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Editorial

On the sectorization of psychiatric services

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Sectorization, the organizational principle of dividing the population into geographic sectors and developing all necessary public hospital and outpatient services within each sector, emerged as part of the broader movement to reform psychiatric services in Europe as early as the 1950s. In France, sectorization began in the 1960s through the joint management of hospitals and new outpatient services and was institutionalized by 1985 laws establishing sectors for 75,000 residents for adults and 150,000 for children and adolescents, today numbering 830 across the country.[1] Another form of sectorization evolved concurrently in the United Kingdom through the development of community psychiatry and later the establishment of mental health trusts.[2] Since then, sectorization has been adopted in most European countries,[3] while in some, like Belgium, community psychiatry has been linked to primary healthcare services.[4]

Sectorization aims to facilitate service accessibility and continuity of care, contributing to the reduction of hospitalizations and readmissions. International experience indeed shows that the implementation of sectorization has been associated with many achievements of community psychiatry[3] and that it has significant long-term positive outcomes for the users of mental health services in terms of functioning and met needs.[5]

In all countries, as expected, there was a gradual transition from the development of units with specific catchment areas to the full establishment of a sectorized system with administrative, managerial, and operational efficiency. In some countries, despite earlier declarations, its implementation progressed only in recent years, as in Portugal[6] and Greece.[7] Additionally, in recent decades, the expansion of community-based interventions has brought about complex problems in the liaison of various service units and the issues caused by the widening gap between growing needs and cuts in public funding.

In Greece, Law 2071/1992 and Framework Law 2716/1999 designated sectorization as the organizational principle of public psychiatric care, while Law 2716/1999 also introduced community mental health as a core principle. However, deinstitutionalization remained the central axis of the reform for a long time, rather than the development of community mental health units, and thus the implementation of sectorization lacked adequate support in practice.[7] In 2019, 38 adult sectors (11 in Attica) and 17 child and adolescent sectors (4 in Attica) were registered, accommodating populations of 250–300,000.[8] However, only a few sectors provide an adequate range of services. The deficiencies lead to bypassing sectorization, especially regarding hospitalizations, and widespread use of private services. This situation undermines continuity of care and contributes to relapses and high rates of involuntary hospitalizations, especially in Athens.

Mental health sectors in Greece include public hospitals and outpatient services as well as many residential and outpatient care units of NGOs. The lack of units' coordination, liaison, and synergy in each sector became evident with the failure of the Mental Health Sectoral Committees established by Law 2716/1999, which only had advisory roles. Law 4461/2017 provided for the establishment of managerial boards of mental health sectors within the health regions, and regional inter-sectoral councils were also established, but its implementation did not continue.

Sectorization has not solved the problem of readmissions so far. For example, in the Psychiatric Hospital of Attica, readmissions within one year currently range from 41% to 45% of total admissions.[9] Nevertheless, it highlighted the central role that community psychiatry can play in the prevention, treatment, and social integration of the most severe cases. However, for its completion, beyond administrative and managerial arrangements, it was necessary to address severe shortages in public services, particularly in hospital beds and staffing of mental health centers, so they could fully meet the various needs in each sector. Additionally, psychosocial rehabilitation interventions remained limited and practically not sectorized. During the pandemic and afterward, the weakening of public services continued, while most of the new projects were given to NGOs and mainly focused on specialized interventions, such as early intervention in psychosis, psychogeriatrics, and autism care. The entire process underscored the

urgency of a preliminary study of needs at a national level and by sector, as well as of advancements in coordination and liaison between different units.

The principle of sectorization was maintained in the 2021–2030 National Action Plan for Mental Health.[10] However, today we face an unprecedented administrative and organizational framework introduced by Law 5129/1.8.2024, which attempts two major shifts. First, it centralizes the management of all psychiatric services in the new Regional Management Board of Mental Health Services in each of the seven health regions. Second, it centralizes the management of all different services for addictions under a private-law entity called the National Organization for the Prevention and Treatment of Addictions. It, therefore, proposes a massive organizational reorganization entrusted to regional management in each health region while abolishing articles from previous laws on the sector-based organization.

It's worrying that these newly established boards will be in charge of all psychiatric units in a "mega-sector" with huge operational needs that didn't seem to have been planned for. Similarly, the immediate abolition of the organizational structures of major psychiatric hospitals in Attika and Thessaloniki without necessary provisions to address potential operational issues is troubling.

The effective operation of mental health service units cannot be achieved without specific catchment areas and a clear organizational structure. Thus, contributions from managerial and scientific leaders of various units, as well as from scientific and professional associations, are needed to provide substantive clarifications and amendments in implementing this new law in a manner consistent with the essence of sectorization.

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Άρθρο σύνταξης

Για την τομεοποίηση των ψυχιατρικών υπηρεσιών

ΙΣΤΟΡΙΚΟ ΑΡΘΡΟΥ: Παραλήφθηκε 1 Ιανουαρίου 2025/Δημοσιεύθηκε Διαδικτυακά 24 Μαρτίου 2025

Η τομεοποίηση, δηλαδή η οργανωτική αρχή της διαίρεσης του πληθυσμού σε γεωγραφικούς τομείς και η ανάπτυξη στον κάθε τομέα όλων των απαραίτητων δημόσιων νοσοκομειακών και εξωνοσοκομειακών υπηρεσιών, αναδείχθηκε εντός της ευρείας κίνησης αναμόρφωσης των ψυχιατρικών υπηρεσιών στην Ευρώπη ήδη από τη δεκαετία του 1950. Στη Γαλλία η τομεοποίηση ξεκίνησε από τη δεκαετία του 1960 μέσα από την κοινή διεύθυνση των νοσοκομειακών και των νέων εξωνοσοκομειακών υπηρεσιών και κατοχυρώθηκε με νόμους του 1985 που εγκαθίδρυσαν τομείς 75.000 κατοίκων για τους ενήλικους και 150.000 για τα παιδιά και τους εφήβους, σήμερα 830 σε ολόκληρη τη χώρα.[1] Μια άλλη μορφή τομεοποίησης εξελίχθηκε παράλληλα στο Ηνωμένο Βασίλειο με την εγκαθίδρυση της κοινοτικής ψυχιατρικής και στη συνέχεια τη δημιουργία των mental health trusts.[2] Έκτοτε η τομεοποίηση υιοθετήθηκε στις περισσότερες χώρες της Ευρώπης,[3] ενώ σε ορισμένες, όπως το Βέλγιο, η κοινοτική ψυχιατρική συνδέθηκε κυρίως με την πρωτοβάθμια φροντίδα υγείας.[4]

Η τομεοποίηση στοχεύει στην εξασφάλιση της προσβασιμότητας των υπηρεσιών και του συνεχούς της φροντίδας και κατά προέκταση συμβάλει στη μείωση των νοσηλειών και των επανεισαγωγών. Η διεθνής εμπειρία όντως δείχνει ότι συνδέθηκε με πολλά επιτεύγματα της κοινοτικής ψυχιατρικής, όπου εφαρμόστηκε[3] και ότι έχει σημαντικά θετικά μακροχρόνια αποτελέσματά στους λήπτες υπηρεσιών ψυχικής υγείας όσον αφορά τη λειτουργικότητά τους και την κάλυψη αναγκών.[5]

Σε όλες τις χώρες, όπως ήταν αναμενόμενο, παρατηρήθηκε μία σταδιακή μετάβαση από τη δημιουργία μονάδων με συγκεκριμένη περιοχή κάλυψης (catchment area) έως την πλήρη εγκαθίδρυση τομεοποιημένου συστήματος, με διοικητική, διαχειριστική και λειτουργική επάρκεια. Σε ορισμένες χώρες, παρά τις παλαιότερες εξαγγελίες μόνο τα τελευταία χρόνια τέθηκε το ζήτημα της εφαρμογής της, όπως για παράδειγμα στην Πορτογαλία[6] και στην Ελλάδα.[7] Επιπλέον, τις τελευταίες δεκαετίες η συνεχής διεύρυνση των παρεμβάσεων στην κοινοτική ψυχιατρική έκανε εμφανή τα σύνθετα προβλήματα στη διασύνδεση των διαφόρων υπηρεσιών και τα διαρκή προβλήματα που δημιουργεί το άνοιγμα της ψαλίδας μεταξύ διεύρυνσης αναγκών και περικοπών στη δημόσια χρηματοδότηση.

Στην Ελλάδα ο νόμος 2071/1992 και ο νόμος πλαίσιο 2716/1999 όρισαν την τομεοποίηση ως βασική οργανωτική αρχή της δημόσιας ψυχιατρικής φροντίδας, ενώ στον 2716/1999 προστέθηκε ως βασική αρχή η κοινοτική ψυχική υγιεινή. Κεντρικός όμως άξονας της μεταρρύθμισης παρέμεινε για μεγάλο διάστημα ο αποϊδρυματισμός και όχι η ανάπτυξη ανοιχτών κοινοτικών μονάδων και έτσι η τομεοποίηση δεν είχε επαρκή στήριξη στην πράξη.[7] Το 2019 καταγράφηκαν 38 τομείς ενηλίκων (11 στην Αττική) και 17 παιδιών και εφήβων (4 στην Αττική) και αυτοί της τάξης των 250–300 κάτοικων.[8] Λίγοι όμως τομείς διαθέτουν ένα στοιχειωδώς επαρκές σύνολο υπηρεσιών. Οι ελλείψεις οδηγούν στην παράκαμψη της τομεοποίησης, κυρίως σε ότι αφορά τις νοσηλείες, και στην ευρεία χρήση ιδιωτικών υπηρεσιών. Αυτή η κατάσταση υπονομεύει το συνεχές της φροντίδας και συμβάλει σε υποτροπές και σε πολυάριθμες ακούσιες νοσηλείες, κυρίως στην Αθήνα.

Στην Ελλάδα εντός των ψυχιατρικών τομέων σήμερα συναντούμε δημόσιες νοσοκομειακές και εξωνοσοκομειακές υπηρεσίες καθώς και πολλές μονάδες των ΜΚΟ, στεγαστικές και ανοικτές. Το πρόβλημα της έλλειψης συντονισμού, διασύνδεσης και συνέργειας των μονάδων του κάθε τομέα έγινε προφανές με την αποτυχία των Τομεακών Επιτροπών Ψυχικής Υγείας του νόμου 2716/1999 οι οποίες διέθεταν μόνο συμβουλευτικές αρμοδιότητες. Ο νόμος 4461/2017 πρόβλεψε τη σύσταση περιφερειακών διοικήσεων τομέων ψυχικής υγείας στις Υγειονομικές Περιφέρειες, συγκροτήθηκαν περιφερειακά διατομεακά συμβούλια, αλλά δεν συνεχίστηκε η εφαρμογή του.

Η τομεοποίηση δεν έλυσε μέχρι στιγμής το πρόβλημα των επανεισαγωγών. Για παράδειγμα, στο ΨΝΑ οι επανεισαγωγές εντός ενός έτους διακυμαίνονται σήμερα σε ποσοστά από 41% έως 45% του συνόλου των εισαγωγών.[9] Ανέδειξε όμως τον κεντρικό ρόλο που μπορεί να παίξει η κοινοτική ψυχιατρική στην πρόληψη, την παρακολούθηση και την κοινωνική ένταξη των σοβαρότερων περιστατικών. Ωστόσο, για την ολοκλήρωση της χρειαζόταν, πέρα από διοικητικές και διαχειριστικές ρυθμίσεις, να καλυφθούν οι σοβαρές ελλείψεις σε δημόσιες υπηρεσίες, ιδιαίτερα σε κλίνες και στελέχωση κέντρων ψυχικής υγείας, ώστε αυτές να ανταποκρίνονται στο σύνολο των αναγκών σε κάθε τομέα. Επίσης η ψυχοκοινωνική αποκατάσταση παρέμεινε περιορισμένη και ουσιαστικά διατομεακή. Τα χρόνια της πανδημίας και μετά συνεχίστηκε η αποδυνάμωση των δημόσιων υπηρεσιών ενώ τα περισσότερα νέα προγράμματα δόθηκαν σε ΜΚΟ και κυρίως για εξειδικευμένες παρεμβάσεις, όπως έγκαιρη παρέμβαση στην ψύχωση, ψυχογηρι-

ατρική, φροντίδα του αυτισμού. Το σύνολο της πορείας ανέδειξε την επείγουσα ανάγκη προκαταρκτικής μελέτης των αναγκών σε εθνικό επίπεδο και ανά τομέα, αλλά και οργάνωσης της διασύνδεσης μεταξύ των διαφορετικών μονάδων.

Στο Εθνικό Σχέδιο Δράσης για την Ψυχική Υγεία 2021–2030 διατηρήθηκε η αρχή της τομεοποίησης.[10] Ωστόσο, σήμερα βρισκόμαστε μπροστά σε μια πρωτόγνωρη διοικητικά και οργανωτικά νομική ρύθμιση με τον νόμο 5129/1.8.2024, που επιχειρεί δύο μείζονες τομές. Πρώτο, συγκεντρώνει τη διοίκηση όλων των ψυχιατρικών υπηρεσιών στις νέες Περιφερειακές Διοικήσεις Υπηρεσιών Ψυχικής Υγείας σε κάθε μία από τις επτά υγειονομικές περιφέρειες. Δεύτερο, συγκεντρώνει τη διοίκηση όλων των διαφορετικών υπηρεσιών του τομέα της απεξάρτησης στο ΝΠΙΔ που ονομάζεται Εθνικός Οργανισμός Πρόληψης και Αντιμετώπισης Εξαρτήσεων (ΕΟΠΑΕ). Επιχειρεί λοιπόν μία τεράστια διοικητική αναδιοργάνωση, την οποία εναποθέτει σε περιφερειακές διοικήσεις σε κάθε υγειονομική περιφέρεια, ενώ καταργεί τα άρθρα των προηγούμενων νόμων για την ισχύ της τομεοποίησης.

Δεν μπορεί παρά να γεννά προβληματισμό ότι οι νεοπαγείς αυτές διοικήσεις θα εποπτεύουν όλες τις ψυχιατρικές μονάδες σε έναν «μεγα-τομέα» με τεράστιες λειτουργικές ανάγκες που δεν φαίνεται να προβλέφθηκαν. Αντιστοίχως προβληματισμό προκαλεί η άμεση κατάργηση του οργανισμού των μεγάλων ψυχιατρικών νοσοκομείων, ΨΝΑ και ΨΝΘ, χωρίς τις αναγκαίες προβλέψεις για αντιμετώπιση των προβλημάτων λειτουργίας που μπορούν να προκύψουν.

Δεν μπορεί να υπάρξει ομαλή λειτουργία των μονάδων ψυχικής υγείας χωρίς συγκεκριμένο πληθυσμό αναφοράς και χωρίς σαφές οργανωτικό σχήμα. Γίνεται λοιπόν απαραίτητη η συμβολή των διοικήσεων και των επιστημονικών διευθύνσεων των διαφόρων μονάδων καθώς και των επιστημονικών/επαγγελματικών ενώσεων ώστε να υπάρξουν ουσιαστικές διευκρινίσεις και τροποποιήσεις κατά την εφαρμογή του νέου αυτού νόμου σύμφωνες με την ουσία της τομεοποίησης.

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Research article

Sleep quality and associated factors in teachers

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ABSTRACT

Sleep is an essential part of life, accounting for about one third of an individual's life expectancy and plays an important role in quality of life and professional performance. This study focuses specifically on primary school teachers, a group that often faces high levels of stress. Restorative sleep is vital for dealing with this stress, and when its quality is unsatisfactory, it can contribute to the development of burnout. The aim of the study was to assess the prevalence of poor sleep quality among state schoolteachers in Minas Gerais and to identify the factors associated with this condition. The cross-sectional study included 1,907 teachers who took part in a web survey. It included sociodemographic variables, work characteristics, lifestyle, and health conditions. The data was collected between October and December 2021, using validated instruments such as the Pittsburgh Sleep Quality Index (PSQI) to assess sleep quality. The results showed that 39.1% of teachers reported poor or very poor sleep quality. The main variables associated with poor sleep quality included working more than 40 hours a week (OR=1.618), low control over work (OR=1.235), professional dissatisfaction (OR=2.234), poor diet (OR=3.240), smartphone dependence (OR=2.265) and high fear of COVID-19 (OR=1.532). It was noted that mental health problems, such as anxiety (OR=1.728), were also significantly related to sleep quality. In addition, although sleep quality varied with age, older teachers had fewer sleep problems. The study suggests that working conditions and psychosocial factors play a crucial role in sleep quality, highlighting the importance of interventions that consider the specific needs of teachers. The recommendations include carrying out regular psychological assessments and applying sleep hygiene practices in order to mitigate these problems and improve the quality of life of this group.

KEYWORDS: Sleep quality, school teachers, public health.

Introduction

Human beings spend an average of one third of their lives sleeping, which is why personal satisfaction with the physiological experience of sleep is a fundamental characteristic of individuals that has a direct impact on their quality of life and work. Sleep should be restorative, re-establishing the body's basic functions and preparing it to face the challenges of everyday life.[1,2]

Regarding teachers, this aspect takes on considerable particularities, given that this is the professional category that suffers most from the repercussions of stress when compared to other professions.[3] Sleep is an important component of recovery from stress, and when it doesn't occur satisfactorily, it contributes to a condition known as Burnout.[4]

Factors of various kinds are associated with the quality of teachers' sleep,[5,6] but those that fall within a block of variables defined as working conditions seem to have a more direct impact on the experience of sleep. Aspects such as working hours, overtime, high de-

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mands, and low control over the work process seem to increase the likelihood of a negative sleep experience.[6]

The aim of this study was to estimate the prevalence of self-reported poor and extremely poor sleep quality and associated factors among public school teachers in the state of Minas Gerais, Brazil.

Material and Method

This study represents a cross-sectional (baseline) section of the ProfSMinas Project "Health and Working Conditions of Basic Education Teachers in the State of Minas Gerais: Longitudinal Study". This is an epidemiological, cross-sectional, analytical, web survey-type study conducted with basic education teachers from public schools in the state of Minas Gerais, Brazil.

Participants and procedures

Ensuring total control over the number of participants in the data collection is difficult as this is a web survey.[7] Even so, the sample size was calculated. A formula based on the prevalence of a disease or event was used, considering an infinite population, a prevalence of 50% of the event of interest, a tolerable error of 3%, with a 20% increase in sample size to compensate for losses (non-response rate). We therefore estimated the need to collect data from at least 1,282 teachers.

To compose the sample, the steps in the flowchart shown in figure 1 were followed. Only those who held a teaching position at the time of collection and who agreed to take part in the survey were included. Teachers who were not performing their teaching duties and those who had retired were excluded from the survey.

Data collection took place from October to December 2021. An online data collection form was made available to participants via the Google Forms platform, based on validated instruments/scales. The link to the form was provided by the State Department of Education SEE-MG via the teachers' institutional email. The teacher's SEE registration number was requested to avoid duplicate responses.

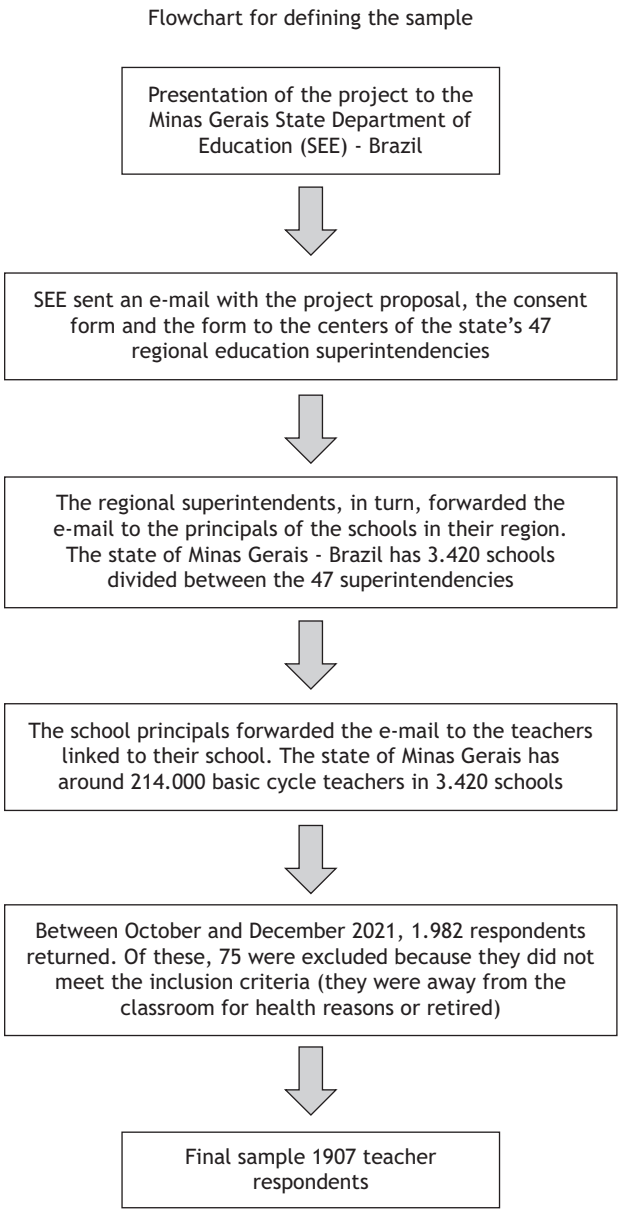

Figure 1. Flowchart defining the final sample of teachers taking part in the study.

Measures

The dependent variable "sleep quality" was obtained by answering the question, "During the last month, how would you rate the quality of your sleep in general?". This question was taken from the Pittsburgh Sleep Quality Index (IQSP),[8] and this procedure was based on the work of Kottwitz, who measured the quality of sleep among Swiss teachers.[6]

The independent variables were organized into four thematic blocks, inspired by adaptations of the theoretical models presented by Amaral (2017)[9] to investigate sleep quality and by Vieira et al (2020)[10] who considered the influence of teaching work on health outcomes.

The first block was made up of sociodemographic and economic characteristics: gender, age, self-declared skin color, area of work (whether rural or urban), marital status, family income, and whether they are the main breadwinner.

The second block was made up of work characteristics: weekly working hours, work shift, whether they had another job, type of employment relationship, and job satisfaction. The variables control over work, social support and psychological demand were assessed using the "Job Stress Scale", in its abridged version validated for Portuguese.[11]

The behavior and lifestyle variables made up the third block: alcohol consumption, smoking; dietary assessment, which used an instrument based on the Food Guide for the Brazilian population, containing 24 questions, with answers presented on a four-point Likert scale (0 to 3). The total score was categorized as up to 31 points=inadequate diet, between 31 and 41 points=needs modification, and above 41=healthy diet.[12] The question "physical activity habit for at least 6 months" was based on the transtheoretical model of behavior change for health, which proposes that change towards physical activity is divided into 5 stages. Subsequently, this question was dichotomized into insufficiently active/sedentary, covering the first four stages, and active, the last stage.[13–15] Smartphone dependence was measured using the SPAI-BR, which is a smartphone dependence screening instrument made up of 26 items with yes and no answer options. The total score is obtained from the sum of the items, ranging from 0 to 26 points, and the cut-off point must be 9 or more positive responses to identify addiction. The interviewees were then categorized as dependent or non-dependent.[16]

The fourth block presents the variables relating to clinical and health conditions: fear of COVID-19, obtained from the Fear of COVID-19 scale,[17,18] which is an instrument for investigating people's fear of COVID-19. The scale has 7 items that are answered on a Likert-type scale (1 to 5 points). The total score is obtained from the sum of the items (7 to 35 points), and the higher the score, the greater the fear. This variable was dichotomized into "a lot of fear" (cut-off point 27) and "little/moderate fear". Other variables in the block: self-rated health and quality of life,[19] medical diagnosis of depression and/or anxiety, symptoms of common mental disorder (CMD). CMD was measured using the Self Reporting Questionnaire (SRQ-20), which assesses elements relating to mental health. It is a questionnaire made up of 20 questions with dichotomous answers (yes or no) about the presence of physical and psychological symptoms in the last 30 days. The score ranges from 0 to 20 points. The cut-off point for classifying suspected CMD was set at 7 or more positive responses,[20] medical diagnosis of Chronic Non-Communicable Disease (CNCD), Body Mass Index (BMI), which was calculated from the teachers' self-reported weight and height and classified according to the World Health Organization,[21] and reports of back pain.

Statistical analysis

The data were analyzed using the Statistical Package for the Social Sciences, version 24.0®. Initially, a descriptive analysis was conducted on all the variables considered. Bivariate analyses were then conducted using Pearson's Chi-Square Test. Variables with a p value ≤0.25 in the bivariate analysis were selected for multiple modeling. Hierarchical ordinal logistic regression with proportional odds was used in the multiple models. The selected variables were entered into the multiple modeling grouped by thematic block, following the order in which the blocks were entered. The backward step method was then utilized to enter the variables into the partial models. The magnitude of the associations between the independent variables and the outcome was verified using Odds Ratios (OR) with a 95% confidence interval. The quality of the final model was assessed using the parallel lines test.

The first block to be included in the modeling was the socio-demographic variables, with the variables that were not contributing to the quality of the model's fit being removed one by one, to have a partially adjusted model. Next, the work characteristics block was introduced and proceeded in the same way, keeping, however, the socio-demographic variables that remained significant at the first stage. Then the third block was added, the behavioral and lifestyle variables, keeping what had remained significant in the first and second partial models. Finally, the block of variables related to clinical and health conditions was added, and the variables that lost significance within this block were removed. The parallel lines test was conducted at each stage to check that the principle of homogeneity of the slopes was not violated. The Odds Ratio (OR) of the independent variables that remained in the final model, their 95% confidence intervals, and descriptive level (p value) were estimated.

Ethical issues

The research was approved by the Research Ethics Committee of the State University of Montes Claros - Unimontes (Opinion 4.964.125/2021). All participants signed an informed consent form. This work was funded by the Minas Gerais State Research Foundation (FAPEMIG) under grant APQ-00901-22.

Results

A total of 1,982 forms were collected from basic education teachers in state schools in Minas Gerais. Of the forms collected, 75 were excluded because they did not meet the inclusion criteria. After this procedure, 1.907 forms were considered valid and were used in this study. State schools from 352 municipalities in Minas Gerais (41.3%) were represented. Of the total number of schools, the majority, 3,058 (89.4%), were in the urban areas of the municipalities.

The majority were women aged between 40 and 59. They are professionals who live on a monthly income of 3–5 minimum wages, are the main breadwinners in the household, and their marital status is defined as being in a union, self-declared white, and work mainly in urban areas (table 1). Regarding sleep quality, 29.5% of teachers rated their sleep quality as poor and 9.6% as very poor.

In the bivariate analysis, variables related to the working conditions of these teachers were associated with a poorer quality of sleep, such as working more than 40 hours a week, the type of employment contract, low control over work, low social support, low psychological demand, and job dissatisfaction (table 1).

Regarding behaviors and habits, inadequate diet or diet in need of modification, insufficient physical activity or sedentary lifestyle, and dependence on smartphones in the bivariate analysis were associated with poor or very poor sleep quality (table 1).

Regarding clinical and health conditions, in the bivariate analysis, increased fear of COVID-19 and poor/very poor self-rated health were associated with worse sleep quality. Some medical diagnoses were associated with a self-reported negative sleep quality condition in these teachers, such as diabetes, cardiovascular disease, reflux, respiratory problems, depression, anxiety, common mental disorder, and back pain (table 1).

Table 2 shows the final adjusted model in which variables from the four blocks remained. It can be seen that being female, the main breadwinner, working more than 40 hours a week, having little control over work, low social support, high psychological demand, dissatisfaction with work, having an inadequate diet or needing to change it, smartphone dependency, fear of COVID-19, poor or very poor self-rated health, anxiety, common mental disorder, and back pain significantly increased the chance of being in a worse sleep category. The body mass index was kept as an adjustment factor so as not to violate the assumption of homogeneity of slopes.

Discussion

The prevalence of self-reported poor and extremely poor sleep quality among the teachers in this study was 39.1%. Sleep-related problems in the Brazilian population were reported by 28.9% of individuals in a population-based study.[22] Freitas et al[23] identified a 61.3% proportion of poor sleep quality among higher education teachers. Silva et al[24] pointed to a 63.6% prevalence of poor sleep quality among medical students. Another study pointed out poor sleep quality in 64.3% of nurses in a hospital unit. Lima et al[26] found a 67% prevalence of loss of sleep quality among climacteric women, especially post-menopausal women. Machado et al reported sleep problems in the rural population of the municipality of Pelotas in southern Brazil.[27] In general, the teachers in this study seem to have worse sleep quality than the Brazilian population.

Regarding age, the study by Garjado et al[22] carried out with the Brazilian population shows that sleep quality worsens with advancing age. In this study, older teachers were less likely to be in a category of poorer sleep quality, a situation that points in the same direction as the study by Pereira et al[28] which found good subjective sleep quality in 73% of the sample of individuals over 60 years old. This suggests that with advancing age, the factors that negatively impact sleep quality seem to fade away, or the perceived condition becomes more resigned in the face of greater acceptance of limitations.[29]

Among women, there is also an increased chance of being in a category of poorer sleep quality compared to men. Lima et al[26] presented a group of proximal variables in relation to sleep quality in climacteric women, including intense climacteric symptoms such as hot flushes (PR: 1.18 95%CI: 1.10–1.27), and others such as anxiety (PR: 1.17 95%CI: 1.10–1.27), depression (PR: 1.08 95%CI: 1.01–1.15) and arthritis/arthrosis (PR: 1.07 95%CI: 1.01–1.14). Hypoestrogenism appears to be the most common physiological finding and seems to be implicated in the genesis of the condition that impacts sleep quality in women. Among the teachers investigated, there was a predominance of women (77.2%) who may be in the climacteric phase due to their age (61.5% between 40 and 59 years).

Being the main breadwinner in the household represented an increase in the chance of being in a worse

Table 1. Characterization of the sample and bivariate analysis for levels of sleep quality in public school teachers in the state of Minas Gerais, Brazil, 2021 (n = 1.907)

Variables	Characterization		Sleep Quality						p value
	N	%	Very good/ good	%	Bad	%	Very bad	%	
Socio-economic factors									
Age									
Up to 39 years*	627	32.9	356	56.8	209	33.3	62	9.90	0.047**
40 to 59 years	1173	61.5	730	62.2	328	28.0	115	9.80	
60 years and over	106	5.6	73	68.9	27	25.5	6	5.70	
Gender									
Male*	434	22.8	283	65.2	115	26.5	36	8.30	0.102**
Female	1473	77.2	877	59.5	449	30.5	147	10.0	
Area									
Rural*	202	10.6	139	68.8	51	25.2	12	5.90	0.031**
Urban	1705	89.4	1021	59.9	513	30.1	171	10.0	
Skin Color									
White*	1040	54.5	625	60.1	312	30.0	103	9.9	0.753
Non-White	867	45.5	535	61.7	252	29.1	80	9.2	
Income									
6 minimum wages or more*	342	17.9	202	59.1	109	31.9	31	9.1	0.201**
3 to 5	1089	57.1	647	59.4	332	30.5	110	10.1	
Up to 2	476	25.0	311	65.3	123	25.8	42	8.8	
Marital status									
With union*	1160	60.8	726	62.6	328	28.3	106	9.1	0.146**
Without union	747	39.2	434	58.1	236	31.6	77	10.3	
Main provider									
No*	765	40.1	481	62.9	221	28.9	63	8.2	0.170**
Yes	1142	59.9	679	59.5	343	30.0	120	10.5	
Work Condition									
Working hours									
< 40 hours per week*	1253	65.7	829	66.2	338	27.0	86	6.9	<0.001**
> 40 hours per week	654	34.3	331	50.6	226	34.6	97	14.8	
Night Shift									
No*	1348	70.8	838	62.2	387	28.7	123	9.1	0.151**
Yes	555	29.2	319	57.5	176	31.7	60	10.8	
Type of Relationship									
Permanent*	1096	57.5	594	54.2	364	33.2	138	12.6	<0.001**
Contracted/designated	811	42.5	566	69.8	200	24.7	45	5.5	
Other job									
No*	1277	67.0	785	61.5	367	28.7	125	9.8	0.515
Yes	630	33.0	375	59.5	197	31.3	58	9.2	
Control over work									
High*	982	51.5	553	56.3	305	31.1	124	12.6	<0.001**
Low	925	48.5	607	65.6	259	28.0	59	6.4	

Continues

Table 1. Continued.

Variables	Characterization		Sleep Quality						p value
	N	%	Very good/ good	%	Bad	%	Very bad	%	
Social Support									
High*	834	43.7	403	48.3	310	37.2	121	14.5	<0.001**
Low	1073	56.3	757	70.5	254	23.7	62	5.8	
Psychological demand									
High*	725	38.0	537	74.1	154	21.2	34	4.7	<0.001**
Low	1182	62.0	623	52.7	410	34.7	149	12.6	
Job satisfaction									
Satisfied*	1592	83.5	1048	65.8	432	27.1	113	7.1	<0.001**
Dissatisfied	315	16.5	112	35.6	133	42.2	70	22.2	
Behaviors/Habits									
Smoker									
No*	1583	83.0	938	62.1	450	28.4	150	9.5	0.066**
Yes	115	6.0	57	49.6	44	38.3	14	12.2	
Ex-smoker	209	11.0	120	57.4	70	33.5	19	9.1	
Alcoholism									
Never/almost never*	1274	66.8	795	62.4	364	28.6	115	9.0	0.134**
Monthly frequency (2x/month)	456	23.9	272	59.6	136	29.8	48	10.5	
Weekly frequency	177	9.3	93	52.5	64	36.2	20	11.3	
Nutrition									
Healthy*	971	50.9	708	72.9	217	22.3	46	4.7	<0.001**
Needs modification	738	38.7	385	52.2	265	35.9	88	11.9	
Inadequate	198	10.4	67	33.8	82	41.4	49	24.7	
Physical AtivAge									
Yes (active)*	286	16.9	194	67.8	73	25.5	19	6.6	0.023**
No (insufficient/sedentary)	1407	83.1	836	59.4	433	30.8	138	9.8	
Dependence on the smartphone									
No*	1554	81.5	1039	66.9	398	25.6	117	7.5	<0.001**
Yes	353	18.5	121	34.3	166	47.0	66	18.7	
Medical and health conditions									
Fear of COVID-19									
Little/moderate*	1313	68.9	898	68.4	330	25.1	85	6.5	<0.001**
A lot	594	31.1	262	44.1	234	39.4	98	16.5	
Self-assessment of health									
Excelent*	931	48.8	693	74.4	196	21.1	42	4.5	<0.001**
Regular	913	47.9	452	49.5	341	37.3	120	13.1	
Bad/poor	63	3.3	15	23.8	27	42.9	21	33.3	
Diabetes									
No*	1789	93.8	1104	61.7	519	29.0	166	9.3	0.007**
Yes	118	6.2	56	47.5	45	38.1	17	14.4	
Hypertension									
No*	1483	77.8	922	62.2	424	28.6	137	9.2	0.080**
Yes	424	22.2	238	56.1	140	33.0	46	10.8	

Continues

Table 1. Continued.

Variables	Characterization		Sleep Quality						p value
	N	%	Very good/ good	%	Bad	%	Very bad	%	
Cardiovascular disease									
No*	1830	96.0	1129	61.7	528	28.9	173	9.5	0.001**
Yes	77	4.0	31	40.3	36	46.8	10	13.0	
Reflux									
No*	1574	82.5	1020	64.8	418	26.6	136	8.6	<0.001**
Yes	333	17.5	140	42.0	146	43.8	47	14.1	
Respiratory issues									
No*	1459	76.5	956	65.5	382	26.2	121	8.3	<0.001**
Yes	448	23.5	204	45.5	182	40.6	62	13.8	
Depression									
No*	1658	86.9	1091	65.8	455	27.4	112	6.8	<0.001**
Yes	249	13.1	69	27.7	109	43.8	71	28.5	
Anxiety									
No*	1171	61.4	880	75.1	244	20.8	47	4.0	<0.001**
Yes	736	38.6	280	38.0	320	43.5	136	18.5	
Common mental disorder									
Absent*	1222	64.1	982	80.4	212	17.3	28	2.3	<0.001**
Present	685	35.9	178	26.0	352	51.4	155	22.6	
BMI									
Eutrophic*	654	34.7	411	63.7	173	26.8	61	9.5	0.075**
Overweight	746	39.1	459	61.5	221	29.6	66	8.8	
ObesAge	466	24.4	259	55.6	155	33.3	53	11.2	
Back pain									
No*	646	33.9	545	84.4	81	12.5	20	3.1	<0.001**
Yes	1261	66.1	615	48.8	483	38.3	163	9.6	

* Reference category

** Variable with p-value ≤0.25 for the multiple model

sleep category (OR=1.243). Moreira et al[30] found a prevalence of worse IQSP scores (5.96) in women compared to men (3.90) and attributed this finding to the overload of work performed by women (mother/housewife and professional). One study pointed to a disadvantage in the living conditions and health of female teachers who were the main breadwinners compared to female co-braeadwinners,[31] and economic responsibility for the household may be implicated in this association. In the period of this study, there was an association between reduced income among public school teachers and difficulty sleeping (PR=1.21 p<0.001).[32]

Work-related psychosocial aspects associated with sleep quality were pointed out by Kottwitzi et al,[6] such as emotional dissonance, social exclusion, and the experience of failure in school. Freitas et al[23] listed the most frequent complaints of teachers: the need to maintain more than one employment relationship and high psychological demands with low control over work. These characteristics were strongly associated with the outcome of poor sleep quality.

This set of factors seems to point to a common mechanism, stress, which triggers organic reactions engendered by adrenaline and noradrenaline, which in turn modulates a state of continuous alertness, preventing the relaxation necessary for restful sleep. In addition, the elevated level of cortisol promotes an organic environment of oxidative stress. With prolonged exposure

Table 2. Hierarchical ordinal logistic regression model for predictor variables of sleep quality Age in public school teachers in the state of Minas Gerais, Brazil, 2021 (n = 1.907)

Variable	Models							
	Model 1		Model 2		Model 3		Model 4	
Socio-economic factors	OR [IC95%]	P-value						
Age								
Up to 39 years*	1							
40 to 59 years	0.808 [0.666-0.979]	0.030						
60 years and over	0.577 [0.373-0.893]	0.014						
Gender								
Male*	1							
Female	1.294 [1.037-1.615]	0.023						
Main supplier								
No*	1							
Yes	1.243 [1.031-1.498]	0.023						
Work Condition			OR [IC95%]	P-value				
Working hours								
< 40 hours per week*			1					
> 40 hours per week			1.618 [1.324-1.977]	<0.001				
Type of relationship								
Civil service employee*			1					
Hired/designated			0.685 [0.559 -0.840]	<0.001				
Control over work								
High *			1					
Low			1.235 [1.015-1.503]	0.034				
Social support								
High *			1					
Low			1.598 [1.299-1.965]	<0.001				
Psychological demand								
Low*			1					
High			1.868 [1.509-2.312]	<0.001				
Job satisfaction								
Satisfied*			1					
Dissatisfied			2.234 [1.720-2.902]	<0.001				
Behaviors/Habits								

Continues

Table 2. Continued.

Variable	Models				
	Model 1	Model 2	Model 3		Model 4
Nutrition			OR [IC95%]	P-Value	
Healthy*			1		
Needs modification			2.008 [1.625-2.481]	<0.001	
Inadequate			3.240 [2.343-4.479]	<0.001	
Dependence on the smartphone					
No*			1		
Yes			2.265 [1.785-2.875]	<0.001	
				OR [IC95%]	P-Value
Medical and health conditions					
Fear of COVID-19					
Little/moderate*				1	
A lot				1.532 [1.220-1.925]	<0.001
Self-assessment of health					
Excelente/Good*				1	
Regular				1.413 [1.120-1.783]	0.004
Bad/Poor				2.711 [1.567-4.690]	<0.001
Anxiety					
No*				1	
Yes				1.728 [1.365 -2.188]	<0.001
Common mental disorder					
Absent*				1	
Present				4.413 [3.388-5.747]	<0.001
Back pain					
No*				1	
Yes				2.029 [1.526-2.697]	<0.001
BMI					
Eutrophic*				1	
Overweight				0.936 [0.727-1.203]	0.604
Obese				1.074 [0.810-1.417]	0.627
*Reference category					

to this biophysical state, the individual will soon reach a state of physical and psychological exhaustion.[33]

Two behaviors/lifestyle habits remained strongly associated with poorer sleep quality: poor diet (OR: 3.240) and smartphone dependence (OR: 2.265). In a study conducted in South Korea at a sleep clinic, participants considered to be more stressed consumed more grains, meat, and eggs, and had poorer sleep quality compared to less stressed participants who consumed more vegetables and had better sleep quality (p=0.023).[34] In another study, higher protein intake in weight loss diets was associated with better sleep quality in North American adults.[35] North American data shows that there is a scarcity of studies on the impact of diet on sleep.[34]

Smartphone addiction reduced sleep time among adolescents from public schools in northeastern Brazil (OR=0.715–95%CI: 0.538–0.949).[36] A study conducted in Indonesia, also among adolescents, showed a positive correlation between smartphone use at night and sleep disorders (r=0.374).[37] Exposure to screen light is a factor that acts as a signal to the circadian timing system, which mimics daylight conditions by sending information that it is still daytime. This impairs the release of melatonin, which has an impact on sleep latency.[22] Smartphone addiction is a problem that has become very prominent today and deserves attention and measures aimed at the rational use of this device.

In the set of variables related to clinical aspects, fear of COVID-19 was a factor that increased the chance of being in a worse sleep category (OR=1.532 95%CI 1.220–1.925). According to Barros et al[38] anxiety triggered by the fear of acquiring the disease could be at the root of sleep disorders or aggravate previous ones. In relation to self-rated health, the more negative the self-perception, the greater the chance of being in a worse category of poor/extremely poor sleep quality. Garbin et al[39] point out that negative self-rated health is more related to disability than established chronic or acute illnesses. The individual considers their health condition to be bad to the extent that they are unable to conduct certain activities, i.e. the limitation(s) imposed by a health condition seem to have an impact on sleep quality.

Back pain remained associated with the chance of being in the worst sleep category [OR=2.029 (1.526–2.697)]. Alves et al[40] identified an association between severe chronic pain (6 months or more) and worse sleep quality among elderly people assisted by the Family Health Units of a municipality in São Paulo. Machado et al[41] observed the presence of back pain strongly associated with poorer quality of life among university professors, and this included repercussions on sleep. Two factors are correlated: ergonomics and working hours outside of class. Ergonomics in schools seems to be an unsolvable issue, given that chairs, tables, and blackboards are usually standardized in classrooms.

CMD among primary school teachers in Uberlândia was studied by Machado and Limongi.[42] The authors found a prevalence of 43.9% of CMD and among the related factors were the use of medication to sleep, being female, and psychological/moral violence in the school territory practiced by students towards teachers. In this study, the issue of sleep is part of a set of symptoms that point to the onset of CMD. These authors recommend frequent psychological assessment of teachers.

The multiple hierarchical ordinal logistic regression model revealed the influence of certain variables on the probability of being in a category of poorer sleep quality when compared to other individuals from the same population who do not have the factor in question. The grouping of these variables showed that the influence can be proximal or distal as we include or remove blocks of variables.

Face-to-face classes were suspended until the middle of the second semester of 2021, when they gradually began to be resumed in basic education in Brazil, when the data for this study was collected.

This study has some limitations. The fact that exposure and outcome were observed at the same time limits its inferences of causality, but this is a limitation of the cross-sectional design. Furthermore, as it is a web survey, there is no sample control by the researchers, and it is a self-report. However, the size of the sample obtained by the return of respondents to the instrument makes generalizations feasible.

New longitudinal approaches should be carried out in order to better understand the relationship between exposure and outcome with regard to teachers' sleep quality, as well as to provide public policymakers with information on how to intervene in the factors associated with poorer sleep quality, either by minimizing and/or eliminating such predictors. In this direction, some aspects are emerging, such as the psychological assessment of teachers, which should be considered within the scope of periodic examinations, which currently take into account the approach of speech therapy and clinical medicine. In addition, recommenda-

tions regarding sleep hygiene should be administered. These are some strategies for improving teachers' quality of sleep and quality of life.

This study indicates that there is a significant proportion of public elementary school teachers in the state of Minas Gerais with self-reported poor and very poor sleep quality, which may have been determined by sociodemographic variables, habits and behaviors, clinical and health conditions, and, above all, working conditions that need to be monitored more closely.

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Ερευνητική εργασία

Ποιότητα ύπνου και σχετιζόμενοι παράγοντες σε δασκάλους

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ΠΕΡΙΛΗΨΗ

Ο ύπνος είναι ένα ουσιώδες μέρος της ζωής, αποτελώντας περίπου το ένα τρίτο του προσδόκιμου ζωής ενός ατόμου και παίζοντας σημαντικό ρόλο στην ποιότητα ζωής και την επαγγελματική απόδοση. Η παρούσα μελέτη επικεντρώνεται συγκεκριμένα στους δασκάλους της πρωτοβάθμιας εκπαίδευσης, μια ομάδα που συχνά αντιμετωπίζει υψηλά επίπεδα στρες. Ο αναζωογονητικός ύπνος είναι ζωτικής σημασίας για την αντιμετώπιση αυτού του στρες και, όταν η ποιότητά του είναι μη ικανοποιητική, μπορεί να συμβάλει στην εμφάνιση επαγγελματικής εξουθένωσης. Σκοπός της μελέτης ήταν να εκτιμηθεί η επικράτηση της κακής ποιότητας ύπνου μεταξύ των δασκάλων δημόσιων σχολείων στην πολιτεία Minas Gerais και να εντοπιστούν οι παράγοντες που σχετίζονται με αυτήν την κατάσταση. Η συγχρονική μελέτη περιλάμβανε 1.907 δασκάλους που συμμετείχαν σε διαδικτυακή έρευνα. Συμπεριέλαβε κοινωνικοδημογραφικές μεταβλητές, χαρακτηριστικά εργασίας, τρόπο ζωής και συνθήκες υγείας. Τα δεδομένα συλλέχθηκαν μεταξύ Οκτωβρίου και Δεκεμβρίου 2021, χρησιμοποιώντας επικυρωμένα εργαλεία, όπως ο Δείκτης Ποιότητας Ύπνου του Πίτσμπουργκ (PSQI), για την αξιολόγηση της ποιότητας του ύπνου. Τα αποτελέσματα έδειξαν ότι το 39,1% των δασκάλων ανέφεραν κακή ή πολύ κακή ποιότητα ύπνου. Οι κύριες μεταβλητές που σχετίζονταν με την κακή ποιότητα ύπνου περιλάμβαναν εργασία άνω των 40 ωρών την εβδομάδα (OR=1,618), χαμηλό έλεγχο στην εργασία (OR=1,235), επαγγελματική δυσαρέσκεια (OR=2,234), κακή διατροφή (OR=3,240), εξάρτηση από το smartphone (OR=2,265) και έντονο φόβο για την COVID-19 (OR=1,532). Παρατηρήθηκε επίσης ότι τα προβλήματα ψυχικής υγείας, όπως το άγχος (OR=1,728), σχετίζονταν σημαντικά με την ποιότητα του ύπνου. Επιπλέον, παρόλο που η ποιότητα του ύπνου διέφερε ανάλογα με την ηλικία, οι μεγαλύτεροι σε ηλικία δάσκαλοι παρουσίαζαν λιγότερα προβλήματα ύπνου. Η μελέτη υποδεικνύει ότι οι εργασιακές συνθήκες και οι ψυχοκοινωνικοί παράγοντες διαδραματίζουν κρίσιμο ρόλο στην ποιότητα του ύπνου, υπογραμμίζοντας τη σημασία παρεμβάσεων που λαμβάνουν υπόψη τις συγκεκριμένες ανάγκες των εκπαιδευτικών. Οι συστάσεις περιλαμβάνουν τη διενέργεια τακτικών ψυχολογικών αξιολογήσεων και την εφαρμογή πρακτικών υγιεινής του ύπνου, με σκοπό τη μείωση αυτών των προβλημάτων και τη βελτίωση της ποιότητας ζωής αυτής της ομάδας.

ΛΕΞΕΙΣ ΕΥΡΕΤΗΡΙΟΥ: Ποιότητα ύπνου, δάσκαλοι, δημόσια υγεία.

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Research article

Death anxiety, life's meaninglessness, and mental resilience among women with symptoms of behavioral addictions and alcohol use disorder: Using the existential approach

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ABSTRACT

In recent decades, a growing body of research has emphasized the unique nature of substance abuse among women, necessitating a gender-specific approach and thus individualized therapeutic interventions.The purpose of this study, based on the existential approach, was to examine whether symptoms of several behavioral addictions (shopping, sex, gambling and betting, eating) and alcohol use disorder correlate with death anxiety, lack of meaning in life, and levels of mental resilience in a convenience sample of women. A total of 3,176 women participated in this online study and completed a ddemographic ccharacteristics' qquestionnaire, the Shorter PROMIS Questionnaire (SPQ), the Meaning in Life Questionnaire (MLQ), the Connor-Davidson Resilience Scale (CD-RISC), and the Death Anxiety Scale (DAS).The results showed a significant negative correlation between the "Presence of meaning in life" subscale and all addiction symptoms subscales (shopping, $p<0.001$; sex, $p<0.001$; gambling and betting, $p=0.006$; food, $p<0.001$, and alcohol use, $p<0.001$). Conversely, the "Search for meaning in life" subscale showed a significant positive correlation with all addiction symptoms subscales (shopping, sex, gambling and betting, food, and alcohol use, $p<0.001$). Resilience emerged as a protective factor, showing significant negative correlations with symptoms of sex addiction ($p<0.001$), alcohol use disorder ($p<0.001$), shopping addiction ($p<0.001$), and food addiction ($p<0.001$) addiction, although the correlation coefficients were small (ranging from −0.07 to -0.21), indicating a weak or no correlation. Participants with higher death anxiety also showed more symptoms of gambling and betting addiction ($p<0.001$), shopping addiction ($p<0.001$), and food addiction ($p<0.001$). Women who were married and had a university degree showed fewer symptoms of sex addiction ($\beta=-0.079$; $p=0.004$ / $\beta=-0.118$; $p=0.001$), alcohol use disorder ($\beta=-0.105$; $p=0.011$ / $\beta=-0.158$; $p=0.004$), and gambling addiction ($\beta=-0.055$; $p<0.001$ / $\beta=-0.091$; $p<0.001$), while women aged 18-25 displayed significantly lower symptoms of shopping and food addiction. Marriage and higher levels of education emerged as protective factors against certain types of addictive behaviors. In conclusion, this research showed a meaningful relationship between the lack of meaning in life and death anxiety with the manifestation of behavioral addiction symptoms and alcohol use. Also, the presence of mental resilience may act as a protective factor against gambling and betting addiction, shopping addiction, and food addiction, but not against sex addiction and alcohol use disorder.

KEYWORDS: Addiction, behavioral addictions, alcohol use disorder, death anxiety, meaning in life, mental resilience, existentialism.

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Introduction

Addiction is a complex phenomenon, viewed from many perspectives, including hereditary influences, moral frailty, social pathology, and neurophysiological and psychopathological dimensions.[1] Within this framework, addiction is understood as a psychopathological phenomenon that emphasizes the interactive dynamics and relationship of the individual with his or her environment.[2]

There has been a great deal of research on behavioral addictions,[3] focusing on online gambling and betting,[4] shopping,[5] sex,[6] and food consumption.[7] These behaviors, like alcohol and substance use, significantly activate the reward system,[8] alter self-perception and provide an escape from psychological distress. However, the long-term consequences often include increased feelings of shame, pain, and decreased self-esteem.[9]

Gender differences as risk factors for addictive behavior reflect a complex interplay of biological, psychological, and social influences. A review focusing on addiction in animal models suggests that the transition from initial exposure to dependence is more rapid in females than males, which may also be based on biological and psychosocial factors.[10] In addition, females have been shown to be more susceptible to addiction and relapse following stress-related cues, particularly in the presence of a history of trauma, whereas males are more sensitive to stimulus-related cues such as paraphernalia.[11] Coping mechanisms also differ between genders. Men are more likely to use substances to cope with external stressors, while women are more likely to engage in compulsive behaviors to cope with internal stressors.[12] Furthermore, women may face unique challenges related to hormonal factors that contribute to their increased susceptibility to addiction.[13] Additionally, internalizing disorders, such as depression and anxiety, are more prevalent among women, contributing to behaviors such as compulsive shopping or pathological eating behaviors.[14] Accordingly, pathological women gamblers are more likely to engage in gambling activities as a means of coping with emotional distress, particularly in the context of depression and other forms of emotional discomfort, than their male counterparts.[15] It is also possible that socioeconomic factors may exert an influence on gender differences. It has been proposed that social norms may act as a deterrent to gambling among women, which could explain the lower prevalence of problem gambling among the female population. Of note, research conducted in the Greek population demonstrated that the onset of problem gambling was exclusively observed in women during the period of economic recession.[16] This association may be attributed to a sustained increase in the prevalence of depression in Greece because of the economic crisis,[17,18] coupled with women's inclination to engage in gambling as a means of alleviating depressive feelings.[19,20]

The existential approach suggests that substance abuse initially serves as a coping mechanism for individuals struggling with existential anxiety, including the absence of meaning in life, the inevitability of death, issues related to individual freedom, existential loneliness, and personal responsibility regarding their choices in life.[21] Tomer and Eliason's theoretical model (1996) posits a link between death anxiety and past- and future-related regrets, indicating that the anticipation of premature death intensifies feelings of guilt for unfulfilled aspirations.[22] Furthermore, research has demonstrated a positive correlation between a sense of meaning in life and overall well-being, life satisfaction, perceived life control, and mental health.[23–27] Conversely, the absence of meaning has been linked to the development of mental disorders.[28] Other studies have also shown that individuals who exhibit better resilience following psycho-traumatic experiences are more likely to find meaning in those experiences,[29] process them emotionally,[30,31] understand them,[32] accept and transform the negative aspects of the experience by enhancing their positive emotions,[33,34] thereby avoiding seeking consolation in alcohol and behavioral addictions.

The intricate interplay between gender, behavioral addictions, and substance use disorders represents a crucial area for further investigation. Accordingly, the present study, from an existential perspective, examines the relationship between various behavioral addiction symptoms and alcohol use disorder symptoms with death anxiety, the absence of meaning in life, and mental resilience in the female population.

The objective of this study was twofold: firstly, to examine the association between death anxiety, lack of meaning in life, and mental resilience in women with symptoms of behavioral and alcohol use disorder; and secondly, to investigate the predictability of death anxiety, life meaninglessness, and resilience on symptoms of addictions among women. It was hypothesized that (i) there is a positive correlation between death anxiety, life meaninglessness and behavioral addictions and alcohol use disorder, (ii) there is a negative correlation

between resilience and behavioral addictions and alcohol use disorder; and (iii) death anxiety, life meaninglessness, and resilience will predict symptoms of these addictions.

Material and Method

Participants

A total of 3,176 women participated in the study. To be included, women had to be at least 18 years of age and possess a good command of the Greek language. Participants who were enrolled in therapeutic rehabilitation programs during the study period were excluded from the study.

Procedure

An online cross-sectional study was conducted for the purpose of this investigation. The study was granted ethical approval by the Steering Committee of the MSc program in "Addictology" at the National and Kapodistrian University of Athens. The study information form, informed consent, and the questionnaires were made available in the form of online Google forms, which were distributed to various groups through a snowball sampling procedure that utilized a range of social media and websites. Additionally, the study was disseminated via email. All individuals interested in participating in the study were required to first read the information sheet and then complete the consent form. Those who were at least 18 years of age were subsequently granted access to the questionnaires. The study was conducted in an anonymous manner, and participants were not required to provide any personal data.

Measures

The demographic characteristics questionnaire consists of seven questions regarding gender, age, educational level, marital status, employment status, and potential participation in a therapeutic rehabilitation program.

The Shorter PROMIS Questionnaire (SPQ)[35] assesses behaviours and attitudes regarding alcohol, nicotine, recreational drugs, prescription drugs, gambling, sex, caffeine, food bingeing, food starving, exercise, shopping, work, dominant and submissive relationships, and compulsive helping, dominant and submissive. The scale contains 16 subscales, each containing 10 items, which are rated on a 6-point Likert scale (ranging from 0, indicating that the item is "not like" the respondent, to 5, indicating that the item is "like" the respondent). This yields a scale score range of 0–50. In the present study, five of the sixteen subscales were utilized: alcohol consumption, shopping, sex addiction, gambling and betting, and food. The psychometric properties of the scale are satisfactory, and it is a widely accepted research tool.[35] In the present study, Cronbach's alpha was found to be between 0.76–0.90.

The Meaning in Life Questionnaire (MLQ)[36] is a psychometric instrument designed to assess the presence of meaning (the extent to which respondents feel their lives have meaning) and the search for meaning in life (the extent to which respondents seek to find meaning and understanding in their lives). It comprises ten items, rated on a 7-point Likert-type scale, ranging from 1 (absolutely true) to 7 (absolutely untrue). The scale is a reliable psychometric tool that has been validated in the Greek population.[37] Cronbach's alpha was 0.86 for the subscale of presence of meaning and 0.86 for the subscale of search for meaning.

The Connor-Davidson Resilience Scale (CD-RISC)[38] employs a 5-point Likert scale to measure resilience, comprising five factors: personal competence, tolerance, acceptance of change, control, and spiritual influences. The scale measures the subject's feelings over the past month. Total scores range from 0 to 100, with higher scores indicating greater resilience.[35] The scale demonstrates good internal consistency (Cronbach's alpha=0.89), following testing in the general population.[39] In our sample, Cronbach's alpha was 0.91.

The Death Anxiety Scale (DAS)[40] measures attitudes toward death as a psychodynamic process with social and learning components. It consists of fifteen true/false items. The psychometric properties of the scale are satisfactory with a high internal consistency and test-retest reliability.[41] In our study, Cronbach's alpha was 0.71.

Statistical analysis

Quantitative variables are presented as mean, standard deviation (SD), and qualitative variables as absolute and relative frequencies. Spearman correlation coefficients (rho) were employed to investigate the relationship between ordinal and continuous variables. A multiple linear regression analysis was conducted, incorporating age, area of residence, family status, educational level, occupation, MLQ, CD-RISC, and DAS, was used with the addiction subscales designated as dependent variables. Adjusted regression coefficients (β) with standard errors (SE) were calculated. All reported

p-values are two-tailed, with statistical significance set at p<0.05. The analyses were performed using the SPSS statistical software (version 26.0).

Results

The demographic characteristics of the sample (n=3,176 women) are presented in table 1. Most of the sample (53.6%) held university degrees and resided in Athens. Of the remaining respondents, 47.7% were married or living with a partner, 40.1% were aged 26–35 years, and 47.1% were employed in the private sector.

The means and standard deviations (SD) of the study variables (i.e., Death Anxiety, Meaning in Life, Mental Resilience) are presented in table 2.

The results of the correlation analysis (table 3) indicated that there were significant positive correlations between the dimensions of "Search for meaning in life," "Presence of meaning in life," "Death Anxiety," and "Mental Resilience" with all addiction dimensions. The "Presence of meaning in life" subscale demonstrated a statistically significant negative correlation with all addiction subscales, including symptoms of sex addiction (rho=–0.16; p<0.001), symptoms of alcohol use disorder (rho=–0.21; p<0.001), symptoms of gambling and betting addiction (rho=–0.05; p=0.006), symptoms of shopping addiction (rho=–0.14; p<0.001) and symptoms of food addiction (rho=–0.20; p<0.001). The "Search for meaning in life" subscale showed a significant positive correlation with symptoms of sex addiction (rho=0.11; p<0.001), symptoms of alcohol use disorder (rho=0.11; p<0.001), symptoms of gambling and betting addiction (rho=0.12; p<0.001), symptoms of shopping addiction (rho=0.16; p<0.001) and symptoms of food addiction (rho=0.11; p<0.001). Regarding the dimensions of resilience, significant negative correlations were observed with symptoms of sex addiction (rho=–0.07; p<0.001), alcohol use disorder (rho=–0.11; p<0.001), shopping addiction (rho=–0.13; p<0.001) and food addiction (rho=–0.21; p<0.001). Additionally, a positive correlation was observed between greater death anxiety and symptoms of gambling and betting (rho=0.08; p<0.001), shopping (rho=0.21; p<0.001), and food addiction (rho=0.14; p<0.001).

Multiple linear regressions were also conducted with the addiction subscales as dependent variables (table 4). As shown, fewer symptoms of sex addiction were associated with women over 45 years of age (β=–0.112; p=0.041), those who were married (β=–0.079; p=0.004), university graduates (β=–0.118; p=0.001), and master's degree/Ph.D. holders (β=–0.115; p=0.004). More symp-

Table 1. Demographic Characteristics of the study sample.

	N (%)
Age range	
18–25	566 (17.8)
26–35	1274 (40.1)
36–45	931 (29.3)
46+	405 (12.8)
Residence	
Athens	1702 (53.6)
Other	1474 (46.4)
Education	
Primary/Secondary/High school	536 (16.9)
University	1559 (49.1)
Master's & Ph.D. degree	1081 (34.0)
Marital status	
Married	1094 (34.4)
Single	1459 (45.9)
Divorced	186 (5.9)
Widowed	15 (0.5)
Living with partner	422 (13.3)
Work	
Private sector employee	1495 (47.1)
Public sector employee	493 (15.5)
Freelancer	507 (16.0)
Student	323 (10.2)
Unemployed	358 (11.3)

Table 2. Descriptive statistics for "Presence of meaning in life," "Search for meaning in life," "Death Anxiety," "Mental Resilience" and Addiction Subscales.

	Mean	SD
Death Anxiety	9.58	2.99
Meaning in life Scale		
Presence of meaning in life	4.79	1.28
Search for meaning in life	4.91	1.37
Mental resilience scale	3.75	0.61
Symptoms of sex addiction	0.59	0.71
Symptoms of alcohol use disorder	1.18	1.08
Symptoms of gambling/betting addiction	0.29	0.85
Symptoms of shopping addiction	1.68	0.85
Symptoms of food addiction	1.79	1.12

Table 3. Spearman Correlation coefficients (rho) between Sex, Alcohol, Gambling and Betting, Shopping and Food Addiction Subscales and "Presence of meaning in life," "Search for meaning in life," "Death Anxiety," and "Mental Resilience".

	Presence of meaning in life	Search for meaning in life	Mental resilience	Death Anxiety
Symptoms of sex addiction	–0.16***	0.11***	–0.07***	0.02
Symptoms of alcohol use disorder	–0.21***	0.11***	–0.11***	0.01
Symptoms of gambling / betting addiction	–0.05**	0.12***	0.02	0.08***
Symptoms of shopping addiction	–0.14***	0.16***	–0.13***	0.21***
Symptoms of food addiction	–0.20***	0.11***	–0.21***	0.14***

**p<0.01; ***p<0.001

toms of sex addiction were associated with private sector employees (β=0.096; p=0.014) and freelancers (β=0.090; p=0.046) compared to public sector employees. Also, a lower "presence of meaning in life" score (β=–0.074; p<0.001) and a higher "search for meaning in life" score (β=0.054; p<0.001) were significantly associated with more sex addiction symptoms.

Significantly fewer symptoms of alcohol use disorder were found in participants aged 26 –35 years (β=–0.247; p<0.001), participants aged 36 –45 years (β=–0.343; p<0.001) and participants older than 46 years (β=–0.446; p<0.001) compared with those aged 18 –25 years. Moreover, married participants (β=–0.105; p=0.011) and university graduates (β=–0.158; p=0.004) had significantly fewer symptoms of alcohol use disorder. A lower "presence of meaning in life" score (β=–0.148; p<0.001) and a higher "search for meaning in life" score (β=0.072; p<0.001) were significantly associated with more symptoms of alcohol use disorder.

Regarding symptoms of gambling and betting addiction, it was found that residents of Athens (β=–0.072; p<0.001), married participants (β=–0.055; p<0.001), university graduates (β=–0.091; p<0.001) and master's degree/Ph.D. holders (β=–0.123; p<0.001) had significantly fewer symptoms than the other groups. Also, lower "presence of meaning in life" scores (β=–0.025; p=0.001) and higher "search for meaning in life" scores (β=0.032; p<0.001) were significantly associated with more symptoms of gambling and betting addiction. Higher mental resilience scores were significantly associated with fewer symptoms of gambling and betting addiction (β=–0.052; p=0.001), while higher death anxiety scores were significantly associated with more symptoms (β=0.011; p<0.001).

Significantly more symptoms of shopping addiction were found in participants aged 26 to 35 years of age (β=0.115; p=0.021) and in participants aged 46 and older (β=0.156; p=0.014) than in those aged 18 to 25. In addition, married participants reported significantly more symptoms of shopping addiction (β=0.096; p=0.003), whereas the unemployed reported significantly fewer symptoms (β=–0.157; p=0.008). A lower "presence of meaning in life" score (β=–0.074; p<0.001) and a higher "search for meaning in life" score (β=0.098; p<0.001) were significantly associated with more shopping addiction symptoms. Furthermore, higher mental resilience was significantly associated with fewer shopping addiction symptoms (β=–0.086; p=0.004), and higher death anxiety with more symptoms (β=0.049; p<0.001).

As the final set of findings, significantly more food addiction symptoms were observed in participants aged 26 to 35 (β=0.206; p=0.002), 36 to 45 (β=0.322; p<0.001), and those older than 46 (β=0.421; p<0.001), when compared with the 18 to 25 age group. Additionally, university graduates (β=–0.123; p=0.027) and those holding master's degree/Ph.D. holders (β=–0.144; p=0.018) reported significantly fewer symptoms of food addiction. Lower scores for "presence of meaning in life" (β=–0.111; p<0.001) and higher scores for "search for meaning in life" scores (β=0.109; p<0.001) were significantly associated with more food addiction symptoms. Moreover, greater mental resilience was associated with fewer food addiction symptoms (β=–0.278; p<0.001), while higher levels of death anxiety correlated with more symptoms (β=0.031; p<0.001).

Discussion

The primary aim of this study was to examine the relationship between symptoms associated with various behavioral addictions (shopping, sex, gambling and betting, and food) and alcohol use disorder with death anxiety, the absence of meaning in life, and the

Table 4. Multiple Linear Regression with dependent variables Sex, Alcohol, Gambling and Betting, Shopping and Food Addiction Subscales and independent variables the demographic variables, "Search for meaning in life," "Presence of meaning in life," "Death Anxiety," and "Mental Resilience".

		β+	SE++	Beta	t	P
Symptoms of sex addiction F (15, 3160) =11,38; p<.001; R^2 = 0,05	Age					
	26–35 vs 18–25	0.006	0.042	0.004	0.14	0.885
	36–45 vs 18–25	–0.040	0.047	–0.025	–0.85	0.394
	46+ vs 18–25	–0.112	0.055	–0.052	–2.05	0.041
	Residents of Athens (yes vs no)	0.009	0.025	0.006	0.34	0.734
	Married/ Living with partner (yes vs no)	–0.079	0.028	–0.055	–2.88	0.004
	Education					
	University vs Primary/ Secondary/ High school	–0.118	0.036	–0.083	–3.25	0.001
	Master's & Ph.D. degree vs Primary/ Secondary/ High school	–0.115	0.040	–0.077	–2.91	0.004
	Work					
	Private sector employee vs Public sector employee	0.096	0.039	0.067	2.45	0.014
	Freelancer vs Public sector employee	0.090	0.045	0.046	1.99	0.046
	Student vs Public sector employee	–0.074	0.062	–0.032	–1.19	0.233
	Unemployed vs Public sector employee	0.029	0.050	0.013	0.58	0.565
	Presence (MLQ)	–0.074	0.012	–0.134	–5.98	<0.001
	Search (MLQ)	0.054	0.009	0.104	5.80	<0.001
	Resilience (CD–RISC)	0.009	0.026	0.008	0.36	0.717
	Death Anxiety Scale	–0.001	0.004	–0.003	–0.16	0.872
Symptoms of alcohol use disorder F (15, 3160)=18; p<.001; R^2=0,07	Age					
	26–35 vs 18–25	–0.247	0.064	–0.112	–3.88	<0.001
	36–45 vs 18–25	–0.343	0.070	–0.144	–4.92	<0.001
	46+ vs 18–25	–0.446	0.082	–0.137	–5.46	<0.001
	Residents of Athens (yes vs no)	–0.063	0.038	–0.029	–1.68	0.093
	Married/ Living with partner (yes vs no)	–0.105	0.041	–0.048	–2.54	0.011
	Education					
	University vs Primary/ Secondary/ High school	–0.158	0.055	–0.073	–2.88	0.004
	Master's & Ph.D. degree vs Primary/ Secondary/ High school	–0.075	0.059	–0.033	–1.26	0.206
	Work					
	Private sector employee vs Public sector employee	0.073	0.058	0.034	1.25	0.212
	Freelancer vs Public sector employee	0.111	0.067	0.038	1.65	0.099
	Student vs Public sector employee	–0.018	0.093	–0.005	–0.19	0.846
	Unemployed vs Public sector employee	0.051	0.076	0.015	0.68	0.497
	Presence (MLQ)	–0.148	0.019	–0.174	–7.93	<0.001
	Search (MLQ)	0.072	0.014	0.091	5.15	<0.001
	Resilience (CD–RISC)	0.009	0.039	0.005	0.23	0.819
	Death Anxiety Scale	–0.008	0.006	–0.021	–1.18	0.237

Continues

Table 4. Continued.

		β+	SE++	Beta	t	P
Symptoms of gambling and betting addiction F (15, 3160)= 10,89; p<.001; R^2=0,04	Age					
	26–35 vs 18–25	–0.035	0.026	–0.038	–1.32	0.188
	36–45 vs 18–25	–0.041	0.029	–0.042	–1.41	0.159
	46+ vs 18–25	0.051	0.034	0.039	1.51	0.132
	Residents of Athens (yes vs no)	–0.072	0.016	–0.081	–4.62	<0.001
	Married/Living with partner (yes vs no)	–0.055	0.017	–0.062	–3.21	0.001
	Education					
	University vs Primary/Secondary/High school	–0.091	0.023	–0.103	–4.02	<0.001
	Master's & PhD degree vs Primary/Secondary/ High school	–0.123	0.025	–0.131	–4.97	<0.001
	Work					
	Private sector employee vs Public sector employee	–0.026	0.024	–0.029	–1.07	0.283
	Freelancer vs Public sector employee	–0.025	0.028	–0.021	–0.89	0.374
	Student vs Public sector employee	–0.046	0.039	–0.031	–1.18	0.239
	Unemployed vs Public sector employee	–0.003	0.031	–0.002	–0.10	0.920
	Presence (MLQ)	–0.025	0.008	–0.071	–3.19	0.001
	Search (MLQ)	0.032	0.006	0.099	5.51	<0.001
	Resilience (CD–RISC)	–0.052	0.016	–0.071	–3.20	0.001
	Death Anxiety Scale	0.011	0.003	0.077	4.30	<0.001
Symptoms of shopping addiction F (15, 3160)=21,6; p<.001; R^2=0,09	Age					
	26–35 vs 18–25	0.115	0.050	0.066	2.32	0.021
	36–45 vs 18–25	0.100	0.054	0.053	1.84	0.066
	46+ vs 18–25	0.156	0.064	0.061	2.45	0.014
	Residents of Athens (yes vs no)	0.003	0.029	0.002	0.10	0.917
	Married/ Living with partner (yes vs no)	0.096	0.032	0.056	2.98	0.003
	Education					
	University vs Primary/Secondary/High school	–0.052	0.043	–0.031	–1.23	0.218
	Master's & PhD degree vs Primary/Secondary/ High school	0.014	0.046	0.008	0.31	0.758
	Work					
	Private sector employee vs Public sector mployee	–0.021	0.045	–0.012	–0.47	0.640
	Freelancer vs Public sector employee	–0.077	0.052	–0.033	–1.47	0.142
	Student vs Public sector employee	–0.140	0.073	–0.050	–1.92	0.055
	Unemployed vs Public sector employee	–0.157	0.059	–0.058	–2.67	0.008
	Presence (MLQ)	–0.074	0.015	–0.111	–5.08	<0.001
	Search (MLQ)	0.098	0.011	0.158	8.99	<0.001
	Resilience (CD–RISC)	–0.086	0.030	–0.062	–2.85	0.004
	Death Anxiety Scale	0.049	0.005	0.172	9.87	<0.001

Continues

Table 4. Continued.

		β+	SE++	Beta	t	P
Symptoms of food addiction F (15, 3160)=21; p<.001; R^2=0,09	Age					
	26–35 vs 18–25	0.206	0.065	0.090	3.16	0.002
	36–45 vs 18–25	0.322	0.071	0.132	4.52	<0.001
	46+ vs 18–25	0.421	0.083	0.126	5.04	<0.001
	Residents of Athens (yes vs no)	–0.016	0.038	–0.007	–0.41	0.683
	Married/Living with partner (yes vs no)	0.052	0.042	0.023	1.24	0.216
	Education					
	University vs Primary/Secondary/High school	–0.123	0.056	–0.055	–2.21	0.027
	Master's & PhD degree vs Primary/Secondary/ High school	–0.144	0.061	–0.061	–2.38	0.018
	Work					
	Private sector employee vs Public sector employee	–0.027	0.060	–0.012	–0.46	0.648
	Freelancer vs Public sector employee	–0.057	0.069	–0.019	–0.82	0.411
	Student vs Public sector employee	–0.081	0.095	–0.022	–0.85	0.396
	Unemployed vs Public sector employee	–0.078	0.077	–0.022	–1.01	0.313
	Presence (MLQ)	–0.111	0.019	–0.127	–5.82	<0.001
	Search (MLQ)	0.109	0.014	0.133	7.57	<0.001
	Resilience (CD–RISC)	–0.278	0.040	–0.152	–7.00	<0.001
	Death Anxiety Scale	0.031	0.007	0.082	4.70	<0.001

+regression coefficient; ++Standard Error; Beta = Standardized regression coefficient

level of mental resilience among women. The findings indicated significant correlations between the study variables, offering valuable insights into the intricate interplay of psychological factors and addiction symptoms in the female population. These results align with those of previous studies examining the existentialist perspective, death anxiety, and absence of meaning in life across various addictions.[42–47] All of them indicate that individuals may utilize various escape strategies to cope with the underlying existential distress. Our findings corroborate this notion. Those who are ensnared in the cycle of addiction may exhibit a lack of motivation, a sense of meaninglessness in life, and a deficiency in a safe and supportive social and family environment.[42]

It is noteworthy that the "Presence of meaning in life" subscale exhibited a significant negative correlation with all addiction subscales, including shopping, sex, gambling and betting, and food addiction. Similarly, the "Search for meaning in life" subscale demonstrated a significant and positive correlation with the addiction subscales. These findings corroborate prior research associating existential concerns and the absence of meaning in life with various forms of addiction.[41,42] This underscores the therapeutic value of prioritizing personal values and promoting engagement in meaningful pursuits as an integral aspect of the addiction treatment.[43] Notably, studies have indicated that for women in particular, a diminished sense of meaning in life is associated with an increased likelihood of substance misuse, both legal and illegal.[44–46]

Interestingly, participants exhibiting elevated levels of death anxiety displayed a greater propensity for symptoms of addiction, particularly in the domains of gambling and betting, shopping, and food. This highlights the intricate relationship between existential concerns, such as death anxiety, and the emergence of addictive behaviors. A review of the literature supports a robust connection between the existential issue of death and sexual addiction. This connection emphasizes that sex serves as a coping mechanism for the fear of mortality. It has been demonstrated that death anxiety is frequently associated with sexual dysfunction. Many individuals perceive sexual activity as a drive for life

and, therefore, as a way of combating death through the reproductive process.[47]

Furthermore, the present study identified mental resilience as a protective factor, showing a significant negative correlation with symptoms of sex, alcohol, shopping, and food addiction. However, the low correlation coefficients (ranging from –0.07 to –0.21) indicate a weak correlation or a lack of linkage. These findings are consistent with the results of previous studies and literature reviews that highlight the importance of resilience in mitigating the impact of traumatic experiences and reducing the vulnerability to addictive behaviors.[45–49]

It has been shown that traumatic experiences can evoke distressing emotions that may result in the use of substances or the engagement in addictive behaviors. In such instances, individuals tend to perceive themselves as inferior to others and may exhibit a tendency to withdraw to conceal their inferiority and vulnerability.[50]

In addition, early-onset stressful life events, in conjunction with a lack of mental resilience, represent significant risk factors for the development of mental disorders, including emotional disorders, behavioral disorders, and substance use disorders.[45,46,48,49,51] The present study examined demographic predictors and found that married women and university graduates exhibited fewer symptoms of sex, alcohol, and gambling and betting addiction. Conversely, women aged 18–25 displayed significantly fewer symptoms of shopping and food addiction. Therefore, marriage and a higher level of education emerged as protective factors against certain types of addictive behaviors in women, which agrees with another recent survey.[52]

It is important to acknowledge certain limitations of study. Initially, the utilization of convenience sampling techniques inherently restricts the generalizability of the findings. However, the extensive sample size enables the formulation of some meaningful inferences. Secondly, a self-report measure (SPQ) was employed to identify symptoms of behavioral addictions and alcohol use disorder, which limits the significance of the findings. Nevertheless, this instrument is clinically useful and widely used to broadly assess these symptoms.[34]

Conclusions

In conclusion, the present study offers significant insights into the relationship between death anxiety, a lack of meaning in life, and mental resilience in women with symptoms of behavioral addictions and alcohol use disorder in the general population in Greece. The findings highlight the value of the existential perspective in comprehending and treating various addiction symptoms, examining the development of addiction, and enhancing insights into the psychology of individuals struggling with addiction. Moreover, these findings have significant implications for health professionals engaged in therapeutic rehabilitation programs. They underscore the importance of enhancing mental resilience as a crucial protective factor against gambling and betting, shopping, and food addiction. However, they do not extend this conclusion to sex addiction and alcohol use disorder. Although the coefficients between gambling and betting, shopping and food addiction, and psychological resilience were low, suggesting a weak correlation or no relationship, this study may be an important step in advancing our understanding of addiction dynamics. It provides mental health professionals with valuable insights into the role of death anxiety, meaning of life, and resilience in female

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Ερευνητική εργασία

Άγχος θανάτου, απουσία νοήματος ζωής και ψυχική ανθεκτικότητα σε γυναίκες με συμπτώματα συμπεριφορικών εθισμών και διαταραχής χρήσης αλκοόλ: Υπαρξιακή προσέγγιση

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ΠΕΡΙΛΗΨΗ

Τις τελευταίες δεκαετίες, ένας αυξανόμενος αριθμός ερευνών υπογραμμίζει την ιδιαίτερη φύση της χρήσης ουσιών μεταξύ των γυναικών, γεγονός που καθιστά αναγκαία μια προσέγγιση με βάση το φύλο και κατ' επέκταση εξατομικευμένες θεραπευτικές παρεμβάσεις. Η παρούσα μελέτη, η οποία βασίστηκε στην υπαρξιακή προσέγγιση, αποσκοπούσε να διερευνήσει κατά πόσον τα συμπτώματα διαφόρων συμπεριφορικών εθισμών (αγορές, σεξ, τυχερά παιχνίδια και στοιχηματισμός, φαγητό) και η διαταραχή χρήσης αλκοόλ συσχετίζονται με το άγχος θανάτου, την απουσία νοήματος στη ζωή και το επίπεδο ψυχικής ανθεκτικότητας σε ένα δείγμα ευκολίας γυναικών. Συνολικά 3.176 γυναίκες συμμετείχαν σε αυτή τη διαδικτυακή μελέτη, συμπληρώνοντας: ένα ερωτηματολόγιο δημογραφικών στοιχείων, το σύντομο ερωτηματολόγιο PROMIS (SPQ), το ερωτηματολόγιο για το Νόημα της Ζωής (MLQ), την κλίμακα Ανθεκτικότητας Connor-Davidson (CD-RISC) και την Κλίμακα Άγχους Θανάτου (DAS). Τα αποτελέσματα έδειξαν μια στατιστικά σημαντική αρνητική συσχέτιση μεταξύ της υποκλίμακας «Παρουσία νοήματος στη ζωή» και όλων των υποκλιμάκων για τα συμπτώματα εθισμού (αγορές, p<0,001, σεξ, p<0,001, τυχερά παιχνίδια και στοιχηματισμός, p=0,006, τροφή, p<0,001, και χρήση αλκοόλ, p<0,001). Αντίθετα, η υποκλίμακα «Αναζήτηση νοήματος στη ζωή» παρουσίασε σημαντική θετική συσχέτιση με όλες τις υποκλίμακες συμπτωμάτων εθισμού (αγορές, σεξ, τυχερά παιχνίδια και στοιχηματισμός, τροφή και χρήση αλκοόλ, p<0,001). Η ψυχική ανθεκτικότητα αναδεικνύεται ως προστατευτικός παράγοντας, επιδεικνύοντας σημαντικές αρνητικές συσχετίσεις με τα συμπτώματα του εθισμού στο σεξ (p<0,001), στο αλκοόλ (p<0,001), στις αγορές (p<0,001) και στην τροφή (p<0,001), αν και οι συντελεστές συσχέτισης κυμαίνονταν σε χαμηλά επίπεδα (από -0,07 έως -0,21), υποδηλώνοντας ασθενή ή μη συσχέτιση. Επιπλέον, οι συμμετέχουσες με υψηλότερο άγχος θανάτου εκδήλωσαν περισσότερα συμπτώματα εθισμού σε τυχερά παιχνίδια και στοιχηματισμό (p<0,001), στις αγορές (p<0,001) και στην τροφή (p<0,001). Οι γυναίκες που ήταν έγγαμες και απόφοιτες πανεπιστημίου εμφάνιζαν χαμηλότερα συμπτώματα εθισμού στο σεξ (β=−0,079, p=0,004/β=−0,118; p=0,001), το αλκοόλ (β=−0.105, p=0,011/β=−0,158, p=0,004), και τα τυχερά παιχνίδια (β=−0,055, p<0,001/β=−0,091, p<0,001), ενώ οι γυναίκες ηλικίας 18–25 ετών εμφάνιζαν σημαντικά χαμηλότερα συμπτώματα εθισμού στις αγορές και στην τροφή. Ο γάμος και το υψηλότερο επίπεδο εκπαίδευσης αναδείχθηκαν ως προστατευτικοί παράγοντες έναντι ορισμένων τύπων εθισμού. Συνοπτικά, η παρούσα έρευνα έδειξε μια ουσιαστική σχέση μεταξύ της απουσίας νοήματος στη ζωή και του άγχους θανάτου με την εκδήλωση συμπτωμάτων συμπεριφορικών εθισμών και τη χρήση αλκοόλ. Αντιθέτως, η παρουσία ψυχικής ανθεκτικότητας μπορεί να λειτουργήσει ως προστατευτικός παράγοντας έναντι του εθισμού στον τζόγο και στο στοιχηματισμό, στις αγορές και στην τροφή, αλλά όχι στον εθισμό στο σεξ και στη διαταραχή χρήσης αλκοόλ.

ΛΕΞΕΙΣ ΕΥΡΕΤΗΡΙΟΥ: Εξάρτηση, συμπεριφορικοί εθισμοί, διαταραχή χρήσης αλκοόλ, άγχος θανάτου, νόημα ζωής, ψυχική ανθεκτικότητα, υπαρξισμός.

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Research article

Clozapine/norclozapine plasma concentrations and their ratio in treatment resistant, early psychosis patients

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ABSTRACT

Treatment-resistant schizophrenia affects approximately 30% of schizophrenia patients, and clozapine is the antipsychotic of choice for their treatment. Despite its effectiveness, clozapine is under-prescribed for those patients' group, probably due to its severe side effects. Measurement of plasma concentrations of clozapine and its active metabolite, norclozapine, in plasma could help clinicians to monitor compliance with treatment and reduce the possibility of severe side effects. Such measurements are currently not included in routine clinical practice, although clozapine plasma concentrations are influenced by many different factors and do not usually reflect the prescribed dose. The aim of the present study was to measure clozapine and norclozapine plasma concentrations and their ratio in a group of early psychosis, treatment-resistant, schizophrenia patients and to investigate possible associations among the prescribed clozapine daily dose and socio-demographic variables. Thirty-eight patients were included in the study, and 342 blood samples were collected. Clozapine and norclozapine plasma concentration measurements were performed by UHPLC-MS/MS. Mixed-effects linear regression models were performed to associate blood clozapine and norclozapine levels and their ratio to clozapine dose. The median clozapine dose, clozapine, norclozapine plasma concentrations, and their ratio at first and last measurement were as follows: 400 mg/day (IQR=350 mg/day to 500 mg/day) and 425 mg/day (IQR=350 mg/day to 600 mg/day), 335 ng/ml (IQR=191 ng/ml to 427 ng/ml) and 389 ng/ml (IQR= 276 ng/ml to 523 ng/ml), 129 ng/ml (IQR=62 ng/ml to 218 ng/ml) and 135 ng/ml (IQR=82 ng/ml to 209 ng/ml), 2.5 (IQR=1.6 to 4.8) and 2.9 (IQR=1.7 to 4.4). An increase of clozapine dose by 50mg/day was associated with higher blood clozapine and norclozapine levels but with lower clozapine/norclozapine ratio. Clozapine dose was positively associated with blood clozapine and norclozapine levels and negatively with the clozapine/norclozapine ratio.

KEYWORDS: Clozapine, norclozapine, clozapine/norclozapine ratio, treatment resistant schizophrenia, early psychosis patients.

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Introduction

Treatment-resistant schizophrenia (TRS) is defined as non-responsiveness to two trials with two antipsychotics, at least one of which is a second-generation antipsychotic, used in adequate doses and for an appropriate duration of 4 to 6 weeks[1] and affects approximately 30% of patients with schizophrenia.[2] Clozapine has been proved to be more effective than any other antipsychotic in patients suffering from TRS and is considered to be the antipsychotic of choice for their treatment.[3] Literature suggests that clozapine is associated with reduced suicide attempts,[4] mortality risk,[5] relapses[6] and hospitalizations.[7] Despite these facts, there is a considerable under-prescription of clozapine for the aforementioned patients' group.[8] Only 2–3% and 7% of TRS patients are treated with clozapine in the United States[9] and Canada,[10] respectively. Severe and life-threatening side effects like agranulocytosis, myocarditis, pneumonic embolism, bowel obstruction, and paralytic ileus have significantly contributed to the under-prescription of clozapine.[11]

There is also a considerable delay of at least 2–5 years in the initiation of clozapine in TRS patients,[12] with the duration of untreated TRS being correlated with reduced effectiveness of the medication.[13] There seems to be a critical treatment window for the effectiveness of clozapine of approximately 3 years, like the Duration of Untreated Psychosis (DUP) in First Episode Psychosis-FEP.[14]

Clozapine is metabolized by N-demethylation, N-oxidation, and aromatic hydroxylation. The cytochrome CYP450 isoenzymes CYP1A2 and CYP3A4 are involved in its metabolism.[15] Clozapine has two major metabolites, the pharmacologically active norclozapine and the inactive clozapine N-oxide.[16] Norclozapine has similar but not the same affinities as clozapine. It is a D2/D3 partial agonist, while clozapine is a D2/D3 inverse agonist/antagonist, and it contributes to the low incidence of extrapyramidal adverse effects and to the amelioration of cognitive symptoms.[17]

According to the protocol by Hiemke et al,[18] Clozapine plasma concentrations (CLPC) should range between 350 and 600 ng/ml, although plasma concentrations between 200 and 300 ng/ml have also been proven effective. CLPC between 700 and 1000 ng/ml have been associated with increased risk of side effects and concentrations above 1000 ng/ml with toxicity.

Many factors can influence CLPC.[19] According to Perry's nomogram,[20] 47% of clozapine concentration variability could be explained by dose, sex, and smoking status in agreement with the study of Rostami-Hodjegan[21] that attributed 48% of the variability to the aforementioned factors and body weight.

Women tend to have 17% higher CLPC than men when they receive equal doses of clozapine.[21] This is due to several factors, among them lower cytochrome P450A2 (CYP1A2) activity in women, slower gastric emptying, more adipose tissue, lower liver blood flow, and estrogens because they inhibit CYP1A2.[22]

Cigarette smoking reduces CLPC, and smokers need much higher doses to reach the same PC than non-smokers because polycyclic aromatic hydrocarbons induce CYP1A2.[23] According to a meta-analysis by Tsuda et al[24] smoking causes a reduction of approximately 50% in CLPC. Smoking cessation because of reversal of enzymatic induction can lead to toxic CLPC if the daily doses are not adjusted properly.[15]

Age influences CLPC in at least two ways: The activity of CYP1A2 decreases as the age advances.[25] Decreases in liver function because of aging can cause a reduction in clozapine metabolism and increased CLPC.[26] The impact of BMI on CLPC remains controversial, with different studies reporting contradictory results.[27,21] Infection and inflammation increase CLPC,[28] while constipation, a frequent side effect, may delay the absorption of clozapine.[15] Caffeine can increase CLPC by inhibiting CYP1A2 if a patient is taking the equivalent of three cups of coffee per day.[29]

For all the above-mentioned reasons, Therapeutic Drug Monitoring (TDM) is strongly recommended in patients under clozapine treatment to maximize therapeutic benefit using the appropriate dose and to avoid relapses and intoxications.[18,28]

The aim of this study was to measure clozapine and norclozapine PC and calculate their ratio in early psychosis treatment-resistant schizophrenia patients to investigate correlations between the aforementioned parameters, clozapine doses, clinical, and socio-demographic variables.

Material and Method

Patients and plasma samples

Patients were recruited from the "Early Intervention in Psychosis Unit" of the Department of Psychiatry of the "University Hospital of Ioannina" between September 2017 and July 2021. The patients included in the study were early psychosis patients who proved to be treatment resistant and were introduced to treatment with clozapine.

Inclusion criteria were: (a) a diagnosis of TRS; (b) the time from the diagnosis of TRS to first clozapine use was less than 3 years; (c) they should be in antipsychotic monotherapy (they did not take any other antipsychotics or antidepressants); (d) have normal renal and hepatic function (as reflected by the relevant biochemical analyses for plasma urea, creatinine, aspartate transaminase (AST), alanine transaminase (ALT), and gamma-glutamyl-transferase (gamma-GT); and (g) clozapine should have achieved steady-state levels at the day of samples collection. Steady state was defined as the time of 5 half-lives of clozapine (clozapine's half-life=14 hours).[30,31] We considered the following exclusion criteria: (a) Diagnostic and Statistical Manual of Mental Disorders (DSM-5)[32] diagnostic criteria for alcohol or substance abuse; (b) a serious physical disorder; (c) patients were also excluded if they refused to give informed consent. We contacted forty-three patients, and three of them were excluded from the study because they refused to give informed consent.

All patients were stabilized at the time of sample collection and received stable clozapine dosages. However, in cases when it was required due to clinical indications, doses were adjusted within the prescribed range. Patients received only clozapine and no other antipsychotic or antidepressant during the study).

All patients had a complete physical examination by an internist before the inclusion in the study. A urine test was performed in all subjects to exclude current substance use. We collected a total of 342 samples from 38 patients (min 3 samples, max 19 samples). All participants had the blood samples taken at 08:00 in the morning, twelve hours after the evening dose of clozapine and before the morning medication, at least seven days after a change in clozapine dosages for determination of clozapine concentration. Samples were collected once a month during regular follow-up visits of the patients.

Plasma was retained after samples were centrifuged at 2500 rpm for 10 min, divided into aliquots of 1.0 mL, frozen immediately, and stored at −20 °C until analysis. Analysis for clozapine/norclozapine was performed after selection of all plasma samples.

Quantification of Clozapine and Norclozapine in Plasma

The samples were prepared and analyzed by ultra-high-performance liquid chromatography-tandem mass spectrometry (UHPLC-MS/MS) according to a previously published method by the authors.[33] In brief, 200 µL of plasma to which 20 µLof acetonitrile, 20 µL of an internal standard working solution containing isotopically labeled clozapine, and 50 µL of a carbonate buffer (1 M; pH 9.5) were added, was extracted with 1 mL of methyl-t-butyl ether (MTBE). The upper organic layer was transferred and evaporated to dryness. The extract was reconstituted in 50 µL of acetonitrile, and an aliquot of 5 µL was injected into the UHPLC–MS/MS system. Targeted LC-MS/MS analyses of clozapine and norclozapine were performed on a Dionex UHPLC system (Thermo Scientific) coupled to a Q-Trap +5500™ mass spectrometer (Sciex, Darmstadt, Germany) operated in multiple reaction monitoring (MRM) mode and an electrospray ionization (ESI) Turbo V Source in positive mode. The liquid chromatograph system consisted of a degasser, a binary pump, autosampler, and column oven. Gradient elution was performed on an Accupore C18 (50 mmx3 mm, 2.6 µm particle size) column from Thermo Scientific, Waltham, MA, USA, operating at 300C equipped with a precolumn cartridge (2.1 mm×0.2 µm). The mobile phases consisted of 10 mM aqueous ammonium acetate adjusted to pH 3.5 with 0.1% formic acid (eluent A) and acetonitrile UHPLC-MS grade with 0.1% formic acid (eluent B), which were degassed by the Elmasonic S ultrasonic, Germany. The flow rate was 0.5 mL/min, and the column oven was maintained at 30°C. Total run time was 6.50 min. The autosampler was operated at 5°C, and the autosampler needle was rinsed with 200 µLmethanol before and after each injection. Injection volume was 5 µL. For detection and quantitation, the following ESI inlet conditions were applied: gas 1, nitrogen (55 psi; 620.5 kPa); gas 2, nitrogen (55 psi; 620.5 kPa); ion spray voltage, 5500 V in positive mode; ion-source temperature, 450 °C; curtain gas, nitrogen (55 psi; 379.2 kPa). The dwell times were optimized using the scheduled MRM algorithm incorporated in Sciex Analyst® software version 1.7.1. All other settings were analyte-specific and were determined using Analyst® software in the automatic quantitative optimization mode. All data processing was performed using SciexOS 1.6 software.

Statistical analysis

We have collected 342 blood samples from 38 participants for measurement of clozapine and norclozapine plasma concentrations. Descriptive statistics were applied to calculate the participants' characteristics and their distribution by first and last sample collection. Continuous variables were described as median [interquartile range IQR)]; categorical variables were described as frequency rates and percentages. A Wilcoxon signed-rank test was used to compare body mass index

(BMI), PANSS scales and subscales, clozapine, norclozapine, clozapine/norclozapine ratio, and clozapine dose between the first and the final measurement. We have created a plot for the distribution of blood clozapine, norclozapine, and clozapine doses of each participant across measurements. Furthermore, we plotted the geometric means for all measurements for all clozapine and norclozapine levels and the respective clozapine doses. Among participants, we performed mixed-effects linear regression models for the association between blood clozapine and norclozapine levels and their ratio with clozapine dose. Models were adjusted for age, sex, smoking, BMI, duration of untreated psychosis (DUP), PANSS total score, and antipsychotic prescribed before clozapine initiation. We also performed linear regression models to evaluate the association of clozapine dose with final values of BMI and PANSS scale and its subscales, accounting for age, sex, DUP, smoking, antipsychotic medication before clozapine, the baseline value of each variable, and the number of clozapine/norclozapine PC measurements. We further investigated the changes between the first and final clozapine measurements of the variables in a comparable manner. Results were considered statistically significant if the p-value was <0.05. Analysis was performed using Stata (version 16.1; StataCorp, College Station, TX, USA).

Results

Table 1 presents the characteristics of the sample. We included 38 patients (29 male, 76.3%) with a median age of 26.5 years (IQR=23.8 to 34.5). The median DUP was 10 weeks (IQR=8 to 12.5). DUP was crudely assessed through combined information received from the patients themselves and a key informant regarding the first evidence of the appearance of delusional ideas and/or hallucinations and/or odd behavior (estimated as the day or the week of a month). The majority were smokers (n=25, 65.8%) and the most frequent drug before clozapine was olanzapine (n=21, 55.3%). Information about smoking was collected from the patients themselves and their closest relatives. We did not observe statistically significant differences between males and females, except for smoking status with 77.8% (n=21) male smokers in contrast to 33.3% (n=3) female smokers (p=0.01) (Supplement Table S2).

In total, we collected and analyzed 342 samples from 38 participants. Of those, seventy-five samples (23.4%) were from 9 females and 267 samples (75.7%) from 29 males. CLPC <250 ng/ml were observed in 83 samples (24.3%), while concentrations within the expected 251–750 ng/ml range were found in 237 samples (69.3%). CLPC exceeding 750 ng/ml were found in 22 samples (6.4%). Of those, 4 samples from one male patient (1.2% of the total samples) showed toxic plasma concentrations >1000 ng/ml), but the patient did not present toxicity symptoms or other side effects. For females, out of the 75 samples, 18 (24%) had CLPC<250 ng/ml, 65 (70.7%) within the 251–750 ng/ml range, and 4 samples had CLPC exceeding 750 ng/ml. Among males, from the 267 samples, 65 (24.3%) had CLPC<250 ng/ml, 184 (68.9%) in the 251–750 ng/ml range and 18 (6.8%) had CLPC exceeding 750 ng/ml. 24.8% of the smokers and 13.3% of NS had CLPC<250 ng/ml, 73.8% of smokers and 67.3% of NS between 251 and 750 and 1% of smokers and 13.3% of NS above 750 ng/ml. All NS and 92.3% of smokers received daily Clozapine dosages >250 mg. 7.7% of smokers received less than 250 mg clozapine/day.

The median clozapine dose at baseline was 400 mg/day (IQR=350 mg/day to 500 mg/day) and at the final visit, 425 mg/day (IQR=350 mg/day to 600 mg/day) (table 1). The p-value for the comparison between the two time-points was statistically significant (p=0.030). The median clozapine blood levels were 335 ng/ml (IQR=191 ng/ml to 427 ng/ml) at the first measurement and 389 ng/ml (IQR=276 ng/ml to 523 ng/ml) at the final one. As above, a significant p-value was observed between the first and last measurements (p<0.001). Norclozapine levels had a median value of 129 ng/ml (IQR=61.9 ng/ml to 218 ng/ml) at the first measurement and 135 ng/ml (IQR=82–209 ng/ml) at the final measurement. Their median ratio, clozapine/norclozapine, was 2.5 (IQR=1.6 to 4.8) and 2.9 (IQR=1.7 to 4.4) for the first and last measurements, respectively. None of the last two variables were significant (pnorclozapine=0.694 and pclozapine/norclozapine=0.743 respectively). BMI, PANSS-Positive, PANSS-Negative, PANSS-General, PANSS-Total were assessed before clozapine initiation and at the last follow-up. Their corresponding median values were 22.6 kg/m^2 (IQR=22.0 kg/m^2 to 23.7 kg/m^2), 35 (IQR=32 to 37), 28.5 (IQR=16 to 32), 41 (IQR=34 to 44), and 102 (IQR=88 to 110) at baseline and 24.9 kg/m2 (IQR=24.0 kg/m^2 to 25.8 kg/m^2),10 (IQR=8 to 14), 14 (IQR=10 to 17), 20 (IQR=18 to 22) and 45 (IQR=37 to 56) at the last visit. For all the above variables, their corresponding p-values were statistically significant. All patients proved to be clozapine responders, as is shown by the PANSS values at the last visit.

Figures 1–3 show the clozapine dose and clozapine and norclozapine levels for each participant across visits. In general, the blood levels of the clozapine and norclozapine followed similar trends with the received dose.

Table 1. Descriptive characteristics of the participants at baseline and final blood sample.

	Baseline visit		Final visit		p-value
	N	Median [IQR] or Frequency (%)	N	Median [IQR] or Frequency (%)	
Age (years)	38	26.5 [23.8; 34.5]		-	
Sex	38				
Female		9 (23.7)		-	
Male		29 (76.3)		-	
Smoking	38				
No		13 (34.2)		-	
Yes		25 (65.8)		-	
DUP (weeks)	38	10.0 [8.0; 12.5]		-	
Drugbefore	38				
Amisulpride		1 (2.6)		-	
Aripiprazole		2 (5.3)		-	
Haloperidole		1 (2.6)		-	
Olanzapine		21 (55.3)		-	
Risperidone		13 (34.2)		-	
Clozapine dose (mg/day)	36	400 [350; 500]	36	425 [350; 600]	0.030
Clozapine (ng/mL)	38	335 [191; 427]	38	389 [276; 524]	<0.001
Nor-clozapine (ng/mL)	36	129 [62; 218]	36	135 [82; 209]	0.694
Clozapine/Nor-clozapine ratio	36	2.5 [1.6; 4.8]	36	2.9 [1.7; 4.4]	0.743
BMI	38	22.6 [22.0; 23.7]	38	24.9 [24.0; 25.8]	<0.001
PANSS-Positive	38	35 [32; 37]	38	10 [8; 14]	<0.001
PANSS-Negative	38	29 [16; 32]	38	14 [10; 17]	<0.001
PANSS-General	38	41 [34; 44]	38	20 [18; 22]	<0.001
PANSS-Total	38	102 [88; 110]	38	45 [37; 56]	<0.001

Abbreviations: BMI, body mass index; IQR: interquartile range;PANSS: Positive and Negative Syndrome Scale

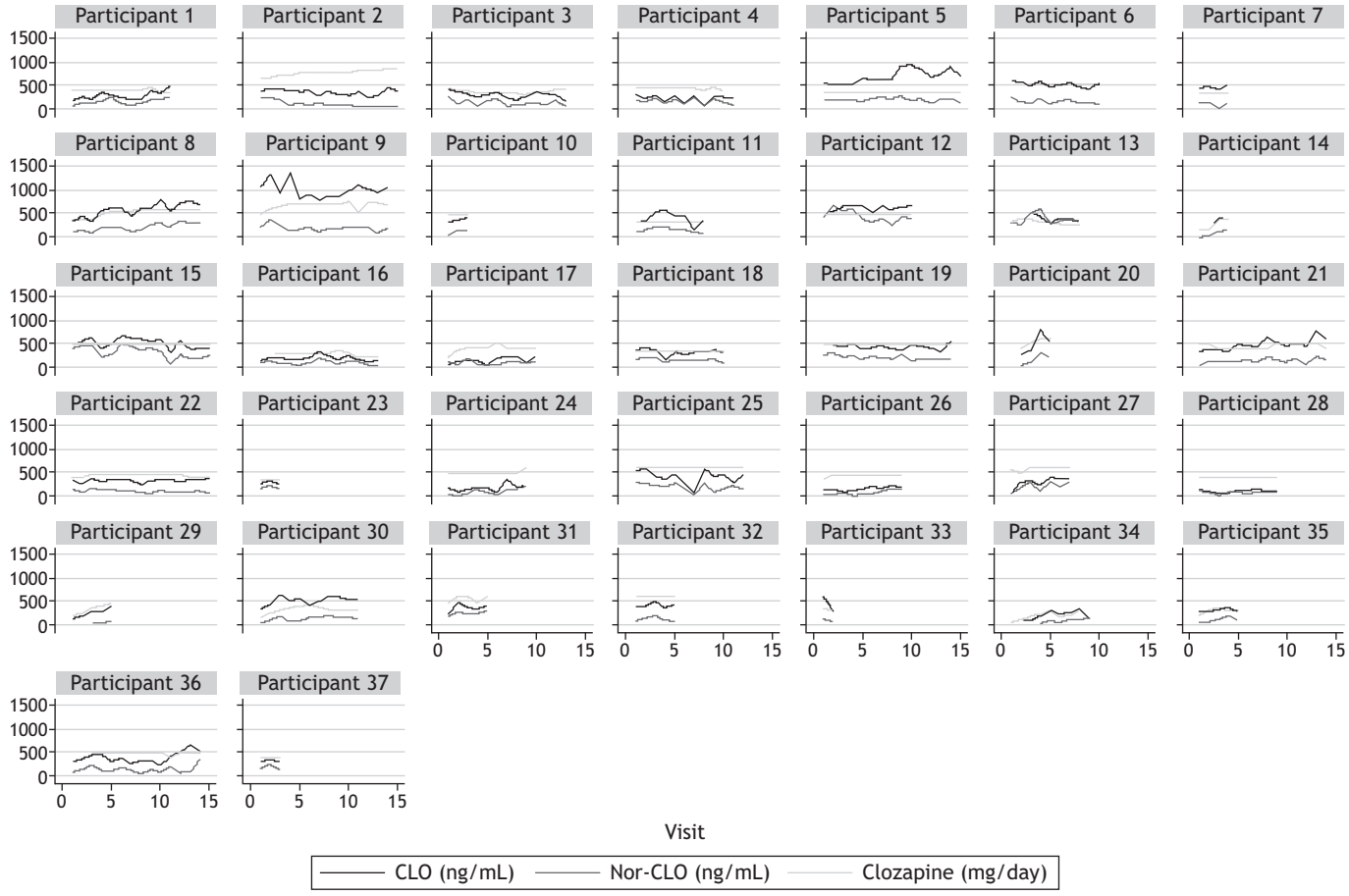

Figure 1. Clozapine dose and blood levels from baseline visit. Participants with a single visit at baseline are not presented in the figure.

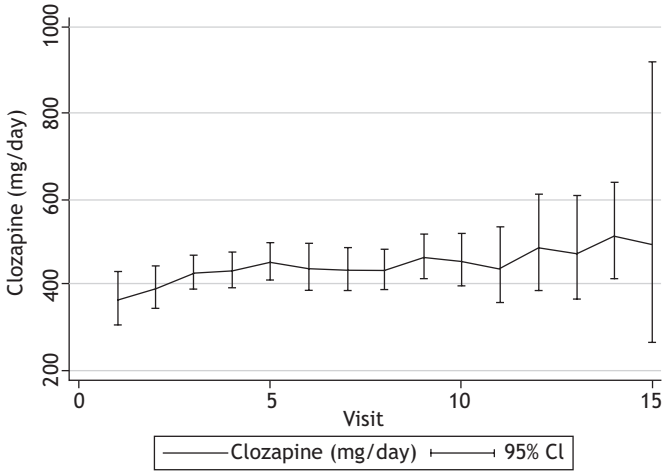

Figure 2. Distribution of mean clozapine dose across visits.

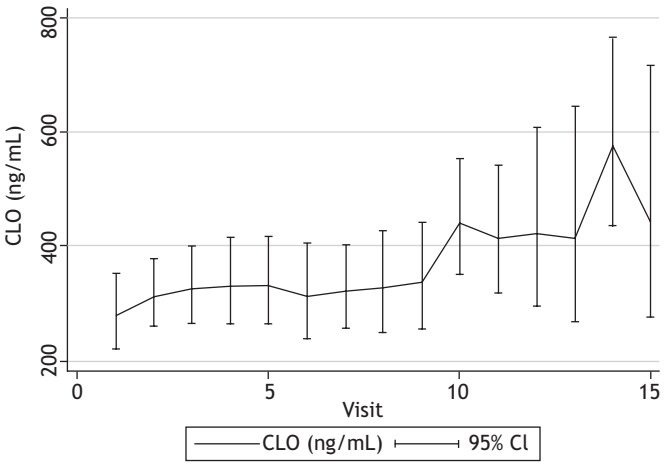

Figure 3. Distribution of mean blood clozapine levels across visits.

However, some participants had disproportionately high clozapine and norclozapine levels compared to the doses received. Figures 4–5 show that the mean norclozapine levels and clozapine/norclozapine ratio remain stable across the visits.

In the multivariable adjusted analysis (table 2), none of the included covariates were statistically significantly associated with dose levels, although there was an indication of a positive association with DUP (p=0.082). In a sensitivity analysis, by excluding one participant with only one visit, the results remained unchanged (Supplement Table S2). Clozapine dose is associated with blood clozapine (table 3) and norclozapine levels (table 4) and with a lower clozapine/norclozapine ratio (table 5). Specifically,

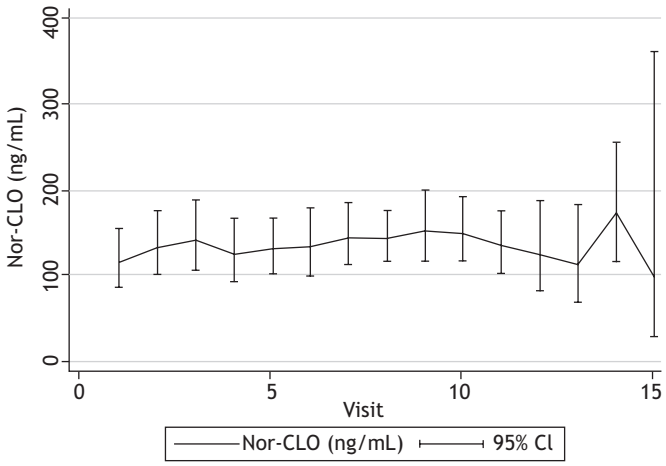

Figure 4. Distribution of mean blood clozapine levels across visits.

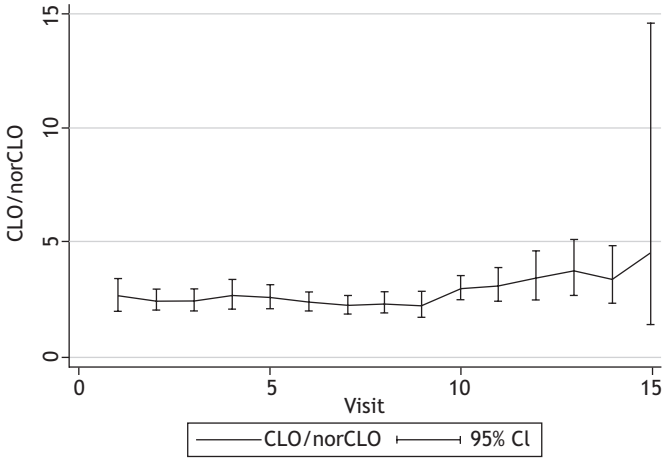

Figure 5. Distribution of mean blood clozapine levels across visits.

an increase of clozapine dose by 50mg/day was associated with higher blood clozapine (β=28.6 ng/mL, 95% CI=17.9 ng/mL to 39.2 ng/mL, p<0.001) and norclozapine levels (β=10.6 ng/mL, 95% CI=3.29 ng/mL to 17.9 ng/mL, p=0.004) but with lower clozapine/norclozapine ratio (β=–0.18, 95%CI=–0.37 to 0.00, p=0.054). As shown in table 6, in visit 5 patients receiving 250–500 mg clozapine/day (mean clozapine dose 409 mg) had a mean CLPC of 345 ng/ml and a mean norclozapine PC of 138 ng/ml and those receiving >500 mg clozapine/day (mean clozapine dose 629 mg) showed a mean of 493 ng/ml of CLPC and a mean of 203 ng/ml for norclozapine PC.

Clozapine levels were not associated with BMI, the PANSS scale and its subscales at follow-up or their changes from baseline. (Supplement Tables S6–S15).

Discussion

In our study, we did not observe differences in CLPC between males and females, although other studies[21,22] report higher CLPC in female patients for the same clozapine dose. This finding could be explained by the small number of female participants in our study (N=9). More smokers have CLPC<250 ng/ml compared to NS (24.8% vs 13.3%), and only 1% of smokers have CLPC> 750ng/ml compared with 13.3% of NS. This is an indication that smokers had lower CLPC than NS for similar clozapine dosages.

Mayerova et al (2018)[22] reported that 67% of the study participants had CLPC outside the suggested reference range, with 43% of them having supratherapeutic and

Table 2. Multivariable adjusted model for clozapine dose (mg/day) and risk factors (n=38, visits=342).

Covariate	β	95% Confidence Interval		p-value
Age (per year)	4.39	–4.73	13.51	0.346
Sex				
Female*	0			
Male	44.83	–59.93	149.59	0.402
Smoking				
No*	0			
Yes	–90.34	–193.76	13.07	0.087
Drug before clozapine	0			0.352
Amisulpride	191.74	–211.70	595.19	0.396
Aripiprazole	180.10	–236.19	596.38	0.216
Haloperidole	213.41	–124.54	551.36	0.168
Olanzapine	227.06	–95.88	550.00	
Risperidone				
DUP (per week)	15.61	–2.01	33.23	0.082
BMI (before clozapine), per kg/m^2	1.39	–37.38	40.16	0.944
PANSS-Total (Before clozapine), per unit	–3.03	–6.82	0.75	0.116

Abbreviations: BMI, body mass index; DUP: duration of untreated psychosis; PANSS: Positive and Negative Syndrome Scale

Table 3. Multivariable adjusted model for blood clozapine levels (ng/mL) and risk factors (n=38, visits=342).

Covariate	β	95% Confidence Interval		p-value
Clozapine (per 50 mg/day)	28.56	17.94	39.19	<0.001
Age (per year)	–0.99	–13.48	11.50	0.876
Sex		–93.04	193.71	0.491
Female*	0			
Male	50.33			
Smoking	0	–235.35	49.43	0.201
No*	–92.96			
Yes				
Drug before clozapine	0	–728.86	370.90	0.524
Amisulpride*	–178.98	–525.83	605.61	0.890
Aripiprazole	39.89	–645.39	275.92	0.432
Haloperidole	–184.73	–492.35	389.15	0.819
Olanzapine	–51.60			
Risperidone				
DUP (per week)	–6.79	–31.04	17.46	0.583
BMI (before clozapine), per kg/m^2	–6.68	–59.41	46.04	0.804
PANSS-Total (Before clozapine), per unit	0.06	–5.12	5.25	0.980

* Reference category

Abbreviations: BMI, body mass index; DUP: duration of untreated psychosis; PANSS: Positive and Negative Syndrome Scale

Table 4. Multivariable adjusted model for blood nor-clozapine levels (ng/mL) and risk factors (n=38, visits=342).

Covariate	β	95% Confidence Interval		p-value
Clozapine (per 50 mg/day)	10.60	3.29	17.91	0.004
Age (per year)	–1.33	–8.23	5.58	0.706
Sex	0	–86.10	72.67	0.868
Female*	–6.71			
Male				
Smoking	0	–107.69	50.12	0.475
No*	–28.79			
Yes				
Drug before clozapine	0	–426.23	179.65	0.425
Amisulpride	–123.29	–201.25	420.74	0.489
Aripiprazole	109.74	–344.24	162.88	0.483
Haloperidole	–90.68	–312.41	173.16	0.574
Olanzapine	–69.63			
Risperidone				
DUP (per week)	–4.81	–18.25	8.63	0.483
BMI (before clozapine), per kg/m^2	3.80	–25.23	32.83	0.798
PANSS-Total (Before clozapine), per unit	0.75	–2.12	3.62	0.608

Abbreviations: BMI, body mass index; DUP: duration of untreated psychosis; PANSS: Positive and Negative Syndrome Scale

24% subtherapeutic CLPC. Similarly, Couchman et al. (2010)29 reported in 104,127 samples from 26,796 patients that 70.9% of the samples were outside the suggested reference range, with 42.5% of the samples showing lower and 28.4% higher plasma concentrations. CLPC seems to be correlated with clinical response more than clozapine doses.[17] CLPC less than 250 ng/ml are associated with relapse, while CLPC of more than 750 ng/ml is associated with an increased risk of side effects.[26] However, because of its complex metabolism, clozapine levels for a given dose vary considerably. Patients receiving the same dose of clozapine have shown a 7 to 45 –fold inter– individual variation in serum concentration levels.[34,35] Factors that influence CLPC are, among others, sex, age, smoking

Table 5. Multivariable adjusted model for clozapine/nor–clozapine ratio and risk factors (n=38, visits=342).

Covariate	β	95% Confidence Interval		p-value
Clozapine (per 50 mg/day)	–0.18	–0.37	0.00	0.054
Age (per year)	0.04	–0.12	0.20	0.608
Sex	0	–1.33	2.36	0.582
Female*	0.52			
Male				
Smoking	0	–1.59	2.08	0.792
No*	0.25			
Yes				
Drug before clozapine	0	–5.29	8.73	0.630
Amisulpride*	1.72	–7.53	6.84	0.925
Aripiprazole	–0.34	–4.61	7.12	0.676
Haloperidole	1.25	–4.17	7.07	0.613
Olanzapine	1.45			
Risperidone				
DUP (per week)	0.04	–0.27	0.36	0.781
BMI (before clozapine), per kg/m^2	–0.56	–1.23	0.11	0.103
PANSS-Total (Before clozapine), per unit	–0.01	–0.08	0.06	0.744
DUP (per week)	36.06	–1553.05	1625.17	0.961
Number of visits (per unit)	293.51	–434.94	1021.96	0.397
PANSS-Total (before clozapine), per unit	–357.43	–928.28	213.43	0.198

*Reference category
Abbreviations: BMI, body mass index; DUP: duration of untreated psychosis; PANSS: Positive and Negative Syndrome Scale; DUP, duration of untreated psychosis; PANSS, Positive and Negative Syndrome Scale

Table 6. Clozapine Plasma Concentrations per dose and per measurement in visit 5 (n=30).

Variable	Obs	Mean	Std. Dev.	Min.
Dose=250-500				
Max				
Clozapine	22	409.0909	71.77406	300
500				
CLOngmL	22	345.2	168.2677	40.7
669				
NorCLOngmL	22	138.0182	91.00743	22.26
394.6				
CLOnorCLO	22	3.05295	1.677206	.8340164
6.567487				
Dose=>500				
Max				
Clozapine	7	628.5714	69.86381	550
750				
CLOngmL	7	493	168.0563	382.5
820.7				
NorCLOngmL	7	202.5314	86.7944	74.92
287.8				
CLOnorCLO	7	2.990094	1.655803	1.329048=
5.448478				

status, caffeine, BMI, concomitant medications, and genetic factors.[36,22]

On the contrary, in our study, by analyzing 342 samples from 38 patients, we found that clozapine and norclozapine plasma concentrations were correlated with clozapine daily dosages. Clozapine dose was positively associated with blood clozapine and norclozapine levels and negatively with the clozapine/norclozapine ratio. More specifically, an increase of clozapine dose by 50mg/day was associated with higher blood clozapine and norclozapine levels but with a lower clozapine/norclozapine ratio, due to the longer half-life of norclozapine.

Ding et al (2024)[37] reported in a retrospective study of clozapine and norclozapine PC a linear correlation between CLPC and the prescribed clozapine dose. 9.18% of the samples showed CLPC>600 ng/ml, 22.19% showed CLPC between 350–600 ng/ml, while 68.63% of the samples showed values <350 ng/ml. In the female group, clozapine and norclozapine PC were higher than in the male group, and a higher proportion of CLPC within the therapeutic window of 350–600 ng/ml was found in females compared to males. Clozapine/rorclozapine ratio did not differ between sexes. Patteet et al (2014)[38] reported that only 22.3% (72 out of 323) of the samples were within therapeutic range, and a similar percentage (26.9) was found in a recent study by Baldelli et al. (2021).[39]

Wickramarachchi et al (2022)[40] found in a sample of 247 patients that 87 (19.7%) had norclozapine PC higher than CLPC, and the lowest clozapine/norclozapine ratio was 0.47. In these patients' group, norclozapine levels were more than twofold higher than the ones of clozapine. Given the fact that norclozapine has been associated with adverse effects such as sedation, hypersalivation, and weight gain, routine monitoring of norclozapine levels is strongly recommended for this subgroup of patients. Clozapine, norclozapine PC, and their ratio were significantly lower in females compared to males.

The clozapine/norclozapine ratio could provide us with useful information regarding clozapine metabolism due to the fact that norclozapine has a longer half-life than the parent compound. As such, a ratio <0.5 could suggest poor adherence to treatment in the previous 24 hours or rapid metabolism of clozapine, while a ratio >3 may suggest saturation of metabolism or possible inhibition by concomitant medications.[29] In our study, one sample had a clozapine/norclozapine ratio <0.5, 11 samples out of a total of 342 (3.21%) had a clozapine/norclozapine ratio between 0.5 and 1. A ratio between 1 and 3 was found in 194 (56.7%) samples and a ratio >3 in 136 samples (39.7%). These results confirm that our study participants were compliant with treatment.

Elevated norclozapine rather than clozapine levels seem to be correlated with increases in weight, BMI, and disturbances in metabolic parameters such as triglyceride and fasting glucose levels (Lu et al 2004).[41] In our study, CLPC was not associated with BMI at follow-up or its change from baseline.

We found an indication of an association between higher CLPC and longer DUP, probably because these patients need higher clozapine doses to achieve clinical response.

CLPC emphasizes the individualized medication model "one patient, one dosage" that is replacing the traditional paradigm of "multiple patients, one dosage". Therapeutic Drug Monitoring (TDM) represents a particularly important tool in clinical practice for psychiatric disorders. Inter-individual variability in drug pharmacokinetics and pharmacodynamics contributes significantly to either subtherapeutic plasma concentrations or toxicity at standard recommended dosage. We emphasize the importance of regular monitoring of clozapine and other antipsychotics in patients receiving these medications as a chronic treatment.[37]

Clozapine has a narrow therapeutic range (the range between an effective and a potentially toxic dose)[41,42] as reflected in its narrow therapeutic index (1.71). For any medication with a narrow therapeutic index (<3), TDM is strongly recommended to minimize the possibility of dose-dependent side effects and toxicity; importantly, clozapine's side effects are strongly correlated with CLPC.

CLPC may vary from day to day in the same patient, even with the same daily dosage. For each patient, a mean of several measurements represents better his/her metabolism. Repeated measurements over time may help the clinicians explain better the variability observed in one or more samples. Probably many factors are implicated in normal variations of CLPC, with poor compliance and changes in smoking habits being the ones better understood.[43]

We acknowledge the following limitations in our study:

Our study group was small, and the number of samples we obtained is also relatively small.

Smoking was not used as a continuous variable. Even more, smokers differ in the intensity with which they smoke and tend to understate the number of cigarettes they smoke per day. Even small increases or reductions

in the number of cigarettes smoked per day may require a clozapine dose adjustment and influence CLPC.[42]

DUP was crudely assessed using information from patients and close relatives.

A strength of our study is the fact that we followed a homogeneous group of early psychosis, TRS patients who were switched early on to clozapine; they were in antipsychotic monotherapy with clozapine and exhibited high levels of compliance and consistent improvement.

In conclusion, the clozapine dose was associated with blood clozapine and norclozapine levels but not with the clozapine/norclozapine ratio. More specifically, an increase of clozapine dose by 50 mg/day was associated with higher blood clozapine and norclozapine levels but with a lower clozapine/norclozapine ratio (β=–0.18, 95%CI=–0.37 to 0.00, p=0.054).

Acknowledgments

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi: https://doi.org/10.22365/jpsych.2025.001

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Ερευνητική εργασία

Συγκεντρώσεις κλοζαπίνης και νορκλοζαπίνης στο πλάσμα και ο λόγος αυτών (κλοζαπίνη/νορκλοζαπίνη) σε ασθενείς με νεοδιαγνωσθείσα σχιζοφρένεια που αποδείχθηκαν ανθεκτικοί στη θεραπεία

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ΠΕΡΙΛΗΨΗ

Η ανθεκτική στη θεραπεία σχιζοφρένεια αφορά περίπου το 30% των ασθενών με σχιζοφρένεια, για τους οποίους η κλοζαπίνη αποτελεί τη θεραπεία εκλογής. Η κλοζαπίνη παραμένει ένα αντιψυχωτικό που υποσυνταγογραφείται εξαιτίας και των σοβαρών ανεπιθύμητων ενεργειών του. Η μέτρηση των επιπέδων κλοζαπίνης και του ενεργού μεταβολίτη της, της νορκλοζαπίνης στο πλάσμα θα συνέβαλε στον περιορισμό των ανεπιθύμητων ενεργειών αλλά και στην διαπίστωση της τήρησης της φαρμακευτικής αγωγής. Η μέτρηση των συγκεντρώσεων αυτών δεν αποτελεί μέχρι σήμερα συνήθη κλινική πρακτική, παρά το γεγονός ότι οι συγκεντρώσεις της κλοζαπίνης στο πλάσμα φαίνεται να επηρεάζονται από πολλούς παράγοντες και δεν αντικατοπτρίζουν πάντα τη λαμβανόμενη δόση. Σκοπός της μελέτης αυτής ήταν η μέτρηση συγκεντρώσεων κλοζαπίνης και νορκλοζαπίνης στο πλάσμα ομάδας ασθενών με νεο διαγνωσθείσα σχιζοφρένεια που αποδείχθηκαν ανθεκτικοί στη θεραπεία με άλλα αντιψυχωτικά και ο υπολογισμός του λόγου κλοζαπίνης προς νορκλοζαπίνη, ώστε να διαπιστώσουμε αν οι συγκεντρώσεις του φαρμάκου στο πλάσμα συσχετίζονται με τη χορηγούμενη ημερήσια δοσολογία και εάν και κατά πόσο επηρεάζονται από κοινωνικο-δημογραφικούς παράγοντες. Τριάντα οκτώ ασθενείς σε μονοθεραπεία με κλοζαπίνη συμπεριελήφθησαν στη μελέτη και συγκεντρώθηκαν συνολικά 342 δείγματα αίματος. Η μέτρηση των συγκεντρώσεων κλοζαπίνης και νορκλοζαπίνης πραγματοποιήθηκε με τη μέθοδο της υγρής χρωματογραφίας υψηλής απόδοσης σε συνδυασμό με δίδυμη φασματομετρία μάζας (UHPLC-MS/MS). Εφαρμόστηκαν μοντέλα γραμμικής παλινδρόμησης σε αναζήτηση πιθανών συσχετίσεων μεταξύ συγκεντρώσεων κλοζαπίνης και νορκλοζαπίνης στο πλάσμα και των χορηγούμενων δόσεων. Η διάμεση δόση κλοζαπίνης και οι διάμεσες συγκεντρώσεις κλοζαπίνης, νορκλοζαπίνης και ο λόγος τους στην πρώτη και την τελευταία αιμοληψία είχαν ως εξής: 400mg/ημέρα (IQR = από 350mg/ημέρα ως 500mg/ημέρα) και 425mg/ημέρα (IQR=από 350mg/ημέρα ως το 600 mg/ημέρα), 335 ng/ml (IQR=191 ng/ml ως 427 ng/ml) και 389 ng/ml (IQR=276 ng/ml ως 523 ng/ml), 129 ng/ml (IQR= 2 ng/ml ως 218 ng/ml) και 135 ng/ml (IQR=82 ng/ml ως 209 ng/ml), 2.5 (IQR=1.6 to 4.8) και 2.9 (IQR=1.7 ως 4.4). Μια αύξηση στην ημερήσια δόση της κλοζαπίνης κατά 50mg συσχετιζόταν με αύξηση των συγκεντρώσεων κλοζαπίνης και νορκλοζαπίνης αλλά με χαμηλότερο λόγο κλοζαπίνης προς νορκλοζαπίνη. Συμπερασματικά, οι ημερήσιες δόσεις κλοζαπίνης συσχετίζονται θετικά με τις συγκεντρώσεις κλοζαπίνης και νορκλοζαπίνης στην ομάδα των υπό μελέτη ασθενών και αρνητικά με το λόγο κλοζαπίνης/νορκλοζαπίνης.

ΛΕΞΕΙΣ ΕΥΡΕΤΗΡΙΟΥ: Κλοζαπίνη, νορκλοζαπίνη, λόγος κλοζαπίνης/νορκλοζαπίνης, ανθεκτική στη θεραπεία σχιζοφρένεια, πρώτο ψυχωτικό επεισόδιο.

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Review

Under pressure: A systematic review of the mental health impact of COVID-19 pandemic on mental health workers

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ABSTRACT

The COVID-19 pandemic emerged suddenly, profoundly impacting the lives of us all, including mental health workers (MHW). This unprecedented crisis introduced significant challenges for MHW, exposing them to increased risks of psychological distress. This systematic review aims to evaluate the psychopathological effects of the COVID-19 pandemic on MHW. Additionally, it seeks to explore factors –social, regional, occupational, and others– influencing these effects. A systematic search was conducted across PubMed, PsycINFO, and Embase databases following PRISMA guidelines. A total of 2621 citations were screened, with 29 studies meeting the inclusion criteria for analysis. Our review focused exclusively on studies utilizing validated measurement tools to ensure reliability. Our findings revealed a high prevalence of anxiety, depression, stress, trauma-related disorders, and burnout among mental health nurses and other MHW during the COVID-19 pandemic, with significant variations based on regional, occupational, gender, and other demographic factors. Depressive symptoms ranged from 16.8% to 52.2%, and anxiety levels varied from 9.7% to 63% among MHW. Interestingly, MHW exhibited lower rates of depression and anxiety compared to other healthcare workers and the general population, indicating higher resilience. Factors such as younger age, female gender, profession, work setting, fear of COVID-19, and workload were associated with increased psychological distress. Our review also underscores the need for more systematically accurate trauma research, particularly in how trauma is defined and assessed during global crises. While the consistency in study findings highlights the considerable effect of the pandemic, we observed differences that suggest the influence of multiple interacting factors. The lack of longitudinal studies and comparative data limits the ability to determine changes over time and differences with other groups. The COVID-19 pandemic significantly affected the mental health of those responsible for caring for the mental health of others, with considerable variations influenced by multiple interacting factors. Our findings highlight the critical need for protective protocols and psychological support systems to mitigate adverse effects on MHW during global crises. The variance in impact across different countries, in relation to local, political, cultural, and other factors, provides a foundation for future research.

KEYWORDS: COVID-19, mental health workers, depression, anxiety, trauma, systematic review.

Introduction

The COVID-19 pandemic exposed significant vulnerabilities in healthcare systems worldwide. Inadequate preparation and the virus's objective danger led to unprecedented challenges.[1,2] WHO reported a 25% increase in global rates of depression and anxiety in the first year of the pandemic.[3] Mental health workers (MHW) faced this burden magnified by deficiencies of health systems.[4] Reviews and meta-analyses assessed the mental health impact of COVID-19 on healthcare workers (HW), reveal-

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ing significant levels of depression, anxiety, PTSD, and insomnia.[5–8] The meta-analysis by Lee et al[6] found that HW experienced depression (28.5%), anxiety (28.7%) and PTSD (25.5%). Another meta-analysis involving frontline HW demonstrated that 44.6% reported depression, 43% anxiety, and 53% stress.[7] These rates exceeded the general population (33.7%, 31.9%, 29.6%)[9] and were closer to COVID-19 patients (45%, 47%, 34%).[10]

Crocker et al found COVID-19 significantly impacted MHW work-related and personal outcomes, increasing depression, anxiety, fear, stress, and insomnia.[4] However, their review included studies with varying methodologies, some using non-validated tools and semi-structured interviews.

To our knowledge, no review focused on psychopathology among MHW during the COVID-19 pandemic. Our study addresses this gap by systematically reviewing MHW psychopathology during the COVID-19 pandemic, focusing exclusively on studies using validated measures. We aim to highlight factors in MHW symptom manifestation, providing insights into cultural, systemic, and contextual components.

Material and Method

This review followed PRISMA guidelines.[11] We developed a search strategy incorporating keywords related to MHW, mental health settings, and COVID-19. The search included terms like "mental health workers", "COVID-19", "pandemic", and synonyms. The search was conducted on PubMed and PsycINFO in February 2023. Reference lists of three systematic reviews[12–14] and Crocker et al[4] were screened for additional articles.

Inclusion criteria focused on peer-reviewed articles in English, investigating the impact of COVID-19 on the mental health of MHW. Exclusion criteria encompassed studies with heterogeneous samples, no specific MHW outcomes, conference proceedings, abstracts, dissertations/theses, preprint articles, and letters to the editor. Additionally, qualitative studies and studies not utilizing at least one standardized measure were omitted.

Titles and abstracts were screened, followed by full-text examination against inclusion criteria. The PRISMA flow diagram tool was utilized for guidance and transparency (figure 1). A structured data extraction template captured relevant information, including study characteristics, demographics, measurement tools, outcomes measured, and results (table 1). Themes were identified, including the impact of COVID-19 on psychopathology, associations with factors like age, specialty, etc., and the implications for MHW job.

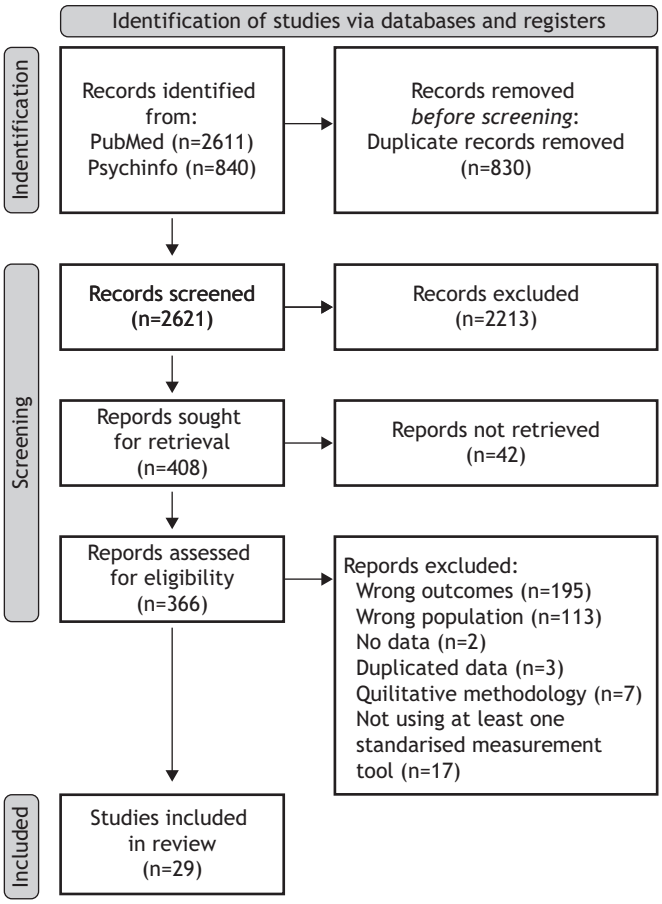

Figure 1. PRISMA 2020 flow diagram for systematic reviews.

Results

The search yielded 2621 citations, 366 underwent full-text examination, and twenty-nine met our inclusion criteria (figure 1). Findings were categorized into two main themes: "Psychopathological impact of COVID-19 on MHW" and "Factors associated with psychopathological impacts on MHW".

AXIS tool assessment found most studies of moderate quality.[15] One main issue was the use of convenience samples that did not represent the population; some studies also had unclear population definitions due to mixed clinical and community samples. [supplementary material_1].

Psychopathological impact of the COVID-19 pandemic on MHW

Depression

Depression symptoms were explored across 13 studies.[16–26] Prevalence ranged from 16.8% to 52.2%[16,18,20,21,23,25,26] with severity ranging from mild[18,19] to moderate or severe in most studies.[16,20–26] One study noted 65% of mental health nurses with depressive symptoms during the pandemic had not previously experienced similar symptoms.[19]

Table 1. Characteristics of the studies included, the measures utilized and their main and secondary findings regarding psychopathology.

Author, Year, Origin	Sample Size	SEX	Age (years) M±SD	MH specialty	Validated Psycho-pathological Outcome Measures	Other Validated Measures	Key findings	Secondary findings
Aafjes-van Doorn et al 2020, United States	N=339	249F	55±16.36	Clinical Psychologist (162) Social Worker (60) Medical Doctor (57) Counselling Psychologist (28) Other (33)	VTS		Around 15% of therapists experienced elevated levels of VT during the COVID-19 pandemic. Higher levels of trauma was associated with younger age, less clinical experience, and negative online therapy experiences.	Increased fatigue during therapy sessions (74.9%), decreased competency (34.7%), decreased connection with clients (43.0%), moderate to high vicarious trauma (77.6%)
Ali et al 2022, Pakistan	N=435 (145*3)	370F 65M	30	Doctors, Nurses, and Psychologists	SAM PSS	Brief COPE Inventory FCCQ	Subscales of cognitive appraisal (threat, challenge, centrality, stressfulness and uncontrollable) and coping strategies positively correlated with stress and fear. Psychologists used more "self-control appraisal" and "control by others appraisal" were more fearful of contracting COVID-19 than doctors.	Psychologists focus on awareness of emotions that helps in approaching, tolerating, and accepting of their emotional states. The present study finding stated that doctors and psychologists used more coping of humor as compared to nurses to deal with the pandemic of COVID-19
Alkhamees et al 2021, Saudi Arabia	N=121	51F	24–38	Psychiatry Residents	MBI, PHQ		26.4% had high emotional exhaustion, 10.7% met the criteria for high depersonalization, 24.0% demonstrated low personal accomplishment. About a quarter of the population suffered from burnout 27.3% of the population were determined to suffer from depressive symptoms, moderate depressive symptoms in 60.6%, moderately severe depressive symptoms in 21.2%, and severe depressive symptoms 18.2%. Burnout was significantly associated with depressive symptoms, with those experiencing burnout being 9 times more likely to have depressive symptoms. High scores on all burnout subscales predicted depressive symptoms. Receiving mental health help in the past two years was significantly associated with both burnout and depressive symptoms. Younger age, being male, and being in later years of residency were associated with lower rates of depressive symptoms. Singles were more likely than their married counterparts to experience burnout or depression but not significantly.	

Continues

Table 1. Continued.

Author, Year, Origin	Sample Size	SEX	Age (years) M±SD	MH specialty	Validated Psycho-pathological Outcome Measures	Other Validated Measures	Key findings	Secondary findings
Anzola et al 2022, Canada	N=146/91	NS	<65	HCP in Psychiatric Hospital vs General Hospital	DASS-21	CAS WRQoL ULS CD-RISC	Half of the participants showed no symptoms across all subscales of DASS-21 and CAS, while the remaining half displayed varying degrees of severity, ranging from mild to extremely severe. scores for coronavirus anxiety. However, a notable portion of healthcare professionals at both sites appeared to be facing challenges and experiencing difficulties.	Over a quarter of respondents exhibited positive. These findings suggest that, during the data collection period, most participants demonstrated resilience and effective coping mechanisms.
Brillon et al 2021, Canada	N =616 (plus 658 in other profession)	1136F	42.06±12.58	Psychologist (204) Psychosocial Counsellor (137) Social Worker (74) Clinical Counsellor (55) Other types of mental health providers (e.g psychiatrists, art therapists, criminologists; 146)	English and French versions of PHQ-9 GAD-7	UCLA Loneliness Scale CD-RISC	MHW reported fewer symptoms of depression and anxiety compared to the general population. In regions heavily affected by COVID-19, MHWs exhibited heightened symptoms of anxiety and depression.	MHW experienced higher levels of loneliness and vulnerability. MHWs exhibited increased loneliness, and lower resilience compared to those in regions with lower COVID-19 incidence rates.
Cabeza et al 2022, Colombia	N =429	282F	33.4±2.68	NS	PSQI		A sizable portion of individuals reported poor sleep quality (48.7%), with COVID-19 negatively impacting sleep for about one-third of respondents (33.0%). Additionally, a notable percentage experienced dreams related to COVID-19 (10.4%), including nightmares centered around fears of infection or spreading the virus to others (7.2%).	
Dahan et al 2022, Israel	N=183	F=65	47,3	Mental Health nurses	GAD-7 PTG inventory	CD- RISC National Resilience Questionnaire	Participants reported moderate levels of worry (M=3.20, SD=0.82), low levels of anxiety (M=1.50, SD=0.49), and moderate levels of post-traumatic stress disorder (PTSD) symptoms (M=3.01, SD=0.81). Notably, there were significant negative correlations between resilience and levels of worry and stress.	Higher religiosity was linked with greater resilience, and increased work experience was associated with higher levels of resilience.
Doan et al 2020, United Kingdom	N=106	50F	25–50	Psychiatrists	MBI		A burnout rate surpassing the tool's threshold was identified in 44% of the participants. A significant majority, approximately two-thirds, reported an increase in screen time by an average of 4 hours, attributed to the adoption of telemedicine during the pandemic. Of these, 41% expressed dissatisfaction with remote sessions. Moreover, 62% of participants associated strained relationships with patients with the use of face masks.	

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Table 1. Continued.

Author, Year, Origin	Sample Size	SEX	Age (years) M±SD	MH specialty	Validated Psycho-pathological Outcome Measures	Other Validated Measures	Key findings	Secondary findings
Jokic-Begic et al 2020, Croatia	N=165	115F	48.3±11.26	Psychiatrists (165)	CORE-YP	CAS BRS	In comparison to general health physicians, psychiatrists reported lower levels of anxiety.	There were no significant differences in resilience, psychological distress, or concerns related to the COVID-19 pandemic.
Kameg et al 2021, China	N=151;	116F, 23M, 1NB	N/A	APRN (54) RN (74) Other MH Worker (10)	PHQ-8, GAD-7,	PFI CAS WEMWBS	Participants exhibited mild symptoms of anxiety and depressive symptomatology, with mean scores of 7.72 and 7.48, respectively.	They reported moderate levels of job satisfaction (mean 12.7) and mental well-being (mean 45.09). Mental well-being showed positive associations with occupational fulfillment and negative associations with COVID-19-related stress, burnout, depressive symptoms, and anxiety-related symptoms. No significant association found between gender and mental well-being in the study.
King et al 2021, Ireland	N=161	82F	20–50	MH Nurses	IES-R SAS		Among the participants, 12% had an IES-R total score ranging from 24 to 32, indicative of clinically significant symptoms of post-traumatic stress disorder (PTSD), while 38% had an IES-R total score exceeding thirty-two, suggesting a potential diagnosis of PTSD. The mean score on the SAS index was 40.78 (SD=9.25), indicating moderate levels of anxiety and somatic symptoms. Thirty percent of mental health nurses experienced moderate to extreme levels of stress.	
Langdon et al 2021 United Kingdom	N=97	19M 78F		Registered Psychologist (97)	MSIT	WEMWBS	A substantial proportion of respondents reported worry about their own health (87.3%) and the health of their patients (80.9%).	These respondents demonstrated lower well-being scores compared to the general population.

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Table 1. Continued.

Author, Year, Origin	Sample Size	SEX	Age (years) M±SD	MH specialty	Validated Psycho-pathological Outcome Measures	Other Validated Measures	Key findings	Secondary findings
Minelli et al 2022, Italy	N=271	198F 73M	45.37±10.94	Nurse (86) Psychiatrist/Training psychiatrist (60) PRT/ Educator (59) Psychologist/ Psychotherapist (44) Other mental health professions (22)	LEC-5 IES-R DASS-21		19.2% of participants scored above the cut-off point for the IER-S, while no participants passed the cutoff for the DASS-21. The largest range of values for all 3 subscales was noted by psychologists. The strongest risk factors were older age, professional role, increased workload, worse team relationship, and separation from family members. Being a psychiatrist or psychologist/psychotherapist and good team relations were protective factors. Exposures to toxic substances, unwanted sexual experiences and severe human suffering were risk factors of moderate or severe depressive symptoms. Unwanted sexual experience was a risk factor of moderate or severe symptoms on the DASS Anxiety subscale. Unwanted sexual experience and severe human suffering were risk factors of moderate and severe distress symptoms.	
Napoli 2022, Italy	N=266	80F186M	25–50	Mental health nurses	PSS-10, PHQ-9		The sample mean on the stress questionnaire was 19.78, indicating moderate levels of stress. On the anxiety scale, the mean score was 9.95 indicating borderline mild depressive symptomatology since a score >10 is required to be considered mild.	
Northwood et al 2021, Australia	N=138	91F 46M 1NS	18–65	Psychiatrists, nurses, psychologists, social workers	DASS-21, CBI		52.2% and 63.0% of respondents reported moderate or more severe levels of depression or anxiety, respectively. Only 20.3% had a moderate or higher stress score. Respondents' self-rated anxiety correlated with their score on the anxiety subscale of the DASS-21.	
Ogutlu et al 2021, Turkey	N=217	150F 67M	33	Adult psychiatrists (109) Child psychiatrists (108)	CBI		60.8% of psychiatrists experienced moderate or high intensity burnout, 49.8% experienced patient-related burnout, and 31.8% experienced moderate or high intensity personal burnout. Patient-related burnout scores were significantly higher in the child psychiatry group than in the adult psychiatry group. The majority (58.1%) reported either moderate or higher levels of stress associated with the COVID-19 pandemic. Workload, reluctance to retrain in psychiatry, and feeling undervalued at work were associated with higher levels of burnout.	

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Table 1. Continued.

Author, Year, Origin	Sample Size	SEX	Age (years) M±SD	MH specialty	Validated Psycho-pathological Outcome Measures	Other Validated Measures	Key findings	Secondary findings
Pappa et al 2021, United Kingdom	N=387	78M 201F 4NS	16–20: 1 21–30: 64 31–40: 57 41–50: 71 51–65: 83 ≥66: 7	Doctors (45) Nurses (46) Psychologists (52) Health Care Assistant (21) Administrative/ Management (41) Other (76)	MBI, PHQ-9, GAD-7, AIS, NFRS	RS-14	15.9% experienced moderate to severe anxiety symptoms, and 21.9% moderate to severe depressive symptoms. Insomnia was observed by 52% of respondents. Women scored statistically significantly higher stress levels	Elevated levels of resilience were observed in 70% of participants. Women had a lower resilience score than men.
Phillips et al 2021, United States	N=207;	165F 39M 1NB 2NS	52.90±12.22	Psychologist (71) Licensed Counsellor (17) Licensed Marriage and Family Therapist (5) Social Workers (94) Other Licence (12)	PSS		Participants exhibited moderate stress levels, commonly related to concerns about COVID-19, childcare issues due to shutdowns, needing to care for a nonchild loved one. MHW cited financial stressors such as reduced caseloads, insurance uncertainties, and the cost of remote office space rental as contributing factors.	
Rapisarda et al 2021, Italy	N=241	185F	46,5±12.22	Psychologist (73) Counsellor (68) Medical doctor (28) Social Worker (15) Nurse (27) Peer Supporter (9) Support Worker (7) Manager/coordination (7) Other (7)	MBI, PHQ-9, GAD-7		Twenty percent of the participants exhibited a weighted score indicative of burnout on at least one dimension. The average anxiety score for the entire sample was 5.1, with 11.6% reporting moderate to severe anxiety levels. A moderately significant correlation was observed between GAD-7 and PHQ-9 scores. GAD-7 scores were significantly correlated with the exhaustion subscale of the MBI.	
Rapisarda et al 2022, Italy/ Canada	N=395	299F	44.4±12.2 41.8±11.1	Rehabilitation counselor 62 (29.2%) 39 (21.2%) Psychologist 59 (27.8%) 14 (7.6%) Nurse 22 (10.4%) 42 (22.8%) Medical Doctor 22 (10.4%) 15 (8.2%) Social Worker 14 (6.6%) 43 (23.4%) Peer Supporter 15 (7.1%) 0 (0.0%) Manger or Administration Officer 7 (3.3%) 17 (9.2%) Other 11 (5.2%) 13 (7.1%)	MBI, GAD-7, PHQ-9		The most common difficulties in both samples were related to job design, organizational support, and deterioration in the quality of care. Fear of COVID-19 contagion, burnout signs and common mental health symptoms were confirmed factors in both samples. Burnout signs had the strongest association with common mental health symptoms, followed by fear of COVID-19 contagion. Lack of organizational support was positively associated with burnout signs in both samples. Working in an inpatient service was associated with FCC in Quebec and with burnout signs in Lombardy. Restrictions and safety issues were associated with concerns of contracting COVID-19 at work.	

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Table 1. Continued.

Author, Year, Origin	Sample Size	SEX	Age (years) M±SD	MH specialty	Validated Psycho-pathological Outcome Measures	Other Validated Measures	Key findings	Secondary findings
Reno-Chanca et al 2021, Spain	N=413	361F	43,06	Psychologists	DASS-21, Y-BOCS		Moderate to concerning symptoms were observed in 23% of participants for depression, 24% for anxiety, and 30% for stress. Only 1.9% of participants exhibited symptoms above the mild threshold on the Y-BOCS scale. Elevated scores on the anxiety scale were predictive of higher scores on the Y-BOCS scale.	
Sadek et al 2021, Scotland	N=60	N/A	N/A	Physician 3 Nurse 43 Other Allied Healthcare professional 14	DASS-21, MBI		Most participants demonstrated values exceeding the cutoff points on at least one of the two assessment tools (75.5% and 93.5%). Median severity levels on both the DASS-21 and MBI were moderate, with the younger age group (20–35 years) showing significantly higher burnout scores.	
Schneider et al 2021, United States	N=400;	347F 46M 7NS	30.87±5.23	Psychology Intern (259) Psychology Postdoctoral Fellow/ Resident (143)	GAD-2, PHQ-2		Clinically significant anxiety symptoms were reported by 40.8% of participants, 21.7% experienced depressive symptoms. 16.9% expressed concerns about transmitting the virus to others, including family members and patients, and a notable portion reported feeling unsafe.	
Serrão et al 2022, Portugal	N=83	70F	N/S	Psychologists	CBI, DASS- 21		Most psychologists exhibited elevated levels of burnout across various dimensions, with a significant portion experiencing high work-related, personal, and client-related burnout. Participants scored below midpoint levels for depression, anxiety, and stress, indicating lower levels of these symptoms. Teleworking psychologists showed significantly higher levels of personal burnout, depression, and stress compared to those working in the workplace or not working. Having children under 12 years old was associated with higher levels of personal and work-related burnout, while teleworking was linked to increased client-related burnout. Teleworking was associated with higher levels of depression and stress, while being single was also correlated with higher depression levels.	

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Table 1. Continued.

Author, Year, Origin	Sample Size	SEX	Age (years) M±SD	MH specialty	Validated Psycho-pathological Outcome Measures	Other Validated Measures	Key findings	Secondary findings
Sklar et al 2021, United States	N=93	77F 14M 1NS 1NR	41,7	Drug/Alcohol Counselling (13) Social Work (44) Child Development (2) Marriage and Family Therapy (2) Psychology (16) Other (15)	CBI		Changes at work due to COVID-19 had a significant indirect effect on burnout. The extent of this indirect impact differed depending on factors such as job resources, organizational trust, and perceived support within the organization.	
Stefanatou et al 2022, Greece	N=224	171F 53M	38.27±10.28	Occupational therapist 127 (56.7%) Nurse 33 (14.7%) Psychologist 27 (12.1%) Psychiatrist 10 (4.5%) Social worker 13 (5.8%) Counsellors 14 (6.2%)	ProQOL	FCV-19	ProQOL scores showed moderate levels of compassion satisfaction and burnout, with low levels of STS. MHW, with extreme FCV-19 had higher scores in STS and burnout but not in compassion satisfaction compared to those with non-extreme FCV-19. FCV-19 contributed to additional variance in burnout and STS, but not in compassion satisfaction, after controlling for sociodemographic and professional factors. Younger age and female gender were associated with higher burnout and STS.	Mean FCV-19 score among MHWs was 13.76, with 23.7% experiencing extreme fear.
Sun et al 2021, China	N=536	370F 166M	39±9.63	General Physician (389) General Nurse (147)	PHQ-9, GAD-7, PANAS	GSES	18.8% reported scores greater than the cutoff point for the PHQ-9 scale, and 9.7% for the GAD-7. Those who provided services to patients suspected of having COVID-19 had higher scores on the depression and anxiety scales. Those of the nurses who had received psychiatric training showed higher positive emotions and self-efficacy, while the provision of online psychological help increased self-efficacy.	The mean GSES score was 26.29±6.45 with scores higher than 31 indicating higher self-efficacy.

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Table 1. Continued.

Author, Year, Origin	Sample Size	SEX	Age (years) M±SD	MH specialty	Validated Psycho-pathological Outcome Measures	Other Validated Measures	Key findings	Secondary findings
Vita et al 2023, Italy	N=124	87F 37M	45.52±10.99	Nurses (33.9%), Psychiatrist or psychiatry residents (28.2%), Psychiatric rehabilitation therapists and professional educators (13.7%), Psychologists and psychotherapists (14.5%), Other MHWs (9.7%)	IES-R, DASS-21		Significant symptoms of post-traumatic stress, depression, anxiety, and stress were observed in 29.8%, 16.9%, 16.1% and 21.8% respectively. Higher age was positively correlated with higher scores on the Impact of Event Scale - Revised (IES-R) and higher depression scores on the Depression Anxiety Stress Scales 21. Years of education were negatively correlated with all outcomes. A higher work burden was correlated with higher PTSD, depression, and anxiety scores, while worse team relationships were correlated with higher stress scores. In terms of depressive symptoms, the professional role and having a Covid-19-positive family member emerged as potential predictors. For anxiety symptoms, being a nurse and having more years of professional experience were potential predictors. Predictors of stress symptoms included higher years of professional experience and experiencing the death of a loved one. Being a nurse, having more years of professional experience, and experiencing the death of a patient emerged as individual predictors of higher IES-R scores. Being a nurse emerged as the only predictor of more severe depressive symptoms, while being a nurse and having more years of professional experience predicted more severe anxiety symptoms. More years of professional experience, higher workloads, worse team relationships, and experiencing the death of a loved one were individual predictors of more severe stress symptoms.	
Zhu et al 2022, China	N=270	203F 67M	35.33±8.21	Nurse (173) Doctor (83) Technician (14)	MBI-GS	CAI	Moderate and severe burnout was experienced by 8.1% of the participants. Work factors such as occupation, work shift, work pressure, work-family conflict, satisfaction with internship environment, satisfaction with salary were significantly associated with burnout.	79.6% of the participants showed low levels on the empathy ability tool.

Only measures that are associated with the reported results are listed in the table.
General abbreviations: F, female; M, male, NS, not stated; NB, non-binary; HCP, health care providers, PRT, psychiatric rehabilitation therapist, MHW, mental health workers
Validated tools abbreviations: VTS, Vicarious Trauma Survey; SAM, Stress Appraisal Measure; PSS, Perceived Stress Scale; MBI, Maslach Burnout Inventory; PHQ, Patient Health Questionnaire; DASS-21, Depression, Anxiety, and Stress Scale-21; GAD-7, Generalized Anxiety Disorder 7-item scale; CORE-YP ,Clinical Outcomes in Routine Evaluation - Youth Population; SAS, Zung Self-Rating Anxiety Scale; MSIT, The United Kingdom Health and Safety Executive Management Standards Indicator Tool; LEC-5, Life Events Checklist for DSM-5; IES-R, Impact of Event Scale – Revised; PSS, Perceived Stress Scale; PSQI, Pittsburgh Sleep Quality Index; CBI, Copenhagen Burnout Inventory; AIS, Athens Insomnia Scale; NFRS, Numerical Fear Rating Scale; Y-BOCS, Yale-Brown Obsessive-Compulsive Scale; PANAS, Positive and Negative Affect Schedule.

Another study found lower depression rates among MHW compared to workers from other sectors.[17] Psychologists had lower rates of mild (14.1%), moderate (9.4%), severe (2.4%), and extremely severe depression (1.5%) compared to HW and the public.[22]

No study employed a longitudinal design to investigate changes in depression symptoms before and after the pandemic.

Anxiety and stress

Anxiety and stress were examined across 18 studies.[5,17–22,24–31] The prevalence of anxiety among MHW ranged from 9.7%[25] to 63%,[20] and severity varied from minimal and mild[18,19] to moderate and severe.[20,31] Moderate to severe anxiety symptoms ranged from 11.6%[31] to 20.3%.[20]

One study found MHW mean scores below cutoff scales,[24] while most others revealed stress levels from mild to severe, with prevalence ranging from 14.1% to 58.1%.[22,26,32,33]

One study noted that 20.3% of MHW experienced moderate or higher stress levels,[20] while another reported that 30% of mental health nurses experienced moderate to extreme stress.[29] MHW were found to exhibit lower levels of anxiety than both the public and general health physicians.[17,28]

No study utilized a longitudinal design to assess changes in anxiety, worry, or stress symptoms before, during, and after the COVID-19 pandemic.

Trauma and post-traumatic stress symptoms

Trauma and post-traumatic stress symptoms (PTSS) were explored in 6 studies.[26,29,30,34,35]

Three studies reported PTSS among MHW in regards to the COVID-19 pandemic and the lockdown measures[29] or the COVID-19 emergency in general.[26,29,30] The prevalence ranged from 19.2% to 38%.[29,30] One study found PTSD a clinical concern for 12% and probable in 32% (29), while in another, significant PTSS were observed in 29.8% of the sample.[26]

A study on vicarious traumatization (VT) employed the Vicarious Traumatization Scale (VTS)[36] and revealed that 62.7% of therapists experienced moderate VT, while approximately 15% reported high levels.[34]

Stefanatou et al used the STS subscale of the ProQOL-5, proven to measure symptoms of secondary traumatic stress (STS). They report low levels of STS among MHW.[35]

Burnout syndrome

Burnout syndrome in MHW during the COVID-19 pandemic was investigated in 13 studies.[16,18,24,31,33,35,37–41] Prevalence varied, ranging from 20%[31] to 60.8%,[33] with most reporting burnout in over a quarter of their sample with moderate to high levels of burnout.[16,24,33,35,37,39,41]

One study found 60.8% of psychiatrists experienced moderate or high burnout, with 49.8% reporting patient-related and 31.8% personal burnout.[16] Another study found 37.3% of psychologists had high work-related burnout, 33.7% personal burnout, and 16.9% client-related burnout.[24] Burnout was a significant factor across two MHW samples from different cities.[38]

Compassion satisfaction was moderate,[35] while empathy was affected.[41] MHW reported increased fatigue, decreased competency, and reduced connection during therapy.[34]

Other psychopathological findings

One study documented 10.7% of MHW to experience depersonalization.[16] More than 50% of the MHW studied experienced poor sleep quality and insomnia.[42,21] One study reported above-mild symptoms of obsessive-compulsive disorder only in 1.9% of MHWs.[22]

Differences and similarities between countries

Depression

In the US, 21.7% of MHW experienced depressive symptoms, similar to the UK (21.9%).[23,21] Lower rates were reported in China (18.9%)[25] and Italy (16.9%).[26] In Canada, MHW reported fewer depression and anxiety symptoms than the general population.[17]. Saudi Arabia reported high rates, with 27.3% of MHW experiencing depressive symptoms (21.2% moderately severe and 18.2% severe symptoms).[16]

Anxiety, stress, and worry

In the US, 40.8% of MHW reported significant anxiety, with 16.9% concerned about transmitting the virus.[23]

In the UK, only 15.9% experienced moderate to severe anxiety.[21] In Ireland, 30% of mental health nurses exhibited moderate to extreme stress.[29] In Spain, 23% of psychologists reported anxiety, with 17% ranging from moderate to extremely severe.[22] In Italy, 11.6–16.9% had moderate to severe anxiety,[26,31] while nobody surpassed the DASS-21 cutoff in another study.[30]

In Canada, 16% scored above the anxiety cut-off, compared to 29% of the public, with heightened symptoms in regions with high COVID-19 rates.[17] In Israel, MHW reported moderate worry but low anxiety.[27]

In Australia, 63% had anxiety symptoms, though only 20.3% had moderate or higher stress levels.[20]

Trauma and PTSS

In the US, around 15% of therapists experienced high VT, with higher trauma linked to younger age, less clinical experience, and negative online therapy experiences.[34] In Greece, low levels of STS were reported, though extreme fear of COVID-19 (FOC) increased STS.[35] In Italy, 19.2–29.8% of participants scored above the IES-R cutoff, with older age, professional role, increased workload, and poor team relationships as risk factors, while being a psychiatrist or psychologist and having good team relations were protective against PTSS.[26,30] In Ireland, a striking 50% exhibited significant PTSS, 12% had scores indicative of the syndrome, and 38% potentially qualified for PTSD diagnosis.[29]

Burnout syndrome

In the US, burnout in MHW was significant: 74.9% reported increased fatigue, 34.7% decreased competency, and 43.0% felt less connected with clients (34). Work changes, influenced by job resources and organizational trust, played a significant role.[40] Similarly, 44% of UK participants surpassed the threshold, indicating burnout.[37]

In Portugal, 37.3% of psychologists had high work-related, 33.7% personal, and 16.9% client-related burnout. Teleworking was linked to increased client-related burnout.[24] In Italy, 20% exhibited burnout symptoms.[31] In China, only 8.1% experienced moderate and severe burnout, with 79.6% scoring low on empathy.[41] Greece reported moderate burnout.[35] In Saudi Arabia, 26.4% experienced high emotional exhaustion, 10.7% high depersonalization, and 24.0% low personal accomplishment, and about a quarter of MHW suffered from burnout syndrome.[16]

Extremely high burnout rates were found in Scotland (93.5% had at least one pathologic MBI score and 56.5% scored on three subtypes), particularly among the age group 20–35 years old.[39] In Turkey, 60.8% of MHW experienced moderate to high burnout, with higher rates of patient-related burnout in child psychiatry.[33]

Factors associated with the psychopathological impact of the pandemic on MHW

Age

The relationship between age and mental health outcomes is conflicting. Some studies associate younger age with increased burnout,[35,39] while others suggest it may protect against burnout[16,29] and depression.[16] In a study only MHW over 50 years scored below 24 in the IES-R scale, indicating no PTSD concerns.[29] Higher age was positively correlated with distress,[30] PTSS, and depression.[26] However, one study found no significant effects on burnout, depression, or anxiety.[31]

Gender

Regarding gender, most studies suggest that female MHW are more prone to burnout,[16,31,35] depression,[16,31] stress,[21] and STS.[35] Two studies found no significant association between gender and burnout[41] or mental well-being in general.[18]

Profession and work setting

Working as a mental health nurse has been identified as a predictor of PTSS, depression, and anxiety.[26] Among MHW, nurses exhibited the highest anxiety scores, while psychiatrists had the lowest.[30]

Full-time nurses with less than one year of experience were prone to PTSD, and ward-based nurses showed an increase in PTSS.[29] Those who have received psychiatric training had higher levels of positive emotions and self-efficacy.[25]

Other studies have highlighted doctors to be more prone to burnout than mental health nurses[41] with higher scores in the child psychiatrists group.[16]

Psychologists experienced high levels of burnout,[24] though their role was protective against depression and PTSD.[30]

Other occupational factors

Longer professional experience was associated with anxiety and PTSS,[26] while VT was associated with less clinical experience.[34] Poor team relationships contributed to depression, PTSS, and stress.[26,30] Workload and high work pressure were strongly associated with burnout, emotional exhaustion, depersonalization, and stress[33,26,41] Work-family conflict increased burnout, emotional exhaustion, and depersonalization.[41]

Working with COVID-19 patients, especially in outpatient services, perceiving a risk of infection and lack of organizational support were linked to higher burnout.[31]

However, factors like available protective equipment, workload changes, and staff psychological support had no effect on burnout.[31] Higher satisfaction with the work environment, humanistic care ability, and salary were linked to reduced burnout, emotional exhaustion, and depersonalization.[41] On the other hand, feeling undervalued increased burnout.[33]

Working full-time on-site led to more anxiety and depression compared to working from home, with less support reported.[23] In another study, providing online

psychological assistance was protective for self-efficacy.[25] Conversely, in another study, teleworking psychologists exhibited higher levels of personal burnout, depression, and stress.[24] Additionally, negative online therapy experiences were associated with VT.[34]

Workplace changes indirectly affected burnout, influenced by job resources, organizational trust, and perceived support.[40,41]

Impact of Fear of COVID-19

FOC significantly affected MHW. In particular, both fear of infection and infecting others have been reported.[42]

MHW with FOC had higher scores in STS and burnout,[34,35] but not in compassion satisfaction.[35] FOC contributed to burnout and STS even after controlling for sociodemographic and professional factors.[35]

Perceived risk of contracting COVID-19 at work was linked to increased anxiety and depression, while working with non-infected individuals correlated with lower anxiety.[31] MHW serving suspected COVID-19 patients reported higher depression and anxiety.[25] In high-prevalence regions, MHW experienced more anxiety, depression, loneliness, and lower resilience.[17] Trainees who felt at risk at work showed elevated anxiety and depressive symptoms.[23] Having a family member test positive for COVID-19 was linked to higher depression.[26]

Other factors related to COVID-19 impact on MHW's mental health

Recent studies highlight that MHWs who sought mental help before the pandemic were more prone to depressive symptoms.[16] Being single, divorced, or separated from family increased the risk of PTSD and depression.[16,24,30] Parents of young children faced higher burnout.[24] Exposure to trauma, such as toxic substances or sexual experiences, elevated the risk of severe depressive, anxiety, and distress symptoms.[30] The death of a loved one significantly predicted stress, and the death of a patient was linked to PTSS.[26] Education levels were inversely correlated with PTSS, depression, anxiety, and stress scores.[26]

Discussion

In our review, we investigated the impact of COVID-19 on the mental health of the MHW, aiming to shed light on the challenges faced by those whose task is to care for the mental health of others. We tried to address the factors that contributed to these issues and investigate differences and similarities with the public, other HW, and between different countries.

We identified 29 studies that met our criteria. MHW experienced a wide range of mental health issues during the pandemic, including symptoms of depression, anxiety, stress, trauma-related disorders, and burnout. While studies agreed on the impact, prevalence varied.

Depressive symptoms ranged from 16.8% to 52.2% of MHW and from mild to severe. Notably, 65% of mental health nurses with depressive symptoms experienced depression for the first time during the pandemic. MHW exhibited lower depression rates than both the general population and other HW.

Anxiety symptoms varied widely from 9.7% to 63% and ranged from moderate to severe. Significant proportions of MHW reported moderate to extreme stress. However, MHW had lower anxiety and stress levels compared to the public and HW.

Burnout ranged from 20% to 60.8%, with fatigue, decreased competency, and diminished client connection reported by MHW.

PTSS were significant, with 19.2% to 38% of MHWs scoring above the cutoff of the scales for PTSD. Secondary trauma levels varied across countries, with therapists in the US showing high VT and MHW in Greece exhibiting low STS.

We feel the need to make a special remark concerning the studies that assessed trauma and post-traumatic symptoms. One significant limitation is the lack of comprehensive assessment of PTSD symptoms according to diagnostic criteria. Instead, they focused on scales that assess symptoms of post-traumatic syndromes that are present in other conditions as well. This could result in inflated rates of PTSS and vague estimations of PTSD.

Aafjes-van Doorn et al and Stefanatou et al examined secondary trauma.[34,35] While their results reflect the distress felt by working with patients during the pandemic, they cannot examine if the primary trauma of patients was the pandemic itself or the differences in prevalence of secondary trauma before the pandemic. Minelli et al employed the Life Events Checklist for DSM-5 (LEC-5) but did not specifically link traumatic experiences to the pandemic.[30] Vita et al, King et al, and Minelli et al assessed PTSD symptoms using the Impact of Event Scale-Revised (IES-R) with the first two using "COVID-19 pandemic and the lockdown measures" as the traumatic event and the last noting that "participants were specifically asked to refer to the COVID-19 pandemic emergency" while answering.[26,29,30] IES-R is a scale designed and validated with a specific traumatic event as a reference. The COVID-19 pandemic and the subsequent measures span a wide period and include a variety of different events. Studies that

label the pandemic or lockdowns as inherently traumatic may inflate PTSD prevalence rates. Without referencing a specific traumatic event, IES-R could capture symptoms attributable to other conditions.

Traditional trauma definitions may not fully capture the unique stressors and impact of the pandemic. This calls for a reevaluation of what constitutes a traumatic event in the context of global crises like the COVID-19 pandemic.[43]

A secondary issue is the aspects of some scales used for assessing trauma. For example, Aafjes-van Doorn et al used the VTS, originally developed to measure distress in solicitors working with traumatized clients.[34] Although the VTS has been evaluated for internal consistency and factor structure, its validity is not established.

Our study has certain limitations. Despite the decent quality of our data, no longitudinal studies assessed changes in symptoms before and after the pandemic. There was a lack of comparative studies with other population groups or the general population. Prior to 2019, there is limited systematic or meta-analytical evidence on the prevalence of psychopathology in MHW. Two studies of that sort focused on burnout (44,45) report emotional exhaustion to be 34.5–40% already before the pandemic. Another study reported high prevalence of stress among psychiatrists, reaching 25%.[46] Finally, regarding STS, studies prior to 2019 reported conflicting results.[47] We tried to compensate for the inherent limitations of systematic reviews, such as publication bias, by incorporating robust methodology (PRISMA).

Prevalence rates vary, complicating conclusions regarding differences between MHW, HW, and the public. Comparative studies found a lower prevalence of depression and anxiety in MHW. An arising question would be if these differences preceded the pandemic or are associated with it. Lower MHW rates might be due to higher resilience, linked to their working situation. MHW may have worked more frequently during restrictive measures, being more protected than HW at the workplace. Conflicting reports about teleworking add to this complexity.

Mental health nurses, especially those in inpatient services or with less than a year of experience, were particularly vulnerable to PTSS, depression, and anxiety. Psychologists and psychotherapists showed lower depression and PTSS but higher burnout. High workload, poor team relationships, and close contact with COVID-19 patients or perceived infection risk were linked to increased burnout, depression, PTSD, and stress. On the other hand, satisfaction with the work environment, perceived organizational support, and humanistic care ability were associated with reduced burnout and emotional exhaustion.

FOC was associated with increased anxiety, depression, and stress. The perceived risk of contracting COVID-19 amplified these effects. Fear of the virus also contributed to higher burnout levels, particularly in settings with inadequate protective measures or organizational support. This highlights the critical need for protective protocols and psychological support systems to mitigate the adverse effects on MHW.

We reported the significant mental health impact of the COVID-19 pandemic on MHWs across different countries. However, the variation suggests that local factors, healthcare systems, policies, and pandemic severity play crucial roles in outcomes. Our results contribute to the examination of these differences for future research.

Our findings demonstrate that COVID-19 left a considerable impact on the mental health of MHW. Consistency across studies highlights the pandemic's significant effect, while differences emphasize its complexity. Variability across countries implies that governmental, structural, cultural differences, and pandemic response strategies may influence mental health outcomes, making this a promising area for future research to inform better prevention strategies for similar events.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.22365/jpsych.2024.025

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Ανασκόπηση

Υπό πίεση: Συστηματική ανασκόπηση του αντίκτυπου της πανδημίας COVID-19 στην ψυχική υγεία των εργαζόμενων στην ψυχική υγεία

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ΠΕΡΙΛΗΨΗ

Η πανδημία COVID-19 εμφανίστηκε ξαφνικά, επηρεάζοντας βαθιά τη ζωή όλων μας, συμπεριλαμβανομένων των εργαζομένων στην ψυχική υγεία (ΕΨΥ). Αυτή η πρωτοφανής κρίση εισήγαγε σημαντικές προκλήσεις για τους ΕΨΥ, εκθέτοντάς τους σε αυξημένους κινδύνους ψυχολογικής επιβάρυνσης. Η παρούσα συστηματική ανασκόπηση στοχεύει στην αξιολόγηση των ψυχοπαθολογικών επιδράσεων της πανδημίας COVID-19 στους ΕΨΥ. Επιπλέον, επιδιώκει να διερευνήσει παράγοντες – δημογραφικούς, γεωγραφικούς, επαγγελματικούς και άλλους – που συνέβαλαν σε αυτές τις επιπτώσεις. Μετά από μια συστηματική αναζήτηση στις βάσεις δεδομένων PubMed, PsycInfo και Embase, ακολουθώντας τις κατευθυντήριες γραμμές PRISMA, εντοπίστηκαν 2621 δημοσιεύσεις, εκ των οποίων 29 μελέτες πληρούσαν τα κριτήρια ένταξης στην ανάλυση. Η ανασκόπηση μας επικεντρώθηκε αποκλειστικά σε μελέτες που χρησιμοποίησαν επικυρωμένα εργαλεία, διασφαλίζοντας την αξιοπιστία των αποτελεσμάτων. Τα ευρήματά μας αποκάλυψαν υψηλό επιπολασμό άγχους, κατάθλιψης, διαταραχών που σχετίζονται με το τραύμα και επαγγελματικής εξουθένωσης στους ΕΨΥ κατά τη διάρκεια της πανδημίας COVID-19, με σημαντικές διακυμάνσεις ανάλογα με γεωγραφικούς, επαγγελματικούς, δημογραφικούς παράγοντες, όπως το φύλο. Τα καταθλιπτικά συμπτώματα κυμαίνονταν από 16,8% έως 52,2% και τα επίπεδα άγχους από 9,7% έως 63%. Είναι ενδιαφέρον ότι οι ΕΨΥ παρουσίασαν χαμηλότερα ποσοστά κατάθλιψης και άγχους σε σύγκριση με άλλους εργαζόμενους στον τομέα της υγείας και τον γενικό πληθυσμό, πιθανώς λόγω υψηλότερης ανθεκτικότητας. Παράγοντες όπως η νεότερη ηλικία, το γυναικείο φύλο, το επάγγελμα, ο φόρτος εργασίας και ο φόβος του COVID-19 συσχετίστηκαν με δυσμενέστερα αποτελέσματα. Η ανασκόπηση μας υπογραμμίζει επίσης την ανάγκη για πιο ακριβή και συστηματική έρευνα γύρω από το τραύμα, ιδιαίτερα όσον αφορά τον ορισμό και την αξιολόγησή του σε παγκόσμιες κρίσεις. Ενώ η συνέπεια στα ευρήματα υπογραμμίζει τη σημαντική επίδραση της πανδημίας, παρατηρήθηκαν διαφορές που υποδηλώνουν την επίδραση πολλαπλών αλληλεπιδρώντων παραγόντων. Η έλλειψη διαχρονικών μελετών και συγκριτικών δεδομένων περιορίζει την ικανότητα να προσδιοριστούν οι αλλαγές στο χρόνο και οι διαφορές με άλλες ομάδες. Η πανδημία COVID-19 επηρέασε σημαντικά την ψυχική υγεία όσων είναι υπεύθυνοι για τη φροντίδα άλλων, με διακυμάνσεις που οφείλονται σε αλληλεπιδρώντες παράγοντες. Τα ευρήματά μας τονίζουν την ανάγκη για προστατευτικά πρωτόκολλα και συστήματα ψυχολογικής υποστήριξης για την άμβλυνση των δυσμενών επιπτώσεων στους ΕΨΥ κατά τη διάρκεια παγκόσμιων κρίσεων. Η διακύμανση των επιπτώσεων στις διάφορες χώρες, σε σχέση με τοπικούς, πολιτικούς, πολιτιστικούς και άλλους παράγοντες, προσφέρεται ως πεδίο για μελλοντική έρευνα.

ΛΕΞΕΙΣ ΕΥΡΕΤΗΡΙΟΥ: COVID-19, εργαζόμενοι ψυχικής υγείας, κατάθλιψη, άγχος, τραύμα, συστηματική ανασκόπηση.

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Review

A systematic review of depressive and anxiety symptoms in caregivers of dementia patients

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ABSTRACT

The current number of dementia cases in Europe stands at 7.7 million, a figure projected to double by 2050. Caregivers of individuals with dementia experience a heightened burden compared to those caring for other chronically ill individuals, increasing the risk of depression and stress disorders. This systematic literature review, following PRISMA guidelines, explores the prevalence of anxiety and depressive symptoms in dementia caregivers. Searches in academic databases, restricted to studies from the last 15 years, identified eighty-five articles with 16 meeting the inclusion criteria. Results indicate a significant caregiver burden, diminished self-reported quality of life, and a propensity for clinical depression. Depression and anxiety symptoms were more pronounced among female caregivers. Caregiver depression correlated with increased emergency department utilization by dementia patients, with a surge in depressive symptoms reported during the COVID-19 pandemic. Caregiving for dementia patients was associated with burnout, adversely impacting caregiver quality of life. Depression and anxiety symptoms in caregivers correlate with substance use. Sociodemographic variables, including low socioeconomic status, high urbanization levels, and older age, were associated with caregiver depression. Caregivers of individuals with Alzheimer's disease reported higher anxiety, burden, and depression scores compared to those assisting individuals with other dementias, particularly when neuropsychiatric symptoms were evident. The identification of the factors that are linked to the mental burden of caregivers allows mental health professionals to enhance symptom detection and provide tailored support, alleviating caregiver burden and improving dementia care quality. Systematic professional assistance and training opportunities through health policies can effectively alleviate caregiver burden.

KEYWORDS: Depression, anxiety, dementia, Alzheimer, caregivers.

Introduction

The current number of dementia cases in Europe is reported to be 7.7 million individuals, and projections suggest a twofold increase by the year 2050.[1] The Alzheimer's World Report 2015 indicates a global number of cases of 46.8 million individuals living with dementia in 2015, with a projected doubling approximately every two decades, reaching 74.7 million in 2030 and 131.5 million in 2050.[2] Regional variations are evident, notably in Japan where the aging population constituted 26.3% in 2015, surpassing rates in Western countries (19% in the European Union, 15% in the USA, and 8% worldwide).[2] This demographic shift signifies a considerable proportion of the elderly population, with estimates suggesting 1 in 4 individuals being elderly. Moreover,

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the trajectory of population aging is anticipated to persist, with projections indicating that by 2060, 39.9% and 26.9% of the Japanese population will be aged over 65 and 75, respectively.[3]

The provision of care for dementia afflicted individuals places a considerable strain on familial caregivers, extending beyond the financial costs to include reduced productivity and significant emotional impacts. This caregiving responsibility has pervasive implications, which have an impact on psychological well-being and the overall quality of life and they also increase the susceptibility to psychopathological conditions, including anxiety and depression. Comparative studies indicate that family caregivers of dementia patients experience a greater burden than those caring for individuals with other chronic illnesses, leading to a higher risk of depression.[4]

Identifying factors that increase psychological distress among caregivers is essential, as their sustained well-being is crucial for delivering effective care to individuals with dementia.[5] Research highlights several demographic determinants that heighten mental health challenges for caregivers, including lower educational attainment, limited income, being a spousal caregiver, female gender, and identifying as white.[6–9]

Psychological and behavioral determinants, including a less favorable self-rated health, reduced social networks, use of dysfunctional (emotion-focused) coping mechanisms, and stress manifesting as role overload, restriction, or burden, have been identified as contributors to depressive symptoms.[10–13] The burden indicators of the caregivers, are associated with the spectrum and intensity of the symptoms that are exhibited by elderly patients, including heightened behavioral issues, increased levels of physical disability [deficits in activities of daily living (ADL)], and diminished cognitive functioning, which have been documented as risk factors.[6–7,14]

Material and Method

This review was conducted following the guidelines of the preferred reporting items for systematic reviews and meta-analysis (PRISMA). The purpose of the present study is to investigate the anxiety and depression experienced by caregivers of patients with dementia.

Search strategy

Systematic searches on computerized databases were performed, in order to retrieve English language material that has been published and developed over the last 15 years. The search was conducted through the electronic databases of academic research Google Scholar, PubMed and Scopus. The following combinations of words were set as criteria for the search: caregivers AND dementia; caregivers AND dementia AND depression; caregivers AND dementia AND anxiety.

Screening criteria

Inclusion criteria: (a) Study type: single quantitative study, qualitative analysis of interviews, systematic review, systematic review and meta-analysis, cohort randomized controlled trial (b) Population of study: caregivers of patients with dementia. (c) Outcome: affective symptom outcome (including but not limited to depression, anxiety, distress, etc.). Each study underwent a critical appraisal, initially assessing its title and subsequently scrutinizing its content. Studies deemed partially unrelated to the research subject were excluded during this phase. Subsequently, the remaining studies were further evaluated, and those lacking methodological rigor or exhibiting incomplete relevance to the research topic were excluded. This meticulous process culminated the compilation of the final list of studies included in the research.

Data extraction

Data from retained articles were manually extracted into a data extraction table using Microsoft Excel. Data extracted from the retained articles included: authors, title of the study, type of study, results (see table 1). The records screening process are shown through the flowchart in figure 1.

Data synthesis and analysis

The diverse nature of the across studies data, in particular the methods of reporting symptoms or psychopathology, lead to an inability to construct a meta-analysis, therefore a narrative synthesis was used.

Results

A total of 85 records were retrieved from searching databases (Fig 1; Flow diagram of the search process). After removing twenty-three duplicates, 62 records were screened, of which 46 were excluded as not relevant. We included a total of sixteen studies, all of which were assessed for quality and included in the systematic review.

Characteristics of the studies meeting inclusion criteria are presented in table 1 and more detailed information regarding the characteristics of the studies can be found in table S1 in the appendix. Most studies were cross-sectional studies. Qualitative studies, systematic

Table 1. Data extracted from the retained articles.

S/N	Authors	Title of study	Type of study	Results
1	Ma et al 2018[15]	Alzheimer's' disease and caregiving: a meta-analytic review comparing the mental health of primary caregivers to controls	Systematic Review and Meta-Analysis	Caregivers of dementia patients have poor mental health compared to the general population, with female caregivers disproportionately affected.
2	Fong et al 2021[16]	Depression, anxiety and stress on caregivers of persons with dementia (CGPWD) in Hong Kong amid COVID-19 pandemic	Quantitative study-Cross-sectional design	High prevalence of symptoms of depression in caregivers of patients with dementia during the pandemic.
3	Alfakhri et al 2018[17]	Depression among caregivers of patients with dementia	Quantitative study-Cross-sectional design	Caregivers of patients with dementia experience significant psychological burden and lower health-related quality of life and are predisposed to develop clinical depression.
4	Guterman et al 2019[18]	Association between caregiver depression and emergency department use among patients with dementia	Longitudinal Cohort Randomized Controlled Trial	Dementia caregiver depression appears to be significantly associated with increased emergency department use by patients, revealing a key caregiver vulnerability that, if addressed with patient- and caregiver-centered dementia care, could improve health quality and reduce costs for this high-risk population.
5	Matsumoto et al 2007[19]	Caregiver burden associated with behavioral and psychological symptoms of dementia in elderly people in the local community	Quantitative study-Cross-sectional design	Certain symptoms such as hyperarousal, aggression, irritability and immobility in dementia patients can significantly affect the anxiety and depression symptoms of their caregivers, although their frequency and severity are low.
6	Huang et al 2012[20]	Caregiver burden associated with behavioral and psychological symptoms of dementia (BPSD) in Taiwanese elderly	Quantitative study-Cross-sectional design	Patient delusions had the highest mean score on the caregiver distress scale, followed by agitation/aggression, anxiety, irritability/unsteadiness, and distress/depression. The frequency of symptoms of anxiety, delusions and agitation/aggression showed a statistically significant positive correlation with the score on the caregiver distress scale. Improving treatments for delusions, agitation/aggression, anxiety, irritability/instability, and distress/depression among dementia patients may reduce caregiver burden.
7	Mougias et al 2015[21]	The burden of caring for patients with dementia and its predictors	Quantitative study-Cross-sectional design	Younger caregiver age, high behavioral symptoms of dementia patients, and caregiver depression were found to be independently associated with caregiver burnout.
8	Alves et al 2019[22]	Burnout syndrome in informal caregivers of older adults with dementia: A systematic review	Systematic Review	Burnout syndrome negatively affects the quality of life of caregivers and was associated with depression and anxiety symptoms and abusive behavior by the caregiver.
9	De Fazio et al 2015[23]	Symptoms of depression in caregivers of patients with dementia: demographic variables and burden	Quantitative study-Cross-sectional design	The study confirms the presence of symptoms of depression in a large number of high-burden caregivers. However, it demonstrates that these symptoms are mainly associated with sociodemographic variables.
10	Del-Pino-Casado et al 2019[24]	The association between subjective caregiver burden and symptoms of depression in caregivers of older relatives: A systematic review and meta-analysis	Systematic Review and Meta-Analysis	Caregiver burden is an important risk factor for developing symptoms of depression in elderly caregivers and may lead to clinical depression. Those who take care of people with dementia face a greater burden.

Continues

Table 1. Continued.

S/N	Authors	Title of study	Type of study	Results
11	Watson et al 2019[25]	Depression and anxiety among partner and offspring caregivers of people with dementia: a systematic review	Systematic Review	Depression and anxiety symptoms were related to demographic factors, patient dementia characteristics, various caregiver psychological and social factors, and dyadic relationship factors. A number of important factors were consistently associated with symptoms of depression across studies. Female caregivers and adult-child caregivers, were more likely to experience such symptoms rather than husbands . It was also found that caregivers' coping strategies and activity limitation were strongly associated with symptoms of depression. The severity of dementia-related problematic behaviors was related to caregivers' symptoms of depression and anxiety. Additionally, significant factors associated with symptoms of depression were relationship type and quality of relationships.
12	Haley et al 2008[26]	Long-term effects of bereavement and caregiver intervention on dementia caregiver symptoms of depression	Qualitative interview analysis by conducting repeat interviews	Patient death led to the diminishment of symptoms of depression for caregivers. The enhanced support intervention resulted in milder symptoms of depression both before and after bereavement.
13	Monteiro et al 2018[27]	Coping strategies used by caregivers of people with Alzheimer disease: a systematic review	Systematic Review	The use and development of coping strategies reduces the effect of depression symptoms, anxiety and the burden of responsibility experienced by caregivers.
14	Sallim et al 2015[28]	Prevalence of mental health disorders among caregivers of patients with Alzheimer disease	Systematic Review and Meta-Analysis	Caregivers of patients with Alzheimer have a higher prevalence of mental health disorders, particularly depression and anxiety, compared to the general population and their counterparts caring for patients with other diseases. The higher prevalence is mainly observed in female caregivers, caregivers with male care-recipients, and caregivers who have a spousal relationship with care-recipients.
15	Truzzi et al 2012[29]	Burnout in familial caregivers of patients with dementia	Quantitative study-Cross-sectional design	42.1% of the sample, showed high levels of emotional exhaustion, and depersonalization was found in 22.8%. Depression was one of the most important predictors of their emotional exhaustion.
16	Valente et al 2011[30]	Self-perception of health by dementia family caregivers: sociodemographic and clinical factors	Quantitative study-Cross-sectional design	The diminished perception of caregivers' health exhibited a correlation with elevated levels of emotional exhaustion, burden, as well as symptoms of depression and anxiety.

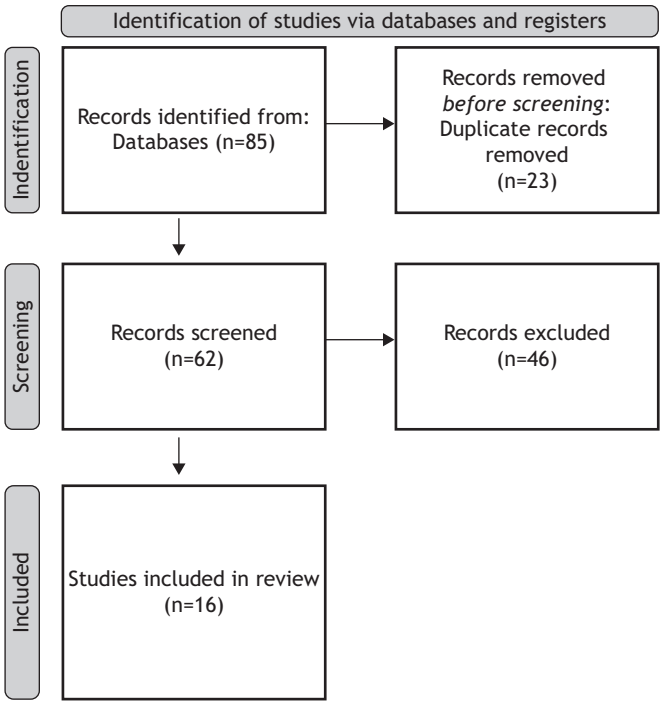

Figure 1. Prisma flow-chart of inclusion and exclusion of publications derived from the database searches.

reviews and meta-analyses were included in our study. Our systematic review of symptoms of depression and anxiety among caregivers of dementia patients reveals a concerning prevalence of psychological distress within this population. The findings consistently demonstrate that caregivers experience significantly higher rates of depression and anxiety compared to the general population, with female caregivers being disproportionately affected.[15,28] The review identifies numerous factors contributing to caregiver distress. Notably, elevated levels of caregiver burden, associated with behavioral and psychological symptoms exhibited by dementia patients, are strongly linked to increased symptoms of depression and anxiety. For instance, caregivers managing behaviors such as aggression and irritability in patients report heightened anxiety and depressive symptoms.[19–20] Our analysis also highlights the correlation between caregiver burnout and mental health outcomes. Younger caregivers and those dealing with significant behavioral issues in patients are at an increased risk for burnout, which in turn correlates with depressive symptoms.[21] Furthermore, the presence of sociodemographic variables, such as caregiver age and relationship type, influences the severity of depression experienced.[23,25] Coping strategies employed by caregivers emerge as a crucial factor in mitigating the effects of psychological distress. The effective use and development of coping mechanisms can significantly reduce symptoms of depression and anxiety, emphasizing the need for targeted interventions that enhance caregiver resilience.[27] Overall, our review underscores the urgent need for comprehensive support systems for caregivers of dementia patients. By addressing the unique challenges faced by this demographic, we can improve their mental health outcomes and overall quality of life.[18,22] Implementing patient- and caregiver-centered interventions can enhance the caregiving experience, reduce psychological burdens, and improve healthcare outcomes for this high-risk population.

Discussion

This study aimed to assess anxiety and depression levels among caregivers of individuals with dementia. To our knowledge, it is the first systematic review to apply the PRISMA methodology to explore these symptoms specifically in dementia caregivers.

Research findings indicate that caregivers of individuals with dementia encounter substantial burden and exhibit diminished health-related quality of life, with a notable susceptibility to clinical depression.[17] Moreover, symptoms of depression and anxiety are discerned to be more pronounced among female caregivers, suggesting a disproportionate impact in comparison to their male counterparts.[7] One possible explanation for the observed gender differences in caregiving may stem from stress-coping theory.[31] Research suggests that women are more likely to employ maladaptive coping strategies, such as denial, escape, and avoidance, compared to men, who more frequently utilize effective strategies like problem-solving, acceptance, and distancing.[32] Women may also experience caregiving in a more emotionally intense way than men, whose challenges may manifest differently, such as through poor health or disrupted sleep patterns. As a result, common assessment tools for measuring the negative aspects of caregiving may not fully capture men's experiences and could be more attuned to the challenges faced by female caregivers.[33]

Additionally, the studies highlight a correlation between caregiver depression and heightened emergency department use for dementia patients.[18] The ongoing COVID-19 pandemic is further identified as a contributing factor to an elevated prevalence of primarily symptoms of depression, along with other psychological effects, among caregivers of individuals with dementia.[16]

Several studies have illuminated the fact that the caregiver burden associated with the behavioral and psychological symptoms of dementia exhibits variability across different symptoms, indicating that the impact

does not uniformly correlate with the frequency and severity of the disease.[20] Specific symptoms such as agitation/aggression and irritability/immobility were identified in two studies as exerting significant effects on caregivers, notwithstanding their relatively low frequency and severity. Notably, in the context of Greece, caregiving practices diverge from those in other developed nations, with a predominant trend of familial care at home.[21] This study revealed that nearly half of the caregivers displayed pronounced signs of mental fatigue, and almost a quarter of them experienced symptoms of depression. Factors such as the caregiver's early age, heightened behavioral symptoms in dementia patients, and caregiver depression were identified as independently associated with the manifestation of mental fatigue. The study underscores the complexity of mental fatigue, emphasizing its intricate interplay with various patient and caregiver factors, thus advocating for its incorporation into routine clinical assessments in dementia care practices.

Research consistently shows that caregiving roles can lead to burnout syndrome, negatively impacting caregivers' quality of life and correlating with depressive and anxiety symptoms in care recipients, as well as instances of abusive behavior by caregivers. [22] Depression in caregivers is frequently linked to sociodemographic factors such as lower socioeconomic status, heightened urbanization, and advanced age. Additionally, a substantial body of research highlights a robust positive association between caregiver burden and symptoms of depression, with dementia caregivers exhibiting a higher effect size compared to those caring for frail elderly individuals and stroke survivors.[24] Converging evidence suggests that caregivers of individuals with Alzheimer's disease have to deal with elevated stress, burden, and depression, particularly in the presence of neuropsychiatric symptoms. Effective coping strategies can mitigate the impact of stressful situations, consequently improving caregivers' quality of life. Some studies suggest that enhanced supportive interventions were associated with reduced symptoms of depression in caregivers, implying that clinical strategies can potentially safeguard caregivers from chronic manifestations of depression. These findings underscore the need for new research focused on targeted interventions to address the complex challenges faced by caregivers.

Prevalence of mental health disorders within the caregiver population attending to individuals with Alzheimer's disease remains indeterminate. In a specific investigation, the aggregate prevalence rates were reported as follows: depression at 34.0%, anxiety at 43.6%, and psychotropic medication use at 27.2%. This study discerned that the likelihood of experiencing depression was 1.53 times higher for female caregivers, 1.86 times higher for male caregivers, and 2.51 times higher for spousal caregivers.[28] Caregivers of Alzheimer's patients exhibited an elevated prevalence of mental health disorders, notably depression and anxiety, in contrast to both the general population and caregivers attending to individuals with diverse medical conditions.

In the broader context, the existing literature on the subject is limited, and lacks randomized controlled trials. Numerous contemporary clinical studies rely on cross-sectional research designs. Given the progressive deterioration of behavioral symptoms and daily life functions in dementia, there is a need for longitudinal studies with extended follow-up periods to ascertain whether caregivers' depressive symptoms undergo temporal changes.[34] The lack of standardized methodologies across studies has made it challenging to establish definitive indicators of psychopathology or related symptoms. Variability exists both in the methods used and, in the tools employed to assess depression and anxiety, while diverse data processing approaches further contribute to inconsistencies in reported outcomes across studies. Achieving greater consensus and uniformity in the scales employed for assessing these outcomes in future research endeavors would enhance the comprehension of the prevalence of anxiety, depression symptoms, or psychopathology in dementia caregivers. Consequently, the generation of more robust clinical evidence may necessitate an increase in high-quality randomized controlled trials with consistent methods for outcome evaluation. While evaluation criteria have been delineated, the potential for bias in results persists.

Considering the systematic literature review's findings, future research endeavors examining anxiety and depression in dementia caregivers should center on delineating the impact of specific behavioral and psychological symptoms of dementia, such as agitation/aggression and irritability/immobility. As suggested by Huang,[31] comprehending the clinical mechanisms underpinning depression and anxiety necessitates an exploration of psychosocial, physiological, and biological factors. Furthermore, there is a need to investigate the role of the COVID-19 pandemic in amplifying the prevalence of depressive symptoms among dementia caregivers. Exploring interventions targeting the mitigation of burden and enhancing the health-related quality of life for caregivers, particularly those tending to Alzheimer's patients with neuropsychiatric symptoms, should be a priority in such research initiatives. Insights from such

research can inform the development of targeted support and interventions tailored to the unique challenges faced by dementia caregivers, leading to an improvement in their overall quality of life. The identified findings offer valuable insights for policymakers in shaping innovative programs and services aimed at alleviating and mitigating the strain experienced by caregivers, with consideration of diverse social and cultural contexts. A prevalent theme in the literature underscores the imperative for additional research, a broader array of cultural approaches to caregiving.[34–35] The formulation and execution of individualized treatment plans emerge as pivotal elements in addressing depression and anxiety among dementia caregivers. Advocating for increased attention, policy measures, and financial allocations is warranted to support forthcoming research endeavors focused on the multifaceted challenges faced by dementia caregivers.

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Ανασκόπηση

Συστηματική ανασκόπηση συμπτωμάτων κατάθλιψης και άγχους σε φροντιστές ασθενών με άνοια

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ΠΕΡΙΛΗΨΗ

Ο αριθμός των ατόμων με άνοια στην Ευρώπη είναι επί του παρόντος 7,7 εκατομμύρια και αναμένεται να διπλασιαστεί έως το έτος 2050. Οι φροντιστές ατόμων με άνοια αντιμετωπίζουν μεγαλύτερη επιβάρυνση από τους φροντιστές άλλων ατόμων με χρόνια ασθένεια και διατρέχουν μεγαλύτερο κίνδυνο να αναπτύξουν κατάθλιψη και διαταραχές άγχους. Μέσα από την παρούσα συστηματική βιβλιογραφική ανασκόπηση (PRISMA Analysis) επιχειρούμε να διερευνήσουμε τον επιπολασμό συμπτωμάτων και διαταραχών άγχους και κατάθλιψης σε φροντιστές ασθενών με άνοια. Πραγματοποιήθηκε μία αναζήτηση σε ακαδημαϊκές ηλεκτρονικές βάσεις δεδομένων με τον χρονικό περιορισμό οι μελέτες να έχουν δημοσιευτεί εντός των τελευταίων 15 ετών. Εντοπίστηκαν 85 άρθρα και συμπεριλήφθηκαν 16 τα οποία πληρούσαν τα κριτήρια. Τα αποτελέσματα των μελετών έδειξαν ότι οι φροντιστές βιώνουν σημαντική επιβάρυνση και μειωμένη αυτοαναφερόμενη ποιότητα ζωής , ενώ παράλληλα εμφανίζουν τάσεις για ανάπτυξη κλινικής κατάθλιψης. Τα συμπτώματα κατάθλιψης και άγχους βρέθηκαν να είναι πιο σοβαρά στις περιπτώσεις των γυναικών φροντιστών. Η κατάθλιψη των φροντιστών σχετίζεται με την αυξημένη χρήση του τμήματος επειγόντων περιστατικών από ασθενείς με άνοια και κατά την περίοδο της πανδημίας COVID-19 αποτυπώθηκε αύξηση του επιπολασμού καταθλιπτικών συμπτωμάτων σε φροντιστές ατόμων με άνοια. Η φροντίδα ατόμων με άνοια συνδέθηκε με την επαγγελματική εξουθένωση, επηρεάζοντας αρνητικά σε πολύ μεγάλο βαθμό την ποιότητα ζωής των φροντιστών. Αποτυπώθηκε συσχέτιση ανάμεσα στα συμπτώματα κατάθλιψης και άγχους των φροντιστών και την χρήση ουσιών από την πλευρά των φροντιστών. Η κατάθλιψη στους φροντιστές συσχετίστηκε με κοινωνικοδημογραφικές μεταβλητές όπως το χαμηλό κοινωνικοοικονομικό επίπεδο, το υψηλότερο επίπεδο αστικοποίησης και τη μεγαλύτερη ηλικία. Οι φροντιστές ατόμων με νόσο Alzheimer αναφέρουν σημαντικά υψηλότερες τιμές στα συμπτώματα άγχους, επιβάρυνσης και κατάθλιψης σε σύγκριση με φροντιστές που παρέχουν υπηρεσίες σε άτομα με άλλες άνοιες, ειδικά όταν τα νευροψυχιατρικά συμπτώματα είναι εμφανή. Με τον εντοπισμό παραγόντων που συνδέονται με την ψυχική επιβάρυνση των φροντιστών ατόμων με άνοια, οι επαγγελματίες ψυχικής υγείας θα έχουν τη δυνατότητα να προχωρούν σε έγκαιρη ανίχνευση συμπτωμάτων και να παρέχουν κατάλληλη υποστήριξη για να ανακουφίσουν το βάρος των φροντιστών και να ενισχύσουν την ποιότητα της φροντίδας για τα άτομα με άνοια. Μέσα από πολιτικές υγείας θα είναι χρήσιμο οι φροντιστές να λαμβάνουν περισσότερη και πιο συστηματική επαγγελματική βοήθεια και να έχουν ευκαιρίες κατάρτισης ώστε να μειωθεί η επιβάρυνση τους.

ΛΕΞΕΙΣ ΕΥΡΕΤΗΡΙΟΥ: Κατάθλιψη, άγχος, άνοια, alzheimer, φροντιστές.

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Letter to the Editor

New guidelines for the effectiveness of exercise in the prevention of dementia: Implications for psychiatry

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To the Editors,

We recently published evidence-based guidelines for the role of exercise in the prevention of dementia.[1] The guidelines combined an umbrella review and expert consensus, and has important implications for psychiatry.

Evidence from published studies was evaluated using the GRADE assessment. We found scarce and relatively low-quality evidence in the literature, particularly for the primary prevention of dementia.

Our GRADE-informed evidence synthesis yielded the following conclusions:

- For Primary prevention of dementia: Physical activity may be considered for the primary prevention of dementia. In people without dementia or MCI, exercise may be no better than health education for the primary prevention of dementia and MCI. Quality of evidence: Very low for physical activity; very low for exercise.
- For Secondary prevention of dementia: In people with MCI there is continued uncertainty about the role of physical activity and exercise in slowing the conversion to dementia. Quality of evidence: Very low for physical activity; very low for exercise.
- For Tertiary prevention of dementia: In people with moderate dementia, physical activity/exercise could be considered for maintaining cognition and exercise could be considered for stabilizing disability compared to usual care. Quality of evidence: Exercise: very low for cognitive outcomes; low for disability.

Following a consensus process, we recommended physical activity/exercise for all three purposes, namely primary, secondary, and tertiary prevention (improve cognition and reduce disability) of dementia. The recommendation of exercise was largely contingent on its positive effects on mental health,[2,3] in conjunction with the extensive body of evidence linking mental disorder with dementia.[4]

The guidelines highlight the need for further research on multidisciplinary interventions for both the primary and secondary prevention of dementia. A question remains whether the positive effect of physical activity on mood/behaviour applies to the MCI group, as it does to the dementia group. More research is required in people with established dementia and in less common forms of dementia. The guidelines also make an implicit research recommendation in support of heurism, in the sense that they integrate the evidence-based expectation that exercise is likely to be beneficial both for mental and physical health. Indeed, employing heurism may be inherently necessary in prevention research.[5]

Overall, these guidelines offer an evidence-based insight into the effectiveness of physical activity/exercise for the prevention (primary, secondary, and tertiary) of dementia. Importantly, they necessitate the inclusion of mental health in a multi-component approach. In doing so, they emphasize the necessity of mental health promotion and mental illness prevention in the prevention and management of dementia.

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