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## Social Distance in COVID-19: Drawing the line between protective behavior and stigma manifestation

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Social stigma has long been defined by Ervin Goffman as an attribute that it is deeply discrediting and reduces the individual who bears it from a whole and usual person to a tarnished one, unfit to be included into the mainstream society.<sup>1</sup> As stigma spans time and space and has been documented in other social species such as ants and chimpanzees, one might argue for its adaptive potential. Neuberg et al<sup>2</sup> have suggested that humans generate stigmas against threats to effective group functioning, with a notable case being infectious diseases. A similar explanation has been put forward by other researchers who consider stigma to have evolved from disease-avoidance mechanisms.<sup>3</sup> Hence, it is not surprising that tuberculosis, HIV and leprosy have been surrounded by stigma and discrimination.<sup>4,5</sup> More recently, people who had survived the 2013–2016 Ebola outbreak tackled social exclusion and unemployment after returning to their neighborhoods.<sup>6</sup>

Nowadays, the global community faces an unprecedented challenge of grappling with the COVID-19 pandemic. From the very outset, social distance measures were introduced in order to contain the spread of the virus, ranging from maintaining 1.5 meters physical distance to strict lockdowns. However, this may easily escalate into stigmatizing and discriminatory behaviours (desired social distance is a proxy of discrimination) against people who have suffered from COVID-19, their relatives and their caregivers, with the United Nations stating that “fear, rumours and stigma” are the key challenges surrounding COVID-19.<sup>7</sup> Apart from the psychological distress experienced by the stigmatized individuals, due to anticipated stigma people might start concealing their illness, avoid or delay seeking medical advice or testing until they are seriously ill and be reluctant to collaborate with authorities on tracing contacts. Therefore, timely identifying stigma and addressing it is an integral part of an effective health response to the ongoing pandemic.

In spite of its importance, research on COVID-19 related stigma is scarce. From the perspective of the stigmatized individuals, a study in China<sup>8</sup> demonstrated that COVID-19 survivors faced heightened levels of overall stigma, social rejection, financial insecurity, internalized shame and social isolation, compared to healthy controls. From the perspective of the general population, a study in US<sup>9</sup> substantiated low levels of anticipated stigma and stereotype endorsement; however, respondents who anticipated greater stigma were less likely to seek a COVID-19 test. It is therefore clear that the international literature is still on its infancy with respect to COVID-19 related stigma.

In this context, in the First Department of Psychiatry, University of Athens, we conducted a survey on public attitudes to COVID-19 and to mental disorders. The study would inform the design and implementation of anti-stigma initiatives, funded by the Regional Governor of Attica. As physical distancing and social distancing are interwoven, with some researchers and practitioners using the terms interchangeably, and social distancing is also a protective public health measure against COVID-19, we enquired about attitudes and desired social distance from people who had recovered from COVID-19. Nonetheless, it merits noting that evidence from other diseases indicates that stigma may persist even after recovery.<sup>10</sup> Moreover, rather than describing public attitudes overall, we were more interested in investigating where COVID-19 related stigma stands as compared to the most stigmatizing health condition to date, i.e., severe mental illness.<sup>11</sup> Interestingly enough, which elements of severe mental illness render it the most stigmatized as compared to other conditions is still speculative: is it the fear of madness? the severity and the type of symptoms? the purported incurability or its chronicity?

In our study, evidence from a convenience sample of 370 residents of Attica indicates that the general population holds more negative attitudes towards people who have recovered from COVID-19 than towards people with mental disorders. Nonetheless, respondents reported lower levels of desired social distance from recovered COVID-19 cases as compared to mental illness cases in social interactions of graded intimacy; however, the difference between the two groups was found to decrease as the level of intimacy decreased as well. In other words, desired social distance from COVID-19 cases is more easily discernible in transient social encounters, like talking to a stranger.

It is therefore clear that social distance is still a public health protective measure rather than a stigma manifestation. For social encounters of greater intimacy, usually a sign of discriminatory behaviours, having recovered from COVID-19 is not a deterrent to interaction. Findings can be explained by the acute (non-chronic) nature of the disease, both in terms of

symptoms as well as the 10-day period since symptom onset for being contagious. Nonetheless, with emerging evidence substantiating the notion of long COVID-19, defined as the persistence of symptoms for 3 weeks after infection,<sup>12</sup> this might quickly change. Moreover, with many public health protective measures available, such as the use of mask, diagnostic testing and vaccination, people who become infected are more likely to be blamed for contracting the disease and thus deemed responsible for this, in line with the Attribution Theory.<sup>13</sup> Specifically, overarching evidence from stigma research in many diseases/conditions indicates that when an illness or a social condition, such as economic disadvantage, is attributed to internal causes, as compared to external, lay people are more likely to hold stigmatizing attitudes.<sup>14–16</sup> Therefore, as attitudes towards COVID-19 are worse compared to those towards people with mental illness, if tailored anti-stigma action is not undertaken, it is only a matter of time for prejudices to evolve into discriminatory behaviours, with devastating consequences on both the individuals and the course of the pandemic. Concomitantly, as severe mental illness is neither life threatening nor contagious, but COVID-19 is, it is interesting to explore how stigma is related to evolutionary mechanisms favouring adaptability and survival as well as which elements are the drivers of stigma development and establishment. Therefore, comparing and contrasting the stigma surrounding these conditions may shed light on the underpinnings of social stigma and facilitate effective interventions to reduce it and eventually eliminate it.

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## Άρθρο σύνταξης

# Κοινωνική απόσταση και COVID-19: Θέτοντας τα όρια μεταξύ προστατευτικής συμπεριφοράς και εκδήλωσης στιγματισμού

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Το κοινωνικό στίγμα έχει ορισθεί εδώ και αρκετά χρόνια από τον Ervin Goffman ως ένα χαρακτηριστικό, το οποίο είναι βαθιά δυσφημιστικό και υποβιβάζει τον άνθρωπο που το φέρει από μια θέση ολοκληρωμένου και κανονικού ατόμου σε μια θέση φθαρμένου ατόμου, ακατάλληλου να αποτελεί μέρος της κοινωνίας.<sup>1</sup> Καθώς το στίγμα διατρέχει τον χρόνο και τον τόπο και έχει καταγραφεί και σε άλλα κοινωνικά είδη, όπως τα μυρμήγκια και οι χιμπατζήδες, μπορεί κάποιος να ισχυρισθεί ότι εξυπηρετεί τη δυνατότητα προσαρμογής των οργανισμών. Οι Neuberg et al<sup>2</sup> έχουν διατυπώσει την υπόθεση ότι οι άνθρωποι παράγουν το στίγμα ως άμυνα απέναντι σε απειλές της εύρυθμης λειτουργίας της ομάδας, με την περίπτωση των μεταδοτικών λοιμώξεων να είναι χαρακτηριστική. Μια παρόμοια εξήγηση έχει διατυπωθεί και από άλλους ερευνητές που θεωρούν πως το στίγμα αποτελεί μετεξέλιξη μηχανισμών αποφυγής της νόσου.<sup>3</sup> Επομένως δεν προκαλεί έκπληξη πως η φυματίωση, το HIV/AIDS και η λέπρα έχουν περιβληθεί από στίγμα και διακρίσεις.<sup>4,5</sup> Πιο πρόσφατα, άτομα που επιβίωσαν της νόσησης από τον ιό Ebola την περίοδο 2013–2016, ήρθαν αντιμέτωπα με κοινωνικό αποκλεισμό και δυσκολίες στην ανεύρεση και διατήρηση της εργασίας τους μετά την ανάρρωσή.<sup>6</sup>

Αυτή την περίοδο, η διεθνής κοινότητα αντιμετωπίζει μια τεράστιας εμβέλειας πρόκληση παλεύοντας με την πανδημία της COVID-19. Ακόμη και από τα πολύ αρχικά στάδια της έξαρσης της πανδημίας, μέτρα φυσικής και κοινωνικής απόστασης υιοθετήθηκαν προκειμένου να ελεγχθεί η διασπορά του ιού, τα οποία κυμαίνονταν από τη διατήρηση φυσικής απόστασης μέχρι αυστηρά lockdown. Ωστόσο, τα μέτρα αυτά συχνά μπορούν να κλιμακωθούν ανεξέλεγκτα και να πάρουν τη μορφή στιγματιστικών συμπεριφορών και διακρίσεων (είναι γνωστό εξάλλου ότι η επιθυμητή κοινωνική απόσταση αποτελεί έναν βασικό δείκτη κοινωνικού στιγματισμού) σε βάρος όσων έχουν νοσήσει από COVID-19, τους συγγενείς και τους φροντιστές τους, με τα Ηνωμένα Έθνη να αναφέρουν πως «ο φόβος, οι φήμες και το στίγμα» αποτελούν τις βασικές προκλήσεις που περιβάλλουν την COVID-19.<sup>7</sup> Πέραν της ψυχικής δυσφορίας που βιώνουν τα άτομα που φέρουν το στίγμα, εξαιτίας του φόβου επικείμενου στιγματισμού μπορεί να κρύβουν την ασθένεια, να αποφεύγουν ή να καθυστερούν την αναζήτηση βοήθειας από επαγγελματία υγείας ή τη διενέργεια εξετάσεων ανίχνευσης του ιού μέχρι να νοσήσουν βαριά, ενώ μπορεί επίσης να είναι απρόθυμα να συνεργαστούν με τις αρχές για την ιχνηλάτηση των επαφών τους. Επομένως η έγκαιρη αναγνώριση και διαχείριση του στίγματος αποτελεί αναπόσπαστο μέρος μιας αποτελεσματικής στρατηγικής υγείας για την τρέχουσα πανδημία.

Παρά τη σημασία του στίγματος της COVID-19, η υπάρχουσα έρευνα είναι ελλιπής. Από την οπτική γωνία των ατόμων που στιγματίζονται, μια έρευνα στην Κίνα<sup>8</sup> κατέδειξε πως τα άτομα που νόσησαν από COVID-19 βίωσαν αυξημένα επίπεδα συνολικού στίγματος, κοινωνικής απόρριψης, οικονομικής ανασφάλειας, εσωτερικευμένης ντροπής και κοινωνικής απομόνωσης συγκριτικά με την ομάδα ελέγχου των «υγιών» ατόμων. Από την οπτική γωνία του γενικού πληθυσμού, μελέτη στις ΗΠΑ<sup>9</sup> ανέδειξε χαμηλά επίπεδα αναμενόμενου στίγματος και στερεοτύπων σχετικά με την COVID-19, ωστόσο αυτοί που ανέφεραν περισσότερο στιγματιστικές στάσεις ήταν λιγότερο πιθανό να υποβληθούν σε test ανίχνευσης για τον κορωνοϊό. Καθίσταται επομένως σαφές ότι η διεθνής βιβλιογραφία αναφορικά με το στίγμα της COVID-19 βρίσκεται ακόμα στην αρχή της.

Σε αυτό το πλαίσιο, στην Α΄ Ψυχιατρική Κλινική του Πανεπιστημίου Αθηνών διενεργήσαμε μελέτη για τις στάσεις του γενικού πληθυσμού απέναντι στη νόσο COVID-19 και την ψυχική ασθένεια. Η μελέτη χρηματοδοτείται από την Περιφέρεια Αττικής και τα ευρήματά της αναμένεται να συμβάλουν στον σχεδιασμό και την υλοποίηση κατάλληλων αντι-στιγματιστικών παρεμβάσεων. Καθώς η φυσική απόσταση και η κοινωνική απόσταση αλληλοσυνδέονται, με ορισμένους ερευνητές και επαγγελματίες να χρησιμοποιούν τους δυο όρους εναλλάξ, ενώ παράλληλα η κοινωνική απόσταση αποτελεί επίσης ένα μέτρο προστασίας από την COVID-19, διερευνήσαμε επίσης τις στάσεις και την επιθυμητή κοινωνική απόσταση από τα άτομα που ανάρρωσαν από τη νόσο. Ωστόσο, αξίζει να σημειωθεί ότι σύμφωνα με δεδομένα από έρευνες στο πεδίο του στίγματος που συνοδεύει άλλες ασθένειες, φαίνεται ότι στιγματιστικές στάσεις και συμπεριφορές παρατηρούνται σε βάρος των ασθενών ακόμη και μετά την ανάρρωσή τους από τη νόσο.<sup>10</sup> Επιπλέον, αντί να περιγράψουμε τις στάσεις συνολικά, μας ενδιέφερε περισσότερο να μελετήσουμε πως αποτυπώνεται το στίγμα της COVID-19 σε σχέση με την πιο στιγματισμένη-μέχρι σήμερα- νόσο, τη σοβαρή ψυχική ασθένεια.<sup>11</sup> Κατά ενδιαφέροντα τρόπο, παραμένει το ερώτημα ποια στοιχεία της σοβαρής ψυχικής ασθένειας την καθιστούν ως την πιο στιγματισμένη συγκριτικά με τις άλλες νόσους; είναι ο φόβος της τρέλας; η βαρύτητα και ο τύπος των συμπτωμάτων; η υποτιθέμενη μη θεραπευσιμότητά της; ή η χρονιότητά της;

Στη μελέτη μας, στοιχεία από δείγμα ευκολίας 370 κατοίκων της Αττικής καταδεικνύουν πως ο γενικός πληθυσμός διατηρεί πιο αρνητικές στάσεις απέναντι στα άτομα που έχουν αναρρώσει από COVID-19 απ' ό,τι απέναντι στα άτομα με ψυχική νόσο. Ωστόσο, οι συμμετέχοντες ανέφεραν χαμηλότερα επίπεδα επιθυμητής κοινωνικής απόστασης από τα άτομα που έχουν αναρρώσει από COVID-19 συγκριτικά με εκείνα από ψυχική νόσο σε κοινωνικές αλληλεπιδράσεις διαβαθμιζόμενης εγγύτητας. Ωστόσο, η διαφορά ανάμεσα στις δύο ευάλωτες ομάδες βρέθηκε να μειώνεται όσο ο βαθμός εγγύτητας επίσης μειωνόταν. Συνεπώς, η επιθυμητή κοινωνική απόσταση από τα άτομα που νόσησαν από COVID-19 ήταν πιο ευδιάκριτη στις εφήμερες κοινωνικές επαφές, όπως το να ξεκινήσει κανείς συζήτηση με έναν άγνωστο.

Καταδεικνύεται επομένως σαφώς από την έρευνά μας ότι η κοινωνική και φυσική απόσταση αποτελούν προς το παρόν περισσότερο ένα μέτρο προστασίας της δημόσιας ψυχικής υγείας παρά μια έκφραση στίγματος. Για τις κοινωνικές επαφές μεγαλύτερης εγγύτητας, που συχνά αποτελούν ένδειξη διακρίσεων, το να έχει αναρρώσει κανείς από COVID-19 δεν αποτελεί αποτρεπτικό παράγοντα για αλληλεπίδραση. Τα ευρήματα μπορούν να εξηγηθούν από την οξεία και συγκεκριμένης μικρής διάρκειας (μη χρόνια) φύση της νόσου, τόσο όσον αφορά στα συμπτώματα όσο και στην περίοδο των 10 ημερών από την έναρξη των συμπτωμάτων, όπου η νόσος θεωρείται μεταδοτική. Ωστόσο, λόγω των αναδυόμενων ερευνητικών δεδομένων που τεκμηριώνουν την έννοια της μακροχρόνιας COVID-19, η οποία ορίζεται ως η διατήρηση των συμπτωμάτων για 3 εβδομάδες μετά τη μόλυνση,<sup>12</sup> αυτή η άποψη ενδέχεται σύντομα να αλλάξει. Επιπλέον, καθώς υπάρχουν πολλά διαθέσιμα μέτρα προστασίας της δημόσιας υγείας, όπως η χρήση μάσκας, οι διαγνωστικές εξετάσεις και ο εμβολιασμός, τα άτομα που μολύνονται είναι πιο πιθανό να κατηγορηθούν για τη μόλυνση από τη νόσο και έτσι να θεωρηθούν υπεύθυνα για αυτήν, σύμφωνα με τη Θεωρία Απόδοσης Αιτιών.<sup>13</sup> Πιο συγκεκριμένα, συγκλίνοντα ευρήματα από τη μελέτη του στίγματος σε διάφορες ασθένειες και καταστάσεις δείχνουν ότι όταν μια ασθένεια ή μια συνθήκη, όπως η οικονομική δυσπραγία, αποδίδεται σε εσωτερικές αιτίες, δηλαδή εντός της σφαίρας επιρροής και ευθύνης του ίδιου του ατόμου, σε σύγκριση με εξωτερικές, ο γενικός πληθυσμός είναι πιο πιθανό να υιοθετήσει στιγματιστικές στάσεις.<sup>14-16</sup> Ως εκ τούτου, καθώς οι στάσεις απέναντι στη νόσο COVID-19 είναι χειρότερες από εκείνες για την ψυχική νόσο, αν δεν σχεδιαστούν εγκαίρως κατάλληλα προσαρμοσμένες αντι-στιγματιστικές παρεμβάσεις, είναι θέμα χρόνου οι προκαταλήψεις να εξελιχθούν σε διακρίσεις με δυσμενείς συνέπειες για τους νοσούντες από τη μια αλλά και τη συνολική έκβαση της πανδημίας από την άλλη. Ταυτόχρονα και με βάση ότι η σοβαρή ψυχική ασθένεια δεν είναι απειλητική για τη ζωή και δεν είναι μεταδοτική, όπως η νόσος COVID-19, έχει ενδιαφέρον να μελετηθεί ο τρόπος με τον οποίο το στίγμα μπορεί να σχετίζεται με τους εξελικτικούς μηχανισμούς προσαρμοστικότητας και επιβίωσης, καθώς και ποια είναι τελικά εκείνα τα συστατικά στοιχεία που έχουν τη μεγαλύτερη βαρύτητα στη διαδικασία ανάπτυξης και εγκαθίδρυσης του στιγματισμού. Επομένως, η σύγκριση του στίγματος ανάμεσα στις δύο νοσολογικές οντότητες μπορεί να φωτίσει πτυχές του υποστρώματος του κοινωνικού στίγματος και να ευνοήσει τις αποτελεσματικές παρεμβάσεις μείωσης και εν τέλει εξάλειψής του.

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## Research article

# Atrial fibrillation: The impact of anxiety and depression on patients' needs

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### ABSTRACT

Atrial fibrillation (AF) is a common sustained cardiac arrhythmia, which is expected to expand enormously due to population ageing. The aim of the present study was to explore the significance of AF patients' needs and the associated factors as well as the impact of anxiety and depression on these needs. The sample of the study included 215 AF hospitalized patients. Data were collected by the completion of a questionnaire which, in addition to patients' characteristics, it also included the Hospital Anxiety and Depression Scale (HADS) and the questionnaire "Needs of hospitalized patients with coronary artery disease", that is evaluating the significance of the following 6 categories of needs: (a) for support and guidance, (b) for information from medical and nursing staff, (c) for communication with other patients and family, (d) for individualization of care and participation, (e) to trust the medical and nursing staff and f) to meet emotional and physical needs. The statistical significance level was  $p < 0.05$ . Of the 215 participants, 68.4% were men and 67.5% were  $> 60$  years old. Moreover, 47.5% of the participants experienced anxiety and 29.5% depression. The need for support, to be informed and to trust the medical and nursing staff considered to be of high significance by the patients (median 29,20 and 6, respectively). Anxiety and depression were significantly associated with all patients' needs ( $p < 0.05$ ) apart from the need to meet the emotional and physical needs and the need to trust the medical and nursing staff, which were not associated with anxiety levels. In terms of patients' needs, those who reported to be little or not at all informed about their disease considered of a higher significance the need for support and guidance ( $p = 0.030$ ), the need to be informed and to trust the medical and nursing staff ( $p = 0.001$  and  $p = 0.012$ , respectively) and the need for communication with other patients and family ( $p = 0.007$ ). The need for individualization of care and participation in it, was considered more significant by patients aged  $> 70$  years and those having no children ( $p = 0.039$  and  $p = 0.029$ , respectively) while the need for communication with other patients and family was considered more significant by women ( $p = 0.028$ ). The present findings emphasize the importance of providing care tailored to meet the needs of AF patients who experience anxiety and depression.

**KEYWORDS:** Anxiety, depression, patients' needs, atrial fibrillation.

### Introduction

Atrial fibrillation (AF) which was discovered more than 100 years ago, it is nowadays a most common cardiac arrhythmia, worldwide.<sup>1–3</sup> In Australia, Europe and USA, the current estimated prevalence of AF is about between 1% to 4%, with lower prevalence in Asia (0.49–1.9%). The higher prevalence rates of AF are found in developed countries, especially in North America, whereas the lowest in the Asia–Pacific area.<sup>1</sup> Given the prolonga-

tion of life expectancy and the improvements in survival resulting from the progress in medical therapies, AF is anticipated to affect 6–12 million people in the USA by 2050 and 17.9 million in Europe by 2060.<sup>3</sup> Additionally, geographical variations are reported; more elevated AF prevalence in high-income countries compared to low-middle ones.<sup>3</sup> These discrepancies are attributed to several limitations in health care services or to the diminished clinical data registry records.<sup>3</sup> AF is predominantly

a disease of the elderly. In Western Europe, Australia and North America 70% of AF patients are aged >65 years.<sup>4,5</sup>

The most common type is permanent AF occurring in 40–50% of patients, followed by the paroxysmal and persistent AF occurring in 20–30% of cases.<sup>2</sup> Irrespective of type, this common sustained arrhythmia is associated with elevated health care expenditures (frequent and long hospitalizations or multiple emergency room visits), hypertension,<sup>6</sup> increased risk of stroke,<sup>7</sup> high morbidity and mortality.<sup>1,2</sup> The nature of AF including unexpected onset or recurrent events, various symptoms (shortness of breath, palpitations, chest discomfort), complex treatment and several daily limitations may trigger psychological distress, in the form of anxiety and depression.<sup>5,8,9</sup>

Optimal management of this complex arrhythmia demands a patient centered care which is responsive to patient's preferences, needs and values. The ultimate goal of this approach is to empower patients to become active participants in their care. Patient-centered approach is associated with benefits such as stress alleviation, effective patient self-care, satisfaction from health care and adherence to therapy.<sup>10–12</sup> Needs' orientated approach becomes more demanding especially when patients experience depression or anxiety. Needs of depressed hospitalized cardiac patients are mainly determined by the severity of disease, physical and cognitive impairment, co-morbidities, difficulties to comply with the hospital's rules, and demographic factors (gender, and single).<sup>13</sup> Providing treatment to alleviate psychological distress to this population may achieve worldwide reductions in AF-related morbidity, mortality, and healthcare burden.<sup>13,14</sup>

To the best of our knowledge, data exploring needs of AF patients and the associated factors as well as the impact of anxiety/depression on needs are limited. Thus, the aim of this cross-sectional study was to explore the level of significance of AF patients' needs and the associated factors as well as the impact of anxiety and depression on patients' needs.

## Material and Method

### Study population

In the present study, were enrolled 215 hospitalized patients diagnosed with permanent AF. This was a convenience sample. Patients were classified according to the current guidelines regarding type of AF.<sup>14</sup> Criteria for inclusion of patients in the study were: (a) diagnosis of permanent AF, (b) ability to write and read the Greek language fluently and (c) be hospitalized for at least 2 days. The exclusion criteria were: (a) age <18 years, and (b) diagnosis of paroxysmal and persistent AF.

### Data collection and procedure

Collection of data was performed by interview using a questionnaire which was developed by the researcher so as to fully serve the purposes of the study. Completion of each questionnaire lasted approximately 15 min and took place for each participant at evening shift when patients were free of examinations or other medical procedures.

The data collected for each patient included socio-demographic characteristics (e.g., gender, age, education level, marital status, and number of children), clinical characteristics (e.g., years having the disease), and other self-reported characteristics (e.g., relations with the medical-nursing staff).

The study was approved by the Ethical Committee of the hospital where it was conducted. Patients who met the inclusion criteria were informed by the researcher for the purposes of this research. All patients participated only after they had given their written consent. Data collection guaranteed anonymity and confidentiality. All subjects had been informed of their rights to refuse or discontinue participation in the study, according to the ethical standards of the Declaration of Helsinki (1989) of the World Medical Association.

### Measures

The Hospital Anxiety and Depression Scale (HADS)<sup>15</sup> was used for the assessment of depression and anxiety. The scale consists of 14 questions that assess how patients felt during the previous week. Patients were able to answer every question in a 4-point Likert scale from 0–3. Seven of 14 questions assess the level of depression and seven evaluate the anxiety level. Scores attributed to questions are summed separately for anxiety and depression, leading to two scores with range 0–21. Higher score indicates higher levels of anxiety and depression, respectively. In addition, the following categorization has been proposed and is widely used: score 0–8 indicating no stress or depression, score above 8 indicating clinically significant anxiety or depression. The Greek version of the HADS has been tested for its validity and reliability.<sup>16</sup>

The questionnaire "Needs of hospitalized patients with coronary artery disease" was used in order to assess the needs of AF patients. This questionnaire includes 39 statements regarding the significance of potential needs of cardiac patients during their hospitalization. This questionnaire consists of 6 sub-scales of potential needs. Patients were able to answer every question in a 4-point Likert scale from 1–4. Scores attributed to questions are summed separately for each sub-scale. Higher score indicates that the need was considered of high signifi-

cance. The questionnaire 'Needs of hospitalized patients with coronary artery disease' had good reliability and validity in Greek population. More in detail, Cronbach's  $\alpha$  for each sub-scale was as following: 17 Need for support and guidance, 0.922; Need to be informed from the medical-nursing staff, 0.918; Need for communication with other patient groups, and ensuring communication with family, 0.865; Need for individualization of care and patient participation in patient care, 0.861; Need to meet the emotional needs (e.g. anxiety, fear, loneliness) and the physical needs (such as relaxation, sleep, better conditions during hospitalization), 0.859; Need to trust the medical-nursing staff, 0.923.

### Statistical analysis

To test the existence of association between patient's needs and patient's anxiety/depression or patient's characteristics the Kruskal-Wallis test or the Mann-Whitney test was used, as well as the Spearman's rho correlation coefficient. Multiple linear regression was performed to estimate the effect of anxiety/depression and patient

characteristics on the patient's needs (dependent variable). The results are presented with  $\beta$  coefficients and 95% confidence intervals. The level of statistical significance was set to  $\alpha=5\%$ . The analysis was performed with the statistical package SPSS, version 22 (SPSS Inc, Chicago, IL, USA).

## Results

### Patients' characteristics

68.4% of participants were men, approximately 67% over 60 years, 74.4% was married, 53.7% had primary education, 65.1% were pensioners, 67.4% lived in Attica and 47% had two children. In terms of clinical characteristics, 43.9% of participants had also another disease, 57.2% had been previously hospitalized, 45.1% had the disease for less than a year while the median duration of hospitalization was 5 days. The majority of the sample reported to be very informed about their problem (51.6%) and to have very good relations with nursing and medical staff (76.2% and 73.2%, respectively) (table 1).

**Table 1.** Patients' characteristics (N=215).

	N (%)		N (%)
Gender (male)	147 (68.4%)	Informed about health	
Age		Very	111 (51.6%)
<50	27 (12.6%)	Enough	77 (35.8%)
51–60	43 (20.0%)	Less/Not at all	27 (12.6%)
61–70	70 (32.6%)	Years having the disease	
>70	75 (34.9%)	<1 year	97 (45.1%)
Marital status		2–5 years	54 (25.1%)
Married	160 (74.4%)	6–10 years	64 (29.8%)
Single	55 (25.6%)	Relations with nursing staff	
Educational Level		Very good	163 (76.2%)
Primary	115 (53.7%)	Good	36 (16.8%)
Secondary	69 (32.2%)	Moderate/Bad	15 (7.0%)
University	30 (14.0%)	Relations with medical staff	
Job		Very good	156 (73.2%)
Employee	75 (34.9%)	Good	46 (21.6%)
Pensioner /Household	140 (65.1%)	Moderate/Bad	11 (5.2%)
Place of residence		Other disease (yes)	94 (43.9%)
Attica	145 (67.4%)	Previous hospitalization (yes)	123 (57.2%)
Other	70 (32.6%)		
No of children			
None	22 (10.2%)		
One	41 (19.1%)		
Two	101 (47.0%)		
More than two	51 (23.7%)		
Days in hospital	5 (4–6)*		

\*Data presented as Median (Interquartile Range)

### Levels of Anxiety/Depression

As presented in table 2, almost half of the patients had clinically significant anxiety (47.5%) and 29.5% had depression. Cronbach's  $\alpha$  coefficients of HADS subscales were above 0.7 indicating high reliability.

### Patients' needs

Table 3 presents patients' self-report about the significance of their needs. Patients considered of low significance the 3 following needs: (a) for communication, (b) for individualization of care and (c) to meet the emotional needs, since the median scores of these needs are close to the lower limit of the needs' ranges. On the contrary, patients considered of high significance the 3 following needs: (a) for support, (b) to be informed and (c) to trust the medical and nursing staff (median, 29, 20 and 6, respectively).

### Association between patients' needs and their characteristics

The associations between patients' characteristics and their needs based on univariate analysis are presented in table 4. It was found that the degree of information was significantly associated with the need for support and guidance. In particular, patients who reported to be little or not at all informed considered this need of higher significance than patients who reported to be very or enough informed (median 31 vs 29 and 23,  $p=0.030$ ). Likewise, patients who reported to be little or not at all

informed considered the need to be informed from the medical and nursing staff of higher significance than those very or enough informed (median 24 vs 20 and 19,  $p=0.001$ ).

The need for communication with other patient groups, and for communication with family was significantly associated with gender and degree of information ( $p=0.028$  and  $p=0.007$ , respectively). In particular, female patients considered this need of higher significance than males (median 12 vs 10). Patients who reported to be little or not at all informed considered this need to be of a higher significance than those very or enough informed (median 14 vs 10 and 9).

The need for individualization of care and patient participation in their care was significantly associated with age and number of children ( $p=0.039$  and  $p=0.029$ , respectively). Patients aged above 70 years considered this need of a higher significance than younger patients (median 10 vs 7 and 9). Similarly, for patients that did not have any children compared to those with one or more children (median 11 vs 7 and 9).

The need to meet the emotional and the physical needs was not found to be statistically significant associated with any patient's characteristic.

The need to trust the medical and nursing staff was associated with the degree of information ( $p=0.012$ ). Patients who reported to be little or not at all informed considered this need of a higher significance than patients that are very or enough informed (median, IQR was higher).

### Association between patients' needs and anxiety/depression

The association between anxiety/depression and needs based on univariate analysis is presented in table 5. It was found that all needs were statistically significant associated with depression levels and anxiety levels ( $p<0.05$ ) apart from the need to meet the emotional and physical needs and the need to trust

**Table 2.** Levels of anxiety/depression of patients (N=215).

	N (%)
Anxiety (Cronbach's $\alpha=0.779$ )	
No (Score $\leq 8$ )	110 (52.1%)
Yes (Score $> 8$ )	101 (47.9%)
Depression (Cronbach's $\alpha=0.844$ )	
No (Score $\leq 8$ )	148 (70.5%)
Yes (Score $> 8$ )	62 (29.5%)

**Table 3.** Descriptive data of the sub-scales assessing the significance of the needs of patients (N=215).

Patients' needs (range)	Median (IQR)
Need for support and guidance (9–36)	29 (23–32)
Need to be informed from the medical and nursing staff (8–32)	20 (14–27)
Need for communication with other patient groups, and ensurance for communication with family (6–24)	10 (6–14)
Need for individualization of care and patient participation in patient care (6–24)	9 (6–12)
Need to meet the emotional needs (e.g., anxiety, fear, loneliness) and physical needs (such as relaxation, sleep, better conditions of treatment) (7–28)	9 (7–12)
Need to trust the medical and nursing staff (2–8)	6 (5–7)

**Table 4.** Association between patients' characteristics and their needs (N=215).

	Need for support and guidance		Need to be informed from the medical/nursing staff		Need for communication with other patient, and family		Need for individualization of care and their participation		Need to meet the emotional and physical needs		Need to trust the medical/nursing staff	
	Median (IQR)	p	Median (IQR)	p	Median (IQR)	p	Median (IQR)	p	Median (IQR)	p	Median (IQR)	p
Male	29 (23-31)		19 (19-27)		10 (6-14)		8 (6-12)		8 (7-12)		6 (5-7)	
Female	30 (23-33)		24 (19-28)		12(7,5-15)		9(6,5-12)		9.5 (7-13)		6 (5-7)	
Age		0.517		0.485		0.296		0.039		0.238		0.985
<60	29,5 (23-30)		20 (19-27)		10 (7-13)		9 (6-12)		8 (7-11)		6 (5-7)	
61-70	29 (23-31)		19 (19-27)		9 (6-15)		7 (6-10)		7.5 (7-12)		6 (5-7)	
>70	30 (23-33)		20 (19-27)		12 (6-15)		10 (6-12)		9 (7-13)		6 (5-7)	
Marital status		0.315		0.135		0.245		0.485		0.293		0.274
Married	29 (23-31)		19 (19-27)		10 (6-14)		8 (6-12)		8 (7-12)		6 (5-7)	
Single	31 (23-33)		24 (19-28)		11 (6-15)		10 (6-12)		9 (7-14)		6 (5-7)	
Educational Level		0.511		0.383		0.368		0.342		0.869		0.059
Primary	29 (23-31)		20 (19-27)		9 (6-14)		8 (6-12)		9 (7-13)		6 (5-7)	
Secondary	29 (23-34)		19 (19-26)		12 (6-15)		9 (6-12)		9 (7-12)		6 (5-7)	
University	29 (23-31)		20 (19-24)		10 (7-15)		10 (6-13)		8 (7-11)		6 (5-7)	
Job		0.577		0.220		0.517		0.268		0.965		0.242
Employee	29 (23-33)		20 (19-28)		10 (6-15)		9 (6-13)		9 (7-12)		6 (5-7)	
Pensioner	29 (23-31)		19 (19-26,5)		10 (6-14)		8 (6-12)		9 (7-13)		6 (5-7)	
Place of residence		0.934		0.061		0.200		0.402		0.351		0.491
Attica	29 (23-31)		19 (19-26)		9 (6-15)		8 (6-12)		9 (7-12)		6 (5-7)	
Other	29 (23-33)		24 (19-27)		12 (7-14)		9 (6-12)		8.5 (7-13)		6(5-7)	
No of children		0.561		0.774		0.182		0.029		0.192		0.390
None	31 (23-33)		20 (19-28)		10,5(8-16)		11 (8-13)		11.5 (7-14)		6 (5-7)	
One	29 (23-31)		20 (19-26)		9 (6-13)		7 (6-9)		8 (7-11)		6 (5-7)	
One+	29 (23-32)		20 (19-27)		11 (6-15)		9 (6-12)		8.5 (7-12)		6 (5-7)	
Other disease		0.731		0.530		0.794		0.875		0.558		0.897
Yes	29 (23-31)		20 (19-27)		11 (6-14)		9 (6-12)		9 (7-13)		6 (5-7)	
No	29 (23-32,5)		19 (19-27)		10 (6-15)		8 (6-12)		8.5 (7-11)		6 (5-7)	

Continues

**Table 4.** (Continued).

	Need for support and guidance		Need to be informed from the medical/nursing staff		Need for communication with other patient, and family		Need for individualization of care and their participation		Need to meet the emotional and physical needs		Need to trust the medical/nursing staff	
	Median (IQR)	p	Median (IQR)	p	Median (IQR)	p	Median (IQR)	p	Median (IQR)	p	Median (IQR)	p
Previous hospitalization		0.920		0.157		0.601		0.770		0.821		0.104
Yes	29 (23–32)		19 (19–27)		10 (6–14)		8 (6–12)		9 (7–12)		6 (5–7)	
No	29,5 (23–32)		20 (19–27)		11(6–14,5)		9 (6–12)		9 (7–12)		6 (5–7)	
Informed of the state of their health		0.030		0.001		0.007		0.079		0.102		0.012
Very	23 (23–31)		19 (18–26)		9,5 (6–14)		8 (6–12)		8 (7–11)		6 (5–7)	
Enough	29 (23–33)		20 (19–27)		10 (7–14)		9 (6–12)		9 (7–12)		6 (5–7)	
Less/Not at all	31 (23–34)		24 (20–29)		14 (8–16)		10 (8–13)		10 (7–14)		7 (5–8)	
Years having the disease		0.789		0.854		0.346		0.098		0.090		0.929
<1 year	29 (23–31)		19 (19–27)		10 (6–14)		8 (6–11)		8 (7–12)		6 (5–7)	
2–5 years	29 (23–31)		20 (19–27)		12 (8–15)		9 (7–14)		9 (8–13)		6 (5–7)	
6–10 years	29 (23–33)		19,5 (19–27)		10(6–14,5)		9 (6–12)		8 (7–12)		6 (5–7)	
Relations with nursing staff		0.237		0.409		0.609		0.176		0.529		0.326
Very good	29 (23–32)		19 (19–27)		10 (6–15)		8 (6–12)		9 (7–12)		6 (5–7)	
Good	29 (23–30,5)		20,5(19–27,5)		9,5 (7–13)		8 (6–11,5)		8 (7–12)		6 (5–7)	
Moderate/Bad	31 (23–34)		27 (19–29)		12 (7–17)		12 (8–15)		12 (7–14)		6 (5–8)	
Relations with medical staff		0.106		0.143		0.314		0.133		0.174		0.362
Very good	29 (23–31)		19 (19–26)		10 (6–14)		8 (6–12)		8,5 (7–11,5)		6 (5–7)	
Good	30 (23–33)		20 (19–28)		11 (7–15)		8,5(6–12)		9 (7–13)		6 (5–7)	
Moderate/Bad	31 (31–34)		27 (19–29)		13 (8–15)		12 (9–12)		12 (8–14)		6 (5–8)	
Length of stay	rho	p	rho	p	rho	p	rho	p	rho	p	rho	p
	-0.050	0.463	-0.035	0.616	-0.016	0.816	0.011	0.877	-0.033	0.635	-0.125	0.068



**Table 5.** Association between anxiety/depression and patient's needs (N=215).

	Need for support and guidance		Need to be informed from the medical/nursing staff		Need for communication with other patient, and family		Need for individualization of care and their participation		Need to meet the emotional and physical needs		Need to trust the medical/nursing staff	
	Median (IQR)	p	Median (IQR)	p	Median (IQR)	p	Median (IQR)	p	Median (IQR)	p	Median (IQR)	p
Anxiety		0.002		0.002		0.047		0.048		0.129		0.084
No (Score ≤8)	27 (23–31)		19 (19–26)		9 (6–14)		8 (6–11)		8 (7–11)		6 (5–7)	
Yes (Score >8)	28 (23–33)		23 (19–27)		12 (6–15)		9 (6–12)		9 (7–13)		6 (5–7)	
Depression		0.001		0.001		0.001		0.001		0.001		0.001
No (Score ≤8)	23 (23–31)		19 (19–24)		8 (6–13.5)		8 (6–11)		8 (7–11)		6 (5–7)	
Yes (Score >8)	31 (30–34)		26 (19–29)		13 (10–16)		11 (8–15)		11 (8–14)		7 (5–8)	

the medical and nursing staff, which were not associated with anxiety levels. Patients with high levels of anxiety/depression considered the needs of a higher significance than patients with moderate or low levels (higher medians).

#### Effect of anxiety/depression and characteristics on patient's needs

Multiple linear regression, after adjustment for the patients' characteristics that were significantly associated with the needs in the univariate analysis (table 6), revealed that patients with depression consider the need for support and guidance 3.1 points more significant than patients without depression (95%CI: 1.70, 4.53,  $p=0.001$ ). Likewise, patients with depression consider the need to be informed from the medical and nursing staff and the need for communication with other patient, and family 2.3 and 2.7 points respectively more significant than patients without depression (95%CI: 1.26, 3.34,  $p=0.001$  and 95%CI: 1.38, 4.10,  $p=0.001$  respectively). Moreover, patients that were less or not at all informed for the state of their health considered these needs 1.98 and 1.81 points respectively more significant than patients that were well-informed (95%CI: 0.62, 3.35,  $p=0.005$  and 95% CI: 0.04, 3.59,  $p=0.046$  respectively). Patients with high depression considered the need for individualization of care and their participation 2.67 points more significant than patients without depression (95%CI: 1.51, 3.82,  $p=0.001$ ). Patients with depression consider the need to meet the emotional and physical needs 1.85 points more significant than patients without depression (95%CI: 0.75, 2.95,  $p=0.001$ ). Likewise, patients with depression and those that were less or not at all informed for the state of their health consider the need to trust the medical/nursing staff 0.30 and 0.33 points respectively more significant than patients with without depression and those that were well-informed (95%CI: 0.08, 0.52,  $p=0.001$  and 95%CI: 0.04, 0.62,  $p=0.025$ , respectively).

## Discussion

According to results of the present study, almost half of participants had clinically significant anxiety (47.5%) and 29.5% had depression. A prior study by Thrall et al,<sup>18</sup> showed that one third of AF patients experienced high levels of depression and anxiety which persisted for 6 months. A relevant study in Greece, among 170 AF outpatients showed high anxiety and depression in 34.9% and 20.2% of the participants, respectively.<sup>2</sup> In a population sample of 10.000 individuals (mean age  $56\pm 11$  years, 49.4% women) a higher burden of depressive symptoms in AF individuals was observed.<sup>19</sup> In com-

**Table 6.** Effect of anxiety/depression and characteristics on patients' needs (N=215).

	Need for support and guidance		Need to be informed from the medical/nursing staff		Need for communication with other patient, and family		Need for individualization of care and their participation		Need to meet the emotional and physical needs		Need to trust the medical/nursing staff	
	$\beta$ (95% CI)	p	$\beta$ (95% CI)	p	$\beta$ (95% CI)	p	$\beta$ (95% CI)	p	$\beta$ coef (95% CI)	p-value	$\beta$ coef (95% CI)	p-value
<b>Gender</b>												
Male	Ref.Cat		Ref.Cat		Ref.Cat		Ref.Cat		Ref.Cat		Ref.Cat	
Female	0.52 (-0.74, 1.79)	0.415	0.54 (-0.40, 1.47)	0.259	0.87 (-0.35, 2.09)	0.160	0.36 (-0.69, 1.40)	0.502	0.38 (-0.62, 1.37)	0.455	0.07 (-0.12, 0.27)	0.458
<b>Age (years)</b>												
<60	Ref.Cat		Ref.Cat		Ref.Cat		Ref.Cat		Ref.Cat		Ref.Cat	
61-70	-0.18 (-1.62, 1.26)	0.809	-0.17 (-1.24, 0.90)	0.748	-0.22 (-1.60, 1.16)	0.752	-0.86 (-2.10, 0.38)	0.173	0.15 (-0.99, 1.29)	0.793	-0.04 (-0.27, 0.18)	0.703
>70	0.69 (-0.80, 2.17)	0.363	0.15 (-0.95, 1.26)	0.785	0.43 (-1.00, 1.85)	0.558	0.25 (-0.99, 1.49)	0.694	0.51 (-0.65, 1.67)	0.388	-0.03 (-0.26, 0.21)	0.822
<b>No of children</b>												
None	-		-		-		Ref.Cat		-		-	
One	-		-		-		-1.54 (-3.41, 0.33)	0.105	-		-	
One+	-		-		-		-0.46 (-2.11, 1.20)	0.588	-		-	
<b>Informed</b>												
Very	Ref.Cat		Ref.Cat		Ref.Cat		Ref.Cat		Ref.Cat		Ref.Cat	
Enough	0.43 (-0.85, 1.71)	0.507	0.60 (-0.34, 1.55)	0.210	-0.01 (-1.23, 1.22)	0.992	-		-		0.14 (-0.06, 0.34)	0.157
Less/Not at all	0.74 (-1.11, 2.59)	0.433	1.98 (0.62, 3.35)	0.005	1.81 (0.04, 3.59)	0.046	-		-		0.33 (0.04, 0.62)	0.025
<b>Other disease</b>												
Yes	Ref.Cat		Ref.Cat		Ref.Cat		Ref.Cat		Ref.Cat		Ref.Cat	
No	0.82 (-0.38, 2.02)	0.182	0.06 (-0.84, 0.95)	0.903	0.30 (-0.85, 1.46)	0.606	0.29 (-0.72, 1.30)	0.569	0.10 (-0.85, 1.05)	0.837	-0.01 (-0.19, 0.18)	0.948
<b>Anxiety</b>												
No	Ref.Cat		Ref.Cat		Ref.Cat		Ref.Cat		Ref.Cat		Ref.Cat	
Yes	0.25 (-1.02, 1.52)	0.697	0.42 (-0.53, 1.36)	0.384	0.25 (-0.97, 1.47)	0.688	0.11 (-0.95, 1.17)	0.835	-		-	
<b>Depression</b>												
No	Ref.Cat		Ref.Cat		Ref.Cat		Ref.Cat		Ref.Cat		Ref.Cat	
Yes	3.12 (1.70, 4.53)	0.001	2.30 (1.26, 3.34)	0.001	2.74 (1.38, 4.10)	0.001	2.67 (1.51, 3.82)	0.001	1.85 (0.75, 2.95)	0.001	0.30 (0.08, 0.52)	0.008

Ref.Cat: Reference Category Ci: Confidence Interval

munity-dwelling population of 4979 individuals, (mean age  $78.1 \pm 8.3$  years, 52% males), AF was associated with higher depression prevalence, independently from demographic factors, disabilities and comorbidities (including history of stroke).<sup>20</sup> In the same study, self-reported AF history was associated with 42% increase of suspected depression.<sup>20</sup> Antidepressant treatment is associated with a three-fold higher risk of AF during the first month.<sup>21</sup>

Psychological distress in the form of depression and/or anxiety may be the environment for the initiation and perpetuation of AF and may also contribute to greater symptom severity and recurrence of this arrhythmia.<sup>8,9</sup> Several reasons trigger anxiety and depression among AF patients. More precisely, important sources for anxiety might be the frequent blood tests due to warfarin use, the regular follow-up appointments, the need to follow a strict diet, the potential medication side effects, (stomach bleeding or cerebral hemorrhage) and the fear of palpitations.<sup>22</sup> It is not rare that AF patients face financial losses or disruptions in their professional lives, thus exacerbating an already established anxiety.<sup>22</sup> In terms of depression, the associated behavioural factors such as unhealthy lifestyle and poor treatment adherence are responsible for adverse cardiac prognosis.<sup>8,9</sup>

Furthermore, the presence of depression and anxiety can minimize treatment effectiveness.<sup>9</sup> For instance, diagnosed anxiety among AF adults newly starting warfarin was associated with an increased risk for ischemic stroke and intracranial hemorrhage during follow-up.<sup>23</sup> Hence, recognition of psychological factors and implementation of strategies to reduce this burden in AF patients may improve treatment outcomes and patients' quality of life.<sup>9,24</sup> It is also essential to obtain clinical diagnosis of anxiety for differential diagnosis with depression which might be a comorbidity.<sup>8</sup>

Our results also revealed that participants considered of high significance the need for support, for information and for trust the medical and nursing staff.

After AF diagnosis, patients are facing many challenges and management is crucial in five domains: acute management, treatment of underlying and concomitant cardiovascular conditions, stroke prevention, rate control, and rhythm control.<sup>25</sup> Indeed, this arrhythmia requires multidimensional management that helps patients to understand the complex AF-related issues. Interestingly, patients have to learn medical terminology, to enhance self-care skills, to interpret symptoms and to adhere to medications such as antiarrhythmics and anticoagulants.<sup>9,25-27</sup>

Regarding the use of anticoagulant treatment, the main difficulty is lack of information and understand-

ing<sup>28</sup> while one in four patients to be unable to explain AF.<sup>27</sup> Notably, lack of information is related with distrust of health professionals' options and uncertainties about the disease.<sup>11</sup> Given that limited knowledge is associated with adverse consequences, the need for on-going support to patients is crucial to achieve treatment adherence.<sup>29</sup>

Trust based on effective communication is the cornerstone of participatory decision making. However, trust is not always dominant in clinical settings while perspectives of health professionals and AF patients may differ.<sup>30,31</sup> A trusting relationship permits better understanding of patients' problems preferences, beliefs, attitudes and emotional challenges. More in detail, mutual communication helps health professionals to summarize the problems in a clear manner, to present treatment options with clarity and enables patients to shape their own medical opinion. As a consequence, patients' autonomy is guaranteed and they actively participate in the decision-making process.<sup>30</sup>

With respect to level of information, results showed that participants who reported to be little or not informed about AF considered of higher significance the need for support, for information, for trust medical and nursing staff and for communication with other patients and family. Indeed, AF patients need to acquire knowledge through supportive communication and build up confidence in order to be effectively involved in treatment.<sup>32</sup> The model of care is a "two-way exchange of information" between health professionals and patients.<sup>30</sup> Information should be provided according to patients' readiness to learn, cognitive abilities, learning style and beliefs about the cause, consequences, controllability, duration of symptoms and diagnosis of AF.<sup>2</sup>

From the patients' perspective, the amount of provided information is insufficient and they claim to need elaborate information in regard to treatment including anticoagulation use and dose adjustments. Assessment of gaps knowledge is important when planning educational interventions to facilitate implementation of AF guidelines.<sup>32-34</sup> Significant concerns are raised about constant reassessment of patients' level of information according to disease progression.<sup>11</sup> Equally important is evaluation of patients' personality since unnecessary information may be a source of stress or detailed information may be more beneficial in patients who wish to monitor closely the disease progress.<sup>11</sup>

Last but not least, depressed patients considered all six needs significant. Clinically, this information is helpful when providing care tailored to patients' needs. To the best of our knowledge, data exploring needs of AF

patients' who experience anxiety/depression is diminished.

Interestingly, AF patients who report not to maintain very good relations with nursing staff are more likely to have high levels of anxiety and depression while those who are not informed about their health state have 3.77 times higher chances to experience high levels of depression.<sup>2</sup>

It should be stressed that health professionals put emphasis on psychological and pharmacological treatment while limited attention is paid on the care needs that accompany depression. Possibly, they fail to recognize this psychological distress either because they perceive it as a normal reaction to the stressful AF or they have no education on its' typical and atypical symptoms.<sup>10,11,17</sup> Apart from AF clinical course, health professionals ought to explore both patients' needs and psychological distress. Anxiety and depression along with unmet care needs have a detrimental effect on treatment motivation and on quality of life. Moreover, depression is a significant predictor of an increase in both met and unmet care needs.<sup>35</sup>

Nowadays, the global trend is to provide patient centered care. A well-educated and competent clinician is the essential link in the chain of AF management.<sup>36</sup> Healthcare professionals who understand these concepts may also apply them while managing depressed AF patients.

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## Limitations of the study

This study has some limitations. Convenience sampling is one of the limitations since this method is not representative of all population with AF living in Greece, thus limiting the generalizability of results. Other limitations are related to the study design which was cross-sectional and not longitudinal and therefore does not permit exploring causal relation between patients' needs and anxiety/depression. The sample size was relatively small, although many significant associations were observed. Moreover, there was no next measurement in time that would allow evaluation of possible changes in all dimensions under assessment (needs and anxiety/depression).

The strengths of the study include the use of a wide spread instrument (HADS), that permit comparisons among populations across the world.

## Conclusions

Understanding the association between patients' needs and anxiety/depression should prompt health professionals to provide beneficial care for AF patients. The results offer support to ideas for educational interventions that improve clinicians' ability to manage AF more efficiently. Furthermore, assessment of anxiety and depression is essential immediately after hospital admission and should not be undermined at discharge. The findings of the present study may stimulate and guide future research efforts.

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## Ερευνητική εργασία

# Κολπική μαρμαρυγή: Η επίπτωση του άγχους και της κατάθλιψης στις ανάγκες ασθενών

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### ΠΕΡΙΛΗΨΗ

Η κολπική μαρμαρυγή (ΚΜ) αποτελεί συχνή καρδιακή αρρυθμία, που αναμένεται να λάβει ανησυχητικές διαστάσεις κυρίως λόγω της γήρανσης του πληθυσμού. Σκοπός της μελέτης ήταν η διερεύνηση του βαθμού σημαντικότητας των αναγκών των ασθενών με ΚΜ και των συσχετιζόμενων παραγόντων όπως επίσης της επίπτωσης του άγχους και της κατάθλιψης σε αυτές τις ανάγκες. Το δείγμα της μελέτης αποτέλεσαν 215 νοσηλευόμενοι ασθενείς με ΚΜ. Τα δεδομένα συλλέχθηκαν με τη συμπλήρωση ενός ερωτηματολογίου το οποίο, εκτός από τα χαρακτηριστικά των ασθενών, περιλάμβανε την κλίμακα άγχους και κατάθλιψης σε γενικό νοσοκομείο (HADS) και το ερωτηματολόγιο «Ανάγκες νοσηλευόμενων ασθενών με στεφανιαία νόσο», το οποίο αξιολογεί τις εξής έξι κατηγορίες αναγκών: (α) ανάγκη για στήριξη και καθοδήγηση, (β) ανάγκη για ενημέρωση από το ιατρονοσηλευτικό προσωπικό, (γ) ανάγκη για επικοινωνία με άλλες ομάδες ασθενών και την οικογένεια, (δ) ανάγκη για εξατομίκευση της φροντίδας και συμμετοχή του ασθενούς στη φροντίδα, (ε) ανάγκη για κάλυψη των συναισθηματικών αναγκών και φυσικών αναγκών και (στ) ανάγκη να εμπιστευονται το ιατρικό και νοσηλευτικό προσωπικό. Το επίπεδο της στατιστικής σημαντικότητας ετέθη στο  $p < 0,05$ . Από τους 215 συμμετέχοντες, το 68,4% ήταν άνδρες και το 67,5% ήταν  $>60$  ετών. Επιπλέον, το 47,5% του δείγματος βίωνε άγχος και το 29,5% κατάθλιψη. Οι ασθενείς ανέφεραν ως σημαντικότερη την ανάγκη στήριξης, ενημέρωσης και εμπιστοσύνης από ιατρικό και νοσηλευτικό προσωπικό (διάμεσος, 29, 20 και 6, αντίστοιχα). Το άγχος και η κατάθλιψη συσχετίστηκαν στατιστικά σημαντικά με όλες τις ανάγκες των ασθενών ( $p < 0,05$ ) εκτός από την ανάγκη κάλυψης των συναισθηματικών και σωματικών αναγκών και την ανάγκη εμπιστοσύνης, οι οποίες δεν συσχετίστηκαν με το άγχος. Όσον αφορά τις ανάγκες των ασθενών, όσοι δήλωσαν λίγοι ή καθόλου ενημερωμένοι για την ασθένειά τους ανέφεραν ως σημαντικότερη την ανάγκη στήριξης και καθοδήγησης ( $p = 0,030$ ), την ανάγκη ενημέρωσης και την ανάγκη εμπιστοσύνης από το ιατρικό και νοσηλευτικό προσωπικό ( $p = 0,001$  και  $p = 0,012$ , αντίστοιχα) και την ανάγκη επικοινωνίας με άλλους ασθενείς και την οικογένεια ( $p = 0,007$ ). Η ανάγκη εξατομίκευσης της φροντίδας και συμμετοχής σε αυτή αξιολογήθηκε ως σημαντικότερη από τους ασθενείς ηλικίας  $>70$  ετών και εκείνους που δεν είχαν παιδιά ( $p = 0,039$  και  $p = 0,029$ , αντίστοιχα), ενώ η ανάγκη επικοινωνίας με άλλους ασθενείς και την οικογένεια αξιολογήθηκε ως σημαντικότερη από τις γυναίκες ( $p = 0,028$ ). Τα ευρήματα υπογραμμίζουν τη σημασία της παροχής φροντίδας προσαρμοσμένης στις ανάγκες των ασθενών με ΚΜ που βιώνουν άγχος και κατάθλιψη.

**ΛΕΞΕΙΣ ΕΥΡΕΤΗΡΙΟΥ:** Άγχος, κατάθλιψη, ανάγκες ασθενών, κολπική μαρμαρυγή.

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## Research article

# Assessment of the Mobile Mental Health Units' effectiveness in Cyclades islands

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### ABSTRACT

In Greece, the provision of mental health shows inefficiencies in remote and inaccessible areas due to the lack of appropriate structures and access to healthcare. The purpose of this study was to assess the effectiveness of the Mobile Mental Health Units (MMHUs) in Cyclades with and without MMHUs' operation based on Real-World Evidence (RWE). The study population consisted of 724 people who visited the MMHUs of the western and northeastern Cyclades in 2015. The data derived from the patients' medical records of EPAPSY classified by International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) and the Global Assessment of Functioning (GAF) scale. The analysis revealed that 60.9% of the participants were women and the average age was 50.1. 50.4% of the people who visited MMHUs without referral from primary health care professionals and 18.8% with referral. The calculation of effectiveness was based on DALYs (Disability-Adjusted Life Years) and was performed according to the World Health Organization methodology. In the specific population, there are no recorded deaths caused by mental disorders and thus DALYs are equal to Years Lost due to Disability (YLDs) with MMHUs' operation. 18% of the population was diagnosed with mood disorders (F30-F39) and morbidity burden 9.49 (YLDs), while 17.5% of the patients were diagnosed with neurotic, stress-related and somatoform disorders (F40-F48) and corresponding morbidity burden 4.53 (YLDs). Our results revealed that the effectiveness of MMHUs corresponds to 17.98 Disability-Adjusted Life Years (DALYs) averted in 2015. The mood disorders and the neurotic, stress-related disorders have shown a high morbidity burden. Advanced age, non-permanent employment, existence of psychopathology in the family and referral on patients' own will were found to significantly affect the mental health status of the participants. The implementation and expansion of flexible and alternative community-based interventions, such as MMHUs, constitute a best practice both for obtaining higher clinical outcomes and for facing regional inefficiencies related to population's access to healthcare.

**KEYWORDS:** Mobile Mental Health Units (MMHUs), Disability-Adjusted Life Years (DALYs), mental health, remote areas, Greece.

### Introduction

Health policy experts and analysts have identified deficiencies in the access and provision of the mental health services in remote and inaccessible areas, in Greece and elsewhere.<sup>1–6</sup> The operation of the community-based<sup>7,8</sup> Mobile Mental Health Units (MMHUs) has been shown to be a cost-effective option for decision-making pur-

poses internationally.<sup>9–22</sup> The Scientific Association for the Regional Development and Mental Health (EPAPSY) launched in 2003 the MMHUs in the Northeastern and Western Cyclades in the islands of Paros, Antiparos, Syros, Tinos, Mykonos, Andros, Kea, Kythnos, Serifos, Sifnos, Kimolos and Milos. These units provide free mental health services to children, adolescents and adults,

are funded by the Ministry of Health and are also supported by the local government and other local agencies.<sup>23,24</sup>

It's worth mentioning that in the above islands and before the MMHUs' operation, patients were facing major difficulties in access to mental health services, with adverse consequences on their health condition.<sup>25</sup> Mental care was only delivered at the outpatient units of the Hospital of Syros. The geographical dispersion among the islands, the difficulties in transportation related with the low frequency of itineraries and the unpredictable weather conditions hampered disproportionately patients' access to health services.<sup>23</sup> In addition, the unpropitious fiscal situation in the country had created a climate of uncertainty, unemployment, financial difficulties, etc., which are directly related to the impact of psychiatric morbidity.<sup>6,26-34</sup>

Throughout these years plenty of actions have taken place by the MMHUs covering the islands' population in need and also providing preventive and consultation mental health services. In particular, workshops and training seminars addressed to doctors, teachers, police officers, civil servants and other local professional groups have been organized. Furthermore, the creation of volunteer groups and the undertaking of actions addressed to specific groups of the population, such as the elderly, victims of domestic violence, parents, children, etc. is a significant part of the operation of MMHUs.<sup>23</sup>

Given the MMHUs' operation and the lack of mental health infrastructure in these islands as well as the geographical features of the country, it was considered critical to evaluate patients' clinical outcomes. Thus, the purpose of this study is to assess the effectiveness of the MMHUs in the Northeastern and Western Cyclades population with symptoms of mental disorders.

## Material and Method

### Study population

The data were extracted from the patients' medical records (Real-World Evidence, RWE) addressed to the MMHUs of the Northeastern and Western Cyclades. The collected data was anonymous and referred to patients' demographic and socio-economic characteristics, the diagnosis according to the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10),<sup>35</sup> comorbidities, health services use and the overall cases' management. Figure 1 illustrates the sample's stratification for subsequent analysis. The study was undertaken by the University of Peloponnese and has been approved by the Ethics Committee of EPAPSY.

### Clinical data

Medical records were classified in accordance with the diagnostic categories (ICD-10) and the Global Assessment of Functioning scale (GAF).<sup>36</sup> GAF assesses person's health status and the symptoms of mental disorder that affect his/her daily life. The Disability-Adjusted Life Years Index (DALYs) has been used for the outcomes' assessment. DALYs refer to the present value of future life years lost due to premature mortality and morbidity associated with various mental and physical health conditions.<sup>37-42</sup> DALYs for a disease or health condition are calculated as the sum of Years of Life Lost (YLLs) lost due to premature mortality in the population and Years of Lost due to Disability (YLDs). The methodology of the World Health Organization (WHO) was used to calculate the DALYs:<sup>39-41</sup>

$DALYs = YLLs + YLDs$ , where:

$YLLs = \text{Years of Life Lost due to premature death}$

$YLDs = \text{Years Lost due to Disability}$

YLLs were calculated by the formula:<sup>37-42</sup>

$YLLs = N * L$ , where:

$N = \text{number of deaths}$

$L = \text{standard life expectancy at age of death in years}$

YLDs were estimated by the formula (GBD 2010):<sup>40</sup>

$YLDs = P * D$ , where:

$P = \text{number of prevalent cases (prevalence)}$

$D = \text{disability weight for each disease (0-1)}$

Due to the cases of comorbidities, the calculation was formulated as follows:<sup>39</sup>

$YLD_{1+2} = 1 - (1 - YLD_1) * (1 - YLD_2)$

### Statistical analyses

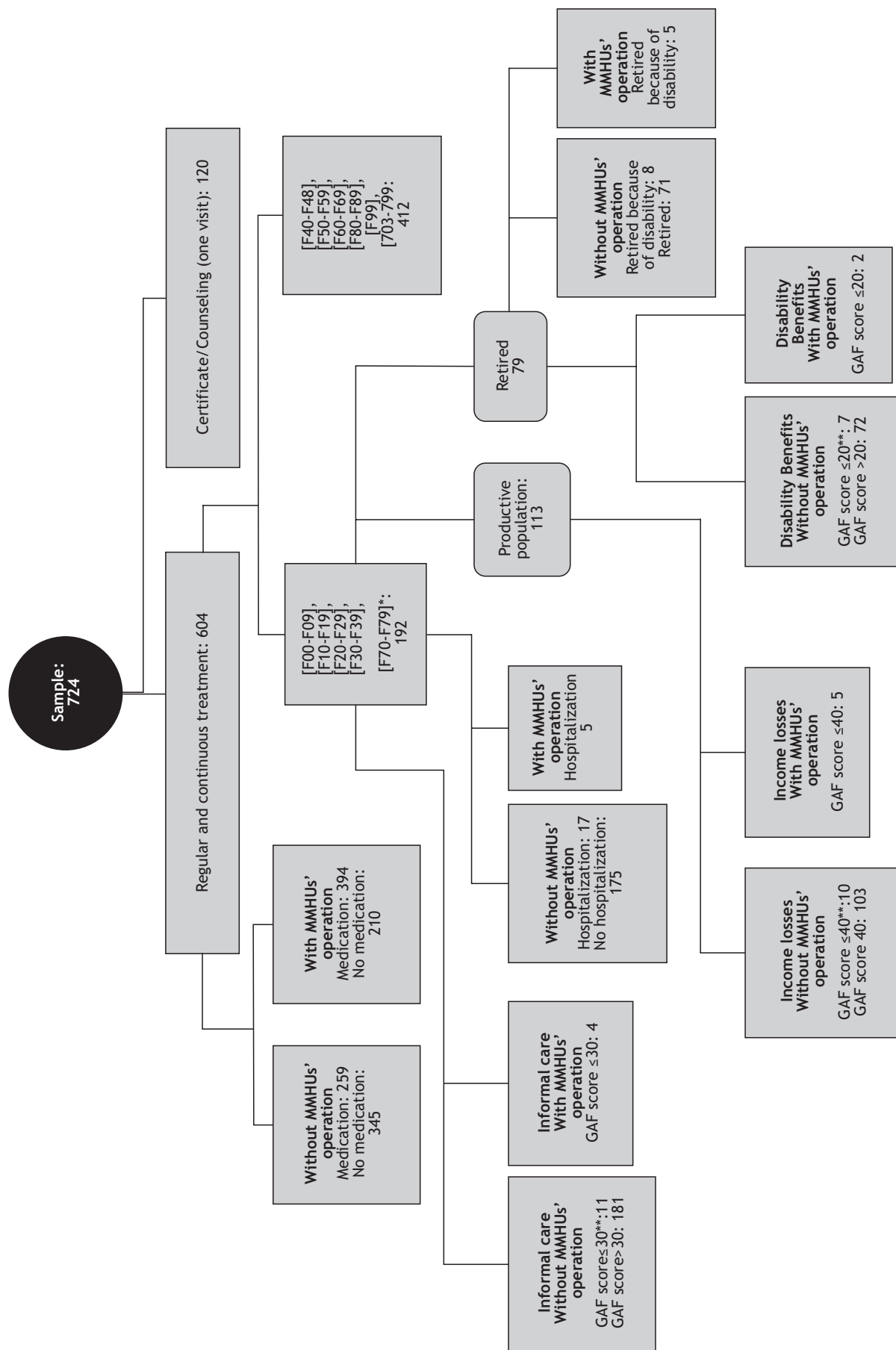
The statistical program IBM SPSS 22.0 was used for data processing (Statistical Package for Social Sciences). The statistical analysis of the results includes descriptive and inferential statistics (linear regression). In the multiple linear regression, DALYs of the mental and physical illnesses were used as dependent variable while the demographic, socio-economic data, health services' use and the cases' overall management were used as independent variables. Logarithmic transformations were performed and the stepwise method was used. Statistical significance levels were set at 0.05.

## Results

### Characteristics of the sample

The study population (table 1) consisted of 724 people, who addressed the MMHUs in 2015. The majority were women, married, secondary and tertiary education graduates and full-time employees. In addition, the





**Figure 1.** Sample Stratification. \*These specific diagnostic categories of diagnoses were selected because they cause greater burden on the population's health and hospitalizations in mental health structures, as evidenced by data from the Hellenic Statistical Authority (2000, 2010–2014). \*\*The GAFscore rating system evaluates the individual's functionality in daily life. The lower the score, the greater the individual's difficulty to cope with everyday life activities. Persons with GAF score 40–31 may not be able to cope with their professional activities. People with GAF score 30–21 need to be cared by their environment. Persons with GAF score between 20–11 are unable to support themselves and need disability allowance and ongoing care.

**Table 1.** Characteristics of the sample.

		N	%
Gender	Male	283	39.1
	Female	441	60.9
	Total	724	100
Marital status	Single	129	18.1
	Married	447	62.9
	Divorced/ Separated	64	9.0
	Widow	52	7.3
	Domestic Partnership	19	2.7
	Total	711	100
Education	No	12	1.7
	Primary school	136	18.8
	Secondary school	70	9.7
	High school	224	30.9
	IEK/College/Vocational training institute	72	9.9
	Technological Educational Institute	62	8.6
	University/Higher Educational Institute	148	20.4
Total	724	100.0	
Occupation	Full-time	327	45.2
	Part-time/seasonal/unemployed	109	15.0
	Household	156	21.5
	Pupil/Student	4	0.6
	Retired	128	17.7
	Total	724	100.0

mean age of the sample was 50.1 years (SD=17.0 years). The 62.9% of participants was married and the median number of children was 2 (1–2 children). 71.0% of the participants lived with their family, while 13.7% lived alone. The majority (91.6%) of the sample were Greeks and 21.4% were lived in Paros, 16.7% in Mykonos and 15.5% in Tinos. 4.3% of participants were uninsured. In addition, 33.7% of people had visited a mental health professional at some point in the past. Specifically, the mean age of the first visit was 44.0 years (SD=17.5 years). The 20.9% reported cases of psychopathology in the family environment. A small number (2.4%) had been hospitalized for mental disorders with an average number of one hospitalization. 28.0% of the participants had serious health problems and 31.4% had been diagnosed with chronic physical illness.

Table 2 presents the reasons for attendance, as well as the referral methods from 2013 to 2017. The reasons for attendance were mainly related to cases of parental counseling, anxiety, depression and relationship or so-

cial problems. It was found that over time, the majority of participants addressed the MMHUs on their own will. It is also worth noting that this method of referral became an increasing trend over time: in 2013 the patients who addressed the units voluntarily approached 61.8% while the percentage reached 82.6% in 2017. As a result, there was a reduction in the other means of referral. In 2015, out of the 365 participants who addressed voluntarily the MMHUs, the majority mentioned as primary reason for their visit the parent counseling (88 patients), anxiety cases (87 patients), and depression cases (66 patients).

### Clinical characteristics

Table 3 presents the patients' diagnosis. The majority was addressed for counseling, mood and neurotic, stress-related and somatoform disorders. Regarding the individualized care plan, 48.9% of participants followed psychological treatments, 21.8% pharmacotherapy and 12.3% a combination of psychological therapies and pharmacotherapy. Specifically, 24.4% followed treatment with antidepressants and 9.4% anxiolytics.

Based on the patients' diagnosis combined with the mortality (YLDs) and morbidity (YLLs) data, DALYs estimation is presented in the table 4 with and without the MMHUs' operation. Thus, 17.98 DALYs were found for the MMHUs' operation and 115.79 in the case of the non MMHUs' operation (table 4).

The results of the multiple linear regression (table 5) were:

- The older the patients, the greater their DALYs.
- Full-time employees had significantly fewer DALYs than the non-permanent work ones.
- Patients who visited MMHUs because of referral had significantly fewer DALYs than those who voluntarily visited MMHUs.
- Patients with a family history of psychopathology had more DALYs than those without family history of psychopathology.

### Discussion

The operation of the MMHUs in the Northeastern and Western Cyclades contributed to the aversion of about 98 DALYs (115.79–17.98) in 2015. This result is due to the prevention of premature mortality and the reduction of the mental health burden. More specifically, before the MMHUs' operation, there were no suitable structures to care for people with symptoms of mental disorders resulting in deficient treatment. It is clear that the MMHUs health services provision cover a significant part of Primary Health Care (PHC) in the field of mental health. The cooperation among PHC and MMHUs health profes-

**Table 2.** Reasons for attendance and referral methods to MMHUs 2013–2017.

	2013		2014		2015		2016		2017	
	N	%	N	%	N	%	N	%	N	%
Reasons for attendance										
Anxiety	75	18.9%	70	17.9%	138	19.1%	72	23.7%	72	18.9%
Depression	76	19.2%	73	18.6%	105	14.5%	52	17.1%	63	16.5%
Psychosis	12	3.0%	12	3.1%	24	3.3%	11	3.6%	9	2.4%
Dementia	16	4.0%	13	3.3%	28	3.9%	14	4.6%	29	7.6%
Drugs	2	0.5%	2	0.5%	6	0.8%	3	1.0%	0	0.0%
Prescription-	45	11.4%	36	9.2%	79	10.9%	30	9.9%	45	11.8%
Problems in relationship-Social-Other	156	39.4%	114	29.1%	98	13.5%	57	18.8%	83	21.8%
Problem of conduct	4	1.0%	4	1.0%	16	2.2%	3	1.0%	5	1.3%
Parents' counseling	10	2.5%	68	17.3%	230	31.8%	62	20.4%	75	19.7%
Total	396	100.0%	392	100.0%	724	100.0%	304	100.0%	381	100.0%
Referral methods										
Without referral/on their own will	275	61.8%	198	50.3%	365	50.4%	199	65.7%	314	82.6%
Primary health care units	35	7.9%	74	18.8%	136	18.8%	36	11.9%	12	3.2%
Private doctor	17	3.8%	32	8.1%	43	5.9%	10	3.3%	3	0.8%
Local municipality	26	5.8%	27	6.9%	53	7.3%	17	5.6%	14	3.7%
Public authorities (police. school etc.)	72	16.2%	55	14.0%	80	11.0%	19	6.3%	14	3.7%
Church	7	1.6%	6	1.5%	10	1.4%	5	1.7%	0	0.0%
Other (family. friends etc.)	13	2.9%	2	0.5%	37	5.1%	17	5.6%	23	6.1%
Total	445	100.0%	394	100.0%	724	100.0%	303	100.0%	380	100.0%

**Table 3.** Sample diagnoses.

Diagnoses according to ICD-10	N	%
Organic, including symptomatic, mental disorders [F00–F09]	39	5.4
Mental and behavioural disorders due to psychoactive substance use [F10–F19]	5	0.7
Schizophrenia, schizotypal and delusional disorders [F20–F29]	20	2.8
Mood [affective] disorders [F30–F39]	130	18
Neurotic, stress-related and somatoform disorders [F40–F48]	127	17.5
Behavioural syndromes associated with physiological disturbances and physical factors [F50–F59]	5	0.7
Disorders of adult personality and behavior [F60–F69]	12	1.7
Mental retardation [F70–F79]	4	0.6
Disorders of psychological development [F80–F89]	1	0.1
Factors influencing health status and contact with health services, counseling [Z03–Z99]	279	38.5
Examination for administrative purposes [Z00–Z02]	62	8.6
Unspecified mental disorder [F99]	40	5.5
Total	724	100.0

sionals would significantly contribute to the continuation of treatment and access to mental care as well as the overall improvement of patients' health status.

Our results indicate that the highest DALYs' scores are found in the diagnostic categories of mood disorders (DALYs: 9.49) and neurotic, stress-related disorders

(DALYs: 4.53) under the MMHUs' operation. These findings are similar to a previous research conducted in Greece indicating high numbers of patients diagnosed with neurotic disorders and mood disorders.<sup>6</sup> It is essential to point out that the results of our study converge with other studies conducted in Greece. In particular,

**Table 4.** DALYs measurement with and without MMHUs' operation.

Diagnostic Categories ICD-10	With MMHUs' operation			Without MMHUs' operation			
	N	YLD	YLL	DALYs	YLD	YLL	DALYs
Organic, including symptomatic, mental disorders [F00–F09]	39	1.17	0.00	1.17	1.69	0.00	1.69
Mental and behavioural disorders due to psychoactive substance use [F10–F19]	5	0.03	0.00	0.03	0.04	0.00	0.04
Schizophrenia, schizotypal and delusional disorders [F20–F29]	20	0.43	0.00	0.43	0.49	79.40	79.89
Mood [affective] disorders [F30–F39]	130	9.49	0.00	9.49	15.60	0.00	15.60
Neurotic, stress-related and somatoform disorders [F40–F48]	127	4.53	0.00	4.53	10.79	0.00	10.79
Behavioural syndromes associated with physiological disturbances and physical factors [F50–F59]	5	0.05	0.00	0.05	0.05	0.00	0.05
Disorders of adult personality and behavior [F60–F69]	12	0.13	0.00	0.13	0.13	0.00	0.13
Mental retardation [F70–F79]	4	0.00	0.00	0.00	0.00	0.00	0.00
Disorders of psychological development [F80–F89]	1	0.00	0.00	0.00	0.00	0.00	0.00
Unspecified mental disorder [F99]	40	0.24	0.00	0.24	0.41	0.00	0.41
Examination for administrative purposes [Z00–Z02]	62	0.15	0.00	0.15	0.65	0.00	0.65
Factors influencing health status and contact with health services, counseling [Z03–Z99]	279	1.75	0.00	1.75	6.53	0.00	6.53
Total	724	17.98	0.00	17.98	36.39	79.40	115.79

**Table 5.** Results of multiple linear regression. Predictors of DALYs.

		$\beta^*$	SE**	P
Age		0.001	0.0001	<0.001
Occupation	Household/Student/Pupil/Retired (refer.)			
	Part-time/Seasonal/Unemployed	–0.004	0.004	0.287
	Full-time/stable	–0.009	0.003	0.003
Referral	No (refer.)			
	Yes	–0.007	0.002	0.006
Existent psychopathology in the family	No (refer.)			
	Yes	0.007	0.003	0.015

\*beta coefficient, \*\*standard error

our finding revealing that patients with psychotic disorders show a higher degree of comorbidity compared to those diagnosed with other mental disorders is also presented in a study conducted in Ioannina-Thesprotia.<sup>43,44</sup> Obviously, these patients have a greater difficulty in finding appropriate treatment and the presence of MMHUs is considered as of added value for the continuation of their treatment. Also, relevant studies have shown that women outnumber men in terms of the onset of mental disorders symptoms,<sup>6,30,31,34</sup> married<sup>30,31,34</sup> as well as people with higher education and higher income have higher incidence of mental disorders.<sup>6</sup> Our results support the above findings since 60.9% of the participants who addressed the MMHUs were women, 62.9% were

married and 20.6% were scientists, businessmen, senior public and private sector executives.

Advanced age, non-permanent employment, existence of psychopathology in the family (heredity) as well patients' referral on their own will, are factors that seem to significantly affect individuals' mental health condition. These findings are in agreement with the international literature that shows increased risk of developing psychopathology and morbidity in these specific population groups.<sup>6,23,26,27,29,31–34,45</sup>

Although DALYs for clinical evaluation of interventions is revealed as among the most valid indices used in the field of mental health internationally,<sup>46–50</sup> it lags far behind

in Greece. The present study measures the effectiveness of an intervention using the DALYs index for the first time in the field of mental health in the country. However, the lack of comparative chronological data on DALYs and the use of only one year for the evaluation of MMHUs constitutes a methodological limitation that should be pointed out. Therefore, DALYs calculation for one year period is indicative and cannot be reproduced over time. The existence of chronological real world evidence data would provide more reliable and robust results.

The results of this study highlighted the contribution of MMHUs to cover unmet mental medical needs. The

expansion of the activities of MMHUs is deemed necessary and beneficial in a country such as Greece where remote areas are inaccessible. Evaluation of health services should be considered as priority in health policy decision making.

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## Ερευνητική εργασία

# Αξιολόγηση της Αποτελεσματικότητας των Κινητών Μονάδων Ψυχικής Υγείας στις Κυκλάδες

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### ΠΕΡΙΛΗΨΗ

Η ύπαρξη ελλείψεων σε απαραίτητες και κατάλληλες δομές του συστήματος παροχής υπηρεσιών ψυχικής υγείας σε απομακρυσμένες και δυσπρόσιτες περιοχές έχει διαπιστωθεί και εντείνεται σημαντικά στη νησιωτική χώρα. Αντικείμενο της παρούσας μελέτης είναι η μέτρηση της αποτελεσματικότητας της λειτουργίας των Κινητών Μονάδων Ψυχικής Υγείας (ΚΜΨΥ) βάσει πραγματικών δεδομένων (Real-World Evidence, RWE) για την αντιμετώπιση περιστατικών με συμπτώματα ψυχικών διαταραχών στις Κυκλάδες. Τον πληθυσμό της μελέτης αποτέλεσαν οι 724 εξυπηρετούμενοι που προσήλθαν στις ΚΜΨΥ των Βορειοανατολικών και Δυτικών Κυκλάδων από τα δώδεκα (12) νησιά ευθύνης κατά το έτος 2015. Τα δεδομένα της ανάλυσης προήλθαν από τους ιατρικούς φακέλους των εξυπηρετούμενων της ΕΠΑΨΥ και ταξινομήθηκαν με βάση τη Διεθνή Στατιστική Ταξινόμηση Νόσων και Συναφών Προβλημάτων Υγείας Δέκατη Αναθεώρηση (ICD-10) και την κλίμακα Global Assessment of Functioning (GAF). Από την ανάλυση προέκυψε ότι το 60,9% των εξυπηρετούμενων ήταν γυναίκες και η μέση ηλικία των εξυπηρετούμενων ήταν 50,1 έτη. Το 50,4% των εξυπηρετούμενων απευθύνθηκε για βοήθεια στις ΚΜΨΥ αυτοβούλως και το 18,8% παραπέμφθηκε από τις μονάδες της Πρωτοβάθμιας Φροντίδας Υγείας (ΠΦΥ). Η μέτρηση της αποτελεσματικότητας βασίστηκε στη χρήση του δείκτη των Σταθμισμένων Ετών Ζωής ως προς την Ανικανότητα (Disability-Adjusted Life Years, DALYs), σύμφωνα με τη μεθοδολογία του Παγκόσμιου Οργανισμού Υγείας. Με δεδομένο ότι στον υπό μελέτη πληθυσμό δεν υπάρχει θάνατος από ψυχική διαταραχή, τα DALYs ισούνται με τα Years Lost due to Disability (YLDs). Το 18% του πληθυσμού διαγνώστηκε με διαταραχές της διάθεσης (F30-F39) και φορτίο νοσηρότητας ίσο με 9,49 (YLDs), ενώ το 17,5% των εξυπηρετούμενων με νευρωσικές διαταραχές, οι οποίες σχετίζονται με άγχος και σωματόμορφες διαταραχές (F40-F48) και αντίστοιχο φορτίο νοσηρότητας 4,53 (YLDs). Η αποτελεσματικότητα της λειτουργίας των ΚΜΨΥ καταγράφεται σε 17,98 DALYs που αποτρέπονται κατά το έτος 2015, όπου οι διαταραχές της διάθεσης και οι νευρωσικές σχετιζόμενες με άγχος διαταραχές εμφανίζουν υψηλό φορτίο νοσηρότητας. Η προχωρημένη ηλικία, η μη σταθερή απασχόληση, η ύπαρξη ψυχοπαθολογίας στην οικογένεια και η παραπομπή με πρωτοβουλία του ασθενή βρέθηκε ότι επηρεάζουν σημαντικά την ψυχική υγεία του ατόμου. Η ανάπτυξη ευέλικτων μορφών παρεμβάσεων που θέτουν στο κέντρο τους την κοινότητα, όπως οι ΚΜΨΥ αποτελεί μια άριστη πρακτική με όρους κλινικής αποτελεσματικότητας και παρέχει λύσεις στο πρόβλημα της γεωγραφικής ιδιαιτερότητας και πληθυσμιακής κατανομής στον ελλαδικό χώρο.

**ΛΕΞΕΙΣ ΕΥΡΕΤΗΡΙΟΥ:** Κινητή Μονάδα Ψυχικής Υγείας (ΚΜΨΥ), Σταθμισμένα Έτη Ζωής ως προς την Ανικανότητα (Disability-Adjusted Life Years, DALYs), ψυχική υγεία, δυσπρόσιτες περιοχές, Ελλάδα.

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## Research article

# Factor structure and psychometric properties of a new 39-item version of the Criteria for Recovery from Eating Disorders questionnaire (CRED-39)

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### ABSTRACT

Eating disorders (ED) are a group of mental disorders, which are quite difficult to treat. In studies on the recovery process of ED, patients' experience is rarely been taken into account. In addition, there seems to be a gap between patients' objective improvement, as assessed by clinicians, and patients' own subjective evaluation of their recovery. Criteria for Recovery from Eating Disorders (CRED) is a questionnaire used to investigate recovery criteria which are considered important from the patients' perspective. The purpose of the present study was to examine the factorial structure of CRED and to evaluate its psychometric properties. A sample of 138 patients in ED treatment were asked to complete the CRED along with the WHO questionnaire on quality of life (WHOQoL-BREF) and the eating disorders questionnaire (EDE-Q). Exploratory factor analysis (EFA) was used to explore the factor structure of the CRED. Internal consistency assessment was based on Cronbach's  $\alpha$ . Convergent validity was assessed through correlations of CRED with WHOQoL-BREF and EDE-Q. The EFA led to the removal of 13 items of the original CRED and yielded a conceptually justifiable seven factor model: Body Experience, Psychological Well-being, Social Relationships, Gastrointestinal Symptoms, Bodily Functions, Eating Behaviours, and Compensatory Behaviours. Cronbach's alphas of the total questionnaire and all seven factors ranged from 0.77 to 0.88. Convergent validity to WHOQoL-BREF and EDE-Q total scores and subscales were found to be quite satisfactory. Our analysis has, thus, led us to propose the CRED-39, a 39-item version of the CRED questionnaire, which seems to be a valid and reliable tool in assessing ED patients' own view of their recovery process. CRED-39 can be used in clinical practice to address personal needs and to direct individualised interventions.

**KEYWORDS:** Eating disorders, patient perspective, validity, reliability, factor analysis.

### Introduction

Eating disorders (ED) are a group of mental disorders, which are quite difficult to treat, as they manifest through several unique characteristics and set a number of clinical challenges. For example, several patients suffering from anorexia nervosa (AN) lack insight on their body image and express relevant delusional beliefs.<sup>1</sup> The diagnosis of ED often does not remain stable over the years, shifting between AN and Bulimia Nervosa (BN), a

fact that has led a number of researchers to suggest a "transdiagnostic" approach to ED classification and therapy.<sup>2,3</sup>

Although psychotherapy is the first line treatment for ED,<sup>4</sup> its effectiveness is limited, especially when symptoms are severe and the duration of illness is long.<sup>5</sup> Moreover, a considerable number of patients, particularly those suffering from AN, drop out of therapy for a variety of reasons.<sup>6</sup> In many cases, patients with ED need several years to recover (average 12–18 years in AN)



and a substantial number of them do not recover fully, if at all (approximately 50% for AN).<sup>5,7</sup> It is alarming that specialised psychotherapeutic interventions have been found only equally or less effective than nonspecific supportive clinical management for the disorder, which is not considered sufficient in ED treatment.<sup>8</sup> Overall, these points stress the necessity for improving the available therapeutic interventions.

On the other hand, in studies on the recovery process of ED, patient experience has rarely been taken into account. Our knowledge on the effectiveness of ED psychotherapeutic interventions is mainly based on open follow-up studies,<sup>9</sup> where the effectiveness of psychotherapy is assessed based on the diagnostic criteria of the EDs, such as weight restoration, reduction or elimination of bulimic episodes, reduction of excessive fear of obesity and restoration of menstruation. Research on the treatment of EDs is aimed primarily at reducing the physical symptoms such as nutrition restoration, normalization of body weight and absence of purging behaviours. In a study, 79% of patients with AN were considered to have recovered, based on the above criteria, but when psychological criteria (such as mental state, body image and insight) were also taken into account, the recovery rate decreased to 49%.<sup>10</sup> This led clinicians and researchers to differentiate full ED remission from just weight recovery. Moreover, a common observation in clinical practice is that when some patients “recover” from ED symptomatology, they become extremely anxious, distressed or even depressed and in some cases, they start weight-reducing behaviours again.<sup>11</sup> Clearly, there is a gap between objective improvement, as measured by the researchers, and patients’ own subjective sense of their recovery.

Patients who have recovered from an ED or have received long-term treatment, report only a small improvement in their quality of life (QoL)<sup>12</sup> and it appears that, in most cases, their QoL index remains poorer than that of controls.<sup>13,14</sup> According to ED patients the most affected areas of their QoL is self-image and well-being.<sup>14</sup> Patients mention that a sense of belonging, having a job or being a student, good physical health, and a general sense of well-being are the most important elements of good QoL.<sup>14</sup>

Lately, it has been suggested that patients’ view on their therapy is very important in order to improve existing treatment practices and to achieve better therapeutic outcomes.<sup>15</sup> There are a limited number of questionnaires assessing patient view in Eds.<sup>16–18</sup> Noordenbos and Seubring<sup>18</sup> have created the most extended of those, the Criteria for Recovery from Eating Disorders (CRED) questionnaire, by selecting criteria which were

considered important by patients and therapists. They first created a list of the core characteristics and consequences of EDs based on the literature and on the criteria for recovery mentioned in effectiveness and follow-up studies. Patients rated a number of these criteria as very important for their recovery, including eating behaviour, body experience, physical concerns, as well as psychological, emotional and social recovery; therapists on the other hand, rated only three criteria as the most important in assessing recovery of their patients, all of which were related to physical recovery.<sup>18</sup> Noordenbos and Seubring reached the conclusion that beyond eating behaviour and weight restoration, one should take into account psychological, emotional and social recovery, in order to prevent dropout, high relapse rate and to achieve full remission of ED symptomatology.<sup>18</sup>

Since the psychometric properties of CRED have not been published yet by the authors,<sup>18</sup> the purpose of the present study was to examine the factorial structure of the questionnaire and to evaluate its validity and reliability for use in research and clinical practice.

## Material and Method

### Procedure

Researchers contacted Dr Greta Noordenbos, the CRED developer, and received permission to translate and to use the questionnaire in a research setting. The CRED questionnaire was translated to Greek by independent Greek and English native speakers, following a forward-backward-forward procedure, according to the instructions of the World Health Organization (WHO) for the translation of self-report questionnaires.<sup>19</sup> In addition, the instrument was split translated using a committee-based approach. Any discrepancies that emerged from the comparison of the two approaches were discussed and a few minor adjustments were applied.

The administration of the questionnaire took place in two contributing centres, the Eating Disorders Outpatient Clinic of the First Department of Psychiatry of the National and Kapodistrian University of Athens and the Day Care Centre for Eating Disorders of the NGO “ANASA”. Participants, according to the Helsinki declaration, were informed in written on the purpose of the study, their ensured anonymity and data protection, the possibility of non-participation without any implications for the treatment they were receiving, and the researchers’ contact details.

### Participants

Participants were consecutive admissions to the outpatient services of the contributing centres with an ED diagnosis (AN, BN or ED Not Otherwise Specified -

EDNOS), who were in treatment for ED at least for the past 3 months. ED diagnosis was made by a psychiatrist in the initial assessment of the patient, according to DSM-5<sup>20</sup> criteria. Exclusion criteria were age less than 18 years, severe mental retardation, psychosis or lack of Greek language comprehension. Recorded demographics included gender and age. Body Mass Index (BMI) and menstruation status (MS; normal menstruation or loss of any menstrual cycle in the last four months) were derived from corresponding questions of the EDE-Q.

## Measures

### Criteria for Recovery from Eating Disorders Questionnaire (CRED)

Noordenbos and Seubring<sup>18</sup> categorised the questionnaire's items into six groups representing behavioural, body experience, somatic, psychological, emotional, and social factors. This procedure resulted in a list of 52 recovery criteria: 9 items on eating behaviour, 5 items on body attitude, 16 items on physical recovery, 8 items on psychological well-being, 9 items on emotional state and 5 items on social adjustment. Each item is rated on a 5-point Likert type scale, with higher scores indicating higher levels of recovery.

### World Health Organization Quality of Life Brief questionnaire (WHOQoL-BREF)

The WHOQoL-BREF questionnaire is a self-report inventory of QoL with 26 original items<sup>21</sup> and 4 additional items (nutrition, work satisfaction, home-life and social life), derived from the validation of the questionnaire within Greek populations.<sup>22</sup> The items fall into four domains: physical health, psychological health, social relationships, and environment. Higher scores indicate better QoL. The Greek version of the WHOQoL-BREF by Ginieri-Coccosis et al.<sup>22</sup> has demonstrated good internal consistency, with Cronbach's  $\alpha$  ranging from 0.67 to 0.81 across the four domains.

### Eating Disorders Examination Questionnaire (EDE-Q) 6.0

The EDE-Q is a self-report questionnaire developed by Fairburn and Wilson,<sup>23</sup> which measures the severity of ED symptomatology. It consists of 28 questions on eating behaviour, clustered in four subscales: restraint eating, eating concern, shape concern and weight concern. Each question is rated on a 6-point Likert type scale and addresses the patient's last 28 days. When appropriate, respondents are requested to provide a frequency count. Each subscale score is presented as a mean score, and Global EDE-Q score is calculated as the mean score

of all the four subscales. In a recent study by Giovazolias et al,<sup>24</sup> the validity of the Greek version of EDE-Q was investigated and the results supported both the internal consistency, as well as the concurrent, convergent and discriminant validity of the EDE-Q and its subscales, with Cronbach's alpha ranging from 0.74 to 0.91.

## Statistical analysis

An Exploratory Factor Analysis (EFA) was conducted in order to investigate the construct validity of the CRED questionnaire and of its factors, using principal components analysis with varimax rotation.<sup>25</sup> For the EFA, the adequacy of the sample was assessed by the Kaiser-Meyer-Olkin test (KMO) and a Bartlett's test of sphericity. Cronbach's alpha was calculated to reflect the internal consistency of each factor, which was produced by the EFA, separately and of the entire questionnaire. Differential validity among diagnoses (AN, BN, EDNOS) was assessed for each factor, based on the non-parametric Kruskal-Wallis test. Convergent validity was assessed through correlations with WHOQoL-BREF and EDE-Q. Statistical significance level was set at 0.05; analyses were conducted using SPSS version 26.

## Results

### Sample characteristics

The ED diagnoses for the 138 participants were AN (N=48), BN (N=53) and EDNOS (N=37). Mean age was 27.38 (Std 8.73) years, females N=132 (95.7%), mean BMI 21.52 (Std 6.23) kg/m<sup>2</sup>. The EDE-Q and WHOQoL-BREF total and subscales mean scores are presented in table 1.

**Table 1.** Descriptive statistics for EDE-Q and WHOQoL-BREF.

	Mean	SD
EDE-Q subscales and Global score		
Global EDE-Q score	2.76	1.44
Eating Concern	2.18	1.50
Restraint	2.42	1.67
Shape Concern	3.35	1.65
Weight Concern	3.09	1.63
WHOQoL-BREF subscales		
Overall Quality of Life	13.30	3.93
General Health	13.10	3.92
Physical Domain	13.15	2.63
Psychological Domain	11.43	3.03
Social Relationships	12.10	3.38
Environment Domain	13.61	2.43

EDE-Q: Eating Disorders Examination Questionnaire; SD: Standard Deviation; WHOQoL-BREF: World Health Organization Quality of Life Brief questionnaire

## Factorial structure

The EFA results indicated a low fit between the data and the original Noordenbos & Seubring six-group model. The EFA yielded a seven-factor solution (based on scree-plots and eigenvalues  $\geq 1.00$ ) with a KMO coefficient equal to 0.74 and a Barlett chi-square value equal to 4512.14 ( $p < 0.001$ ). Seven unique pairs of correlations with an absolute value greater than 0.8 were detected by a Spearman's bivariate correlation of each item to all other items. Thus, one item from each of these pairs was removed, based on a qualitative analysis.<sup>26</sup> Since there were overlapping items in the seven pairs, four items were removed, leaving 48 items in total. A further five items were removed, as they either cross-loaded on more than one factor at more than 75% or had a highest loading of less than 0.4 on any factor. Four additional items were excluded, because their removal improved Cronbach's alpha for the factor they belonged to.

The seven emerging factors were identified as Body Experience, Psychological Well-being, Social Relationships, Gastrointestinal (GI) Symptoms, Bodily Functions, Eating Behaviours and Compensatory Behaviours. Of the 13 items of the Noordenbos & Seubring questionnaire which were left out of the final solution, seven belonged to physical recovery criteria, three to eating behaviour criteria, one each to body attitude, psychological well-being and emotional state criteria. Thus, of our solution's 39 items six came from eating behaviour, four from body attitude, nine from physical recovery, seven from psychological well-being, eight from emotional state and five from social adjustment. The final items which constitute the seven factors and their origin from the Noordenbos & Seubring questionnaire are presented in table 2. Thus, the analysis we conducted resulted in a seven-factor model with 39 items, leading to the proposal for a shorter, 39-items CRED questionnaire (CRED-39), with seven subscales. The final model showed a KMO coefficient equal to 0.76 and a Barlett chi-square value equal to 2783.8 ( $p < 0.001$ ). The proportion of total variance explained was 58.58%. Factor loadings based on the EFA of the 39 items are presented also in table 2.

## Internal consistency and reliability

Cronbach's alpha (reflecting internal consistency) for the total CRED-39 questionnaire was 0.87 and for all subscales (factors) it ranged from 0.77 to 0.88 (table 3). Intercorrelations between the seven subscales are presented in table 4; the average of between subscales correlation coefficients is 0.17. The one-way non-parametric ANOVA (Kruskal-Wallis test), assessing differential validity

based on diagnosis, did not show any statistically significant results for any CRED-39 subscales.

## Correlations between CRED subscales and external validators

Convergent validity coefficients were examined by non-parametric test (Spearman's correlations) due to non-normal distribution in some of the CRED-39 subscales. The correlation coefficients showed significant association with at least one of the WHOQoL-BREF subscales for all CRED subscales (table 5), except for GI Symptoms. The subscales Body Experience, Psychological Well-being, and Eating Behaviours were negatively correlated with all EDE-Q subscales (table 6), whereas Social Relationships and Bodily Functions subscales were negatively correlated with the Eating and Shape Concern EDE-Q subscales. GI Symptoms and Compensatory Behaviours subscales were weakly negatively correlated with presence of normal menstrual cycles (table 6).

## Discussion

The main purpose of the present study was to evaluate the psychometric properties and factorial structure of the CRED questionnaire.<sup>18</sup> Our results did not support the original structure of 52 items for the questionnaire. In the seven subscales solution, suggested by our results, the items of the original emotional state group loaded on Psychological Well-being and Social Relationships. Items reflecting better emotional management (e.g., "I am not depressed"), as well as items reflecting better psychological interaction (e.g., "I dare to express a different opinion") loaded on the Psychological Well-being and Social Relationships, accordingly. The original physical recovery criteria created two distinct subscales, separating Bodily Functions (e.g., "My body temperature is normal") from more specific health recovery criteria related to gastrointestinal problems (e.g., "I have no stomach complaints"). It is known that ED patients experience and focus more on health disturbances related to the gastrointestinal system<sup>27</sup> and this may have led to the creation of a specific subscale for GI Symptoms. Three more of the original physical recovery criteria loaded on the Body Experience subscale. Finally, the new Compensatory Behaviours subscale was created from items of the original eating behaviour group. It seems that healthy eating behaviours (e.g., "I eat three meals a day") are not identical with recovery from eating disorder compensatory behaviours (e.g., "I do not vomit after food intake"). All of these subscale's combinations can be considered conceptually justifiable. Thus, our analysis has led to proposing the CRED-39, a 39-items version

**Table 2.** Final factor loadings based on the results of exploratory factor analysis.

Item number*	Item	Solution Factors**						
		1	2	3	4	5	6	7
B2	I have a more positive body experience	0.775						
B3	I can accept my appearance and figure	0.763						
C15	I have enough energy	0.700				0.337		
D1	I have adequate self-esteem	0.678						
D3	I am sufficiently assertive	0.658	0.325					
C14	I am not often tired	0.655						
C13	My sleep is normal	0.604						
E9	I can cope with stress in a healthy way	0.530						
D5	I can concentrate well	0.504						
E6	I am not very dependent on the opinions of others		0.753					
E5	I am not too often trying to please others		0.741					
D4	I do not criticise myself very often		0.717					
D7	I have no strong fear of failure		0.715					
D2	My self-esteem is no longer dependent on weight		0.661					
B5	I am not obsessed by food and weight		0.612					
E1	I am not depressed		0.562				0.375	
D6	I am not extremely perfectionistic		0.544					
B4	I do not feel the need to diet	0.326	0.500					
E7	I dare to express a different opinion			0.730				
F3	I am able to initiate contact with others			0.706		0.315		
E8	I am able to handle conflicts			0.646				
F5	I dare to talk about personal experiences			0.625				
F4	I have some good friends			0.602				
E4	I am able to express positive emotions	0.339		0.594				
F1	I am not isolated			0.557				
F2	I participate in social activities			0.465				
E3	I am able to express negative emotions			0.458				
C10	I have no stomach complaints				0.834			
C9	I have no intestinal disturbances				0.819			
C8	I have no constipation				0.698			
C7	My blood pressure is normal					0.855		
C6	My heartbeat is normal					0.805		
C5	My body temperature is normal					0.644		
A2	I eat three meals a day						0.819	
A1	My eating behaviour is healthy and regular	0.321					0.769	
A3	The amount of calories I consume is normal						0.735	
A7	I do not use diuretics							0.864
A5	I do not vomit after food intake							0.841
A9	I do not exercise excessively							0.809

\*Item numbers from the original Noordenbos & Seubring questionnaire;<sup>18</sup> the letter refers to Noordenbos & Seubring criteria for recovery (A=eating behaviour, B=body attitude, C=physical recovery, D=psychological recovery, E=emotional state, F=social adjustment)

\*\*The seven factors produced by the solution are: 1 Body Experience, 2 Psychological Well-being, 3 Social Relationships, 4 Gastrointestinal Symptoms, 5 Bodily Functions, 6 Eating Behaviours, 7 Compensatory Behaviours; the loadings to each factor are presented if they exceed 0,3

**Table 3.** Descriptive statistics for and internal consistencies of the CRED-39 subscales.

CRED-39 subscales	Number of items	Mean Score* (SD)	Median	Skewness (SE)	Kurtosis (SE)	Mean Inter-item correlation	Cronbach's alpha
Body Experience	8	3.03 (0.797)	3.13	-0.107 (0.206)	-0.164 (0.410)	0.266	0.881
Psychological Well-being	9	2.88 (0.810)	3,00	-0.057 (0.206)	-0.143 (0.410)	0.154	0.850
Social Relationships	9	3.75 (0.657)	3.78	-0.197 (0.206)	-0.226 (0.410)	0.218	0.806
GI Symptoms	3	3.05 (1.151)	3.33	-0.167 (0.206)	-0.982 (0.410)	0.091	0.823
Bodily Functions	3	3.88 (0.899)	4,00	-0.584 (0.206)	-0.232 (0.410)	0.176	0.774
Eating Behaviours	3	3.21 (1.014)	3.33	-0.239 (0.206)	-0.768 (0.410)	0.201	0.843
Compensatory Behaviours	3	3.05 (1.500)	3.33	-0.034 (0.206)	-1.650 (0.410)	0.081	0.846

CRED-39: Criteria for Recovery from Eating Disorders – 39 items version; GI: Gastrointestinal

\*Each item is rated on a 5-point Likert scale in response to the question “Do you agree with the following statement?” (1=not at all, 2=no, 3=somewhat, 4=yes, 5=strongly), after Noordenbos & Seubring<sup>18</sup>

**Table 4.** Intercorrelations between CRED-39 subscales (values are Spearman's r coefficients).

CRED-39 subscales	Body Experience	Psychological Well-being	Social Relationships	GI Symptoms	Bodily Functions	Eating Behaviours	Compensatory Behaviours
Body Experience	1.000						
Psychological Well-being	0.441	1.000					
Social Relationships	0.422	0.153	1.000				
GI Symptoms	0.022	0.084	0.016	1.000			
Bodily Functions	0.307	0.087	0.269	0.064	1.000		
Eating Behaviours	0.405	0.228	0.280	0.087	0.215	1.000	
Compensatory Behaviours	0.000	-0.067	0.170	0.273	0.115	-0.007	1.000

CRED-39: Criteria for Recovery from Eating Disorders – 39 items version; GI: Gastrointestinal

**Table 5.** Correlation between CRED-39 subscales and WHOQoL-BREF (values are Spearman's r coefficients).

CRED-39 subscales	WHOQoL-BREF subscales					
	Overall Quality	General Health	Physical Domain	Psychological Domain	Social Relationships Domain	Environment Domain
Body Experience	0.477**	0.461**	0.687**	0.795**	0.511**	0.252**
Psychological Well-being	0.125	0.033	0.217**	0.337**	0.180*	-0.036
Social Relationships	0.471**	0.206**	0.424**	0.481**	0.681**	0.383**
GI Symptoms	0.035	-0.009	-0.059	-0.076	-0.114	-0.059
Bodily Functions	0.134	0.399**	0.246**	0.227**	0.205**	0.087
Eating Behaviours	0.388**	0.264**	0.415**	0.377**	0.229**	0.235**
Compensatory Behaviours	-0.189*	-0.109	-0.090	-0.042	-0.046	0.116

CRED-39: Criteria for Recovery from Eating Disorders – 39 items version; GI: Gastrointestinal; WHOQoL-BREF: World Health Organization Quality of Life-Brief questionnaire

\*p<0.05, \*\*p<0.01

**Table 6.** Correlation between CRED-39 subscales and EDE-Q (values are Spearman's r coefficients).

CRED-39 subscales	EDE-Q subscales						
	Global EDE-Q	Eating Concern	Restraint	Shape Concern	Weight Concern	BMI	MS
Body Experience	-0.637**	-0.554**	-0.471**	-0.656**	-0.617**	-0.156*	0.280**
Psychological Well-being	-0.334**	-0.339**	-0.284**	-0.287**	-0.285**	-0.099	0.189*
Social Relationships	-0.124	-0.191*	-0.061	-0.146*	-0.114	-0.097	0.062
GI Symptoms	0.003	0.006	0.018	-0.007	0.035	-0.006	-0.228**
Bodily Functions	-0.117	-0.141*	-0.053	-0.152*	-0.137	0.132	0.005
Eating Behaviours	-0.327**	-0.346**	-0.318**	-0.269**	-0.271**	0.061	0.272**
Compensatory Behaviours	0.004	0.015	0.064	-0.053	-0.031	-0.024	-0.174*

BMI=body mass index; CRED-39: Criteria for Recovery from Eating Disorders – 39 items version; EDE-Q: Eating Disorders Examination Questionnaire; GI: Gastrointestinal; MS=menstrual status (0=not normal, 1=normal cycles in the last 4 months)

\* $p < 0.05$ , \*\* $p < 0.01$

of the original CRED questionnaire, which is shorter, with a more solid structure and seven subscales.

The internal consistency measures (Cronbach's alpha) of the CRED-39 subscales were quite satisfactory, ranging from 0.77 to 0.88, as was the Cronbach's alpha for the entire questionnaire ( $\alpha=0.87$ ). Furthermore, the low average between subscales correlation coefficients (0.17), confirms the relative independence of the seven subscales from each other.<sup>25</sup> In addition, the mean scores of the CRED subscales suggested that the mean level of recovery is not uniform across the seven areas (table 3). Social Relationships and Bodily Functions received the highest means, reflecting that these are the main areas of improvement after treatment. The Psychological Well-being and Body Experience displayed the lowest mean ratings. This finding confirms previous studies, which have shown that physical recovery does not always imply psychological recovery.<sup>10</sup>

Significant associations were observed between the CRED-39 subscales and the WHOQoL-BREF, as expected. This finding indicates that subjective recovery is in accordance with objective improvement in patients' QoL. In addition, Body Experience, Psychological Well-being and Eating Behaviours subscales were moderately to strongly negatively associated with the EDE-Q subscales. The strongest associations were for the Body Experience suggesting that improvement in the way patients perceive their body (shape and function) is related both to recovery from ED and to improvement in QoL. Also, significant associations between Eating Behaviours and all the WHOQoL-BREF and EDE-Q subscales reflect the importance of eating behaviours restoration to the

QoL and to ED symptomatology. Finally, significant negative associations between Psychological Well-being and EDE-Q remind us of the importance of psychological recovery in order to physically recover from an ED. In conclusion, the associations between CRED-39 and EDE-Q show that recovery criteria, as measured by the EDE-Q, are significantly related to the majority of the CRED subscales, most strongly with the subscale related to patients' Body Experience.

The GI Symptoms subscale did not show any significant correlation with the WHOQoL-BREF or the EDE-Q subscales. This finding might be explained based on the fact that GI symptoms are not specifically addressed in any of these two questionnaires.

No significant differences were found in the reported CRED-39 subscales mean scores between different diagnoses of ED. This finding is in line with the literature, which suggests that there is a "transdiagnostic" model for EDs. According to this model, EDs share a common background and the same cognitive and coping mechanisms that maintain the ED.<sup>2,3</sup> Consequently, therapeutic interventions and outcome could be expected to be approximately the same for all ED diagnoses.

The findings of the present study suggest that CRED-39 is a valid and reliable measure that can be used in clinical practice to address the subjective recovery experience in ED patients. There are, however, limitations to the present study, starting with sample size and the need for the results to be replicated in larger samples. Also, a Confirmatory Factor Analysis should be conducted to confirm the fit of the seven-factor model on other populations, as well as, test-retest reliability should be

performed in future research. Finally, the study did not include a sample of fully recovered patients, so we could not test differences between them and patients still being on various stages of treatment.

Patients' view is being increasingly considered to be important in the effort to improve therapies for Eds<sup>15</sup> and to move from a mainly physical approach to a more holistic and individualised one, paying proper attention to psychological, social and emotional criteria; the latter seem to be mentioned as exceptionally important from patients' perspective.<sup>18</sup> In addition, research is recently focused on understanding the psychological and biological mechanisms that drive the illness trajectory over time and on explaining interindividual differences in illness course, severity, and persistence to treatment.<sup>28</sup> Official Clinical Guidelines have addressed the need for more individualised therapeutic approaches as well as for longer treatment duration for severe and enduring ED.<sup>4</sup> It seems that recovery procedure is not completed with weight recovery and in some cases, it could take up to two years, after the completion of therapy, for patients to report a subjective sense of ED recovery.<sup>18</sup>

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## APPENDIX

### Greek translation of CRED-39 questionnaire

#### Ελληνική μετάφραση του ερωτηματολογίου CRED-39

Ερωτηματολόγιο Κριτηρίων Ανάρρωσης από Διαταραχή Πρόσληψης Τροφής – εκδοχή 39 λημμάτων (CRED-39, Noordenbos & Seubring, 2006, Karapavlou et al 2021)

Το παρόν ερωτηματολόγιο αφορά τους παρακάτω επτά τομείς/κριτήρια ανάρρωσης από διαταραχή πρόσληψης τροφής: εικόνα εαυτού, ψυχική ευεξία, κοινωνικές σχέσεις, γαστρεντερικά συμπτώματα, σωματικές λειτουργίες, διατροφικές συνήθειες και αντιρροπιστικές συμπεριφορές. Αφού συμπληρώσετε αυτό το ερωτηματολόγιο, μπορείτε να ελέγξετε σε συνεργασία με τον θεραπευτή σας σε ποιους τομείς έχετε ήδη βελτιωθεί και σε ποιους τομείς μπορεί να χρειάζεται περισσότερη επικέντρωση στην θεραπεία σας, ώστε να προσαθήσετε να βρείτε μαζί ποια θεραπευτική στρατηγική θα μπορούσε να είναι χρήσιμη για την περαιτέρω βελτίωσή σας.

Πόσο σας εκφράζουν οι παρακάτω προτάσεις;

	1=καθόλου,	2=όχι,	3=κάπως	4=ναι	5=πάρα πολύ
<i>I. Εικόνα εαυτού</i>					
1. Έχω πιο θετική στάση απέναντι στο σώμα μου	1	2	3	4	5
2. Μπορώ να αποδεχθώ την εμφάνισή μου	1	2	3	4	5
3. Έχω αρκετή ενέργεια	1	2	3	4	5
4. Έχω αρκετή αυτοπεποίθηση	1	2	3	4	5
5. Αξιολογώ τον εαυτό μου με θετικό τρόπο	1	2	3	4	5
6. Δεν αισθάνομαι κόπωση πολύ συχνά	1	2	3	4	5
7. Ο ύπνος μου είναι φυσιολογικός	1	2	3	4	5
8. Μπορώ να διαχειριστώ το άγχος μου με υγιή τρόπο	1	2	3	4	5
9. Μπορώ να συγκεντρωθώ αρκετά καλά	1	2	3	4	5
<i>II. Ψυχική ευεξία</i>					
10. Δεν εξαρτώμαι υπερβολικά από την αποδοχή των άλλων	1	2	3	4	5
11. Δεν προσπαθώ να ευχαριστώ τους άλλους πολύ συχνά	1	2	3	4	5
12. Δεν κατακρίνω τον εαυτό μου πολύ συχνά	1	2	3	4	5
13. Δεν φοβάμαι συχνά ότι θα αποτύχω	1	2	3	4	5
14. Η αυτοεκτίμησή μου δεν σχετίζεται με το βάρος μου	1	2	3	4	5
15. Δεν έχω εμμονή με το φαγητό και το βάρος	1	2	3	4	5
16. Δεν αισθάνομαι κατάθλιψη	1	2	3	4	5
17. Δεν είμαι υπερβολικά τελειομανής	1	2	3	4	5
18. Δεν νιώθω την ανάγκη να κάνω δίαιτα	1	2	3	4	5

Continues



**APPENDIX**  
**Greek translation of CRED-39 questionnaire**  
**Ελληνική μετάφραση του ερωτηματολογίου CRED-39**

(Continued)

Πόσο σας εκφράζουν οι παρακάτω προτάσεις;					
	1=καθόλου,	2=όχι,	3=κάπως	4=ναι	5=πάρα πολύ
<i>III. Κοινωνικές σχέσεις</i>					
19. Τολμώ να εκφράσω την άποψή μου	1	2	3	4	5
20. Είμαι σε θέση να πάρω την πρωτοβουλία να επικοινωνήσω με άλλους	1	2	3	4	5
21. Δεν φοβάμαι να έχω διαφορετική γνώμη από τους άλλους	1	2	3	4	5
22. Τολμώ να μιλήσω για προσωπικές εμπειρίες μου	1	2	3	4	5
23. Έχω μερικούς καλούς φίλους	1	2	3	4	5
24. Είμαι σε θέση να εκφράζω θετικά συναισθήματα	1	2	3	4	5
25. Δεν είμαι απομονωμένος/η	1	2	3	4	5
26. Συμμετέχω σε κοινωνικές εκδηλώσεις και δραστηριότητες	1	2	3	4	5
27. Είμαι σε θέση να εκφράζω αρνητικά συναισθήματα	1	2	3	4	5
<i>IV. Γαστρεντερικά συμπτώματα</i>					
28. Δεν έχω στομαχικά προβλήματα	1	2	3	4	5
29. Δεν έχω εντερικά προβλήματα	1	2	3	4	5
30. Δεν έχω δυσκοιλιότητα	1	2	3	4	5
<i>V. Σωματικές λειτουργίες</i>					
31. Η αρτηριακή μου πίεση είναι φυσιολογική	1	2	3	4	5
32. Οι σφύξεις μου είναι φυσιολογικές	1	2	3	4	5
33. Η θερμοκρασία σώματός μου είναι φυσιολογική	1	2	3	4	5
<i>VI. Διατροφικές συνήθειες</i>					
34. Τρώω τρία γεύματα την ημέρα	1	2	3	4	5
35. Η διατροφή μου είναι υγιεινή και τακτική	1	2	3	4	5
36. Η ποσότητα των θερμίδων που προσλαμβάνω είναι υγιεινή και αρκετή	1	2	3	4	5
<i>VII. Αντιρροπιστικές συμπεριφορές</i>					
37. Δεν λαμβάνω διουρητικά	1	2	3	4	5
38. Δεν κάνω εμετούς μετά την πρόσληψη τροφής	1	2	3	4	5
39. Δεν κάνω υπερβολική γυμναστική	1	2	3	4	5

## Ερευνητική εργασία

# Παραγοντική Δομή και Ψυχομετρικές Ιδιότητες του Ερωτηματολογίου Κριτηρίων Ανάρρωσης από Διαταραχή Πρόσληψης Τροφής – εκδοχή 39 λημμάτων (CRED-39)

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### ΠΕΡΙΛΗΨΗ

Οι Διαταραχές Πρόσληψης Τροφής (ΔΠΤ) είναι μια ομάδα ψυχικών διαταραχών που είναι δύσκολο να αντιμετωπιστούν. Στις έρευνες που διερευνούν την ανάρρωση ασθενών από ΔΠΤ, παρατηρείται ότι σπάνια διερευνάται η άποψη των ίδιων των ασθενών. Επιπροσθέτως, κάποιες μελέτες διαπιστώνουν ότι υπάρχει χάσμα μεταξύ της αντικειμενικής βελτίωσης των ασθενών, όπως μετρείται από τους ερευνητές, και της υποκειμενικής αίσθησης βελτίωσης, όπως αξιολογείται από τους ίδιους τους πάσχοντες. Ο στόχος της μελέτης ήταν να εξεταστεί η παραγοντική δομή και η αξιολόγηση των ψυχομετρικών ιδιοτήτων του ερωτηματολογίου Κριτηρίων Ανάρρωσης από Διαταραχή Πρόσληψης Τροφής (Criteria for Recovery from Eating Disorders - CRED), το οποίο αξιολογεί κριτήρια ανάρρωσης που αξιολογούνται ως σημαντικά από τον ασθενή. Το CRED και τα σταθμισμένα εργαλεία ποιότητας ζωής (WHOQoL-BREF) και συμπτωμάτων ΔΠΤ (EDE-Q) συμπληρώθηκαν από δείγμα 138 ασθενών με ΔΠΤ. Η διερευνητική παραγοντική ανάλυση οδήγησε στην αφαίρεση 13 από τα αρχικά λήμματα της CRED και παρήγαγε ένα εννοιολογικά συνεκτικό μοντέλο επτά παραγόντων: Εικόνα Εαυτού, Ψυχική Ευεξία, Κοινωνικές Σχέσεις, Γαστρεντερικά Συμπτώματα, Σωματικές Λειτουργίες, Διατροφικές Συνήθειες και Αντιρροπιστικές Συμπεριφορές. Ο δείκτης του Cronbach (άλφα) έδειξε ικανοποιητική εσωτερική συνοχή για το σύνολο του ερωτηματολογίου, καθώς και για καθέναν από τους επτά παράγοντες ( $\alpha=0,77$  έως  $0,88$ ). Η συσχέτιση του ερωτηματολογίου με τα WHOQoL-BREF και EDE-Q έδειξε ικανοποιητική συγκλίνουσα εγκυρότητα. Η ανάλυσή μας οδήγησε στο να προταθεί η εκδοχή 39 λημμάτων του CRED, το CRED-39, το οποίο φαίνεται να είναι έγκυρο και αξιόπιστο ερωτηματολόγιο για την αξιολόγηση της άποψης των ασθενών με ΔΠΤ σχετικά με την εξέλιξη της θεραπείας τους. Το CRED-39 μπορεί να χρησιμοποιηθεί τόσο στην έρευνα όσο και στην κλινική πρακτική για την διερεύνηση προσωπικών αναγκών σε σχέση με τη θεραπεία και την εξατομίκευση των παρεμβάσεων.

**ΛΕΞΕΙΣ ΕΥΡΕΤΗΡΙΟΥ:** Διαταραχές πρόσληψης τροφής, οπτική του ασθενούς, εγκυρότητα, αξιοπιστία, παραγοντική ανάλυση.

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## Review

# Do patients with schizophrenia have higher infection and mortality rates due to COVID-19? A systematic review

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### ABSTRACT

People with mental illness are known to have poorer physical health outcomes. Among them, patients with schizophrenia spectrum disorders are disproportionately burdened. A number of recent studies have highlighted that patients with schizophrenia are particularly at risk from COVID-19. The aim of this systematic review was to clarify whether patients with schizophrenia spectrum disorders are at greater risk for poor COVID-19 outcomes. We conducted a systematic review of the literature following the PRISMA guidelines, using PubMed, PsycINFO (via Ovid) and Scopus as databases, to identify all studies which investigated infection and/or mortality rate from SARS-CoV-2 in patients with schizophrenia spectrum disorders. Following a formal screening process, seven studies met our inclusion criteria. The results of these seven studies were reported using odds ratios or adjusted odds ratios. The collective results indicated a moderate, but statistically significant effect for higher infection rates, and a strong statistically significant effect for higher mortality rates in patients with schizophrenia. Our findings indicate that people with schizophrenia have a high risk of being infected by the new coronavirus and have a significantly higher mortality rate than the general population. There are contradictory findings concerning other outcomes, including the frequency of intensive care unit admissions for this group. Collectively, these results indicate that people with schizophrenia spectrum disorders may be more vulnerable to being infected and more likely to die due to COVID-19, and yet their access to Intensive Care Units does not seem to be higher. We conclude that patients with schizophrenia constitute a vulnerable group for COVID-19 related infection and mortality, consequently there is a necessity for this vulnerable group of people to have better access to healthcare, including priority in nationwide COVID-19 vaccination programs and expedited intensive care treatment. Our conclusion adds to the ongoing debate arguing for equitable access to healthcare for people with schizophrenia spectrum disorders.

**KEYWORDS:** Schizophrenia, COVID-19, mortality, infection, equity, access to care, vaccination.

### Introduction

The relationship between COVID-19 and mental disorders is bidirectional, because mental disorders may be a risk factor for COVID-19, and conversely COVID-19 patients present frequently with psychiatric problems.<sup>1</sup> In addition, the stress resulting from isolation and social alienation during lockdown periods may result in psychological problems.<sup>2</sup>

The COVID-19 pandemic is a great threat to health care systems across the world. The disease mostly affects vulnerable groups with established risk factors,

such as older age, male sex, cardiovascular diseases, diabetes and neoplasms. Many of these factors are found in mental health patients and especially those suffering from schizophrenia.<sup>3,4</sup>

It is reported that mechanical ventilation, admission to an intensive care unit and death are more likely adverse outcomes among COVID-19 patients who are also diagnosed with mental disorders.<sup>5</sup>

Therefore, it would be very interesting to elucidate whether (a) patients with schizophrenia are more frequently infected with SARS-CoV-2, and (b) schizophre-

nia is associated with higher mortality from COVID-19. This is a systematic review which tries to answer these two questions.

## Methods

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.<sup>6</sup>

### Search strategy and inclusion criteria of studies

To identify relevant research papers, the two authors independently searched MEDLINE, Scopus and PsycINFO (via Ovid) up to 21/3/2021 using the key terms “Schizophrenia” AND “COVID-19”. The resulting papers were then screened to include all those examining COVID-19 related infection or mortality, and to exclude thematically irrelevant studies (i.e., those not dealing with the aforementioned themes). Other inclusion/exclusion criteria were English language and adult population. Final paper inclusion was decided by consensus. External arbitration was planned for potential disagreements. References of included articles were also searched for citations of further relevant published and unpublished studies.

### Data synthesis and outcome measures

Data extraction included article ID, time of publication, number of subjects, infection rate and/or mortality rate. The outcome measures were (a) SARS-CoV-2 infection rate in patients with schizophrenia, and (b) death of patients with schizophrenia from SARS-CoV-2. Both outcome rates (infection and mortality) were reported as Odds Ratios (OR)/Adjusted Odds Ratios (AOR).

## Results

### Study characteristics

Our searches in the three databases yielded 605 hits, which were reduced after duplicate and title/abstract screening to 16. Of the remaining 16 articles, 8 were excluded because they did not focus on the infection and/or mortality rate of patients with schizophrenia and COVID-19. Subsequently, one article was excluded at the full-text stage due to irrelevance. Therefore, 7 studies were included in the systematic review. The remaining 7 papers included 90,076 positive patients for SARS-CoV-2, among which 1,989 suffered from schizophrenia.

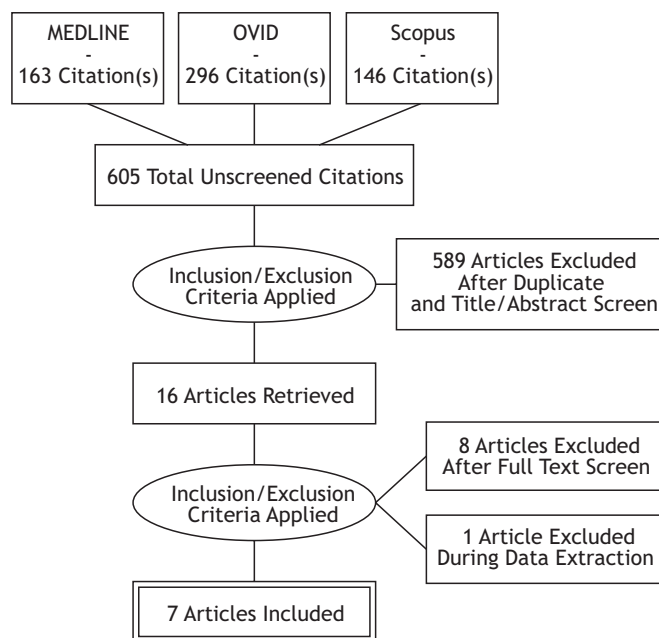


Figure 1. PRISMA flow diagram.

### Infection and mortality rate

A large study from the USA<sup>7</sup> asserts that patients with schizophrenia have a higher infection rate compared to the rest of the population. The authors examined 15,110 patients with COVID-19 and found that patients with a recent diagnosis of schizophrenia had higher odds of contracting SARS-CoV-2 than the rest of the population (AOR=1.53, 95% CI:1.21-1.94,  $p<0.0001$ ).

Two similar studies were conducted in Korea,<sup>8,9</sup> which studied 14,418 SARS-CoV-2 positive people. Patients with schizophrenia-related disorders had a higher risk of infection in both studies (OR=1.50, 95%CI:1.14-1.99, OR, 1.614-1.721). Moreover, schizophrenia patients experienced more severe outcomes of the infection, including death (OR=2.25, 95%CI:0.36-14.03), intensive care unit (ICU) admission, use of mechanical ventilation and acute respiratory distress syndrome (OR=1.27, 95%CI:0.37-4.37).

In Europe, there are two French studies<sup>10,11</sup> with 51,842 COVID-19 positive patients. These studies showed that schizophrenia is associated with increased in-hospital mortality (AOR=4.36, 95%CI:1.09-17.44,  $p=0.038$  and OR 1.30 [95% CI, 1.08-1.56]) but not with increased intensive care unit admission. Schizophrenia patients between 65 and 80 years had a significantly higher risk of death than controls of the same age (+7.89%). Schizophrenia patients younger than 55 years had more ICU admissions (+13.93%) and Schizophrenia patients between 65 and 80 years and older than 80

years had fewer ICU admissions than controls of the same age (−15.44% and −5.93%, respectively).

Conversely, a study from Israel found that individuals with schizophrenia were less likely to test positive for COVID-19; however, they were twice as likely to be hospitalized for COVID-19 (OR 1.88 95% CI 1.39–2.55,  $P < 0.0001$ ). Furthermore, they were 3 times more likely to die from COVID-19 (OR 3.27 95% CI 1.39–7.68,  $P < 0.0001$ ), compared to the rest of the population.<sup>12</sup>

Another important finding in the literature was that patients with schizophrenia have a higher mortality rate for up to 45 days after a laboratory-confirmed positive SARS-CoV-2 test result.<sup>13</sup> In this study, 7348 COVID-19 positive patients, among them 75 with schizophrenia spectrum disorders (SSD), were followed up for 45 days. A pre-morbid diagnosis of schizophrenia spectrum disorders was significantly associated with mortality (OR=2.67; 95% CI, 1.48-4.80).

A summary of the results of these studies is shown in table 1.

## Discussion

Our review shows that patients with schizophrenia have higher infection and mortality rates from SARS-CoV-2 compared to the rest of the population. This finding may be due to many factors.<sup>14</sup>

Firstly, many patients with schizophrenia suffer physical comorbidities, such as the metabolic syndrome. Mortality from COVID-19 is particularly elevated in people with comorbid conditions, in particular cardiovascular disease, diabetes, and chronic respiratory disease, all of which are more common in people with schizophrenia than the general population.<sup>15–17</sup> Moreover, patients with schizophrenia tend not to adhere well to their treatment, including treatment for physical illness. Consequently, their physical health

is often poor. Similarly, it may be harder for people with schizophrenia to adopt and adhere to measures against infection (e.g., hand washing, social distancing or isolation, confinement), thus predisposing them to infection. The combination of poor physical health and a higher infection risk can prove fatal.

Smoking is another important factor for poor outcomes from COVID-19 in people with schizophrenia. Smoking is very prevalent in schizophrenia, with more than 60% of patients smoking. Smoking may worsen prognosis in COVID-19,<sup>18</sup> possibly because of its effect on the respiratory system and immune responsiveness.<sup>19</sup> In addition, many chronic patients with schizophrenia reside in long-term psychiatric facilities, so there is a high chance of conducting the virus to other patients if the environment is crowded.<sup>11</sup>

Furthermore, vulnerability to infection from Sars-Cov-2 may increase by the presence of pro-inflammatory factors postulated to occur in patients with schizophrenia.<sup>20</sup>

Finally, stigma puts people with schizophrenia at great risk for COVID-19. They face difficulties in accessing healthcare and often experience discrimination when they do access care. They are less likely to have a prompt and appropriate diagnostic work-up and therefore they are likely to have physical problems underdiagnosed or misdiagnosed, resulting in poor quality of care overall.<sup>21,22</sup>

## Conclusion

In conclusion, people with schizophrenia spectrum disorders constitute a vulnerable group to COVID-19. Specifically, they suffer higher rates of infection and are more likely to die from COVID-19. Mitigating measures should be taken to ensure that people with schizophrenia are protected. We concur with Suhas23 that people

**Table 1.** Studies with patients with schizophrenia spectrum disorders (SSD) and COVID-19: Infection and mortality rates.

Study	Year	Patients with COVID-19	Infection rate of patients with SSD with COVID-19 (OR/AOR, [95% C.I.])	Mortality rate of patients with SSD from COVID-19 (OR/AOR, [95% C.I.])
Wang et al <sup>7</sup>	2021	15,110	1.53 [1.21-1.94]	
Jeon et al <sup>8</sup>	2021	7,077	1.50 [1.14-1.99]	2.25 [0.36-14.03]
Fond et al <sup>10</sup>	2020	1,092		4.36 [1.09-17.44]
Fond et al <sup>11</sup>	2020	50,750	1.30 [1.08–1.56]	
Nemani et al <sup>13</sup>	2020	7,348		2.67 [1.48-4.80]
Ji et al <sup>9</sup>	2020	7,341	? [1.614–1.721]	
Tzur Bitan et al <sup>12</sup>	2021	1,358		3.27 [1.39–7.68]

Note: OR, Odds Ratio; AOR, Adjusted Odds Ratio

with schizophrenia should be given priority to vaccination. We support that emphasis should be given to infection control measures, early recognition of COVID-19 symptoms, better access to healthcare and in particular

intensive care, and stigma reduction. We conclude that the COVID-19 pandemic has disproportionately affected people with schizophrenia, making measures to ensure equitable care not just an option, but a necessity.

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# Ανασκόπηση

## Έχουν οι ασθενείς με σχιζοφρένεια υψηλότερη συχνότητα λοίμωξης και θνησιμότητας από τον COVID-19; Συστηματική ανασκόπηση

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### ΠΕΡΙΛΗΨΗ

Είναι γνωστό πως ασθενείς με ψυχικές νόσους έχουν επιβαρυνμένη σωματική υγεία σε σχέση με τον γενικό πληθυσμό. Μεταξύ των ασθενών με ψυχικές νόσους, εκείνοι με διαταραχές του φάσματος της σχιζοφρένειας έχουν δυσανάλογα μεγαλύτερη επιβάρυνση. Πρόσφατες μελέτες έχουν επισημάνει ότι αυτοί οι ασθενείς διατρέχουν ιδιαίτερο κίνδυνο από τον COVID-19. Στόχος αυτής της συστηματικής ανασκόπησης είναι να διευκρινιστεί κατά πόσον οι ασθενείς με διαταραχές του φάσματος της σχιζοφρένειας διατρέχουν μεγαλύτερο κίνδυνο για δυσμενείς εκβάσεις της σωματικής τους υγείας λόγω του COVID-19. Πραγματοποιήσαμε αυτή τη συστηματική ανασκόπηση της βιβλιογραφίας σύμφωνα με τις κατευθυντήριες γραμμές PRISMA, χρησιμοποιώντας το PubMed, το PsycINFO και το Scopus ως βιβλιογραφικές βάσεις δεδομένων, για να εντοπίσουμε όλες τις μελέτες που διερεύνησαν τη συχνότητα λοίμωξης ή/και θνησιμότητας από τον SARS-CoV-2 σε ασθενείς με διαταραχές του φάσματος της σχιζοφρένειας. Μετά από συστηματική διαδικασία ελέγχου, επτά μελέτες πληρούσαν τα κριτήρια ένταξης στη μελέτη. Τα αποτελέσματα αυτών των επτά μελετών εκτέθηκαν περιληπτικά χρησιμοποιώντας odds ratios ή adjusted odds ratios. Τα συλλογικά αποτελέσματα έδειξαν μέτρια, αλλά στατιστικά σημαντική επίδραση για υψηλότερα ποσοστά λοίμωξης σε ασθενείς με σχιζοφρένεια και ισχυρή στατιστικά σημαντική επίδραση για υψηλότερα ποσοστά θνησιμότητας σε ασθενείς με σχιζοφρένεια. Τα ευρήματά μας δείχνουν ότι τα άτομα με σχιζοφρένεια έχουν υψηλό κίνδυνο να μολυνθούν από τον νέο κορωνοϊό και έχουν σημαντικά υψηλότερο ποσοστό θνησιμότητας από τον γενικό πληθυσμό. Υπάρχουν αντιφατικά ευρήματα σχετικά με άλλα αποτελέσματα, συμπεριλαμβανομένης της συχνότητας εισαγωγής σε μονάδες εντατικής θεραπείας. Συλλογικά, αυτά τα αποτελέσματα δείχνουν πως οι ασθενείς με διαταραχές του φάσματος της σχιζοφρένειας είναι πιο ευάλωτοι στο να μολυνθούν και πιο πιθανό να πεθάνουν λόγω του COVID-19, και όμως η πρόσβασή τους σε Μονάδες Εντατικής Θεραπείας δεν φαίνεται να είναι υψηλότερη. Καταλήγουμε στο συμπέρασμα ότι οι ασθενείς με σχιζοφρένεια αποτελούν ευάλωτη ομάδα για λοίμωξη και θνησιμότητα που σχετίζεται με τον COVID-19, συνεπώς υπάρχει ανάγκη αυτή η ευάλωτη ομάδα ανθρώπων να έχει καλύτερη πρόσβαση στην υγειονομική περίθαλψη, συμπεριλαμβανομένης της προτεραιότητας σε εθνικά προγράμματα εμβολιασμού COVID-19 και καλύτερη πρόσβαση στην εντατική θεραπεία. Η μελέτη μας συνεισφέρει στην ανάγκη για ισότιμη πρόσβαση στην υγειονομική περίθαλψη για τα άτομα με διαταραχές του φάσματος της σχιζοφρένειας.

**ΛΕΞΕΙΣ ΕΥΡΕΤΗΡΙΟΥ:** Σχιζοφρένεια, COVID-19, θνησιμότητα, λοίμωξη, ισότητα, πρόσβαση στις υπηρεσίες, εμβολιασμός.

## Review

# Religious delusions: Definition, diagnosis and clinical implications

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### ABSTRACT

The prevalence of the biopsychosocial model in psychiatry highlights the importance of investigating the clinical significance of religiosity in patients with psychotic disorders. Due to the spiritual and supernatural nature of religious beliefs, distinguishing them from religious delusions is a challenging endeavour. The self-referential nature of the beliefs, the presence of concomitant psychiatric symptomatology and the effect on functionality seem to play a key role in differential diagnosis. Religious psychotic symptoms are common in clinical practice. The study of these symptoms often becomes difficult due to varying definitions, the fluctuation they present over time and space and the strong influences of the social and cultural environment on them. There seems to be a positive correlation between religiosity and the occurrence of religious delusions in psychotic patients, but it is not clear that this indicates a causal relationship. The content of religious delusions seems to be significantly influenced by the immediate social environment rather than cultural background of the individual, as well as by the beliefs and attitudes of the patient's family environment. Religious delusions are characterized by increased conviction and pervasiveness, permeating to a greater extent the individual's whole experience. Their presence is associated with more severe symptoms, higher medication dosage, and poorer prognosis. The increased severity of psychosis with religious content symptomatology seems to be associated with genetic factors and greater genetic load. In addition, the increased duration of untreated psychosis is a determinant of prognosis. This may reflect a reduced alertness of the immediate environment of patients who develop psychotic symptoms with religious content for the first time. Other important prognostic factors are patients' lack of adherence to treatment, their greater resistance to psychiatric approach of the disorder and their exclusion from religious communities, as well as the special characteristics of religious delusions, which seem more corrosive to the patients' psyche than other delusions. Religion and spirituality are prominent in the lives of the majority of patients with psychosis, but they are often underestimated in clinical practice. Raising the awareness of mental health professionals on issues of a religious and spiritual nature can be beneficial in both preventing and treating psychotic disorders.

**KEYWORDS:** Delusions, religious delusions, religiosity, psychotic disorders.

### Introduction

Despite the progressive “disenchantment” of the world and the secularization of societies, the need for transcendental and religious experiences still seems to be a constant feature of the personal and social lives of the majority of people. The role that religion

and religiosity play, in the development and the prognosis of psychopathological conditions remains unclear and should be thoroughly investigated. A major area of this line of research is psychotic symptoms with religious content, which are so frequently found in clinical practice.



## Differences between religious beliefs and religious delusions

Distinguishing religious delusions from non-delusional religious beliefs seems to be a difficult and multidimensional task, which has aroused the interest of many scholars internationally. As the content of religious beliefs is supernatural and goes beyond the scientific terms of understanding the world, religious beliefs can be misinterpreted as delusional. The DSM's definition of delusional ideas and, consequently, the definition of religious delusional ideas seem to be confusing due to some disadvantages and ambiguities which we will try to list.

Patients with religious delusions seem to maintain their beliefs in a qualitatively different way from healthy religious individuals.<sup>1</sup> The religious person may be possessed by doubts about his/her beliefs or at least recognize that the existence of doubts in others is rational.<sup>2</sup> In addition, he/she may need even a hint of strengthening his/her faith, while the person with religious delusions has an unshakable and self-proven "faith". Geiderman suggests that religious belief exists only when there is doubt.<sup>3</sup> For the religious individual, faith is ultimately a matter of choice, while in the person with delusions "the absolute truth" is revealed to him/her, to which he/she surrenders completely. Spitzer emphasizes that delusions represent "claims of knowledge" and not "claims of faith".<sup>4</sup>

Delusions are not combined with intuition. Patients with psychosis are usually unaware of the impossibility and paradox of their claims and may even "embellish" them, while the non-psychotic individuals usually acknowledge the peculiar nature of their own claims of faith.<sup>1,5</sup>

The way of thinking of the religious people is abstract and spiritual. On the contrary, delusional thoughts, experiences, actions are specific and literal. Typically, when patients with delusions say that they feel God inside them, they say it in a literal way and they can determine exactly where they feel him (for example in a specific organ or part of their body). That is, they describe it as a physical and sensory experience.<sup>6</sup>

In addition, religion (especially the modern "secularized" doctrines) is overwhelmed by symbolic speech, while the understanding of the world in psychosis is possessed by extreme literacy. This thought disorder, the so-called concrete or rigid thinking, characterizes the delusional structure of psychosis.<sup>6</sup> Extreme examples of this delusional aspect are the cases of patients, who performed self- or hetero-amputation operations (castration, amputation of limbs, eye extraction) receiving with extreme literacy the scriptures.<sup>7-9</sup> Ames

in 1987 proposed the naming of such practices of self-castration, in the context of religious delusions, as Klingsor Syndrome,<sup>8</sup> from the homonymous character of Wagner's opera "Parsifal", who castrated himself as he was unable to control his libido. It is noteworthy that patients often report that they feel no pain but relief during the act of castration, and then express little or no remorse, as they do not recognize their behavior as irrational, but as a means of purification and salvation. Most of these patients refuse to undergo remedial surgery and if they reluctantly accept it, they strongly resist the subsequent treatment and rehabilitation process, while there are many cases of patients who re-amputated the rehabilitated body part themselves.<sup>9</sup>

To distinguish between delusions and non-delusional religious beliefs, the DSM-5 adopts the criterion of acceptance of the religious beliefs by other community members ("members of the person's culture or subculture"), instead of a criterion about the control of beliefs' validity. Consequently, religious beliefs could be considered non-delusional despite the blatant lack of scientific validation. On the other hand, this DSM-5 criterion seems to protect the believers of the established religious doctrines and consequently to easily pathologize other temperamental and unpopular beliefs.<sup>10</sup>

This also raises the question: what happens if a delusion is adopted by others. Based on the abovementioned criterion of "sharing", it should be considered by definition a non-delusional belief. Kauffman in 1939 notes that the person who believes he is the Messiah is considered psychotic until there is a group of people who will accept him as such and in this group this belief represents a religious system. Beyond the delusional system of the person claiming to be the Messiah, other parameters in his delusion enable him to have an impact on other people and help him cover some of his needs.<sup>10</sup>

However, delusion can also be shared, which is typically the case in shared psychotic disorder (*follie a deux*). It usually occurs between two individuals, less often in three and four individuals, but there have been also cases involving many more people (*follie a famille* or *follie a douze*).<sup>11</sup> The question is how many people have to share an idea in order to consider it "normal". Religious doctrines present a special challenge for answering this question. In the United States of America, new religious groups with distinctive and idiosyncratic beliefs, often emerge and they are called new religious movements (NRMs). On the other hand, small religious group can become an internationally accepted religion, as has already happened with Mormons or even in the case of Christianity.<sup>10</sup> Scholars who have studied the dynamics that develop

in such groups, the so-called “charismatic groups” or heresies, have found a “charismatic” leader, who forms a belief system, develops a special atmosphere and applies a control mechanism in order to suppress opposing views. In this way, the other members of the group adopt a structure of beliefs, usually with secondary benefits and a sense of belonging somewhere as a mental reward, so they do not meet the criteria of having delusions. This holds true if we accept as characteristic of delusions that they form either in conditions of isolation of an individual, or despite the opposite view of others.<sup>10</sup> However, in the case of a leader with delusional beliefs, the acceptance of his/her delusions could fit the model of shared psychosis, in which the other members of the closed and entrenched group play the role of the submissive and dependent party.<sup>11</sup>

Criteria of functioning are the most practical and applicable for the evaluation of human behavior. Central role in attempting to distinguish “normal” religious beliefs from religious delusions has the criterion of the effect of beliefs on the functioning of the person who embraces them.<sup>5</sup> That is, if the social and professional life of the person who has the religious beliefs or the religious experience is not affected, then they are not considered pathological.

Perhaps the most noticeable difference between a healthy religious person and a person with religious delusions is that the healthy person may consider that he/she has a personal relationship with God, but this is in line with the teachings of his/her religion and in the way it is accepted to exist. In religiosity there is a religious connection with the “sacred” element, but it is generalizable. The believers do not consider that they have any special relationship with God, but that everyone is connected in some way with the divine. On the other hand, patients with delusions believe that they have a unique or privileged relationship with God, or even that they are the religious entities themselves. The self is the center of their religious delusions.<sup>12</sup>

Table 1 summarizes the differences between religious beliefs and religious delusions.

## Religious delusions

Psychotic symptoms with religious content are most commonly presented as religious delusions and religious hallucinations. They are often encountered in clinical practice and their rate has been estimated at 1.1–80% (20–60%).<sup>13</sup> This large variation is due to some methodological difficulties faced in the study of psychotic symptoms with religious content, such as the difficulty of defining them, i.e. distinction between re-

**Table 1.** Characteristics of religious delusions versus non-delusional religious beliefs.

Non-delusional religious beliefs	Religious Delusions
<i>Quality of faith</i>	
<ul style="list-style-type: none"> <li>• Doubts about beliefs</li> <li>• May need a hint of faith</li> <li>• Faith is ultimately a matter of choice</li> </ul>	<ul style="list-style-type: none"> <li>• Unshakable faith</li> <li>• Self-proven faith</li> <li>• Revelation of «the absolute truth», followed by complete surrender</li> </ul>
<ul style="list-style-type: none"> <li>• «Claims of faith»</li> <li>• Acknowledgement of the peculiar nature of the claims of faith</li> </ul>	<ul style="list-style-type: none"> <li>• «Claims of knowledge»</li> <li>• Unaware of the impossibility and paradox of the claims of faith</li> </ul>
<i>Speech – thought</i>	
<ul style="list-style-type: none"> <li>• Abstract and spiritual way of thinking</li> <li>• Symbolic speech and scripts</li> </ul>	<ul style="list-style-type: none"> <li>• Concrete or rigid thoughts</li> <li>• Specific experiences and literal actions</li> </ul>
<i>Share – acceptance of beliefs</i>	
<ul style="list-style-type: none"> <li>• Religious beliefs accepted by other community members</li> </ul>	<ul style="list-style-type: none"> <li>• Delusional beliefs are unpopular and not accepted by others inside the community</li> </ul>
<i>Functioning</i>	
<ul style="list-style-type: none"> <li>• Social and professional life not affected</li> </ul>	<ul style="list-style-type: none"> <li>• Impaired social and professional life</li> </ul>
<i>Relationship with God</i>	
<ul style="list-style-type: none"> <li>• No special relationship with God, religious connection is generalizable</li> <li>• Everyone is connected in some way with the divine</li> </ul>	<ul style="list-style-type: none"> <li>• Unique or privileged relationship with God</li> <li>• The self is in the center of the religious delusions</li> </ul>

ligious delusions religious beliefs, difference between religiosity and spirituality. Moreover, the prevalence of religious delusions varies in different cultures and different time periods.<sup>1,14</sup> In Egypt, for example, fluctuations in the prevalence of religious delusions over a 20-year period have been linked to shifts in the emphasis on religious issues in Egyptian society, in times of socio-political tension and an escalation of religiously motivated violence.<sup>15</sup> In addition, a retrospective 40-year sampling study in patients with schizophrenia in Poland, found a gradual decrease in the prevalence of religious delusions. This can be related to a cultural shift from Catholicism to a more secular society. It is worth noting that religious issues seemed to go hand in hand with socio-political changes in the country, such as the rise of the Polish Pope to the papal throne or the rise of the Communist regime.<sup>16</sup>

Finally, social environment seems to play an important role. In cultural environments that are more tolerant of diversity religious delusions are underestimated, while more conservative environments that maximize the peculiarity of minority's beliefs. Moreover, religious delusions with content compatible with the religious beliefs of each environment are less frequently identified as pathological compared to religious delusions with content different from the dominant religious beliefs.

## Etiology

No causal relationship between increased religiosity and the prevalence of religious delusions in the general population has been found.<sup>17</sup> On the contrary, there appears to be a positive correlation between religiosity and religious delusions in those already suffering from a mental illness.<sup>18</sup> This finding may indicate that when a person develops a mental disorder, his delusions reflect his own prevailing interests and concerns.<sup>6,19</sup> The religiosity level seems not directly related to clinical severity, but it seems to be a better predictor of religious delusions than religious affiliation status.<sup>20</sup> Moreover, people who attribute their symptoms to religious explanations are more likely to form religious delusions.

Recent studies have linked the increased likelihood of religious delusions formation to both environmental and genetic factors. Patients who report high religious activity are more than three times more likely to experience religious delusions. Moreover, patients with schizophrenic disorders who exhibit a high genetic predisposition are more likely to develop psychotic symptoms with religious content.<sup>21</sup>

## Content

Religious delusions may be presented in various ways and their contents differ. The following categories can be distinguished regarding the content of religious delusions:

- (1) Delusions of persecution (by the devil, demonic entities etc.)
- (2) Grandiose identity delusions (Messiah Syndrome, undertaking special mission)
- (3) Delusions of guilt or devaluation (unforgivable sins)
- (4) Delusions of control or passivity phenomena
- (5) Delusional misidentification syndrome or antichrist delusion (the delusional misidentification of oneself or others as the Antichrist, which, although relatively rare, is of particular clinical significance, because it is often accompanied by violent, mostly hetero-destructive, behaviors).<sup>22,23</sup>

## Characteristics

The immediate social living environment has a greater influence than the cultural background on the content of delusions and hallucinations. In a study conducted in UK the content of delusions and hallucinations was compared in 3 groups of patients with schizophrenia, British White (BW), British Pakistani (BP) and Pakistan Pakistani (PP). The results showed a greater degree of similarity of the content between of BW and BP than between BP and PP.<sup>23</sup>

In addition, the influence of beliefs and attitudes of the patients' family environment play an important role on the manifestation of religious delusions. In a survey in Southwestern Greece, the majority of healthy mothers (85%) of patients with delusions with religious or magical content attributed their children's mental illness to demon possession or magical influence. This finding was found mainly in families with low educational level, while it was quite common to resort to "therapeutic" practices, except psychiatric treatment, such as exorcism.<sup>24,25</sup>

According to a study which was conducted in three cities (Vienna, Tübingen, Tokyo), delusions with religious content are more common in European patients (20–21%) than in Japanese patients (6.8%). In fact, while delusions of grandiosity are common in all three regions, delusions of guilt and sin appear only in 2 out of 22 (9.1%) Japanese but in 12 out of 32 (37.5%) Germans and in 9 out of 20 (45%) Austrian patients.<sup>26</sup>

In addition, delusions of guilt and sin seem to be more prevalent in societies with a Christian Jewish religious tradition, while they are uncommon in Islamic, Hindu, and Buddhist societies.<sup>26–28</sup> Catholic Christian patients (15.5%) present more religious delusions of guilt than Protestant or Muslim patients (3.8%).<sup>29</sup> Protestant patients report religious delusions more often than Catholic patients or non-Catholic patients or patients with no religion affiliation.<sup>30</sup>

Members of the New Religious Movements show higher scores on the measurement scales of delusional ideation in relation to members of Christian or no-religious social groups.<sup>31</sup>

Delusions of persecution and religious delusions show the strongest impact on the lives of patients, while there is over-representation of religious delusions in schizophrenic patients compared to bipolar or depressed patients. In fact, religious delusions show higher scores in the dimensions of conviction and pervasiveness (pervasiveness reflects the degree to which delusions permeates the entire experience of the individual).<sup>32</sup>

Finally, the delusional characteristics bizarreness, frequency of psychotic symptoms, and degree of distress were more prevalent for religious delusions than for any other type of delusion.<sup>33</sup>

### Prognosis

As early as in 1996, Thara & Eaton reported that specific symptoms at the time of hospital admission, namely delusions of grandiose or regarding sexuality, bizarre thoughts and blunted affect, are strongly related to poor prognosis of patients with psychosis and religious delusions.<sup>34</sup>

In a study conducted in UK a sample of 193 patients with religious delusions in Manchester hospitals were compared to a group of schizophrenia patients with delusions of different content and found that the first group had higher scores in Positive and Negative Syndrome Scale (PANSS), poorer functionality, measured using the Global Assessment of Functioning (GAF) and higher doses of medication.<sup>18</sup> On the other hand, it has been proposed that possible biases in psychiatrists, who are considered to be less religious, belong to a group with lower rates of religious belief, may result in more aggressive treatments towards patients with religious delusions.<sup>10</sup> In the aforementioned UK study, the response of the above patients to the treatment was re-evaluated two years later. It was found that the symptoms of patients with religious delusions were more severe both before and after treatment, but the response to treatment was similar in both groups.<sup>34</sup>

The increased severity of psychosis with religious content symptomatology seems to be related to genetic factors. Individuals with a higher genetic burden are more likely to experience religious delusions.<sup>21</sup>

The duration of untreated psychosis (DUP) is a particularly crucial factor. It is reported that upon admission patients with religious delusions show a more extensive course of disease, i.e. they have been exposed for a longer period of time to psychotic symptoms.<sup>35</sup> Patients with religious delusions cause less anxiety in their family than patients with delusions of other content. This is a possible explanation for the fact that patients with religious delusions present with a more severe symptoms at the time of admission than other patients with delusions.<sup>18,35</sup>

Another dimension of great prognostic value is patient's compliance with treatment. Religious delusions can have a negative effect on a patient's consistency in treatment when he attributes his psychotic symptoms to supernatural entities.<sup>36</sup> Moreover, cases are often reported of patients refusing to continue medication because it prevents them from praying or because they prefer to hear the voice of God or find answers in the Bible.<sup>36–38</sup>

Previous studies found that patients with religious delusions did not have a worse clinical status than patients with other delusions and concluded that the worst prognosis of the former is due to the greater resistance they show to psychiatric treatment and the less support they receive from religious communities.<sup>20,36</sup> These patients seem to be at a disadvantage as they are far from both science (poorer therapeutic alliance—"competition" between religion and psychiatry) and the religious community (rejection due to dysfunctional behaviors induced by their delusions).<sup>36</sup>

Other studies in schizophrenia patients with religious delusions have shown increased disease severity and the poorer effects of treatment in these patients, which were mainly attributed to: (a) delayed access to mental health services (in religious settings religious delusions skip the attention of their relatives or initially, religious rituals are preferred as "therapy"), (b) to the reduced cooperation in psychiatric treatment (due, for example, to the patients' preference to hear the voice of God), and (c) to the special characteristics of the religious delusional ideas, which seemed more corrosive to the patients' psyche and were maintained with greater vigor.<sup>30,39–43</sup>

### Discussion

We can think of religious beliefs as a continuum ranging from normal religious beliefs to religious delusions. Where a belief lies in this continuous depends on the intensity of the various dimensions of delusionality. Among them, the self-referential nature of the belief, the presence of other psychiatric symptoms and the effect on functionality seem to play a key role in differential diagnosis.

The difficulty of distinguishing religious delusions from religious beliefs is more prominent in multicultural societies (where a person's peculiar beliefs, which seem strange and can be misinterpreted as delusional, may correspond to a peculiar cult). In societies with a dominant religion, like Greece, the problem is not so obvious, but taking into account the constant movement of populations and the increase of the immigrant and refugee communities, it is something that can be a particular challenge in the future.

While religion and religiosity are prominent in the lives of many psychotic patients, in clinical practice issues of a religious and spiritual nature may be overlooked and sometimes devalued by clinicians. Indicatively, it is reported that while 90% of Americans say they believe in the existence of God, only 40–70% of psychiatrists and 43% of psychologists share this belief, and this may be reflected in a bias towards identifying pathological aspects of religiosity.<sup>10</sup> This

divergence is certainly not just a phenomenon of the modern age. As early as the turn of the last century, the founder of psychoanalysis, Sigmund Freud, adopted a strong anti-religious stance that had a great influence on the scientific community.<sup>44</sup> Although there has been a historical rivalry between the fields of psychiatry and religion and prejudices and dogmas have prevailed on both sides, due to their different and largely opposite ontological approach and interpretation of the world, we must not forget that the common denominator is human mental pain and its relief.

It could therefore be considered more than reasonable, if not necessary, for mental health professionals to be aware of issues of a religious nature because of the importance that patients attach to them. Several authors, moreover, suggest the establishment of an alliance between mental health clinicians and religious ministers.<sup>20</sup> Psychiatrists could be more sensitive to re-

ligious and spiritual aspects of patients' personalities and their potential positive effects on mental health, while religious practitioners could better identify the boundaries between healthy religiosity and the pathological experiences or denial of mental illness and treatment due to religious beliefs. The benefits of such a therapeutic partnership can be of great importance both for the prevention and for the more effective treatment of mental disorders.

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# Ανασκόπηση

## Θρησκευτικές παραληρητικές ιδέες: Ορισμός, διάγνωση και κλινική σημασία

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### ΠΕΡΙΛΗΨΗ

Η επικράτηση του βιοψυχοκοινωνικού μοντέλου στην επιστήμη της ψυχιατρικής αναδεικνύει την σπουδαιότητα της διερεύνησης της κλινικής σημασίας της θρησκευτικότητας σε ασθενείς με ψυχωτικές διαταραχές. Λόγω του πνευματικού και υπερφυσικού χαρακτήρα των θρησκευτικών πεποιθήσεων, η διάκριση αυτών από τις θρησκευτικές παραληρητικές ιδέες αποτελεί απαιτητικό εγχείρημα. Καίριο διαφοροδιαγνωστικό ρόλο φαίνεται να διαδραματίζουν η αυτοαναφορική φύση της δοξασίας, η παρουσία συνοδού ψυχιατρικής συμπτωματολογίας και η επίδραση στη λειτουργικότητα. Τα ψυχωτικά συμπτώματα με θρησκευτικό περιεχόμενο απαντώνται συχνά στην ψυχιατρική κλινική πράξη. Η μελέτη των ανωτέρω συμπτωμάτων καθίσταται δυσχερής, λόγω αντικειμενικών δυσκολιών που αφορούν τις διαφοροποιήσεις στον ορισμό αυτών, την διακύμανση που παρουσιάζουν στην πορεία του χρόνου και την ισχυρή επιρροή που ασκείται από το εκάστοτε κοινωνικό και πολιτισμικό περιβάλλον σε αυτά. Φαίνεται να υπάρχει θετική συσχέτιση μεταξύ θρησκευτικότητας και εμφάνισης θρησκευτικών παραληρητικών ιδεών στους πάσχοντες ψυχωτικούς, χωρίς όμως να είναι ξεκάθαρο αν η σχέση είναι αιτιοπαθογενετική. Το περιεχόμενο των θρησκευτικών παραληρητικών ιδεών φαίνεται να επηρεάζεται σημαντικά από το άμεσο κοινωνικό περιβάλλον διαβίωσης του ατόμου καθώς και από τις πεποιθήσεις και στάσεις του οικογενειακού περιβάλλοντος του ασθενούς. Οι θρησκευτικές παραληρητικές πεποιθήσεις χαρακτηρίζονται από αυξημένες τιμές βεβαιότητας διαποτίζοντας σε μεγαλύτερο βαθμό το σύνολο των εμπειριών του ατόμου. Η παρουσία τους σε ασθενείς με ψύχωση συνδέεται με βαρύτερη συμπτωματολογία, υψηλότερη δοσολογία φαρμακευτικής αγωγής και πτωχότερη πρόγνωση. Η αυξημένη βαρύτητα της ψύχωσης με θρησκευτικού περιεχομένου συμπτωματολογία φαίνεται να συνδέεται με γενετικούς παράγοντες και μεγαλύτερο γενετικό φορτίο. Επιπλέον, καθοριστικό προγνωστικό παράγοντα αποτελεί και η αυξημένη διάρκεια της μη θεραπευμένης ψύχωσης (DUP). Αυτό μπορεί να αντανakλά μειωμένη εγγύηση του εγγύτερου περιβάλλοντος των ασθενών που πρωτοεμφανίζουν ψυχωτική συμπτωματολογία με θρησκευτικό περιεχόμενο. Άλλες σημαντικές διαστάσεις προγνωστικού χαρακτήρα αποτελούν η ελλιπής συμμόρφωση των ασθενών στη θεραπεία, η μεγαλύτερη αντίσταση που προβάλλουν απέναντι στην ψυχιατρική αντιμετώπιση της διαταραχής και τον αποκλεισμό τους από τις θρησκευτικές κοινότητες, καθώς και τα ιδιαίτερα χαρακτηριστικά των θρησκευτικών παραληρητικών ιδεών, οι οποίες φαίνονται περισσότερο διαβρωτικές για τον ψυχισμό σε σύγκριση με άλλες παραληρητικές ιδέες. Η θρησκεία και η πνευματικότητα κατέχουν προεξάρχουσα θέση στη ζωή της πλειονότητας των ασθενών με ψύχωση, ωστόσο στην κλινική πράξη συχνά υποτιμούνται. Η ευαισθητοποίηση των επαγγελματιών ψυχικής υγείας πάνω σε ζητήματα θρησκευτικής και πνευματικής φύσεως μπορεί να αποδειχθεί ωφέλιμη τόσο για την πρόληψη όσο και για τη βέλτιστη αντιμετώπιση των ψυχωτικών διαταραχών.

**ΛΕΞΕΙΣ ΕΥΡΕΤΗΡΙΟΥ:** Παραληρητικές ιδέες, παραληρητικές ιδέες θρησκευτικού περιεχομένου, θρησκευτικότητα, ψυχωτικές διαταραχές.

## Review

# The effect of psychosocial interventions on infertility: Inconsistency of research data

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### ABSTRACT

This systematic review aimed to investigate the inconsistency of research data concerning the contribution of systematic psychosocial interventions to infertility treatments. More specifically, the objective of this review was to investigate the cause of the contradictions in the results of contemporary research with respect to the role of systematic psychosocial interventions in the success of fertility treatments. The suspected cause of these contradictions is the heterogeneity of the relevant clinical studies with respect to their methodology. Thus, the specific aim of the current review was to evaluate the degree of heterogeneity of certain parameters in the design of the relevant clinical studies during the last decade, including sample heterogeneity, assisted reproductive technology methods, types of psychosocial interventions and methods of recording and analyzing psychometric data. This investigation may be considered imperative considering that despite the great number of relevant clinical studies and their meta-analyses, there are still no conclusive results concerning the potential of improving fertility through psychosocial support. Search for relevant studies was performed employing the PubMed and Google Scholar databases based on specific criteria. According to these criteria the selected publications have been meta-analyses of clinical studies on humans, evaluating the effect of psychosocial interventions on the success of assisted reproductive treatments during the last decade. The studies may have included all the different infertility etiologies, as well as all types of assisted reproductive treatments. The extensive search based on the specific inclusion/exclusion criteria resulted in reporting results from 6 studies in total. The clinical studies included have reported on various types of interventions for psychosocial support such as individual, couples' or group therapies performed either in facilities offering mental health services or in the form of home-based self-treatment. Moreover, these studies investigated various techniques of stress management ranging from counseling to specialized methods such as biofeedback and diaphragmatic breathing or alternative techniques such as yoga and meditation. Our results suggest that clinical studies designed specifically to evaluate the effect of systematic interventions on the efficacy of fertility treatments are limited. Moreover, their degree of heterogeneity is highly significant with respect to included participants, treatment protocols, psychosocial support techniques as well as methods for the documentation and statistical analysis of psychometric data. Consequently, the conduction of well-design clinical studies based on strict criteria aiming to investigate specific infertility causes, similar fertility treatment protocols or particular types of psychosocial interventions is necessary in order to reach definitive conclusions.

**KEYWORDS:** Systematic review, stress management, psychosocial intervention, Assisted Reproductive Technology, meta-analysis.



## Introduction

Assisted Reproductive Technology (ART) treatment is significantly widespread due to the continuous increasing number of infertile people worldwide.<sup>1</sup> Infertility is a factor of psychological stress for many couples, while ART treatment is regarded painful and time consuming, leading to severe psychosocial consequences.<sup>2,3</sup> This is especially true in the case of multiple failed attempts.<sup>4</sup> The psychosocial consequences have been associated with depression,<sup>5</sup> that affects the relationship and social life of the couple<sup>6,7</sup> often leading to abandonment of reproductive treatment.<sup>8</sup> According to recent studies the increasing anxiety levels lead to oxidative stress<sup>9</sup> and increase of inflammatory factors.<sup>10</sup> Moreover, it has been reported that stress has influence on a variety of biological markers such as cortisol, that could result in decreased fertility.<sup>11,12</sup> The influence of stress in the physiology of reproduction and its impact on the success of ART is an increasingly expanding research field.<sup>13</sup> A number of studies have been conducted investigating the impact of targeted psychosocial support interventions for stress management on the success of the assisted reproduction treatments.<sup>12,14–18</sup> However, despite the large number of studies and relevant meta-analyses, the potential contribution of psychosocial intervention on the improvement of ART remains unclear, mainly attributed to conflicting results. On one hand, studies by Matthiessen et al<sup>19</sup> and Frederiksen et al<sup>20</sup> report a statistically significant improvement in the outcomes of infertility treatments following psychosocial support. On the other hand, Boivin et al<sup>21,22</sup> and Nicoloro-Santa Barbara et al<sup>23</sup> in their meta-analyses failed to report similar conclusion. Consensus point for the majority of studies, is the fact that psychosocial support presents with a positive impact on the general psychosocial welfare of women who undergo infertility treatments, regardless of the outcome of ART.<sup>19,20,22,24</sup> This may be indirectly associated with the improvement of ART success rates since women with lower stress levels are less likely to abandon reproductive treatment.<sup>25,8</sup> Additionally, the majority of meta-analyses reach to conflicting results due to study heterogeneity and all underline the need for further investigation. The conduction of better designed studies employing stricter inclusion/exclusion criteria is of paramount importance.<sup>26,27</sup> The heterogeneity observed, may be attributed to the sample employed in each study, which consists of women whose etiology of infertility differs significantly and may range from idiopathic infertility to male or female pathological infertility. Similarly, the methods and techniques employed for stress management in each study differs significantly. These methods may be based on individual, binary or group conferences<sup>26</sup> and include a variety of techniques namely diaphragmatic respiration,<sup>28,29</sup> progressive muscular relaxation,<sup>30</sup> guided visualization,<sup>31,32</sup>

biofeedback,<sup>33,34</sup> emotional release technique,<sup>35</sup> autogenic education,<sup>36</sup> transcendental meditation,<sup>37</sup> consciousness techniques,<sup>38</sup> body-mind interaction,<sup>39,40</sup> and yoga.<sup>41</sup> Heterogeneity has been similarly reported regarding protocols of assisted reproduction, referring to homologous or heterologous genetic material, surrogate motherhood, different number of embryos transferred, as well as the statistical data evaluation methods.<sup>42</sup> Therefore, it may be of interest to investigate the impact of stress management on the efficacy of the infertility treatments, while taking in consideration the infertility etiologies, the psychosocial support techniques, the treatment protocols and the statistical evaluation methods. This systematic review aimed to investigate the causes of heterogeneity reported in the relevant meta-analyses of the last decade.

## Material and Method

PubMed and Google Scholar were searched for relevant studies. The keywords employed for the search were: (“Infertility” OR “Assisted Reproductive Technology” OR “IVF”) AND (“Psychosocial Interventions” OR “Social Support” OR “Stress” OR “Anxiety”). The search was limited for articles in English from 2000 until 2021. Only systematic reviews and meta-analyses were included. A total of 917 articles, 562 from PubMed and 355 from Google Scholar were screened. A total of 288 duplicate studies were revealed. The inclusion criteria were the keywords of the titles to be relevant and conceptual with the content of the article, the articles to solely constitute meta-analyses or systematic reviews of clinical studies on humans. Only studies evaluating non-pharmaceutical psychosocial support interventions for women undergoing infertility treatment were included. The exclusion criteria were interventions for pathological causes for infertility, animal studies, infertility with genetic etiology or administration of pharmaceutical interventions for infertility. From the initial screening based on the titles and abstracts 588 studies were excluded as non-relevant, 14 studies focused on dealing with male infertility and 11 studies referred to pharmaceutical and surgical interventions for infertility management. Full-text articles of the remaining 12 studies were obtained. One study was excluded, as it did not contain psychosocial interventions and 5 studies did not examine, clarify or exclude the possibility that participants were receiving further psychological support. Of the remaining 6 articles (figure 1) were included in the present systematic review. Data extraction on the included studies was performed in regard to the number of studies, the cause of infertility, the control of the variables for heterogeneity, the methods/techniques of the interventions employed, the ART employed, the methods for collecting psychometric data and the findings of those studies (table 1). The data collection was performed considering the heterogeneity of the studies per outcome.

**Table 1.** Summary of the results.

Bibliographic report	Number of studies	Etiology of infertility	Heterogeneity of studies	Method/technique of stress management	Method/protocol of assisted reproduction	Psychometric data	Findings of study
Frederiksen et al 2015	39 (10 examine pregnancy percentages too).	It could not be clarified in the total of the studies in order to clarify the degree of heterogeneity.	Low to mediocre heterogeneity based on $I^2$ test	Psychosocial interventions (individual, couples, group) including the counselling, meditation, muscular relation, guided visualization etc.	All the ART methods including the IVF. The degree of heterogeneity of the protocols is not clarified.	Psychometric tests for infertility stress, depression, anxiety and balance of married life, before and after the intervention, with or without a control group. A significant decrease of stress and depression was noted.	The psychosocial interventions and especially the CBT and MBI seem to limit stress and to improve significantly the probability for a pregnancy. It is noted that a publication bias is observed in favor of studies with positive correlations, the pooling of which ends up with a non-significant correlation.
Ying et al 2016	20 (10 examine pregnancy percentages too).	It is not examined, it is not mentioned.	The quality of the methodology was deemed satisfying in most studies based on specific quality criteria. Difficulty in the analysis came up from the heterogeneity of the number of participants who withdrew in some studies.	14 different types of intervention including beyond the most common and music therapy, written expression of emotions, hypnosis.	IVF without a clarification on the degree of homogeneity of the applied protocols.	Psychometric tests for infertility stress, depression, anxiety and social consequences, before and after, with or without a control group. No measurements were done during the waiting for the results.	Reference on the positive impact of the interventions on the pregnancy rates but without statistical analysis or emphasis.
Chow et al 2016	12 (8 examine pregnancy rates).	It is not examined, it is not mentioned.	The heterogeneity in the cultural background of the participants is commented on.	Psychosocial interventions (individual, couples, group) including the counselling, meditation, muscular relation, guided visualization etc.	All the ART methods including the IVF. The degree of heterogeneity of the protocols is not clarified.	Heterogeneity in the time of implementation of interventions and transcription of psychometric data.	Reference on the positive impact of the interventions on the pregnancy rates but without statistical analysis or emphasis.
Chu et al, 2017	34 (25 examine pregnancy rates).	It is not examined, it is not mentioned.	Significant heterogeneity based on $I^2$ test. Selection of only RCT studies.	Non-pharmaceutical psychosocial interventions including acupuncture, psychotherapy, improvement of lifestyle.	All the ART methods including the IVF. The degree of heterogeneity of the protocols is not clarified.	Implementation of interventions and initial psychometric tests after the initiation of ART. Final measurements during the waiting time for the ART results.	Non-significant positive impact of psychosocial interventions on the success of assisted reproduction treatments on younger ages and on group interventions compared to individual interventions.

Continues

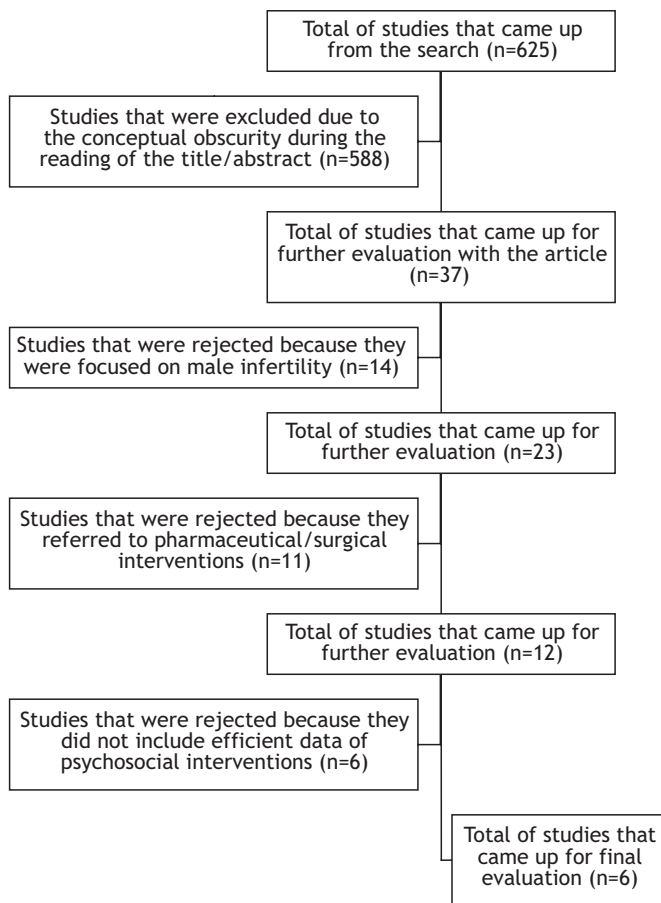
**Table 1.** (Continued).

Bibliographic report	Number of studies	Etiology of infertility	Heterogeneity of studies	Method/technique of stress management	Method/protocol of assisted reproduction	Psychometric data	Findings of study
Massaro et al 2018	11 (5 examine pregnancy rates).	It is not examined, it is not mentioned.	The studies are examined individually without the cumulative statistical data being listed. Cultural heterogeneity since it includes participants from various different countries. Significant heterogeneity of demographic characteristics.	Sole participation of women with subsidiary activities of psychosocial support such as yoga, counselling or acupuncture.	IVF without a clarification on the degree of homogeneity of the applied protocol.	Initiation of interventions prior to the initiation of IVF.	Similar pregnancy rates are mentioned in the intervention groups compared to the control groups, even though the study is not focused on the correlation between the psychosocial support and the successful outcome.
Gaitzsch et al 2020	12 (6 examine pregnancy rates).	Heterogeneity when referring to the etiology and the amount of time for the infertility diagnosis.	The data of the studies were considered to a significant degree as heterogeneous or incomplete so their cumulative statistical analysis was not possible.	Body-mind interaction interventions (yoga, consciousness techniques, etc.).	Heterogeneity of fertility improvement and assisted reproduction methods.	Psychometric data related to stress, depression, life quality and married life quality.	A positive impact of the interventions on the mental welfare, the quality of life and the quality of married life is reported. A possible improvement of the pregnancy rates is mentioned.

## Results

The meta-analysis of Frederiksen et al<sup>20</sup> includes 39 studies and concludes that the psychosocial interventions and especially the ones based on the Cognitive Therapy<sup>43</sup> and the Consciousness<sup>44</sup> seem to limit stress and improve pregnancy rates. However, it was noted that only 10 out of the 39 studies examined pregnancy rates, while publication bias in favor of studies with a significant correlation between psychosocial support and pregnancy rates was observed. When investigating the heterogeneity of the studies examined by Frederiksen et al, the infertility etiology remained unclear, considering that in numerous studies insufficient data were provided. The heterogeneity was evaluated from low to mediocre level based on I<sup>2</sup> test. The psychosocial interventions consisted of several different approaches and techniques, including counselling, meditation, muscular relaxation and guided visualization. In the included studies, all ART treatments were accepted. When evaluating psychometric data, all the included studies employed the pre-post design, noting a statistically significant decline in stress and depression symptoms. However, the selection methods and the statistical analysis employed were not stated in detail. Emphasis should be given to heterogeneity due to attrition bias, which in a number of studies is significantly high.

Similarly, the meta-analysis of Ying et al<sup>7</sup> included 20 clinical studies which consisted of 14 different types of interventions, including special alternative procedures such as musical therapy, hypnosis or written expression of emotions. Beyond the heterogeneity attributed to the type of intervention employed, significant heterogeneity was observed related to the timing of the application of the intervention. It should be noted that in some studies the intervention was performed prior to the initiation of the ART treatment, while in others it was performed during or towards the end of the ART treatment. It should also be highlighted that psychometric data were not collected while awaiting the results, in any of the included studies, as this time is considered quite stressful.<sup>45</sup> Only 10 out of the 20 studies evaluated the outcome of pregnancy rates, while only 2 out of the aforementioned<sup>10</sup> presented with significantly improved pregnancy rates. However, it should be also noted that the result may be again subjected to attrition bias. Moreover, it should be noted that all studies refer to *in vitro* fertilization treatment without clarifying possible differences in the specific protocols that were implemented, the fertilization method employed, the number of embryos transferred or the day of the embryo transfer. The meta-analysis observed a statistically non-significant positive impact of the psychosocial interventions on the success of ART treatment.



**Figure 1.** Diagram of the article selection flow.

The meta-analysis conducted by Chow et al<sup>46</sup> included a limited number of studies. Specifically, 7 prospective and 5 retrospective studies of psychosocial interventions were analyzed. The majority of the included studies were randomized, controlled clinical trials but only 3 evaluated pregnancy rates as an outcome, concluding to significant,<sup>47</sup> marginal<sup>48</sup> and non-significant increase,<sup>49</sup> respectively. In relation to the quality of these studies Chow et al reported that despite the robust design of the studies according to evidence-based medicine, their statistical analysis presented with weaknesses due to the small sample size and the lack of adjustment for confounders. Evaluating the pregnancy outcome, two studies reported a significant increase,<sup>20,27</sup> while the remaining three concluded that the psychosocial interventions did not influence the efficiency of the infertility treatments.<sup>3,21,26</sup> The study concludes that the psychosocial interventions significantly improve the mental health of the participants, while they seem to improve ART outcomes. However, a limitation of the study is that the data examined are insufficient for evaluating the different approaches of psychosocial support due to significant heterogeneity. Thus, it is considered necessary

the design of clinical studies for the evaluation of the different types of interventions.<sup>21</sup> Another covariate that may have significantly increased heterogeneity is the different cultural background of the participants, since the studies originated from countries with cultural differences, hence different perceptions of infertility and its psychosocial repercussion.<sup>50,51</sup>

The meta-analysis of Chu et al<sup>52</sup> examined 34 studies, with pre-post design, evaluating the impact of specific non-pharmaceutical psychosocial interventions on anxiety, stress of infertility, depression and pregnancy rates following ART. Twenty-five studies reported on the pregnancy outcome and the interventions included were acupuncture, psychological support and improvement of lifestyle. According to the inclusion criteria all studies consisted of a control group, while all the initial psychometric tests were performed at the initiation of the ART treatment and the final ones were performed during the time of waiting for the pregnancy results. The heterogeneity of the studies was evaluated as significant, according to a sub-group analysis based on age, type of intervention and gender. The subgroup analysis revealed that the group interventions presented with enhanced results compared to the individual ones, even though evaluation per kind of intervention could not be performed due to the limitation of the sample size. More specifically group interventions presented with improved stress management, but also a steady but non-significant increase on pregnancy rates. The fact that the increase of pregnancy rates was not statistically significant –in disagreement with prior meta-analyses<sup>27,26,20</sup> – was attributed to the stricter inclusion criteria as solely randomized, controlled trials reporting on ART outcomes were selected. Studies investigating the impact of psychosocial interventions on mental welfare without reporting on ART outcomes were excluded.

The meta-analysis of Massaro et al<sup>50</sup> included 11 studies examining the impact of psychosocial interventions on the mental and emotional welfare of women undergoing IVF. Only studies that the intervention was initiated prior to the IVF cycle were included. From the 11 studies, only 5 reported on the impact of the interventions on the IVF cycle result. Significant heterogeneity was observed when evaluating the studies, originating from the study design, the methodology and the statistical analysis performed. Further to this, a number of studies did not clearly present the psychosocial interventions and did not clarify the methodology of psychometric data recording. It is noted, however, that the meta-analysis does not provide cumulative statistical data, but examines each study individually, resembling more to a systematic review than a meta-analysis. However, the 5 studies reporting on IVF outcomes are relative-

ly homogenic, as they are randomized controlled trials including the necessary psychometric data.<sup>49,53-56</sup> The studies reporting on IVF outcomes present with similar pregnancy rates between the intervention and control groups.

Finally, the meta-analysis of Gaitzsch et al<sup>39</sup> includes 12 studies and assessing the impact of the body/mind interaction interventions on mental health of infertile women and on the efficacy of infertility treatments. Body/mind interaction interventions and the provision of psychometric data for stress, depression, life quality and married life of the participants, were the inclusion criteria of this meta-analysis. The included studies were not necessarily either randomized or controlled. Therefore, results were subjected to significant heterogeneity, and statistical analysis could not be performed in a number of outcomes. In cases presenting with significantly high heterogeneity a systematic review was performed. Moreover, significant heterogeneity was observed in infertility etiologies and duration, age of the participants, and the type of ART treatment employed. Moreover, insufficient data were presented regarding the interventions and the contingent infertility treatments. Six studies reported on pregnancy rates, while only 2 of them reported significant improvement. The findings of the study should be interpreted with caution due to significantly high heterogeneity and the limited sample size.

## Discussion

The aim of this systematic review was to investigate the impact of heterogeneity and statistical bias of studies included in past meta-analyses, as the most probable causes of the unclear results reported regarding the evaluation of the psychosocial interventions in the improvement of ART outcome.<sup>26,27</sup> One observation of this systematic review is the limited results uncovered during the search for relevant meta-analyses. Only 6 meta-analyses fulfilled the inclusion criteria that included 128 studies with only 64 of them reporting on pregnancy rates (table 1). Hence, despite the plethora of studies regarding the psychosocial health of infertile couples, the ones that focus on the improvement of fertility through psychosocial support are inadequate for reaching robust conclusions. Evaluation of results may be even more challenging when investigating the heterogeneity of the individual characteristics of the included studies. Examining the main causes of heterogeneity, the infertility etiology is neither examined nor mentioned in the meta-analyses by Ying et al, Chow et al, Chu et al and Massaro et al analysed herein. The meta-analysis by Frederiksen et al does not provide adequate data regarding the main causes of heterogeneity, while in the

meta-analysis by Gaitzsch et al the duration of infertility is regarded as the main cause of heterogeneity. It has been highlighted that the infertility etiology plays a primary role to ART success. Similarly, the duration of infertility is deemed as equally important, since women with long term infertility present with a diminished psychological profile.<sup>27,17</sup> The attempts to perform a meta-analysis were hindered by the fact that the majority of studies included presented with high heterogeneity and statistical bias. Thus, Massaro et al and Gaitzsch et al opted to perform a systematic review instead of a meta-analysis as statistical evaluation was not possible, due to high heterogeneity. Frederiksen et al reported a low to mediocre degree of heterogeneity, while Chu et al reported significantly high heterogeneity. Ying et al discussed the heterogeneity and the lack of statistical precision due to sample size, as well as due to attrition bias observed in a number of studies. The cultural background of the participants as a cause of heterogeneity is highlighted in the studies of Chow et al and Massaro et al. This may be attributed to the fact that the included studies originate from different countries, in which the degree of acceptance of different types of psychosocial interventions or their perceptions of infertility may vary,<sup>51</sup> Significant heterogeneity is also observed in the types of interventions that are included in the meta-analyses. The meta-analysis by Ying et al includes 14 different types of psychosocial interventions in 20 studies, while the meta-analysis by Gaitzsch et al focusses solely on the body/mind interaction interventions. Another significant causation of heterogeneity is the methodology of infertility management, that ranges from lack of employment of ART to IVF. It should be emphasized that, even the meta-analyses including solely studies with IVF (Ying et al, Massaro et al), the specific protocols applied may vary significantly regarding the number of embryos transferred, the day of embryo transfer or the employment of homologous or heterologous genetic material used.<sup>42</sup> Concerning the reporting of psychometric data, significant heterogeneity is observed regarding the synchronization of the interventions and the timing of data recording, in comparison to the initiation of ART treatment. In the meta-analysis by Ying et al only studies that did not perform psychometric evaluation following embryo transfer, albeit prior to pregnancy evaluation, were included, as this is considered quite tense time period.<sup>45</sup> The meta-analysis by Chu et al included solely studies that the final psychometric tests were performed exclusively on the aforementioned timeframe. Further heterogeneity causations observed were the age of the participants, the participation of the spouses/partners in the interventions, the demographic characteristics and the definition of the positive outcome of the ART treatment.

One important finding of this systematic review is the limited number of well-designed studies. The significant heterogeneity observed does not allow for definitive conclusions regarding the impact of the psychosocial interventions on the efficacy of ART treatment. The conduction of novel, better designed, randomized controlled tri-

als, with stricter inclusion and exclusion criteria, as well as better defined outcomes is required. Furthermore, novel meta-analyses of the existing studies based on more specific selection criteria aiming to investigate studies with more homogenic characteristics would possibly enable better evaluation of the existing evidence.

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# Ανασκόπηση

## Η επίδραση των ψυχοκοινωνικών παρεμβάσεων στη γονιμότητα: Η διχογνωμία των επιστημονικών δεδομένων

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### ΠΕΡΙΛΗΨΗ

Σκοπός της παρούσας βιβλιογραφικής ανασκόπησης ήταν η διερεύνηση της διχογνωμίας των αποτελεσμάτων της σύγχρονης έρευνας για τη σχέση μεταξύ της βελτίωσης της ψυχικής ευεξίας υπογόνιμων ζευγαριών μέσω συντονισμένων ψυχοκοινωνικών παρεμβάσεων, με τη βελτίωση των ποσοστών επιτυχίας θεραπειών υπογονιμότητας. Η διχογνωμία των αποτελεσμάτων στο ερευνητικό αυτό πεδίο πιθανολογείται ότι οφείλεται στην ετερογένεια των μελετών ως προς τον σχεδιασμό τους και τις μεθόδους ανάλυσης δεδομένων. Η συστηματική αυτή ανασκόπηση επιχειρεί να αξιολογήσει τον βαθμό ετερογένειας καίριων παραμέτρων μελετών της τελευταίας δεκαετίας όπως την ετερογένεια δείγματος, μεθόδων υποβοηθούμενης αναπαραγωγής, τύπων ψυχοκοινωνικών παρεμβάσεων και μεθόδων καταγραφής και ανάλυσης ψυχομετρικών δεδομένων. Η εν λόγω διερεύνηση κρίνεται σκόπιμη δεδομένου ότι ενώ ο αριθμός των σχετικών κλινικών μελετών και των μετα-αναλύσεων τους είναι μεγάλος εξακολουθεί να υπάρχει αδυναμία διεξοδικής αξιολόγησης της δυνατότητας βελτίωσης της γονιμότητας μέσω ψυχοκοινωνικής στήριξης. Η αναζήτηση άρθρων έγινε μέσω των ηλεκτρονικών βάσεων αποδελτίωσης βιβλιογραφικών δεδομένων PubMed και Google Scholar. Σύμφωνα με τα κριτήρια που τέθηκαν τα άρθρα επιλογής έπρεπε να αποτελούν μετα-αναλύσεις κλινικών μελετών για την επίδραση συντονισμένων ψυχοκοινωνικών παρεμβάσεων στην αποτελεσματικότητα θεραπειών υποβοηθούμενης αναπαραγωγής της τελευταίας δεκαετίας. Οι μετα-αναλύσεις αφορούσαν σε όλες τις αιτιολογίες υπογονιμότητας, καθώς και όλων των ειδών τις μεθόδους υποβοηθούμενης αναπαραγωγής. Κατόπιν αναζήτησης και επιλογής βάσει συγκεκριμένων κριτηρίων η διαδικασία κατέληξε στην επιλογή 6 άρθρων. Τα άρθρα αυτά αφορούσαν σε μετα-αναλύσεις μελετών διαφόρων τύπων παρεμβάσεων ψυχοκοινωνικής στήριξης όπως ατομικές, ζευγαριού, ομαδικές είτε σε επαγγελματικό περιβάλλον παροχής υπηρεσιών ψυχικής υποστήριξης είτε με τη μορφή προσωπικής αυτοβελτίωσης. Επιπλέον τα άρθρα αφορούσαν σε διάφορες τεχνικές και μεθόδους διαχείρισης stress που ποικίλαν από τη συμβουλευτική έως τη χρήση εξειδικευμένων τεχνικών διαχείρισης stress όπως η βιοανάδραση ή η εκμάθηση τεχνικών αναπνοής, αλλά και εναλλακτικές μεθόδους όπως η γιόγκα και ο διαλογισμός. Γενικό συμπέρασμα της συγκριτικής ανασκόπησης είναι ότι ο αριθμός των συστηματικών κλινικών μελετών που επικεντρώνονται αποκλειστικά στη διερεύνηση της επίδρασης στοχευμένων ψυχοκοινωνικών παρεμβάσεων στην επιτυχία θεραπειών υποβοηθούμενης αναπαραγωγής, είναι τελικά σχετικά περιορισμένος, ενώ στη μεθοδολογία τους εντοπίζεται σημαντική ετερογένεια ως προς τη δειγματοληψία, τα πρωτόκολλα θεραπείας, τις τεχνικές ψυχοκοινωνικής στήριξης, τις μεθόδους καταγραφής ψυχομετρικών δεδομένων αλλά και τις μεθόδους στατιστικής ανάλυσης δεδομένων. Συνεπώς, απαραίτητος κρίνεται ο σχεδιασμός συστηματικών τυχαιοποιημένων, ελεγχόμενων μελετών βάση αυστηρών κριτηρίων, οι οποίες να στοχεύουν στη διερεύνηση της διαχείρισης stress για την αντιμετώπιση της υπογονιμότητας αναφορικά με συγκεκριμένες αιτιολογίες υπογονιμότητας, ομοιογενή πρωτόκολλα υποβοηθούμενης αναπαραγωγής και συγκεκριμένους τύπους ψυχοκοινωνικών παρεμβάσεων.

**ΛΕΞΕΙΣ ΕΥΡΕΤΗΡΙΟΥ:** Συστηματική ανασκόπηση, διαχείριση στρες, ψυχοκοινωνική παρέμβαση, μέθοδοι υποβοηθούμενης αναπαραγωγής, μετα-ανάλυση.



## Brief communication

# Short-term reliability of retrospective childhood trauma reports in schizophrenia spectrum psychosis

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### ABSTRACT

Childhood trauma (CT) refers to severe early life adversities, especially experiences of parental abuse and neglect. Patients with schizophrenia spectrum psychosis (SSP) report higher CT rates than the general population. As CT assessment in SSP samples has been mainly conducted retrospectively through adult recollections of childhood adverse events, reservations about the reliability and validity of these reports have arisen. We sought to explore the short-term reliability of retrospective CT reports in sixty-three patients with SSP, by assessing the concurrent validity and test-retest reliability of the data. Two CT self-report measures, the Childhood Experience of Care and Abuse Questionnaire (CECA.Q) and the Parental Bonding Instrument (PBI) were employed for this task. High concurrent validity was detected between CECA.Q antipathy scales and PBI care and overprotection scales; and between CECA.Q neglect scales and PBI care scales. High test-retest reliability was confirmed for all CECA.Q and PBI scales. Our findings indicate that retrospective CT self-report measures are a reliable means of assessing early life adversities in SSP. However, further provisions should be taken to increase the reliability of retrospective reports, especially corroboration of the events through other sources and removal of latent confounders, such as psychopathology, memory fallacies and social desirability biases.

**KEYWORDS:** Childhood trauma, schizophrenia, retrospective reports, test-retest reliability, concurrent validity, parental abuse and neglect.

### Introduction

Childhood trauma (CT) is a comprehensive term encompassing a wide array of early life adversities that negatively impact normal child development and growth.<sup>1</sup> Attention is mainly focused on inadequate or inappropriate parental behaviors that fail to meet the physical and psychological needs of the developing child. These negative child-rearing behaviors may include acts of commission (i.e., emotional, physical, sexual abuse of the child) or acts of omission (i.e., emotional, physical, medical, educational neglect, inadequate supervision

and exposure of the child to violent environments) on the part of the primary caregiver.<sup>1</sup>

Research has repeatedly shown high rates of early life adversities in individuals with clinical or subclinical psychosis,<sup>2</sup> and CT has been identified as a prominent social risk factor for the emergence of psychotic symptoms.<sup>3</sup> However, the validity of these findings has been questioned because research in this domain has been mainly conducted retrospectively, namely through adult recollections of childhood traumatic events. Due to this retrospective design, several concerns have been raised regarding the reliability of the patients' CT reports.<sup>4</sup>

These reservations largely emanate from the intrusion of confounding factors, affecting the accuracy of these recollections, such as fallacies and limitations of normal memory functioning,<sup>5</sup> cognitive impairments associated with trauma and psychosis,<sup>6</sup> social desirability bias and stigmatization avoidance.<sup>7</sup>

### Normal memory fallibility

#### *Caveats of autobiographical memory*

Autobiographical memories, such as those associated with childhood experiences of abuse and neglect, are neither literal reproductions nor radical reconstructions of past events.<sup>8</sup> They can be better conceptualized as partially modified recollections of the original material either due to the expected time-lapse effects and age-related deterioration of normal memory functions,<sup>5</sup> or due to the inherent psychological need of the individual to maintain a viable and consistent self-narrative.<sup>8</sup>

#### *Childhood amnesia*

Childhood amnesia refers to the sparse recollection of personal events occurring in early childhood.<sup>5</sup> Due to this encoding and retrieval deficit, early life experiences are stored in a fragmented and incohesive manner, thus making them prone to loss, later suggestion and inaccuracies.<sup>8</sup>

### Impact of trauma and psychosis

Posttraumatic stress and psychosis may impair normal recall processes and lead to unfaithful or deceptive reconstructions of past events in an effort after meaning.<sup>6</sup> In this sense, retrospective CT reports may deviate from the original material and essentially form an alternative life script, an existential reconstruction seeking to provide a more bearable explanation for one's current affliction and distress.<sup>9</sup>

### Social desirability

The embarrassing and upsetting nature of various CT forms (e.g., sexual abuse) may lead individuals to minimize or deny the occurrence of such events, in an attempt to avoid social stigmatization.<sup>7</sup>

### Research indicating reliability of retrospective CT reports

Despite the aforementioned reservations, research has provided evidence that retrospective CT reports are stable across long periods of time,<sup>4,10</sup> uninfluenced by acute symptomatology,<sup>4,11</sup> and congruous with other sources of relevant information.<sup>4</sup> Furthermore, the effect of CT on risk for psychosis appears to be comparable across

retrospective and prospective study designs.<sup>2</sup> This is a significant finding, since prospective designs are considered more reliable as they usually follow up samples with documented early life adversities.

The present study aimed to explore the short-term reliability (i.e., stability) of retrospective CT reports in schizophrenia spectrum psychosis (SSP), by assessing the concurrent validity and test-retest reliability of these reports. Concurrent validity was chosen as a measure of report similarity, while test-retest reliability as a measure of temporal stability.

## Material and method

### Participants and procedure

Early relational trauma due to abusive or neglectful parenting was assessed in 63 SSP patients (44 men; 19 women) through the employment of two CT self-report measures, the Childhood Experience of Care and Abuse Questionnaire (CECA.Q)<sup>12</sup> and the Parental Bonding Instrument (PBI).<sup>13</sup> Both measures were administered on two separate occasions ( $T_1$ : initial testing, inpatient status;  $T_2$ : outpatient status, three months after  $T_1$ ). At the time of initial testing, all patients received antipsychotic medication.

All patients met DSM-IV criteria for Schizophrenia and other Psychotic Disorders, with the exception of Psychotic Disorder Due to a General Medical Condition and Substance-Induced Psychotic Disorder.

### CT measures

CECA.Q is a self-report measure designed to elicit information about experiences of parental antipathy (i.e., hostile, cold, rejecting, scapegoating behaviors towards the child), parental neglect (i.e., disinterest in child's material care, health, schoolwork, friendships), physical abuse perpetrated by parents, and sexual abuse perpetrated by adults during childhood and adolescence.<sup>12</sup>

PBI is a brief self-report questionnaire evaluating one's perceived parenting during the first 16 years of life. The instrument extracts two scales for each parent, parental care and parental overprotection (excessive control, intrusiveness, restrictiveness), which represent the two principal structural dimensions of parental attitudes towards the child.<sup>13</sup> The intersection of these two scales according to specific cut-off scores provides four parenting styles: optimal parenting (high care+low overprotection), affectionless control (low care+high overprotection), affectionate constraint (high care+high overprotection), neglectful parenting (low care+low overprotection).<sup>14</sup>

## Statistical analysis

Statistical analyses were performed using SPSS version 22.0. software package for Windows. Kolmogorov-Smirnov test was used to check for normality, and variables were also examined for skewness and kurtosis. As the variables of interest were not normally distributed, Spearman's correlation coefficient ( $\rho$ ) was employed to explore the concurrent validity and test-retest reliability of the data.

Whole sample ( $n=63$ ) CECA.Q and PBI  $T_1$  scores were used to test concurrent validity. Test-retest reliability was explored by correlating  $T_1$  and  $T_2$  CECA.Q and PBI scores in those patients who gave positive CT reports at  $T_1$  ( $n=46$ ).

## Results

### Baseline demographics

The SSP group consisted predominantly of male chronic patients with high-school level of education (table 1).

### Childhood trauma rates

At  $T_1$ , 46 SSP patients gave positive CT reports.  $T_2$  re-testing confirmed CT history in 42 of them. Two thirds

of the patients reported at least one severe CT type (table 2). Polytraumatization (i.e., history of  $\geq$  two CT types) was present in 46% of the SSP group, with 17.5% of the patients reporting two and 28.6% more than two CT types.

### Parenting style rates

Patients' perceived parenting experiences revealed high rates of low parental care (63.5% low maternal care; 63.5% low paternal care) and high parental overprotection (73% high maternal overprotection; 65.1% high paternal overprotection).

For both parents, the prevalent combined parenting style was that of maternal and paternal affectionless control (table 2).

### Concurrent validity of CECA.Q vs PBI

High concurrent validity was detected between CECA.Q parental antipathy scales and PBI parental care and overprotection scales; and between CECA.Q parental neglect scales and PBI parental care scales (table 3).

### Test-retest reliability of CECA.Q and PBI scales

High test-retest reliability was confirmed for all CECA.Q and PBI scales (table 4).

## Discussion

Regarding CT rates, our study confirms the high prevalence of childhood abuse and neglect in patients with psychosis.<sup>2</sup> We offer a more detailed analysis on this in a previous paper exploring associations between CT, adult attachment style and psychopathology.<sup>15</sup>

Regarding the perceived parental rearing behaviors, our study corroborates previous results indicating a clear preponderance of the affectionless control style in UHR risk for psychosis<sup>16</sup> and SSP samples.<sup>17</sup>

**Table 1.** Baseline demographics.

	SSP* patients ( $n=63$ )
Gender (% male)	69.84
Age (Mean; SD)	40.44 (10.003)
Level of education in years (Mean; SD)	11.13 (3.270)
Age of SSP onset	29.65 (9.09)
Duration of illness (months)	130.14 (121.11)
Chlorpromazine equivalent dose mg/d (Mean; SD)	1024.1 (669.8)

\*SSP: Schizophrenia-Spectrum Psychosis

**Table 2.** Childhood Trauma rates and perceived parenting experiences in the Schizophrenia-Spectrum Psychosis group ( $n=63$ )

CT rates	n	%	Perceived parenting styles	n	%
Total*	42	66.7	Maternal optimal parenting	12	19.0
Mother Antipathy	15	23.8	Maternal affectionless control	35	55.6
Mother Neglect	11	17.5	Maternal affectionate constraint	11	17.5
Father Antipathy	18	28.6	Maternal neglectful parenting	5	7.9
Father Neglect	11	17.5	Paternal optimal parenting	13	20.6
Mother Physical Abuse	14	22.2	Paternal affectionless control	31	49.2
Father Physical Abuse	14	22.2	Paternal affectionate constraint	10	15.9
Sexual Abuse	13	20.6	Paternal neglectful parenting	9	14.3

\*Presence of at least one severe CT type

**Table 3.** Concurrent validity: Spearman's correlations between Childhood Experiences of Care and Abuse Questionnaire (CECA.Q) and Parental Bonding Instrument (PBI).

	PBI Mother Care		PBI Mother Overprotection	
	rho	p	rho	p
CECA.Q Mother Antipathy	-0.618	<0.001	0.470	<0.001
CECA.Q Mother Neglect	-0.566	<0.001	0.242	0.056
	PBI Father Care		PBI Father Overprotection	
	rho	p	rho	p
CECA.Q Father Antipathy	-0.798	<0.001	0.493	<0.001
CECA.Q Father Neglect	-0.636	<0.001	0.112	0.385

**Table 4.** Test-retest reliability: Spearman's correlations between  $T_1$  vs  $T_2^*$  scores on Childhood Experiences of Care and Abuse Questionnaire (CECA.Q) and Parental Bonding Instrument (PBI).

CECA.Q scales	CECA.Q T1 vs T2		PBI scales	PBI T1 vs T2	
	rho	p		rho	p
Mother Antipathy	0.719	<0.001	Mother Care	0.798	<0.001
Father Antipathy	0.853	<0.001	Father Care	0.852	<0.001
Mother Neglect	0.655	<0.001	Mother Overprotection	0.794	<0.001
Father Neglect	0.713	<0.001	Father Overprotection	0.894	<0.001
Mother Physical Abuse	0.904	<0.001			
Father Physical Abuse	0.956	<0.001			
Sexual Abuse	0.860	<0.001			

\* $T_1$ : initial testing, inpatient status;  $T_2$ : outpatient status, three months after  $T_1$

Our findings stand in accordance with prior research that indicates adequate reliability of CT reports in adult patients with psychosis, especially of CT data gathered retrospectively through brief self-report questionnaires.<sup>4,10,11</sup>

Proper research designs that can reliably explore the occurrence and intensity of early life adversities are necessary for the clarification of the complex CT-psychosis association. The optimal method of assessing the impact of CT on the subsequent development of psychotic symptomatology would be through prospective studies of psychosis emergence in children and adolescents with officially documented early experiences of abuse and neglect. However, the increased cost and practical difficulties of prospective designs severely limit their actual feasibility. Hence, out of practical necessity, research in this area usually resorts to the retrospective assessment of CT in adult samples, either through comprehensive interviews or brief questionnaires, thus raising questions about the reliability of these reports.

While the reliability reservations cannot be answered definitively, we deem that our study offers adequate evidence substantiating the stability of retrospective CT re-

ports in patients with SSP, as these reports did not show significant fluctuation across different measures and different times of testing.

As already mentioned, four patients failed to replicate their initial  $T_1$  positive CT reports at  $T_2$ . This is by no means an unexpected finding, since it has already been documented in related literature.<sup>4</sup> Bearing in mind that  $T_1$  corresponded to the acute phase of illness, these initial false positives may be attributed to the confounding effect of severe psychopathology. As the magnitude of this replication failure was very low, the overall test-retest reliability was not affected.

High levels of concurrent validity were detected between CECA.Q and PBI scales, with the exception of CECA.Q neglect and PBI overprotection scales. These findings are in full agreement with prior research in this area.<sup>4</sup>

Our study did not remove the potential confounding effect of psychopathology on retrospective CT reports, a failure that weakens the strength of our results.

Regarding the matter of validity, that is whether retrospective CT reports reflect true life events, we cannot provide any meaningful insights, since this issue exceeded the scope of our study. Retrospective designs cannot

fully exclude the intrusion of invalid CT reports, unless there is some corroboration of reported events through third-party accounts or official child abuse and neglect registries. Despite our inability to productively address the validity issue, we may point out that the observed temporal stability can be regarded a necessary, albeit not sufficient, condition for a retrospective report to be valid.

In conclusion, we propose that retrospective CT data, based on brief self-evaluation questionnaires, are

adequately reliable in assessing early experiences of abuse and neglect in patients with SSP. At the same time, we acknowledge the inherent limitations of this method and we strongly suggest the inclusion of further provisions to increase the reliability of the reports, especially corroboration of the events through other sources and removal of latent confounders, such as psychopathology, social desirability biases and memory fallacies.

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## Σύντομο άρθρο

# Η βραχυπρόθεσμη αξιοπιστία των αναδρομικών αναφορών παιδικού ψυχικού τραύματος στις ψυχώσεις σχιζοφρενικού φάσματος

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### ΠΕΡΙΛΗΨΗ

Ο όρος Παιδικό Ψυχικό Τραύμα (ΠΨΤ) αναφέρεται σε αντίξοες εμπειρίες της παιδικής ηλικίας, ιδιαίτερες εμπειρίες γονεϊκής κακοποίησης και παραμέλησης, που επηρεάζουν την ομαλή ψυχολογική ανάπτυξη του ατόμου. Οι ασθενείς με ψυχώσεις του σχιζοφρενικού φάσματος (ΨΣΦ) αναφέρουν υψηλότερα ποσοστά ΠΨΤ σε σχέση με το γενικό πληθυσμό. Επειδή η αξιολόγηση του ΠΨΤ στους ασθενείς με ΨΣΦ διενεργείται συνήθως αναδρομικά, έχουν διατυπωθεί επιφυλάξεις ως προς την αξιοπιστία και την εγκυρότητα αυτών των αναφορών. Η παρούσα μελέτη διερεύνησε τη βραχυπρόθεσμη αξιοπιστία των αναδρομικών αναφορών ΠΨΤ σε ένα δείγμα 63 ασθενών με ΨΣΦ, μέσω του ελέγχου της συντρέχουσας εγκυρότητας και της αξιοπιστίας εξέτασης-επανεξέτασης. Χορηγήθηκαν δύο ερωτηματολόγια αναδρομικής αξιολόγησης του ΠΨΤ, το Ερωτηματολόγιο Εμπειριών Φροντίδας και Κακοποίησης στην Παιδική Ηλικία (CECA.Q) και το Όργανο Μέτρησης του Γονεϊκού Δεσμού (PBI). Διαπιστώθηκε υψηλή συντρέχουσα εγκυρότητα μεταξύ των κλιμάκων γονεϊκής αντιπάθειας του CECA.Q και των κλιμάκων γονεϊκής φροντίδας και υπερπροστασίας του PBI, όπως επίσης και μεταξύ των κλιμάκων γονεϊκής παραμέλησης του CECA.Q και των κλιμάκων γονεϊκής φροντίδας του PBI. Οι καταγραφές αμφοτέρων των ερωτηματολογίων παρουσίασαν υψηλή αξιοπιστία εξέτασης-επανεξέτασης. Τα ανωτέρω ευρήματα υποδεικνύουν ότι οι αναδρομικές αναφορές ΠΨΤ σε ασθενείς με ΨΣΦ έχουν επαρκή βραχυπρόθεσμη αξιοπιστία. Για την πληρέστερη, όμως, διερεύνηση του ΠΨΤ, απαιτείται η επιβεβαίωση των αναδρομικών αναφορών μέσω πρόσθετων πηγών και η απομάκρυνση συγχυτικών παραγόντων που μπορεί να επηρεάζουν την αξιοπιστία και εγκυρότητα των καταγραφών, όπως η ψυχοπαθολογία, τα εγγενή σφάλματα της μνήμης και ο φόβος κοινωνικού στιγματισμού.

**ΛΕΞΕΙΣ ΕΥΡΕΤΗΡΙΟΥ:** Παιδικό ψυχικό τραύμα, σχιζοφρένεια, αναδρομικές αναφορές, αξιοπιστία εξέτασης-επανεξέτασης, συντρέχουσα εγκυρότητα, γονεϊκή κακοποίηση και παραμέληση.

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## Case report

# Suicidal thoughts in a patient after administration of infliximab

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### ABSTRACT

Infliximab (IFX) is a chimeric monoclonal antibody biologic drug that works against tumor necrosis factor alpha (TNF- $\alpha$ ) and is used to treat autoimmune diseases. This is case of a 45year old female patient who had suicidal thoughts after receiving infusions with IFX. She did not report any family psychiatric history. She was diagnosed with ulcerative colitis. She had many relapses and she was treated with azathioprine and prednisolone. After many incidents of diarrhea, she started therapy with infliximab infusions. She had totally 13 infusions during a period of 13 months. The last year and in particular during the time of Infliximab intake, she reported suicidal ideation. Due to lack of improvement in her physical symptoms, she voluntarily discontinued medication and resorted to a nutritionist and a mental health counselor, where she followed cognitive and behavioral interventions. Treatment of autoimmune disorders with infliximab raise an awareness among medical and paramedical staff involved in the care of these patients about the psychiatric side effects of the drug.

**KEYWORDS:** Infliximab, Side effects, suicidal ideation, depression, ulceral colitis.

### Introduction

Infliximab (IFX) is a chimeric monoclonal antibody biologic drug that works against tumor necrosis factor alpha (TNF- $\alpha$ ) and is used to treat autoimmune diseases. Infliximab exerts its influence by binding to TNF- $\alpha$ . TNF- $\alpha$  is a chemical messenger (cytokine) and plays an integral part in autoimmune reaction. It was originally developed as a mouse antibody in mice. As humans have immune reactions to mouse proteins, the mouse common domains were replaced by similar human antibody domains.<sup>1</sup> IFX is as second line therapy in patients with ulcerative colitis who fail to respond in

intravenous steroids.<sup>2</sup> Psychiatric side effects are rare.<sup>3</sup> We present a case of a female patient who had suicidal thoughts after receiving infusions with IFX.

### Case Presentation

This is case of a 45year old female patient who attended a community mental health center due to depressive mood. She did not report any family psychiatric history. Ten years ago she was diagnosed with ulcerative colitis. She had many relapses and she was treated with azathioprine 100–150 mg p.o., prednisolone 30 mg p.o. After many incidents of diarrhea, she

started therapy with infliximab infusions. She had totally 13 infusions during a period of 13 months. The patient reported considerable psychological burden from the early days of the disease; however, with good adaptation in the ensuing years. Mild symptoms of irritability and sleep disturbances were reported. Her clinical condition worsened in 2010 after a new relapse of the disease when she manifested decreased mood and energy, fatigue, generalized anxiety and irritability. The intensity of the symptoms was hand in hand with her physical condition and was consonant with the exacerbations and remissions of the disease. In addition, for a considerable time period she described reduced functionality in her work, social withdrawal, and strenuous gastrointestinal symptoms, feeding fear, anxiety and avoidance behaviors (distant parts, control of the toilet - agoraphobia). She endeavored to regulate and control her defecation before leaving for her work on a daily basis in the form of a ritual. During the last year and in particular during the time of infliximab intake, she reported suicidal ideation. She had thoughts that she wanted to hurt herself and specifically she started thinking that she wanted to fall out the window but he never got to try it. Suicidal ideation occurred almost two months after starting treatment with infliximab and appeared suddenly. She had no symptoms of depression before starting treatment. The patient had also cognitive disorders and specifically she forgot things more often, important events such as appointments or social engagements and also, she became more impulsive or showed increasingly poor judgment. Due to lack of improvement in her physical symptoms, she voluntarily discontinued medication and resorted to a nutritionist and a mental health counselor, where she followed cognitive and behavioral interventions. Since then both her physical and mental well-being were significantly improved one month after the discontinuation of the treatment, restoring thus a large part of her functionality, undertaking and fulfilling family responsibilities, mobilizing with greater autonomy, improving mood and alleviating suicidal ideation. Irritability, impatience, cognitive disorders, avoidance behaviors, and pre-morning preparation rituals ("waking up two hours earlier, drinking a large amount of coffee, using toilet and leaving for work") remain. The patient has provided informed consent for this report and her anonymity has been preserved.

## Discussion

In our patient there was a time interrelation between the IFX therapy and the suicidal thoughts. The patient was not receiving any other treatment during IFX infusion. In the literature two other cases have also demon-

strated suicide attempts after IFX therapy.<sup>4,5</sup> Side effects with psychological or psychiatric implications are rare during infliximab therapy; while in relevant clinical trials the following side effects have been documented: amnesia, confusion, somnolence depression and apathy.<sup>6</sup> In another case report a 16-year-old male with a 2-year history of disabling symptoms and complications of Crohn's disease was initiated on a trial of infliximab. Within days of the first infliximab infusion, he experienced symptoms of depression, which intensified over weeks and resulted in a serious suicide attempt.<sup>7</sup> In a cohort study analyzing data from the French national hospital higher risks were observed for certain pairs of adverse events and underlying pathologies: psychotic disorders in patient treated for ulcerative colitis, manic episodes in patients treated for severe psoriasis, and suicide attempts in patients treated for rheumatoid arthritis.<sup>8</sup> Infliximab neutralizes the biological activity of TNF- $\alpha$  by binding with high affinity to the soluble (free floating in the blood) and transmembrane (located on the outer membranes of T cells and similar immune cells) forms of TNF- $\alpha$ , and inhibits or prevents the effective binding of TNF- $\alpha$  with its receptors. Infliximab and adalimumab (another TNF antagonist) are in the subclass of "anti-TNF antibodies" (they are in the form of naturally occurring antibodies), and are capable of neutralizing all forms (extracellular-, transmembrane-, and receptor-bound) TNF- $\alpha$ .<sup>9</sup> A large body of evidence corroborates an association among tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ), inflammation and depression. Immune activation and the concomitant upregulation of TNF- $\alpha$  is usually followed by a series of physiological, behavioral and motivational changes including fever, increased slow wave sleep, hyperalgesia, anorexia, anhedonia, disturbed mood and impaired concentration.<sup>10</sup> Childhood abuse has been associated with increased TNF- $\alpha$  mRNA consistent with extant studies of increased inflammation in subjects with history of childhood abuse.<sup>11</sup> TNF- $\alpha$  mRNA also continued to be increased in SA even after controlling for childhood abuse. Similar to HCC, TNF- $\alpha$  mRNA was also associated with perceived stress; however, TNF- $\alpha$  mRNA was associated with several clinical predictors of suicidal behavior of increased severity of depression and anxiety symptoms, impulsivity, aggression, hopelessness, and sleep disturbances. TNF- $\alpha$  is a potent pro-inflammatory cytokine and is one of the cytokines that can cross the blood brain barrier (BBB) without BBB disruption and affect brain function.<sup>12</sup> In this case, in addition to being at increased risk for depression due to the medical history of Crohn's disease, our patient had no previous psychiatric history and suicidal ideation came late after the start of treatment compared to other incidents in



the literature and the escape time of suicidal ideation in the literature usually is withdrawn after discontinuation of treatment.<sup>13</sup>

## Conclusion

Considering that infliximab remains a highly effective standard treatment of autoimmune disorders,

there is an imperative need to raise awareness among medical and paramedical staff involved in the care of these patients about the psychiatric side effects of the drug. Psychiatrists and gastroenterologists must liaison on inflammatory bowel disease therapy, so as to ensure success, reduce side effects and minimize the likelihood of relapse.

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## Ενδιαφέρουσα περίπτωση

# Αυτοκτονικός ιδεασμός σε ασθενή ύστερα από χορήγηση ινφλιξιμάμπης

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### ΠΕΡΙΛΗΨΗ

Η ινφλιξιμάμπη (infliximab) (IFX) είναι ένα βιολογικό φάρμακο χιμαιρικού μονοκλωνικού αντισώματος που λειτουργεί ενάντια στον παράγοντα νέκρωσης όγκου άλφα (TNF-α) και χρησιμοποιείται για τη θεραπεία αυτοάνοσων ασθενειών. Περιγράφεται η περίπτωση ασθενούς 45 ετών που είχε αυτοκτονικές σκέψεις μετά από λήψη εγχύσεων με IFX. Δεν ανέφερε κανένα οικογενειακό ψυχιατρικό ιστορικό. Διαγνώστηκε με ελκώδη κολίτιδα. Είχε πολλές υποτροπές και υποβλήθηκε σε θεραπεία με αζαθειοπρίνη και πρεδνιζολόνη. Μετά από πολλά περιστατικά διάρροιας ξεκίνησε θεραπεία με εγχύσεις ινφλιξιμάμπης. Είχε συνολικά 13 εγχύσεις για μια περίοδο 13 μηνών. Τον τελευταίο χρόνο και ιδιαίτερα κατά τη διάρκεια της πρόσληψης ινφλιξιμάμπης, ανέφερε αυτοκτονικό ιδεασμό. Λόγω της έλλειψης βελτίωσης των σωματικών της συμπτωμάτων, διέκοψε οικειοθελώς τη φαρμακευτική αγωγή και κατέφυγε σε διατροφολόγο και σύμβουλο ψυχικής υγείας, όπου ακολούθησε νοητικές και συμπεριφορικές παρεμβάσεις. Η θεραπεία αυτοάνοσων διαταραχών με ινφλιξιμάμπη αυξάνει την ευαισθητοποίηση του ιατρικού και παραϊατρικού προσωπικού που εμπλέκεται στη φροντίδα αυτών των ασθενών σχετικά με τις ψυχιατρικές παρενέργειες του φαρμάκου.

**ΛΕΞΕΙΣ ΕΥΡΕΤΗΡΙΟΥ:** Ινφλιξιμάμπη, παρενέργειες, αυτοκτονικός ιδεασμός, κατάθλιψη, ελκώδης κολίτιδα.

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