SF-SY.

The Arabic-translated IPAQ-SF-SY had been previously utilized by other Arab populations as an interview short form in Arabic [19,20]. It assessed walking, moderate, and vigorous PA levels across various domains like work, transportation, household chores, gardening activities, and leisure time on both weekdays and weekends. Trained research assistants conducted all measurements in person following standardized protocols.

Statistical analysis

Participants included in the analysis had data from both the IPAQ-SF-SY and AG accelerometer. Statistical analyses were conducted using the Statistical Package for Social Science (SPSS) software (Version 24, 2016, SPSS Inc., Chicago, USA). Continuous variables were presented as mean ± standard deviation (SD), while categorical variables (such as total PA, moderate PA, vigorous PA, moderate-to-vigorous intensity PA (MVPA), and sitting time) across different demographics like sex, age, BMI, education, and smoking categories were expressed as frequencies and percentages. Statistical significance was set at $p \leq 0.05$. To address skewed distributions of many accelerometer factors, log transformation was applied before analysis. Given the non-normal distribution of IPAQ and accelerometer measurements, descriptive statistics including mean, median, and interquartile ranges (IQR) were utilized [18].

RESULTS

Objective and self-reported PA and sitting time

The mean minutes per day for the PA variables (total PA, vigorous PA, moderate PA and moderate-to-vigorous intensity PA (MVPA) and sitting time) assessed by IPAQ-SF-SY and AG accelerometer are presented in Table 1. The variations were significant with PA being over-estimated and sitting time under-estimated in the IPAQ-SF-SY. Compared to AG accelerometer derived total PA (mean of 607 min per day; IQR 488–681), and MVPA (mean of 43 min per day; IQR 27–52), participants under-estimated their self-reported IPAQ derived levels of total PA (mean of 763 min per day; IQR 303–1069), and MVPA (mean of 122 min per day; IQR 36–169) (Table 1).

When analyses were carried out by gender, both men and women under self-estimated their level of total PA and MVPA. Males reported a mean of 996 minutes (IQR 405–1448) and 148 minutes (IQR 13–240) of total PA and MVPA per day, respectively. Whereas, the AG accelerometer recorded a mean of 670 min (IQR 521–812) of total PA, and 60 min (IQR 46–72) of MVPA. Females reported a mean of 650 minutes (IQR 297–910) of total PA and 110 (IQR 43–137) of MVPA per day using the IPAQ-SF-SY, whereas, the AG accelerometer recorded a mean of 576 min (IQR 467–649) of total PA, and 35 minutes per day (IQR 22–47) of MVPA per day (Table 1).

When analyses were carried out by age groups, all groups (18 – 29 years), (30-45 years), and (>45 years) under self-estimated their level of total PA and MVPA. (18-29 years) reported a mean of 306 minutes per day (IQR 206–473) of total PA, and 49 minutes per day (IQR 26–69) of MVPA using the IPAQ-SF-SY, whereas the AG accelerometer recorded a mean of 37 min per day (IQR 32–47). The age of (30-45 years) reported a mean of 861 minutes per day (IQR 346–1177) of total PA, and 131 minutes per day (IQR 28–176) of MVPA, whereas the accelerometer recorded a mean of 598 min per day (IQR 477–681) of total PA, and 39 min per day (IQR 24–52) of MVPA. While, the age of (>45 years) reported a mean of 790 min per day (IQR 387–1268) of total PA, and 138 minutes per day (IQR 69–210) of MVPA, whereas the accelerometer recorded a mean of 633 min per day (IQR 481–732) of total PA, and 51 min per day (IQR 29–61) of MVPA.

Table 1 compares total time spent on PA reported in the IPAQ-SF-SY to AG accelerometer readings, by subgroup according to BMI (more or less than 25). On every variable, the self-report questionnaire produced much higher measurements of time spent in vigorous, moderate and total PAs than the objective device. Normal weight participants (BMI>25) reported a mean of 539 min per day (IQR 289–780) of total PA, and 87 minutes per day (IQR 26–120) of MVPA, whereas the accelerometer recorded a mean of 598 min per day (IQR 547–654) of total PA, and 43 min per day (IQR 33–54) of MVPA. While overweight or obese participants (BMI>25) reported a mean of 838 min per day (IQR 366–1211) of total PA, and 134 (IQR 34–180) of MVPA using the IPAQ, whereas the accelerometer recorded a mean of 610 min per day (IQR 467–726) of total PA, and 43 minutes per day (IQR 23–52) of MVPA (Table 1).

The average differences in reported physical activity (PA) times between IPAQ-SF-SY and AG accelerometer readings, categorized by education levels, are detailed in Table 1. Participants with lower education levels (<secondary school) reported higher total PA (1195 minutes per day) (IQR 527–1922) and moderate to vigorous physical activity (MVPA) (180 minutes per day) (IQR 77–296) on IPAQ-SF-SY compared to AG accelerometer readings of 703 minutes per day for total PA (IQR 497–891) and 55 minutes per day for MVPA (IQR 36–75). Conversely, the discrepancies between IPAQ-SF-SY and AG accelerometer data were less significant among participants with higher education levels. For instance, those with secondary education reported 366 minutes per day of total PA (IQR 93–523) and 49 minutes per day of MVPA (IQR 9–88), while participants with >secondary education reported 801 minutes per day of total PA (IQR 317–1245) and 132 minutes for MVPA (IQR 56–195), compared to AG accelerometer readings of 612 minutes per day for total PA (IQR 508–670) and 42 minutes per day for MVPA (IQR 23–52).

When stratified by smoking status, both smoking and non-smoking participants underestimated their total PA and MVPA levels. Smoking participants self-reported a mean of 704 minutes per day of total PA (IQR 122–1181) and 104 minutes per day of MVPA (IQR 13–171), while the accelerometer recorded means of 611 minutes per day for total PA (IQR 546–630) and 41 minutes per day for MVPA (IQR 27–51). Non-smoking participants reported a mean of 798 minutes per day of total PA (IQR 311–1052) and 133 minutes of MVPA (IQR 60–171) using IPAQ, whereas the accelerometer captured means of 604 minutes per day for total PA (IQR 474–719) and 44 minutes per day for MVPA (IQR 28–55) as shown in Table 1.

The results indicated an underestimation of sitting time by the tested sample (Table 1). The average sedentary time reported using IPAQ-SF-SY was 447 minutes per day (IQR 315–600), which was lower than the objective AG accelerometry findings showing an average sedentary time of 643 minutes per day (IQR 595–693) (Table 1).

In Figure 1, the distribution of weekly moderate-equivalent minutes of physical activity (PA) from self-reported data (IPAQ-SF-SY) and AG accelerometer measurements is depicted. The figure illustrates a wide variation in PA levels across the sample, with a significant number of participants exhibiting low activity levels during the week and a notable percentage engaging in relatively high levels of activity. The self-reported PA data from IPAQ-SF-SY displayed a broader range of values compared to the AG accelerometer data, with notably higher values. For instance, based on self-reports, 34.6% of participants reported 960 or more minutes of PA, whereas less than 1% reached this level based on AG accelerometer data. The skewed distribution indicates that relying on mean values for correlational analysis between the two measures can be misleading.

Figure 2 illustrates the impact of outlier values on the estimated mean PA minutes from self-reports (IPAQ-SF-SY). The mean weekly PA minutes reported through self-assessment were considerably higher than those determined by AG accelerometers. However, median values were more aligned, suggesting that outlier values influenced the agreement between the two measurement methods. Even when considering medians, self-reported PA minutes exceeded those captured by AG accelerometers, indicating an overestimation in self-reported PA minutes.

DISCUSSION

The present study aimed to measure factors related to time spend in different PA intensities using IPAQ-SF-SY and AG accelerometers in a population-based sample. We used a common metric (minutes per week) to compare the outcome variables. Comparing the AG accelerometer and IPAQ-SF-SY our results found, in general, higher values of PA with IPAQ-SF-SY than with AG accelerometer, but lower time in sitting time activities on the IPAQ-SF-SY. This figure is also confirmed by the study of [21], and shows a tendency to overestimate PA carried out. However, Barnaba et al [22] found lower results in general with IPAQ-SF; these participants spent on average of 257.1 min (females 201.9, males 325.7) with vigorous and 348.9 with moderate activity weekly. If we convert our result, Syrian adults spent 203 min with vigorous and 658 with moderate activity weekly when determined by IPAQ-SF-SY. Time spent in moderate-to-vigorous PA was 2.8 times more according to the IPAQ-SF-SY than to AG accelerometers. Accumulated results over 7 days (min per week) as measured by AG accelerometer and IPAQ-SF-SY were total MVPA 330 vs 1086, vigorous PA 41 vs 645 and moderate PA 289 vs 441 respectively. Comparing the accelerometer and IPAQ data, several studies reported higher vigorous and moderate activities in questionnaire compared to objective results [23,24]. Comparably, several other studies found the self-report vigorous category to report the largest discrepancy in mean min per week of PA when compared with accelerometer [1,18,25]. However, population-based estimations of PA are based on self-reported dated, which indicated overestimation [7,25,26]. At the same time the AG may have underestimated PA level, and it is possible that the accelerometer, unlike IPAQ was unable to measure or underestimated the specific PA such as heavy lifting, bicycling, household work… that could have been performed [18], also, the accelerometer is not waterproof and therefore cannot be worn during water activities such as swimming [27]. Accelerometers are known for being not enough when determining steps at the low speeds that some of the participants may walk at [28,29].

These results indicate that the IPAQ-SF-SY

overestimation of PA practice should be taken into account in prevalence studies and hence consistent efforts are necessary to correct this limitation. Results from this study extend previous findings by using both objective and self-reported measures, and by explicitly investigating PA intensity [22,25,30,31].

Analyzing the data to SB activities differences vs. time are observed and these outcomes are similar to those reported by Hagstromer et al. [32], who reported also an overestimation of sedentary activity and an increase of the differences in relation to time.

Larger IQRs were found for PA and sitting time when measured by the IPAQ-SF-SY in comparison to the accelerometer. This may indicate that the IPAQ-SF-SY may not be the applicable method to use on an subject basis when aiming to measure PA or sitting time in adults. Nevertheless, it is moderate acceptable when used in large population studies. it may possible to more strengthen the validity scores by providing more detail of the kinds of activities and behaviors. This is in line with recommendations from Cleland et al. [7] who suggested the addition of relevant examples to provide clarity.

We observed some differences in the correlations by gender, Age, BMI, education statues, and smoking (for total PA, vigorous PA, moderate PA, MVPA and sitting time). BMI was related to less time spent in low-intensity activity. Higher education was related to less time spent in MVPA intensity activity. For all correlations, there were no significant differences between sub groups.

Unexpectedly, our investigation found no significant difference in standing and sitting time between normal weight (BMI<25) and overweight (BMI>25) groups. There are some possible reasons why these overweight individuals spent more time in standing than did the normal weight subjects. It is possible that the measured time period in this assessment may have been too short. It should be indicated that, for standing, because all of the participant in this work were initially sedentary, the expected variations, between the overweight and normal weight subjects are not showed in these data [33].

We found differences between genders according to the AG accelerometer and IPAQ-SF-SY. According to both methods, men spent more time in vigorous, moderate, and MVPA intensity of activities. Sitting time was slightly higher in men than in women for both IPAQ-SF-SY and AG accelerometer measured variables. The overestimation factor of total PA in the IPAQ-SF-SY compared to AG accelerometer data was 1.5 in men and 1.1 in women. Males are generally more active than females, and PA is lower in successive age groups. Acs et al. [22] presented their findings with respect to age and found similar activity patterns in the group of adults. The higher activity levels in boys in our experiment is in agreement with previous study indicated that boys were more physical active than girls, as they accumulated MVPA [26].

AG Accelerometer and IPAQ-SF-SY data revealed that those over 45 years were most active than younger individuals for all PA variables. Thus, overestimation in the IPAQ-SF-SY compared to AG accelerometer data was highest in the oldest age group (more than 45 years) (1.2) and lower in the younger age group (30-45 years) (1.4). While, the underestimation in the IPAQ-SF-SY compared to AG accelerometer data was observed in the youngest age group (18-29 years). Both IPAQ-SF-SY and AG accelerometer data showed that the oldest age group was more active in vigorous, moderate and total PA compared to younger age groups. AG accelerometer sitting time was almost 1.4 times as high as IPAQ-SF-SY sitting time. Both the IPAQ-SF-SY and old age substantially over-reported the total mean time spent in MVPA when compared with the AG accelerometer and young age. We found that higher age was associated with more time spent in MVPA. These results are in agreement with previous results from cross-sectional and longitudinal research's, including 24h-accelerometry-based data [34,35].

Compared to never smoking, current smoking spent less time in MVPA. These findings are acceptable, given the negative impact of smoking on cardio vascular diseases and oxygen metabolism [34]. A previous study indicated that smoking versus non-smoking is synchronized with a lower likelihood of being persistently moderately or vigorously active [35]. This assumption is supported by our observation that former compared to never smokers tended to spent less time in PA; however, this association was not statistically significant

Strength

This assessment's robustness lies in the utilization of a validated accelerometer with established cut points and the administration of a physical activity (PA) self-report questionnaire in Arabic, the participants' native language. Furthermore, a quality control protocol was implemented, involving random validity checks conducted by the authors to assess the precision of individual interviews.

Limitations

The study utilized an equation to predict physical activity (PA), a method that may introduce errors requiring thorough scrutiny. It is imperative to conduct further evaluations of the questionnaire across diverse age groups, occupations, and various populations in Arab-speaking regions. The study's limitations stem from a relatively small sample size confined to one location in Damascus, limiting the generalizability of the findings to other Syrian populations with differing characteristics. Moreover, the AG accelerometer has notable drawbacks, including its lack of waterproofing, rendering it ineffective during water-related activities like swimming or showering. Additionally, accelerometers fail to account for the energy expenditure of strenuous

upper body movements or water-based exercises. [36].

CONCLUSION

The current research reveals a significant disparity in physical activity (PA) and sedentary time when assessed using IPAQ-SF-SY versus AG accelerometers, irrespective of the activity pattern. There is notable over-reporting and overestimation of PA duration (minutes per week) with IPAQ-SF-SY. In the Syrian population, PA levels determined by IPAQ-SF-SY compared to AG accelerometers vary based on gender, age, employment status, education level, body mass index (BMI), and smoking habits. Inaccurate PA levels pose a critical public health challenge, necessitating further studies to enhance PA adherence to recommended standards. Future research focusing on identifying individuals with low PA levels and tailoring interventions for these specific groups could greatly benefit health officials.

CONFLICT OF INTEREST

The authors declare no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Table 1. Descriptive physical activity data from IPAQ-SF-SY and Actigraph, by sex, age, BMI, education and smoking; median and interquartile Ranges (IQR).

	Total PA*		Vigorous PA		Moderate PA*		MVPA*		Sitting*	
Variables	**IPAQ MET min.d-1**	**Actigraph† counts.min-1**	**IPAQ min.d-1**	**Actigraph† min.d-1**	**IPAQ min.d-1**	**Actigraph† min.d-1**	**IPAQ min.d-1**	**Actigraph† min.d-1**	**IPAQ min.d-1**	**Actigraph† min.d-1**
All‡	763 (660)	607 (149)	29 (57)	1 (0.2)	94 (76)	42 (22)	122 (106)	43 (22)	447 (180)	643 (93
Median (IQR)	552 (303; 1069)	552 (488; 681)	2 (0; 32)	1 (0.2; 1)	77 (26; 127)	42 (27; 52)	103 (36; 169)	42 (27; 52)	450 (315; 600)	631 (595; 693)
Sex										
Men‡	996 (793)	670 (181)	49 (74)	2 (2)	98 (99)	58 (25)	148 (134)	60 (25)	383 (217)	647 (71)
Median (IQR)	889 (405; 1448)	649 (521; 812)	13 (0; 73)	1 (0; 2)	60 (5; 206)	52 (44; 68)	137 (13; 240)	55 (46; 72)	360 (240; 510)	655 (593; 706)
women‡	650 (564)	576 (122)	19 (44)	1 (1)	91 (64)	34 (15)*	110 (90)	35 (15)	478 (152)	641 (102)
Median (IQR)	480 (297; 910)	582 (467; 649)	0 (0; 17)	0 (0' 1)	77 (34; 120)	34 (22; 44)	94 (43; 137)	34 (22; 47)	480 (360; 600)	624 (596; 692)
Age										
18-29‡	306 (132)	575 (161)	8 (9)	1 (2)	41 (31)	36 (11)	49 (32)	37 (12)	446 (124)	684 (199)
Median (IQR)	297 (206; 373)	604 (481; 649)	3 (0; 17)	1 (0; 3)	26 (17; 69)	37 (31; 46)	43 (26; 69)	38 (32; 47)	480 (300; 540)	631 (577; 803)
30-45‡	861 (736)	598 (130)	34 (64)	1 (1)	98 (78)	39 (17)	131 (122)	39 (17)	449 (188)	627 (61)
Median (IQR)	684 (346; 1177)	603 (477; 681)	6 (0; 34)	0 (0; 1)	82 (26; 158)	36 (24; 52)	110 (28; 176)	37 (24; 52)	480 (300; 600)	622 (592; 682)
>45‡	790 (600)	633 (177)	29 (56)	2 (2)	109 (81)	49 (30)	138 (88)	51 (30)	445 (193)	651 (71)
Median (IQR)	499 (387; 1268)	639 (481; 732)	0 (0; 42)	1 (0; 3)	103 (39; 150)	46 (28; 57)	120 (69; 210)	48 (29; 61)	360 (360; 600)	655 (595; 722)
BMI (kgm-2)										
< 25‡	539 (404)	598 (112)	19 (50)	1 (1)	68 (69)	43 (14)	87 (70)	43 (14)	439 (126)	673 (133)
Median (IQR)	373 (289; 780)	616 (547; 654)	0 (0; 12)	0 (0; 1)	60 (4; 120)	43 (33; 53)	89 (26; 120)	44 (33; 54)	480 (300; 540)	631 (586; 695)
> 25‡	838 (715)	610 (161)	32 (59)	1 (2)	102 (78)	41 (24)	134 (114)	43 (24)	450 (196)	633 (74)

Median (IQR)	605 (366; 1211)	582 (467; 726)	4 (0; 34)	1 (0; 1)	86 (34; 171)	38 (23; 52)	111 (34; 180)	39 (23; 52)	420 (360; 600)	631 (595; 687)
Education										
< Secondary‡	1195 (912)	703 (203)	58 (104)	2 (2)	122 (59)	53 (23)	180 (144)	55 (23)	336 (178)	622 (78)
Median (IQR)	1074 (527; 1922)	737 (497; 891)	0 (0; 145)	3 (1; 4)	120 (69; 176	53 (33; 73)	154 (77; 296)	55 (36; 75)	360 (180; 480)	651 (543; 687)
Secondary‡	366 (258)	529 (116)	3 (6)	1 (1)	46 (41)	37 (11)	49 (41)	38 (11)	460 (167)	646 (61)
Median (IQR)	408 (93; 523)	566 (419; 634)	0 (0; 7)	1 (0; 1)	60 (3; 82)	38 (28; 44)	60 (9; 88)	39 (28; 45)	480 (330; 600)	638 (597; 700)
> Secondary‡	801 (657)	612 (143)	31 (55)	1 (2)	101 (81)	41 (23)	132 (106)	42 (24)	459 (182)	645 (101)
Median (IQR)	579 (317; 1245)	609 (508; 670)	6 (0; 34)	0 (0; 1)	82 (26; 140)	42 (23; 52)	120 (56; 195)	43 (23; 52)	480 (345; 600)	627 (595; 694)
Smoking										
Yes‡	704 (6040	611 (165)	22 (41)	1 (2)	83 (74)	40 (23)	104 (92)	41 (24)	508 (148)	622 (61)
Median (IQR)	488 (122; 1181)	604 (546; 630)	3 (0; 17)	1 (0; 2)	77 (9; 129)	34 (26; 51)	94 (13; 171)	34 (27; 51)	540 (360; 600)	606 (577; 667)
No‡		604 (142)	33 (64)	1 (1)	100 (79)	43 (21)	133 (114)	44 (21)	412 (189)	655 (106)
Median (IQR)	565 (311; 1052)	616 (474; 719)	0 (0; 34)	0 (0; 2)	86 (38; 125)	43 (28; 53)	111 (60; 171)	44 (28; 55)	420 (270; 570)	651 (596; 695)

**- Significant difference between IPAQ-SF-SY-Actigraph tested for total PA, vigorous, moderate, Moderate-to-Vigorous PA, and sitting, respectively, using T- test, $p \leq 0.05$; †_Cut-off values for sitting, moderate and vigorous were <100, 1952–5724, and >5724 counts, respectively; ‡_ Mean (±Standard deviation); _ IQR_ Interquartile range; BMI_ Body Mass Index; PA_ Physical Activity.*

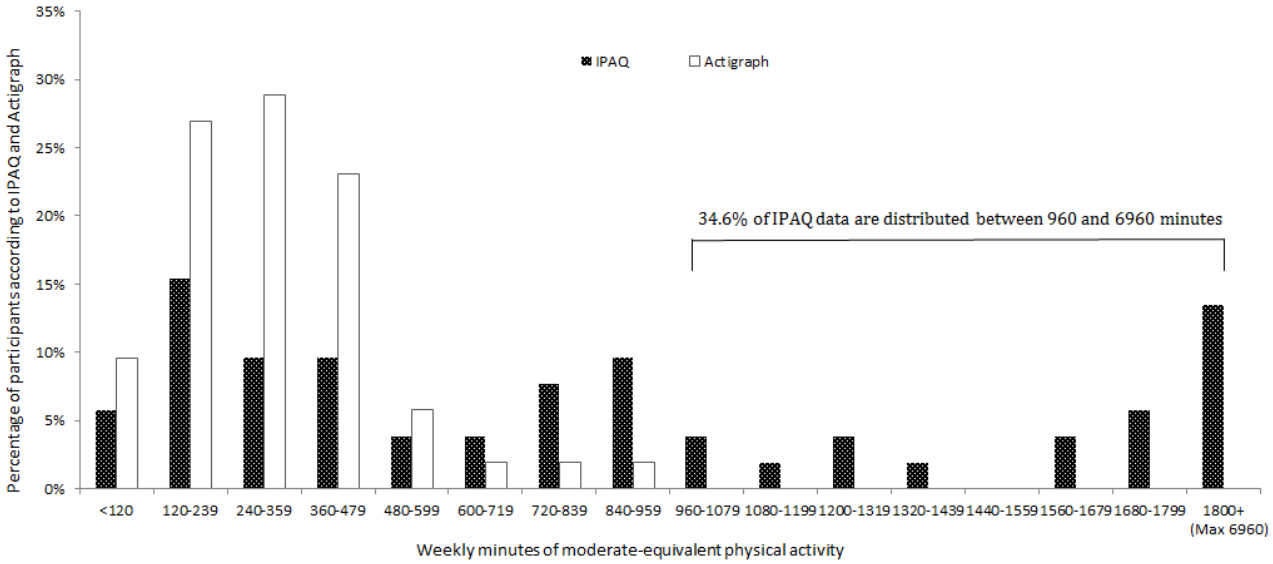

Figure 1. Distribution of weekly moderate-equivalent minutes as measured by IPAQ and Actigraph

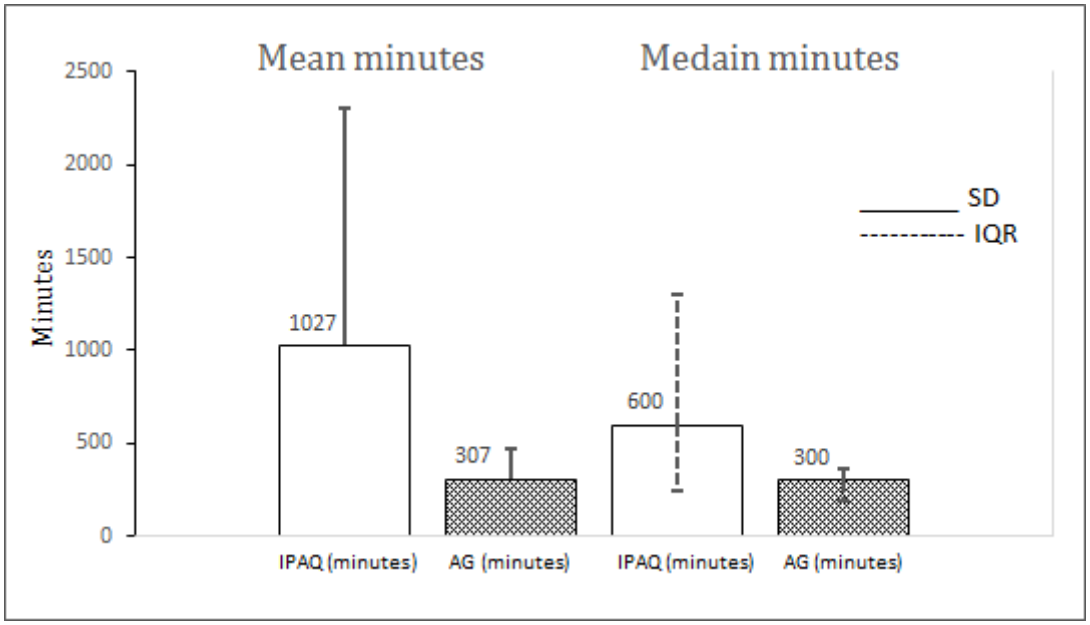

Figure 2. Physical Activity by Actigraph and IPAQ (mean and median weekly minutes)

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Crack Cocaine Use and Mortality Risk: A Follow-Up Study on 178 Individuals in Drug Treatment for Crack Cocaine Problems

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SUMMARY

Background: In Europe, crack cocaine use is mainly observed in vulnerable and marginalized groups, many of whom have other substance use problems, including heroin-related problems.
Objectives: To examine mortality risk and causes of death in a cohort of crack users.
Methods: We performed a follow-up study to assess mortality in a cohort of patients who entered drug treatment for crack cocaine problems in the metropolitan area of Bologna (Northern Italy) from 1992 to 2020.
Results: Most of participants were polydrug users, 75% reported concomitant heroin, 55% cocaine and 24% alcohol use; 43% have injected a substance. Mortality was six times higher than in the general population, and overdose and infectious diseases were among the leading causes of death.
Conclusions: Longitudinal epidemiological studies are needed to systematically assess the health outcomes of crack cocaine use.

Keywords: Crack; Cocaine; Mortality; Cohort study; Public Treatment Centre for Addiction.

INTRODUCTION

Cocaine is available in Europe mainly in two forms: cocaine hydrochloride, a salt often referred to as 'cocaine powder' that can be snorted, swallowed or injected; and 'crack cocaine', which has been processed into a freebase form using cocaine hydrochloride as the starting material and can be smoked, swallowed or injected.

While cocaine powder has been used for decades, crack cocaine (crack) emerged as a sub-type in the 1980s [1]. Crack use is often characterized by high-frequency consumption, leading to mental and physical health problems and aggressive behaviour, making the delivery of treatment and harm reduction responses challenging [2]. As with other illegal drugs, crack use crosses social strata but is particularly associated with poverty, homelessness, incarceration and limited access to or uptake of health and social services [3].

The high availability of cocaine is likely to have contributed to increased levels of crack use in western and southern Europe. In Europe, crack use is mainly observed in vulnerable and marginalized groups [4], many of whom have other substance use problems, including heroin-related problems [5, 6]. Crack injection, often in combination with heroin, is common in England and Wales, with 52% of people who inject drugs reporting recent crack injection in 2020–21 [7].

Long-term trends point to an estimated 7000 clients entering drug treatment for crack problems in Europe in 2020, which is triple the number reported in 2016 and suggests its growing use [2]. The proportion of crack among cocaine as primary substance treatment entrants varied considerably: Italy 3,4%, Switzerland 8,1%, Ireland 11,8%, Spain 12,9%, France 30,8%, Belgium 32,3%, England 34%, The Netherlands 37,1% [8].

In Italy, while the number of crack users received in treatment centres increased by 378% from 2014 to 2022 (905 in 2014; 3417 in 2022), the total number of clients entering treatment for drug problems

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decreased by 6% [9]. The estimated number of crack users aged 15–64 years is believed to have tripled in France from 2010 to 2017, with prevalence below 1‰ [10], while in England in 2016/2017 it was around 5‰ [11]. A 2021 analysis of municipal wastewater in 13 European cities found crack residues in all cities on all sampling days [12], while 13% of patients presenting to 22 emergency departments in 14 European countries with acute cocaine toxicity were crack consumers [13].

It should however be noted that the label "crack user" is profoundly stigmatizing and people entering drug treatment with less risky cocaine use profiles, not using other stimulants, with high socioeconomic level, have higher odds of using the less stigmatizing "smoked cocaine" [14].

Pipes used for crack cocaine smoking are often homemade and/or in short supply, leading to pipe sharing and injuries from use of unsafe materials. This increases risk of viral infection and respiratory harm among a marginalised underserved population [15]. Crack injection is associated with elevated blood-borne virus (HCV, HIV) and bacterial infection risk [16], given increased injection frequency compared to opioid use [17].

Meta-analyses showed positive associations between crack use and blood/sexually transmitted diseases (HIV, hepatitis C virus [HCV], etc.); and moderate evidence and meta-analyses supported associations with neonatal health and violence. There were mixed associations for mental and other health outcomes, yet insufficient evidence to perform meta-analyses for mortality. Most underlying research was of limited or poor quality, with crack commonly assessed as a secondary covariate [18].

From reviews, elevated all-cause crude mortality rates (CMR = 12.4 per 1000 person-years) and standardized mortality ratios (SMR = 6.3) among people with regular or problematic cocaine use have emerged. Drug-related, suicide, accidental injury, homicide and AIDS-related mortality were all elevated compared with age- and gender-matched peers in the general population [19]. Mortality risk and excess mortality were significantly greater among those with cocaine and heroin use disorder than among people with only cocaine use disorder or cocaine and alcohol use disorder [20]. In the only two follow-up studies, individuals arrested for crack use [21] and crack-dependent patients [22, 23] experienced 5-fold and 12-fold elevated mortality rates, respectively, compared to the general population. Homicide, overdose and AIDS were the main causes of death [24].

The aim of this retrospective cohort study, which targeted residents of the Emilia-Romagna region (North Italy) who turned to a Public Treatment Centre for Addiction (PATS) following problems due to crack use between 1992 and 2020, was to examine mortality risk and causes of death in the Emilia-Romagna region. We estimated overall mortality rates and excess mortality by age and gender.

MATERIALS AND METHODS

People residing in the Emilia-Romagna Region (Northern Italy) aged 18 years and older who entered drug treatment for crack problems were enrolled. The reference period was between 01/01/1992 and 31/12/2020 and the territory was the metropolitan area of Bologna. The cases were selected from the IT systems of 10 PATS. All information was obtained retrospectively.

At the PATS, a digital regional folder was used to collect the data at first admission, as well as personal data, health data, treatments undertaken and substances of use (including crack).

The information was collected at first contact. Variables related to age, gender, country of birth, residence, social situation (homeless, imprisonment), professional condition, marital status, educational degree, health situation (HIV positive, HCV positive), substance of use and date of first admission were used.

Person-years (PY) were calculated from the first documented episode to 31 December 2020 or up to the date of death. Based on the ICD-9 (until 2002) and ICD-10 (from 2003) codes, mortality was verified at the registry offices of the municipality where the patients were living at the end of the study period (i.e. 31 December 2020) or at death. Patients who were lost to follow-up were included in PY until the date they moved out of their last known stable place of residence.

Continuous and categorical variables were analysed with Student's t-test and the chi-squared test, respectively. CMRs per 1000 person-years and relative confidence intervals (CIs) at 95% were calculated. To compare the mortality rates of crack patients with those of the general population, we calculated the SMRs, adjusted for gender, age and calendar year (standard: Emilia-Romagna region), and the relative 95% CIs.

Data analyses were performed using STATA 15.1 statistical software.

The study protocol was approved by the local research ethics committee (Cod. CE:201
83).

RESULTS

The cohort was made up of 178 subjects, 24 (13%) female and 48 (28%) non-natives: 26 (15%) Mediterranean African, 11 (6%) Eastern Europe, 6 (3%) other European countries. One hundred and twenty-seven people (73%) were unmarried, 16 (9%) were widowed, separated or divorced, 26 (15%) were homeless, 57 (32%) had been to prison at least once, 134 (77%) did not finish a high school/university degree and 93 (53%) were unemployed. Among the females, a lower percentage of non-natives and a higher quota of those with a high school degree were observed.

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Furthermore, 37 (21%) were HCV positive and 6 (3%) were HIV positive, 138 (77%) smoking crack and 40 (23%) injecting crack with an average age at first admission of 35 years. (Table 1).

In the entire period, 131 (75%) reported concomitant heroin use, 96 (55%) cocaine, 42 (24%) alcohol, 29 (17%) cannabis, 11 (6%) benzodiazepines, 7 (4%) barbiturates, 6 (3%) amphetamines and 5 (3%) hallucinogens; almost 76 (43%) have injected a substance.

The average period of contact with the PATS was 4.3 years. By the end of the follow-up, 52 (29%) had completed the therapeutic programme and had been dismissed, 57 (32%) had an ongoing therapeutic programme, 56 (31%) had already left treatment, 8 (5%) were arrested and 5 (3%) died during the treatment programme.

Follow-up continued until 31 December 2020 or the date of death for 96% of the subjects (eight subjects were lost to follow-up). The average follow-up period was 7.6 years. There were 1355 PY (145 females, 1210 males). Nine patients (5% of the whole cohort) died, all males (6% of men). The mean age at death was 48.1 ± 8 years.

Proportional mortality

There was one death of ill-defined or unknown causes. The main causes of death were external causes (2, heroin overdose; 1, suicide), infectious diseases (1, viral hepatitis; 1, AIDS), all tumours (1, malignant neoplasm of oesophagus; 1, malignant neoplasm of liver and intrahepatic bile ducts) and digestive system disease (1, gastritis and duodenitis).

Mortality rates

The CMR was 6.6 (95% CI = 3.5–12.8) per 1000 person-years, increasing with age.

Regarding the causes of death, the CMR was higher for external, followed by infectious diseases and all tumours (Table 2).

Mortality rates were higher among Italian-born patients (natives: CMR = 7.3, 95% CI = 3.7–14.6; non-natives: CMR = 3.8, 95% CI = 0.5–27.1), individuals with a low school degree (primary/secondary school: CMR = 7.5, 95% CI = 3.7–14.9; high school diploma/university: CMR = 3.5, 95% CI = 0.5–25.2), patients using alcohol (using alcohol: CMR = 8.5, 95% CI = 2.7–26.3; not using alcohol: CMR = 6.0, 95% CI = 2.7–13.3) and patients injecting any substance (injecting: CMR = 7.6, 95% CI = 3.4–16.9; not injecting: CMR = 5.3, 95% CI = 1.7–16.4).

It should be noted that there was no difference in mortality rates between patients using (CMR = 6.7, 95% CI = 3.4–16.9) and not using heroin (CMR = 6.7, 95% CI = 3.2–14.1).

Standardized mortality ratios

SMRs were at least six times higher among males and thirteen times higher among patients aged 35–44 years. Elevated and statistically significant SMRs were found for any single cause of death (Table 2).

DISCUSSION

This study targeted a cohort of people who accessed health services following problems caused by crack use, many of whom reported concomitant heroin and alcohol use, and results confirmed what has been reported in the literature concerning the characteristics [3, 5, 6, 20] and the elevated mortality risk connected to crack cocaine use [18, 21, 22, 23, 25].

From studies crack-cocaine use was associated with a range of health outcomes, although it was unclear if there was direct causal impact, interactions between risk factors, or external drivers of both crack-cocaine use and outcomes [18].

The cohort, composed of 178 individuals who turned to a public addiction service for problems due to crack use over a 30-year period, is distinguished by specific demographic (non-natives, most from Mediterranean African countries) and socio-economic (low education, unemployed) characteristics, social marginalization (homeless, imprisonment) and particular physical (HIV, hepatitis) problems. Many of them have injected a substance; heroin, cocaine and alcohol were the other principal substances used. It should be noted that the majority had either completed or entered an ongoing therapeutic programme at the end of the follow-up.

The results highlight elevated SMRs for males (no deaths among females), being higher for patients aged 35–44 years. Mortality rates were higher among older patients, Italian-born patients, individuals with a low school degree and those using alcohol and injecting any substance. Similar to other mortality studies on cocaine [19] and crack users [24], excess mortality was six times higher than in the general population, and overdose and infectious diseases (AIDS) were among the leading causes of death. Furthermore, we highlight a mortality excess for digestive system disease and malignant neoplasm of the liver. The prevalence of HIV, HCV and other infectious diseases is often higher among people who use crack cocaine relative to the general population [26, 27], driving AIDS-related mortality and probably contributing to excess mortality from liver disease [19].

It should be noted that in our study there were no deaths by homicide; this most probably reflects both the characteristics of Italian crack users, who turn to services for treatment, and the resulting changes in substance consumption and lifestyle.

This study presents some limitations that reduce the generalizability of the results and therefore further

research is required with specifically targeted studies. The number of people recruited and the person-years are quite low; also, the data used are those available from first admission, so data regarding average consumption variations or the use of other substances over time are lacking. Furthermore, it has not been possible to consider data concerning age at first use, because it was not collected uniformly.

Despite these limitations, several interesting aspects have emerged in identifying the vital statistics and mortality risks in a cohort of a population of patients treated for Crack use. In particular, it was possible to calculate the excess mortality compared to the general population adjusted for gender, age and calendar year.

The difficulties in carrying out studies in this field are well known [18]. Indeed, from the studies on crack use, significant problems and shortcomings regarding case definition, prevalence, morbidity and mortality have emerged.

CONCLUSION

The results of our study show that those who turned to a health service following problematic crack consumption have a high mortality excess compared to the general population, similar to that of problem cocaine users.

Furthermore, we observed a higher mortality risk among males, older patients, those with a low school degree, those using alcohol and those injecting any substance.

Rigorous epidemiological studies are needed to systematically assess health outcomes of crack-cocaine use and underlying pathways, also to inform evidence-based interventions.

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Table 1. Characteristics

		All cases (178)	**Males** (154)	**Females** (24)	P
		N (%)	**N (%)**	**N (%)**	
Period of first admission	<=2010	54 (30.3)	49 (31.8)	5 (20.8)	0.487
	2011/2015	59 (33.2)	49 (31.8)	10 (41.7)	
	2016/2020	65 (36.5)	56 (36.4)	9 (37.5)	
Age at first admission	Mean (± standard dev.)	35.1±9.6	35.2±9.3	34.3±11.7	0.3357
Country of birth	Natives	130 (74.7)	107 (69.5)	23 (95.8)	0.007
	Non-natives	48 (27.6)	47 (30.5)	1 (4.2)	
Social situation	Homeless	26 (14.9)	26 (16.9)	-	0.029
	Any imprisonment	57 (32.0)	56 (36.4)	1 (4.2)	0.002
Professional condition	Regular income	33 (19.0)	31 (20.1)	2 (8.3)	0.384
	Unemployed	93 (53.4)	80 (51.9)	13 (54.2)	
	Student	3 (1.7)	3 (1.9)	-	
	Missing	49 (28.2)	40 (26.0)	9 (37.5)	
Educational degree	Primary/Secondary school	134 (77.0)	119 (77.3)	15 (62.5)	0.021
	High school diploma/University	33 (19.0)	4 (2.6)	9 (37.5)	
	Missing	11 (6.3)	11 (7.1)	-	
Marital status	Unmarried	127 (73.0)	110 (71.4)	17 (70.8)	0.916
	Married	17 (9.8)	15 (9.7)	2 (8.3)	
	Widow/separated/divorced	16 (9.2)	13 (8.4)	3 (12.5)	
	Missing	18 (10.3)	16 (10.4)	2 (8.3)	
Substances	Heroin	131 (75.3)	112 (72.7)	19 (79.2)	0.506
	Cocainie	96 (55.2)	83 (53.9)	13 (54.2)	0.980
	Alcohol	42 (24.1)	38 (24.7)	4 (16.7)	0.390
	Cannabis	29 (16.7)	25 (16.2)	4 (16.7)	0.957
	Benzodiazepines	11 (6.3)	11 (7.1)	-	0.176
	Any Injecting	76 (42.7)	64 (41.6)	12 (50.0)	0.437
	Injecting crack	40 (22.5)	36 (23.4)	4 (16.7)	0.464
Health situation	HIV positive	6 (3.4)	6 (3.9)	-	0.325
	HCV positive	37 (21.3)	33 (21.4)	4 (16.7)	0.593

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*Table 2 Crude Mortality Rates and Standardized Mortality Ratios**

	All cases (PY 1355)					Males (PY 1210)				
	O/E	CMR	95% CI	SMR	95% CI	O/E	CMR	95% CI	SMR	95% CI
Total	9/1.6	6.6	3.5-12.8	5.72	2.98-11.0	9/1.4	7.4	3.9-14.3	6.30	3.28-12.11
Age group										
35-44 years	4/0.3	8.4	3.1-22.3	13.18	4.95-35.12	4/0.3	9.2	3.4-24.4	13.90	5.22-37.03
>44 years	5/1.1	11.8	4.9-28.4	4.38	1.82-10.51	5/1.0	12.7	5.3-30.6	4.88	2.03-11.72
Infectious diseases	2/0.06	1.5	0.4-5.9	35.40	8.85-141.54	2/0.05	1.7	0.4-6.6	38.14	9.54-152.48
Viral hepatitis	1/0.01	0.7	0.1-5.2	91.20	12.85-647.47	1/0.01	0.8	0.1-5.9	94.02	13.24-667.43
AIDS	1/0.02	0.7	0.1-5.2	43.22	6.08-306.83	1/0.02	0.8	0.1-5.9	44.67	6.29-317.08
All tumors	2/0.6	1.5	0.4-5.9	3.30	0.83-13.21	2/0.5	1.7	0.4-6.6	3.83	0.96-15.33
Malignant neoplasm of oesophagus	1/0.01	0.7	0.1-5.2	91.29	12.86-648.10	1/0.01	0.8	0.1.5.9	95.94	13.51-681.05
Malignant neoplasm of liver and intrahepatic bile ducts	1/0.04	0.7	0.1-5.2	24.24	3.42-172.10	1/0.04	0.8	0.1-5.9	25.43	3.58-180.51
Digestive system	1/0.1	0.7	0.1-5.2	14.41	2.03-102.30	1/0.1	0.8	0.1-5.9	15.37	2.16-109.08
Gastritis and duodenitis	1/0	0.7	0.1-5.2	1334	188-9476	1/0	0.8	0.1-5.9	1499	211-10638
External causes	3/0.3	2.2	0.7-6.9	10.32	3.33-31.98	3/0.3	2.5	0.8-7.7	10.72	3.46-33.22
Overdose	2/0.02	1.5	0.4-5.9	114.18	28.56-456.54	2/0.02	1.7	0.4-6.6	118.05	29.52-472.03
Suicide	1/0.1	0.7	0.1-5.2	8.68	1.22-61.60	1/0.1	0.8	0.1-5.9	9.01	1.27-63.99

* Adjusted for age and calendar year (Standard: Emilia Romagna Region)
O, observed death; **E**, expected death; **CMR**, crude mortality rate per 1000 PY; **SMR**, standardized mortality ratios; **CI**, confidence interval

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Pregnancy-associated Cancers: A Narrative Review

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SUMMARY

Pregnancy-associated cancers are malignancies diagnosed during pregnancy or within one year of delivery or abortion. These cancers present unique challenges because of the delicate balance required for maternal-fetal health. Diagnosis can be made complex by physiological changes associated with pregnancy, and treatment decisions must take into account potential harm to the fetus. Multidisciplinary collaboration between oncologists and obstetricians is essential. Despite the complexities, early detection and tailored management can optimise outcomes for both the mother and child. A systematic approach is currently lacking; further research into prenatal exposure to maternal cancer is recommended to formulate evidence-based guidelines for the management of cancer in pregnancy.

Keywords: cancer, chemotherapy, pregnancy.

INTRODUCTION

Pregnancy-associated cancers are malignancies diagnosed during pregnancy or within one year of birth or abortion. Neoplasms diagnosed in the first year after the end of pregnancy are presumed to have originated in the previous months of pregnancy.

The clinical management of a pregnant patient with oncological disease is certainly a complex scenario due to the co-presence of the mother and the fetus: an accurate diagnosis and timely treatment may save the life of the mother, but may have irreparable consequences for the fetus. The psychological impact on the woman, the couple, and the family of an oncological disease during pregnancy is also significant.

It is therefore important to quantify this event and assess its impact.

METHODS

This is a narrative review of published data on cancer associated with pregnancy. The Scale for the Assessment of Narrative Review Articles (SANRA) was used to report and qualitatively assess the review [1]. We conducted the review using a narrative review approach [2]. PubMed was searched up to 1 December 2023 for relevant publications in English, focusing on, but not limited to, the use of the keywords listed. Key search terms were: pregnancy associated cancer OR ((cancer OR neoplasm OR chemotherapy OR malignancy) AND (pregnancy OR pregnant OR postpartum)). The most relevant articles providing useful information on definition, diagnosis, treatment options, and clinical management of pregnancy-associated cancers were selected. The bibliography was also analyzed to include articles that could have been missed.

Epidemiology

Cancer complicates approximately 1 in 1000 pregnancies, with about 25% diagnosed during pregnancy and the majority diagnosed after pregnancy [3]. The literature on the incidence or prevalence of pregnancy-associated cancers is difficult to compare. Firstly, many studies have focused on a specific type of cancer. Secondly, there are many differences in study design, inclusion criteria, inconsistent follow-up periods, and different reference populations (i.e., pregnancies or births) between studies.

Northern European countries [4-9] have a tradition of epidemiological studies on this topic, as for North

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Table 1. Result from selected population-based studies about pregnancy-associated breast cancer

Study	Country	Sample size	Incidence rate per 1000	Post-partum follow-up (months)
Sullivan et al., 2022 [22]	Australia New Zealand	-	0.072 0.090	-
Shechter Maor et al., 2018 [23]	USA	11,846,300	0.065	-
Abenhaim et al., 2012 [24]	USA	8,826,137	0.065	-
Andersson et al., 2009 [25]	Sweden	4,156,190	0.279	24
Rodriguez et al., 2008 [26]	California	4,846,505	0.164	12

America [10-12] and Australia [13, 14]. A few evidence are available also from Asia [15, 16]. Studies from southern Europe, particularly in Italy, are more recent [17-21]. The incidence measures range from 0.65 per 1000 in Finland (1950-1969) [7] to 1.73 per 1000 in Korea (1995-2013) [16].

Pregnant women are more likely to experience cancers that are more common in women of reproductive age, with an incidence generally similar to that of women of the same age who are not pregnant [14]; the most commonly diagnosed is the breast cancer [3].

Table 1 lists selected population-based studies regarding pregnancy-associated breast cancer; specifically, incidence rate, and the postpartum follow-up period are described.

Diagnostic challenge

Regardless of pregnancy status, early diagnosis of cancer is essential for successful treatment. The diagnosis of cancer in pregnancy is often delayed because it can be made complex by the fact that many of the symptoms of malignancy mimic the physiological changes of pregnancy, including nausea, breast changes, abdominal pain, anaemia, and fatigue.

The diagnosis of breast cacer during pregnancy represents a challenging situation for the patient and physicians, because variations in hormone levels can cause changes in the breast that can hide small new formations [27]. Specifically, pregnancy increases breast density and nodularity, complicating clinical and radiological examinations [28]. Although biopsy of a suspected breast lesion can be problematic due to the hypervascularisation and oedema typical of the gravid state, histopathology from core biopsies is the gold standard and should follow standard procedures as for non-pregnant women, but the pathologist needs to be aware of the pregnancy status to properly account for changes that may occur due to the physiology of the breast tissue during pregnancy [29].

The awareness of pregnancy-associated hyperpigmentation can also affect how potential malignant lesions or melanoma are interpreted and manifested. Therefore, any pigmented lesion that changes clinical or dermoscopic characteristics during pregnancy should be considered suspicious [30].

On the contrary, pregnancy favours early diagnosis of cervical cancer: women in this period are strictly monitored and the screening for this type of cancer is considered safe during pregnancy using correct sampling tool to minimize bleeding risk [31]. However, also for cervical cancer, the physiological changes associated with pregnancy can lead to false-positive results, so the cytopathologist must be well informed; a Papanicolaou smear taken from a pregnant woman

Table 2. American College of Obstetricians and Gynecologists (ACOG) guidelines for the use of x-rays, ultrasound, magnetic resonance imaging and radioisotopes during pregnancy and lactation. Source: [32, 33]

"Ultrasonography and magnetic resonance imaging (MRI) are not associated with risk and are the imaging techniques of choice for the pregnant patient, but they should be used prudently and only when use is expected to answer a relevant clinical question or otherwise provide medical benefit to the patient".
"With few exceptions, radiation exposure through radiography, computed tomography (CT) scan, or nuclear medicine imaging techniques is at a dose much lower than the exposure associated with fetal harm. If these techniques are necessary in addition to ultrasonography or MRI or are more readily available for the diagnosis in question, they should not be withheld from a pregnant patient".
"The use of gadolinium contrast with MRI should be limited; it may be used as a contrast agent in a pregnant woman only if it significantly improves diagnostic performance and is expected to improve fetal or maternal outcome".
"Breastfeeding should not be interrupted after gadolinium administration".

may show squamous metaplasia or trophoblastic cells that could be mistaken for dysplasia [27].

Diagnosis by instrumental examination may have been delayed because exposure to procedures during pregnancy and lactation is avoided in the absence of a strong indication. There are, however, a large number of imaging techniques that can be used as diagnostic tools in pregnancy. Guidelines for the use of x-rays, ultrasound, magnetic resonance imaging, and radioisotopes during pregnancy and lactation are reported in Table 2. In the case of x-rays and nuclear medicine, the exposure of the patient and fetus to ionising radiation must be limited. Other diagnostic procedures such as incisional or excisional biopsies, endoscopies and bone marrow punctures can be performed safely [27, 32, 33].

Treatment options

1. A multidisciplinary approach

A comprehensive assessment is needed when considering how best to manage a pregnant patient with cancer. This involves an analysis of the complex interplay between the progression of the tumour and the decision about whether to continue the pregnancy. This includes a thorough evaluation of the stage and type of cancer, its potential impact on the health of the mother and baby, and the therapies that can be given safely during pregnancy. Equally important is an understanding of how the continuation of the pregnancy may affect the approach to tumour treatment, taking into account the safety of the fetus and the potential need for adjustments to the treatment plan to ensure the best possible outcome for both mother and baby.

Management of this situation requires a joint strategy by a multidisciplinary team of obstetricians, oncologists, surgeons, radiologists, neonatologists, psychologists, and other specialists [34]. It is therefore important that cancers during pregnancy are managed in referreal obstetrics hospitals togher with comprehensive cancer centers, with access to the resources and specialists needed to manage all aspects of treatment. [35]. As for non-pregnant women, the approaches to cancer include: radiotherapy, chemotherapy, and surgery. The choice of treatment and its timing cannot be separated from the wishes of the mother and the couple, and is a challenge for each member of the medical and support team [34].

2. Surgical intervention

Planning surgery during pregnancy is based on assessing the potential risks for both progression of maternal disease and fetus health. Where indicated, the procedure can be performed at any time during the course of the pregnancy [36]. Maternal surgery may result in preterm labour and altered uteroplacental perfusion with a resulting risk of hypoxia, brain injury, and fetal intrauterine death [37]. Complications are more common with major abdominal or pelvic surgery due to the increased blood supply to the pelvis [36]. However, a systematic review including pregnant women who underwent non-obstetric surgery found no increased rate of miscarriage or adverse birth outcomes compared with the general population [38]. In the case of gynaecological malignancies, it is preferably performed in the early second trimester when the risk of miscarriage and the size of the uterus allows access [39].

With regard to anaesthesia, the US Food and Drug Administration suggests minimising the time under general anaesthesia, minimising the dose and concentration of the agent, and avoiding inhalational anaesthetics, propofol, and midazolam [40]. The physiological changes of pregnancy require an adapted anaesthesiological approach with an additional safety margin to keep the blood pressure and the oxygenation of the mother as stable as possible [41].

3. Radiotherapy

Radiotherapy should be limited to a few patients; for others, chemotherapy allows safe deferral of radiotherapy [42]. If strictly recommended, limited upper body use can be considered, as the uterus is out of the field and shielded from radiation, with care taken to protect the patient's abdomen with a shield [37, 43].

Fetal exposure to radiotherapy depends on several factors, including gestational age (the fetus is most vulnerable during the first weeks of organogenesis), target dose (doses between 0.05 and 0.5 Gy are generally considered safe for the fetus during the second and third trimesters), the size of the radiation fields, and the distance from the edges of the fields to the fetus [44, 45].

Careful planning using appropriate shielding techniques or other dose reduction techniques is therefore essential when treating a pregnant patient [46, 47].

In the specific case of breast cancer, breastfeeding during radiotherapy is not recommended because the suckling effect of the infant may potentially increase radiotherapy-induced skin toxicity, leading to discomfort, skin breakdown, and infection [48].

4. Chemotherapy

The physiological changes induced by pregnancy may have an effect on the pharmacokinetics and pharmacodynamics, i.e. the absorption, distribution, metabolism, excretion and mechanism of action of the drug. These changes include an increase in plasma volume by approximately 50%, an increase in renal clearance and an increase in hepatic metabolism. The result is a reduction in the active concentration of the drug in comparison with the same dose in a non-pregnant woman of the same weight [49].

Over the past two decades, the use of chemotherapy during pregnancy has gradually increased [50]. Most chemotherapy is discouraged in the first trimester

as it may lead to increased morbidity, particularly congenital malformations [37, 49, 51-53]. The second and third trimester chemotherapy may be associated with intrauterine growth restriction, preterm delivery, low birth weight, and stillbirth [54]. No consistent evidence of major effects on long-term fetal neurodevelopment has been reported. However, longer and more thorough follow-up is certainly needed to draw firm conclusions [52, 55].

The mechanisms underlying the association between prenatal exposure to chemotherapy and adverse outcomes depend on several factors, including the duration and timing of exposure, the dose delivered to the embryo/fetus, and the disruption of cellular metabolism [56].

Not all chemotherapic drugs are dangerous [57, 58]. Table 3 shows the most commonly used chemotherapic treatment against breast cancer.

As for the potential effects on lactation, more than half of the women who underwent prenatal chemotherapy reported reduced milk production and breastfeeding difficulties, with the need to supplement infant feeding [59].

With evidence limited to a few case reports, little is known about the safety of chemotherapy for infants during breastfeeding. In addition to chemotherapy, cancer patients are usually given other drugs that can pass into breast milk and endanger the health of their babies. Despite the well known benefits for both mothers and their babies, breastfeeding during chemotherapy is discouraged, even though neonatal toxicity depends on the oral bioavailability of the drug, the pharmacokinetics of the newborn, and the amount of milk [60].

Management of pregnancy, delivery, and breastfeeding

The pregnancies in women with a diagnosis of malignancy are considered high-risk and should be monitored in a highly specialised centre with an effective multidisciplinary team. Regular ultrasound scans are required for early detection of malformations, assessment of fetal growth, placental flow, and amniotic fluid regularity [34, 36, 61, 62].

If treatment of the neoplasm is planned, the precautions must be taken. In the case of surgery after 24 weeks, cardiotocographic monitoring of the fetus should be performed in order to ensure his well-being throughout the intervention. In addition, the woman needs to be made aware of the possible complications, so her consent needs to be obtained for an emergency caesarean section [34]. During surgery, the patient should be placed in the left lateral decubitus position from 20 weeks' gestation to avoid compression of the inferior vena cava. Tocolytics should not be administered during surgery unless there is evidence of uterine contractions. Post-operative tocolytics may be considered for 48 hours from late second trimester if uterine manipulation is unavoidable [63].

In the case of chemotherapy, monitoring of fetal well-being is a requirement after each course of treatment. It is desirable to plan these treatments carefully according to gestational age. Chemotherapy is generally avoided in the first trimester and should not be administered later than 35 weeks and stopped approximately three weeks before delivery [34, 41, 49]. This interval allows the drugs to be excreted by the fetus across the placenta. Otherwise, the drugs would remain in the infant's circulation [49].

Wherever possible, delivery should be planned and managed on the basis of obstetric indications, with full-term delivery desirable to avoid the consequences of preterm birth [34, 36, 49, 61]. If a premature birth is necessary, it is important to ensure that the baby adapts well, for example by ensuring that the lungs mature through the administration of cortisone [34]. In general, vaginal delivery is appropriate, but the mode of delivery needs to be assessed on a case-by-case basis, in particular depending on the type of cancer. For those that affect the pelvic-abdominal region, such as colorectal or gynaecological cancers, a caesarean section may be more appropriate. For cervical cancer, caesarean section is recommended if the tumor is more than 3 mm deep because of the risk of bleeding or obstructed labor [37].

Histological examination of the placenta should always be carried out after delivery; this is particularly important for leukaemia and melanoma [34, 36, 61]. However, placental metastases are rare [36].

As for postpartum, a potentially safe combination

Table 3. Most common chemotherapic treatment during pregnancy

Chemotherapic options	Evidence
FAC regimen (5-fluorouracil, doxorubicin, cyclophosphamide)	FAC regimen was commolnly well tollerated. Doxorubicin and epirubicin were used either as single agents or in combination with 5-fluorouracil, in both cases well tollerated.
AC regimen (doxorubicin, cyclophosphamide)	
FEC regimen (5-fluorouracil, epirubicin, cyclophosphamide)	
EC regimen (epirubicin, cyclophosphamide)	
Trastuzumab as HER2/neu targeted agent	Short-term use of trastuzumab did not appear to put pregnancy at risk. Prolonged exposure was associated with adverse events.

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of breastfeeding and chemotherapy with minimal risk to the infant may be achieved by discarding the breast milk. It has been suggested that exposure to cyclophosphamide and paclitaxel is negligible when breast milk was discarded for as little as 2 days, whereas doxorubicin should be discarded for at least 6 days [64, 65].

CONCLUSIONS

Over recent decades, there has been an increase in research into the feasibility and safety of oncological treatment during pregnancy, which has led to an increase in the number of ongoing pregnancies with timely treatment of the mother's cancer. However, a systematic approach is currently lacking due to the relative rarity of this situation. This will be useful in formulating evidence based guidelines for the management of cancer in pregnancy.

CONFLICT OF INTERESTS

The authors declare that they have no conflicts of interest to disclose.

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Healthy and Unhealthy Plant-Based Diets and Body Weight in Breast Cancer Survivors

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SUMMARY

Obesity in breast cancer (BC) survivors increase the risk of BC recurrence, second primary BC, BC-specific mortality, and overall mortality. Guidelines for BC survivors encourage healthy lifestyles by promoting healthy diets, engage in physical activity and avoid weight gain to achieve longer survival and improved quality of life. In recent years, there has been a growing interest in the possible beneficial role of plant-based diets in body weight control and in BC risk and prognosis. Plant-based diets can be evaluated using dietary indices which provide a quantitative measure of how closely an individual's diet aligns with a plant-based dietary pattern. However, there is a need to distinguish plant-based diets in healthy and unhealthy. This approach would address a research gap that often overlooks the quality and specific types of plant foods consumed. The aim of this narrative review is to analyze how a plant-based diet may impact on body weight in BC survivors, synthesizing existing evidence and discussing the potential mechanisms and implications. The findings suggest the importance of considering the quality of plant-based diets, as some may include vegetarian foods with a low nutritional profile which may negatively impact on body weight. This aspect could be crucial in preventing weight gain in women with BC, as body weight is considered a risk factor for poor BC prognosis and reduced survival.

Keywords: plant-based diet, dietary patterns, body weight, body mass index, waist circumference, breast cancer

INTRODUCTION

Obesity in breast cancer (BC) survivors, at or after diagnosis, increase the risk of BC recurrence, second primary BC, BC-specific mortality, and overall mortality [1, 2, 3]. Specifically, in postdiagnosis, for every 5 kg/m^2 of BMI increase, there was an estimated 7% higher risk of all-cause mortality, 10% higher risk of BC-specific mortality, and 14% higher risk of developing a second primary BC [3].

Obesity is commonly defined using body mass index (BMI), which is calculated from the formula body weight (kg) / height (m^2). The World Health Organization classifies levels of adiposity based on BMI as follows: underweight, ≤ 18.5 kg/m^2; normal, 18.5 – 24.9 kg/m^2; overweight, 25.0 – 29.9 kg/m^2; obese, ≥ 30 kg/m^2.

Obesity has a complex relationship with BC risk that differs in pre-menopause versus post-menopause. Higher BMI is associated with a lower risk of BC before menopause and with an increased risk of cancer after menopause, especially among postmenopausal women who have never received hormone replacement therapy [4].

Before menopause, the ovaries are the primary site of estrogen production in women. This is because the enzyme aromatase, which is responsible for converting androgens to estrogens, is predominantly expressed in the ovaries. Only a small portion of estrogen is produced by fat tissue during this stage [5]. After menopause, when the ovaries cease estrogen production, the primary site of estrogen synthesis shifts to adipose tissue, with fat tissue becoming the predominant source of estrogen. Additionally, decreased levels of sex-hormone binding globulin

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result in elevated circulating estrogen levels [6]. Having a higher amount of fat tissue after menopause can result in raised estrogen levels, thereby increasing the risk of developing BC in postmenopausal women with obesity [6].

Body fat deposits are typically located in the upper abdominal region and in lower sites around the hips and thighs. In clinical studies, the waist-to-hip circumference ratio (WHR) is commonly utilized to evaluate body fat distribution, with waist circumference (WC) being identified as a more reliable indicator of visceral abdominal fat distribution [7]. High WC is an indicator of central obesity. In particular, the evaluation of central adiposity may be a more specific indicator of the metabolic effects of obesity and another predictor of BC risk than body weight alone [7]. It was observed that postmenopausal women with BMI ≥ 35 kg/m^2 and WC ≥ 90 cm were more likely to develop BC [8]. Intra-abdominal (visceral) adipose tissue is associated with a higher risk of metabolic disorders such as type 2 diabetes, cardiovascular disease (CVD), and insulin resistance [9]. Fat cells in the abdominal area are metabolically active and release higher levels of free fatty acids, as a product of lipolysis, and inflammatory cytokines, which contribute to chronic subclinical inflammation. The levels of adipokines are altered, with an increase in pro-inflammatory leptin and a decrease in adiponectin, resulting in reduced anti-inflammatory and insulin-sensitizing effects [10]. These pathways are associated with the development of highly aggressive biological features in tumors, creating an environment that may promote cancer invasion and metastasis in women with obesity [11, 12].

Exercise and weight loss decrease the inflammatory microenvironment in obese patients, improve antitumor immunity, decrease estrogen levels, and are associated with reduced BC risk, better outcomes and it may indeed improve BC survival [10, 13]. These findings highlight the importance of maintaining a healthy body weight in order to improve the prognosis and outcomes of individuals diagnosed with BC. Long-term lifestyle changes, beyond a single year, may be required for sustained weight loss [13].

While there is a well-established association between being overweight or obese in menopause and having a sedentary lifestyle with an increased risk of BC [4], the relationship between diet and BC risk is not yet fully understood. The impact of diet on BC risk, recurrence, and mortality is still an active and ongoing area of research. It is estimated that 30% to 50% of all cancers could be prevented through a healthy lifestyle by being at a healthy weight, being physically active, and making sustainable long-term changes to dietary habits [14]. Therefore, nutritional interventions play a critical role in determining cancer prognosis, improving patient quality of life, and enhancing the effectiveness of anti-tumor therapies. Among BC patients, diet, physical activity, and weight management, are indeed essential to improving survival rates. In these patients, nutritional intervention should be considered as an integral part of the multimodal therapeutic approach in oncology to reduce the risk of recurrence, mortality and the development of BC co-morbidities (e.g., obesity, hypertension, hyperlipidemia, and diabetes mellitus) [14,15]. A healthy lifestyle and dietary habits are advised to BC patients before, during, and after treatment in order to have better long-term survival and quality of life [15]. The dietary pattern promoted by the World Cancer Research Fund / American Institute for Cancer Research (WCRF / AICR) to improve the survival of women with BC after diagnosis emphasizes a diet rich in plant-based foods such as vegetables, fruit, whole grains, and legumes, especially soy. Conversely, it de-emphasizes the consumption of refined grains and animal products. In particular, the WCRF / AICR guidelines recommend limiting consumption of red meat (e.g., beef, pork, and lamb) and avoiding processed meat by limiting consumption of "fast foods" and other processed foods high in saturated fatty acids (SFA), starches, or sugars (e.g., sweets, desserts). Additionally, it suggests reducing the consumption of sugar-sweetened beverages (SSBs), avoiding alcohol, and not using supplements for cancer prevention [11, 16, 17].

PLANT-BASED DIET AND BREAST CANCER

In recent years, there has been growing interest in the potential protective effects of plant-based diets against BC. The term "plant-based diet" may both be used to describe a diet rich in plant foods or as an umbrella term for various types of vegetarian patterns that excludes some or all animal foods [18, 19]. Despite the increasing popularity of vegetarian or vegan diets, the majority of individuals in Western countries still consume a combination of foods from both animal and plant sources [20].

Evaluating diets only as a dichotomy of vegetarian and omnivorous, categorizing study populations into participants who do or do not consume some or all animal foods, has several limitations that are overcome by using dietary indices that evaluate progressive adherence to a plant-based dietary pattern [18]. It is important to understand whether the gradual reduction of animal food intake with a concomitant increase in the consumption of plant-based foods can reduce the risk and recurrence of BC. If effective, this approach could have broader implications, as it may be more feasible and sustainable for individuals compared to the complete exclusion of animal foods [21]. Another limitation in studies focusing on vegetarian diets is that all plant-based foods are treated equally, but the nutritional quality is not equivalent across all plant foods [19]. Satija et al. [22] proposed three different approaches for plant-based dietary indices, which are numerical scores designed to assess adherence to an overall pattern of plant-based eating (Figure 1). An overall plant-based diet index (PDI) was created,

equivalent to the original pro-vegetarian dietary pattern, which emphasizes consumption of all plant foods while reducing intake of animal foods. Another plant-based dietary index is the healthful plant-based diet index (hPDI), which focuses on the intake of healthy plant foods that have been associated with improved health outcomes. This includes whole grains, legumes, vegetables, fruits, nuts, vegetables oils, and beverages like tea and coffee. The last index, the unhealthful plant-based diet index (uPDI), places emphasis on the consumption of less healthy plant foods, which have been linked to a higher risk of various diseases. Examples of these foods include refined grains, potatoes, fruit juices, sweets, desserts, and SSBs [23]. These three indices provide a quantitative measure of how closely an individual's diet aligns with a plant-based dietary pattern. This approach is particularly interesting as it addresses a significant gap in current research, which often overlooks the quality and specific types of plant foods consumed in comparison to the proportion and frequency of animal food intake within a plant-based diet. Plant-based diets have been associated with lower risk of chronic diseases, such as type 2 diabetes, with a stronger inverse association for hPDI and a positive association for uPDI [22], CVD [19], and some cancers [24]. Recent studies have provided evidence suggesting the potential benefits of plant-based diets in reducing the risk and recurrence of BC. The Nurses' Health Studies have shown that healthful plant-based diets were significantly associated with lower BC risk, especially for ER-negative BC [21, 25] where a healthful plant-based diet adherence was not a full vegetarian diet, but one composed of both plants and some animal foods. Furthermore, adopting healthful plant-based dietary patterns has been found to potentially improve overall survival among BC survivors [23]. While some studies suggest potential benefits of plant-based diets in reducing BC risk and promoting BC prevention and survivorship, the specific relationship is still unclear although some suggest a dose-response with the highest prevalence of overweight and obesity found among omnivores compared to semi-vegetarians, lacto-vegetarians, and vegans [26]. Other randomized controlled trials have demonstrated that a vegetarian diet is an effective intervention for weight loss, with vegan dietary treatments achieving the greatest weight loss among different vegetarian dietary patterns [27, 28]. However, only a few studies investigating BMI in women with BC have made the distinction between healthy and unhealthy plant-based diets. The assessment of the quality of plant-based food using three plant-based dietary indices (PDI, hPDI, and uPDI) is a fairly new concept and has been defined by Satija et al. [19, 22]. PDIs are numerical scores designed to measure adherence to an overall pattern of plant-based dietary patterns. These scores are designed to understand common dietary patterns that incorporate a range of progressively increasing proportions of plant foods while reducing the consumption of animal foods.

In an analysis of the combined data from the Nurses' Health Study I and II and the Health Professionals' Study, 3 ongoing US prospective cohort studies involving healthy women and men, three variations of plant-based diet indices (overall, healthful, and unhealthful), and weight fluctuations were investigated over 4-year intervals spanning more than 20 years. The authors found that different types of plant-based diet indices were associated with different amounts of weight gain or loss and that healthier plant-based diets were associated with less weight gain over 4-year intervals, whereas unhealthful plant-based diets were associated with greater weight gain during midlife [29].

A systematic review, summarizing findings from 9 prospective cohort studies of adults 18 years and older, without BC, on the association between the level of adherence to a plant-based dietary patterns and obesity risk, demonstrated that adherence to a plant-based diet, especially if rich in healthy plant foods, was associated with lower obesity risk, lower body adiposity, and better body weight management [18]. In this review, no significant association was found between the uPDI and the risk of overweight or obesity, but a positive association was observed with the risk of central obesity [18].

Another study demonstrated that adherence to a healthful plant-based diet was associated with favorable long-term changes in adiposity-related inflammatory and metabolic biomarkers concentrations in women [30]. Higher hPDI score was significantly associated with lower plasma concentrations of leptin, insulin, and higher plasma concentrations of adiponectin. On the other hand, a higher uPDI score was significantly associated with higher concentrations of leptin and insulin [30].

Findings suggest broad variations in nutritional quality of plant foods, with the healthier options showing higher levels of diet quality indicators, while the less healthy ones are poorer in quality [31]. The observations align with the results of a prospective cohort study conducted in a Mediterranean population, emphasizing the significant importance of considering the diverse nutritional quality of plant foods within plant-based diets, particularly for BC prevention [31]. Not all plant foods offer equal nutritional benefits, making it essential to prioritize fiber-rich, micronutrient-dense options like fruits, vegetables, whole grains, and legumes to maximize health benefits [31].

Within plant-based diets, carbohydrates play a major role, and their quality has been investigated in relation to body weight changes in a reanalysis of the 3 prospective cohort studies of the Harvard group, highlighting the importance of carbohydrate quality and source for long-term weight management [32]. These authors found that a 10 unit increase in glycemic index was associated with 1.2 kg greater weight gain, and a 100 g/day increase in starch or added sugar was associated with 1.5 kg and 0.9 kg greater weight gain, respectively, over four years. Conversely, a 10 g/day increase in dietary fiber was associated with

0.8 kg less weight gain. These associations were stronger among participants with overweight or obesity compared with those with normal weight and were also stronger among women than men [32].

Plant-based diets may have benefits beyond body weight control. They have also been associated with a lower risk of chronic diseases such as type 2 diabetes, CVD, and some cancers [19, 22]. Healthful plant-based dietary patterns have been directly associated with greater overall survival in BC survivors [23] as well as in healthy individuals, as the analyses of the large UK Biobank data on a quarter million women demonstrated [33].

Potential Mechanism

The possible inverse associations of a healthful plant-based dietary score with BMI in women with BC could be partly explained by higher intake of several beneficial components of plant-based foods, which may indicate a better diet quality compared to an unhealthy plant-based diet.

A diet high in healthful plant-based foods would be rich in dietary fiber, unsaturated fatty acids (MUFA and PUFA), antioxidants, and micronutrients such as calcium, magnesium, potassium, but low in SFA [22]. For example, vegetables and fruits are the main sources of fiber and antioxidants, nuts are rich in PUFA, soy and pulses are main sources of plant protein, and coffee and tea are rich in antioxidants, theaflavins and chlorogenic acid respectively [33, 34]. These food groups have been suggested to promote weight loss/maintenance, reduce adiposity, and potentially lower the risk of obesity through various pathways and intermediate factors, including satiety, inflammation, oxidative stress and gut microbiome modulation [18, 22, 34]. Studies have shown that dietary fiber increases satiation and satiety at a low caloric density and regulates lipid metabolism to reduce adiposity and promoting weight loss/maintenance [18], it is also associated with reduced levels of inflammatory markers [35]. High intakes of unsaturated fatty acids and low intakes of SFA in diets have also been shown to have anti-inflammatory properties [22]. In addition, plant-based dietary patterns have been shown to enhance insulin sensitivity, improve glycemic control, lower blood pressure, reduce long-term weight gain, and mitigate systemic inflammation [19, 21, 36], all factors linked to BC risk and recurrence [14, 11]. The abundance of antioxidants, vitamins, and polyphenols may confer antioxidant, anti-inflammatory, and antiproliferative benefits [37], and may also neutralize free radicals and prevent DNA damage [21]. BC survivors are at increased risk for low bone mineral density, loss of muscle mass, coupled with increased fat mass and increased metabolic syndrome rates, due in part to the treatments received [38]. Therefore, the high presence of minerals in health plant-based foods is important for BC survivors. Dietary calcium intake has an important impact on bone metabolism and bone health. Chronic calcium deficiency, resulting from inadequate intakes plays a role in reduced bone mass and osteoporosis [39]. In addition, a calcium-only intervention could have a marginal protective effect against cancer [40]. Magnesium is required for protein synthesis and essential for the regulation of muscular contraction [41]. Potassium intake lowers blood pressure and may impact muscle function, overall muscle health, and potentially contribute to the prevention of falls [42].

On the other hand, an unhealthy plant-based diet would have a higher glycemic index and glycemic load, reduced fiber which may lead to decreased satiety and increased hunger signals [22, 29]. This could adversely affect the pathways mentioned earlier, contributing to potential negative health outcomes. A diet that includes mainly animal foods and unhealthy plant foods like refined grains, potatoes, desserts and SSBs, tends to be richer in energy, in sodium, sugar, SFA, fast-release carbohydrates, and poorer in fiber, vitamin, minerals, antioxidants, flavonoids, and other beneficial phytocomponents [22, 31]. Moderate increases in usual glycemic index and glycemic load, starch, refined grains, added sugar, and starchy vegetables have been associated with more concurrent weight gain throughout midlife, particularly among individuals who are already obese or overweight [32]. Excessive consumption of carbohydrates from low-quality food sources (refined cereals, sweets and SSB), leads to fat storage and, over time, promotes insulin resistance [22]. Insulin resistance, in turn, contributes to additional fat storage and accumulation in the liver, further aggravating insulin resistance [18]. Moreover, a high intake of SFA from animal foods activates pro-inflammatory pathways, increasing oxidative stress and systemic inflammation, which perpetuates obesity [18]. High intake of SSBs, which are rich in added sugar, provides a significant amount of rapidly absorbable energy [43]. Consuming these liquid calories is associated with less satiety and an incomplete compensatory reduction in energy intake at subsequent meals, leading to overconsumption of total daily calories and potentially promote weight gain, contributing to an increased risk of general and abdominal obesity, type 2 diabetes, fatty liver disease, and metabolic syndrome [31, 43].

Implications

Investigating the relationship between weight control and dietary choices in BC survivors could have significant implications for public health, especially considering the substantial increase in overweight and obesity rates in more developed countries [44]. Preventing weight gain in BC survivors is crucial, not only for preventing the comorbidities associated with excess weight but also for enhancing patient quality of life and prognosis, while reducing the risks

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of recurrence and mortality [45, 46]. Chief among obesity determinants is diet that can be utilized for timely and sustainable interventions among individuals and populations. Healthful plant-based diets have been associated with lower BMI in women with BC, thereby increasing the potential for population-wide positive impact on survival. Adopting a healthful plant-based diet to improve body weight does not require a total elimination of animal foods, but instead a moderate decrease in the latter while avoiding unhealthy plant foods and increasing healthy plant-based food.

According to the American Cancer Society guidelines for cancer survivors, those who have finished the acute phase of treatment are encouraged to maintain a healthy weight, engage in regular physical activity, and adopt healthier dietary patterns [11]. High quality dietary patterns are generally characterized by a predominance of plant-based foods, including whole grains, vegetables, and fruits, and de-emphasize red, processed meat intake and refined grains [1]. These align with the recommendations for BC survivors, CVD prevention and health promotion. For BC, especially if diagnosed at an early stage, CVD is more common as a cause of death than cancer [47]. Following a healthful plant-based diet is also expected to help reduce the risk of other non-communicable diseases, such as diabetes and osteoporosis [11]. Additionally, plant-based diets are considered beneficial for planetary health [48]. Dietary recommendations focus on promoting moderate adherence to a healthful plant-based diet, along with the encouragement of consuming a variety of minimally processed, possibly locally produced, plant-based foods. This approach contributes to environmental sustainability and may have a lower environmental impact since plant-based food systems generally use fewer resources compared to those heavily reliant on animal foods [19, 21]. By adopting plant-based dietary patterns, individuals can improve not only their own health but also contribute to reducing the environmental impact of food production and consumption [48].

Adopting a plant-based diet without completely eliminating animal foods is preferable, as this approach allows for flexibility and enables individuals to make gradual adjustments to their eating habits. This also preserves "cultural traditions" that involve the moderate consumption of animal foods as in the Mediterranean diet. Moreover, excluding all animal foods may not be suitable for every demographic, as moderate intakes of animal products like fish, poultry, and fermented dairy have been associated with certain health benefits [49]. In contrast, exclusively plant-based diets may lead to deficiencies in essential nutrients, such as vitamin B12 and calcium [50]. From this standpoint, a healthy plant-based diet encourages a progressive shift towards a healthy vegetarian diet without the necessity of entirely removing a specific food group.

CONCLUSION

In conclusion, it is important to consider the quality of plant-based diets, as some may include vegetarian foods with a low nutritional profile which may negatively impact on body weight. Increased adherence to a healthful plant-based diet, which emphasized intake of high-quality plant foods such as whole grains, vegetables, fruits, and nuts, could be associated with lower BMI and an overall better quality of diet in women with BC. The findings suggest that the observed beneficial effects are attributed to the consumption of healthy plant-based foods while reducing the intake of unhealthy plant-based options and the balance with animal food sources. The international guidelines for BC survivors and the recent updated meta-analysis of international data emphasize the importance of body weight control and dietary fiber intake after BC diagnosis to reduce total mortality [1, 2, 3]. Increasing dietary fiber intakes translates into higher plant-based food consumption; however, increasing adherence to a plant-based diet requires knowledge to avoid the unhealthy vegetarian versions, which may be detrimental to body weight control, cardiometabolic risk, and BC prognosis. There is a need to educate the public on the quality of plant-based diets and the public food courts in governmental buildings, commercial centers, and schools. Additional research involving women with BC will be crucial for a better comprehension of the relationship between BMI and the distinction between healthy and unhealthy plant-based diets. Taking into consideration the quality of plant-based foods may be crucial in preventing weight gain, a risk factor for a poor BC prognosis and reduced survival.

Figure 1. Characteristics of the plant-based diet indices (PDI, uPDI, hPDI).

	Plant-based diet index (PDI)	Healthy plant-based diet index (hPDI)	Unhealthy plant-based diet index (uPDI)
Healthy plant foods  Whole grains, legumes, nuts, vegetables, fruits, vegetables oils, tea, coffee	↑	↑	↓
Less healthy plant foods  Refined grains, potatoes, fruit juices, sweets and desserts, sugar-sweetened beverages	↑	↓	↑
Animal foods  Animal fats, fish/seafood, eggs, dairy, meat	↓	↓	↓

PDI, hPDI, and uPDI are indices derived from the listed food groups. Each food group's consumption is assigned a positive (↑) or negative (↓) score based on the index of interest.

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Social and Environmental Factors Influencing COVID-19 Transmission and Mortalities in Developing and Developed Nations

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SUMMARY

Background: The study sought to establish environmental and social factors that influenced the transmission and mortalities of COVID-19 in developing and developed nations. The factors that were assessed included temperature, average age of the population, urbanization, population density, and percentage of old-aged people in the population. The dependent variables were COVID-19 transmission and COVID-19-related deaths.
Methods: The study employed a pragmatism research philosophy. It also relied on a deductive research approach and a descriptive research design. It adopted a mixed-method approach as it used both qualitative and quantitative data. It was a cross-sectional study, given its data measurement at a particular point in time. Data was analyzed and presented using descriptive techniques.
Results: Statistical analyses were conducted to quantify the relationships between various factors and COVID-19 outcomes. A Kendall's Tau test revealed a robust negative correlation between COVID-19 cases and temperature (Tb = -0.560, $p<0.005$). This result was further confirmed by Spearman's rank correlation, showing a strong negative correlation with $r(13) = -0.684$, $p<0.007$. Similarly, a strong negative correlation was observed between COVID-19 deaths and average annual temperature using both Kendall's Tau (Tb = -0.495, $p<0.014$) and Spearman's rank correlation ($r(13) = -0.648$, $p<0.012$). Age emerged as a significant factor, with a strong positive correlation found between age and both COVID-19 infections (Tb = 0.516, $p<0.010$; $r(13) = 0.670$, $p<0.009$) and COVID-19-related mortalities ($r(13) = 0.516$, $p<0.029$). Urbanization was also positively correlated with COVID-19 infections (Tb = 0.530, $p<0.008$; $r(13) = 0.640$, $p<0.014$) and COVID-19 deaths (Tb = 0.398, $p<0.048$; $r(13) = 0.561$, $p<0.037$). Interestingly, no significant correlation was found between population density and COVID-19 infections or deaths in both developed and developing countries, as evidenced by Kendall's Tau (TB = 0.331, $p<0.1$; Tb = 0.133, $p<0.511$) and Spearman's rank correlation ($r(13) = 0.425$, $p<0.130$; $r(13) = 0.161$, $p<0.583$), respectively. Moreover, the percentage of elderly individuals in a country exhibited a strong positive correlation with both COVID-19 infections (Tb = 0.464, $p<0.021$; $r(13) = 0.642$, $p<0.013$) and COVID-19-related deaths ($r(13) = 0.541$, $p<0.046$).
Conclusion: The study focused on social, demographic, and environmental factors influencing COVID-19 incidence and mortality in developing and developed nations. The study highlights significant COVID-19 transmission and mortality disparities between developed and developing countries. Developed countries exhibited higher infection and mortality rates, coupled with elevated death rates per million and infection rates per million, as compared to their developing counterparts. The research identified a correlation between lower average annual temperatures and increased mortality in developed countries. Contrary to this, high average annual temperatures were associated with a decline in COVID-19 infections.
Moreover, developed countries, characterized by higher urbanization levels, population densities, and percentages of aged individuals, experienced elevated COVID-19 infection rates. The study also unveiled a positive correlation between age and COVID-19 infections, with developed countries hosting signifi-

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cantly older populations than their developing counterparts. However, population density did not clearly correlate with COVID-19 infections or deaths.

Keywords: Medical Education; Competition; Young medical doctor; Medical specialities; Career choice.

INTRODUCTION

The outbreak of COVID-19 resulted in the infection of hundreds of millions of people globally and left millions of others dead. The COVID-19 pandemic had significant social and economic ramifications. However, the patterns of its effects in developed and developing countries significantly differed. At the earlier stages of the pandemic, predictions had been made that developing nations would be significantly more affected by the pandemic than developed countries. However, it became apparent that developed nations had higher disease prevalence and deaths than low-income countries [1]. Studies established that high-income countries had three times higher disease prevalence rates than low-income countries [1, 2]. The disparity has been linked to ecological and environmental factors such as average population age, average annual temperature in specific countries, population density, urbanization, and percentage of aged people in each country. Other studies have also mentioned the factors influencing COVID-19 transmission and mortality [3-5]. However, a critical limitation of our study is its reliance on country-reported data, which introduces a degree of uncertainty. Disparities in testing infrastructure among countries may contribute to an underestimation of the actual burden of COVID-19. Our findings illuminate a stark reality, with less than 20% of populations in developing countries having been tested for the virus. Our study brings to light the stark contrast in testing efforts between developed and developing nations, with the former conducting more extensive testing, thus providing a more comprehensive picture of the pandemic's impact.

Controlling for economic factors, it is evident that other factors influenced the disparities in infections and deaths from COVID-19 in high-income and low-income countries [6]. It is, therefore, significant to understand the factors that influenced the transmission of the disease and eventual deaths in both developed and developing countries. Several models suggested that environmental factors were responsible for the morbidities and mortalities of COVID-19, while other investigations point to social factors [6, 7]. Suggestions indicate that environmental and social factors influenced these disparities in the disease's transmission and fatalities [7]. However, there are contrasting findings in current investigations on the extent to which environmental and social factors influence the spread of the disease. Therefore, this study aims to investigate the following social and environmental factors, like temperature, population density, urbanization, average age, and the percentage of aged people in the population, influencing COVID-19 transmission and mortality in developing and developed nations.

MATERIALS AND METHODS

Theoretical perspectives

The study utilizes the transmission mechanism theory of disease dynamics [8]. Therefore, the theory seeks to help individuals understand a single-level interaction between a pathogen, an organism, and its environment. In the case of this study, the organisms are human beings. The theory has four significant assumptions. The first assumption asserts that infectious disease patterns result from two transmission models: direct transmission and environmental transmission processes. The direct transmission of disease is mediated through the direct contact of an infected individual with a vulnerable individual [8]. However, in environmental transmission, a disease is transmitted when a vulnerable individual comes into contact with an environment contaminated by an infectious pathogen. The direct transmission process of disease transmission focuses on the infectiousness of the disease host, such as the individual being mildly infectious, symptomatic, asymptomatic, or vaccinated [9].

The second assumption of the theory is that a communicable disease has seven primary levels of organization it can emanate at, in a hierarchical order from the simplest to the most complex: at the cell level, the tissue level, the organ, level, the microecosystem level, the organism level, the community level, and at the microecosystem level [8]. The third assumption is that the spread of an illness can be local through a pathogen or both local and global spread of the infectious agent [8]. The local spread of the infection is through direct contact between the vulnerable victim and the infectious agent. However, global transmission of the ailment happens when the infectious agents are transported by other agents like wind, which blows it over distances locally, nationally, regionally, or globally. The fourth assumption is that a virulent infection results from interactions between the host, the disease agent, and the environment [8]. This may help explain the relationship between high population density and COVID-19 infections and the influence of temperature on COVID-19 infections.

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Conceptual framework

The conceptual framework is based on the interactions between factors influencing COVID-19 infections and deaths. The factors that form the independent variables are average annual temperature, average population age in respective countries, percentage urbanization in respective countries, population densities in respective countries, and percentage of aged people in respective countries. The dependent variables are COVID-19 infections and COVID-19 deaths because the aforementioned independent variables influence them.

Research philosophy

The study relied on a pragmatism research design. The philosophy was selected for this study because it would help explain the interconnectedness of the issues under study [10]. Besides, it provided grounds for explaining the complex issue quickly because it accommodated both expected and unexpected results. Moreover, the pragmatism philosophy approach was ideal for the study as it provided avenues for generalizing the findings to a larger population.

Research approach

The study relied on a deductive research approach. The deductive approach was ideal for this study because it would enable using both observable phenomena and subjective meanings to help explain the study issue under study [11]. It allowed for the generalization of the research findings. Also, the approach was ideal as it would allow for mixed research approaches to help explain the phenomenon. Moreover, the deductive approach provided the ideal ground for testing the research theory.

Research design

The study employed a descriptive research design. The design was appropriate for this study as it provided grounds for an in-depth understanding of the issue. The design was also selected for this study as it enabled a comprehensive and accurate description of the issue under study by describing the trends and patterns that arose from the data [12]. Besides, the design was the best in describing the natural behavior of the target population in their various natural settings.

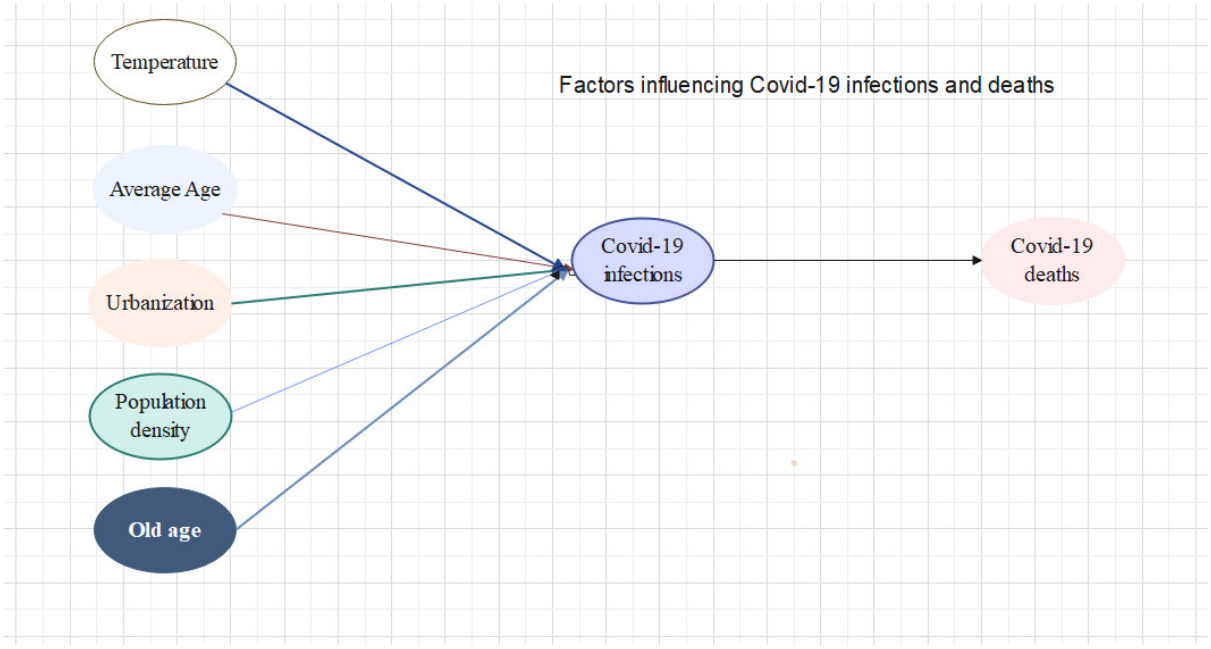
Research choice

The study was based on a mixed research choice. This is because it utilized both qualitative and quantitative approaches. The choice was appropriate for this study because quantitative or qualitative data alone was insufficient to explain the phenomenon, therefore calling for the use of both qualitative and qualitative data to understand the issue under study comprehensively [13]. This provided a broader perspective of understanding the complex issue being examined.

Time horizon

The study relied on a cross-sectional research approach. The approach was appropriate because the study needed more time and resources. As such, the approach would enable the completion of the study in a short time. Besides, the cross-sectional approach enabled the observation of the study phenomenon at

Figure 1: Factors influencing COVID-19 infections and deaths in developing and developed countries



a specific time [14]. It was also the best approach in analyzing data based on group differences, as the aim was to establish whether there were differences in developing and developed countries.

Study sample

The study population was all the countries affected by COVID-19, from developing and developed nations. The researcher used stratified sampling to get a sample for this study. Stratified sampling enabled the grouping of countries by region and economic strata of developing and developing countries. Based on this approach, the researchers selected developed countries from North America, Europe, and Asia as they are the only regions with developed nations. The researcher also used the stratified sampling approach to select six countries from South America, Africa, and Asia. The final sample comprised 14 countries, including the USA, the UK, Italy, Spain, Germany, South Korea, and Japan, for developed nations. Peru, Bolivia, Mozambique, Uganda, Kenya, India, and Cambodia represented developing nations.

The selection of our study sample was guided by a deliberate and thoughtful approach aimed at ensuring a meaningful and representative analysis of the diverse global landscape in the context of COVID-19. One aim was to strike a balance between the depth and manageability of our analysis. A smaller, more focused sample allowed for a thorough examination of each country's social and environmental factors, ensuring a comprehensive understanding of the nuanced relationships between these variables and COVID-19 outcomes. Including both developed and developing nations was intentional, enabling a comparative analysis that sheds light on the potential disparities in COVID-19 transmission and mortality between the two categories. Resource constraints, including time and data availability, played a role in determining the sample size. Analyzing a smaller set of countries allowed us to thoroughly examine and validate the data while adhering to practical limitations. This approach ensures a rigorous and focused analysis, enhancing the reliability and robustness of our findings.

Data collection approach

The researchers employed the secondary data collection approach. This is because data was accessed from already collected sources. To ensure data reliability, data was accessed only from revered sources, including the World Bank, the World Health Organization, and government websites. The researcher also collected quantitative and qualitative data from peer-reviewed journals, books, government websites, and other organization websites.

Data analysis

The collected data was checked for completeness and clarity before it was analyzed. It was then analyzed quantitatively using descriptive techniques that included means and cross-tabulations. The data was summarized and presented in table format. Using the data analysis tool IBM's SPSS, the researcher performed Spearman's rank correlation, Kendall's Tau test, and Pearson's moment correlations. The correlation approaches were selected because they enabled the establishment of the relationship between the variables besides indicating the direction of the relationship [15]. This enabled the establishment of relationships, or lack of it, between the environmental and social factors and the transmission of COVID-19 and death rates in developing and developed nations.

The utilization of the three distinct correlation coefficients, Kendall's Tau, Spearman's rank correlation, and Pearson correlation, reflects a deliberate choice to assess the relationships between various quantitative variables comprehensively. This decision was influenced by the nature of our data, which primarily consisted of numerical measurements of social and environmental factors across the selected countries. Kendall's Tau was employed to gauge the strength and direction of correlation between non-parametric variables. This coefficient is robust in handling data with ties and is particularly suitable for assessing associations between variables when the normality assumptions are unmet [16]. Given the diverse range of social and environmental factors considered in our study, Kendall's Tau offered a valuable tool for capturing relationships robustly and distribution-free.

Spearman's rank correlation complemented our analysis, offering an alternative non-parametric measure that assesses monotonic relationships between variables. This coefficient is particularly useful when dealing with ordinal data or situations where the assumption of linearity may not hold [16]. While our variables were primarily non-parametric, including Pearson correlation provided a helpful comparison. Pearson correlation is well-suited for detecting linear relationships between variables [17]. Its use allowed us to explore potential linear associations among the quantitative factors considered in our study, providing a comprehensive perspective on the nature of these relationships.

Research ethics

The study sought to observe the principles of ethical research. Firstly, the researcher sought the original researcher's consent to use data. Care was also taken to ensure that data used in the study was publicly available. Besides, the study ensured that there was no social profiling in the study by not referring to any region or its population in derogatory terms. However, it ensured objective reporting of the findings as they

ISSN 2282-0930 • Epidemiology Biostatistics and Public Health - 2023, Volume 18, Issue 2

were established. Besides, the principle of provenance was observed by first establishing the origin of the data accessed for this study before it was analyzed. Only data from authentic sources was employed to generate the findings [18]. To ensure anonymity and confidentiality, the researcher took all measures to ensure no subjects would be reidentified from the analysis outcomes. Finally, the researcher made the research findings available to the scientific community for critique by publishing the findings.

RESULTS

The study carried out a descriptive analysis of selected developed and developing countries. The data are summarized in Table 1. The study revealed that developed countries had the highest number of cases. In descending order, the most affected countries were the USA, Germany, Japan, Italy, the UK, Spain, Peru, Bolivia, Kenya, Mozambique, and Uganda. The tests established a significantly higher number of cases per million populations in the developed countries.

COVID-19 cases per million

The descriptive analysis revealed the COVID-19 cases in each country per million population. The cases in Germany were 461,467 per million population; in Italy, were 440,360; in the UK, 364,011; in the USA, 304,229; in South Korea, 665,885; and 294,201 in Spain. Therefore, although the USA had significantly higher infections overall, South Korea, Germany, the UK, and Italy had higher infections per million people. This could indicate that other variables influenced the higher infection rates in these countries compared to the USA. Besides, the findings reveal that about a third of the population in developed countries contracted COVID-19 infections.

This can be deciphered from Table 2, where three particular variables stand out: population density, average age, and percentage of older adults. While the USA has a population density of 35 people per square kilometer, the UK has 277, Spain 94, Italy 196, Japan 338, South Korea 516, and Germany 233. This would indicate that the higher population densities in these countries influenced higher infection rates among their populations. Secondly, while the USA has an average age of 39 years, the other countries have significantly higher average ages in their populations where the UK's average age is 41 years, Spain is 44 years, Italy is 46 years, Japan is 49 years, South Korea is 43 years, and Germany stands at 48 years. Thirdly, the USA has a lower percentage of old-aged people than the other developed nations. While the USA's percentage of old-aged people in its population stands at 17%, it is 19% in the UK, 20% in Spain, 23.5% in Italy, 29.8% in Japan, 17.5% in South Korea, and 22.3% in Germany.

In developing nations, COVID-19 cases are relatively low. In Kenya, there were 6,242 cases per million; in Mozambique, 6,886 cases per million; in Uganda, 3,535 cases per million; in Bolivia, 97,383 cases per million; Peru had 131,490 cases per million; India had 31,989; Cambodia recorded 8,200 cases per million. This indicates that less than 10% of the population in developing countries contracted COVID-19 infections. This is three times less than the infection rate in developed nations.

COVID-19 tests and their relation with COVID-19 Infections

The results for developing nations indicate that Kenya had a test rate of 71,997 tests per million, Mozambique carried out 40,449 tests per million, Uganda did 62,006 tests per million, Bolivia carried out 218,771 tests per million, Peru had 1,128,095 tests per million, India had 661,721 tests per million, and Cambodia had 182,440 tests per million. The results reveal that less than 20% of populations in developing countries were ever tested for COVID-19. While this does not influence infection rates, it helps to explain the lower infection rates officially reported, as some cases might have been underreported. Alvarez et al. (2023) state that developing nations recorded significantly low COVID-19 tests due to a lack of test kits and trained staff. The low testing rates would have led to missed cases and lower official cases being reported [19].

The study revealed that more tests were carried out in developed nations than in developing ones. The USA carried out 3.474,844 tests per million, Spain did 9,912,458 tests per million, the UK carried out 7,714,071 tests per million, Italy had 4,664,194 tests per million, and Germany had 1,468,671 tests per million. In comparison, Japan had 814,431 tests per million. The data reveals that other than Japan, people in developed nations underwent more than one test, with countries like Spain and the UK carrying out 9 and 7 tests per person, on average. The high test rates would correlate to the high COVID-19 cases established in these countries. Correspondingly, Van Gordon et al. [20] argue that the high testing rates of COVID-19 in developed countries partly indicated their higher COVID-19 cases compared to developing nations.

Death rates

The study compared mortality rates between developed countries and developing countries. As illustrated in Table 1, the USA had 3,315 COVID-19-related deaths per million population; the UK had 3,375 deaths per million population; Spain had 2,564 deaths per million population; Italy had 3,246 deaths per million population; Japan had 606 deaths per million population, South Korea had 1,451 deaths per million, while Germany had 2,101 deaths per million

Table 1: COVID-19 country specific data

	Population	COVID-19 cases	COVID-19 deaths	COVID-19 Tests	Infection Rate	Testing Rate	Mortality Rate
Kenya	55100586	343,918	5,689	3,967,062	6,242	71,997	103
Mozambique	33897354	233,417	2,243	1,371,127	6,886	40,449	66
India	1430687966	44,996,919	531,928	930,797,975	31,989	661,721	378
Uganda	48582334	171,729	3,632	3,012,408	3,535	62,006	75
Bolivia	12388571	1,206,420	22,399	2,710,261	97,382	218,771	1,808
Peru	34352719	4,517,034	221,364	38,753,114	131,490	1,128,095	6,444
Cambodia	16944826	138,940	3,056	3,091,420	8,200	182,440	180
USA	339996563	103,436,829	1,127,152	1,181,435,124	304,229	3,474,844	3,315
UK	67736802	24,656,914	228,622	522,526,476	364,011	7,714,071	3,375
Spain	47519628	13,980,340	121,852	471,036,328	294,201	9,912,458	2,564
Italy	58870762	25,924,308	191,118	274,584,632	440,360	4,664,194	3,246
Japan	123294513	33,803,572	74,694	100,414,883	274,169	814,431	606
Germany	83294633	38,437,756	174,979	122,332,384	461,467	1,468,671	2,101
South Korea	51777405	34,179,800	35,687	15,804,065	665,885	307,892	1451

population. Among the developing nations, Kenya had 103 deaths per million population, Mozambique had 66 deaths per million population, Uganda had 75 deaths per million population, Bolivia had 1,808 deaths per million population, Peru had 6,444 deaths per million population, India had 378 deaths per million, and Cambodia had 180 deaths per million population. Other than Peru, which had a significantly high death rate, the COVID-19-related death rates among developing countries were relatively lower than those in developed countries.

Demographic data of each country

The demographic data from each country was significant for this study as it provided independent variables that would have influenced the rate of COVID-19 infections and deaths. The data represents averages of the country's annual temperature, age, urbanization, population density, and percentage of older adults in the country as of the end of 2022. The data was obtained from the Worlddata.info website. The results are summarized in Table 2.

The study sought to establish whether temperature was linked to high COVID-19 infections and deaths. The study compared the average annual temperatures in both developed and developing countries. The study revealed that the USA had an average annual temperature of 10 °C, the UK had 9 °C, Spain had 14 °C, Italy had 12.44 °C, Japan had 12.4 °C, South Korea had 13.04 °C, and Germany had 9.5 °C. Comparatively, in the developing countries, Kenya had an average annual temperature of 26 °C, Mozambique had 25 °C, Uganda had 23 °C, Bolivia had an average annual temperature of 21 °C, Peru had 20 °C, India had 24.99 °C, and Cambodia had 27 °C. The outcome revealed that developing countries had higher average annual temperatures than developed countries. A correlation analysis in subsequent sections will seek further to explain the relationship between temperature and country-specific COVID-19 cases.

The study established that developing countries had relatively younger populations than developed countries. In developing countries, the average age was 20 years in Kenya, 17 years in Mozambique, 16 years in Uganda, 25 years in Bolivia, 29 years in Peru, 29 years in India, and 26 years in Cambodia. In the developed world, the average age was 39 years in the USA, 41 years in the UK, 44 years in Spain, 46 years in Italy, 49 years in Japan, 43 years in South Korea, and 48 years in Germany.

The study analyzed the urbanization levels in the targeted countries. It was revealed that developing countries had relatively low levels of urbanization. The urbanization rate in Kenya was 28%; in Mozambique, it was 37%; it was 25% in Uganda; 70% in Bolivia; 78% in Peru; India was 34.9% urbanized, while it was 24% in Cambodia. The developed countries were highly urbanized. The USA was 83% urbanized; the UK was 84% urbanized; Spain 81%; Italy 71.4%; Japan 91.7% urbanized; South Korea 81.4% urbanized; while Germany was 78%.

The study carried out an analysis of population density in the targeted countries. The population densities in developing countries were relatively low, except in Uganda, which had a population density of

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Table 2: Country specific demographic data

Country	Temperature (°C)	Average Age (Years)	Urbanization (%)	Population Density (people/km²)	Percentage of Old People (%)
Kenya	26	20	28	93	3
Mozambique	25	17	37	42	3
Uganda	23	16	25	201	2
Bolivia	21	25	70	11	5
Peru	20	29	78	27	8
Cambodia	27	26	24	94	6
India	24.99	29	34	435	6.9
USA	10	39	83	35	17
UK	9	41	84	277	19
Spain	14	44	81	94	20
Italy	12.44	46	71.4	196	23.5
Japan	12.4	49	91.7	338	29.8
Germany	9.5	48	78	233	22.4
South Korea	13.04	43	81.4	516	17.5

201 people/km²; in Kenya, it was 93 people/km²; in Mozambique, it was 42 people/km²; in Bolivia, it was 11 people/km², in Peru it was 27 people/km², in India it was 435 people/km², and in Cambodia it was 94 people/km². Other than the USA, with 35 people/km², the developed nations had relatively high population densities. The UK had a population density of 277 people/km², Spain had 94 people/km², Italy had 196 people/km², Japan had 338 people/km², South Korea had 516 people/km², and Germany had 233 people/km².

The study sought to establish the percentage of older adults in the targeted countries. The aged people were those aged 60 years and above. It was established that developing nations had significantly low percentages of aged people in their populations. Kenya had a composition of 3% of its population being aged, Mozambique had 3%, Uganda 2%, Bolivia had 5%, Peru had 8%, India had 6.9%, and Cambodia had 6%. Developed countries had higher percentages of their population ageing. In the USA, 17% of their population were aged, in the UK, it was 19%, Spain had a 20% aged population, Italy had 23.5% of its population, Japan had 29.8% of its population, South Korea had 17.5% while Germany's 22.4% of its population aged.

Discussion of the correlation analysis

Table 3 shows correlation analysis results for COVID-19 variables and Social/Environmental factors.

i) Infection Rate

As illustrated in Table 2, developing countries had significantly higher average temperatures than developed countries, yet lower COVID-19 cases. The study conducted a correlation analysis to establish the significance of the correlation between temperature and COVID-19 cases. Correlation analysis revealed a strong negative correlation between COVID-19 cases and average annual temperature, supported by both Kendall's Tau ($Tb = -0.560$, $p<0.005$) and Spearman's rank correlation ($r(13) = -0.684$, $p<0.007$). This suggests that higher temperatures are associated with a decline in COVID-19 infections, aligning with previous studies indicating a potential impact of climate on virus transmission. This affirmed that countries with higher temperatures had lower COVID-19 infections. Therefore, the high COVID-19 cases witnessed in developed nations would be correlated to the average lower temperatures the countries experienced. In contrast, the significantly lower COVID-19 cases in developing nations would partly be explained by their relatively high annual temperatures.

A positive correlation was established between age and COVID-19 infections, supported by both Kendall's Tau ($Tb = 0.516$, $p<0.010$) and Spearman's rank correlation ($r(13) = 0.670$, $p<0.009$). This indicates that for every unit increase in age, there is a corresponding rise in COVID-19 infections. Developed countries, characterized by higher elderly populations, exhibited higher infection rates. This underscores the vulnerability of older age groups to the virus. The results concluded that countries with lower average ages had lower COVID-19 infections while those with higher ages had higher COVID-19 infections. The demographic data in Table 2 indicates that developed countries had higher average ages than developing countries. A positive correlation was established between the percentage of older adults in a country and COVID-19 infections, supported by both Kendall's Tau ($Tb = 0.464$, $p<0.021$) and Spearman's rank

Table 3: Correlation analysis results

Variables	Correlation coefficient (r)	p-value
COVID-19 Cases vs. Temperature	-0.684	<0.007
COVID-19 Deaths vs. Temperature	-0.648	<0.012
COVID-19 Infections vs. Age	0.670	<0.009
COVID-19 Deaths vs. Age	0.516	<0.029
COVID-19 Infections vs. Urbanization	0.640	<0.014
COVID-19 Deaths vs. Urbanization	0.561	<0.037
COVID-19 Infections vs. Population Density	No Correlation	>0.1
COVID-19 Deaths vs. Population Density	No Correlation	>0.511
COVID-19 Infections vs. Percentage of Old People	0.642	<0.013
COVID-19 Deaths vs. Percentage of Old People	0.541	<0.046

correlation (r(13) = 0.642, p<0.013). The findings indicated that there was a related rise in COVID-19 infections for every unit rise in old age. As illustrated in Table 2, developed countries with higher proportions of elderly individuals recorded higher infection rates, emphasizing the vulnerability of this demographic. Developed nations were more vulnerable to COVID-19 infections than developing nations with relatively younger populations. This would help explain the high COVID-19 infections noted in developed countries compared to developing countries.

Urbanization demonstrated a positive correlation with COVID-19 infections, as indicated by both Kendall's Tau (Tb = 0.530, p<0.008) and Spearman's rank correlation (r(13) = 0.640, p<0.014). Developed nations with higher urbanization levels experienced elevated infection rates, emphasizing the role of population density and social interactions in virus transmission. Interestingly, no significant correlation was found between population density and COVID-19 infections. Both Kendall's Tau (TB = 0.331, p<0.1) and Spearman's rank correlation (r(13) = 0.425, p<0.130) indicated a lack of a clear association. This suggests that population density may not be a predominant factor influencing infection rates.

ii) Mortality Rate

Similar to infection rates, a negative correlation was observed between COVID-19 deaths and average annual temperature, supported by both Kendall's Tau (Tb = -0.495, p<0.014) and Spearman's rank correlation (r(13) = -0.648, p<0.012). This suggests that higher temperatures may contribute to lower mortality rates, aligning with the notion that milder climates may mitigate the severity of the disease. The results led to the conclusion that higher temperatures were partly responsible for lower COVID-19 cases witnessed in developing countries compared to the higher COVID-19 death rates in developed countries with relatively lower temperatures.

Positive correlations were established between age and both COVID-19 infections (r(13) = 0.516, p<0.029) and COVID-19 related mortalities (r(13) = 0.541, p<0.046). The increased mortality risk among older age groups is consistent with existing evidence, emphasizing the critical importance of age in understanding COVID-19 outcomes. This leads to the conclusion that older populations are more prone to COVID-19-related deaths. As illustrated in Table 2, developed nations have relatively older populations than developing nations.

Urbanization demonstrated a positive correlation with COVID-19 deaths, as indicated by both Kendall's Tau (Tb = 0.398, p<0.048) and Spearman's rank correlation (r(13) = 0.561, p<0.037). Higher urbanization levels in developed countries were associated with elevated mortality rates, reflecting the potential challenges in managing the pandemic within densely populated urban areas. The outcome indicates that an increment in urbanization would help explain the high number of COVID-19 deaths.

No significant correlation was found between population density and COVID-19 deaths, supported by both Kendall's Tau (Tb = 0.133, p<0.511) and Spearman's rank correlation (r(13) = 0.161, p<0.583). This suggests that, unlike infection rates, population density may not be a decisive factor influencing mortality rates. The findings would be explained by the stringent lockdowns that various nations imposed soon after the pandemic started to spread.

Positive correlations were established between the percentage of older adults in a country and both COVID-19 infections (r(13) = 0.642, p<0.013) and COVID-19-related deaths (r(13) = 0.541, p<0.046).

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This underscores the vulnerability of older populations not only to infection but also to more severe outcomes, emphasizing the need for targeted interventions for this demographic. This helps explain why countries like Germany, Italy, and Spain had higher death rates per million as compared to the USA, which had the highest infections.

SUMMARY AND CONCLUSIONS

Main findings of this study

The study was carried out to compare COVID-19 infections and deaths in developed countries and developing countries. The selected developed countries were the USA, UK, Spain, Italy, Germany, South Korea and Japan. The developing countries selected for this study included Kenya, Mozambique, Uganda, Bolivia, Peru, India, and Cambodia. Care was taken to select countries from every region globally. The results indicated that developed countries had higher COVID-19 infections and deaths than developing countries. They also had higher death rates per million and higher infection rates per million as compared to developing countries.

The study also reviewed demographic factors that would have influenced COVID-19 infections and deaths in developing and developed countries. The factors selected for this study were average age in the population; average annual temperature, percentage of urbanization in each country, population density, and percentage of old age in the country's population. The study revealed that developed countries had relatively lower temperature averages than developing countries. Developed countries also had higher urbanization levels, higher population densities, and high percentages of aged people.

The study established that high average annual temperature resulted in a decline in COVID-19 infections. This helped explain the low infection rates in developing countries with relatively high average annual temperatures. However, developed countries recorded high COVID-19 infections due to their relatively low average annual temperatures. The explanation for this was that high temperatures reduced the transmission of the COVID-19 virus and made it less severe in higher temperatures. The study also established that developed countries had higher mortality levels than developing countries due to their lower average annual temperatures.

The study established a positive correlation between age and COVID-19 infections, where a rise in average age also led to a rise in COVID-19 infections. Developed countries had significantly elderly populations compared to the relatively younger populations in developing countries. This helped explain the high COVID-19 infection rates in developed countries and low infection rates in developing countries. Older populations were also indicated to be more vulnerable to COVID-19 infections, which helped to explain the higher death rates in developed countries than in developing countries. Older people were found to have other comorbidities and weak immunities that compromised their resilience to COVID-19 infections.

The study established a correlation between urbanization and COVID-19 infections. It was revealed that the more urbanized a country is, the higher its COVID-19 infection rates. Developed countries had the highest urbanization levels and higher COVID-19 infection rates than the less urbanized developing countries. Urbanization was linked to high COVID-19 infections due to the attendant high population densities in such environments that led to the rapid spread of the disease. Urbanized areas were also linked to high infection rates due to their regional, global and local linkages as they served as transport hubs. Given similar reasons, urbanization and population density were linked to COVID-19 deaths where developed countries suffered more COVID-19 deaths than developing countries simply because urbanization had exposed them to higher infection rates that led to higher death rates.

The study did not establish any correlation between population densities and COVID-19 infections or deaths. This was linked to the stringent lockdowns that were imposed by various countries. The lockdowns helped to level out the influence of population densities in COVID-19 infections and deaths to a level that did not correlate by the end of the pandemic.

The study establishes a positive correlation between old age and COVID-19 infections. It was indicated that the higher the percentage of older adults in a given population, the higher the COVID-19 infection rates and deaths. Developed countries had higher percentages of aged people than developing countries; therefore, they had higher COVID-19 infections and deaths than developing countries. The explanation was that older people had other comorbidities, weak immunity, and were on other treatments that compromised their resilience against the COVID-19 virus.

Strengths of this study

The study had two major strengths. Firstly, it selected countries from every global region, providing a more comprehensive comparison than if countries had been selected from a given geographical region. The other strength was that the study relied on the latest COVID-19 statistics on infections and deaths as of May 2023, which means that the findings were more reliable as they covered the entire period of the COVID-19 pandemic. Also, the demographic data was based on data from the end of 2022, which was within the pandemic period. This helped eliminate errors on spurious data spikes before and after the pandemic.

Limitations of this study

However, the study had several limitations. Firstly, the sample size for the study was relatively small, as only 14 countries were selected, which would limit the generalization of the study findings. Secondly, the study relied on country-reported data. Therefore, the data may have disparities in its comprehensibility, especially among countries with limited testing capabilities that may have underreported actual cases. This was noted at the testing levels, where some developed countries had more than 800% testing levels above their populations.

In comparison, most developing countries had less than 10% testing levels of their populations. This may limit the accurate picture of actual morbidity and mortality rates, especially in the under-tested developing nations. Finally, the study focused on a cross-sectional difference in COVID-19 morbidities and mortalities at a given time. It did not investigate how and whether the independent variables influenced COVID-19 infections and deaths in specific countries. This would require a time series analysis model to explore the time lag influence of each factor in each country.

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