UNIWERSYTET MEDYCZNY
IM. PIASTÓW ŚLĄSKICH WE WROCŁAWIU

Praca doktorska

# *„Psychopatologiczne konsekwencje pandemii COVID-19 i strategie radzenia sobie pacjentów chorych przewlekle"*

lek. Mateusz Łuc

Promotor: prof. dr hab. n. med. Joanna Rymaszewska

Wrocław, 2023

# PODZIĘKOWANIA

*Dziękuję prof. Joannie Rymaszewskiej za wsparcie merytoryczne, sprawność działania oraz motywację.*

*Dziękuję dr. n. med. Marcie Woźniak za wdrożenie w świat nauki i pokazanie, że może być on źródłem radości i satysfakcji.*

*Składam podziękowania dla lek. Marcina Pawłowskiego, mgr Karoliny Fili-Pawłowskiej, lek. Tomasza Wieczorka oraz dr n. med. Doroty Szcześniak za ich wkład oraz pomoc w zebraniu oraz opracowaniu materiału badania.*

*Szczególne podziękowania kieruję do mych bliskich i przyjaciół, których zrozumienie i nieustanne wsparcie gwarantowały wytrwałość w dążeniu do celu.*

*Dziękuję także wszystkim współautorom artykułów oraz uczestnikom przeprowadzonych przeze mnie badań.*

**Wyniki pracy badawczej prowadzonej przez doktoranta zostały ujęte w cyklu trzech publikacji stanowiących podstawę niniejszej rozprawy doktorskiej:**

Łuc M, Woźniak M, Rymaszewska J. Neuroinflammation in dementia - therapeutic directions in a COVID-19 pandemic setting. Cells, 2022, vol. 11, nr 19, art.2959 [17 s.], DOI:10.3390/cells11192959.

IF = 7,666; Pkt. MEiN: 140,00

Łuc M, Pawłowski M, Jaworski A, Fila-Witecka K, Szcześniak D, Augustyniak-Bartosik H, Zielińska D, Stefaniak A, Pokryszko-Dragan A, Chojdak-Łukasiewicz J, Krajewska M, Pawłowski T, Szepietowski JC., Rymaszewska J. Coping of chronically-ill patients during the COVID-19 pandemic: comparison between four groups. Int J Environ Res Public Health, 2023, vol. 20, nr 6, art.4814 [14 s.], DOI:10.3390/ijerph20064814.

IF = 4,614; Pkt. MEiN: 140,00

Łuc M, Pawłowski M, Jaworski A, Fila-Witecka K, Kamińska D, Poznański P, Rymaszewska JE, Krajewski P, Szcześniak D, Rymaszewska J. Determinants of sleep disturbances in chronically-ill patients during the COVID-19 pandemic. Archives of Psychiatry and Psychotherapy, 2023, Nr 21: 1-15 [15 s.], DOI:10.12740/APP/166394.

Pkt. MEiN: 70,00

Sumarycznie punkty MEiN = 350; Sumaryczny IF = 12,280

## SPIS TREŚCI

# 1. Streszczenie

**Wstęp:**

Pojawienie się nowego wariantu koronawirusa, SARS-CoV-2, i jego gwałtowne globalne rozprzestrzenianie doprowadziło do poważnego kryzysu zdrowotnego na całym świecie. Zalecenia zachowania dystansu społecznego, nakładane kwarantanny poekspozycyjne oraz izolacje osób chorych wywarły znaczny wpływ na zdrowie psychiczne osób cierpiących na choroby przewlekłe. Grupa ta, ze względu na swój stan somatyczny była z jednej strony bardziej zagrożona ciężkim przebiegiem COVID-19. Z drugiej zaś, unikanie większych zbiorowisk ludzkich czy placówek medycznych było dla niej niemożliwe z powodu konieczności uzyskania niezbędnych świadczeń medycznych.

**Cele:**

1. Przegląd literatury dotyczącej biologicznego wpływu SARS-CoV-2 na ośrodkowy układ nerwowy, ze szczególnym uwzględnieniem powiązań z chorobami neurodegeneracyjnymi.
2. Ocena wykorzystywanych strategii radzenia sobie ze stresem i ich skuteczności z uwzględnieniem występowania objawów psychopatologicznych wśród chorych przewlekle.
3. Analiza występowania zaburzeń snu oraz ich determinant wśród osób chorych przewlekle w okresie pandemii COVID-19.

**Materiał i metody:**

Uczestnikami badania byli dorośli pacjenci leczeni przewlekle z rozpoznaniem łuszczycy, biorcy przeszczepu nerki, pacjenci dializowani, a w ramach drugiego artykułu, także pacjenci z rozpoznaniem stwardnienia rozsianego. Uczestnicy, którzy po zapoznaniu się z informacją o badaniu, wyrazili zgodę na udział, uzupełnili kwestionariusz w formie papierowej lub formularz internetowy CAWI (ang. Computer-assisted web interviewing). Pierwszy cel badania został zrealizowany poprzez analizę dotychczasowej literatury na temat biologicznego wpływu SARS-CoV-2 na ośrodkowy układ nerwowy psychicznego. Cel drugi i trzeci zrealizowano

za pomocą danych zebranych wśród uczestników badania zawierających kwestionariusz socjodemograficzny, Skalę Odczuwanego Stresu (PSS-10), Inwentarz do Pomiaru Radzenia Sobie ze Stresem (Mini-COPE), Kwestionariusz Ogólnego Stanu Zdrowia (GHQ-28) oraz Skalę Nasilenia Bezsenności (ISI).

**Wyniki:**

Przeprowadzone analizy wykazały, że wśród uczestników badania poziom odczuwanego stresu w związku z pandemią COVID-19 miał w dominującej mierze umiarkowany stopień. Najczęściej stosowanymi strategiami radzenia sobie ze stresem w tej grupie były strategie skupiające się na problemie, a zwłaszcza aktywne radzenie sobie, planowanie oraz pozytywne przewartościowanie. Spośród strategii skupiających się na emocjach najczęściej stosowanymi były akceptacja oraz wsparcie emocjonalne, a najrzadziej stosowaną był humor. Najrzadziej stosowaną grupą strategii radzenia sobie wśród osób przewlekle chorych stanowiły strategie unikające, a szczególnie zażywanie substancji psychoaktywnych. W odniesieniu do uczestników badania płci męskiej, uczestniczki częściej deklarowały stosowanie strategii z grupy skupiającej się na emocjach oraz unikającej. Zaobserwowano również korelację między wiekiem a zwrotem ku religii, podczas gdy większość z pozostałych strategii radzenia sobie była ujemnie skorelowana z wiekiem. Wraz ze wzrostem poziomu odczuwanego stresu wzrastał silnie wskaźnik strategii obwiniania siebie, natomiast w stopniu umiarkowanym rósł poziom strategii ukierunkowanych na unikanie, strategii zaprzestania działań, zaprzeczania oraz wyładowania. Wśród uczestników badania 25,2% spełniało kryteria umiarkowanej lub ciężkiej bezsenności klinicznej. Najczęstszymi skargami dotyczącymi snu były niezadowolenie z jego jakości, wpływ zaburzeń na funkcjonowanie oraz zauważalność problemu dla innych. Całkowite nasilenie zaburzeń snu było silnie związane ze wskaźnikiem GHQ-28, korelowało umiarkowanie dodatnio z odczuwanym poziomem stresu oraz ujemnie z długością trwania choroby.

**Wnioski:**

Przedstawione powyżej wyniki cyklu trzech spójnych tematycznie prac dowodzą istotnego wpływu pandemii COVID-19 na zdrowie psychiczne pacjentów chorych przewlekle w zakresie konsekwencji krótkoterminowych w postaci występowania objawów psychopatologicznych na skutek zagrożenia i stresu związanego z możliwym zakażeniem, a także długoterminowych na skutek aktywacji prozapalnej wynikającej z zachorowania na COVID-19.

Wyniki przeprowadzonych analiz pozostają zgodne z dostępną literaturą naukową, choć pojawiają się w nich pewne istotne różnice, wynikające między innymi z czynników o charakterze społecznym i kulturowym, ale także z charakterystyki badanej grupy osób chorujących przewlekle. Wcześniejsze leczenie psychiatryczne i psychoterapia korelowały ze znacząco wyższymi wynikami w skali ISI, a także mniej adaptacyjnym profilem stosowanych strategii radzenia sobie ze stresem. W związku z tym, populacja pacjentów chorych przewlekle z wcześniejszymi zaburzeniami psychicznymi może być szczególnie narażona na negatywne konsekwencje zdrowotne w okolicznościach pandemii.

Podczas gdy wspomniane wyniki prac oryginalnych opisują nasilenie objawów psychopatologicznych, ze szczególnym uwzględnieniem zaburzeń snu, oraz stosowane strategie radzenia sobie ze stresem w populacji pacjentów przewlekle chorych, poznanie skali długoterminowego wpływu nowego czynnika zakaźnego na ośrodkowy układ nerwowy możliwe będzie dopiero w przyszłości i wymagać będzie dalszych analiz.

# 2. Abstract

**Introduction:**

The emergence of a novel coronavirus variant, SARS-CoV-2, and its rapid global spread have led to a serious health crisis worldwide. Recommendations for social distancing, post-exposure quarantines, and isolation of infected individuals have had a significant impact on the mental health of people with chronic diseases. On one hand, this group was more vulnerable to severe COVID-19 due to their somatic condition.

On the other hand, avoiding large gatherings or medical facilities was impossible for them due to the need for receiving necessary medical care.

**Objectives:**

1. Literature review on the biological impact of SARS-CoV-2 on the central nervous system, with particular emphasis on its associations with neurodegenerative diseases.
2. Evaluation of used coping strategies and their effectiveness in relation to the occurrence of psychopathological symptoms among chronically-ill patients.
3. Analysis of the occurrence of sleep disturbances and their determinants among chronically-ill individuals during the COVID-19 pandemic.

**Materials and methods:**

The study included adult patients with chronic conditions such as psoriasis, kidney transplant recipients, dialysis patients, and, in case of the second article, patients diagnosed with multiple sclerosis. Participants who after obtaining information about the study consented to participate completed a questionnaire in paper form or with the us of an online Computer-Assisted Web Interviewing (CAWI). The first objective of the study was achieved through an analysis of existing literature on the biological impact of SARS-CoV-2 on the central nervous system. The second and third objectives were accomplished using data collected from study participants, including a socio-demographic questionnaire, Perceived Stress Scale (PSS-10), Mini-COPE (Inventory to Measure Coping Strategies), General Health Questionnaire (GHQ-28), and Insomnia Severity Index (ISI).

**Results:**

The conducted analyses showed that among study participants, the level of stress related to the COVID-19 pandemic was predominantly moderate. The most commonly used coping strategies in this group were problem-focused strategies, especially active coping, planning, and positive reframing. Among emotion-focused strategies, acceptance and emotional support were the most frequently used, while humor was the least used. Avoidant strategies, particularly substance use, were the least reported

coping strategies among chronically-ill individuals. Female participants more frequently used emotion-focused and avoidant strategies when compared to male participants. A correlation was also observed between age and turn to religion, while other coping strategies were mostly negatively correlated with age. As the level of perceived stress increased, the self-blame strategy significantly increased, and moderate increases were observed in avoidant strategies, behavioral disengagement, denial and venting. Among study participants, 25.2% met the criteria for moderate to severe clinical insomnia. The most common sleep complaints were dissatisfaction with sleep quality, impact of sleep disorders on daily functioning, and the noticeability of the problem to others. The overall severity of sleep disorders was strongly associated with the GHQ-28 score, moderately positively correlated with perceived stress levels, and negatively correlated with the duration of illness.

**Conclusions:**

The presented results from this set of studies demonstrate the significant impact of the COVID-19 pandemic on the mental health of chronically-ill patients, both in terms of short-term consequences, such as the occurrence of psychopathological symptoms due to the threat and stress associated with possible infection, and long-term consequences resulting from proinflammatory activation due to the COVID-19 infection.

The results of the conducted analyses are consistent with the available scientific literature, although there are some significant differences resulting from social and cultural factors, as well as the characteristics of the studied group of chronically-ill individuals. Previous psychiatric treatment and psychotherapy correlated with significantly higher scores on the ISI scale and less adaptive coping strategy profiles. Therefore, the population of chronically-ill patients with pre-existing mental disorders may be particularly susceptible to negative health consequences in the circumstances of pandemic.

While the mentioned results of the original studies describe the severity of psychopathological symptoms, with a particular focus on sleep disorders, and coping strategies employed in the population of chronically-ill patients, the full extent of the

long-term impact of the new infectious agent on the central nervous system requires further analysis and will be described more comprehensively in the future.

# 3. Wstęp

## 3.1 Wpływ pandemii COVID-19 na opiekę zdrowotną nad przewlekle chorymi

Pojawienie się nowego wariantu koronawirusa, SARS-CoV-2, i jego gwałtowne globalne rozprzestrzenianie doprowadziło do poważnego kryzysu zdrowotnego na całym świecie. Brak odporności populacyjnej na nowy czynnik zakaźny wymagał wprowadzenia szeroko zakrojonych restrykcji mających na celu spowolnienie dalszej transmisji SARS-CoV-2. Zalecenia zachowania dystansu społecznego, nakładane kwarantanny poekspozycyjne oraz izolacje osób chorych wywarły znaczący wpływ na zdrowie społeczne a pośrednio również zdrowie psychiczne ogółu populacji (1). Szczególne piętno mogły wywrzeć jednak na osobach cierpiących na choroby przewlekłe. Grupa ta, ze względu na swój stan somatyczny była z jednej strony bardziej zagrożona ciężkim przebiegiem COVID-19. Z drugiej zaś, często niemożliwe było dla niej unikanie większych zbiorowisk ludzkich czy placówek medycznych celem uzyskania niezbędnych świadczeń medycznych. Istotny wpływ wywarły również ograniczenia dotyczące społecznego i codziennego funkcjonowania pozbawiając wiele osób możliwości radzenia sobie ze zwiększonym stresem w dotychczasowy sposób (2). Zarówno bezpośrednie skutki infekcji, jak i wpływ izolacji społecznej, niepewności i obaw dotyczących przyszłości, ograniczeń w codziennym życiu, a także ekonomiczne konsekwencje pandemii, wywierają kumulujący się negatywny wpływ na zdrowie ludzi (1,3).

Do końca roku 2020 na świecie rozpoznano niemal 5 milionów przypadków zachorowań na COVID-19 a bezpośrednia śmiertelność z powodu choroby wynosiła ponad 1,8 miliona (https://covid19.who.int, dostęp z dnia 13.05.2023). Należy podkreślić,

że liczba ta nie uwzględnia pogorszenia stanu zdrowia bądź śmierci związanych z nieuzyskaniem świadczeń zdrowotnych zarówno z powodu braku ich dostępności, jak i indywidualnych obaw związanych z udaniem się do placówek medycznych w trakcie kolejnych fal pandemii (4,5). Pod tym względem, sytuacja osób chorujących przewlekle w okresie przed wprowadzeniem powszechnych szczepień przeciwko COVID-19 ponownie nabiera szczególnego znaczenia. Zastosowanie środków telemedycyny prowadzonej bez narażenia pacjenta na zakażenie nie umożliwia przeprowadzenia wszystkich niezbędnych procedur, w tym badania fizykalnego, rehabilitacji czy prowadzenia regularnych terapii takich jak hemodializa.

### 3.2 Zdrowie psychiczne osób przewlekle chorych

Rozpoznanie przewlekłej choroby somatycznej oraz konieczność regularnego korzystania ze świadczeń medycznych w znaczący sposób wpływa na zdrowie psychiczne pacjentów. Poza wpływem objawów choroby podstawowej na jakość życia pacjentów choroby przewlekłe, takie jak niewydolność nerek, choroby dermatologiczne czy neurologiczne, wymagają regularnego monitorowania, a także długotrwałego leczenia, aby zminimalizować ryzyko potencjalnych powikłań. W związku z tymi czynnikami, konieczność radzenia sobie z chorobą przewlekłą może prowadzić do nasilenia odczuwanego stresu, a w konsekwencji wpływa negatywnie na ich zdrowie psychiczne i może wiązać się z pojawieniem objawów psychopatologicznych, takich jak objawy depresyjne bądź lękowe (6). Pacjenci często doświadczają negatywnych emocji związanych z koniecznością ciągłego monitorowania stanu zdrowia, regularnych wizyt u lekarza oraz stosowania leków. Ponadto, niektóre choroby przewlekłe mogą wpłynąć na funkcjonowanie ośrodkowego układu nerwowego i powodować objawy psychopatologiczne (7,8).
Poza postępowaniem medycznym, kontrolowanie choroby przewlekłej wymaga od pacjentów wprowadzenia istotnych zmian w zakresie stylu życia, takich jak

stosowanie odpowiedniej diety, aktywność fizyczna czy unikanie stosowania używek. Te zmiany mogą być trudne do zaakceptowania dla niektórych pacjentów, a jednocześnie pozbawiać ich możliwości radzenia sobie ze stresem za pomocą dotychczas stosowanych strategii i zachowań. Powyższe czynniki czynią populację pacjentów chorych przewlekle szczególnie podatną na rozwój bądź nasilenie wcześniej występujących zaburzeń psychicznych w trakcie pandemii COVID-19.

### 3.3 Wpływ pandemii COVID-19 na zdrowie psychiczne osób przewlekle chorych.

Skutki pandemii na indywidualne zdrowie psychiczne wywierane są dwutorowo. Z jednej strony bezpośredni biologiczny wpływ wirusa na ludzki organizm może prowadzić do intensywnej uogólnionej reakcji układu immunologicznego, hipoksemii czy zakrzepicy, których wpływ może prowadzić do znacznych uszkodzeń ośrodkowego układu nerwowego a tym samym również do wynikających z nich objawów psychopatologicznych (9,10). Dotychczas opisano powikłanie COVID-19 w postaci zespołu post-covidowego, którego czas trwania cechuje się znacznym zróżnicowaniem a wśród objawów wymieniane są między innymi przewlekłe zmęczenie, obniżenie nastroju, objawy lękowe czy obniżenie sprawności funkcji poznawczych (11). Jednak mechanizm rozwoju powikłań w zakresie działania ośrodkowego układu nerwowego, całkowite rozpowszechnienie, a także znaczenie długoterminowych konsekwencji COVID-19 zostaną zweryfikowane w przyszłości.
Wpływ nowego czynnika zakaźnego, SARS-CoV-2 na ludzki organizm wiąże się z nasiloną prozapalną odpowiedzią układu immunologicznego. Szereg mechanizmów, takich jak produkcja i przenikanie cytokin obwodowych do ośrodkowego układu nerwowego, infiltracja zakażonymi leukocytami czy wzrost przepuszczalności bariery krew-mózg w wyniku obwodowych procesów zapalnych, może umożliwiać dalszą

propagację aktywacji prozapalnej w mózgu (12–15). Jej konsekwencje w postaci zmiany fenotypu komórek glejowych a następnie również utraty neuronów i uszkodzenia połączeń synaptycznych stanowią zaś podłoże do rozwoju chorób neurodegeneracyjnych (16–19).

Z drugiej strony liczne doniesienia wskazują na znacznie zwiększone rozpowszechnienie występowania objawów psychopatologicznych powstałych w wyniku przewlekłego utrzymywania się poważnego stresora w postaci pandemii. Obawy związane z przyszłością, stanem zdrowia własnym oraz osób bliskich skutkują odczuwaniem podwyższonego poziomu stresu, któremu towarzyszyć mogą objawy lękowe, depresyjne czy zaburzenia snu (20). W obliczu ograniczonej edukacji dotyczącej zdrowia psychicznego oraz nadal występującej stygmatyzacji osób z zaburzeniami psychicznymi, u części populacji strategie radzenia sobie ze stresem mogą przybierać dezadaptacyjny charakter, jak na przykład stosowanie używek bądź zaniechanie aktywności, prowadząc do dalszego pogarszania zdrowia psychicznego w mechanizmie błędnego koła (2). Istotne jest zatem rozpatrywanie wskaźników zdrowia psychicznego w odniesieniu do indywidualnie stosowanych strategii radzenia sobie ze stresem, tak aby możliwe było wskazanie wpływu poszczególnych strategii na dobrostan psychiczny.

# 4. Cel pracy

Pierwszy artykuł o charakterze przeglądowym miał na celu analizę biologicznego wpływu nowego wariantu koronawirusa, SARS-CoV-2, na ośrodkowy układ nerwowy. Omówiono w nim kluczowe biologiczne szlaki uczestniczące w rozwoju patologii oraz ich potencjalne długoterminowe skutki w postaci zaburzeń psychicznych. Za pomocą przeprowadzonego przeglądu literatury wskazano również farmakologiczne i niefarmakologiczne metody redukcji nasilenia procesów neurodegeneracyjnych.

W drugim artykule badano krótkoterminowe konsekwencje pojawienia się czynnika stresowego, pandemii COVID-19, w postaci objawów psychopatologicznych oraz stosowane metody radzenia sobie ze stresem w szczególnie narażonej grupie pacjentów przewlekle chorych.

Celem trzeciego artykułu było określenie rozpowszechnienia zaburzeń snu w trakcie pierwszej fali pandemii COVID-19 wśród pacjentów przewlekle chorych, wskazanie różnic pomiędzy poszczególnymi grupami pacjentów oraz socjodemograficznych czynników związanych z nasileniem omawianych zaburzeń.

# 5. Materiał i metoda badań

## 5.1. Uczestnicy badań

Uczestnikami badań prac oryginalnych byli dorośli pacjenci leczeni przewlekle z rozpoznaniem łuszczycy, biorcy przeszczepu nerki, pacjenci dializowani, a w ramach drugiego artykułu także pacjenci z rozpoznaniem stwardnienia rozsianego. Ze względu na obowiązujące w tym czasie obostrzenia i bezpieczeństwo uczestników część materiału została zebrana za pomocą formularzy internetowych CAWI (ang. Computer-assisted web interviewing), podczas gdy część osób odbywających już wizytę w placówce medycznej uzupełniła kwestionariusz w formie papierowej.

Uczestnicy zostali poinformowani o dobrowolnym oraz anonimowym charakterze badania, możliwości rezygnacji z udziału w badaniu w dowolnym momencie, a także braku negatywnych konsekwencji wynikających z udziału w nim. Informacje te zostały zawarte w opisie badania. Wysłanie formularza internetowego uznane było jako potwierdzenie pełnoletności, zapoznania się z opisem i celem badania, a także wyrażenie zgody na udział. Do dalszych analiz włączono jedynie formularze, które zostały uzupełnione w całości lub z ewentualnymi pojedynczymi pominięciami odpowiedzi, co zostało uwzględnione w analizach.

Badanie zostało zatwierdzone prze Komisję Bioetyczną przy Uniwersytecie Medycznym we Wrocławiu (numery zgód dla poszczególnych grup pacjentów: KB-468/2020; KB-469/2020; KB-470/2020 oraz KB-417/2020) i zostały przeprowadzone zgodnie z zasadami Deklaracji Helsińskiej.

Rekrutację do badania prowadzono w trakcie pierwszej fali zakażeń SARS-CoV-2 w Polsce, w okresie od kwietnia 2020 do sierpnia 2020. Ze względu na obowiązujące w tym czasie obostrzenia, rekrutację do badania prowadzono również za pośrednictwem mediów społecznościowych stowarzyszeń zrzeszających pacjentów z diagnozą łuszczycy oraz stwardnienia rozsianego.

### 5.2. Wykorzystane narzędzia

Pierwszy oraz drugi artykuł oryginalny z cyklu bazują na autorskim kwestionariuszu socjodemograficznym oraz następujących narzędziach psychometrycznych: Skali Odczuwanego Stresu PSS-10, kwestionariuszu MiniCOPE**,** polskiej adaptacji Ogólnego Kwestionariusza Zdrowia-28 (General Health Questionnaire, GHQ-28) oraz Krótkiej Skali Nasilenia Bezsenności (Insomnia Severity Index – ISI)**.**

A. Autorski kwestionariusz socjodemograficzny zawierał pytania o płeć, wiek, wykształcenie, stan cywilny bądź status związku, ilość dzieci, czas trwania choroby podstawowej, zmiany w organizacji wykonywanej pracy na skutek rozwoju pandemii COVID-19 oraz kwarantanny i izolacje nałożone na uczestnika badania oraz jego bliskich w ostatnich miesiącach.
B. Skala Odczuwanego Stresu 10 (PSS-10; polska adaptacja: Juczyński & Ogińska-Bulik, 2009) służy do oceny poziomu odczuwanego stresu w ciągu ostatniego miesiąca (21). Składa się z 10 pytań zaprojektowanych celem pomiaru subiektywnego poziomu stresu. Uczestnicy wskazują swoje odpowiedzi na 5-stopniowej skali, gdzie 0 (nigdy) oznacza brak stresu, a 4 (bardzo często) oznacza silne odczuwanie stresu. Wynik PSS-10 jest obliczany przez

sumowanie wyników poszczególnych pytań. Im wyższy wynik, tym wyższy poziom doświadczanego stresu. Wyniki w przedziale 0-13 interpretowane są odpowiednio jako niski, 14-26 jako umiarkowany, a 27-40 jako wysoki poziom stresu. Kwestionariusz został zatwierdzony dla polskiej populacji i uznany za zadowalający pod względem walidacji (Cronbach's alpha wynosi około 0.8).

C. Kwestionariusz MiniCOPE składa się z 28 elementów, które są podzielone na 14 podskal. Kwestionariusz umożliwia identyfikację używanych przez badanego strategii radzenia sobie w sytuacji zagrożenia lub stresu (Juczyński & Ogińska-Bulik, 2010) (22). Respondenci proszeni są o wybór najbardziej odpowiedniej odpowiedzi w czteropunktowej skali Likerta, gdzie 0 oznacza, że nigdy nie stosują danej strategii, a 3 - prawie zawsze to robią. W skład podskal wchodzą: aktywne radzenie sobie, planowanie, pozytywne przewartościowanie, akceptacja, poczucie humoru, zwrot ku religii, poszukiwanie wsparcia emocjonalnego, poszukiwanie wsparcia instrumentalnego, zajmowanie się czymś innym, zaprzeczenie, wyładowanie, zażywanie substancji psychoaktywnych, zaprzestanie działań, a także obwinianie siebie. Każda z podskal ma możliwą do uzyskania punktację między 0 a 3, gdzie im wyższy wynik, tym częściej badany stosuje daną strategię radzenia sobie. Wyróżniane są również 3 grupy strategii radzenia sobie: skupiające się na problemie (aktywne radzenie sobie, korzystanie z wsparcia informacyjnego, pozytywne przewartościowanie i planowanie), skupiające się na emocjach (wsparcie emocjonalne, wyładowanie, poczucie humoru, akceptacja, religia i obwinianie siebie) oraz unikające (odwracanie uwagi, zaprzeczenie, zażywanie substancji psychoaktywnych i zaprzestanie działań).

D. Ogólny Kwestionariusz Zdrowia-28 (GHQ-28) składa się z 28 pytań i wyróżnia cztery kategorie objawów: objawy somatyczne (pytania 1, 3, 4, 8, 12, 14 i 16), lęk i bezsenność (pytania 2, 7, 9, 13, 15, 17 i 18), zaburzenie funkcjonowania społecznego (pytania 5, 10, 11, 25, 26, 27 i 28) oraz objawy depresyjne (pytania

6, 19, 20, 21, 22, 23 i 24). Odpowiedzi udzielane są na czterostopniowej skali Likerta, gdzie 0 oznacza "wcale", 1 - "nie więcej niż zwykle", 2 - "raczej więcej niż zwykle" i 3 - "dużo więcej niż zwykle". Wynik całkowity stanowi sumę poszczególnych odpowiedzi i mieści się w przedziale od 0 do 84. Im wyższy wynik, tym bardziej intensywne są badane objawy, a punkt odcięcia dla istotnego nasilenia objawów wynosi 24 punkty. Pierwotnie kwestionariusz został opracowany przez Goldberga i wsp. w 1979 roku, a polska wersja została przetłumaczona i dostosowana przez Makowską i wsp. w 2002 roku (23,24).

E. Indeks Nasilenia Bezsenności (ISI) dostarcza informacji na temat istniejących zaburzeń snu, ich charakteru oraz wpływu na codzienne życie (25). Składa się z 7 pytań, na które udzielana jest odpowiedź na 5-stopniowej skali od 0 do 4, gdzie wyższe wyniki odpowiadają bardziej nasilonym trudnościom ze snem. Wynik całkowity jest obliczany poprzez zsumowanie każdej udzielonej odpowiedzi, a zgodnie z literaturą może być interpretowany jako: 0-7 – Brak klinicznie istotnej bezsenności; 8-14 – Podprogowa bezsenność; 15-21 – Bezsenność kliniczna (o umiarkowanym nasileniu); 22-28 – Bezsenność kliniczna (o ciężkim nasileniu). Kwestionariusz został zwalidowany za pomocą alfy Cronbacha, której wartości wahały się od 0,72 do 0,9 (26).

## 5.3 Analiza statystyczna

### 5.3.1 Pierwsza praca oryginalna

W pierwszym kroku analizy danych obliczone zostały statystyki opisowe wskaźników odczuwanego stresu oraz strategii radzenia sobie ze stresem. Aby określić kształty uzyskanych rozkładów obliczono statystyki takie jak: zakres (min-maks), miary tendencji centralnej (średnia) i rozproszenia (odchylenie standardowe), miary asymetrii i koncentracji (skośność, kurtoza). Aby sprawdzić czy uzyskane rozkłady różnią się od teoretycznego rozkładu normalnego obliczono testy

Kołmogorow-Smirnowa, sugerowane w przypadku prób o relatywnie dużej liczebności.

Aby odpowiedzieć na pytanie, czy poszczególne grupy pacjentów różnią się w zakresie stosowanych strategii radzenia sobie ze stresem, przeprowadzono serię porównań międzygrupowych z użyciem testu rang H Kruskalla-Wallisa, do którego następnie użyto testu post hoc Bonferroniego-Dunn. Wybór testu wynikał z faktu występowania istotnych rozbieżności wyników w podgrupach w stosunku do rozkładu normalnego.

Do obliczenia miary związków pomiędzy strategiami radzenia sobie ze stresem a długością choroby podstawowej oraz obecnym nasileniem odczuwanego stresu zastosowano nieparametryczny test korelacji rho Spearmana oparty na rangach, którego właściwości pozwalają na dobre oszacowanie współczynników korelacji w przypadku rozkładów normalnych odbiegających w sposób istotny od rozkładu normalnego. Do oceny wpływu płci, wcześniejszego leczenia psychiatrycznego oraz wcześniejszych oddziaływań psychologicznych na stosowane obecnie strategie radzenia sobie przeprowadzono test rang U Manna-Whitneya.

W celu sprawdzenia czy istnieją różnice w stosowaniu ogólnych strategii radzenia sobie ze stresem w interakcji z czterema grupami pacjentów, przeprowadzono mieszany model analizy wariancji w schemacie (3) x 4. W modelu czynnikami wewnątrzobiektywnymi były ogólne wskaźniki strategii (skoncentrowane na problemie, ukierunkowane na emocje, ukierunkowane na unikanie), natomiast czynnik międzygrupowy stanowiły cztery grupy pacjentów z różnymi stanami medycznymi. Do przeprowadzenia i porównania poszczególnych par średnich zastosowano poprawkę Bonferroniego.

Opisane analizy statystyczne zostały przeprowadzone przy użyciu oprogramowania IBM SPSS Statistics v. 26.

### 5.3.2 Druga praca oryginalna

Na początkowym etapie analizy danych obliczone zostały statystyki opisowe wskaźników oceny zdrowia psychicznego, poziomu odczuwanego stresu oraz ogólnego nasilenia bezsenności. Aby określić kształty uzyskanych rozkładów obliczono statystyki takie jak: zakres (min-maks), miary tendencji centralnej (średnia) i rozproszenia (odchylenie standardowe), miary asymetrii i koncentracji (skośność, kurtoza) oraz testy normalności rozkładu. Aby sprawdzić czy uzyskane rozkłady różnią się od teoretycznego rozkładu normalnego obliczono testy Kołmogorow-Smirnowa sugerowane w sytuacji prób o relatywnie dużej liczebności. Oprócz standardowych statystyk opisowych obliczono również rozkłady procentowe dla odpowiedzi na pojedyncze pytania kwestionariusza ISI.

Analizy międzygrupowe, porównujące wskaźniki oceny zdrowia psychicznego, poziomu odczuwanego stresu, ogólnego nasilenia bezsenności oraz szczegółowych skarg dotyczących snu u pacjentów z łuszczycą, u pacjentów dializowanych i u pacjentów po transplantacjach, przeprowadzono z użyciem testu rang H Kruskalla-Wallisa z testem post hoc Bonferroniego-Dunn. Wybór testu ponownie wynikał z faktu wystąpienia istotnych rozbieżności wyników w podgrupach w stosunku do rozkładu normalnego. Celem określenia związku pomiędzy wskaźnikiem nasilenia bezsenności a wiekiem, czasem trwania choroby, oceną stanu zdrowia psychicznego i poziomem odczuwanego stresu obliczono macierz korelacji rho Spermana.

Za pomocą testu U Manna-Whitneya dokonano porównań międzygrupowych nasilenia zaburzeń snu ze względu na płeć oraz wywiad w kierunku wcześniejszego leczenia psychiatrycznego lub korzystania z pomocy psychologicznej. Przeprowadzono również analizę kowariancji ANCOVA oraz wielokrotną regresję liniową celem wskazania najistotniejszych parametrów przewidujących nasilenie zaburzeń snu.

Analiz statystycznych dokonano przy użyciu oprogramowania IBM SPSS Statistics v. 26.

# 6. Cykl publikacji stanowiący podstawę pracy doktorskiej

## 6.1 Neuroinflammation in Dementia—Therapeutic Directions in a COVID-19 Pandemic Setting

cells

MDPI

*Review*

# Neuroinflammation in Dementia—Therapeutic Directions in a COVID-19 Pandemic Setting

**Mateusz Łuc [1,*], Marta Woźniak [2] and Joanna Rymaszewska [1]**

[1] Department of Psychiatry, Wroclaw Medical University, 50-367 Wroclaw, Poland
[2] Department of Pathology, Wroclaw Medical University, 50-367 Wroclaw, Poland
* Correspondence: mateusz.luc@student.umw.edu.pl

**Abstract:** Although dementia is a heterogenous group of diseases, inflammation has been shown to play a central role in all of them and provides a common link in their pathology. This review aims to highlight the importance of immune response in the most common types of dementia. We describe molecular aspects of pro-inflammatory signaling and sources of inflammatory activation in the human organism, including a novel infectious agent, SARS-CoV-2. The role of glial cells in neuroinflammation, as well as potential therapeutic approaches, are then discussed. Peripheral immune response and increased cytokine production, including an early surge in TNF and IL-1β concentrations activate glia, leading to aggravation of neuroinflammation and dysfunction of neurons during COVID-19. Lifestyle factors, such as diet, have a large impact on future cognitive outcomes and should be included as a crucial intervention in dementia prevention. While the use of NSAIDs is not recommended due to inconclusive results on their efficacy and risk of side effects, the studies focused on the use of TNF antagonists as the more specific target in neuroinflammation are still very limited. It is still unknown, to what degree neuroinflammation resulting from COVID-19 may affect neurodegenerative process and cognitive functioning in the long term with ongoing reports of chronic post-COVID complications.

**Keywords:** neuroinflammation; TNF; SARS-CoV-2; COVID-19; glial cells; TNF antagonists



**Citation:** Łuc, M.; Woźniak, M.; Rymaszewska, J. Neuroinflammation in Dementia—Therapeutic Directions in a COVID-19 Pandemic Setting. *Cells* **2022**, *11*, 2959. https://doi.org/10.3390/cells11192959

Academic Editor: Dolores Viña

Received: 8 August 2022
Accepted: 20 September 2022
Published: 22 September 2022



## 1. Introduction

Although dementia is a heterogenous group of diseases, inflammation has been shown to play a central role in all of them and provides a common link in their pathology. This review aims to highlight the importance of immune response in the most common types of dementia, discuss essential mechanisms and sources of neuroinflammation and potential therapeutic strategies.

Prolonged activation of pro-inflammatory responses in Alzheimer's disease (AD) alters function of glial cells and in turn, further accelerates neuroinflammation [1]. Subsequent synaptic dysfunction and loss of neurons are responsible for clinical symptoms of the disease. Additionally, factors such as insufficient sleep length and subsequent reduction in amyloid clearance via the glymphatic system lead to amyloid accumulation, while simultaneously aggravating systemic inflammatory response [2]. Inflammation in vascular dementia (VaD) contributes to the three-hit hypothesis, along with hypertension and hypoxia [3]. Vasculitis is responsible for restricted blood circulation in microvessels and leads to decreased oxygen supply and regional glial activation favoring neuroinflammation in the central nervous system (CNS) [4,5]. In the following cascade, blood vessels undergo remodeling, the blood-brain barrier (BBB) becomes more permeable and microthrombi cause regional hypoxia and neural death [3,4,6]. While neuroinflammation in frontotemporal dementia (FTD) is evident with both pro- and anti-inflammatory cytokines levels increased in the brain, the impact of the systemic inflammatory activation remains inconclusive [7]. However, some studies indicate that FTD is associated with autoimmune

activation and more frequent comorbidities such as thyroid and rheumatoid diseases but also with elevated TNF concentrations [8,9] These observations reflect the need to account for peripheral immune response in understanding pathology of the disease [10]. Lewy bodies, α-synuclein aggregates present in neurons are a hallmark trait of Lewy body dementia (LBD) [11]. Microglial phagocytosis of α-synuclein aggregates leads to a release of pro-inflammatory cytokines, such as IL-6, contributing to increased iron sequestration in neurons and exacerbating neural death [12]. α-synuclein acts as an agonist of microglial Toll-like Receptor 2 (TLR-2) resulting in oxidative stress and production of TNF, IL-1 and IL-6 [13]. Addressing evidence from Parkinson's disease studies, extracellular α-synuclein stimulates leucine rich repeat kinase 2 (LRRK2) expression in monocytes, favoring their infiltration of the brain parenchyma [14,15]. Additionally, α-synuclein oligomers induce release of calcium from astrocytes leading in turn to glutamatergic neurotoxicity and synapse loss [16].

As briefly discussed above, source and role of inflammation varies widely depending on specific dementia type. However, recent research highlights the role of peripheral cytokines and immune cells in the neurodegenerative processes [17–19]. Numerous comorbidities, which are considered to be risk factors of cognitive decline, are linked to dementia pathology via several mechanisms, among which, inflammation plays a significant role. While some studies detected a small association between inflammatory markers and global cognition in the elderly or function disability in dementia patients, life-long immune response could not be accounted for in any of those studies [20–22]. Hence, it is currently argued that the total impact of systemic life-long pro-inflammatory activation, such as occurs in obesity or rheumatoid diseases, and its role in cognitive decline require further exploration. In the following sections we describe molecular aspects of pro-inflammatory signaling and sources of inflammatory activation in the human organism, with a special regard to a novel infectious agent, SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2). The role of glial cells in neuroinflammation, as well as potential therapeutic approaches, are discussed.

## 2. Tumor Necrosis Factor Triggers Dementia Pathology

Among various cytokines involved in the immune response, tumor necrosis factor (TNF) is considered to play a significant upstream role in dementia pathology on a molecular level. Its pleiotropic effects vary from physiological neuroprotective and repair activities to pathological neuronal loss occurring in neurodegenerative and autoimmune conditions which are dependent on TNF form and activated receptor [23]. TNF receptor type 1 (TNFR1) is commonly expressed and can be bound by both transmembrane and soluble TNF forms, while TNF receptor type 2 (TNFR2), expressed by myeloid and endothelial cells but also by CNS-residing glia and neurons, is mainly bound by transmembrane TNF [24]. Protective versus deleterious outcomes of receptor activation depend on various factors including TNF concentration, activation of other signaling pathways or cell susceptibility resulting from cell type and age-related priming [25,26]. TNF signaling activates intracellular pathways with transcription factors such as NFκB (nuclear factor kappa-light-chain-enhancer of activated B cells) leading to pro-inflammatory cytokine production and, in conditions of prolonged signaling, aggravation of inflammation [27,28].

Exposure to TNF in an in vitro AD model has been shown to result in aggregation of extracellular proteins which are considered characteristic traits of AD and LBD pathology [29]. Interestingly, exposure to TNF does not need to be sustained in order to maintain increased secretion and aggregation of amyloid-β or α-synuclein in such models. This mechanism may demonstrate profound effects of TNF signaling on pro-inflammatory activation and cytokine production of astrocytes and microglia, leading to prolonged neuroinflammation [30]. This phenomenon has been reflected in a cohort study by Lindbergh et al., in which TNF plasma concentration of participants were assessed annually. Increased systemic TNF resulted in reduction in grey matter volumes in further assessments in a curvilinear correlation, with initially-increased TNF correlating with following loss of volume [31].

Additionally, within-person increases in TNF correlated with lower scores obtained in neuropsychological evaluation with the use of Mini Mental State Examination.

## 3. Mechanisms of Chronic Low-Grade Inflammation

Chronic low-grade inflammation stems from various conditions such as obesity, autoimmune and metabolic diseases, but also from psychosocial stressors. Adipokines released by white adipose tissue favor low-grade chronic inflammation and it has been shown that resulting changes to cytokine levels in mouse hippocampi can be elicited by simple fat tissue transplantation [32,33]. Obesity in humans is associated with greater neuroinflammation and worse cognitive performance, as shown by Samara et al., in a cohort study [34]. The impact of obesity on cognition is mediated both by adipokine dysfunction and increased production of pro-inflammatory cytokines by activated adipocytes [35,36]. Rheumatoid diseases are linked to a higher risk of atherosclerotic lesions and the proposed mediator is low-grade inflammation [37]. Both metabolic syndrome and type 2 diabetes have also been implicated in low-grade inflammation [38]. Moreover, in a longitudinal study chronic work-related stressors were associated with increased inflammatory index in men [39].

Another important factor in pro-inflammatory activation of the immune system seems to be composition of gut microbiota, which interestingly, has also been associated with above-mentioned causes of chronic inflammation [40]. Recent studies highlight the influence of diverse and complex environments present in the gastrointestinal tract on various health outcomes, including neurodegenerative diseases [41]. The bidirectional relations between gut microbiota and brain are reflected by the term gut-brain axis in which both blood and vagus nerve serve as mediators. In Parkinson's disease α-synuclein aggregates are detected in intestinal submucosal plexus in a prodromal stage of disease [42]. Additionally, pathological α-synuclein was shown to be reversely transported via vagus nerve in animal models [43]. A similar mechanism has also been hypothesized for amyloid-β in AD [44]. The noteworthy mechanisms of microbial impact on the CNS include (1) intestinal production of cytokines; (2) entry of bacterial toxins, such as lipopolysaccharides, to the bloodstream; (3) microbial production of neurotransmitters; (4) direct passage of microbes to bloodstream and reactive production of cytokines by immune cells, but also (5) microbial entry to the CNS. Several highly adapted bacterial species, such as *Streptococcus pneumoniae* or *Neisseria meningitidis* are able to cross the BBB, often leading to its disruption and clinical manifestations of neurological infection. However, most of the microbial interactions with the CNS are considered to occur in a chronic, life-long fashion [45,46]. On the other hand, it is argued that activation of hypothalamic-pituitary-adrenal axis by circulating lipopolysaccharides constitutes CNS response and affects the gastrointestinal tract in a feedback loop manner [47].

## 4. SARS-CoV-2—A Novel Source of Neuroinflammation?

Recently, global exposure to the novel infectious agent, SARS-CoV-2, raises a question about neuroinflammatory consequences of COVID-19 (Coronavirus Disease 2019). Despite the fact that most cases of the infections are mild, their long-term effects in humans remain unknown [48]. SARS-CoV-2 has proven neurotropism and was shown to enter the CNS and disrupt the BBB integrity [49–52]. The entry of the virus to the CNS could occur via the olfactory nerve retrograde route but also with viral particles infecting endothelial cells and in conditions of BBB impairment, also pericytes and astrocytes [53,54].

So far, insufficient data exists on hypothesized retrograde axonal transport of the SARS-CoV-2. However, potential cellular mechanisms for this pathway could include ESCPE-1 retrograde trafficking. This endosomal transport system is responsible for sorting of neuropilin-1, which was shown to be a host factor for SARS-CoV-2 infection but further studies are required in order to confirm this pathway [55]. While evidence exists that virus present in the blood infects endothelial cells causing loss of the BBB integrity and allowing for entry to the CNS [56,57], it is still unclear whether disruption of BBB occurs

due to tight junctions alterations [58] or basement membrane remodeling [59]. Another hypothesized pathway is the 'Trojan horse' mechanism observed in HIV infection, with infected circulating macrophages crossing the BBB and transporting SARS-CoV-2 to the brain compartment [60].

The apolipoprotein E4 (ApoE4) genotype has been associated with decreased antiviral defense gene expression resulting in increased risk of neuronal or astrocytic infection and more aggravated inflammatory response in astrocytes [61,62]. This finding links COVID-19 to AD pathology, for which ApoE4 gene is a well-established risk factor. Brain-residing cells, such as neurons, glia or pericytes have been shown to express the angiotensin-converting enzyme (ACE2) receptor, which facilitates viral infection in other organs such as lungs or heart [63–65]. Studies conducted in vitro indicate that SARS-CoV-2 infection in neurons results in synapse loss along with a decreased number and impaired morphology of neurites [61]. Furthermore, a multimodal omics approach revealed correlations between COVID-19 neuroinflammation and cognitive decline, with special emphasis on AD microvascular injury pathways [62].

While acute infection has been documented to cause neurological conditions such as encephalopathy and meningoencephalitis, their occurrence does not require the viral invasion of the CNS but can also result from other neuroinflammatory pathways [66]. In a study of 29 COVID-19 patients with neurological manifestations of the disease, most of them did not test positively for SARS-CoV-2 RNA in the cerebrospinal fluid (CSF) samples [67]. The total impact of the inflammatory activation in the CNS by SARS-CoV-2 is yet to be described. Peripheral immune response and increased cytokine production, including an early surge in TNF and IL-1β concentrations, impact the CNS-residing cells and favor their priming [53,54,66,68–71] (Figure 1). One of the proposed mechanisms of this phenomenon is entry of the peripheral pro-inflammatory signaling to the CNS via endothelial cells [72]. The effects of systemic inflammation observed in the brain compartment during COVID-19 have been described in several reports in which CSF pro-inflammatory cytokines levels were elevated throughout the course of the disease [73,74]. Additionally, cardiovascular consequences of COVID-19, such as coagulopathy and stroke, also contribute to cognitive decline [68,70,75]. As it turns out, despite some reports of viral presence in the CNS, the relevant consequences of COVID-19 in regard to neurodegeneration may actually occur without infiltration or replication of SARS-CoV-2 in the brain compartment. So far, a novel somatic symptomatology similar to chronic fatigue syndrome has been reported and described as post-COVID syndrome or long COVID [76], but other long-term consequences of COVID-19 may be reported in the future and more mechanistic studies are required in order to answer which pathways are of importance in their development.

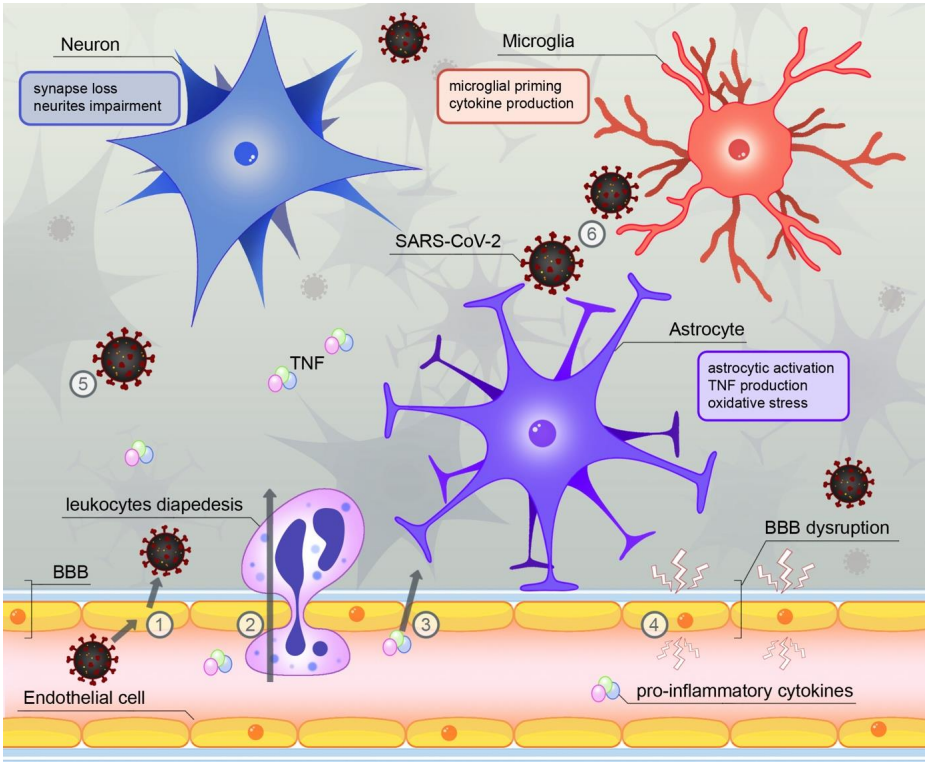



**Figure 1.** SARS-CoV-2 infection impacts the CNS via several potential pathways: (1) Infection of endothelial cells by viral particles present in the blood; (2) infiltration of the CNS by activated leukocytes from the bloodstream; (3) entrance of pro-inflammatory cytokines into the CNS; (4) loss of the BBB integrity due to increased immune response; (5) hypothetic direct passage of viral particles via olfactory nerve and (6) activation of pro-inflammatory phenotypes of CNS-residing cells.

## 5. Glial Involvement in Neuroinflammation

Research shows that the physiological neuroprotective immune response becomes impaired in conditions of prolonged pro-inflammatory activation in the CNS. The intricate interplay between different cell types residing in the CNS, such as neurons, microglia or astrocytes, becomes disturbed, eventually altering their function and leading to progressive aggravation of molecular pathology. Glial cells take part in nourishment of neurons but also affect their maturation, synapse formation and proper function [77,78]. It has been shown that both astrocytes and microglia exhibit neuroprotective and neuroinflammatory phenotypes, though these two main phenotypes may vary widely [79–81]. Loss of neuroprotective glial functions may in fact be associated with age-related decrease in acetylcholine receptors which are responsible for anti-inflammatory glial actions [80,82].

Astrocytes, the most numerous cells in the CNS maintain proper neurotransmission, regulate neural metabolism and oxidative status and contribute to glymphatic clearance of deleterious substrates [83,84]. Along with neurons and endothelial cells they allow for neurovascular coupling crucial for separation but also equilibrium maintenance in blood and brain compartments [85]. However, in neurodegenerative diseases their neuroprotective and neuroregulatory roles are impaired. Evidence indicates that astrocytes exhibit

more pro-inflammatory phenotype with older age [86]. Exposure to phosphorylated tau oligomers evokes a pro-inflammatory astrocyte phenotype in AD and FTD patients resulting in a further increase in TNF production and activation of inflammatory phenotypes in surrounding cells [87]. Additionally, activated astrocytes are implicated in amyloid production increasing amyloid burden in the CNS, while their effectiveness in amyloid clearance decreases with time [79]. In LBD, α-synuclein aggregates accumulate in astrocytes leading to their chronic activation [83]. Microangiopathy impairs function of the neurovascular unit. In such conditions, astrocytes lose their buffering function leading to potassium imbalance and altered neuronal excitability [88]. In an animal model of VaD, reactive astrocytes significantly influenced survival of hypoxic neurons, which was mediated by lipocalin-2 expression [89]. Use of human-induced pluripotent stem cells and their differentiation into astrocytes led to remyelination and axonal sprouting enabling improvement of cognitive functions in another rodent model of VaD [90].

Microglia are primary immune cells responsible for phagocytosis, cytokine production and immune surveillance in the CNS [91,92]. However, their longevity and low turnover facilitate development of age-related neurodegenerative diseases [93]. It is currently believed that throughout life microglia respond to various stressors and become primed leading to often exaggerated and prolonged inflammatory responses to stimuli present in older age [94–96]. Primed microglia are characterized by less efficient amyloid phagocytosis and greater production of pro-inflammatory cytokines, such as TNF [97,98]. Interestingly, TNF has been shown to inhibit microglial clearance and increase production of amyloid in the CNS [99]. The primed microglia are also characterized with overexpression of immune surface protein TREM 2 (triggering receptor expressed on myeloid cells 2), which initially helps to alleviate amyloid burden [80,100]. In the brain compartment TREM2 is expressed by microglia only and promotes their survival, activation and phagocytosis [101,102]. CSF concentration of its soluble form, sTREM2, is indicative of neurodegeneration, with its higher levels correlating with slower cognitive decline in AD patients [103]. TREM gene variants have been implicated in pathologies of AD, FTD, along with α-synucleinopathies [101]. However, conflicting results from animal studies lead to the conclusion that the role of TREM2 in dementia pathology may actually be dependent on the stage of disease, with TREM2 reducing amyloidogenesis at early stages but eventually increasing development of amyloid plaques [104–107]. The reasons for the changed outcome of this signaling pathways may result from prolonged peripheral inflammatory activation influencing the CNS and therefore, activation of other signaling pathways.

Apparently, impaired microglial function resulting in ineffective amyloid plaque clearance favors development of microgliosis. In neurodegenerative diseases such as AD and LBD, the total number of microglia is increased, while number of activated microglia correlates with observed tau pathology [99,108]. Tau aggregates, have in turn been shown to induce NLRP3 inflammasome activation, leading to further production of IL-1β by microglia and aggravation of neuroinflammation [109]. Of note, pharmacological reduction in microgliosis and alteration of the glial pro-inflammatory phenotype leads to alleviation of tau-related pathology and improvement of cognitive functioning in an animal model [110]. Evidence exists, that activated glia may in fact facilitate propagation of α-synuclein pathology in in vitro models of α-synucleinopathies [111–113]. Additionally, microglia and astrocytes have been implicated in defective autophagy and glutamate excitotoxicity in FTD [114–116].

## 6. Methods for Reduction of Pro-Inflammatory Activation—Critical Appraisal

Since TNF signaling exerts a triggering effect in the development of cognitive decline [29,31], the question arises, whether interventions focused on reduction in TNF concentrations or inhibition of its signaling pathway may play a role in dementia prevention or treatment. There are several methods of reducing an inflammatory state in the human organism, including dietary and pharmacological interventions.

Diet has been implicated in pathology of numerous neurodegenerative diseases, including dementia. A well-balanced diet provides all nutritional ingredients necessary for maintaining healthy and functional neurons [117]. On the other hand, it is believed that diet largely impacts inflammatory activation and immune response, which in turn influences regional inflammatory response in the brain. Various studies, including large cohorts, have associated inflammatory dietary patterns with faster cognitive decline and subsequent cognitive impairment [118–120]. The correlation between inflammatory diet and cognition is especially apparent in regard to several cognitive functions, such as episodic memory, semantic-based memory, executive functions and working memory [121].

The Western diet which comprises highly-processed food rich in fructose and saturated fat is known to increase TNF concentration in animal models [122]. Mice immunized against *Klebsiella pneumoniae* were shown to have lower levels of inflammasome-related inflammation, providing yet another link between gut microbiota and inflammation. This phenomenon was mediated by the presence of apolipoprotein E and was not observed in ApoE −/− animals [122]. Although individually tailored diets are not yet within reach and require further exploration, some conclusions regarding the influence of particular diets on neurodegenerative processes can be made based on existing studies [123]. For example, use of Dietary Inflammatory index (DII), which takes into account individual's dietary composition and characteristics, allows us to indicate the general influence of one's diet on systemic cytokine levels and inflammatory activation [124]. Higher scores of DII were shown to strongly correlate with worse cognitive performance [125]. It stands to reason, that the influence of environmental factors such as diet in preserving cognition cannot be underestimated. On the other hand, it seems that the inflammatory potential of the consumed food may be related not only to the specific products but also to the gut microbiota composition resulting from the daily diet. A summary of findings associated with specific diets can be found in Table 1 [126–135].

**Table 1.** Summary of findings associated with diet and inflammation.

| Study (Type) | Outcomes | Diet/Intervention | Group | Key Findings |
|---|---|---|---|---|
| Ostan et al., 2015 [126] (cohort study) | Inflammatory and metabolic parameters | RISTOMED diet (personalized and balanced) +/− nutraceutics | 125 participants | RISTOMED diet alone or with each nutraceutical supplementation significantly decreased erythrocyte sedimentation rate |
| Kim et al., 2022 [127] (non-randomized intervention study) | Inflammatory parameters Insulin sensitivity | Short-term ketogenic diet (3 days) | 15 participants | Short-term Ketogenic diet resulted in lower IL-1β and TNF secretion; Improved insulin sensitivity |
| Al-Abauidy et al., 2021 [128] (randomized clinical trial) | Oxidative stress and inflammatory parameters | Mediterranean diet (12 weeks) | 19 participants | Mediterranean diet reduced IL-6 levels by 49% and levels of oxidative stress marker, 8-OHdG, by 32.4% |
| Georgoulis et al., 2021 [129] (randomized clinical trial) | Oxidative stress and inflammatory parameters | Mediterranean diet (6 months) | 187 patients with obstructive sleep apnea | Mediterranean diet reduced hs-CRP levels in patients |
| Casas et al., 2017 [132] (randomized clinical trial) | Cytokine levels | Mediterranean diet +/− extra virgin olive oil (5 years) | 66 participants | Mediterranean diet reduced IL-6, IL-8, MCP-1, and MIP-1β levels. Addition of extra virgin olive oil reduced IL-1β, IL-5, IL-7, IL-12p70, IL-18, TNF-α, IFN-γ, GCSF, GMCSF, and ENA78 |

**Table 1.** *Cont.*

| Study (Type) | Outcomes | Diet/Intervention | Group | Key Findings |
|---|---|---|---|---|
| Omorogieva et al., 2021 [130] (meta-analysis) | Lipid profiles, LPS, BMI, inflammatory markers | Diet rich in fiber | 10 studies included in meta-analysis | Dietary fiber reduces total cholesterol, BMI and CRP, but no significant changes were observed for IL-6 and TNF |
| Shivappa et al., 2016 [131] (cross-sectional study) | Inflammatory markers | - | 532 adolescents | Higher dietary inflammatory index scores were associated with increased levels of various inflammatory markers: TNF-α, IL-1, 2, IFN-γ and VCAM |
| Mazzoli et al., 2020 [133] (animal study) | Inflammatory markers, insulin sensitivity, BDNF | Western diet (4 weeks) | 16 rats | Western diet increased TNF levels in white adipose tissue and hippocampus of rats; brain BDNF and synaptotagmin I were decreased, while PSD-95 was increased. |
| Jena et al., 2020 [134] (animal study) | Interleukin-17, PD-95, BDNF | High sugar and high fat diet (FPC diet) for 3 months, and 5 months +/− inulin supplementation | 12 mice | FPC diet elevated RORγ and IL-17A signaling. Accompanied by microglia activation and reduced hippocampal long-term potentiation, FPC diet intake also reduced postsynaptic density-95 and brain derived neurotrophic factor. |
| Godfrey et al., 2020 [135] (animal study) | CRP levels, CSF dopamine concentrations Functional connectivity | 12 months of obesogenic diet | 34 female rhesus monkeys | CSF dopamine concentrations decreased, and CRP concentrations increased. Resting-state magnetic resonance neuroimaging showed that higher CRP concentrations were associated with decreased functional connectivity. |

Non-steroidal anti-inflammatory drugs (NSAIDs), the most commonly used anti-inflammatory drugs, were considered as potential dementia preventive agents in numerous studies. Some animal and human cohort studies suggested a beneficial influence of a daily intake of specific NSAIDs in preventing development or progression of most common types of dementia via reducing distinct dementia pathology [136–138]. However, large randomized clinical-trials or meta-analyses did not provide strong evidence supporting their recommended use, with a special regard to the dangerous side effects of their daily intake, such as potential gastrointestinal bleeding [139–146].

TNF antagonists offer yet another interesting approach to reducing inflammatory activation in humans. These agents are commonly used in autoimmune diseases, such as rheumatoid arthritis, psoriasis or inflammatory bowel diseases [147]. Their effects in controlling excessive immune response are mediated by binding TNF but the exact mechanisms and affinity to soluble and transmembrane TNF vary, hence their clinical use can also differ [26,148,149]. Moreover, some other mechanisms of action have been described, such as lymphotoxin-α blocking by etanercept. Additionally, infliximab has been proven to reduce expression of GM-CSF (granulocyte-macrophage colony stimulating factor) [150,151], while infliximab and adalimumab are able to induce production of immunosuppressive IL-10 by macrophages in vitro [152]. Psoriasis patients treated with etanercept had decreased

expression of IL-1 and IL-8 genes which correlated with reduction in total pro-inflammatory immune response [153]. Importantly, although molecular weight and properties do not allow for free entry of TNF antagonists into the CNS, evidence indicates that these drugs may have protective influence against brain aging.

It seems that both BBB-nonpenetrating and modified, BBB-penetrating, etanercept reduce tauopathy, microgliosis and therefore, neuronal loss in a mouse model of AD. Additionally, they increase PSD95 protein levels indicating synaptic health. This phenomenon may be related to the peripheral effects of the drug and underlines the importance of tackling chronic inflammatory activation in order to maintain physiological neuronal function [154]. Similar observations had been made previously, in a study by Chang et al. [155]. Administration of BBB-penetrating TNF-inhibitor, cTfRMAb-TNFR, resulted in a significant decrease in neuroinflammatory markers, amyloid burden and BBB disruption in an AD mouse model. These results were comparable to those obtained with the use of etanercept in regard to amyloid burden and BBB integrity but not for neuroinflammation portrayed with ICAM-1 concentration. The cognitive performance of tested mice was highest in a group treated with cTfRMAb-TNFR highlighting the crucial role of neuroinflammation in cognitive decline [155]. Use of BBB-penetrating agents remains especially interesting in regard to FTD pathology, in which cytokine production seems to take place mainly in the brain [7].

An experiment conducted in an animal model of metabolic syndrome proved that intraperitoneal administration of infliximab improved lipid profiles in rats—i.e., decreased triglycerides and increased HDL. Additionally, the study group had lower adiponectin concentrations compared to the control, impacting low-grade inflammation. Noteworthy, not all metabolic aspects were normalized and cognitive tests were not included in the study protocol [156]. It may be hypothesized that an up-stream role of TNF in obesity-induced pathology, limits the potential protective effects of TNF inhibition in conditions of already present metabolic syndrome. On the other hand, intracerebroventricular administration of infliximab in a transgenic mouse model of AD resulted in a significant decrease in brain TNF levels, reduction in amyloid burden and tau pathology [157]. Another study conducted in a rat model of VaD, revealed a therapeutic effect of adalimumab administration in treating cognitive deficits resulting from cerebral hypoperfusion. This finding was associated with a reduction in neuronal loss and of microglial activation mediated by NFκB suppression [158].

A systematic literature review of TNF antagonist effects on AD revealed beneficial influence of TNF inhibition on cognition [27]. Most commonly studied agents, etanercept, infliximab and adalimumab, used in rheumatoid arthritis coincided with up to 60–70% reduction in AD incidence in large epidemiological analyzes of rheumatoid arthritis patients, whereas other methods of treatment did not affect AD incidence [159]. Similar results were obtained in patients with psoriasis who were treated with etanercept, infliximab or adalimumab [160]. Rheumatoid arthritis and psoriasis, among other autoimmune diseases, are known risk factors of AD due to the occurrence of persistent inflammatory activation which may constitute a confounding factor for generalized conclusions [161–163]. However, these observations warrant further research in other populations in order to establish a protective role of TNF inhibition on development and progression of various types of dementia. Updates on current clinical trials can be found in Table 2.

**Table 2.** Updates on clinical trials with the use of agents which potentially reduce neuroinflammation.

| Anti-Inflammatory Agent | Clinicaltrial.gov Indentifier | Clinical Trial Phase | Results |
| --- | --- | --- | --- |
| Etanercept (TNF antagonist) | NCT01068353, NCT01716637, NCT00203359, NCT00203320 | 1–2 | Etanercept was well tolerated and showed some trends toward cognitive, functional, and behavioral benefits |

**Table 2.** *Cont.*

| Anti-Inflammatory Agent | Clinicaltrial.gov Indentifier | Clinical Trial Phase | Results |
|---|---|---|---|
| XPro1595/DN-TNF (TNF antagonist) | NCT03943264, NCT05321498, NCT05522387, NCT05318976 | 1,2 | In phase 1 XPro1595 reduced white matter free water and increased the axonal integrity in adults with mild to moderate Alzheimer's disease with signs of inflammation. Phase 2 trials are currently active |
| Dapagliflozin (selective sodium-glucose cotransporter 2 inhibitor) | NCT03801642 | 1/2 | Trial ongoing; Alongside beneficial metabolic effects a potential anti-inflammatory effect via reduction in oxidative stress |
| ALZT-OP1/cromolyn + ibuprofen (mast cell stabilizer + NSAID) | NCT04570644, NCT02547818 | 1/2, 3 | The combination of cromolyn and ibuprofen was safe and well tolerated. The concentrations of cromolyn and ibuprofen observed in the CSF are considered sufficient to titrate the estimated daily amyloid production and the associated inflammatory response in patients with AD. Phase 3 results are to be published. |
| Senicapoc (KCa3.1 blocker) | NCT04804241 | 2 | Phase 2 trial is currently active. Previous animal studies show reduced neuroinflammation, decreased cerebral amyloid load, and enhanced hippocampal neuronal plasticity [164]. |

## 7. Conclusions

TNF, a key pro-inflammatory cytokine, plays a central role in the pathology of several types of dementia. Neuroinflammatory aspects of neurodegenerative diseases are related to various factors, both peripheral and located in the CNS. Pro-inflammatory cytokines prime glial cells, leading to aggravation of neuroinflammation. Unsurprisingly, lifestyle factors, such as diet, have a large impact on cognitive outcomes and should be considered as a crucial step in dementia prevention. So far, insufficient data exists on the use of TNF antagonists in dementia prevention and treatment. The predominance of studies conducted in AD models and the few experiments exploring their effects in other types of dementia may constitute a relevant research gap. Focused randomized clinical trials are warranted in order to establish the efficacy of anti-TNF agents and their mechanisms of action in most common types of dementia. It is still unknown, to what degree neuroinflammation resulting from COVID-19 may affect neurodegenerative processes and cognitive functioning in the long term with ongoing reports of chronic post-COVID complications. However, neuroinflammatory aspects of novel common infectious agents need to be taken into account in order to plan potential interventions focused on reduction in immune senescence in dementia treatment.

**Author Contributions:** Conceptualization, M.Ł. and J.R.; Investigation, M.Ł. and M.W.; Writing—Original Draft Preparation, M.Ł.; Writing—Review and Editing, M.W. and J.R.; Visualization, M.Ł.; Supervision, M.W. and J.R.; Funding Acquisition, M.Ł. and J.R. All authors have read and agreed to the published version of the manuscript.

**Funding:** The publication was prepared under the project financed from the funds granted by the Ministry of Education and Science in the "Regional Initiative of Excellence" program for the years 2019–2022, project number 016/RID/2018/19, the amount of funding 9 354 023,74 PLN.

**Conflicts of Interest:** The authors declare no conflict of interest.

## References

1. Ozben, T.; Ozben, S. Neuro-inflammation and anti-inflammatory treatment options for Alzheimer's disease. *Clin. Biochem.* **2019**, *72*, 87–89. [CrossRef] [PubMed]
2. Irwin, M.R.; Vitiello, M.V. Implications of sleep disturbance and inflammation for Alzheimer's disease dementia. *Lancet Neurol.* **2019**, *18*, 296–306. [CrossRef]
3. Rosenberg, G.A. Extracellular matrix inflammation in vascular cognitive impairment and dementia. *Clin. Sci.* **2017**, *131*, 425–437. [CrossRef] [PubMed]
4. Wang, X.X.; Zhang, B.; Xia, R.; Jia, Q.Y. Inflammation, apoptosis and autophagy as critical players in vascular dementia. *Eur. Rev. Med. Pharmacol. Sci.* **2020**, *24*, 9601–9614. [PubMed]
5. Zhang, L.Y.; Pan, J.; Mamtilahun, M.; Zhu, Y.; Wang, L.; Venkatesh, A.; Shi, R.; Tu, X.; Jin, K.; Wang, Y.; et al. Microglia exacerbate white matter injury via complement C3/C3aR pathway after hypoperfusion. *Theranostics* **2020**, *10*, 74–90. [CrossRef] [PubMed]
6. Frantellizzi, V.; Pani, A.; Ricci, M.; Locuratolo, N.; Fattapposta, F.; De Vincentis, G. Neuroimaging in Vascular Cognitive Impairment and Dementia: A Systematic Review. *J. Alzheimer's Dis.* **2020**, *73*, 1279–1294. [CrossRef]
7. Sjogren, M. Increased intrathecal inflammatory activity in frontotemporal dementia: Pathophysiological implications. *J. Neurol. Neurosurg. Psychiatry* **2004**, *75*, 1107–1111. [CrossRef]
8. Miller, Z.A.; Rankin, K.P.; Graff-Radford, N.R.; Takada, L.T.; Sturm, V.E.; Cleveland, C.M.; Criswell, L.A.; Jaeger, P.A.; Stan, T.; Heggeli, K.A.; et al. TDP-43 frontotemporal lobar degeneration and autoimmune disease. *J. Neurol. Neurosurg. Psychiatry* **2013**, *84*, 956–962. [CrossRef]
9. Miller, Z.A.; Sturm, V.E.; Camsari, G.B.; Karydas, A.; Yokoyama, J.S.; Grinberg, L.T.; Boxer, A.L.; Rosen, H.J.; Rankin, K.P.; Gorno-Tempini, M.L.; et al. Increased prevalence of autoimmune disease within C9 and FTD/MND cohorts Completing the picture. *Neurol. Neuroimmunol. Neuroinflamm.* **2016**, *3*, e301. [CrossRef]
10. McCauley, M.E.; Baloh, R.H. Inflammation in ALS/FTD pathogenesis. *Acta Neuropathol.* **2019**, *137*, 715–730. [CrossRef]
11. Hallett, P.J.; Engelender, S.; Isacson, O. Lipid and immune abnormalities causing age-dependent neurodegeneration and Parkinson's disease. *J. Neuroinflamm.* **2019**, *16*, 153. [CrossRef] [PubMed]
12. Lim, S.; Chun, Y.; Lee, J.S.; Lee, S.J. Neuroinflammation in Synucleinopathies. *Brain Pathol.* **2016**, *26*, 404–409. [CrossRef] [PubMed]
13. Kim, C.; Ho, D.H.; Suk, J.-E.; You, S.; Michael, S.; Kang, J.; Joong Lee, S.; Masliah, E.; Hwang, D.; Lee, H.-J.; et al. Neuron-released oligomeric α-synuclein is an endogenous agonist of TLR2 for paracrine activation of microglia. *Nat. Commun.* **2013**, *4*, 1562. [CrossRef] [PubMed]
14. Ahmadi Rastegar, D.; Hughes, L.P.; Perera, G.; Keshiya, S.; Zhong, S.; Gao, J.; Halliday, G.M.; Schüle, B.; Dzamko, N. Effect of LRRK2 protein and activity on stimulated cytokines in human monocytes and macrophages. *NPJ Parkinson's Dis.* **2022**, *8*, 34. [CrossRef]
15. Xu, E.; Boddu, R.; Abdelmotilib, H.A.; Sokratian, A.; Kelly, K.; Liu, Z.; Bryant, N.; Chandra, S.; Carlisle, S.M.; Lefkowitz, E.J.; et al. Pathological α-synuclein recruits LRRK2 expressing pro-inflammatory monocytes to the brain. *Mol. Neurodegener.* **2022**, *17*, 7. [CrossRef]
16. Trudler, D.; Sanz-Blasco, S.; Eisele, Y.S.; Ghatak, S.; Bodhinathan, K.; Akhtar, M.W.; Lynch, W.P.; Piña-Crespo, J.C.; Talantova, M.; Kelly, J.W.; et al. α-Synuclein Oligomers Induce Glutamate Release from Astrocytes and Excessive Extrasynaptic NMDAR Activity in Neurons, Thus Contributing to Synapse Loss. *J. Neurosci.* **2021**, *41*, 2264–2273. [CrossRef]
17. Cyprien, F.; Courtet, P.; Maller, J.; Meslin, C.; Ritchie, K.; Ancelin, M.-L.; Artero, S. Increased serum C-reactive protein and corpus callosum alterations in older adults. *Aging Dis.* **2019**, *10*, 463–469. [CrossRef]
18. Si, S.; Li, J.; Tewara, M.A.; Xue, F. Genetically Determined Chronic Low-Grade Inflammation and Hundreds of Health Outcomes in the UK Biobank and the FinnGen Population: A Phenome-Wide Mendelian Randomization Study. *Front. Immunol.* **2021**, *12*, 720876. [CrossRef]
19. Tao, Q.; Ang, T.F.A.; DeCarli, C.; Auerbach, S.H.; Devine, S.; Stein, T.D.; Zhang, X.; Massaro, J.; Au, R.; Qiu, W.Q. Association of Chronic Low-grade Inflammation with Risk of Alzheimer Disease in ApoE4 Carriers. *JAMA Netw. Open* **2018**, *1*, e183597. [CrossRef]
20. Fard, M.T.; Cribb, L.; Nolidin, K.; Savage, K.; Wesnes, K.; Stough, C. Is there a relationship between low-grade systemic inflammation and cognition in healthy people aged 60–75 years? *Behav. Brain Res.* **2020**, *383*, 112502. [CrossRef]

21. Cervellati, C.; Trentini, A.; Bosi, C.; Valacchi, G.; Morieri, M.L.; Zurlo, A.; Brombo, G.; Passaro, A.; Zuliani, G. Low-grade systemic inflammation is associated with functional disability in elderly people affected by dementia. *GeroScience* **2018**, *40*, 61–69. [CrossRef] [PubMed]
22. Janowitz, D.; Habes, M.; Toledo, J.B.; Hannemann, A.; Frenzel, S.; Terock, J.; Davatzikos, C.; Hoffmann, W.; Grabe, H.J. Inflammatory markers and imaging patterns of advanced brain aging in the general population. *Brain Imaging Behav.* **2020**, *14*, 1108–1117. [CrossRef] [PubMed]
23. Probert, L. TNF and its receptors in the CNS: The essential, the desirable and the deleterious effects. *Neuroscience* **2015**, *302*, 2–22. [CrossRef] [PubMed]
24. Decourt, B.; Lahiri, D.K.; Sabbagh, M.N. Targeting Tumor Necrosis Factor Alpha for Alzheimer's Disease. *Curr. Alzheimer Res.* **2016**, *14*, 412–425. [CrossRef]
25. Montgomery, S.L.; Bowers, W.J. Tumor necrosis factor-alpha and the roles it plays in homeostatic and degenerative processes within the central nervous system. *J. Neuroimmune Pharmacol.* **2012**, *7*, 42–59. [CrossRef]
26. Tracey, D.; Klareskog, L.; Sasso, E.H.; Salfeld, J.G.; Tak, P.P. Tumor necrosis factor antagonist mechanisms of action: A comprehensive review. *Pharmacol. Ther.* **2008**, *117*, 244–279. [CrossRef]
27. Torres-Acosta, N.; O'Keefe, J.H.; O'Keefe, E.L.; Isaacson, R.; Small, G. The rapeutic Potential of TNF-α Inhibition for Alzheimer's Disease Prevention. *J. Alzheimer's Dis.* **2020**, *78*, 619–626. [CrossRef]
28. Brás, J.P.; Bravo, J.; Freitas, J.; Barbosa, M.A.; Santos, S.G.; Summavielle, T.; Almeida, M.I. TNF-alpha-induced microglia activation requires miR-342: Impact on NF-kB signaling and neurotoxicity. *Cell Death Dis.* **2020**, *11*, 415. [CrossRef]
29. Whiten, D.R.; Brownjohn, P.W.; Moore, S.; De, S.; Strano, A.; Zuo, Y.; Haneklaus, M.; Klenerman, D.; Livesey, F.J. Tumour necrosis factor induces increased production of extracellular amyloid-β- and α-synuclein-containing aggregates by human Alzheimer's disease neurons. *Brain Commun.* **2020**, *2*, fcaa146. [CrossRef]
30. Raffaele, S.; Lombardi, M.; Verderio, C.; Fumagalli, M. TNF Production and Release from Microglia via Extracellular Vesicles: Impact on Brain Functions. *Cells* **2020**, *9*, 2145. [CrossRef]
31. Lindbergh, C.A.; Casaletto, K.B.; Staffaroni, A.M.; Elahi, F.; Walters, S.M.; You, M.; Neuhaus, J.; Contreras, W.R.; Wang, P.; Karydas, A.; et al. Systemic tumor necrosis factor-alpha trajectories relate to brain health in typically aging older adults. *J. Gerontol Ser. A Biol. Sci. Med. Sci.* **2020**, *75*, 1558–1565. [CrossRef] [PubMed]
32. Olsthoorn, L.; Vreeken, D.; Kiliaan, A.J. Gut Microbiome, Inflammation, and Cerebrovascular Function: Link between Obesity and Cognition. *Front. Neurosci.* **2021**, *15*, 761456. [CrossRef] [PubMed]
33. Erion, J.R.; Wosiski-Kuhn, M.; Dey, A.; Hao, S.; Davis, C.L.; Pollock, N.K.; Stranahan, A.M. Obesity elicits interleukin 1-mediated deficits in hippocampal synaptic plasticity. *J. Neurosci.* **2014**, *34*, 2618–2631. [CrossRef] [PubMed]
34. Samara, A.; Murphy, T.; Strain, J.; Rutlin, J.; Sun, P.; Neyman, O.; Sreevalsan, N.; Shimony, J.S.; Ances, B.M.; Song, S.-K.; et al. Neuroinflammation and White Matter Alterations in Obesity Assessed by Diffusion Basis Spectrum Imaging. *Front. Hum. Neurosci.* **2020**, *13*, 464. [CrossRef]
35. Karczewski, J.; Zielińska, A.; Staszewski, R.; Eder, P.; Dobrowolska, A.; Souto, E.B. Obesity and the Brain. *Int. J. Mol. Sci.* **2022**, *23*, 6145. [CrossRef]
36. Litwiniuk, A.; Bik, W.; Kalisz, M.; Baranowska-Bik, A. Inflammasome nlrp3 potentially links obesity-associated low-grade systemic inflammation and insulin resistance with alzheimer's disease. *Int. J. Mol. Sci.* **2021**, *22*, 5603. [CrossRef]
37. Jeppesen, J. Low-grade chronic inflammation and vascular damage in patients with rheumatoid arthritis: Don't forget "metabolic inflammation". *J. Rheumatol.* **2011**, *38*, 595–597. [CrossRef]
38. Calle, M.C.; Fernandez, M.L. Inflammation and type 2 diabetes. *Diabetes Metab.* **2012**, *38*, 183–191. [CrossRef]
39. Duchaine, C.S.; Brisson, C.; Talbot, D.; Gilbert-Ouimet, M.; Trudel, X.; Vézina, M.; Milot, A.; Diorio, C.; Ndjaboué, R.; Giguère, Y.; et al. Psychosocial stressors at work and inflammatory biomarkers: PROspective Quebec Study on Work and Health. *Psychoneuroendocrinology* **2021**, *133*, 105400. [CrossRef]
40. Scheithauer, T.P.M.; Rampanelli, E.; Nieuwdorp, M.; Vallance, B.A.; Verchere, C.B.; van Raalte, D.H.; Herrema, H. Gut Microbiota as a Trigger for Metabolic Inflammation in Obesity and Type 2 Diabetes. *Front. Immunol.* **2020**, *11*, 571731. [CrossRef]
41. Łuc, M.; Misiak, B.; Pawłowski, M.; Stańczykiewicz, B.; Zabłocka, A.; Szcześniak, D.; Pałęga, A.; Rymaszewska, J. Gut microbiota in dementia. Critical review of novel findings and their potential application. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* **2021**, *104*, 110039. [CrossRef] [PubMed]
42. Liang, Y.; Cui, L.; Gao, J.; Zhu, M.; Zhang, Y.; Zhang, H.L. Gut Microbial Metabolites in Parkinson's Disease: Implications of Mitochondrial Dysfunction in the Pathogenesis and Treatment. *Mol. Neurobiol.* **2021**, *58*, 3745–3758. [CrossRef] [PubMed]
43. Kim, S.; Kwon, S.-H.; Kam, T.-I.; Panicker, N.; Karuppagounder, S.S.; Lee, S.; Lee, J.H.; Kim, W.R.; Kook, M.; Foss, C.A.; et al. Transneuronal Propagation of Pathologic α-Synuclein from the Gut to the Brain Models Parkinson's Disease. *Neuron* **2019**, *103*, 627–641.e7. [CrossRef] [PubMed]
44. Giovannini, M.G.; Lana, D.; Traini, C.; Vannucchi, M.G. The microbiota–gut–brain axis and alzheimer disease. From dysbiosis to neurodegeneration: Focus on the central nervous system glial cells. *J. Clin. Med.* **2021**, *10*, 2358. [CrossRef] [PubMed]
45. Al-Obaidi, M.M.J.; Desa, M.N.M. Mechanisms of Blood Brain Barrier Disruption by Different Types of Bacteria, and Bacterial–Host Interactions Facilitate the Bacterial Pathogen Invading the Brain. *Cell Mol. Neurobiol.* **2018**, *38*, 1349–1368. [CrossRef]
46. Morais, L.H.; Schreiber, H.L.; Mazmanian, S.K. The gut microbiota–brain axis in behaviour and brain disorders. *Nat. Rev. Microbiol.* **2021**, *19*, 241–255. [CrossRef]

47. Jang, S.H.; Woo, Y.S.; Lee, S.Y.; Bahk, W.M. The brain–gut–microbiome axis in psychiatry. *Int. J. Mol. Sci.* **2020**, *21*, 7122. [CrossRef]
48. de Erausquin, G.A.; Snyder, H.; Carrillo, M.; Hosseini, A.A.; Brugha, T.S.; Seshadri, S. The chronic neuropsychiatric sequelae of COVID-19: The need for a prospective study of viral impact on brain functioning. *Alzheimer's Dement.* **2021**, *17*, 1056–1065. [CrossRef]
49. Jacob, F.; Pather, S.R.; Huang, W.K.; Zhang, F.; Wong, S.Z.H.; Zhou, H.; Cubitt, B.; Fan, W.; Chen, C.Z.; Xu, M.; et al. Human Pluripotent Stem Cell-Derived Neural Cells and Brain Organoids Reveal SARS-CoV-2 Neurotropism Predominates in Choroid Plexus Epithelium. *Cell Stem Cell* **2020**, *27*, 937–950.e9. [CrossRef]
50. Hu, J.; Jolkkonen, J.; Zhao, C. Neurotropism of SARS-CoV-2 and its neuropathological alterations: Similarities with other coronaviruses. *Neurosci. Biobehav. Rev.* **2020**, *119*, 184–193. [CrossRef]
51. Buzhdygan, T.P.; DeOre, B.J.; Baldwin-Leclair, A.; Bullock, T.A.; McGary, H.M.; Khan, J.A.; Razmpour, R.; Hale, J.F.; Galie, P.A.; Potula, R.; et al. The SARS-CoV-2 spike protein alters barrier function in 2D static and 3D microfluidic in-vitro models of the human blood–brain barrier. *Neurobiol. Dis.* **2020**, *146*, 105131. [CrossRef] [PubMed]
52. Yachou, Y.; El Idrissi, A.; Belapasov, V.; Ait Benali, S. Neuroinvasion, neurotropic, and neuroinflammatory events of SARS-CoV-2: Understanding the neurological manifestations in COVID-19 patients. *Neurol. Sci.* **2020**, *41*, 2657–2669. [CrossRef] [PubMed]
53. Xu, Y.; Zhuang, Y.; Kang, L. A Review of Neurological Involvement in Patients with SARS-CoV-2 Infection. *Med. Sci. Monit.* **2021**, *27*, e932962. [CrossRef]
54. Karnik, M.; Beeraka, N.M.; Uthaiah, C.A.; Nataraj, S.M.; Bettadapura, A.D.S.; Aliev, G.; Madhunapantula, S.V. A Review on SARS-CoV-2-Induced Neuroinflammation, Neurodevelopmental Complications, and Recent Updates on the Vaccine Development. *Mol. Neurobiol.* **2021**, *58*, 4535–4563. [CrossRef] [PubMed]
55. Simonetti, B.; Daly, J.L.; Simón-Gracia, L.; Klein, K.; Weeratunga, S.; Antón-Plágaro, C.; Tobi, A.; Hodgson, L.; Lewis, P.A.; Heesom, K.J.; et al. ESCPE-1 mediates retrograde endosomal sorting of the SARS-CoV-2 host factor Neuropilin-1. *Proc. Natl. Acad. Sci. USA* **2022**, *119*, e2201980119. [CrossRef] [PubMed]
56. Liu, F.; Han, K.; Blair, R.; Kenst, K.; Qin, Z.; Upcin, B.; Wörsdörfer, P.; Midkiff, C.C.; Mudd, J.; Belyaeva, E.; et al. SARS-CoV-2 Infects Endothelial Cells In Vivo and In Vitro. *Front. Cell. Infect. Microbiol.* **2021**, *11*, 701278. [CrossRef]
57. Krasemann, S.; Haferkamp, U.; Pfefferle, S.; Woo, M.S.; Heinrich, F.; Schweizer, M.; Appelt-Menzel, A.; Cubukova, A.; Barenberg, J.; Leu, J.; et al. The blood-brain barrier is dysregulated in COVID-19 and serves as a CNS entry route for SARS-CoV-2. *Stem Cell Rep.* **2022**, *17*, 307–320. [CrossRef]
58. Yang, R.-C.; Huang, K.; Zhang, H.-P.; Li, L.; Zhang, Y.-F.; Tan, C.; Chen, H.-C.; Jin, M.-L.; Wang, X.-R. SARS-CoV-2 productively infects human brain microvascular endothelial cells. *J. Neuroinflamm.* **2022**, *19*, 149. [CrossRef]
59. Zhang, L.; Zhou, L.; Bao, L.; Liu, J.; Zhu, H.; Lv, Q.; Liu, R.; Chen, W.; Tong, W.; Wei, Q.; et al. SARS-CoV-2 crosses the blood–brain barrier accompanied with basement membrane disruption without tight junctions alteration. *Signal Transduct. Target Ther.* **2021**, *6*, 337.
60. Huang, J.; Zheng, M.; Tang, X.; Chen, Y.; Tong, A.; Zhou, L. Potential of SARS-CoV-2 to Cause CNS Infection: Biologic Fundamental and Clinical Experience. *Front. Neurol.* **2020**, *11*, 659. [CrossRef]
61. Wang, C.; Zhang, M.; Garcia, G.; Tian, E.; Cui, Q.; Chen, X.; Sun, G.; Wang, J.; Arumugaswami, V.; Shi, Y. ApoE-Isoform-Dependent SARS-CoV-2 Neurotropism and Cellular Response. *Cell Stem Cell* **2021**, *28*, 331–342.e5. [CrossRef] [PubMed]
62. Zhou, Y.; Xu, J.; Hou, Y.; Leverenz, J.B.; Kallianpur, A.; Mehra, R.; Liu, Y.; Yu, H.; Pieper, A.A.; Jehi, L.; et al. Network medicine links SARS-CoV-2/COVID-19 infection to brain microvascular injury and neuroinflammation in dementia-like cognitive impairment. *Alzheimer's Res. Ther.* **2021**, *13*, 110. [CrossRef] [PubMed]
63. Hernández, V.S.; Zetter, M.A.; Guerra, E.C.; Hernández-Araiza, I.; Karuzin, N.; Hernández-Pérez, O.R.; Eiden, L.E.; Zhang, L. ACE2 expression in rat brain: Implications for COVID-19 associated neurological manifestations. *Exp. Neurol.* **2021**, *345*, 113837. [CrossRef]
64. Zhang, Y.; Archie, S.R.; Ghanwatkar, Y.; Sharma, S.; Nozohouri, S.; Burks, E.; Mdzinarishvili, A.; Liu, Z.; Abbruscato, T.J. Potential role of astrocyte angiotensin converting enzyme 2 in the neural transmission of COVID-19 and a neuroinflammatory state induced by smoking and vaping. *Fluids Barriers CNS* **2022**, *19*, 46. [CrossRef] [PubMed]
65. Baig, A.M.; Khaleeq, A.; Ali, U.; Syeda, H. Evidence of the COVID-19 Virus Targeting the CNS: Tissue Distribution, Host-Virus Interaction, and Proposed Neurotropic Mechanisms. *ACS Chem. Neurosci.* **2020**, *11*, 995–998. [CrossRef] [PubMed]
66. Pallanti, S.; Grassi, E.; Makris, N.; Gasic, G.P.; Hollander, E. Neurocovid-19: A clinical neuroscience-based approach to reduce SARS-CoV-2 related mental health sequelae. *J. Psychiatr. Res.* **2020**, *130*, 215–217. [CrossRef] [PubMed]
67. Paterson, R.W.; Brown, R.L.; Benjamin, L.; Nortley, R.; Wiethoff, S.; Bharucha, T.; Jayaseelan, D.L.; Kumar, G.; Raftopoulos, R.E.; Zambreanu, L.; et al. The emerging spectrum of COVID-19 neurology: Clinical, radiological and laboratory findings. *Brain* **2020**, *143*, 3104–3120.
68. Bhaskar, S.; Sinha, A.; Banach, M.; Mittoo, S.; Weissert, R.; Kass, J.S.; Rajagopal, S.; Pai, A.R.; Kutty, S. Cytokine Storm in COVID-19—Immunopathological Mechanisms, Clinical Considerations, and Therapeutic Approaches: The REPROGRAM Consortium Position Paper. *Front. Immunol.* **2020**, *11*, 1648. [CrossRef]
69. Gasmi, A.; Tippairote, T.; Mujawdiya, P.K.; Gasmi Benahmed, A.; Menzel, A.; Dadar, M.; Bjørklund, G. Neurological Involvements of SARS-CoV2 Infection. *Mol. Neurobiol.* **2021**, *58*, 944–949.
70. Jarrahi, A.; Ahluwalia, M.; Khodadadi, H.; Da Silva Lopes Salles, E.; Kolhe, R.; Hess, D.C.; Vale, F.; Kumar, M.; Baban, B.; Vaibhav, K.; et al. Neurological consequences of COVID-19: What have we learned and where do we go from here? *J. Neuroinflamm.* **2020**, *17*, 286. [CrossRef]

71. Tizenberg, B.N.; Brenner, L.A.; Lowry, C.A.; Okusaga, O.O.; Benavides, D.R.; Hoisington, A.J.; Benros, M.E.; Stiller, J.W.; Kessler, R.C.; Postolache, T.T. Biological and Psychological Factors Determining Neuropsychiatric Outcomes in COVID-19. *Curr. Psychiatry Rep.* **2021**, *23*, 68. [CrossRef] [PubMed]
72. Murta, V.; Villarreal, A.; Ramos, A.J. Severe Acute Respiratory Syndrome Coronavirus 2 Impact on the Central Nervous System: Are Astrocytes and Microglia Main Players or Merely Bystanders? *ASN Neuro* **2020**, *12*, 1759091420954960. [CrossRef] [PubMed]
73. Muccioli, L.; Pensato, U.; Cani, I.; Guarino, M.; Cortelli, P.; Bisulli, F. COVID-19–Associated Encephalopathy and Cytokine-Mediated Neuroinflammation. *Ann. Neurol.* **2020**, *88*, 860–861. [CrossRef]
74. Pilotto, A.; Padovani, A. Reply to the Letter "COVID-19-Associated Encephalopathy and Cytokine-Mediated Neuroinflammation". *Ann. Neurol.* **2020**, *88*, 861–862. [CrossRef]
75. Connors, J.M.; Levy, J.H. COVID-19 and its implications for thrombosis and anticoagulation. *Blood* **2020**, *135*, 2033–2040. [CrossRef]
76. Tirelli, U.; Taibi, R.; Chirumbolo, S. Post COVID syndrome: A new challenge for medicine. *Eur. Rev. Med. Pharmacol. Sci.* **2021**, *25*, 4422–4425. [CrossRef]
77. Stevenson, R.; Samokhina, E.; Rossetti, I.; Morley, J.W.; Buskila, Y. Neuromodulation of Glial Function During Neurodegeneration. *Front. Cell. Neurosci.* **2020**, *14*, 278. [CrossRef]
78. Ferrer, I. Oligodendrogliopathy in neurodegenerative diseases with abnormal protein aggregates: The forgotten partner. *Prog. Neurobiol.* **2018**, *169*, 24–54. [CrossRef]
79. Acioglu, C.; Li, L.; Elkabes, S. Contribution of astrocytes to neuropathology of neurodegenerative diseases. *Brain Res.* **2021**, *1758*, 147291. [CrossRef]
80. Gamage, R.; Wagnon, I.; Rossetti, I.; Childs, R.; Niedermayer, G.; Chesworth, R.; Gyengesi, E. Cholinergic Modulation of Glial Function During Aging and Chronic Neuroinflammation. *Front. Cell. Neurosci.* **2020**, *14*, 577912. [CrossRef]
81. Zhou, Y.; Song, W.M.; Andhey, P.S.; Swain, A.; Levy, T.; Miller, K.R.; Poliani, P.L.; Cominelli, M.; Grover, S.; Gilfillan, S.; et al. Human and mouse single-nucleus transcriptomics reveal TREM2-dependent and TREM2-independent cellular responses in Alzheimer's disease. *Nat. Med.* **2020**, *26*, 131–142. [CrossRef] [PubMed]
82. Court, J.A.; Lloyd, S.; Johnson, M.; Griffiths, M.; Birdsall, N.J.M.; Piggott, M.A.; Oakley, A.; Ince, P.; Perry, E.; Perry, R. Nicotinic and muscarinic cholinergic receptor binding in the human hippocampal formation during development and aging. *Dev. Brain Res.* **1997**, *101*, 93–105. [CrossRef]
83. Sorrentino, Z.A.; Giasson, B.I.; Chakrabarty, P. α-Synuclein and astrocytes: Tracing the pathways from homeostasis to neurodegeneration in Lewy body disease. *Acta Neuropathol.* **2019**, *138*, 1–21. [CrossRef]
84. Radford, R.A.; Morsch, M.; Rayner, S.L.; Cole, N.J.; Pountney, D.L.; Chung, R.S. The established and emerging roles of astrocytes and microglia in amyotrophic lateral sclerosis and frontotemporal dementia. *Front. Cell. Neurosci.* **2015**, *9*, 414. [CrossRef] [PubMed]
85. Iadecola, C. The neurovascular unit coming of age: A journey through neurovascular coupling in health and disease. *Neuron* **2017**, *96*, 17–42. [CrossRef]
86. Porchet, R.; Probst, A.; Bouras, C.; Dráberová, E.; Dráber, P.; Riederer, B.M. Analysis of gial acidic fibrillary protein in the human entorhinal cortex during aging and in Alzheimer's disease. *Proteomics* **2003**, *3*, 1476–1485. [CrossRef]
87. Gaikwad, S.; Puangmalai, N.; Bittar, A.; Montalbano, M.; Garcia, S.; McAllen, S.; Bhatt, N.; Sonawane, M.; Sengupta, U.; Kayed, R. Tau oligomer induced HMGB1 release contributes to cellular senescence and neuropathology linked to Alzheimer's disease and frontotemporal dementia. *Cell Rep.* **2021**, *36*, 109419. [CrossRef]
88. Price, B.R.; Norris, C.M.; Sompol, P.; Wilcock, D.M. An emerging role of astrocytes in vascular contributions to cognitive impairment and dementia. *J. Neurochem.* **2018**, *144*, 644–650. [CrossRef]
89. Kim, J.H.; Ko, P.W.; Lee, H.W.; Jeong, J.Y.; Lee, M.G.; Kim, J.H.; Lee, W.-H.; Yu, R.; Oh, W.-J.; Suk, K. Astrocyte-derived lipocalin-2 mediates hippocampal damage and cognitive deficits in experimental models of vascular dementia. *Glia* **2017**, *65*, 1471–1490. [CrossRef]
90. Llorente, I.L.; Xie, Y.; Mazzitelli, J.A.; Hatanaka, E.A.; Cinkornpumin, J.; Miller, D.R.; Lin, Y.; Lowry, W.E.; Carmichael, S.T. Patient-derived glial enriched progenitors repair functional deficits due to white matter stroke and vascular dementia in rodents. *Sci. Transl. Med.* **2021**, *13*, eaaz6747. [CrossRef]
91. DiSabato, D.J.; Quan, N.; Godbout, J.P. Neuroinflammation: The devil is in the details. *J. Neurochem.* **2016**, *139*, 136–153. [CrossRef] [PubMed]
92. López-Valdés, H.E.; Martínez-Coria, H. The Role of Neuroinflammation in Age-Related Dementias. *Rev. Investig. Clin.* **2016**, *68*, 40–48.
93. Ginhoux, F.; Greter, M.; Leboeuf, M.; Nandi, S.; See, P.; Gokhan, S.; Mehler, M.F.; Conway, S.J.; Ng, L.G.; Stanley, E.R.; et al. Fate Mapping Analysis Reveals That Adult Microglia Derive from Primitive Macrophages. *Science* **2010**, *330*, 841–845. [CrossRef] [PubMed]
94. Niraula, A.; Sheridan, J.F.; Godbout, J.P. Microglia Priming with Aging and Stress. *Neuropsychopharmacology* **2017**, *42*, 318–333. [CrossRef] [PubMed]
95. Norden, D.M.; Godbout, J.P. Review: Microglia of the aged brain: Primed to be activated and resistant to regulation. *Neuropathol. Appl. Neurobiol.* **2013**, *39*, 19–34. [CrossRef]
96. Wynne, A.M.; Henry, C.J.; Huang, Y.; Cleland, A.; Godbout, J.P. Protracted downregulation of CX3CR1 on microglia of aged mice after lipopolysaccharide challenge. *Brain Behav. Immun.* **2010**, *24*, 1190–1201. [CrossRef]

97. Njie Malick, G.; Boelen, E.; Stassen, F.R.; Steinbusch, H.W.M.; Borchelt, D.R.; Streit, W.J. Ex vivo cultures of microglia from young and aged rodent brain reveal age-related changes in microglial function. *Neurobiol. Aging* **2012**, *33*, 195.e1–195.e12. [CrossRef]
98. Lee, S.; Varvel, N.H.; Konerth, M.E.; Xu, G.; Cardona, A.E.; Ransohoff, R.M.; Lamb, B.T. CX3CR1 deficiency alters microglial activation and reduces beta-amyloid deposition in two Alzheimer's disease mouse models. *Am. J. Pathol.* **2010**, *177*, 2549–2562. [CrossRef]
99. Hampel, H.; Caraci, F.; Cuello, A.C.; Caruso, G.; Nisticò, R.; Corbo, M.; Baldacci, F.; Toschi, N.; Garaci, F.; Chiesa, P.A.; et al. A Path Toward Precision Medicine for Neuroinflammatory Mechanisms in Alzheimer's Disease. *Front. Immunol.* **2020**, *11*, 456. [CrossRef]
100. Lee, C.Y.D.; Daggett, A.; Gu, X.; Jiang, L.L.; Langfelder, P.; Li, X.; Wang, N.; Zhao, Y.; Park, C.S.; Cooper, Y.; et al. Elevated TREM2 Gene Dosage Reprograms Microglia Responsivity and Ameliorates Pathological Phenotypes in Alzheimer's Disease Models. *Neuron* **2018**, *97*, 1032–1048.e5. [CrossRef]
101. Yeh, F.L.; Hansen, D.V.; Sheng, M. TREM2, Microglia, and Neurodegenerative Diseases. *Trends Mol. Med.* **2017**, *23*, 512–533. [CrossRef] [PubMed]
102. Deczkowska, A.; Weiner, A.; Amit, I. The Physiology, Pathology, and Potential Therapeutic Applications of the TREM2 Signaling Pathway. *Cell* **2020**, *181*, 1207–1217. [CrossRef] [PubMed]
103. Ewers, M.; Franzmeier, N.; Suárez-Calvet, M.; Morenas-Rodriguez, E.; Caballero, M.A.A.; Kleinberger, G.; Piccio, L.; Cruchaga, C.; Deming, Y.; Dichgans, M.; et al. Increased soluble TREM2 in cerebrospinal fluid is associated with reduced cognitive and clinical decline in Alzheimer's disease. *Sci. Transl. Med.* **2019**, *11*, eaav6221. [CrossRef] [PubMed]
104. Jay, T.R.; Hirsch, A.M.; Broihier, M.L.; Miller, C.M.; Neilson, L.E.; Ransohoff, R.M.; Lamb, B.T.; Landreth, G.E. Disease progression-dependent effects of TREM2 deficiency in a mouse model of Alzheimer's disease. *J. Neurosci.* **2017**, *37*, 637–647. [CrossRef] [PubMed]
105. Leyns, C.E.G.; Ulrich, J.D.; Finn, M.B.; Stewart, F.R.; Koscal, L.J.; Serrano, J.R.; Robinson, G.O.; Anderson, E.; Colonna, M.; Holtzman, D.M. TREM2 deficiency attenuates neuroinflammation and protects against neurodegeneration in a mouse model of tauopathy. *Proc. Natl. Acad. Sci. USA* **2017**, *114*, 11524–11529. [CrossRef]
106. Parhizkar, S.; Arzberger, T.; Brendel, M.; Kleinberger, G.; Deussing, M.; Focke, C.; Nuscher, B.; Xiong, M.; Ghasemigharagoz, A.; Katzmarski, N.; et al. Loss of TREM2 function increases amyloid seeding but reduces plaque-associated ApoE. *Nat. Neurosci.* **2019**, *22*, 191–204. [CrossRef]
107. Li, C.; Zhao, B.; Lin, C.; Gong, Z.; An, X. TREM2 inhibits inflammatory responses in mouse microglia by suppressing the PI3K/NF-κB signaling. *Cell Biol. Int.* **2019**, *43*, 360–372. [CrossRef]
108. Carmona-Abellan, M.; Martinez-Valbuena, I.; Marcilla, I.; DiCaudo, C.; Gil, I.; Nuñez, J.; Luquin, M.-R. Microglia is associated with p-Tau aggregates in the olfactory bulb of patients with neurodegenerative diseases. *Neurol. Sci.* **2021**, *42*, 1473–1482. [CrossRef]
109. Stancu, I.C.; Cremers, N.; Vanrusselt, H.; Couturier, J.; Vanoosthuyse, A.; Kessels, S.; Lodder, C.; Brône, B.; Huaux, F.; Octave, J.-N.; et al. Aggregated Tau activates NLRP3–ASC inflammasome exacerbating exogenously seeded and non-exogenously seeded Tau pathology in vivo. *Acta Neuropathol.* **2019**, *137*, 599–617. [CrossRef]
110. Mancuso, R.; Fryatt, G.; Cleal, M.; Obst, J.; Pipi, E.; Monzón-Sandoval, J.; Ribe, E.; Winchester, L.; Webber, C.; Nevado, A.; et al. CSF1R inhibitor JNJ-40346527 attenuates microglial proliferation and neurodegeneration in P301S mice. *Brain* **2019**, *142*, 3243–3264. [CrossRef]
111. Radford, R.; Rcom-H'cheo-Gauthier, A.; Wong, M.B.; Eaton, E.D.; Quilty, M.; Blizzard, C.; Norazit, A.; Meedeniya, A.; Vickers, J.; Gai, W.P.; et al. The degree of astrocyte activation in multiple system atrophy is inversely proportional to the distance to α-synuclein inclusions. *Mol. Cell. Neurosci.* **2015**, *65*, 68–81. [CrossRef] [PubMed]
112. Valdinocci, D.; Radford, R.A.W.; Siow, S.M.; Chung, R.S.; Pountney, D.L. Potential modes of intercellular α-synuclein transmission. *Int. J. Mol. Sci.* **2017**, *18*, 469. [CrossRef] [PubMed]
113. Hartnell, I.J.; Blum, D.; Nicoll, J.A.R.; Dorothee, G.; Boche, D. Glial cells and adaptive immunity in frontotemporal dementia with tau pathology. *Brain* **2021**, *144*, 724–745. [CrossRef] [PubMed]
114. Strohm, L.; Behrends, C. Glia-specific autophagy dysfunction in ALS. *Semin. Cell Dev. Biol.* **2020**, *99*, 172–182. [CrossRef] [PubMed]
115. Chandrasekaran, A.; Dittlau, K.S.; Corsi, G.I.; Haukedal, H.; Doncheva, N.T.; Ramakrishna, S.; Ambardar, S.; Salcedo, C.; Schmidt, S.I.; Zhang, Y.; et al. Astrocytic reactivity triggered by defective autophagy and metabolic failure causes neurotoxicity in frontotemporal dementia type 3. *Stem Cell Rep.* **2021**, *16*, 2736–2751. [CrossRef]
116. Ghasemi, M.; Keyhanian, K.; Douthwright, C. Glial cell dysfunction in c9orf72-related amyotrophic lateral sclerosis and frontotemporal dementia. *Cells* **2021**, *10*, 249. [CrossRef]
117. Vasefi, M.; Hudson, M.; Ghaboolian-Zare, E. Diet Associated with Inflammation and Alzheimer's Disease. *J. Alzheimer's Dis. Rep.* **2019**, *3*, 299–309. [CrossRef]
118. Ozawa, M.; Shipley, M.; Kivimaki, M.; Singh-Manoux, A.; Brunner, E.J. Dietary pattern, inflammation and cognitive decline: The Whitehall II prospective cohort study. *Clin. Nutr.* **2017**, *36*, 506–512. [CrossRef]
119. Shin, D.; Kwon, S.C.; Kim, M.H.; Lee, K.W.; Choi, S.Y.; Shivappa, N.; Hébert, J.R.; Chung, H.-K. Inflammatory potential of diet is associated with cognitive function in an older adult Korean population. *Nutrition* **2018**, *55–56*, 56–62. [CrossRef]
120. Hayden, K.M.; Beavers, D.P.; Steck, S.E.; Hebert, J.R.; Tabung, F.K.; Shivappa, N.; Casanova, R.; Manson, J.E.; Padula, C.B.; Salmoirago-Blotcher, E.; et al. The association between an inflammatory diet and global cognitive function and incident dementia in older women: The Women's Health Initiative Memory Study. *Alzheimer's Dement.* **2017**, *13*, 1187–1196. [CrossRef]
121. Frith, E.; Shivappa, N.; Mann, J.R.; Hébert, J.R.; Wirth, M.D.; Loprinzi, P.D. Dietary inflammatory index and memory function: Population-based national sample of elderly Americans. *Br. J. Nutr.* **2018**, *119*, 552–558. [CrossRef]

122. Saita, D.; Ferrarese, R.; Foglieni, C.; Esposito, A.; Canu, T.; Perani, L.; Ceresola, E.R.; Visconti, L.; Burioni, R.; Clementi, M.; et al. Adaptive immunity against gut microbiota enhances apoE-mediated immune regulation and reduces atherosclerosis and western-diet-related inflammation. *Sci. Rep.* **2016**, *6*, 29353. [CrossRef] [PubMed]
123. Milošević, M.; Arsić, A.; Cvetković, Z.; Vučić, V. Memorable Food: Fighting Age-Related Neurodegeneration by Precision Nutrition. *Front. Nutr.* **2021**, *8*, 688086. [CrossRef] [PubMed]
124. Shivappa, N.; Steck, S.E.; Hurley, T.G.; Hussey, J.R.H.J. Dietary Inflammatory Index. *Public Health Nutr.* **2014**, *17*, 1689–1696. [CrossRef] [PubMed]
125. Kesse-Guyot, E.; Assmann, K.E.; Andreeva, V.A.; Touvier, M.; Neufcourt, L.; Shivappa, N.; Hébert, J.R.; Wirth, M.D.; Hercberg, S.; Galan, P.; et al. Long-term association between the dietary inflammatory index and cognitive functioning: Findings from the SU.VI.MAX study. *Eur. J. Nutr.* **2017**, *56*, 1647–1655. [CrossRef]
126. Ostan, R.; Béné, M.C.; Spazzafumo, L.; Pinto, A.; Donini, L.M.; Pryen, F.; Charrouf, Z.; Valentini, L.; Lochs, H.; Bourdel-Marchasson, I.; et al. Impact of diet and nutraceutical supplementation on inflammation in elderly people. Results from the RISTOMED study, an open-label randomized control trial. *Clin. Nutr.* **2016**, *35*, 812–818. [CrossRef]
127. Kim, E.R.; Kim, S.R.; Cho, W.; Lee, S.G.; Kim, S.H.; Kim, J.H.; Choi, E.; Kim, J.-H.; Yu, J.-W.; Lee, B.-W.; et al. Short Term Isocaloric Ketogenic Diet Modulates NLRP3 Inflammasome Via B-hydroxybutyrate and Fibroblast Growth Factor 21. *Front. Immunol.* **2022**, *13*, 843520. [CrossRef]
128. Al-Aubaidy, H.A.; Dayan, A.; Deseo, M.A.; Itsiopoulos, C.; Jamil, D.; Hadi, N.R.; Thomas, C. Twelve-week mediterranean diet intervention increases citrus bioflavonoid levels and reduces inflammation in people with type 2 diabetes mellitus. *Nutrients* **2021**, *13*, 1133. [CrossRef]
129. Georgoulis, M.; Yiannakouris, N.; Tenta, R.; Fragopoulou, E.; Kechribari, I.; Lamprou, K.; Perraki, E.; Vagiakis, E.; Kontogianni, M.D. A weight-loss Mediterranean diet/lifestyle intervention ameliorates inflammation and oxidative stress in patients with obstructive sleep apnea: Results of the "MIMOSA" randomized clinical trial. *Eur. J. Nutr.* **2021**, *60*, 3799–3810. [CrossRef]
130. Ojo, O.; Ojo, O.O.; Zand, N.; Wang, X. The Effect of Dietary Fibre on Gut Microbiota, Lipid Profile, and Inflammatory Markers in Patients with Type 2 Diabetes: A Systematic Review and Meta-Analysis of Randomised Controlled Trials. *Nutrients* **2021**, *13*, 1805. [CrossRef]
131. Shivappa, N.; Hebert, J.R.; Marcos, A.; Diaz, L.E.; Gomez, S.; Nova, E.; Michels, N.; Arouca, A.; González-Gil, E.; Frederic, G.; et al. Association between dietary inflammatory index and inflammatory markers in the HELENA study. *Mol. Nutr. Food Res.* **2017**, *61*, 1–23. [CrossRef]
132. Casas, R.; Urpi-Sardà, M.; Sacanella, E.; Arranz, S.; Corella, D.; Castañer, O.; Lamuela-Raventós, R.-M.; Salas-Salvadó, J.; Lapetra, J.; Portillo, M.P.; et al. Anti-Inflammatory Effects of the Mediterranean Diet in the Early and Late Stages of Atheroma Plaque Development. *Mediat. Inflamm.* **2017**, *2017*, 3674390. [CrossRef] [PubMed]
133. Mazzoli, A.; Spagnuolo, M.S.; Gatto, C.; Nazzaro, M.; Cancelliere, R.; Crescenzo, R.; Iossa, S.; Cigliano, L. Adipose tissue and brain metabolic responses to western diet—is there a similarity between the two? *Int. J. Mol. Sci.* **2020**, *21*, 786. [CrossRef]
134. Jena, P.K.; Sheng, L.; Nguyen, M.; Di Lucente, J.; Hu, Y.; Li, Y.; Maezawa, I.; Jin, L.-W.; Wan, Y.-J.Y. Dysregulated bile acid receptor-mediated signaling and IL-17A induction are implicated in diet-associated hepatic health and cognitive function. *Biomark. Res.* **2020**, *8*, 59. [CrossRef]
135. Godfrey, J.R.; Pincus, M.; Kovacs-Balint, Z.; Feczko, E.; Earl, E.; Miranda-Dominguez, O.; Fair, D.A.; Jones, S.R.; Locke, J.; Sanchez, M.M.; et al. Obesogenic diet-associated C-reactive protein predicts reduced central dopamine and corticostriatal functional connectivity in female rhesus monkeys. *Brain Behav. Immun.* **2020**, *88*, 166–173. [CrossRef]
136. Weng, J.; Zhao, G.; Weng, L.; Guan, J. Aspirin using was associated with slower cognitive decline in patients with Alzheimer's disease. *PLoS ONE* **2021**, *16*, e0252969. [CrossRef]
137. Sekiyama, K.; Fujita, M.; Sekigawa, A.; Takamatsu, Y.; Waragai, M.; Takenouchi, T.; Sugama, S.; Hashimoto, M. Ibuprofen ameliorates protein aggregation and astrocytic gliosis, but not cognitive dysfunction, in a transgenic mouse expressing dementia with Lewy bodies-linked P123H β-synuclein. *Neurosci. Lett.* **2012**, *515*, 97–101. [CrossRef]
138. Szekely, C.A.; Breitner, J.C.S.; Fitzpatrick, A.L.; Rea, T.D.; Psaty, B.M.; Kuller, L.H.; Zandi, P.P. NSAID use and dementia risk in the Cardiovascular Health Study: Role of APOE and NSAID type. *Neurology* **2008**, *70*, 17–24. [CrossRef]
139. Knopman, D.S.; Petersen, R.C. The quest for dementia prevention does not include an aspirin a day. *Neurology* **2020**, *95*, 105–106. [CrossRef]
140. Tabet, N.; Feldman, H. Ibuprofen for Alzheimer's disease. *Cochrane Database Syst. Rev.* **2003**, CD004031. [CrossRef]
141. Ryan, J.; Storey, E.; Murray, A.M.; Woods, R.L.; Wolfe, R.; Reid, C.M.; Nelson, M.R.; Chong, T.T.; Williamson, J.D.; Ward, S.A.; et al. Randomized placebo-controlled trial of the effects of aspirin on dementia and cognitive decline. *Neurology* **2020**, *95*, E320–E331. [CrossRef]
142. Li, H.; Li, W.; Zhang, X.; Ma, X.C.; Zhang, R.W. Aspirin Use on Incident Dementia and Mild Cognitive Decline: A Systematic Review and Meta-Analysis. *Front. Aging Neurosci.* **2021**, *12*, 578071. [CrossRef]
143. Jordan, F.; Quinn, T.J.; McGuinness, B.; Passmore, P.; Kelly, J.P.; Tudur Smith, C.; Murphy, K.; Devane, D. Aspirin and other non-steroidal anti-inflammatory drugs for the prevention of dementia. *Cochrane Database Syst. Rev.* **2020**, CD011459. [CrossRef]
144. Rands, G.; Orrell, M. Aspirin for vascular dementia. *Cochrane Database Syst. Rev.* **2000**, *2012*, CD001296. [CrossRef]
145. Jaturapatporn, D.; Mgekn, I.; Mccleery, J.; Tabet, N. Aspirin, steroidal and non-steroidal anti-inflammatory drugs for the treatment of Alzheimer's disease. *Cochrane Database Syst. Rev.* **2012**, *2*, CD006378. [CrossRef]

146. Veronese, N.; Stubbs, B.; Maggi, S.; Thompson, T.; Schofield, P.; Muller, C.; Tseng, P.; Lin, P.; Carvalho, A.F.; Solmi, M. Low-Dose Aspirin Use and Cognitive Function in Older Age: A Systematic Review and Meta-analysis. *J. Am. Geriatr. Soc.* **2017**, *65*, 1763–1768. [CrossRef]
147. Gottlieb, A.B. Tumor necrosis factor blockade: Mechanism of action. *J. Investig. Dermatol. Symp. Proc.* **2007**, *12*, 1–4. [CrossRef]
148. Levin, A.D.; Wildenberg, M.E.; van den Brink, G.R. Mechanism of Action of Anti-TNF Therapy in Inflammatory Bowel Disease. *J. Crohn's Colitis* **2016**, *10*, 989–997. [CrossRef]
149. Mitoma, H.; Horiuchi, T.; Tsukamoto, H.; Ueda, N. Molecular mechanisms of action of anti-TNF-α agents—Comparison among therapeutic TNF-α antagonists. *Cytokine* **2018**, *101*, 56–63. [CrossRef]
150. Kirman, I.; Whelan, R.L.; Nielsen, O.H. Infliximab: Mechanism of action beyond TNF-α neutralization in inflammatory bowel disease. *Eur. J. Gastroenterol. Hepatol.* **2004**, *16*, 639–641. [CrossRef]
151. Agnholt, J.; Kelsen, J.; Brandsborg, B.; Jakobsen, N.O.; Dahlerup, J.F. Increased production of granulocyte-macrophage colony-stimulating factor in Crohn's disease—A possible target for infliximab treatment. *Eur. J. Gastroenterol. Hepatol.* **2004**, *16*, 649–655. [CrossRef]
152. Vos, A.C.W.; Wildenberg, M.E.; Duijvestein, M.; Verhaar, A.P.; Van Den Brink, G.R.; Hommes, D.W. AntiTumor necrosis factor-α antibodies induce regulatory macrophages in an Fc region-dependent manner. *Gastroenterology* **2011**, *140*, 221–230.e3. [CrossRef] [PubMed]
153. Gottlieb, A.B.; Chamian, F.; Masud, S.; Cardinale, I.; Abello, M.V.; Lowes, M.A.; Chen, F.; Magliocco, M.; Krueger, J.G. TNF Inhibition Rapidly Down-Regulates Multiple Proinflammatory Pathways in Psoriasis Plaques. *J. Immunol.* **2005**, *175*, 2721–2729. [CrossRef]
154. Ou, W.; Yang, J.; Simanauskaite, J.; Choi, M.; Castellanos, D.M.; Chang, R.; Sun, J.; Jagadeesan, N.; Parfitt, K.D.; Cribbs, D.H.; et al. Biologic TNF-α inhibitors reduce microgliosis, neuronal loss, and tau phosphorylation in a transgenic mouse model of tauopathy. *J. Neuroinflamm.* **2021**, *18*, 312. [CrossRef]
155. Chang, R.; Knox, J.; Chang, J.; Derbedrossian, A.; Vasilevko, V.; Cribbs, D.; Boado, R.J.; Pardridge, W.M.; Sumbria, R.K. Blood-Brain Barrier Penetrating Biologic TNF-α Inhibitor for Alzheimer's Disease. *Mol. Pharm.* **2017**, *14*, 2340–2349. [CrossRef]
156. Abdelhamid, Y.A.; Elyamany, M.F.; Al-Shorbagy, M.Y.; Badary, O.A. Effects of TNF-α antagonist infliximab on fructose-induced metabolic syndrome in rats. *Hum. Exp. Toxicol.* **2021**, *40*, 801–811. [CrossRef]
157. Shi, J.Q.; Shen, W.; Chen, J.; Wang, B.R.; Zhong, L.L.; Zhu, Y.W.; Zhu, H.-Q.; Zhang, Q.-Q.; Zhang, Y.-D.; Xu, J. Anti-TNF-α reduces amyloid plaques and tau phosphorylation and induces CD11c-positive dendritic-like cell in the APP/PS1 transgenic mouse brains. *Brain Res.* **2011**, *1368*, 239–247. [CrossRef]
158. Xu, J.J.; Guo, S.; Xue, R.; Xiao, L.; Kou, J.N.; Liu, Y.Q.; Han, J.-Y.; Fu, J.-J.; Wei, N. Adalimumab ameliorates memory impairments and neuroinflammation in chronic cerebral hypoperfusion rats. *Aging* **2021**, *13*, 14001–14014. [CrossRef]
159. Chou, R.C.; Kane, M.; Ghimire, S.; Gautam, S.; Gui, J. Treatment for Rheumatoid Arthritis and Risk of Alzheimer's Disease: A Nested Case-Control Analysis. *CNS Drugs* **2016**, *30*, 1111–1120. [CrossRef]
160. Zhou, M.; Xu, R.; Kaelber, D.C.; Gurney, M.E. Tumor Necrosis Factor (TNF) blocking agents are associated with lower risk for Alzheimer's disease in patients with rheumatoid arthritis and psoriasis. *PLoS ONE* **2020**, *15*, e0229819. [CrossRef]
161. Zhao, J.; Li, T.; Wang, J. Association between psoriasis and dementia: A systematic review. *Neurologia* **2021**. *Online ahead of print*.
162. Trzeciak, P.; Herbet, M.; Dudka, J. Common Factors of Alzheimer's Disease and Rheumatoid Arthritis—Pathomechanism and Treatment. *Molecules* **2021**, *26*, 6038. [CrossRef] [PubMed]
163. Lin, T.M.; Chen, W.S.; Sheu, J.J.; Chen, Y.H.; Chen, J.H.; Chang, C.C. Autoimmune rheumatic diseases increase dementia risk in middle-aged patients: A nationwide cohort study. *PLoS ONE* **2018**, *13*, e0186475. [CrossRef] [PubMed]
164. Jin, L.W.; Lucente, J.D.; Nguyen, H.M.; Singh, V.; Singh, L.; Chavez, M.; Bushong, T.; Wulff, H.; Maezawa, I. Repurposing the KCa3.1 inhibitor senicapoc for Alzheimer's disease. *Ann. Clin. Transl. Neurol.* **2019**, *6*, 723–738. [CrossRef] [PubMed]

## 6.2 Coping of Chronically-Ill Patients during the COVID-19 Pandemic: Comparison between Four Groups

International Journal of
*Environmental Research and Public Health*

MDPI

*Article*

# Coping of Chronically-Ill Patients during the COVID-19 Pandemic: Comparison between Four Groups

**Mateusz Łuc [1,*], Marcin Pawłowski [1], Arkadiusz Jaworski [2], Karolina Fila-Witecka [1], Dorota Szcześniak [1], Hanna Augustyniak-Bartosik [3], Dorota Zielińska [4], Aleksandra Stefaniak [5], Anna Pokryszko-Dragan [6], Justyna Chojdak-Łukasiewicz [6], Magdalena Krajewska [3], Tomasz Pawłowski [1], Jacek C. Szepietowski [5] and Joanna Rymaszewska [1]**

[1] Department of Psychiatry, Wroclaw Medical University, 50-367 Wroclaw, Poland
[2] Students Research Association, Department of Psychiatry, Wroclaw Medical University, 50-367 Wroclaw, Poland
[3] Dialysis Unit, Department of Nephrology and Transplantology, Wroclaw Medical University, 50-556 Wroclaw, Poland
[4] Department of Nephrology and Transplantology, Wroclaw Medical University, 50-556 Wroclaw, Poland
[5] Department of Dermatology, Venerology and Allergology, Wroclaw Medical University, 50-367 Wroclaw, Poland
[6] Department of Neurology, Wroclaw Medical University, 50-556 Wroclaw, Poland
* Correspondence: mateusz.luc@student.umw.edu.pl

**Abstract:** In many countries, the COVID-19 pandemic led to healthcare reorganization limiting access to diagnostic or therapeutic procedures for chronically-ill patients. In this article, we describe the psychological consequences and coping strategies of several groups of chronically-ill patients. During the cross-sectional survey conducted in 2020, we enrolled 398 patients with four different chronic conditions (psoriasis, multiple sclerosis, and patients who have undergone a kidney transplant or received dialysis). The study sample was examined regarding the experienced stress levels (Perceived Stress Scale) and coping strategies (Brief-COPE). All four groups of patients most commonly declared using problem-focused coping strategies and least commonly reported the use of avoidant coping. Higher levels of perceived stress strongly correlated with self-blaming. The participants who declared previous psychiatric treatment or psychotherapy were more likely to use self-blaming, behavioral disengagement, substance use, and avoidant coping, while previous psychotherapy additionally correlated with emotion-focused coping. Group comparison identifies patients with a chronic neurological disease, such as multiple sclerosis, at higher risk of a less beneficial coping profile than kidney transplant recipients. Further focus on education and early interventions in at-risk individuals is needed, and widely targeted mental health programs are indicated in order to improve the mental health of patients suffering from chronic diseases.

**Keywords:** pandemic; COVID-19; SARS-CoV-2; chronic diseases; psychopathology; coping; chronic kidney disease; multiple sclerosis; psoriasis

check for updates

**Citation:** Łuc, M.; Pawłowski, M.; Jaworski, A.; Fila-Witecka, K.; Szcześniak, D.; Augustyniak-Bartosik, H.; Zielińska, D.; Stefaniak, A.; Pokryszko-Dragan, A.; Chojdak-Łukasiewicz, J.; et al. Coping of Chronically-Ill Patients during the COVID-19 Pandemic: Comparison between Four Groups. *Int. J. Environ. Res. Public Health* **2023**, *20*, 4814. https://doi.org/10.3390/ijerph20064814

Academic Editor: Anna Maria Giannini

Received: 13 February 2023
Revised: 26 February 2023
Accepted: 3 March 2023
Published: 9 March 2023



## 1. Introduction

COVID-19 has quickly spread from its place of origin worldwide, leading to a global pandemic emergency. By the end of 2022, the number of confirmed COVID-19 cases has reached over 649 billion worldwide, with reports indicating insufficient testing and detection in numerous regions [1,2]. Initial preventive actions were aimed at the reduction of viral transmission and therefore alleviating the hospitalization burden in order to avoid the collapse of healthcare systems. Prior to the vaccine development, actions oriented toward the reduction of SARS-CoV-2 transmission initially involved long and recurring lockdowns, travel, and social restrictions and resulted in a major reorganization of daily life. These restrictions took a severe toll on the mental health of citizens, the size of which

is yet to be accounted for, along with the long-term consequences of both viral infection and social isolation stemming from introduced restrictions [3,4].

In many countries, healthcare reorganization resulted in limited access to diagnostic or therapeutic options for novel cases of other diseases [5]. Additionally, various factors contributed to decreased availability of required medical services needed for the maintenance of chronic diseases. Among these factors are (1) personnel shortage stemming from exposure to SARS-CoV-2 and following quarantines and/or infections; (2) reorganization of clinical wards, with medical professionals being transferred to temporary COVID-19 wards and thereby decreased number of professionals remaining at their standard placement and (3) necessity to secure back-up hospital beds in case of a rising incidence during following COVID-19 waves. These factors required additional effort from patients and eventually resulted in a transient reduction of planned appointments, administered procedures, and check-ups [6–9]. On the other hand, anxiety related to medical institution visits and potential SARS-CoV-2 infection disabled another group of patients from obtaining regular professional medical care.

Numerous reports illustrate the effects of the pandemic on the mental health of the general population, indicating a large distribution of COVID-19-related anxiety symptoms, with some researchers proposing a separate term, COVID stress syndrome [10]. After the early pandemic phases, the acute stress factor gained chronic character leading to a novel manifestation of pandemic-associated mental disorders. Currently, many researchers report on factors contributing or correlated with mental health outcomes in the general population, in students, or in medical professionals [11–14]. However, much less is known about the consequences of COVID-19-related psychological strain on vulnerable populations, such as individuals at risk for mental disorders, the elderly, and those frequently requiring services of the health care system—patients treated for chronic diseases, such as neurological disorders, dermatological conditions, or patients undergoing dialyses. The early reports indicate a higher incidence of mental disorders such as depression and anxiety in chronically-ill patients [15]. Additionally, studies that focus mostly on the quality of life of people diagnosed with certain chronic medical conditions suggest that the impact of primary diagnosis significantly varies and depends on the characteristics of the disease [16–18]. Our previous research showed that 48% of chronically-ill patients presented clinically significant psychopathological symptoms in the early stages of the pandemic [19]. This scale of mental health burden significantly exceeds the levels in the general population ranging from 14% to 27% during the first wave of the COVID-19 pandemic [20,21], and highlights the importance of the predisposing individual traits and potential differences between groups of patients which have not been described so far.

Individual strategies for dealing with stress are described as coping and are believed to significantly mediate the varied outcomes of global stress factors, such as the COVID-19 pandemic, on one's mental health. The impact of this mediation remains difficult to quantify. However, some studies present results indicating that used coping strategies in response to either acute or chronic stressful events may actually be responsible for over 50% of mental health outcomes, such as anxiety, depression, or somatization [22,23]. For example, people dealing with stress via avoidance were found to be more likely to manifest anxiety, depression, or symptoms of an eating disorder, while people who respond to stress with problem-solving are at lower risk of these outcomes [24]. Patients diagnosed with multiple sclerosis and using positive reframing, emotional support, instrumental support, religion, planning, and self-distraction were found to be more likely to exhibit post-traumatic growth [25]. There are several classifications of coping strategies that are based on the action direction towards/from a stressful stimulus or emotion use. What is important, the adaptive and detrimental characteristics of each coping strategy may vary depending on the chronicity of the stimulus, its range, and characteristics but also on external factors, such as societal or cultural differences [26].

In this article, we describe the psychological consequences and coping strategies of several groups of chronically-ill patients. We aim to distinguish stress-predisposing

characteristics related to ongoing chronic disease or sociodemographic factors and also to indicate beneficial and deleterious coping strategies common in this population. With the rapid occurrence of novel SARS-CoV-2 variants, this knowledge may allow better identification of chronically-ill patients at risk of deterioration of their mental health and implementation of early interventions. Additionally, it may serve for better organization of necessary health care in a potential need of temporary lockdown reintroduction.

## 2. Materials and Methods

### 2.1. Study Design and Settings

We have recruited chronically-ill patients with diagnoses of psoriasis, multiple sclerosis (MS), patients who had had a kidney transplant, and patients with chronic kidney disease receiving dialyses to participate in a cross-sectional survey carried out between May and October 2020. The local Bioethical Committee at the Wroclaw Medical University approved the study (KB-468/2020; KB-469/2020; KB-470/2020; KB-417/2020). For detailed methods and procedures, see Pawłowski et al., 2022 [19].

Participants took part in a survey voluntarily and without financial reward. Participation was anonymous, and data was secured at all stages of the study. Questionnaires were delivered both via an online form and printed format, as a consequence of COVID-19 restrictions and for patients' safety. We used Computer-Assisted Web Interviewing (CAWI) to conduct an online version of a survey and shared it with patients via websites and profiles of MS Societies and Polish Psoriasis. The printed forms were provided to patients at the University Clinical Hospital in Wroclaw, Poland. In the preliminary section of the survey, respondents filled out an informed consent, so participation and processing of data were possible. The online version required confirmation of informed consent so that respondents only then could continue and submit the questionnaire. In the printed version, the respondents confirmed informed consent by signing the form and completing the survey. The participants were evaluated for perceived levels of stress and employed coping strategies. Demographic variables, as well as pandemic-related data, such as previous quarantines, COVID-19 exposures, or infections, were also contained in the survey. We downloaded the data file from an online survey and transcribed manually the information from paper questionnaires to the database.

### 2.2. Participants

The inclusion criteria for the recruitment were: (1) a previous diagnosis of psoriasis (P), multiple sclerosis (MS), being an adult kidney transplant recipient in the past (T) or undergoing dialysis treatments at the present time (D); (2) age over 18 and (3) providing informed consent to participate. Due to the online version of the survey, no medical documents nor confirmations were required in order to preserve anonymity in P and MS groups. Participants from T and D were recruited only at the hospital. Hence, their medical data and documentation were available in order to confirm diagnoses. Exclusion criteria were: (1) age under 18; (2) inability to provide informed consent, and (3) incomplete survey. Psychological and psychiatric data were collected but did not disqualify from participation.

### 2.3. Measurements & Outcomes Measures

The psychometric tools used in the study were selected by a team of experts from different fields (psychiatry, psychology, neurology, dermatology, and nephrology) and were based on appropriate literature. The survey consisted of the following sections:

Sociodemographic and COVID-19 exposure data.

*The Perceived Stress Scale 10* (PSS-10) allows for the assessment of the experienced stress level. It comprises 10 questions intended to evaluate the subjective level of stress [27]. The questionnaire was validated in the Polish population and deemed satisfactory, with validity scores (Cronbach's alpha) around 0.8. Respondents marked their answers on a 5-point scale ranging from 0 (never) to 4 (very often). The results from all items were

summed up to calculate the final score of the PSS-10. The total score reflects the intensity of perceived stress.

*The Brief Coping Orientation to Problems Experienced Inventory* (Brief-COPE; Polish adaptation: *Juczyński & Ogińska-Bulik, 2009*) allows for the assessment of strategies employed in order to cope with a stressful event [28]. The inventory has 28 items (2 questions per each strategy) and was validated in the Polish population. Participants indicate their answers on a 4-point scale ranging from 0 (almost never) to 3 (almost always), and the sum for each strategy is divided by 2. Fourteen strategies can be grouped into three larger categories: problem-focused (active coping, use of informational support, positive reframing and planning), emotion-focused (emotional support, venting, humor, acceptance, religion, and self-blame), and avoidant (self-distraction, denial, substance use, and behavioral disengagement) coping [29].

### 2.4. Statistical Analysis

The statistical analysis of the obtained results was performed with the use of IBM SPSS Statistics v. 26 (SPSS Inc., Chicago, IL, USA) software. All data were assessed for parametric or non-parametric distribution. The minimum, maximum, mean, and standard deviation were calculated, whereas for coping strategies and perceived stress level, parameter distribution was assessed for kurtosis and skewness. Due to the relatively large sample, Kolmogorov–Smirnov test results were calculated. Analyzed variables were evaluated using the Mann–Whitney U test and Spearman correlations. Differences between several groups were assessed by the Kruskal–Wallis 1-way analysis of variance on ranks. We additionally performed the mixed-design analysis of variance with a focus on overall coping strategies in a (3) $\times$ 4 model. Simple effect tests with Bonferroni adjustment were calculated. A 2-sided $p$-value $\leq 0.05$ was considered to be statistically significant. As incomplete surveys were excluded from the study, no missing data was encountered.

## 3. Results

### 3.1. Participants' Characteristics

In the study, 398 participants aged from 18 to 89 (M = 45.74; SD = 17.04) were enrolled. According to their diagnosis, they were divided into 4 subgroups: 95 psoriasis patients, 128 patients with a diagnosis of multiple sclerosis, 102 recipients of kidney transplants, and 73 patients receiving dialyses. There was a moderate predominance of women in the study group (n = 238; 59.8%). More than half of the study participants declared to have a higher education, whereas one-third declared a secondary education. In the early phase of the pandemic, most of the study population did not declare a reduced time of work or change in their responsibilities due to the COVID-19 emergence. Similarly, at that time, most of the participants were not exposed to SARS-CoV-2 at their place of employment, nor had they previously been quarantined. In addition, 18.3% were previously treated by a psychiatrist, and 28% had undergone previous psychotherapy. Measured with the use of PSS-10, 62.4% of participants exhibited a moderate level of perceived stress, while the percentages for high and low intensity were 15.7% and 21.8%, respectively. The detailed characteristics of the study group are summarized in Table 1.

The study groups had dissimilar sociodemographic profiles in terms of sex, age, marital status, psychiatric treatment, psychotherapy, and duration of illness.

The predominant perceived stress level was moderate in all groups except for psoriasis patients, with more than half of them reporting either low or high intensity of perceived stress. The low-stress level was most commonly observed in psoriasis patients (32.6%) and kidney transplant recipients (28.4%). The high-stress level was more frequently reported by patients with multiple sclerosis (25%).

**Table 1.** Detailed sociodemographic data.

| | **Total n = 398** | **Psoriasis (P) n = 95 (23.9%)** | **Multiple Sclerosis (MS) n = 128 (32.2%)** | **Kidney Transplant (T) n = 102 (25.6%)** | **Dialysis (D) n = 73 (18.3%)** | ***p* Value** |
|---|---|---|---|---|---|---|
| **Sex, female** | 238 (59.8%) | 58 (61%) | 97 (76%) | 49 (48%) | 49 (48%) | $p < 0.001$ |
| **Average Age (SD)** | 45.74 (17.04) | 40.19 (16.87) | 35.63 (9.68) | 51.59 (13.42) | 63.40 (15.49) | $p < 0.001$<br>P vs. KT $p < 0.0001$<br>P vs. D $p < 0.0001$<br>MS vs. KT $p < 0.0001$<br>MS vs. D $p < 0.0001$<br>KT vs. D $p < 0.005$ |
| **Illness duration in years (SD)** | 10.71 (10.27) | 16.65 (13.76) | 12.27 (8.92) | 7.77 (6.80) | 3.52 (3.62) | $p < 0.001$<br>P vs. KT $p < 0.0001$<br>P vs. D $p < 0.0001$<br>MS vs. KT $p < 0.001$<br>MS vs. P $p < 0.0001$<br>KT vs. D $p < 0.001$ |
| **Marital status**<br>S—Single<br>R—Relationship<br>M—Married<br>Se—Separated<br>D—Divorced<br>W—Widow(er) | <br>S—69 (17.6%)<br>R—72 (18.4%)<br>M—205 (52.3%)<br>Se—2 (0.5%)<br>D—26 (6.6%)<br>W—18 (4.6%) | <br>S—21 (22.1%)<br>R—20 (21.1%)<br>M—41 (43.2%)<br>Se—0 (0%)<br>D—8 (8.4%)<br>W—4 (4.2%) | <br>S—27 (21.1%)<br>R—36 (28.1%)<br>M—58 (45.3%)<br>Se—1 (0.8%)<br>D—5 (3.9%)<br>W—1 (0.8%) | <br>S—17 (16.7%)<br>R— 10 (9.8%)<br>M—60 (58.8%)<br>Se—0 (0%)<br>D—10 (9.8%)<br>W—2 (2%) | <br>S—4 (5.5%)<br>R—6 (8.2%)<br>M—46 (63%)<br>Se—1 (1.4%)<br>D—3 (4.1%)<br>W—11 (15.1%) | $p < 0.001$<br>P vs. D $p < 0.002$<br>MS vs. KT $p < 0.04$<br>MS vs. D $p < 0.0001$ |
| **Psychiatric treatment** | 73 (18.3%) | 19 (20%) | 38 (29.7%) | 13 (12.7%) | 3 (4.1%) | $p < 0.0001$ |
| **Psychotherapy** | 111 (28%) | 29 (31%) | 68 (53.1%) | 11 (10.8%) | 3 (4.1%) | $p < 0.001$ |
| **Infection or quarantine of a close one** | 6 (2%) | 1 (1%) | 4 (3,1%) | 1 (1%) | 0 (0%) | Not significant (NS) |
| **COVID 19 status** | Contact—2 (2%)<br>Quarantine—12 (5%)<br>Infection—2 (1%) | Contact—2 (2,1%)<br>Quarantine—5 (5,3%)<br>Infection—0 (0%) | Contact—no data<br>Quarantine—7 (5,4%)<br>Infection—2 (1,6%) | no data | no data | NS<br>NS<br>NS |
| **Stress level (PSS-10)**<br>Low<br>Moderate<br>High | <br>86 (21.8%)<br>246 (62.4%)<br>62 (15.7%) | <br>31 (32.6%)<br>46 (48.4%)<br>16 (16.8%) | <br>11 (8.6%)<br>85 (66.4%)<br>32 (25%) | <br>29 (28.4%)<br>69 (67.6%)<br>4 (3.9%) | <br>15 (20.5%)<br>46 (63%)<br>9 (12.3%) | |

### *3.2. Coping Strategies in the Studied Population*

The studied population reported the most common use of problem-focused coping strategies, such as active coping, planning, and positive reframing. Among emotion-focused strategies, emotional support and acceptance were most likely to be employed by the study participants. On the other hand, the studied group of chronically-ill patients claimed to be less likely to use humor and avoidant strategies, with special emphasis on substance use. The detailed data is provided in Table 2.

**Table 2.** Perceived stress and coping strategies.

| | ***R*** | ***M*** | ***SD*** | ***Mdn*** | ***Sk*** | ***Kurt*** | ***D*** |
|---|---|---|---|---|---|---|---|
| Perceived Stress Scale (PSS-10) | | | | | | | |
| Perceived level of stress | 3–37 | 18.95 | 7.22 | 18.00 | 0.15 | −0.43 | 0.07 ** |
| Coping Orientation to Problems Experienced Inventory (Brief-COPE) | | | | | | | |
| Acceptance | 0–3 | 1.74 | 0.84 | 2.00 | −0.49 | −0.39 | 0.20 ** |
| Active coping | 0–3 | 1.84 | 0.84 | 2.00 | −0.52 | −0.29 | 0.17 ** |
| Self-blame | 0–3 | 1.08 | 0.87 | 1.00 | 0.49 | −0.60 | 0.17 ** |
| Planning | 0–3 | 1.76 | 0.84 | 2.00 | −0.42 | −0.43 | 0.20 ** |
| Humor | 0–3 | 0.90 | 0.68 | 1.00 | 0.54 | 0.09 | 0.16 ** |
| Emotional support | 0–3 | 1.60 | 0.92 | 2.00 | −0.15 | −0.86 | 0.18 ** |

**Table 2.** *Cont.*

| | *R* | *M* | *SD* | *Mdn* | *Sk* | *Kurt* | *D* |
|---|---|---|---|---|---|---|---|
| Use of informational support | 0–3 | 1.50 | 0.87 | 1.50 | −0.09 | −0.72 | 0.13 ** |
| Positive reframing | 0–3 | 1.58 | 0.84 | 1.50 | −0.16 | −0.66 | 0.17 ** |
| Venting | 0–3 | 1.20 | 0.73 | 1.50 | 0.04 | −0.58 | 0.16 ** |
| Self-distraction | 0–3 | 1.52 | 0.81 | 1.50 | −0.17 | −0.66 | 0.14 ** |
| Denial | 0–3 | 0.83 | 0.77 | 1.00 | 0.68 | −0.26 | 0.18 ** |
| Behavioral disengagement | 0–3 | 0.78 | 0.74 | 0.50 | 0.70 | −0.32 | 0.19 ** |
| Substance use | 0–3 | 0.33 | 0.64 | 0.00 | 2.20 | 4.66 | 0.42 ** |
| Religion | 0–3 | 0.90 | 0.99 | 0.50 | 0.72 | −0.78 | 0.25 ** |
| Problem-Focused Coping | 0–3 | 1.67 | 0.69 | 1.75 | −0.54 | 0.04 | 0.10 ** |
| Emotion-Focused Coping | 0–3 | 1.24 | 0.50 | 1.25 | −0.35 | 0.48 | 0.07 ** |
| Avoidant Coping | 0–3 | 0.86 | 0.49 | 0.88 | 0.49 | 0.54 | 0.08 ** |

** $p < 0.01$; M—arithmetic mean; SD—standard deviation; Mdn—median; Sk—skewness; Kurt—kurtosis; D—Kolmogorov–Smirnov test result.

### *3.3. The Differences in Coping Strategies between Studied Groups*

Due to the varied characteristics of distinct subgroups, we performed the Kruskall–Wallis H test in order to analyze differences in coping strategies between the groups of patients. MS and T groups were significantly more likely to use acceptance compared to the P group. Additionally, they employed active coping more frequently than D patients. The MS group had a higher tendency to self-blame than T and also to use positive reframing and emotion-focused coping more than P. Moreover, MS claimed to use venting and self-distraction more frequently than P and T.

D employed emotional support more often than P and employed denial more often than P and T. Both MS and D were more prone to behavioral disengagement and avoidant coping than P and T. On the other hand, P and MS reported higher substance use and less religious coping than T and D. The detailed data is provided in Table 3.

**Table 3.** Comparison of coping strategies between study subgroups.

| | **Psoriasis (P) (n = 95)** | | **Multiple sclerosis (MS) (n = 128)** | | **Kidney Transplant (T) (n = 102)** | | **Dialysis (D) (n = 73)** | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *Mdn* | *Mrang* | *Mdn* | *Mrang* | *Mdn* | *Mrang* | *Mdn* | *Mrang* | *H(3)* | *p* | $\varepsilon^2$ | *Post-hoc* |
| a | 1.50 | 166.42 | 2.00 | 223.93 | 2.00 | 206.85 | 2.00 | 189.45 | 15.28 | 0.002 | 0.038 | a.**P** < a.**MS**; a.**P** < a.**T** |
| b | 2.00 | 187.49 | 2.00 | 212.08 | 2.00 | 213.21 | 1.50 | 173.90 | 7.93 | 0.047 | 0.020 | b.**D** < b.**MS**; b.**D** < b.**T** |
| c | 1.00 | 198.41 | 1.00 | 225.46 | 1.00 | 171.11 | 1.00 | 195.06 | 13.35 | 0.004 | 0.034 | c.**T** < c.**MS** |
| d | 1.50 | 178.17 | 2.00 | 203.00 | 2.00 | 215.47 | 2.00 | 198.80 | 5.62 | 0.132 | 0.014 | |
| e | 1.00 | 197.66 | 1.00 | 218.13 | 1.00 | 185.13 | 1.00 | 189.31 | 5.85 | 0.119 | 0.015 | |
| f | 1.50 | 177.38 | 1.50 | 190.33 | 2.00 | 215.01 | 2.00 | 222.68 | 9.56 | 0.023 | 0.024 | f.**P** < f.**D** |
| g | 1.50 | 176.12 | 1.50 | 200.97 | 1.50 | 211.73 | 1.50 | 210.27 | 5.92 | 0.115 | 0.015 | |
| h | 1.50 | 178.48 | 2.00 | 220.18 | 1.50 | 199.25 | 1.50 | 190.93 | 8.02 | 0.046 | 0.020 | h.**P** < h.**MS** |
| i | 1.00 | 187.95 | 1.50 | 228.41 | 1.00 | 173.56 | 1.50 | 200.07 | 14.84 | 0.002 | 0.037 | i.**P** < i.**MS**; i.**T** < i.**MS** |
| j | 1.50 | 181.82 | 1.50 | 220.44 | 1.50 | 183.95 | 1.50 | 207.51 | 9.00 | 0.029 | 0.023 | j.**P** < j.**MS**; j.**T** < j.**MS** |
| k | 0.50 | 176.66 | 1.00 | 211.59 | 0.50 | 185.80 | 1.00 | 227.17 | 11.47 | 0.009 | 0.029 | k.**P** < k.**D**; k.**T** < k.**D** |
| l | 0.50 | 170.66 | 0.50 | 213.01 | 0.50 | 183.95 | 1.00 | 235.08 | 17.61 | 0.001 | 0.044 | l.**P** < l.**MS**; l.**P** < l.**D**; l.**T** < l.**D** |
| m | 0.00 | 227.59 | 0.00 | 227.32 | 0.00 | 163.09 | 0.00 | 165.05 | 48.94 | <0.001 | 0.123 | m.**T** < m.**P**; m.**T** < m.**MS**; m.**D** < m.**P**; m.**D** < m.**MS** |
| n | 0.00 | 167.91 | 0.00 | 182.77 | 1.00 | 226.44 | 1.00 | 232.32 | 23.48 | <0.001 | 0.059 | n.**P** < n.**T**; n.**P** < n.**D**; n.**MS** < n.**T** n.**MS** < n.**D** |
| o | 1.63 | 176.59 | 1.81 | 209.51 | 1.88 | 214.11 | 1.75 | 191.34 | 6.78 | 0.079 | 0.017 | |
| p | 1.17 | 174.92 | 1.33 | 215.76 | 1.25 | 194.11 | 1.33 | 210.51 | 7.82 | 0.050 | 0.020 | p.**P** < p.**MS** |
| q | 0.75 | 182.68 | 0.88 | 230.63 | 0.75 | 164.80 | 0.88 | 215.29 | 22.20 | <0.001 | 0.056 | q.**P** < q.**MS**; q.**T** < q.**MS** q.**T** < q.**D** |

a—acceptance; b—active coping; c—self-blame; d—planning; e—humor; f—emotional support; g—use of informational support; h—positive reframing; i—venting; j—self-distraction; k—denial; l—behavioral disengagement; m—substance use; n—religion; o—problem-focused coping; p—emotion-focused coping; q—avoidant coping. Mdn—median; Mrang—mean range; H—Kruskall-Wallis test result; *p*—*p*-value; $\varepsilon^2$—effect size.

We additionally confirmed our results with the mixed-design analysis of variance with a focus on overall coping strategies, problem-focused coping, emotion-focused coping, and avoidant coping in the studied groups. All four groups of patients most commonly declared using problem-focused coping strategies and least commonly reported the use of avoidant coping.

The P group used problem-focused coping significantly more frequently than MS and T. The MS and D were more likely to employ emotion-focused coping strategies than P. Moreover, MS used avoidant coping more commonly than P and T, whereas T were also less likely to use avoidant coping than D (Figure 1). Additional data is provided in Supplementary File 1.

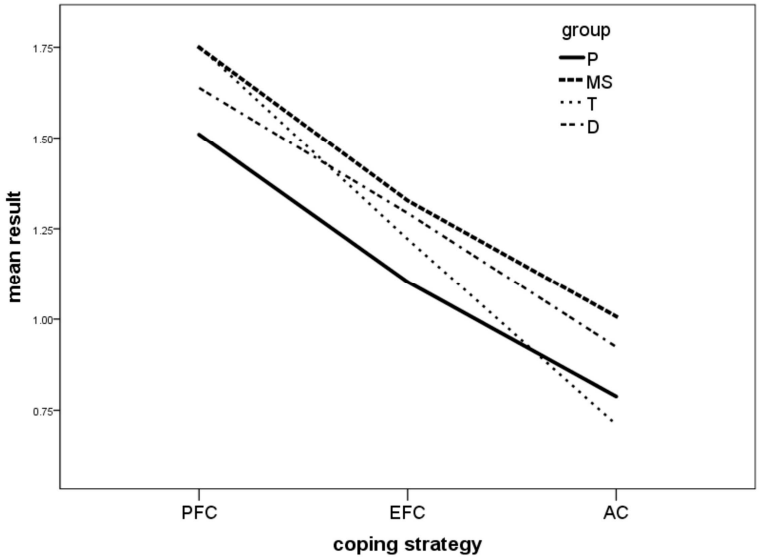



**Figure 1.** Coping strategies in four groups of patients—interaction effect. P—psoriasis, MS—multiple sclerosis, T—kidney transplant recipients, D—dialysis patients. PFC—problem-focused coping, EFC—emotion-focused coping, AC—avoidant coping.

*3.4. The Coping Strategies in Relation to Sociodemographic Characteristics*

In order to assess the influence of age on employed coping strategies, we performed the rho Spearman correlation test. In our population, older age slightly favored religious coping and correlated with a decrease in all of the other coping strategies, with the exception of behavioral disengagement, positive reframing, and denial, for which no statistically significant correlations were found.

The U Mann–Whitney range test revealed that female participants were significantly more likely to cope with the use of self-blame, emotional and informational support, positive reframing, venting, denial, and behavioral disengagement. Considering the classification of coping strategies, they were also more likely than male participants to employ emotion-focused and avoidant coping.

The participants employed at the time of the study were significantly more often using active coping, planning, emotional and instrumental support, venting, self-distraction, substance use, and avoidant coping and had a tendency to problem-focused coping ($p = 0.058$) compared to the unemployed.

Based on analysis with the use of the Kruskall–Wallis test, we observed that participants with a middle or higher level of education were more likely to cope with the use of acceptance, self-blame, and emotion-focused coping. Additionally, a higher level of education also favored coping by planning, humor, positive reframing, and venting.

Considering the amount of performed tests, the results of these analyses are provided in Supplementary File 1.

### 3.5. The Coping Strategies in Relation to Previous Psychiatric Treatment and Psychotherapy Use

We performed the U Mann–Whitney test to evaluate how previous psychiatric treatment and psychotherapy correlate with employed coping strategies (Table 4). We have noticed that participants who declared previous psychiatric treatment were more likely to report self-blaming, behavioral disengagement, substance use, and avoidant coping and less likely to use religious coping. Participants who reported previous psychotherapy were also more likely to cope with the use of the above-mentioned coping strategies (self-blame, behavioral disengagement, substance use, and avoidant coping) but were additionally more inclined to humor, venting, self-distraction, and emotion-focused coping. They were also less likely to report religious coping.

**Table 4.** Coping strategies in relation to previous psychiatric treatment and psychotherapy.

| | **Psychiatric Treatment** | | | | | | | **Psychotherapy** | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **No (n = 325)** | | **Yes (n = 73)** | | | | | **No (n = 286)** | | **Yes (n = 111)** | | | | |
| | ***Mdn*** | ***Mrang*** | ***Mdn*** | ***Mrang*** | ***U*** | ***p*** | ***rg*** | ***Mdn*** | ***Mrang*** | ***Mdn*** | ***Mrang*** | ***U*** | ***p*** | ***rg*** |
| Acceptance | 2.00 | 202.50 | 1.50 | 186.15 | 10,888.00 | 0.262 | 0.08 | 2.00 | 197.21 | 2.00 | 203.62 | 15,360.50 | 0.609 | 0.03 |
| Active coping | 2.00 | 201.67 | 2.00 | 189.85 | 11,158.00 | 0.419 | 0.06 | 2.00 | 200.10 | 2.00 | 196.17 | 15,558.50 | 0.755 | 0.02 |
| Self-blame | 1.00 | 186.04 | 1.50 | 259.40 | 7489.50 | <0.001 | 0.37 | 1.00 | 180.04 | 1.50 | 247.85 | 10,450.50 | <0.001 | 0.34 |
| Planning | 2.00 | 201.30 | 2.00 | 191.47 | 11,276.00 | 0.499 | 0.05 | 2.00 | 199.25 | 2.00 | 198.36 | 15,802.00 | 0.943 | 0.00 |
| Humor | 1.00 | 199.94 | 1.00 | 197.53 | 11,718.50 | 0.868 | 0.01 | 1.00 | 192.90 | 1.00 | 214.73 | 14,127.00 | 0.081 | 0.11 |
| Emotional support | 2.00 | 201.26 | 1.50 | 191.68 | 11,291.50 | 0.511 | 0.05 | 2.00 | 201.48 | 1.50 | 192.62 | 15,164.50 | 0.480 | 0.04 |
| Use of informational support | 1.50 | 199.46 | 1.50 | 199.68 | 11,849.50 | 0.988 | 0.00 | 1.50 | 196.53 | 1.50 | 205.36 | 15,167.00 | 0.484 | 0.04 |
| Positive reframing | 1.50 | 203.77 | 1.50 | 180.49 | 10,475.00 | 0.111 | 0.12 | 1.50 | 198.28 | 1.50 | 200.86 | 15,666.00 | 0.837 | 0.01 |
| Venting | 1.00 | 197.08 | 1.50 | 210.27 | 11,076.00 | 0.366 | 0.07 | 1.00 | 190.41 | 1.50 | 221.14 | 13,415.50 | 0.014 | 0.15 |
| Self-distraction | 1.50 | 197.75 | 1.50 | 207.31 | 11,292.50 | 0.514 | 0.05 | 1.50 | 191.88 | 1.50 | 217.35 | 13,836.50 | 0.044 | 0.13 |
| Denial | 1.00 | 197.07 | 1.00 | 210.34 | 11,071.50 | 0.359 | 0.07 | 0.50 | 194.49 | 1.00 | 210.63 | 14,582.50 | 0.195 | 0.08 |
| Behavioral disengagement | 0.50 | 194.62 | 1.00 | 221.22 | 10,277.00 | 0.066 | 0.13 | 0.50 | 190.83 | 1.00 | 220.06 | 13,535.00 | 0.019 | 0.15 |
| Substance use | 0.00 | 194.00 | 0.00 | 223.97 | 10,076.50 | 0.010 | 0.15 | 0.00 | 190.84 | 0.00 | 220.01 | 13,540.50 | 0.004 | 0.15 |
| Religion | 1.00 | 206.14 | 0.00 | 169.92 | 9703.50 | 0.011 | 0.18 | 1.00 | 206.03 | 0.00 | 180.87 | 13,861.00 | 0.040 | 0.13 |
| Problem-Focussed Coping | 1.75 | 203.56 | 1.63 | 181.40 | 10,541.50 | 0.136 | 0.11 | 1.75 | 200.33 | 1.75 | 195.56 | 15,491.50 | 0.709 | 0.02 |
| Emotion-Focussed Coping | 1.25 | 198.40 | 1.25 | 204.38 | 11,506.50 | 0.688 | 0.03 | 1.25 | 192.84 | 1.33 | 214.88 | 14,110.50 | 0.085 | 0.11 |
| Avoidant Coping | 0.75 | 192.80 | 0.88 | 229.33 | 9685.00 | 0.014 | 0.18 | 0.75 | 186.64 | 0.88 | 230.84 | 12,339.00 | 0.001 | 0.22 |

Mdn—median; Mrang—mean range; U—U Mann-Whitney test result; *p*—*p*-value; rg—Glass's estimator of effect size.

### 3.6. The Coping Strategies in Relation to Time Since Diagnosis and Stress Level

In order to assess the influence of perceived level of stress and disease length on coping strategies, we used the Spearman rho correlation matrix (Table 5). Longer time since initial diagnosis correlated inversely with self-blaming, while the use of other coping strategies was not affected by this variable. However, higher levels of stress strongly correlated with self-blaming and showed a moderate correlation with avoidant coping, behavioral disengagement, denial, and venting. Weak positive associations were detected for substance use, self-distraction, and emotion-focused coping, while weak negative associations were observed for planning, positive reframing, active coping, emotional support, acceptance, and problem-focused coping.

**Table 5.** Rho Spearman range correlations for coping strategies and disease length and coping strategies and perceived stress level.

| | Disease Length (Years) | Perceived Stress Scale |
|---|---|---|
| Acceptance | −0.023 | −0.109 * |
| Active coping | −0.010 | −0.143 ** |
| Self-blame | −0.149 * | 0.522 ** |
| Planning | −0.078 | −0.218 ** |
| Humor | 0.044 | −0.054 |
| Emotional support | 0.043 | −0.115 * |
| Use of informational support | 0.010 | −0.022 |
| Positive reframing | 0.005 | −0.198 ** |
| Venting | −0.083 | 0.311 ** |
| Self-distraction | −0.010 | 0.175 ** |
| Denial | −0.050 | 0.390 ** |
| Behavioral disengagement | −0.109 | 0.405 ** |
| Substance use | −0.114 | 0.251 ** |
| Religion | 0.089 | 0.050 |
| Problem-Focused Coping | 0.005 | −0.193 ** |
| Emotion-Focused Coping | 0.026 | 0.168 ** |
| Avoidant Coping | −0.119 | 0.473 ** |

* $p < 0.05$; ** $p < 0.01$.

## 4. Discussion

In our study, we describe and compare coping strategies used by four groups of chronically-ill patients. It is known that diagnosis of chronic disease poses a significant burden on mental health, resulting in long-term psychological distress manifested, among others, by anxiety or depressive symptoms [30–32]. The individual coping strategies used by people subjected to stress reflect one's ability to adapt to new challenges and, in turn, influence mental health. The final outcome of coping with stress depends on various individual and external factors. While some of them, such as optimism or self-esteem, cannot be rapidly and easily targeted, research highlights the impact of others with the example of social support also in the circumstances of the global pandemic [30,33–35]. While the pandemic-related restrictions largely reduced access to social interactions and, therefore, social support increasing the risk of worsened mental health, the impact on the population of chronically-ill patients was even more deleterious.

We report significant correlations of used coping strategies with sociodemographic factors, such as age, sex, employment status, education, or previous history of psychiatric treatment and psychological interventions. Additionally, we examine the differences between several groups of patients in employed coping strategies and indicate factors related to more adaptive coping. In another analysis conducted in our study group, we observed that almost half of the studied population of chronically-ill patients reported symptoms indicative of a depressive episode or anxiety. According to the General Health Questionnaire 28 (GHQ28) and PSS-10 scores, the highest intensity of symptoms was observed in patients with MS, while the kidney transplant recipients were the least likely to report complaints [19]. Further research in the MS group revealed over 80% of participants experienced high or moderate stress levels, which was more strongly correlated with social restrictions and interactions rather than the current condition resulting from the chronic disease [36]. In this comparison of coping strategies in four groups of chronically-ill patients, we link the previous results with potential higher sensitivity in patients with MS. We hypothesize that these patients are more likely to anticipate, observe and report even less substantial changes to their condition, which may be related to the progressive character of the disease. In our comparison, patients with MS declared higher use of each group of coping strategies than the three remaining groups. While a younger mean of age or lower comorbidity may explain some results, such as higher substance use or less religious coping, the general results profile emphasizes a high level of perceived stress

and indicates the need to include psychoeducation or psychological interventions in the long-term treatment of this population.

Chodkiewicz et al. report that female sex, younger age, and pre-existent disorders were associated with worse mental health outcomes and also with higher use of passive and avoidant coping strategies in healthy participants [37].

We observed similar effects with female participants declaring higher use of self-blame, venting, denial, and behavioral disengagement, while younger participants tended to report higher substance use, self-blame, venting, or denial compared to older participants. However, we observed that a longer time since initial diagnosis was linked to significantly decreased use of self-blame, indicating the potential pro-resilient effect of chronic disease. While recent research highlights the increase in psychoactive substance use in the general population due to the COVID-19 pandemic [38,39], the participants of our study declared low use of this coping strategy, which may be associated with the chronic illness and related treatment.

Our results lie in agreement with previous research on lung transplant recipients and candidates, in which problem-focused coping (task-focused strategy) was also predominant [40]. However, in that population, the least common strategy was emotion-focused, whereas, in our study, all groups of patients were least likely to use avoidant coping.

In regard to patients with MS, we obtained different results than the Turkish study by Altunan et al., which may be related to the sociocultural background [41]. While in both studies, patients with MS declared common use of active coping and acceptance; we rarely observed turning to religion as a relevant coping mechanism in response to the pandemic.

Noteworthy, while our study design only allowed for singular data collection, it is important to mention potential findings regarding increased psychological resilience in chronically-ill patients in response to the COVID-19 pandemic. In the study by Davis et al., participants were found to report less personal suffering and more resilience [42]. In another study by Young et al., older adults were shown to experience less stress and use more problem-focused strategies and less avoidant coping in response to the COVID-19 pandemic compared to younger adults [43]. In our population of chronically-ill patients, older age slightly correlated with turning to religion and with a decrease in other coping strategies, with the exception of behavioral disengagement, positive reframing, and denial. These differences may be related to different sociocultural backgrounds but also to the previous diagnosis of chronic illness as a significant contributor to mental health. According to the study by Bonenkamp et al., no effect of the pandemic on the well-being of dialysed patients was found when measured with the use of health-related quality of life (HRQoL) questionnaires [44]. It seems that previous diagnoses of chronic somatic illness and the necessity of undergoing regular medical procedures may eventually lead to increased psychological resilience in conditions of chronic stress. The inverse correlation between time since diagnosis and the use of self-blaming in our study group may reflect one of the potential underlying mechanisms of this phenomenon.

Interestingly, this finding may also be observed in people suffering from mental disorders. Previous manifestation of mental health complaints, such as depressive, obsessive-compulsive, or anxiety symptoms, was not found to predict poorer mental well-being in response to the COVID-19 pandemic development in a Dutch study comprising three large cohorts [45]. On the other hand, participants who previously did not report such symptoms were more likely to complain of them in response to the pandemic. In a Polish study by Talarowska et al., previous psychiatric treatment alongside non-adaptive coping strategies, such as denial, substance use, self-blame, behavioral disengagement, and venting, correlated with poorer mental health [46]. In our study, we observed that previous psychiatric treatment and psychotherapy strongly correlated with several disadaptive coping strategies, such as self-blaming, behavioral disengagement, substance use, and avoidant coping. We hypothesize that while both psychiatric patients and people choosing psychotherapy are more inclined to disadaptive coping strategies, the latter may also benefit from long-lasting changes to their personalities. Hence, additional more adaptive coping strategies, such

as the use of humor and emotion-focused coping, can be distinguished in their behavior, which was reflected in our study results.

Among numerous alarming reports regarding the general population, the direct impact of the COVID-19 pandemic on the treatment of patients with chronic diseases has been described in several reports. In a study by Singh et al., the interviewed chronically-ill patients declared they had avoided going to hospitals during the pandemic [5]. In Rwanda, almost half (44%) of the participants suffering from chronic diseases reported a lack of access to emergency care or medication and skipping clinical appointments [9]. In a study by Umucu and Lee, patients with chronic conditions who used self-distraction, denial, substance use, behavioral disengagement, venting, planning, religion, and self-blame were found to report higher levels of stress [47]. This finding lies in agreement with our study, in which the participants with higher PSS-10 scores employed similar coping strategies with the exception of planning and religion.

Another study by Girma et al. associated the use of active coping, denial, behavioral disengagement, self-blame, and turning to religion with higher PSS-10 scores in chronically-ill patients [48]. Our results confirm the correlations for self-blaming, behavioral disengagement, and denial. However, we did not observe an association between higher levels of perceived stress and the use of active or religious coping.

Educating and encouraging adaptive coping strategies seems especially relevant in a population of chronically-ill patients considering the psychological burden and potential treatment discontinuation resulting from the aggravated stress. Among such interventions, behavioral activation, mindfulness practice, or acceptance-based coping are indicated in order to improve resilience and reduce stress intensity [49]. Moreover, taking advantage of available ways of telecommunication could facilitate mental state evaluation in vulnerable individuals and, in turn, allow for quicker interventions [50]. This approach could contribute to better compliance and improved treatment results in conditions of generalized stress-inducing factors.

*Limitations*

While our research reports data on coping in a relatively large group of chronically-ill patients, our results are also limited by several factors:

The studied groups were not matched in terms of sociodemographic characteristics, such as sex or education.

Due to the global character of the COVID-19 pandemic, we were unable to recruit a control group. At the time of our study, singular participants were already individually affected by COVID-19 or quarantines. Hence, we were not able to analyze the impact of infections and individual restrictions on the outcomes of the study.

We based our study on two data collection methods, paper questionnaires and an online version, which disabled us from providing a response rate to the study. Considering the large contribution of online questionnaires, we were also unable to confirm the medical diagnosis of patients with psoriasis and multiple sclerosis or to link obtained data with medical data such as laboratory results.

## 5. Conclusions

Compared to previous research, the studied groups of chronically-ill patients possess certain distinct characteristics in regard to coping strategies employed in response to the COVID-19 pandemic. While we confirm some of the previous findings made in the general population, such as the most common use of the problem-focused coping strategies and least frequent use of avoidant coping, or higher coping use correlating with higher perceived stress levels, we also highlight the impact of previously diagnosed chronic illness and its potentially pro-resilient effects on the coping profile. The characteristics of coping profiles in studied groups are dependent on numerous factors, including disease severity, prognosis, and daily burden. Group comparison identifies patients with a chronic neurological disease, such as multiple sclerosis, at higher risk of a less beneficial coping

profile than kidney transplant recipients. Additionally, previous psychiatric treatment and psychotherapy both correlate with several less adaptive coping strategies, such as self-blaming, behavioral disengagement, substance use, and avoidant coping, while psychotherapy is also correlated with several beneficial outcomes, such as humor, venting, self-distraction, and emotion-focused coping. Our findings allow us to distinguish the individual and disease-related characteristics associated with adaptive and disadaptive coping in response to significant stress. Alongside telemedicine, further focus on education and early interventions in at-risk individuals is needed, and wide-targeted mental health programs are indicated in order to improve the mental health of patients suffering from chronic diseases.

**Supplementary Materials:** The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/ijerph20064814/s1, Supplementary File 1.

**Author Contributions:** Conception and design of the study J.R., D.S., K.F.-W., T.P. and M.P.; grant acquisition, D.S., J.R. and M.K.; investigation and data acquisition H.A.-B., M.P., A.S., D.Z. and J.C.-Ł.; formal analysis, M.Ł., A.J. and A.P.-D.; writing—draft preparation, M.Ł., A.J. and K.F.-W.; visualization, M.Ł., A.S. and J.C.-Ł.; writing—critical revising and editing, M.Ł., A.P.-D. and J.C.S.; supervision, M.K., J.C.S., T.P. and J.R. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research was funded by Wroclaw Medical University, grant number SUBZ.C230.22.062.

**Institutional Review Board Statement:** The study was conducted in accordance with the Declaration of Helsinki and approved by the local Bioethical Committee at the Wroclaw Medical University (KB-468/2020; KB-469/2020; KB-470/2020; KB-417/2020).

**Informed Consent Statement:** Informed consent was obtained from all subjects involved in the study.

**Data Availability Statement:** The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

**Acknowledgments:** We want to acknowledge Dorota Kamińska, Paweł Poznański, Piotr K Krajewski, Julia E Rymaszewska and Sławomir Budrewicz and their contribution to the enrollment of the participants.

**Conflicts of Interest:** The authors declare no conflict of interest.

## References

1. WHO. *COVID-19 Weekly Epidemiological Update*; WHO: Geneva, Switzerland, 2022; Volume 123, pp. 1–23.
2. Pullano, G.; Di Domenico, L.; Sabbatini, C.E.; Valdano, E.; Turbelin, C.; Debin, M.; Guerrisi, C.; Kengne-Kuetche, C.; Souty, C.; Hanslik, T.; et al. Underdetection of Cases of COVID-19 in France Threatens Epidemic Control. *Nature* **2021**, *590*, 134–139. [CrossRef] [PubMed]
3. Baker, M.G.; Durrheim, D.; Hsu, L.Y.; Wilson, N. COVID-19 and Other Pandemics Require a Coherent Response Strategy. *Lancet* **2023**, *401*, 265–266. [CrossRef]
4. Dragioti, E.; Li, H.; Tsitsas, G.; Lee, K.H.; Choi, J.; Kim, J.; Choi, Y.J.; Tsamakis, K.; Estradé, A.; Agorastos, A.; et al. A Large-Scale Meta-Analytic Atlas of Mental Health Problems Prevalence during the COVID-19 Early Pandemic. *J. Med. Virol.* **2022**, *94*, 1935–1949. [CrossRef]
5. Singh, K.; Kaushik, A.; Johnson, L.; Jaganathan, S.; Jarhyan, P.; Deepa, M.; Kong, S.; Venkateshmurthy, N.S.; Kondal, D.; Mohan, S.; et al. Patient Experiences and Perceptions of Chronic Disease Care during the COVID-19 Pandemic in India: A Qualitative Study. *BMJ Open* **2021**, *11*, e048926. [CrossRef] [PubMed]
6. Martínez, R.M.; Gómez, R.G.C. Pandemic Iatrogenesis: Exclusion and Lag in Non-COVID Medical Care in Mexico City. *Cienc. Saude Coletiva* **2022**, *27*, 4155–4164. [CrossRef]
7. Akobirshoev, I.; Vetter, M.; Iezzoni, L.I.; Rao, S.R.; Mitra, M. Delayed Medical Care And Unmet Care Needs Due To The COVID-19 Pandemic Among Adults With Disabilities In The US. *Health Aff.* **2022**, *41*, 1505–1512. [CrossRef] [PubMed]
8. Provenzano, D.A.; Sitzman, B.T.; Florentino, S.A.; Buterbaugh, G.A. Clinical and Economic Strategies in Outpatient Medical Care during the COVID-19 Pandemic. *Reg. Anesth. Pain Med.* **2020**, *45*, 579–585. [CrossRef]
9. Nshimyiryo, A.; Barnhart, D.A.; Cubaka, V.K.; Dusengimana, J.M.V.; Dusabeyezu, S.; Ndagijimana, D.; Umutesi, G.; Shyirambere, C.; Karema, N.; Mubiligi, J.M.; et al. Barriers and Coping Mechanisms to Accessing Healthcare during the COVID-19 Lockdown: A Cross-Sectional Survey among Patients with Chronic Diseases in Rural Rwanda. *BMC Public Health* **2021**, *21*, 704. [CrossRef]

10. Taylor, S.; Landry, C.A.; Paluszek, M.M.; Fergus, T.A.; McKay, D.; Asmundson, G.J.G. COVID Stress Syndrome: Concept, Structure, and Correlates. *Depress. Anxiety* **2020**, *37*, 706–714. [CrossRef]
11. Kołodziejczyk, A.; Misiak, B.; Szcześniak, D.; Maciaszek, J.; Ciułkowicz, M.; Łuc, D.; Wieczorek, T.; Fila-Witecka, K.; Chladzinska-Kiejna, S.; Rymaszewska, J. Coping Styles, Mental Health, and the COVID-19 Quarantine: A Nationwide Survey in Poland. *Front. Psychiatry* **2021**, *12*, 625355. [CrossRef]
12. Wieczorek, T.; Kołodziejczyk, A.; Ciułkowicz, M.; Maciaszek, J.; Misiak, B.; Rymaszewska, J.; Szcześniak, D. Class of 2020 in Poland: Students' Mental Health during the COVID-19 Outbreak in an Academic Setting. *Int. J. Environ. Res. Public Health* **2021**, *18*, 2884. [CrossRef]
13. Maciaszek, J.; Ciulkowicz, M.; Misiak, B.; Szczesniak, D.; Luc, D.; Wieczorek, T.; Fila-Witecka, K.; Gawlowski, P.; Rymaszewska, J. Mental Health of Medical and Non-Medical Professionals during the Peak of the COVID-19 Pandemic: A Cross-Sectional Nationwide Study. *J. Clin. Med.* **2020**, *9*, 2527. [CrossRef] [PubMed]
14. Ciułkowicz, M.; Misiak, B.; Szcześniak, D.; Grzebieluch, J.; Maciaszek, J.; Rymaszewska, J. The Portrait of Cyberchondria—A Cross-Sectional Online Study on Factors Related to Health Anxiety and Cyberchondria in Polish Population during SARS-CoV-2 Pandemic. *Int. J. Environ. Res. Public Health* **2022**, *19*, 4347. [CrossRef]
15. Wu, T.; Jia, X.; Shi, H.; Niu, J.; Yin, X.; Xie, J.; Wang, X. Prevalence of Mental Health Problems during the COVID-19 Pandemic: A Systematic Review and Meta-Analysis. *J. Affect. Disord.* **2021**, *281*, 91–98. [CrossRef] [PubMed]
16. Hedemann, T.L.; Liu, X.; Kang, C.N.; Husain, M.I. Associations between Psoriasis and Mental Illness: An Update for Clinicians. *Gen. Hosp. Psychiatry* **2022**, *75*, 30–37. [CrossRef] [PubMed]
17. Brown, E.A.; Zhao, J.; McCullough, K.; Fuller, D.S.; Figueiredo, A.E.; Bieber, B.; Finkelstein, F.O.; Shen, J.; Kanjanabuch, T.; Kawanishi, H.; et al. Burden of Kidney Disease, Health-Related Quality of Life, and Employment Among Patients Receiving Peritoneal Dialysis and In-Center Hemodialysis: Findings From the DOPPS Program. *Am. J. Kidney Dis.* **2021**, *78*, 489–500.e1. [CrossRef]
18. Rodríguez-Agudelo, Y.; Nava-Adán, J.; Paz-Rodríguez, F.; Abundes-Corona, A.; Flores-Rivera, J.; Corona, T. Quality of Life and Mental Health in Multiple Sclerosis Patients during the COVID-19 Pandemic. *Mult. Scler. Relat. Disord.* **2023**, *70*, 104487. [CrossRef]
19. Pawłowski, M.; Fila-Witecka, K.; Rymaszewska, J.E.; Kamińska, D.; Poznański, P.; Augustyniak-Bartosik, H.; Zielińska, D.; Krajewska, M.; Krajewski, P.K.; Stefaniak, A.; et al. Psychopathological Symptoms Among Chronically Ill Patients During SARS-CoV-2 Pandemic in Poland. *Psychol. Res. Behav. Manag.* **2022**, *15*, 2659–2669. [CrossRef]
20. Pierce, M.; Hope, H.; Ford, T.; Hatch, S.; Hotopf, M.; John, A.; Kontopantelis, E.; Webb, R.; Wessely, S.; McManus, S.; et al. Mental Health before and during the COVID-19 Pandemic: A Longitudinal Probability Sample Survey of the UK Population. *Lancet Psychiatry* **2020**, *7*, 883–892. [CrossRef]
21. Ran, M.S.; Gao, R.; Lin, J.X.; Zhang, T.M.; Chan, S.K.W.; Deng, X.P.; Zhang, B.Z.; Zhang, X.F.; Huang, G.P.; Pu, D.S.; et al. The Impacts of COVID-19 Outbreak on Mental Health in General Population in Different Areas in China. *Psychol. Med.* **2022**, *52*, 2651–2660. [CrossRef] [PubMed]
22. Gilhooly, K.J.; Gilhooly, M.L.M.; Sullivan, M.P.; McIntyre, A.; Wilson, L.; Harding, E.; Woodbridge, R.; Crutch, S. A Meta-Review of Stress, Coping and Interventions in Dementia and Dementia Caregiving. *BMC Geriatr.* **2016**, *16*, 106. [CrossRef]
23. Braun-Lewensohn, O.; Abu-Kaf, S.; Al-Said, K. Women in Refugee Camps: Which Coping Resources Help Them to Adapt? *Int. J. Environ. Res. Public Health* **2019**, *16*, 3990. [CrossRef] [PubMed]
24. Compas, B.E.; Jaser, S.S.; Bettis, A.H.; Watson, K.H.; Gruhn, M.A.; Dunbar, J.P.; Williams, E.; Thigpen, J.C. Coping, Emotion Regulation, and Psychopathology in Childhood and Adolescence: A Meta-Analysis and Narrative Review. *Psychol. Bull.* **2017**, *143*, 939–991. [CrossRef] [PubMed]
25. Gil-González, I.; Martín-Rodríguez, A.; Conrad, R.; Pérez-San-Gregorio, M.Á. Coping Strategies Furthering Post-Traumatic Growth in Multiple Sclerosis: A Longitudinal Study. *Int. J. Environ. Res. Public Health* **2022**, *19*, 12679. [CrossRef]
26. Folkman, S.; Moskowitz, J.T. Coping: Pitfalls and Promise. *Annu. Rev. Psychol.* **2004**, *55*, 745–774. [CrossRef] [PubMed]
27. Cohen, S.; Kamarck, T.; Mermelstein, R. A Global Measure of Perceived Stress. *J. Health Soc. Behav.* **1983**, *24*, 385. [CrossRef]
28. Charles, S. Carver. You Want to Measure Coping but Your Protocol's Too Long: Consider the Brief COPE. *Int. J. Behav. Med.* **1997**, *4*, 92–100.
29. Dias, C.; Cruz, J.F.; Fonseca, A.M. The Relationship between Multidimensional Competitive Anxiety, Cognitive Threat Appraisal, and Coping Strategies: A Multi-Sport Study. *Int. J. Sport Exerc. Psychol.* **2012**, *10*, 52–65. [CrossRef]
30. Li, A. Individual and Organizational Health Literacies: Moderating Psychological Distress for Individuals with Chronic Conditions. *J. Public Health (UK)* **2022**, *44*, 651–662. [CrossRef]
31. DeJean, D.; Giacomini, M.; Vanstone, M.; Brundisini, F. Patient Experiences of Depression and Anxiety with Chronic Disease: A Systematic Review and Qualitative Meta-Synthesis. *Ont. Health Technol. Assess. Ser.* **2013**, *13*, 1–33.
32. Yoon, H.; Kim, S.; Naseh, M.; Huang, Y.-C.; Jang, Y. Chronic Conditions and Psychological Distress in Older Asian Americans: The Mediating Role of Subjective Health Perception. *J. Gerontol. Soc. Work* **2022**, *65*, 604–617. [CrossRef] [PubMed]
33. Taylor, S.E.; Stanton, A.L. Coping Resources, Coping Processes, and Mental Health. *Annu. Rev. Clin. Psychol.* **2007**, *3*, 377–401. [CrossRef] [PubMed]
34. Mana, A.; Catz, O.; Mana, Y.; Neuman, M.; Benheim, S.; Sagy, S. How Do People Cope During the COVID-19 Pandemic and Stay Well? A Salutogenic Longitudinal Study in Israel. *Front. Psychol.* **2021**, *12*, 729543. [CrossRef] [PubMed]

35. Leslie-Miller, C.J.; Waugh, C.E.; Cole, V.T. Coping With COVID-19: The Benefits of Anticipating Future Positive Events and Maintaining Optimism. *Front. Psychol.* **2021**, *12*, 646047. [CrossRef]
36. Pokryszko-Dragan, A.; Chojdak-Łukasiewicz, J.; Gruszka, E.; Pawłowski, M.; Pawłowski, T.; Rudkowska-Mytych, A.; Rymaszewska, J.; Budrewicz, S. Burden of COVID-19 Pandemic Perceived by Polish Patients with Multiple Sclerosis. *J. Clin. Med.* **2021**, *10*, 4215. [CrossRef]
37. Chodkiewicz, J.; Miniszewska, J.; Krajewska, E.; Biliński, P. Mental Health during the Second Wave of the COVID-19 Pandemic—Polish Studies. *Int. J. Environ. Res. Public Health* **2021**, *18*, 3423. [CrossRef]
38. Enns, A.; Pinto, A.; Venugopal, J.; Grywacheski, V.; Gheorghe, M.; Kakkar, T.; Farmanara, N.; Deb, B.; Noon, A.; Orpana, H. Evidence-Informed Policy Brief Substance Use and Related Harms in the Context of COVID-19: A Conceptual Model. *Heal. Promot. Chronic Dis. Prev. Can.* **2020**, *40*, 342–349. [CrossRef]
39. Chodkiewicz, J.; Talarowska, M.; Miniszewska, J.; Nawrocka, N.; Bilinski, P. Alcohol Consumption Reported during the COVID-19 Pandemic: The Initial Stage. *Int. J. Environ. Res. Public Health* **2020**, *17*, 4677. [CrossRef]
40. Savary, A.; Hammouda, M.; Genet, L.; Godet, C.; Bunel, V.; Weisenburger, G.; Goletto, T.; Medraoui, C.; Jebrak, G.; Marceau, A.; et al. Coping Strategies, Anxiety and Depression Related to the COVID-19 Pandemic in Lung Transplant Candidates and Recipients. Results from a Monocenter Series. *Respir. Med. Res.* **2021**, *80*, 100847. [CrossRef]
41. Altunan, B.; Unal, A.; Bingöl, A.; Dilek, F.; Girgin, D. Coping with Stress during the First Wave of the COVID-19 Pandemic by Turkish People with Multiple Sclerosis: The Relationship between Perceived Stress and Quality of Life. *Mult. Scler. Relat. Disord.* **2021**, *53*, 103039. [CrossRef]
42. Davis, E.B.; McElroy-Heltzel, S.E.; Lemke, A.W.; Cowden, R.G.; VanderWeele, T.J.; Worthington, E.L.; Glowiak, K.J.; Shannonhouse, L.R.; Davis, D.E.; Hook, J.N.; et al. Psychological and Spiritual Outcomes during the COVID-19 Pandemic: A Prospective Longitudinal Study of Adults with Chronic Disease. *Health Psychol.* **2021**, *40*, 347–356. [CrossRef] [PubMed]
43. Young, N.A.; Waugh, C.E.; Minton, A.R.; Charles, S.T.; Haase, C.M.; Mikels, J.A. Reactive, Agentic, Apathetic, or Challenged? Aging, Emotion, and Coping During the COVID-19 Pandemic. *Gerontologist* **2021**, *61*, 217–227. [CrossRef] [PubMed]
44. Bonenkamp, A.A.; Druiventak, T.A.; van Eck van der Sluijs, A.; van Ittersum, F.J.; van Jaarsveld, B.C.; Abrahams, A.C. The Impact of COVID-19 on the Mental Health of Dialysis Patients. *J. Nephrol.* **2021**, *34*, 337–344. [CrossRef] [PubMed]
45. Pan, K.Y.; Kok, A.A.L.; Eikelenboom, M.; Horsfall, M.; Jörg, F.; Luteijn, R.A.; Rhebergen, D.; van Oppen, P.; Giltay, E.J.; Penninx, B.W.J.H. The Mental Health Impact of the COVID-19 Pandemic on People with and without Depressive, Anxiety, or Obsessive-Compulsive Disorders: A Longitudinal Study of Three Dutch Case-Control Cohorts. *Lancet Psychiatry* **2021**, *8*, 121–129. [CrossRef]
46. Talarowska, M.; Chodkiewicz, J.; Biliński, P.; Nawrocka, N.; Miniszewska, J. Mental Health and the SARS-CoV-2 Epidemic—Polish Research Study. *Int. J. Environ. Res. Public Health* **2020**, *17*, 7015. [CrossRef]
47. Umucu, E.; Lee, B. Examining the Impact of COVID-19 on Stress and Coping Strategies in Individuals with Disabilities and Chronic Conditions. *Rehabil. Psychol.* **2020**, *65*, 193–198. [CrossRef]
48. Girma, A.; Ayalew, E.; Mesafint, G. COVID-19 Pandemic-Related Stress and Coping Strategies among Adults with Chronic Disease in Southwest Ethiopia. *Neuropsychiatr. Dis. Treat.* **2021**, *17*, 1551–1561. [CrossRef]
49. Polizzi, C.; Lynn, S.J.; Perry, A. Stress and Coping in the Time of COVID-19: Pathways to Resilience and Recovery. *Clin. Neuropsychiatry* **2020**, *17*, 59–62. [CrossRef]
50. Ćosić, K.; Popović, S.; Šarlija, M.; Kesedžić, I. Impact of Human Disasters and COVID-19 Pandemic on Mental Health: Potential of Digital Psychiatry. *Psychiatr. Danub.* **2020**, *32*, 25–31. [CrossRef]

## 6.3 Determinants of sleep disturbances in chronically-ill patients during the COVID-19 pandemic

Archives of Psychiatry and Psychotherapy Online First Nr 21: 1–14

Published ahead of print 27 May 2023
10.12740/APP/166394

# Determinants of sleep disturbances in chronically-ill patients during the COVID-19 pandemic

Mateusz Łuc, Marcin Pawłowski, Karolina Fila-Pawłowska, Dorota Kamińska, Paweł Poznański, Julia Rymaszewska, Piotr Krajewski, Dorota Szcześniak, Joanna Rymaszewska

**Abstract:**

Rapid emergence and transmission of SARS-CoV-2 significantly impacted mental health. Restrictions, lockdowns and quarantines issued during the wait for vaccines resulted in additional psychological distress in most populations. We aim to describe the impact of perceived stress related to the pandemic and sociodemographic determinants on sleep disturbances in the population of patients with chronic medical conditions, such as psoriasis, kidney transplant recipients and undergoing dialysis. During the cross-sectional survey conducted between May and October 2020, we enrolled 270 patients with three different chronic medical conditions. Study sample was examined regarding the reported sleep complaints (Insomnia Severity Index), occurrence of psychopathological symptoms (General Health Questionnaire 28) and their perceived levels of stress related to pandemic (Perceived Stress Scale). We observed 25,2% prevalence of ISI scores indicative of clinical insomnia in the group of chronically-ill patients during the first phase of the pandemic. ISI scores were found to be strongly correlated with GHQ28 and moderately correlated with PSS-10 scores. The profiles of reported complaints varied significantly between groups. There are varied outcomes related to sleep disturbances measured with ISI in the general population depending on the country and phase of pandemic with most of them ranging from 11.5 to 20%. Findings of our study suggest that population of patients with chronic conditions, with special emphasis on those who have a simultaneous history of psychiatric or psychological treatment, requires additional attention in order to objectivize and maintain sleep disorders during occurrence of severe stress conditions such as the COVID-19 pandemic.

**stress; sleep disturbances; chronic disease; COVID-19 pandemic**

**Mateusz Łuc[1], Marcin Pawłowski[1], Karolina Fila-Pawłowska[1], Dorota Kamińska[2], Paweł Poznański[2], Julia Rymaszewska[3], Piotr Krajewski[3], Dorota Szcześniak[1], Joanna Rymaszewska[1]:**
[1]Department of Psychiatry, Wroclaw Medical University Poland; [2]Nephrology and Transplantology Department, Wroclaw Medical University Poland; [3]Department of Dermatology, Venerology and Allergology, Wroclaw Medical University

## 1. AIM OF THE STUDY

Rapid emergence and transmission of the novel coronavirus variant, SARS-CoV-2, significantly impacted mental health [1]. Psychopathological consequences of the COVID-19 pandemic are related not only to the direct influence of SARS-CoV-2 on human organism. Widely issued restrictions, lockdowns and quarantines during the wait for vaccination to become avail-

able resulted in additional psychological distress in most populations. These changes lead to decreased social contacts and social support, while at the same time increased the stress levels and anxiety related to worries about health and future of individuals and their close ones [2,3] It stands to reason that the impact and profile of the resulting mental disorders will vary dependent on the population characteristics.

Significant global stress factor and associated changes to the daily life of the general population resulted in increased levels of anxiety and depressive symptoms, but also affected the sleep quality and quantity. Early reports from large groups of Chinese participants indicate that over 20% of them met criteria of clinical insomnia according to Insomnia Severity Index (ISI) and 18.2% were identified to have poor sleep quality with Pittsburgh Sleep Quality Index (PSQI) [4,5]. In another study by Gualano et al. 42.2% of Italian respondents reported to experience sleep disturbances and in 17.4% their ISI score indicated moderate or severe insomnia [6]. Among factors predisposing to pandemic-induced insomnia female sex, younger age or a diagnosis of a chronic disease were listed. Additionally, age, depressive symptoms and perceived stress level were identified as factors responsible for cognitive pre-sleep arousal, while female gender, depressive symptoms, increased stress levels and interruption of regular work were associated with somatic pre-sleep arousal, both leading to aggravation of sleep disturbances [7]. A large international survey study conducted in 13 countries, including Poland, identified 36.7% and 17.4% from a 22 300 group of respondents to manifest insomnia symptoms and probable clinical insomnia, respectively. Similarly, females, younger participants and Polish participants were identified as groups at greater risk of insomnia symptoms [8]. Other studies, including meta-analyses of multi-national studies, reported sleep complaints ranging from 29.7% up to 69.9% of participants from the general population confirming common occurrence of this phenomenon [9–12].

While sleep disturbances described in the general population remain a common complaint during the COVID-19 pandemic, their frequency and pandemic-related changes in patients with previously diagnosed chronic diseases remain underexplored. As it turns out, when a person is diagnosed with a somatic illness, treatment for sleep disorders is frequently inadequate, which lowers quality of life. However, some evidence links insomnia with an increased risk of morbidity and mortality, which has important ramifications for the fields of psychiatry and psychology [13–15]. Research shows that various chronic diseases, such as rheumatoid arthritis or multiple sclerosis, significantly impact sleep quality in several mechanisms both related to symptoms of a primary disease and psychological distress, including distress resulting from the primary diagnosis [16,17]. According to a systematic review by Henry et al., patients diagnosed with psoriasis complaining of sleep difficulties range from 0.05 up to even 85.4% depending on a study and research design indicating a need for further exploration and methods alignment [18]. In a study by Sahin et al., patients with psoriasis slept 1 hour less on average than the healthy control group and pruritus, anxiety or depressive symptoms significantly mediated the effect [19]. These findings lie in agreement with another systematic review, which additionally underscores the impact of alleviating symptoms of the primary disease on improving sleep length and quality [20]. On the other hand, evidence exists on aggravation of psoriasis in response to sleep disorders indicating more complex and bidirectional interactions of a chronic dermatological disease and sleep disorders [21].

Similarly, chronic kidney disease has also been linked to various sleep-related problems, including insomnia, obstructive sleep apnea, hypersomnia, parasomnias or restless legs syndrome [22,23]. A recent meta-analysis by Tan et al. reports that frequency of poor sleep quality or insomnia in patients with chronic kidney is associated with the method of treatment. There was a 48% prevalence of insomnia in patients who were not receiving kidney replacement therapy and only 26% in patients who received kidney transplant. Interestingly, undergoing both peritoneal dialysis and hemodialysis has been associated with worse sleep quality, while undergoing peritoneal dialysis is related to increased prevalence of insomnia [24]. Dialysis impacts sleep and circadian rhythm by depleting patients of melatonin but also elevated serum urea

nitrogen and phosphorus levels have been associated with worse outcomes [25].

Our previous research focused on describing psychological well-being and perceived stress level in patients diagnosed with several chronic conditions, such as psoriasis, multiple sclerosis, kidney transplant recipients and patients undergoing dialysis. [26]. In this study we analyze occurrence of self-reported sleep complaints in three groups of chronically-ill patients who were undergoing regular medical visits and treatment during the first phase of COVID-19 pandemic. We hypothesize that patients with chronic medical conditions will be characterized with significant sleep disturbances and that this effect will be associated with experienced stress related to the pandemic alongside the sociodemographic determinants. This research may contribute to future recommendations regarding organization of health care for chronically-ill patients during similar global health crisis.

## 2. MATERIAL AND METHODS

### *2.1. Study design*

We have recruited chronically-ill patients with diagnoses of psoriasis, patients who had had a kidney transplant and patients with chronic kidney disease receiving dialyses, to participate in a cross-sectional survey carried out between May and October 2020, during the first phase of COVID-19 pandemic. The local Bioethical Committee at the Wroclaw Medical University accepted the study (KB-468/2020; KB-469/2020; KB-470/2020). The study has been conducted in accordance with the STROBE guidelines [27]. For detailed methods and procedures see Pawłowski et al, 2022 [26].

### *2.2. Settings*

The participants took part in the survey voluntarily, with no financial reward. Participation was anonymous and data was secured at all stages of the study. Questionnaires were provided either online or in print, as a consequence of COVID-19 restrictions and patients safety. The printed forms were provided to all groups of patients at the University Clinical Hospital in Wroclaw, Poland. Additionally, we used Computer-Assisted Web Interviewing (CAWI) to conduct an online version of the survey and shared it via the website and the social media profile of Polish Association for Psoriasis patients. In the preliminary section of the survey respondents filled an informed consent, so participation and processing of data was possible. Participants were evaluated for occurrence and intensity of sleep disorders. Demographic variables, as well as pandemic-related data, such as previous quarantines, COVID-19 exposures or infections, were also included in the survey.

### *2.3. Participants*

The inclusion criteria were as follows: 1) a previous diagnosis of psoriasis (P group), current dialysis therapy (D group) or being an adult kidney transplant recipient in the past (T group); 2) age over 18 and 3) informed consent to participate. Due to the online version of the survey no medical documents nor confirmations were required in order to preserve anonymity in P group. Participants from D and T groups were recruited only at the hospital. Hence, their medical data and documentation were available in order to confirm diagnoses. Exclusion criteria were: 1) age under 18; 2) inability to provide informed consent and 3) surveys with incomplete sections. Psychological and psychiatric history was collected but did not disqualify from participation.

### *2.4. Variables:*

The psychometric tools used in the study were selected by a team of experts from different medical specialties (psychiatry, psychology, dermatology and nephrology) and were based on appropriate literature. The survey consisted of following sections:

*Sociodemographic data.*

*Insomnia Severity Index* (ISI) provides information on existing sleep disturbances, their character and impact on daily life. It consists of 7 items which are answered on a 5-point scale from 0 to 4, with higher scores corresponding with more aggravated sleep difficulties. The total score is

calculated by summing up each answer and according to the literature can be interpreted as: 0-7 – No clinically significant insomnia; 8-14 – Subthreshold insomnia; 15-21 – Clinical insomnia (moderate severity) and 22-28 – Clinical insomnia (severe). The questionnaire was validated with Cronbach's alpha ranging from 0,72 to 0,9 [28,29].

*The General Health Questionnaire* (GHQ-28) is a self-administered screening tool designed to detect and measure the presence of psychopathological symptoms. It consists of 28 items and its maximum score is 84 points. The questionnaire was validated in the Polish population and deemed satisfactory with validity scores (Cronbach's alpha) around 0.8. Based on the previous literature, the cut-off score was established at 24 points [30,31]. In order to correlate ISI with GHQ28 without the contribution of two questions directly evaluating sleep, we additionally distinguished sleep-excluded GHQ (seGHQ).

*The Perceived Stress Scale 10 (PSS-10)* assesses the level of experienced stress during last month. It contains 10 questions designed to measure the subjective level of stress. The general result reflects the intensity of perceived stress. Participants indicate their answers on a 5-point scale ranging from 0 (never) to 4 (very often). The PSS-10 score is calculated by summing up the item scores. The higher the score, the higher the level of stress experienced. The questionnaire was validated in the Polish population and deemed satisfactory with the validity scores (Cronbach's alpha) around 0.8 [32].

### *2.5. Statistical methods*

The statistical analysis of obtained results was performed with the use of IBM SPSS Statistics v. 26 (SPSS INC., Chicago, USA) software. All data was assessed for parametric or non-parametric distribution. The minimum, maximum, mean and standard deviation were calculated, whereas for GHQ28, PSS-10 and ISI, parameters distrubution was also assessed for curtosis and skewness. Due to the relatively large sample, Kolmogorov-Smirnov test results were calculated. Analyzed variables were evaluated using the Mann–Whitney U test and the Spearman correlation. Differences between several groups were assessed by Kruskal-Wallis 1-way analysis of variance on ranks and Bonferroni-Dunn post-hoc test was performed. Additionally, ANCOVA and multivariate linear stepwise regression with backward elimination were conducted in order to increase sensitivity. In case of the variable "diagnosis" the renal transplant group was automatically set as a control group (as the subgroup with the highest quantitiy of participants) and other subgroups were compared to this group. The rho Spearmann matrix was performed to establish correlation between variables. A 2-sided $p$ value ≤0.05 was considered to be statistically significant.

## 3. RESULTS:

### *3.1. Participants characteristics:*

We recruited 270 participants aged from 18–89 into the study. According to their primary diagnosis they were divided into 3 groups: 95 patients with psoriasis (P group), 102 recipients of kidney transplants (T group) and 73 patients receiving dialyses (D group). The study groups had relatively dissimilar sociodemographic profiles in terms of age, marital status, psychiatric treatment, psychotherapy and duration of illness and similar gender distribution.

There was a slight predominance of women in the study group (n = 141; 52.2%). The mean age was 50.46 years (*SD* = 17,68). 13% of the participants had previously been treated by a psychiatrist and 16% had been subjected to psychotherapy. The detailed characteristics of the study group are summarized in Table 1.

**Table 1.** Detailed sociodemographic data.

| group | Psoriasis (N=95) | Kidney Transplant recipients (N=102) | Dialyzed patients (N=73) | Total (N=270) |
|---|---|---|---|---|
| gender (female) | 58 (61%) | 49 (48%) | 34 (47%) | 141 (52.2%) |

| | | | | |
|---|---|---|---|---|
| age | 40.24 ± 16.9 | 51.59 ± 13.42 | 63.40 ± 15.49 | 50.46 ± 17.68 |
| illness duration (years) | 16.65 ± 13.76 | 7.77 ± 6.80 | 3.52 ± 3.62 | 9.75 ± 9.22 |
| relationship status | | | | |
| single | 21 | 18 | 4 | 43 |
| in relationship | 20 | 10 | 6 | 36 |
| married | 42 | 62 | 48 | 152 |
| separated | 0 | 0 | 1 | 1 |
| divorced | 8 | 10 | 3 | 21 |
| widow/widower | 4 | 2 | 11 | 17 |
| previous psychiatric treatment (yes) | 19 (20%) | 13 (12.75%) | 3 (4.1%) | 35 (13%) |
| previous psychotherapy (yes) | 29 (30.5%) | 11 (10.8%) | 3 (4.1%) | 43 (16%) |

*3.2. ISI, PSS-10 and GHQ-28 in the studied population.*

The mean ISI score was 9.04 (with Cronbach's alpha at 0.932), whereas mean PSS-10 and GHQ-28 scores in the whole study group were 19.03 and 29.07, respectively. Considering the cut-off points of these psychometric tools, the mean scores corresponded with subthreshold insomnia, moderate level of perceived stress and indication of significant psychopathology.

Due to a relatively large sample size, we performed the Kolmogorov-Smirnov test in order to establish data distribution. All analyzed variables were significantly different than normal distribution. Additionally, PSS-10 scores had a leptokurtotic distribution indicating similar perception of currently experienced stress in the studied group. The detailed data is provided in Table 2.

**Table 2.** Mental well-being, perceived stress related to pandemic level and sleep disturbances in the studied population (N = 270).

| | R | M | SD | Mdn | Sk | Kurt | D |
|---|---|---|---|---|---|---|---|
| | | | | | | | |
| GHQ28 | 0-84 | 29.07 | 18.73 | 23 | 0.93 | 0.37 | 0.13** |
| sleep-excluded GHQ28 (seGHQ) | 0-78 | 27.25 | 17.74 | 22 | 0.94 | 0.34 | 0.13** |
| | | | | | | | |
| PSS-10 | 0-40 | 19.03 | 6.20 | 20 | -0.66 | 1.17 | 0.13** |
| | | | | | | | |
| ISI | 0-28 | 9.04 | 6.69 | 8 | 0.51 | -0.74 | 0.12** |
| Difficulty falling asleep | 0-4 | 1.03 | 1.18 | 1 | 0.81 | -0.45 | 0.28** |
| Difficulty staying asleep | 0-4 | 1.12 | 1.15 | 1 | 0.56 | -0.83 | 0.26** |
| Problems waking up too early | 0-4 | 1.01 | 1.17 | 1 | 0.89 | -0.30 | 0.28** |
| Satisfaction with current sleep pattern | 0-4 | 2.17 | 1.13 | 2 | 0.25 | -0.38 | 0.17** |
| Interference of sleep problem with daily functioning | 0-4 | 1.47 | 1.18 | 2 | 0.17 | -1.04 | 0.19** |
| Noticeability of current sleep problem | 0-4 | 1.29 | 0.99 | 1 | 0.51 | -0.36 | 0.25** |
| Distress about current sleep problem | 0-4 | 1.09 | 1.12 | 1 | 0.67 | -0.58 | 0.24** |

* $p < 0.05$;** $p < 0.01$; R – range; M – arithmetic mean; SD – standard deviation; Mdn – median; Sk – skewness; Kurt – kurtosis; D– Kolmogorov-Smirnov test result

*3.3. Frequency of sleep-related complaints in the studied population.*

Table 3 summarizes the frequency of each answer to specific ISI items. Less than half of the participants denied having difficulty falling asleep or waking up too early, whereas 13.1% and 13.9% of participants reported severe or very severe problems. The most frequently reported complaints according to the mean scores (Figure 1) involved dissatisfaction with current sleep quality, interference of reported sleep disorders with daily functioning of the participants and that experienced sleep problems were noticeable to others. On the other hand, problems with waking up too early and difficulty falling asleep were the least frequently reported by the chronically-ill patients.

**Table 3.** Answers to ISI items in the whole study group

| % | difficulty falling asleep | difficulty staying asleep | problems waking up too early | satisfaction with current sleep pattern | interference of sleep problem with daily functioning | noticeability of current sleep problem | distress about current sleep problem | **total Insomnia Severity Index** |
|---|---|---|---|---|---|---|---|---|
| 0 | 47.6% | 42.5% | 47.4% | 4.5% | 29.3% | 22.3% | 40.8% | - |
| 1 | 18.4% | 18.4% | 21.8% | 27.1% | 18.8% | 41.3% | 24.5% | **47.8%** |
| 2 | 21.0% | 25.6% | 16.9% | 28.6% | 31.2% | 23.1% | 21.5% | **27.0%** |
| 3 | 9.7% | 11.3% | 10.5% | 28.9% | 17.3% | 11.7% | 10.9% | **21.1%** |
| 4 | 3.4% | 2.3% | 3.4% | 8.3% | 3.4% | 1.5% | 2.3% | **4.1%** |

0 – none/very satisfied; 1 – mild/satisfied; 2 – moderate; 3 – severe/dissatisfied; 4 – very severe/very dissatisfied

1 – no clinically significant insomnia; 2 – subthreshold insomnia; 3 – clinical insomnia (moderate) 4 – clinical insomnia (severe)

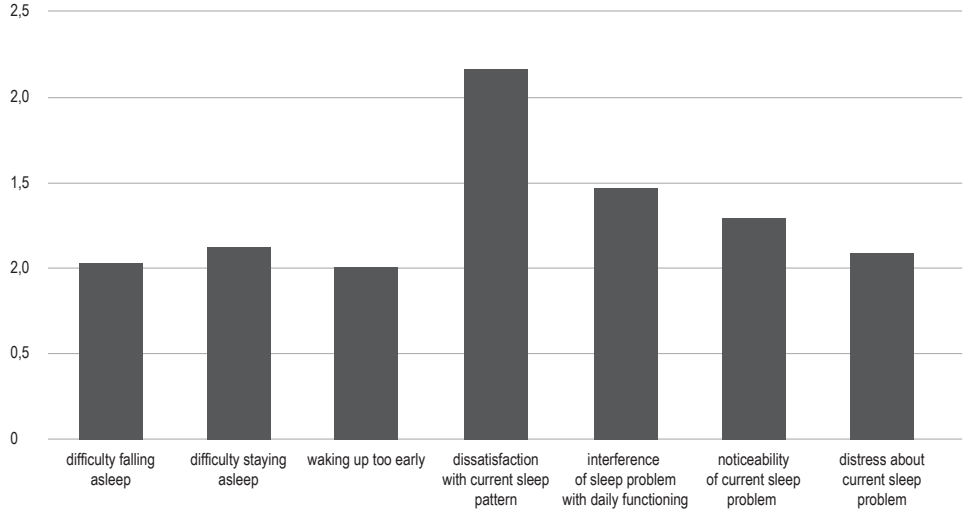



**Figure 1.** Mean profile of answers to Insomnia Severity Index in the whole study group.

Total ISI score indicative of moderate and severe clinical insomnia was observed in 25.2% of the participants, whereas 27% was categorized as subtreshold insomnia and 47.8% of the participants did not manifest symptoms indicative of sleep disorders.

*3.4. ISI in relation to PSS-10, GHQ28 and sociodemographic data.*

In order to assess the correlation between ISI and sociodemographic data or PSS-10 and GHQ28 we used the rho Spearman correlation matrix. U Mann-Whitney test was used in order to analyse qualitative sociodemographic data (sex, history of previous psychiatric treatment, history of previous psychotherapy).

In the rho Spearman analysis ISI scores in the whole group was found to be strongly correlated with GHQ28 scores and moderately correlated with PSS-10 score and seGHQ (GHQ28 after removal of questions directly assessing sleep). Additionally, we observed weak inverse correlation between ISI and duration of the chronic disease. The correlation between ISI scores and age was statistically insignificant. We observed a tendency of higher ISI scores in female participants (p=0.063). Interestingly, previous psychiatric treatment or psychotherapy correlated with higher ISI scores in chronically-ill patients during the COVID-19 pandemic (Tables 4, 5).

**Table 4.** The rho Spearmann correlation coefficients between ISI scores and age, duration off the primary disease, GHQ-28, sleep-excluded GHQ-28 and PSS-10 scores in the whole study group.

| | ISI (total) |
|---|---|
| Age | -0.007 |
| Duration of the primary disease | -0.234* |
| GHQ-28 | 0.504** |
| seGHQ28 | 0.466** |
| PSS-10 | 0.323** |

* $p < 0.05$;** $p < 0.01$

**Table 5.** The U Mann-Whitney test result of correlation between sex, previous psychiatric treatment, previous psychotherapy and total ISI scores in the whole study group.

| | Mdn | Mrang | Mdn | Mrang | U | p | rg |
|---|---|---|---|---|---|---|---|
| sex | female (n = 141) | | male (n = 129) | | | | |
| ISI | 10 | 143.94 | 6 | 126.27 | 7904.00 | 0.063 | 0.13 |
| previous psychiatric treatment | no (n = 235) | | yes (n = 35) | | | | |
| ISI | 7 | 129.59 | 15 | 175.17 | 2724.00 | 0.001 | 0.34 |
| previous psychotherapy | no (n = 226) | | yes (n = 43) | | | | |
| ISI | 7 | 129.18 | 12 | 165.57 | 3544.50 | 0.005 | 0.27 |
| | Mdn | Mrang | Mdn | Mrang | U | p | rg |

Mdn – median; Mrang – mean range; *U* – U Mann-Whitneya test result; *p* – p-value; *rg* – Glass's estimator of effect size

*3.5 Differences in psychometric scores between 3 groups.*

We performed the Kruskal-Wallis test in order to compare the obtained outcomes between the three studied groups of patients. We did not detect any statistically significant differences in total ISI of P, T or D groups. However, we observed the lowest PSS-10 scores in the P group. Additionally, both T group and D group were shown to report lower GHQ28 scores and seGHQ scores than P group (Table 6).

**Table 6.** Psychometric scores in relation to the chronic medical condition.

| | | I: Psoriasis | | II: Kidney transplant | | III: Dialysis | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Mdn | Mrang | Mdn | Mrang | Mdn | Mrang | H(2) | p | $\varepsilon^2$ | Post-hoc |
| A | GHQ28 | 43.00 | 190.08 | 17.50 | 97.01 | 21.00 | 118.25 | 74.81 | < 0.001 | 0.278 | A.II < A.I**<br>A.III < A.I** |
| B | seGHQ | 42.00 | 192.08 | 15.50 | 96.29 | 20.00 | 116.65 | 79.89 | < 0.001 | 0.297 | B.II < B.I**<br>B.III < B.I** |
| C | PSS-10 | 18.00 | 108.93 | 20.00 | 144.90 | 21.00 | 156.95 | 18.07 | < 0.001 | 0.067 | C.I < C.II**<br>C.I < C.III** |
| D | ISI | 10.00 | 138.16 | 6.00 | 129.11 | 10.00 | 140.96 | 1.16 | 0.561 | 0.004 | n.i. |

Mdn– median; Mrang– mean range; H– Kruskall-Wallis test result; *p*– p-value; *ε2*– effect size

After analysis of each ISI item, we observed several statistically significant differences. D group respondents were more likely to complain of difficulties with falling asleep than T group. They also more frequently reported having difficulties staying asleep or waking up too early. Additionally, the distress about their current sleep problem was reported more frequently than in T group. Despite this, dissatisfaction with current sleep pattern was higher in T group than D group. P group reported more complaints on interference of experienced sleep problem with their daily functioning than T group. They also more frequently reported distress related to the sleep problem. There were no statistically significant differences in noticeability of experienced sleep problem between the three groups (Table 7).

**Table 7.** Comparison of sleep complaints measured with ISI between participants wich different chronic medical conditions.

| | | I: Psoriasis | | II: Kidney transplant | | III: Dialysis | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Mdn | Mrang | Mdn | Mrang | Mdn | Mrang | H(2) | p | $\varepsilon^2$ | Post-hoc |
| A | Difficulty falling asleep | 1.00 | 136.03 | 0.00 | 119.01 | 1.00 | 152.85 | 9.29 | 0.010 | 0.035 | A.II < A.III** |
| B | Difficulty staying asleep | 1.00 | 134.09 | 0.00 | 119.90 | 1.50 | 152.52 | 8.31 | 0.016 | 0.031 | B.II < B.III* |
| C | Problems waking up too early | 0.00 | 131.96 | 0.00 | 122.13 | 1.00 | 152.14 | 7.26 | 0.026 | 0.027 | C.II < C.III* |
| D | Dissatisfaction with current sleep pattern | 2.00 | 138.56 | 2.00 | 140.75 | 2.00 | 116.14 | 5.24 | 0.073 | 0.020 | D.III < D.II |
| E | Interference of sleep problem with daily functioning | 2.00 | 143.29 | 1.00 | 120.23 | 2.00 | 139.69 | 5.37 | 0.068 | 0.020 | E.II < E.I |
| F | Noticeability of current sleep problem | 1.00 | 124.00 | 1.00 | 136.71 | 1.00 | 137.94 | 2.01 | 0.366 | 0.008 | n.i. |
| G | Distress about current sleep problem | 1.00 | 140.69 | 0.00 | 113.27 | 1.00 | 151.68 | 13.02 | 0.001 | 0.049 | G.II < G.I*<br>G.II < G.III** |

Mdn– median; Mrang– mean range; H– Kruskall-Wallis test result; *p*– p-value; *ε2*– effect size

*3.6 ANCOVA and multivariate linear stepwise regression results.*

After performing analysis of covariance, we observed total ISI score was mainly mediated by the GHQ-28, PSS-10 and to smaller extent, inversely by previous psychiatric treatment. Among three studied chronic conditions, diagnosis of psoriasis was a potential weak protective factor (compared to T group, which in case of this variable was a control group) in regard to occurrence of sleep disturbances measured with the total ISI score and all its items with exception of noticeability and distress related to the current sleep problem. Additionally, undergoing dialysis was a risk factor of more complaints on noticeability of current sleep problem compared to T group.

Multivariate linear stepwise regression models with backward elimination were built with the use of age, GHQ-28 and PSS-10 and were characterized with moderate predictive values ranging from 0,351 for the whole studied group up to 0,445 for the D group (Table 8). We hypothesize that missing information on current intensity of the symptoms related to the primary disease could further improve the accuracy of the models.

**Table 8.** Multivariate linear stepwise regression models with backward elimination, predictive of the total ISI for the whole study group (N=270), patients with psoriasis, kidney transplant recipients and patients undergoing dialysis. Variables eliminated from the final model are reported with the "p to eliminate" value.

| total ISI score for the whole study group (N=270) | | | | | |
|---|---|---|---|---|---|
| | MS | F | p | β | $R^2$ |
| Intercept | 76.9422 | 2.62444 | 0.106481 | - | 0.351 |
| Age | 129.4704 | 4.41613 | 0.036594 | 0.107825 | |
| GHQ28 | 876.4665 | 29.89557 | 0.000000 | 0.339196 | |
| PSS-10 | 931.3144 | 31.76638 | 0.000000 | 0.346714 | |
| total ISI score for the P group | | | | | |
| Intercept | 16.7987 | 0,55357 | 0.458801 | - | 0.373 |
| Age | Not included in the final model (p=0.66) | | | | |
| GHQ | 191.2090 | 6.30093 | 0.013854 | 0.264621 | |
| PSS-10 | 485.2178 | 15.98944 | 0.000130 | 0.421540 | |
| total ISI score for the T group | | | | | |
| Intercept | 191.706 | 7.92851 | 0.005906 | - | 0.256 |
| Age | Not included in the final model (p=0.45) | | | | |
| GHQ | 1434.340 | 59.32075 | 0.000000 | 0.618000 | |
| PSS-10 | Not included in the final model (p=0.17) | | | | |
| total ISI score for the D group | | | | | |
| Intercept | 31.550 | 1.14400 | 0.288891 | - | 0.445 |
| Age | Not included in the final model (p=0.77) | | | | |
| GHQ | 1440.481 | 52.23169 | 0.000000 | 0.673257 | |
| PSS-10 | Not included in the final model (p=0.06) | | | | |

## 4. DISCUSSION:

In our study we analyze self-reported sleep disturbances in relation to perceived stress level related to the COVID-19 pandemic and psychological wellbeing in three groups of chronically-ill patients. In our previous research we have observed that almost half of the studied population of chronically-ill patients reported symptoms indicative of a depressive episode or anxiety [26]. Previous studies conducted in the general population, students or medical professionals associate diagnosis of a chronic disease with more aggravated sleep disturbances, reporting increased severity of insomnia symptoms in participants who reported a diagnosis of chronic condition [33–36]. In a study by Wankowicz et al. patients with a diagnosis of lupus erythematosus were shown to score twice higher in ISI than control group [37]. Additionally, multimorbidity has been linked to both increased number of missed medical appointments and worse sleep-related outcomes during the COVID-19 pandemic [38].

In a study by Alhadi and Alhuwaydi the mean ISI score of the university students was 12.9, whereas we recorded a lower mean score of 9.04 [39]. We hypothesize that, alongside to the older age of our participants, this difference may be related to the later phase of the pandemic during which we collected the data and in which partial habituation to the stressor could have been developed. On the other hand, we recorded lower percentage of clinical insomnia according to ISI than patients with fibromyalgia in a study by Aloush et al. [40].

It has been shown that while psychological distress measured with psychometric tools such as the Patient Health Questionnaire-9, the Generalized Anxiety Disorder-7 or the Impact of Event Scale-Revised correlates with the current stage of the chronic kidney disease, undergoing dialysis directly correlates with increased ISI score only [41]. This additional impact of regular medical procedures may be related to the necessity of frequent hospital visits and associated fear of infection in this group of patients prior to the SARS-CoV-2 vaccines development. In a study by Yu et al., patients with end-stage kidney disease undergoing hemodialysis were shown to exhibit higher ISI scores than the group receiving peritoneal dialysis during the COVID-19 pandemic [42]. This finding emphasizes the impact of regular medical procedures on the mental health of patients at risk of SARS-CoV-2 infection. In our study, we observed similar ISI scores in all three groups regardless of the primary diagnosis and associated therapeutic plan. However, these results were obtained in the presence of different GHQ-28 and PSS-10 scores, with P group patients reporting significantly higher GHQ-28 and significantly lower PSS-10, which may suggest a moderating impact of mental wellbeing and perceived stress on sleep complaints. Compared to the study by Yu et al., we obtained similar mean ISI scores, despite the fact that we recorded more participants reporting symptoms indicative of moderate and severe clinical insomnia. This difference may also be related to the slightly earlier phase of the pandemic during our study and lesser time for adaptation to the new stress factor in our study group.

Another study conducted during the early phase of the COVID-19 pandemic revealed that prevalence of insomnia measured with ISI in a group of 305 Chinese organ recipients was 11.8% [43]. There are varied outcomes related to sleep disturbances measured with ISI in the general population depending on the country and phase of pandemic with most of them ranging from 11.5 to 20% [44–47]. In our study group of chronically-ill patients, we recorded 25.2% of the participants above the cut-off point (scores 15 and more) with no significant differences between kidney transplant recipients and other groups. We hypothesize that in addition to a primary chronic condition the higher prevalence of moderate and severe clinical insomnia may be mediated by sociocultural differences. Moreover, our results show resemblance to 30-32% prevalence of insomnia obtained in the meta-analyses of the studies conducted at the early phase of the pandemic with inclusion of medical professionals who were even more frequently exposed to potential SARS-CoV-2 infection at their place of work [48,49]. However, further research on larger groups is required in order to establish the mechanism of increased sleep complaints in the patients with chronic conditions during the pandemic conditions.

We observed a high frequency of complaints regarding satisfaction with current sleep pattern,

which stands out in relation to relatively fewer complaints regarding difficulties with falling or staying asleep. Moreover, main complaints reported by the study participants concerned interference of the sleep problem with their daily functioning and noticeability of their decreased sleep quality to others. It seems that in circumstances of a global stress factor presence, satisfaction with current sleep pattern may be a sensitive indicator of experienced stress even without acknowledging it during daily life. We believe that this profile of answers to ISI, with less substantiation by the more objective sleep indicators may indicate the underlying anxiety in the chronically-ill patients during the uncertain pandemic conditions. Previous research links sleep satisfaction to individual health status but also to frequency of healthcare seeking behaviors [50]. While the participants of our study are at risk of dissatisfaction with current sleep quality due to their primary diagnosis, objectivization of their symptoms is recommended in order to reduce unnecessary self-medicating behavior.

Prior to the COVID-19 pandemic, patients with a diagnosis of psoriasis have been shown to manifest increased psychological distress measured with a 12-item General Health Questionnaire [51]. In our study we used a 28-item version of this tool and observed significantly increased GHQ-28 scores in P group compared to T and D groups. Interestingly, these outcomes could not be fully explained by correlation with PSS-10 or ISI scores indicating initially increased psychological distress related to a psoriasis diagnosis and potentially to the associated significantly higher duration of the disease. Additionally, potential bias resulting from online version of the questionnaire could contribute to these results. What is more, we observed higher interference of reported sleep problem with daily functioning and higher distress directly associated with sleep in P group, whereas the same group also reported lower level of dissatisfaction with current sleep pattern. It is our understanding that the perceived distress and daily functioning were not fully related to the sleep quality linking these findings with the increased GHQ-28 scores.

The core ISI complaints related to difficulties with falling and staying asleep or waking up too early were found to be significantly more frequently reported in the D group. The necessity of undergoing long and regular medical procedures, such as hemodialysis, at varied time of a day has been shown to impact the sleep of patients regardless of the COVID-19 pandemic. Hence, this finding is consistent with existing knowledge [24,25].

After correlating ISI scores with GHQ28 and seGHQ scores we obtained similar results of 0.504 and 0.466 respectively indicating a small contribution of two questions used for assessment of sleep in GHQ28 to this association. More importantly, our research confirms previous finding on the correlations of female sex and perceived stress with ISI [6,12]. However, we did not observe a significant correlation with younger age [8], which may indicate that its effect size is decreased in the presence of a chronic disease in comparison to the general population. Previous psychiatric treatment and psychotherapy corresponded with significantly increased ISI scores which suggests that the population of people with previous mental disorders may be at risk for sleep disturbances in the circumstances of the pandemic. Our findings are consistent with a meta-analysis of polysomnographic research conducted by Baglioni et al. in patients with mental disorders who were shown to have significantly altered sleep profiles [52].

Although sleep disturbances during the COVID-19 pandemic may have a transient character, research shows that they have a large impact on the health-related quality of life [53]. Therefore, additional focus is required in order to screen for and reduce sleep complaints. So far, most non-pharmacological interventions aimed at improving sleep are characterized as low certainty in existing studies and require further prospective studies [54]. However, several reports shed light onto interventions especially relevant during the COVID-19 pandemic. Research shows that cognitive behavioral therapy is effective in reducing ISI scores in patients with SARS-CoV-2 infection [55]. Psychoeducational interventions aimed at sufficient exercise and good sleep hygiene remain especially important in circumstances of reorganized daily life with less time spent outside and working from home. Similarly, beneficial impact of social support has been highlighted in the recent findings on sleep quality during the COVID-19 pandemic [12,56,57]. In a study by

Grey et al., participants with high social support were 52% less likely to report poor sleep quality. These findings remain especially relevant in the population of patients diagnosed with chronic conditions who were advised to refrain from social contacts and therefore are at risk of worsened social support.

Our study reports findings on occurrence and intensity of insomnia in chronically-ill patients during the first wave of the COVID-19 pandemic. We were able to recruit a relatively large group of participants with diagnoses of psoriasis, recipients of kidney transplant and patients undergoing regular dialysis. However, our results are limited by several factors: 1) The studied groups were not matched in terms of sociodemographic characteristics, such as sex or education; 2) The clinical symptoms of each disease were not measured leading to a lack of control over the influence of these variables on the sleep disturbances and potentially decreasing the adjustment of the obtained regression models and 3) Due to the global character of COVID-19 pandemic we were unable to recruit control group. At the time of our study, only few participants were already individually affected by COVID-19 or quarantines. Hence, we were not able to analyze the impact of infections and individual restrictions on the outcomes of the study.

## 5. CONCLUSIONS

We observed 25.2% prevalence of results indicative of clinical insomnia in the group of chronically-ill patients during the first wave of pandemic. We hypothesize that a relatively large portion of the participants reporting sleep-related complaints may be associated with the necessity of frequent hospital visits during the COVID-19 pandemic, like in patients after renal transplant or dialysis patients, or to the pre-existent psychological distress, as in case of psoriasis patients who also scored higher in GHQ-28. Our research confirms association of female sex and chronic disease with more aggravated sleep disturbances. However, we did not confirm a correlation of younger age with insomnia symptoms. Findings of our study suggest that population of patients with chronic medical conditions, with special emphasis on those who have a simultaneous history of psychiatric or psychological treatment, requires additional attention in order to objectivize and maintain sleep disorders, especially during stressful conditions such as pandemic. Wide-targeted screening and interventions focused on psychoeducation should be implemented alongside non-pharmacological and pharmacological methods of treatment in order to improve sleep patterns and significantly increase health-related quality of life of patients with chronic medical conditions.

## REFERENCES

1. Chen PJ, Pusica Y, Sohaei D, Prassas I, Diamandis EP. An overview of mental health during the COVID-19 pandemic. Diagnosis. 2021;8(4):403–12.
2. Banerjee D, Rai M. Social isolation in Covid-19: The impact of loneliness. Int J Soc Psychiatry. 2020;66(6):525–7.
3. Brown LA, Hamlett GE, Zhu Y, Wiley JF, Moore TM, DiDomenico GE, et al. Worry about COVID-19 as a predictor of future insomnia. J Sleep Res. 2022;31(5):1–11.
4. Lin L yu, Wang J, Ou-yang X yong, Miao Q, Chen R, Liang F xia, et al. The immediate impact of the 2019 novel coronavirus (COVID-19) outbreak on subjective sleep status. Sleep Med. 2021;77:348–54.
5. Huang Y, Zhao N. Generalized anxiety disorder, depressive symptoms and sleep quality during COVID-19 outbreak in China: a web-based cross-sectional survey. Psychiatry Res. 2020;288(March).
6. Gualano MR, Lo Moro G, Voglino G, Bert F, Siliquini R. Effects of Covid-19 Lockdown on Mental Health and Sleep Disturbances in Italy. Int J Environ Res Public Health [Internet]. 2020 Jul 2;17(13):4779. Available from: https://www.mdpi.com/1660-4601/17/13/4779
7. Gorgoni M, Scarpelli S, Mangiaruga A, Alfonsi V, Bonsignore MR, Fanfulla F, et al. Pre-sleep arousal and sleep quality during the COVID-19 lockdown in Italy. Sleep Med. 2021;88:46–57.
8. Morin CM, Bjorvatn B, Chung F, Holzinger B, Partinen M, Penzel T, et al. Insomnia, anxiety, and depression during the COVID-19 pandemic: an international collaborative study. Sleep Med. 2021;87:38–45.
9. Alharbi AS, Alshahrani SM, Alsaadi MM, AL-Jahdali HH, Wali SO, BaHammam AS. Sleep quality and insomnia during the covid-19 lockdown among the saudi public. Saudi Med J. 2021;42(4):384–90.
10. Pinto J, van Zeller M, Amorim P, Pimentel A, Dantas P, Eusébio E, et al. Sleep quality in times of Covid-19 pandemic. Sleep Med. 2020;74:81–5.
11. Zhang SX, Chen RZ, Xu W, Yin A, Dong RK, Chen BZ, et al. A Systematic Review and Meta-Analysis of Symptoms of

Anxiety, Depression, and Insomnia in Spain in the COVID-19 Crisis. Int J Environ Res Public Health. 2022;19(2):1–15.

12. Yuan K, Zheng YB, Wang YJ, Sun YK, Gong YM, Huang YT, et al. A systematic review and meta-analysis on prevalence of and risk factors associated with depression, anxiety and insomnia in infectious diseases, including COVID-19: a call to action. Mol Psychiatry. 2022;(May).
13. Halioua B, Chelli C, Misery L, Taieb J, Taieb C. Sleep Disorders and Psoriasis: An Update. Acta Derm Venereol. 2022;102(25):1–8.
14. Lindner A V., Novak M, Bohra M, Mucsi I. Insomnia in Patients With Chronic Kidney Disease. Semin Nephrol [Internet]. 2015;35(4):359–72. Available from: http://dx.doi.org/10.1016/j.semnephrol.2015.06.007
15. Pierratos A, Hanly PJ. Sleep disorders over the full range of chronic kidney disease. Blood Purif. 2011;31(1–3):146–50.
16. White CP, White MB. Sleep problems and fatigue in chronically ill women. Behav Sleep Med. 2011;9(3):144–61.
17. Kotronoulas G, Wengström Y, Kearney N. Sleep and sleep-wake disturbances in care recipient-caregiver dyads in the context of a chronic illness: A critical review of the literature. J Pain Symptom Manage. 2013;45(3):579–94.
18. Henry AL, Kyle SD, Bhandari S, Chisholm A, Griffiths CEM, Bundy C. Measurement, Classification and Evaluation of Sleep Disturbance in Psoriasis: A Systematic Review. PLoS One. 2016;11(6):1–18.
19. Sahin E, Hawro M, Weller K, Sabat R, Philipp S, Kokolakis G, et al. Prevalence and factors associated with sleep disturbance in adult patients with psoriasis. J Eur Acad Dermatology Venereol. 2022;36(5):688–97.
20. Gupta MA, Simpson FC, Gupta AK. Psoriasis and sleep disorders: A systematic review. Sleep Med Rev [Internet]. 2016;29:63–75. Available from: http://dx.doi.org/10.1016/j.smrv.2015.09.003
21. Controne I, Scoditti E, Buja A, Pacifico A, Kridin K, Fabbro M Del, et al. Do Sleep Disorders and Western Diet Influence Psoriasis? A Scoping Review. Nutrients. 2022;14(20):1–16.
22. Nigam G, Camacho M, Chang E, Riaz M. Exploring sleep disorders in patients with chronic kidney disease. Nat Sci Sleep [Internet]. 2018 Jan;Volume 10:35–43. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5797456/pdf/nss-10-035.pdf
23. Maung SC, Sara A El, Chapman C, Cohen D, Cukor D. Sleep disorders and chronic kidney disease. World J Nephrol [Internet]. 2016;5(3):224. Available from: http://www.wjgnet.com/2220-6124/full/v5/i3/224.htm
24. Tan LH, Chen PS, Chiang HY, King E, Yeh HC, Hsiao YL, et al. Insomnia and Poor Sleep in CKD: A Systematic Review and Meta-analysis. Kidney Med [Internet]. 2022;4(5):100458. Available from: https://doi.org/10.1016/j.xkme.2022.100458
25. Scherer JS, Combs SA, Brennan F. Sleep Disorders, Restless Legs Syndrome, and Uremic Pruritus: Diagnosis and Treatment of Common Symptoms in Dialysis Patients. Am J Kidney Dis [Internet]. 2017 Jan;69(1):117–28. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0272638616304188
26. Pawłowski M, Fila-Witecka K, Rymaszewska JE, Kamińska D, Poznański P, Augustyniak-Bartosik H, et al. Psychopathological Symptoms Among Chronically Ill Patients During SARS-CoV-2 Pandemic in Poland. Psychol Res Behav Manag. 2022;15:2659–69.
27. Cuschieri S. The STROBE guidelines. Saudi J Anaesth. 2019;13(5):S31–4.
28. Bastien CH, Vallières A, Morin CM. Validation of the insomnia severity index as an outcome measure for insomnia research. Sleep Med. 2001;2(4):297–307.
29. Morin CM, Belleville G, Bélanger L, Ivers H. The insomnia severity index: Psychometric indicators to detect insomnia cases and evaluate treatment response. Sleep. 2011;34(5):601–8.
30. Goldberg DP, Hillier VF. A scaled version of the General Health Questionnaire. Psychol Med. 1979;9(1):139–45.
31. Makowska Z, Merecz D, Mościcka A, Kolasa W. The validity of General Health Questionnaires, GHQ-12 and GHQ-28, in mental health studies of working people. Int J Occup Med Environ Health. 2002;15(4):353–62.
32. Cohen S, Kamarck T, Mermelstein R. A Global Measure of Perceived Stress. J Health Soc Behav [Internet]. 1983 Dec;24(4):385. Available from: https://www.jstor.org/stable/2136404
33. Özçelik N, Kesin HV, Telatar G, Özyurt S, Yılmaz Kara B, Gümüş A, et al. "COVID-Somnia" in healthcare workers during the pandemic. Hosp Pract (1995) [Internet]. 2022;50(4):273–81. Available from: https://doi.org/10.1080/21548331.2022.2102777
34. Alkahtani RF, Alomar AA, Alkanhal AF, Alhinti MF, Alatoui SE, Alrashidi RR, et al. Prevalence of Anxiety, Depression, and Sleep Disturbances Associated With the COVID-19 Outbreak in Riyadh, Saudi Arabia. Cureus. 2022;14(5).
35. Wańkowicz P, Szylińska A, Rotter I. Insomnia, anxiety, and depression symptoms during the COVID-19 pandemic may depend on the pre-existent health status rather than the profession. Brain Sci. 2021;11(8).
36. Wańkowicz P, Szylińska A, Rotter I. The impact of the covid-19 pandemic on psychological health and insomnia among people with chronic diseases. J Clin Med. 2021;10(6):1–8.
37. Wańkowicz P, Szylińska A, Rotter I. Evaluation of mental health factors among people with systemic lupus erythematosus during the sars-cov-2 pandemic. J Clin Med. 2020;9(9):1–8.
38. Shan Wong SY, Zhang D, Shan Sit RW, Kei Yip BH, Chung RY, Man Wong CK, et al. Impact of COVID-19 on loneliness, mental health, and health service utilisation: A prospective cohort study of older adults with multimorbidity in primary care. Br J Gen Pract. 2020;70(700):E817–24.

39. Alhadi AN, Alhuwaydi AM. Insomnia Prevalence and Associated Factors Among University Students in Saudi Arabia During the COVID-19 Pandemic and Lockdown: A Large-Scale Survey. Nat Sci Sleep. 2022;14(September):1651–63.
40. Aloush V, Gurfinkel A, Shachar N, Ablin JN, Elkana O. Physical and mental impact of COVID-19 outbreak on fibromyalgia patients. Clin Exp Rheumatol [Internet]. 2021 Jun 21;39(3):108–14. Available from: https://www.clinexprheumatol.org/abstract.asp?a=16897
41. Lee KM, Kim JS, Hwang S, Cho NJ, Park S, Gil HW, et al. The Higher the CKD Stage, the Higher the Psychological Stress in Patients with CKD during COVID-19 Pandemic. J Clin Med. 2022;11(16).
42. Yu JY, Kim JS, Hong CM, Lee KY, Cho NJ, Park S, et al. Psychological distress of patients with endstage kidney disease undergoing dialysis during the 2019 coronavirus disease pandemic: A cross-sectional study in a University Hospital. PLoS One [Internet]. 2021;16(12 December):1–14. Available from: http://dx.doi.org/10.1371/journal.pone.0260929
43. Cai Z, Cai X, Song Y, Wang D, Zhang Y, Ma S, et al. Psychological Distress and Its Association With Quality of Life in Organ Transplant Recipients During COVID-19 Pandemic. Front Psychiatry. 2021;12(June).
44. Habbash F, Salah A Ben, Almarabheh A, Jahrami H. Insomnia and Related Factors During the Delta Wave of the COVID-19 Pandemic in the Kingdom of Bahrain: A Cross-Sectional Study. Nat Sci Sleep. 2022;14(October):1963–75.
45. Kokou-Kpolou CK, Megalakaki O, Laimou D, Kousouri M. Insomnia during COVID-19 pandemic and lockdown: Prevalence, severity, and associated risk factors in French population. Psychiatry Res [Internet]. 2020;290:113128. Available from: https://doi.org/10.1016/j.psychres.2020.113128
46. Pieh C, Budimir S, Probst T. The effect of age, gender, income, work, and physical activity on mental health during coronavirus disease (COVID-19) lockdown in Austria. J Psychosom Res [Internet]. 2020;136(May):110186. Available from: https://doi.org/10.1016/j.jpsychores.2020.110186
47. Alqahtani JS, Alrabeeah SM, Aldhahir AM, Siraj R, Aldabayan YS, Alghamdi SM, et al. Sleep Quality, Insomnia, Anxiety, Fatigue, Stress, Memory and Active Coping during the COVID-19 Pandemic. Int J Environ Res Public Health. 2022;19(9):1–11.
48. Pappa S, Ntella V, Giannakas T, Giannakoulis VG, Papoutsi E, Katsaounou P. Prevalence of depression, anxiety, and insomnia among healthcare workers during the COVID-19 pandemic: A systematic review and meta-analysis. Brain Behav Immun [Internet]. 2020 Aug;88(1):901–7. Available from: https://linkinghub.elsevier.com/retrieve/pii/S088915912030845X
49. Krishnamoorthy Y, Nagarajan R, Saya GK, Menon V. Prevalence of psychological morbidities among general population, healthcare workers and COVID-19 patients amidst the COVID-19 pandemic: A systematic review and meta-analysis. Psychiatry Res. 2020;293(May).
50. Abraham O, Pu J, Schleiden LJ, Albert SM. Factors contributing to poor satisfaction with sleep and healthcare seeking behavior in older adults. Sleep Heal [Internet]. 2017;3(1):43–8. Available from: http://dx.doi.org/10.1016/j.sleh.2016.11.004
51. Finzi A, Colombo D, Caputo A, Andreassi L, Chimenti S, Vena G, et al. Psychological distress and coping strategies in patients with psoriasis: The PSYCHAE Study. J Eur Acad Dermatology Venereol. 2007;21(9):1161–9.
52. Baglioni C, Nanovska S, Regen W, Spiegelhalder K, Feige B, Nissen C, et al. Sleep and mental disorders: A meta-analysis of polysomnographic research. Psychol Bull [Internet]. 2016 Sep;142(9):969–90. Available from: https://pubmed.ncbi.nlm.nih.gov/27165699%0Ahttps://www.ncbi.nlm.nih.gov/pmc/articles/PMC5664198/%0Afile:///C:/Users/Carla Carolina/Desktop/Artigos para acrescentar na qualificação/The impact of birth weight on cardiovascular disease risk in the.pdf
53. Soh HS, Cho BL. Long COVID-19 and Health-Related Quality of Life of Mild Cases in Korea: 3-Months Follow-up of a Single Community Treatment Center. J Korean Med Sci. 2022;37(46):1–14.
54. Natale P, Ruospo M, Saglimbene VM, Palmer SC, Strippoli GF. Interventions for improving sleep quality in people with chronic kidney disease. Cochrane Database Syst Rev [Internet]. 2019 May 26; Available from: https://doi.wiley.com/10.1002/14651858.CD012625.pub2
55. He J, Yang L, Pang J, Dai L, Zhu J, Deng Y, et al. Efficacy of simplified-cognitive behavioral therapy for insomnia (S-CBTI) among female COVID-19 patients with insomnia symptom in Wuhan mobile cabin hospital. Sleep Breath. 2021;25(4):2213–9.
56. Grey I, Arora T, Thomas J, Saneh A, Tomhe P, Abi-Habib R. The role of perceived social support on depression and sleep during the COVID-19 pandemic. Psychiatry Res. 2020;293(May).
57. Xiao H, Zhang Y, Kong D, Li S, Yang N. The effects of social support on sleep quality of medical staff treating patients with coronavirus disease 2019(COVID-19) in January and February 2020 in China. Med Sci Monit. 2020;26:1–8.

# 7. Podsumowanie wyników

Pierwsza z prac opublikowana w ramach tego cyklu (27) stanowi przegląd literatury i analizuje dotychczasową wiedzę dotyczącą procesów neurozapalnych i neurodegeneracyjnych w kontekście wpływu wirusa SARS-CoV-2 na ośrodkowy układ nerwowy. Ponadto, omówione w niej zostały również potencjalne czynniki ochronne mające na celu redukcję intensywności procesów neurodegeneracyjnych.

Aktywacja układu immunologicznego stanowi jeden z kluczowych elementów chorób neurodegeneracyjnych, a szczególnie zespołów otępiennych takich jak choroba Alzheimera, otępienia naczyniopochodnego, czołowo-skroniowego czy otępienia z ciałami Lewy'ego (28). Przewlekła aktywacja prozapalna w organizmie prowadzi do zwiększenia przepuszczalności bariery krew-mózg, wzrostu stężenia cytokin prozapalnych w ośrodkowym układzie nerwowym oraz do aktywacji komórek glejowych. Na skutek wymienionych procesów dochodzi do dalszej produkcji cytokin prozapalnych w obrębie mózgu, nasilenia lokalnej odpowiedzi immunologicznej oraz do uszkodzenia neuronów, w tym połączeń synaptycznych (29).

Źródłem przewlekłej aktywacji prozapalnej mogą być choroby przewlekłe, takie jak choroby autoimmunologiczne, cukrzyca typu 2 czy otyłość. Obecnie w rozwoju patologii wymienia się również inne czynniki, takie jak dieta, skład mikrobioty jelitowej czy nawet czynniki stresowe o charakterze psychospołecznym (30–32). Szerokie rozpowszechnienie nowego czynnika infekcyjnego z grupy koronawirusów, SARS-CoV-2, zyskało szczególne znaczenie w kontekście procesów neurozapalnych ze względu na udowodniony neurotropizm wirusa oraz doniesienia dotyczące pojawiania się powikłań neuropsychiatrycznych na skutek przechorowania COVID-19 (12,33). Do krótkoterminowych powikłań należą między innymi encefalopatie i zapalenie opon mózgowo-rdzeniowych, jednak wczesne doniesienia wskazują na powiązanie zachorowania na COVID-19 z występowaniem tzw. „zespołu pocovidowego" (ang. *Post-COVID syndrome*) oraz długotrwałym spadkiem sprawności funkcji poznawczych (11,34). Choć mechanizm powstawania tych powikłań nie został dotychczas w pełni opisany, to do ich rozwoju może dochodzić

między innymi na skutek dostawania się obwodowych cytokin prozapalnych, takich jak czynnik martwicy nowotworów (*Tumor Necrosis Factor*, TNF), produkowanych w przebiegu infekcji, do ośrodkowego układu nerwowego poprzez komórki endotelialne współtworzące barierę krew-mózg (35).

W wyniku procesów zapalnych komórki glejowe, astrocyty i mikroglej, zmieniają swój fenotyp tracąc funkcję ochronną wobec neuronów. Aktywowane komórki glejowe uczestniczą w lokalnej produkcji cytokin prozapalnych zaburzając między innymi degradację amyloidu, prowadząc do mikroglejozy oraz upośledzając funkcję synaps (16,19,36).

Wśród interwencji mających na celu zmniejszenie aktywacji prozapalnej wyróżnić można metody farmakologiczne i niefarmakologiczne. Do tych ostatnich należą diety o niskim indeksie zapalnym (ang. *Dietary Inflammatory index*), których przykładem jest dieta śródziemnomorska (37). Spośród metod farmakologicznych, wymieniane są niesteroidowe leki przeciwzapalne oraz biologiczne leki z grupy inhibitorów TNF, takie jak etanercept czy infliximab. Dotychczasowe meta-analizy wskazują na niewielkie korzyści ze stosowania niesteroidowych leków przeciwzapalnych celem podtrzymania sprawności funkcji poznawczych przy istotnym ryzyku występowania działań niepożądanych, takich jak krwawienia z przewodu pokarmowego, przy ich długotrwałym stosowaniu (38,39). W przypadku inhibitorów TNF udowodniony został ich korzystny wpływ w redukcji procesów neurodegeneracyjnych na poziomie molekularnym i modelach zwierzęcych (40,41). Prowadzone obecnie badania kliniczne odpowiedzą na pytanie, czy dzięki ich zastosowaniu możliwe będzie podtrzymanie sprawności funkcji poznawczych osób rozwijających objawy zespołu otępiennego.

Celem pierwszej z prac oryginalnych w cyklu (42) jest analiza strategii radzenia sobie ze stresem w postaci pandemii COVID-19 w grupie przewlekle chorych pacjentów. Badanie zostało przeprowadzone w trakcie pierwszej fali zachorowań na COVID-19 a

jego uczestnikami były następujące grupy pacjentów: pacjenci z rozpoznaniem łuszczycy, stwardnienia rozsianego, biorcy przeszczepu nerki oraz pacjenci dializowani. Strategie radzenia sobie zostały zbadane w odniesieniu do poziomu odczuwanego stresu oraz czynników socjodemograficznych.

Przeprowadzone analizy wykazały, że wśród uczestników badania poziom odczuwanego stresu w związku z pandemią COVID-19 miał w dominującej mierze umiarkowany stopień. Najczęściej stosowanymi strategiami radzenia sobie ze stresem w tej grupie były strategie skupiające się na problemie, a zwłaszcza aktywne radzenie sobie, planowanie oraz pozytywne przewartościowanie. Spośród strategii skupiających się na emocjach najczęściej stosowanymi były akceptacja oraz wsparcie emocjonalne, a najrzadziej stosowaną był humor. Najrzadziej stosowaną grupę strategii radzenia sobie wśród osób przewlekle chorych stanowiły strategie unikające, a szczególnie zażywanie substancji psychoaktywnych.

Przeprowadzone porównania grup pacjentów ze względu na stan zdrowia wykazały szereg interesujących różnic. Badani ze stwardnieniem rozsianym i biorcy przeszczepu nerki w istotnie większym stopniu posługiwali się strategią akceptacji, w porównaniu do pacjentów z łuszczycą, oraz istotnie częściej korzystali ze strategii aktywnego radzenia sobie ze stresem niż pacjenci dializowani. Pacjenci ze stwardnieniem rozsianym w odniesieniu do grupy pacjentów po przeszczepie nerki w większym stopniu przejawiali strategię obwiniania siebie, a także częściej niż pacjenci z łuszczycą sięgali po strategie oparte o pozytywne przewartościowanie i ukierunkowane na emocje. Ponadto, badani z rozpoznaniem stwardnienia rozsianego w istotnie większym stopniu wykorzystywali strategie wyładowania oraz zajmowania się czymś innym, niż pacjenci cierpiący na łuszczycę i pacjenci po przeszczepie nerki. Okazało się również, że pacjenci dializowani częściej sięgali po poszukiwanie wsparcia emocjonalnego niż pacjenci z łuszczycą, a także częściej niż pacjenci z łuszczycą i biorcy przeszczepu nerki wykorzystywali strategię zaprzeczania. Zaobserwowano również, że zarówno pacjenci ze stwardnieniem rozsianym, jak i pacjenci dializowani, częściej stosowali strategię zaprzestania działań

i strategie ukierunkowane na unikanie w odniesieniu do pozostałych grup. Z kolei pacjenci z rozpoznaniem łuszczycy i stwardnienia rozsianego w istotnie większym stopniu sięgali po substancje psychoaktywne w celu radzenia sobie ze stresem, oraz istotnie rzadziej zwracali się w kierunku religii.

Stosowane strategie radzenia sobie ze stresem w istotnym stopniu korelowały również z poszczególnymi czynnikami socjodemograficznymi. W odniesieniu do uczestników badania płci męskiej, uczestniczki częściej deklarowały stosowanie strategii z grupy skupiającej się na emocjach, w tym obwiniania siebie, wsparcia emocjonalnego, wyładowania, a także strategii z grupy unikającej, a zwłaszcza zaprzestania działań oraz zaprzeczenia. Zaobserwowano również korelację między wiekiem a zwrotem ku religii, podczas gdy większość z pozostałych strategii radzenia sobie była ujemnie skorelowana z wiekiem.

Aktywni zawodowo uczestnicy badania istotnie częściej deklarowali stosowanie aktywnego radzenia sobie, planowania, poszukiwania wsparcia emocjonalnego, poszukiwania wsparcia instrumentalnego, wyładowania, zajmowania się czymś innym, zażywania substancji psychoaktywnych oraz strategii skoncentrowanych na problemie i strategii ukierunkowanych na unikanie, niż osoby niepracujące. Osoby z wykształceniem średnim i wyższym cechowały się istotnie częstszym stosowaniem akceptacji, obwiniania siebie, a także częstszym wykorzystywaniem strategii skupiających się na emocjach, niż osoby z wykształceniem podstawowym i zawodowym.

Co ciekawe, uczestnicy którzy zgłaszali wcześniejsze leczenie psychiatrycznie w istotnie większym stopniu wykorzystywali strategie obwiniania siebie, zażywania substancji psychoaktywnych oraz grupy strategii ukierunkowanych na unikanie, a jednocześnie istotnie rzadziej wykorzystywały zwrot ku religii. Osoby deklarujące wcześniejsze oddziaływania psychologiczne wykazywały istotnie wyższe wyniki na wymiarach obwiniania siebie, poczucia humoru, wyładowania, zajmowania się czymś innym, zaprzestania działań, zażywania substancji psychoaktywnych, a także istotnie

wyższe wykorzystywanie strategii ukierunkowanych na emocje i ukierunkowanych na unikanie.

W badanej próbie wraz ze wzrostem czasu trwania choroby spadał w stopniu słabym poziom wykorzystywania strategii obwiniania siebie. Odnotowano również, że wraz ze wzrostem poziomu odczuwanego stresu wzrastał silnie wskaźnik strategii obwiniania siebie, natomiast w stopniu umiarkowanym rósł wskaźnik strategii ukierunkowanych na unikanie, strategii zaprzestania działań, zaprzeczania oraz wyładowania.

Wyniki przeprowadzonych analiz pozostają zgodne z dostępną literaturą naukową, choć pojawiają się w nich różne pewne istotne różnice, które wynikać mogą między innymi z czynników o charakterze społecznym i kulturowym, ale także z charakterystyki badanej grupy osób chorujących przewlekle. Porównanie grup chorych identyfikuje pacjentów ze stwardnieniem rozsianym jako grupę o mniej korzystnym profilu radzenia sobie niż biorcy przeszczepu nerek.

Badania przeprowadzone w polskiej populacji ogólnej wykazały związek między płcią żeńską, młodszym wiekiem oraz wcześniejszym rozpoznaniem choroby przewlekłej a stosowaniem mniej adaptacyjnych strategii radzenia sobie ze stresem i występowaniem objawów psychopatologicznych (43). Wyniki przeprowadzonego badania potwierdzają zależność między profilem stosowanych strategii radzenia sobie a płcią. Zaobserwowany spadek częstości obwiniania siebie wraz z dłuższym czasem od postawienia rozpoznania choroby podstawowej może jednak sugerować adaptacyjne zwiększenie prężności psychicznej w związku z długotrwałym utrzymywaniem stresora w postaci choroby (44). Uczestnicy badania wykazali również znacząco rzadsze stosowanie strategii unikającej w postaci zażywania środków psychoaktywnych w odniesieniu do populacji ogólnej, co wiązać należy z większą troską o własne zdrowie wynikającą z postawionego rozpoznania choroby przewlekłej oraz stosowanego leczenia (45,46).

Otrzymane wyniki potwierdzają również wcześniej opisywaną zależność między wyższym nasileniem odczuwanego stresu a stosowaniem odwracania uwagi,

zażywaniem środków psychoaktywnych, wyładowania, zaprzeczenia, zaprzestania działań oraz obwiniania siebie wśród pacjentów chorujących przewlekle (47,48). W grupie badanej nie potwierdzono jednak związku między wyższym poziomem odczuwanego stresu a aktywnym radzeniem sobie, planowaniem czy zwrotem ku religii.

W przeprowadzonych analizach zaobserwowano silną korelację między wcześniejszym leczeniem psychiatrycznym i psychoterapią a kilkoma nieadaptacyjnymi strategiami radzenia sobie, takimi jak obwinianie siebie, zaprzestanie działań, zażywanie substancji psychoaktywnych oraz unikających strategii radzenia sobie. Możliwe jest, że podczas gdy zarówno pacjenci z historią leczenia psychiatrycznego, jak i osoby wybierające psychoterapię, są początkowo bardziej skłonne do stosowania nieadaptacyjnych strategii radzenia sobie, ci ostatni mogą również odnosić korzyści w postaci uzyskania długotrwałych zmian i wypracowania bardziej adaptacyjnych strategii. Wskazuje na to częstsze wykorzystanie humoru i strategii skupiających się na emocjach, które można wyróżnić w ich zachowaniu.

Omówione powyżej wyniki charakteryzują się również pewnymi ograniczeniami wynikającymi z charakteru badania. Grupy pacjentów nie były dopasowane pod względem charakterystyk socjodemograficznych, takich jak płeć czy wykształcenie. Ponadto, ze względu na zastosowanie kwestionariuszy online, rekrutacja pacjentów z łuszczycą i stwardnieniem rozsianym do badania nie została poprzedzona potwierdzeniem diagnozy za pomocą dokumentacji medycznej.

Ostatnia z prac w cyklu analizuje występowanie subiektywnych skarg dotyczących zaburzeń snu w trzech grupach pacjentów z chorobami przewlekłymi, którzy poddawani byli regularnym wizytom medycznym i leczeniu podczas pierwszej fazy pandemii COVID-19. W badaniu uczestniczyli pacjenci z rozpoznaniem łuszczycy, biorcy przeszczepu nerki oraz pacjenci dializowani.

Pośród uczestników badania, 25,2% spełniało kryteria umiarkowanej lub ciężkiej bezsenności klinicznej. Średnie nasilenie odczuwanego stresu zmierzonego przy użyciu PSS-10 wynosiło 19,03, a średni wynik GHQ-29 wynosił 29,07 wskazując odpowiednio umiarkowany na umiarkowany poziom odczuwanego stresu oraz prawdopodobieństwo występowania istotnych objawów psychopatologicznych. Wśród wymienianych problemów ze snem dominowało niezadowolenie z jego jakości. W dalszej kolejności zgłaszano wpływ zaburzeń na funkcjonowanie oraz zauważalność problemu dla innych, choć miary tendencji centralnej w tym wypadku plasowały się poniżej mediany teoretycznej, co wskazuje na relatywnie niski poziom rzeczonych problemów. Najrzadziej zgłaszanymi trudnościami były problemy z powodu budzenia się zbyt wcześnie.

Testy rang H Kruskalla-Wallisa oraz post hoc Bonferroniego-Dunn wykazały, że pacjenci z łuszczycą cechowali się istotnie niższym wskaźnikiem zdrowia psychicznego. Jednocześnie pacjenci po przeszczepie nerki i dializowani wykazywali istotnie wyższe nasilenie doświadczanego stresu w odniesieniu do pacjentów z łuszczycą. Nie zaobserwowano różnic między grupami pacjentów pod względem ogólnego wskaźnika nasilenie bezsenności.

W analizie poszczególnych skarg dotyczących zaburzeń snu zaobserwowane istotne różnice między poszczególnymi stanami medycznymi. W przypadku pacjentów dializowanych nasilenie trudności z zasypaniem, trudności z utrzymaniem snu oraz problemów z powodu budzenia się zbyt wcześnie były istotnie wyższe w porównaniu do pacjentów po przeszczepie nerki. Odwrotny efekt odnotowano w przypadku niezadowolenia z jakości snu, które było istotnie wyższe wśród pacjentów po przeszczepie nerki, niż u pacjentów dializowanych. Pacjenci z rozpoznaniem łuszczycy deklarowali istotnie wyższy wpływ zaburzeń snu na funkcjonowanie niż pacjenci po przebytych transplantacjach, natomiast grupa pacjentów z łuszczycą i dializowanych wskazywała na istotnie wyższy stopień zmartwienia z powodu zaburzeń snu niż pacjenci po przeszczepie nerki.

Macierz korelacji obliczona pomiędzy wskaźnikiem nasilenia bezsenności a wiekiem, czasem trwania choroby, oceną stanu zdrowia psychicznego i poziomem odczuwanego stresu wykazała, że w badanej próbie nasilenie zaburzeń snu było silnie związane ze wskaźnikiem oceny stanu zdrowia psychicznego, oraz korelowało umiarkowanie dodatnio z odczuwanym poziomem stresu. Ponadto, nasilenie zaburzeń snu korelowało ujemnie z długością trwania choroby. Nie zaobserwowano istotnego statystycznie związku z wiekiem.

Porównania międzygrupowe przeprowadzone za pomocą testu U Manna-Whitneya wykazały, że w porównaniu do grupy mężczyzn, kobiety wykazywały wyższe nasilenie zaburzeń snu z wynikiem na poziomie tendencji (p=0,063). Okazało się również, że wśród osób, które korzystały z wcześniejszego leczenia psychiatrycznego i pomocy psychologicznej całkowite nasilenie zaburzeń snu było istotnie statystycznie wyższe.

Na podstawie analizy kowariancji zaobserwowano, że całkowity wynik ISI był głównie zależny od GHQ-28, PSS-10 i w mniejszym stopniu, odwrotnie przez poprzednie leczenie psychiatryczne. Spośród trzech badanych grup, diagnoza łuszczycy była potencjalnym słabym czynnikiem ochronnym (w porównaniu z grupą po przeszczepie, która ze względu na największą liczebność była dla tej zmiennej grupą kontrolną) w zakresie występowania zaburzeń snu mierzonych całkowitym wynikiem ISI i jego poszczególnymi elementami z wyjątkiem zauważalności problemu dla innych i poziomu zmartwienia aktualnym problemem ze snem. Ponadto, odbywanie dializ stanowiło czynnik ryzyka bardziej nasilonych skarg na zauważalność aktualnego problemu ze snem. Otrzymane modele regresji liniowej oparte na wieku, GHQ-28 i PSS-10 charakteryzowały się umiarkowanymi wartościami predykcyjnymi, od 0,351 dla całej badanej grupy do 0,445 dla grupy pacjentów dializowanych.

Badania przeprowadzone na populacjach studentów, pracowników medycznych oraz populacji ogólnej wiążą występowanie choroby przewlekłej z wyższym nasileniem zaburzeń snu (49–51). W zależności od kraju i fazy pandemii, wyniki dotyczące

zaburzeń snu mierzonych przy użyciu ISI w populacji ogólnej są zróżnicowane i plasują się w przedziale 11,5% do 20% (52–55). W omawianym badaniu wyniki wskazujące na występowanie istotnych zaburzeń snu (powyżej 15 punktów) obserwowano u 25,2% uczestników z chorobami przewlekłymi niezależnie od stanu chorobowego, co może mieć związek z różnicami społeczno-kulturowymi w badanej populacji.

Szczególną uwagę zwraca profil skarg dotyczących zaburzeń snu z wysoką częstością skarg dotyczących satysfakcji z obecnego wzorca snu, wpływu zaburzeń snu na codzienne funkcjonowanie oraz zauważalności problemu przez innych. Stosunkowo mniejsza ilość skarg dotyczyła bardziej obiektywnych aspektów, takich jak trudności z zasypianiem lub podtrzymaniem snu. Wydaje się, że w sytuacji odczuwanej niepewności i zagrożenia pandemią, satysfakcja z obecnego wzorca snu może stanowić czuły wskaźnik doświadczanego stresu u pacjentów z chorobami przewlekłymi.

Otrzymane wyniki potwierdzają wcześniejsze obserwacje dotyczące korelacji między płcią żeńską a odczuwanym stresem oraz wynikami w skali ISI (56,57). W badanej grupie nie zaobserwowano jednak znaczącej korelacji ISI z młodszym wiekiem (58), co może wskazywać na zmniejszenie wpływu wieku w obecności choroby przewlekłej w porównaniu z populacją ogólną. Wcześniejsze leczenie psychiatryczne i psychoterapia korelowały ze znacząco wyższymi wynikami w skali ISI, co sugeruje, że populacja ludzi z wcześniejszymi zaburzeniami psychicznymi może być narażona na zaburzenia snu w okolicznościach pandemii.

Podobnie jak w przypadku poprzedniej pracy, omawiane badanie charakteryzuje się pewnymi ograniczeniami dotyczącymi braku dopasowania uczestników badania pod względem danych socjodemograficznych czy braku grupy kontrolnej. Ponadto, nasilenie objawów związanych z chorobą podstawową nie zostało zmierzone, co potencjalnie mogło przełożyć się na silniejsze dopasowanie modeli otrzymanych przy pomocy regresji liniowej.

# 8. Wnioski

Przedstawione powyżej wyniki cyklu trzech spójnych tematycznie prac dowodzą istotnego wpływu pandemii COVID-19 na zdrowie psychiczne pacjentów chorych przewlekle w zakresie konsekwencji krótkoterminowych w postaci występowania objawów psychopatologicznych na skutek zagrożenia i stresu związanego z możliwym zakażeniem, a także konsekwencji długoterminowych na skutek aktywacji prozapalnej wynikającej z zachorowania na COVID-19. Podczas gdy wspomniane wyniki prac oryginalnych opisują nasilenie objawów psychopatologicznych, ze szczególnym uwzględnieniem zaburzeń snu, oraz stosowane strategie radzenia sobie ze stresem w populacji pacjentów przewlekle chorych, poznanie skali długoterminowego wpływu nowego czynnika zakaźnego na ośrodkowy układ nerwowy możliwe będzie dopiero w przyszłości i wymagać będzie dalszych analiz.

# 9. Referencje


1. Dragioti E, Li H, Tsitsas G, Lee KH, Choi J, Kim J, et al. A large-scale meta-analytic atlas of mental health problems prevalence during the COVID-19 early pandemic. J Med Virol. 2022;94(5):1935–49.
2. Kołodziejczyk A, Misiak B, Szcześniak D, Maciaszek J, Ciułkowicz M, Łuc D, et al. Coping Styles, Mental Health, and the COVID-19 Quarantine: A Nationwide Survey in Poland. Front Psychiatry. 2021;12(March):1–8.
3. Wu T, Jia X, Shi H, Niu J, Yin X, Xie J, et al. Prevalence of mental health problems during the COVID-19 pandemic: A systematic review and meta-analysis. J Affect Disord. 2021;281(August 2020):91–8.
4. Akobirshoev I, Vetter M, Iezzoni LI, Rao SR, Mitra M. Delayed Medical Care And Unmet Care Needs Due To The COVID-19 Pandemic Among Adults With Disabilities In The US. Health Aff. 2022;41(10):1505–12.
5. Nshimyiryo A, Barnhart DA, Cubaka VK, Dusengimana JMV, Dusabeyezu S,

Ndagijimana D, et al. Barriers and coping mechanisms to accessing healthcare during the COVID-19 lockdown: a cross-sectional survey among patients with chronic diseases in rural Rwanda. BMC Public Health. 2021;21(1):1–11.

6. DeJean D, Giacomini M, Vanstone M, Brundisini F. Patient experiences of depression and anxiety with chronic disease: A systematic review and qualitative meta-synthesis. Ont Health Technol Assess Ser. 2013;13(16):1–33.
7. Yoon H, Kim S, Naseh M, Huang Y-C, Jang Y. Chronic Conditions and Psychological Distress in Older Asian Americans: The Mediating Role of Subjective Health Perception. J Gerontol Soc Work [Internet]. 2022 Aug 18;65(6):604–17. Available from: https://www.who.int/publications/m/item/covid-19-weekly-epidemiological-update
8. Li A. Individual and organizational health literacies: Moderating psychological distress for individuals with chronic conditions. J Public Heal (United Kingdom). 2022;44(3):651–62.
9. Pallanti S, Grassi E, Makris N, Gasic GP, Hollander E. Neurocovid-19: A clinical neuroscience-based approach to reduce SARS-CoV-2 related mental health sequelae. J Psychiatr Res [Internet]. 2020 Nov;130(December):215–7. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1359610121000186
10. Jarrahi A, Ahluwalia M, Khodadadi H, Da Silva Lopes Salles E, Kolhe R, Hess DC, et al. Neurological consequences of COVID-19: What have we learned and where do we go from here? J Neuroinflammation. 2020;17(1):1–12.
11. Tirelli U, Taibi R, Chirumbolo S. Post COVID syndrome: a new challenge for medicine. Eur Rev Med Pharmacol Sci [Internet]. 2021;25(12):4422–5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/34227079
12. Xu Y, Zhuang Y, Kang L. A Review of Neurological Involvement in Patients with SARS-CoV-2 Infection. Med Sci Monit. 2021;27:1–11.
13. Karnik M, Beeraka NM, Uthaiah CA, Nataraj SM, Bettadapura ADS, Aliev G, et al. A Review on SARS-CoV-2-Induced Neuroinflammation,

Neurodevelopmental Complications, and Recent Updates on the Vaccine Development. Mol Neurobiol [Internet]. 2021;58(9):4535–63. Available from: https://doi.org/10.1007/s12035-021-02399-6

14. Liu F, Han K, Blair R, Kenst K, Qin Z, Upcin B, et al. SARS-CoV-2 Infects Endothelial Cells In Vivo and In Vitro. Front Cell Infect Microbiol. 2021;11(July):1–13.
15. Krasemann S, Haferkamp U, Pfefferle S, Woo MS, Heinrich F, Schweizer M, et al. The blood-brain barrier is dysregulated in COVID-19 and serves as a CNS entry route for SARS-CoV-2. Stem Cell Reports. 2022;17(2):307–20.
16. Acioglu C, Li L, Elkabes S. Contribution of astrocytes to neuropathology of neurodegenerative diseases. Brain Res [Internet]. 2021;1758(December 2020):147291. Available from: https://doi.org/10.1016/j.brainres.2021.147291
17. Gamage R, Wagnon I, Rossetti I, Childs R, Niedermayer G, Chesworth R, et al. Cholinergic Modulation of Glial Function During Aging and Chronic Neuroinflammation. Front Cell Neurosci. 2020;14(October):1–26.
18. Njie eMalick G, Boelen E, Stassen FR, Steinbusch HWM, Borchelt DR, Streit WJ. Ex vivo cultures of microglia from young and aged rodent brain reveal age-related changes in microglial function. Neurobiol Aging [Internet]. 2012 Jan;33(1):195.e1-195.e12. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0197458010002228
19. Hampel H, Caraci F, Cuello AC, Caruso G, Nisticò R, Corbo M, et al. A Path Toward Precision Medicine for Neuroinflammatory Mechanisms in Alzheimer's Disease. Front Immunol. 2020;11(March).
20. Ciułkowicz M, Misiak B, Szcześniak D, Grzebieluch J, Maciaszek J, Rymaszewska J. The Portrait of Cyberchondria—A Cross-Sectional Online Study on Factors Related to Health Anxiety and Cyberchondria in Polish Population during SARS-CoV-2 Pandemic. Int J Environ Res Public Health. 2022;19(7).
21. Cohen S, Kamarck T, Mermelstein R. A Global Measure of Perceived Stress. J

Health Soc Behav [Internet]. 1983 Dec;24(4):385. Available from: https://www.jstor.org/stable/2136404

22. Charles S. Carver. You want to measure coping but your protocol's too long: Consider the brief COPE. Int J Behav Med. 1997;4(1):92–100.
23. Goldberg DP, Hillier VF. A scaled version of the General Health Questionnaire. Psychol Med. 1979;9(1):139–45.
24. Makowska Z, Merecz D, Mościcka A, Kolasa W. The validity of General Health Questionnaires, GHQ-12 and GHQ-28, in mental health studies of working people. Int J Occup Med Environ Health. 2002;15(4):353–62.
25. Morin CM, Belleville G, Bélanger L, Ivers H. The insomnia severity index: Psychometric indicators to detect insomnia cases and evaluate treatment response. Sleep. 2011;34(5):601–8.
26. Bastien CH, Vallières A, Morin CM. Validation of the insomnia severity index as an outcome measure for insomnia research. Sleep Med. 2001;2(4):297–307.
27. Łuc M, Woźniak M, Rymaszewska J. Neuroinflammation in Dementia—Therapeutic Directions in a COVID-19 Pandemic Setting. Cells [Internet]. 2022 Sep 22;11(19):2959. Available from: https://www.mdpi.com/2073-4409/11/19/2959
28. López-Valdés HE, Martínez-Coria H. The Role of Neuroinflammation in Age-Related Dementias. Rev Invest Clin. 2016;68(1):40–8.
29. Lindbergh CA, Casaletto KB, Staffaroni AM, Elahi F, Walters SM, You M, et al. Systemic tumor necrosis factor-alpha trajectories relate to brain health in typically aging older adults. Journals Gerontol - Ser A Biol Sci Med Sci. 2020;75(8):1558–65.
30. Calle MC, Fernandez ML. Inflammation and type 2 diabetes. Diabetes Metab [Internet]. 2012;38(3):183–91. Available from: http://dx.doi.org/10.1016/j.diabet.2011.11.006
31. Olsthoorn L, Vreeken D, Kiliaan AJ. Gut Microbiome, Inflammation, and Cerebrovascular Function: Link Between Obesity and Cognition. Front

Neurosci. 2021;15(December):rheuma.pdf.

32. Duchaine CS, Brisson C, Talbot D, Gilbert-Ouimet M, Trudel X, Vézina M, et al. Psychosocial stressors at work and inflammatory biomarkers: PROspective Quebec Study on Work and Health. Psychoneuroendocrinology. 2021;133(April).

33. Yachou Y, El Idrissi A, Belapasov V, Ait Benali S. Neuroinvasion, neurotropic, and neuroinflammatory events of SARS-CoV-2: understanding the neurological manifestations in COVID-19 patients. Neurol Sci. 2020;41(10):2657–69.

34. Zhou Y, Xu J, Hou Y, Leverenz JB, Kallianpur A, Mehra R, et al. Network medicine links SARS-CoV-2/COVID-19 infection to brain microvascular injury and neuroinflammation in dementia-like cognitive impairment. Alzheimer's Res Ther. 2021;13(1):1–19.

35. Murta V, Villarreal A, Ramos AJ. Severe Acute Respiratory Syndrome Coronavirus 2 Impact on the Central Nervous System: Are Astrocytes and Microglia Main Players or Merely Bystanders? ASN Neuro. 2020;12(1121).

36. Carmona-Abellan M, Martinez-Valbuena I, Marcilla I, DiCaudo C, Gil I, Nuñez J, et al. Microglia is associated with p-Tau aggregates in the olfactory bulb of patients with neurodegenerative diseases. Neurol Sci. 2021;42(4):1473–82.

37. Frith E, Shivappa N, Mann JR, Hébert JR, Wirth MD, Loprinzi PD. Dietary inflammatory index and memory function: Population-based national sample of elderly Americans. Br J Nutr. 2018;119(5):552–8.

38. Jordan F, Quinn TJ, McGuinness B, Passmore P, Kelly JP, Tudur Smith C, et al. Aspirin and other non-steroidal anti-inflammatory drugs for the prevention of dementia. Cochrane Database Syst Rev [Internet]. 2020 Apr 30;2020(4). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD011459.pub2/full

39. Jaturapatporn D, Mgekn I, Mccleery J, Tabet N. Aspirin , steroidal and non-

steroidal anti-inflammatory drugs for the treatment of Alzheimer ' s disease ( Review ). 2012;(2).

40. Ou W, Yang J, Simanauskaite J, Choi M, Castellanos DM, Chang R, et al. Biologic TNF-$\alpha$ inhibitors reduce microgliosis, neuronal loss, and tau phosphorylation in a transgenic mouse model of tauopathy. J Neuroinflammation [Internet]. 2021;18(1):1–19. Available from: https://doi.org/10.1186/s12974-021-02332-7
41. Chang R, Knox J, Chang J, Derbedrossian A, Vasilevko V, Cribbs D, et al. Blood-Brain Barrier Penetrating Biologic TNF-$\alpha$ Inhibitor for Alzheimer's Disease. Mol Pharm. 2017;14(7):2340–9.
42. Łuc M, Pawłowski M, Jaworski A, Fila-Witecka K, Szcześniak D, Augustyniak-Bartosik H, et al. Coping of Chronically-Ill Patients during the COVID-19 Pandemic: Comparison between Four Groups. Int J Environ Res Public Health. 2023;20(6):4814.
43. Chodkiewicz J, Miniszewska J, Krajewska E, Biliński P. Mental health during the second wave of the covid-19 pandemic—polish studies. Int J Environ Res Public Health. 2021;18(7).
44. Davis EB, McElroy-Heltzel SE, Lemke AW, Cowden RG, VanderWeele TJ, Worthington EL, et al. Psychological and spiritual outcomes during the COVID-19 pandemic: A prospective longitudinal study of adults with chronic disease. Health Psychol. 2021;40(6):347–56.
45. Enns A, Pinto A, Venugopal J, Grywacheski V, Gheorghe M, Kakkar T, et al. Evidence-informed policy brief substance use and related harms in the context of covid-19: A conceptual model. Heal Promot Chronic Dis Prev Canada. 2020;40(11–12):342–9.
46. Chodkiewicz J, Talarowska M, Miniszewska J, Nawrocka N, Bilinski P. Alcohol consumption reported during the COVID-19 pandemic: The initial stage. Int J Environ Res Public Health. 2020;17(13):1–11.
47. Umucu E, Lee B. Examining the impact of COVID-19 on stress and coping

strategies in individuals with disabilities and chronic conditions. Rehabil Psychol. 2020;65(3):193–8.

48. Girma A, Ayalew E, Mesafint G. Covid-19 pandemic-related stress and coping strategies among adults with chronic disease in Southwest Ethiopia. Neuropsychiatr Dis Treat. 2021;17:1551–61.

49. Özçelik N, Kesin HV, Telatar G, Özyurt S, Yılmaz Kara B, Gümüş A, et al. "COVID-Somnia" in healthcare workers during the pandemic. Hosp Pract (1995) [Internet]. 2022;50(4):273–81. Available from: https://doi.org/10.1080/21548331.2022.2102777

50. Wańkowicz P, Szylińska A, Rotter I. Evaluation of mental health factors among people with systemic lupus erythematosus during the sars-cov-2 pandemic. J Clin Med. 2020;9(9):1–8.

51. Wańkowicz P, Szylińska A, Rotter I. Insomnia, anxiety, and depression symptoms during the COVID-19 pandemic may depend on the pre-existent health status rather than the profession. Brain Sci. 2021;11(8).

52. Habbash F, Salah A Ben, Almarabheh A, Jahrami H. Insomnia and Related Factors During the Delta Wave of the COVID-19 Pandemic in the Kingdom of Bahrain: A Cross-Sectional Study. Nat Sci Sleep. 2022;14(October):1963–75.

53. Kokou-Kpolou CK, Megalakaki O, Laimou D, Kousouri M. Insomnia during COVID-19 pandemic and lockdown: Prevalence, severity, and associated risk factors in French population. Psychiatry Res [Internet]. 2020;290:113128. Available from: https://doi.org/10.1016/j.psychres.2020.113128

54. Pieh C, Budimir S, Probst T. The effect of age, gender, income, work, and physical activity on mental health during coronavirus disease (COVID-19) lockdown in Austria. J Psychosom Res [Internet]. 2020;136(May):110186. Available from: https://doi.org/10.1016/j.jpsychores.2020.110186

55. Alqahtani JS, Alrabeeah SM, Aldhahir AM, Siraj R, Aldabayan YS, Alghamdi SM, et al. Sleep Quality, Insomnia, Anxiety, Fatigue, Stress, Memory and Active Coping during the COVID-19 Pandemic. Int J Environ Res Public

Health. 2022;19(9):1–11.

56. Gualano MR, Lo Moro G, Voglino G, Bert F, Siliquini R. Effects of Covid-19 Lockdown on Mental Health and Sleep Disturbances in Italy. Int J Environ Res Public Health [Internet]. 2020 Jul 2;17(13):4779. Available from: https://www.mdpi.com/1660-4601/17/13/4779

57. Yuan K, Zheng YB, Wang YJ, Sun YK, Gong YM, Huang YT, et al. A systematic review and meta-analysis on prevalence of and risk factors associated with depression, anxiety and insomnia in infectious diseases, including COVID-19: a call to action. Mol Psychiatry. 2022;(May).

58. Morin CM, Bjorvatn B, Chung F, Holzinger B, Partinen M, Penzel T, et al. Insomnia, anxiety, and depression during the COVID-19 pandemic: an international collaborative study. Sleep Med. 2021;87:38–45.

# 10. Załączniki

## 10.1 Oświadczenia współautorów prac

**Prof. dr hab. Joanna Rymaszewska** Wrocław, 18.05.2023

Katedra Psychiatrii, Uniwersytet Medyczny im. Piastów Śląskich we Wrocławiu

OŚWIADCZENIE

Oświadczam, że w pracy Łuc M., Woźniak M., Rymaszewska J.: Neuroinflammation in dementia - therapeutic directions in a COVID-19 pandemic setting, Cells, 2022, vol. 11, nr 19, art.2959 [17 s.], DOI:10.3390/cells11192959 mój udział polegał na współtworzeniu koncepcji pracy, superwizji nad manuskryptem oraz pozyskaniu funduszy.

Podpis

Oświadczam, że w pracy Łuc M., Pawłowski M., Jaworski A., Fila-Witecka K., Szcześniak D., Augustyniak-Bartosik H., Zielińska D., Stefaniak A., Pokryszko-Dragan A., Chojdak-Łukasiewicz J., Krajewska M., Pawłowski T., Szepietowski JC., Rymaszewska J.: Coping of chronically-ill patients during the COVID-19 pandemic: comparison between four groups, International Journal of Environmental Research and Public Health, 2023, vol. 20, nr 6, art.4814 [14 s.], DOI:10.3390/ijerph20064814 mój udział polegał na współtworzeniu koncepcji badania, metodyki oraz superwizji nad manuskryptem, w tym sprawdzeniu referencji i ostatecznym zatwierdzeniu pracy.

Podpis

Oświadczam, że w pracy Łuc M., Pawłowski M., Fila-Witecka K., Kamińska D., Poznański P., Rymaszewska J.E., Krajewski P., Szcześniak D., Rymaszewska J.: *Determinants of sleep disturbances in chronically-ill patients during the COVID-19 pandemic.* Archives of Psychiatry and Psychotherapy, *2023* mój udział polegał na współtworzeniu koncepcji pracy i metodyki badania oraz ostatecznym zatwierdzeniu pracy.

Podpis

**Dr n. med. Marta Woźniak** Wrocław, 26.04.2023

Katedra Patomorfologii, Uniwersytet Medyczny im. Piastów Śląskich we Wrocławiu

OŚWIADCZENIE

Oświadczam, że w pracy Łuc M., Woźniak M., Rymaszewska J.: Neuroinflammation in dementia - therapeutic directions in a COVID-19 pandemic setting, Cells, 2022, vol. 11, nr 19, art.2959 [17 s.], DOI:10.3390/cells11192959 mój udział polegał na zgromadzeniu literatury, tworzeniu manuskryptu oraz superwizji nad manuskryptem, w tym sprawdzeniu referencji.

Podpis

Marta Woźniak

**Lek. Marcin Pawłowski** Wrocław, 18.05.2023

Katedra Psychiatrii, Uniwersytet Medyczny im. Piastów Śląskich we Wrocławiu

**OŚWIADCZENIE**

**Oświadczam, że w pracy Łuc M., Pawłowski M., Jaworski A., Fila-Witecka K., Szcześniak D., Augustyniak-Bartosik H., Zielińska D., Stefaniak A., Pokryszko-Dragan A., Chojdak-Łukasiewicz J., Krajewska M., Pawłowski T., Szepietowski JC., Rymaszewska J.: Coping of chronically-ill patients during the COVID-19 pandemic: comparison between four groups, International Journal of Environmental Research and Public Health, 2023, vol. 20, nr 6, art.4814 [14 s.], DOI:10.3390/ijerph20064814 mój udział polegał na współtworzeniu koncepcji badania oraz zbieraniu danych.**

**Podpis** Marcin Pawłowski lekarz 3856819

**Oświadczam, że w pracy Łuc M., Pawłowski M., Fila-Witecka K., Kamińska D., Poznański P., Rymaszewska J.E., Krajewski P., Szcześniak D., Rymaszewska J.: *Determinants of sleep disturbances in chronically-ill patients during the COVID-19 pandemic.* Archives of Psychiatry and Psychotherapy, *2023* mój udział polegał na współtworzeniu protokołu badania.**

**Podpis** Marcin Pawłowski lekarz 3856819

**Mgr Karolina Fila-Pawłowska** Wrocław, 18.05.2023

Katedra Psychiatrii, Uniwersytet Medyczny im. Piastów Śląskich we Wrocławiu

OŚWIADCZENIE

Oświadczam, że w pracy Łuc M., Pawłowski M., Jaworski A., Fila-Witecka K., Szcześniak D., Augustyniak-Bartosik H., Zielińska D., Stefaniak A., Pokryszko-Dragan A., Chojdak-Łukasiewicz J., Krajewska M., Pawłowski T., Szepietowski JC., Rymaszewska J.: Coping of chronically-ill patients during the COVID-19 pandemic: comparison between four groups, International Journal of Environmental Research and Public Health, 2023, vol. 20, nr 6, art.4814 [14 s.], DOI:10.3390/ijerph20064814 mój udział polegał na współtworzeniu koncepcji badania oraz tworzeniu manuskryptu.

Podpis Fila - Pawłowska

Oświadczam, że w pracy Łuc M., Pawłowski M., Fila-Witecka K., Kamińska D., Poznański P., Rymaszewska J.E., Krajewski P., Szcześniak D., Rymaszewska J.: *Determinants of sleep disturbances in chronically-ill patients during the COVID-19 pandemic.* Archives of Psychiatry and Psychotherapy, *2023* mój udział polegał na współtworzeniu koncepcji pracy.

Podpis Fila - Pawłowska

**Dr hab.n.med. Anna Pokryszko-Dragan, prof. UMW** Wrocław, 26.04.2023

Katedra i Klinika Neurologii

Uniwersytet Medyczny im. Piastów Śląskich we Wrocławiu

OŚWIADCZENIE

Oświadczam, że w pracy Łuc M., Pawłowski M., Jaworski A., Fila-Witecka K., Szcześniak D., Augustyniak-Bartosik H., Zielińska D., Stefaniak A., Pokryszko-Dragan A., Chojdak-Łukasiewicz J., Krajewska M., Pawłowski T., Szepietowski JC., Rymaszewska J.: Coping of chronically-ill patients during the COVID-19 pandemic: comparison between four groups, International Journal of Environmental Research and Public Health, 2023, vol. 20, nr 6, art.4814 [14 s.], DOI:10.3390/ijerph20064814 mój udział polegał na analizie danych oraz tworzeniu manuskryptu.

Podpis

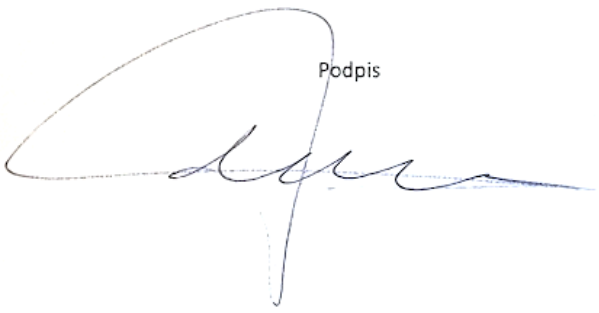
**Lek. Paweł Poznański** Wrocław, 18.05.2023

Katedra Nefrologii i Medycyny Transplantacyjnej, Uniwersytet Medyczny im. Piastów Śląskich we Wrocławiu

OŚWIADCZENIE

Oświadczam, że w pracy Łuc M., Pawłowski M., Fila-Witecka K., Kamińska D., Poznański P., Rymaszewska J.E., Krajewski P., Szcześniak D., Rymaszewska J.: *Determinants of sleep disturbances in chronically-ill patients during the COVID-19 pandemic.* Archives of Psychiatry and Psychotherapy, *2023* mój udział polegał na zbieraniu danych oraz opracowaniu celu badania.

Podpis



**Prof. dr hab. Tomasz Pawłowski**

Wrocław, 26.04.2023

Katedra Psychiatrii, Uniwersytet Medyczny im. Piastów Śląskich we Wrocławiu

OŚWIADCZENIE

Oświadczam, że w pracy Łuc M., Pawłowski M., Jaworski A., Fila-Witecka K., Szcześniak D., Augustyniak-Bartosik H., Zielińska D., Stefaniak A., Pokryszko-Dragan A., Chojdak-Łukasiewicz J., Krajewska M., Pawłowski T., Szepietowski JC., Rymaszewska J.: Coping of chronically-ill patients during the COVID-19 pandemic: comparison between four groups, International Journal of Environmental Research and Public Health, 2023, vol. 20, nr 6, art.4814 [14 s.], DOI:10.3390/ijerph20064814 mój udział polegał na współtworzeniu koncepcji badania oraz superwizji nad manuskryptem.

Podpis

Prof. dr hab. med.
Tomasz Pawłowski
specjalista psychiatra
4718681

**Lek. Julia Ewa Rymaszewska**

Wrocław, 18.05.2023

Katedra Dermatologii, Wenerologii i Alergologii, Uniwersytet Medyczny im. Piastów Śląskich we Wrocławiu

OŚWIADCZENIE

Oświadczam, że w pracy Łuc M., Pawłowski M., Fila-Witecka K., Kamińska D., Poznański P., Rymaszewska J.E., Krajewski P., Szcześniak D., Rymaszewska J.: *Determinants of sleep disturbances in chronically-ill patients during the COVID-19 pandemic.* Archives of Psychiatry and Psychotherapy, *2023* mój udział polegał na opracowaniu celu badania oraz zbieraniu danych.

Podpis

Julia Rymaszewska

**Dr n. med. I n. o zdr. Aleksandra Stefaniak**

Wrocław, 26.04.2023

Katedra Dermatologii, Wenerologii i Alergologii, Uniwersytet Medyczny im. Piastów Śląskich we Wrocławiu

OŚWIADCZENIE

Oświadczam, że w pracy Łuc M., Pawłowski M., Jaworski A., Fila-Witecka K., Szcześniak D., Augustyniak-Bartosik H., Zielińska D., Stefaniak A., Pokryszko-Dragan A., Chojdak-Łukasiewicz J., Krajewska M., Pawłowski T., Szepietowski JC., Rymaszewska J.: Coping of chronically-ill patients during the COVID-19 pandemic: comparison between four groups, International Journal of Environmental Research and Public Health, 2023, vol. 20, nr 6, art.4814 [14 s.], DOI:10.3390/ijerph20064814 mój udział polegał na zbieraniu danych.

Podpis

Stefaniak Aleksandra

**Dr n. med. Justyna Chojdak-Łukasiewicz**

Wrocław, 26.04.2023

Katedra Neurologii, Uniwersytet Medyczny im. Piastów Śląskich we Wrocławiu

OŚWIADCZENIE

Oświadczam, że w pracy Łuc M., Pawłowski M., Jaworski A., Fila-Witecka K., Szcześniak D., Augustyniak-Bartosik H., Zielińska D., Stefaniak A., Pokryszko-Dragan A., Chojdak-Łukasiewicz J., Krajewska M., Pawłowski T., Szepietowski JC., Rymaszewska J.: Coping of chronically-ill patients during the COVID-19 pandemic: comparison between four groups, International Journal of Environmental Research and Public Health, 2023, vol. 20, nr 6, art.4814 [14 s.], DOI:10.3390/ijerph20064814 mój udział polegał na zbieraniu danych.

Podpis

**Lek. Dorota Zielińska**

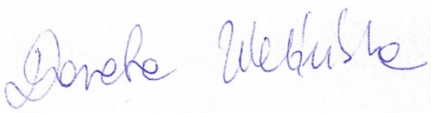
Wrocław, 26.04.2023

Katedra Nefrologii i Medycyny Transplantacyjnej, Uniwersytet Medyczny im. Piastów Śląskich we Wrocławiu

OŚWIADCZENIE

Oświadczam, że w pracy Łuc M., Pawłowski M., Jaworski A., Fila-Witecka K., Szcześniak D., Augustyniak-Bartosik H., Zielińska D., Stefaniak A., Pokryszko-Dragan A., Chojdak-Łukasiewicz J., Krajewska M., Pawłowski T., Szepietowski JC., Rymaszewska J.: Coping of chronically-ill patients during the COVID-19 pandemic: comparison between four groups, International Journal of Environmental Research and Public Health, 2023, vol. 20, nr 6, art.4814 [14 s.], DOI:10.3390/ijerph20064814 mój udział polegał na zbieraniu danych.

Podpis



**Lek. Piotr Krajewski**

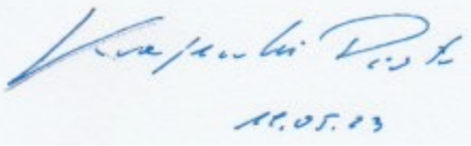
Wrocław, 18.05.2023

Katedra Dermatologii, Wenerologii i Alergologii, Uniwersytet Medyczny im. Piastów Śląskich we Wrocławiu

OŚWIADCZENIE

Oświadczam, że w pracy Łuc M., Pawłowski M., Fila-Witecka K., Kamińska D., Poznański P., Rymaszewska J.E., Krajewski P., Szcześniak D., Rymaszewska J.: *Determinants of sleep disturbances in chronically-ill patients during the COVID-19 pandemic.* Archives of Psychiatry and Psychotherapy, *2023* mój udział polegał na zbieraniu danych oraz opracowaniu celu badania.

Podpis



**Dr n. med. Hanna Augustyniak-Bartosik** Wrocław, 26.04.2023

Katedra Nefrologii i Medycyny Transplantacyjnej, Uniwersytet Medyczny im. Piastów Śląskich we Wrocławiu

OŚWIADCZENIE

Oświadczam, że w pracy Łuc M., Pawłowski M., Jaworski A., Fila-Witecka K., Szcześniak D., Augustyniak-Bartosik H., Zielińska D., Stefaniak A., Pokryszko-Dragan A., Chojdak-Łukasiewicz J., Krajewska M., Pawłowski T., Szepietowski JC., Rymaszewska J.: Coping of chronically-ill patients during the COVID-19 pandemic: comparison between four groups, International Journal of Environmental Research and Public Health, 2023, vol. 20, nr 6, art.4814 [14 s.], DOI:10.3390/ijerph20064814 mój udział polegał na zbieraniu danych.

Podpis

**Arkadiusz Jaworski** Wrocław, 26.04.2023

Studenckie Koło Naukowe Psychiatrii, Uniwersytet Medyczny im. Piastów Śląskich we Wrocławiu

OŚWIADCZENIE

Oświadczam, że w pracy Łuc M., Pawłowski M., Jaworski A., Fila-Witecka K., Szcześniak D., Augustyniak-Bartosik H., Zielińska D., Stefaniak A., Pokryszko-Dragan A., Chojdak-Łukasiewicz J., Krajewska M., Pawłowski T., Szepietowski JC., Rymaszewska J.: Coping of chronically-ill patients during the COVID-19 pandemic: comparison between four groups, International Journal of Environmental Research and Public Health, 2023, vol. 20, nr 6, art.4814 [14 s.], DOI:10.3390/ijerph20064814 mój udział polegał na analizie danych oraz tworzeniu manuskryptu.

Podpis A Jaworski

**Prof. dr hab. Magdalena Krajewska** Wrocław, 26.04.2023

Katedra Nefrologii i Medycyny Transplantacyjnej, Uniwersytet Medyczny im. Piastów Śląskich we Wrocławiu

OŚWIADCZENIE

Oświadczam, że w pracy Łuc M., Pawłowski M., Jaworski A., Fila-Witecka K., Szcześniak D., Augustyniak-Bartosik H., Zielińska D., Stefaniak A., Pokryszko-Dragan A., Chojdak-Łukasiewicz J., Krajewska M., Pawłowski T., Szepietowski JC., Rymaszewska J.: Coping of chronically-ill patients during the COVID-19 pandemic: comparison between four groups, International Journal of Environmental Research and Public Health, 2023, vol. 20, nr 6, art.4814 [14 s.], DOI:10.3390/ijerph20064814 mój udział polegał na pozyskaniu funduszy oraz superwizji nad manuskryptem.

Podpis

**Dr hab. n. med. Dorota Kamińska**

Wrocław, 18.05.2023

Katedra Nefrologii i Medycyny Transplantacyjnej, Uniwersytet Medyczny im. Piastów Śląskich we Wrocławiu

OŚWIADCZENIE

Oświadczam, że w pracy Łuc M., Pawłowski M., Fila-Witecka K., Kamińska D., Poznański P., Rymaszewska J.E., Krajewski P., Szcześniak D., Rymaszewska J.: *Determinants of sleep disturbances in chronically-ill patients during the COVID-19 pandemic.* Archives of Psychiatry and Psychotherapy, *2023* mój udział polegał na opracowaniu metod badania.

Podpis

Dorota Kamińska

**Prof. dr hab. Jacek C. Szepietowski**

Wrocław, 26.04.2023

Katedra Dermatologii, Wenerologii i Alergologii, Uniwersytet Medyczny im. Piastów Śląskich we Wrocławiu

OŚWIADCZENIE

Oświadczam, że w pracy Łuc M., Pawłowski M., Jaworski A., Fila-Witecka K., Szcześniak D., Augustyniak-Bartosik H., Zielińska D., Stefaniak A., Pokryszko-Dragan A., Chojdak-Łukasiewicz J., Krajewska M., Pawłowski T., Szepietowski JC., Rymaszewska J.: Coping of chronically-ill patients during the COVID-19 pandemic: comparison between four groups, International Journal of Environmental Research and Public Health, 2023, vol. 20, nr 6, art.4814 [14 s.], DOI:10.3390/ijerph20064814 mój udział polegał na współtworzeniu manuskryptu oraz superwizji nad manuskryptem.

Podpis

Uniwersytet Medyczny we Wrocławiu
KATEDRA I KLINIKA DERMATOLOGII, WENEROLOGII I ALERGOLOGII
ul. T. Chałubińskiego 1, 50-368 Wrocław
tel. 71 327 09 41, faks: 71 327 09 42
(2)

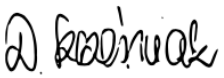
Uniwersytet Medyczny we Wrocławiu
KATEDRA I KLINIKA DERMATOLOGII, WENEROLOGII I ALERGOLOGII
kierownik
prof. dr hab. Jacek Szepietowski

**Dr n. med. Dorota Szcześniak** Wrocław, 18.05.2023

Katedra Psychiatrii, Uniwersytet Medyczny im. Piastów Śląskich we Wrocławiu

OŚWIADCZENIE

Oświadczam, że w pracy Łuc M., Pawłowski M., Jaworski A., Fila-Witecka K., Szcześniak D., Augustyniak-Bartosik H., Zielińska D., Stefaniak A., Pokryszko-Dragan A., Chojdak-Łukasiewicz J., Krajewska M., Pawłowski T., Szepietowski JC., Rymaszewska J.: Coping of chronically-ill patients during the COVID-19 pandemic: comparison between four groups, International Journal of Environmental Research and Public Health, 2023, vol. 20, nr 6, art.4814 [14 s.], DOI:10.3390/ijerph20064814 mój udział polegał na współtworzeniu koncepcji badania oraz pozyskaniu funduszy.

Podpis 

Oświadczam, że w pracy Łuc M., Pawłowski M., Fila-Witecka K., Kamińska D., Poznański P., Rymaszewska J.E., Krajewski P., Szcześniak D., Rymaszewska J.: *Determinants of sleep disturbances in chronically-ill patients during the COVID-19 pandemic.* Archives of Psychiatry and Psychotherapy, *2023* mój udział polegał na opracowaniu metod badania.

Podpis 

## 10.2 Zgody Komisji Bioetycznej



KOMISJA BIOETYCZNA
przy
Uniwersytecie Medycznym
we Wrocławiu
ul. Pasteura 1; 50-367 WROCŁAW

OPINIA KOMISJI BIOETYCZNEJ Nr KB –468/2020

Komisja Bioetyczna przy Uniwersytecie Medycznym we Wrocławiu, powołana zarządzeniem Rektora Uniwersytetu Medycznego we Wrocławiu nr 133/XV R/2017 z dnia 21 grudnia 2017 r. oraz działająca w trybie przewidzianym rozporządzeniem Ministra Zdrowia i Opieki Społecznej z dnia 11 maja 1999 r. (Dz.U. nr 47, poz. 480) na podstawie ustawy o zawodzie lekarza z dnia 5 grudnia 1996 r. (Dz.U. nr 28 z 1997 r. poz. 152 z późniejszymi zmianami ) w składzie:

prof. dr hab. Jacek Daroszewski (choroby wewnętrzne, endokrynologia, diabetologia)
prof. dr hab. Krzysztof Grabowski (chirurgia)
dr Henryk Kaczkowski (chirurgia szczękowa, chirurgia stomatologiczna)
mgr Irena Knabel-Krzyszowska (farmacja)
prof. dr hab. Jerzy Liebhart (choroby wewnętrzne, alergologia)
ks. dr hab. Piotr Mrzygłód, prof. nadzw. (duchowny)
mgr Luiza Müller (prawo)
dr hab. Sławomir Sidorowicz (psychiatria)
prof. dr hab. Leszek Szenborn, (pediatria, choroby zakaźne)
Danuta Tarkowska (pielęgniarstwo)
prof. dr hab. Anna Wiela-Hojeńska (farmakologia kliniczna)
dr hab. Andrzej Wojnar, prof. nadzw. (histopatologia, dermatologia) przedstawiciel Dolnośląskiej Izby Lekarskiej)
dr hab. Jacek Zieliński (filozofia)

pod przewodnictwem
prof. dr hab. Jana Kornafela ( ginekologia i położnictwo, onkologia)

Przestrzegając w działalności zasad Good Clinical Practice oraz zasad Deklaracji Helsińskiej, po zapoznaniu się z projektem badawczym pt.

„Ocena obciążenia psychicznego pacjentów chorujących na łuszczycę w okresie pandemii koronawirusa SARS-CoV-2"

zgłoszonym przez **prof. dr hab. n. med. Joannę Rymaszewską** zatrudnioną w Katedrze i Klinice Psychiatrii Uniwersytetu Medycznego im. Piastów Śląskich we Wrocławiu oraz złożonymi wraz z wnioskiem dokumentami, w tajnym głosowaniu postanowiła **wyrazić zgodę** na przeprowadzenie badania w Klinice Psychiatrii oraz Klinice Dermatologii, Wenerologii i Alergologii Uniwersyteckiego Szpitala Klinicznego im. Jana Mikulicza Radeckiego we Wrocławiu **pod warunkiem zachowania anonimowości uzyskanych danych**.

Uwaga: Badanie to zostało objęte ubezpieczeniem odpowiedzialności cywilnej Uniwersytetu Medycznego we Wrocławiu z tytułu prowadzonej działalności.

Pouczenie: W ciągu 14 dni od otrzymania decyzji wnioskodawcy przysługuje prawo odwołania do Komisji Odwoławczej za pośrednictwem Komisji Bioetycznej UM we Wrocławiu.

Opinia powyższa dotyczy projektu badawczego realizowanego poza działalnością statutową.

Opinia jest ważna do dnia 1 sierpnia 2021 r. (1 rok)

Wrocław, dnia 9 lipca 2020 r.

Uniwersytet Medyczny we Wrocławiu
KOMISJA BIOETYCZNA
przewodniczący
prof. dr hab. Jan Kornafel

KOMISJA BIOETYCZNA
przy
Uniwersytecie Medycznym
we Wrocławiu
ul. Pasteura 1; 50-367 WROCŁAW

OPINIA KOMISJI BIOETYCZNEJ Nr KB – 417/2020

Komisja Bioetyczna przy Uniwersytecie Medycznym we Wrocławiu, powołana zarządzeniem Rektora Uniwersytetu Medycznego we Wrocławiu nr 133/XV R/2017 z dnia 21 grudnia 2017 r. oraz działająca w trybie przewidzianym rozporządzeniem Ministra Zdrowia i Opieki Społecznej z dnia 11 maja 1999 r. (Dz.U. nr 47, poz. 480) na podstawie ustawy o zawodzie lekarza z dnia 5 grudnia 1996 r. (Dz.U. nr 28 z 1997 r. poz. 152 z późniejszymi zmianami ) w składzie:

prof. dr hab. Jacek Daroszewski (choroby wewnętrzne, endokrynologia, diabetologia)
prof. dr hab. Krzysztof Grabowski (chirurgia)
dr Henryk Kaczkowski (chirurgia szczękowa, chirurgia stomatologiczna)
mgr Irena Knabel-Krzyszowska (farmacja)
prof. dr hab. Jerzy Liebhart (choroby wewnętrzne, alergologia)
ks. dr hab. Piotr Mrzygłód, prof. nadzw. (duchowny)
mgr prawa Luiza Műller (prawo)
dr hab. Sławomir Sidorowicz (psychiatria)
prof. dr hab. Leszek Szenborn, (pediatria, choroby zakaźne)
Danuta Tarkowska (pielęgniarstwo)
prof. dr hab. Anna Wiela-Hojeńska (farmakologia kliniczna)
dr hab. Andrzej Wojnar, prof. nadzw. (histopatologia, dermatologia) przedstawiciel Dolnośląskiej Izby Lekarskiej)
dr hab. Jacek Zieliński (filozofia)

pod przewodnictwem
prof. dr hab. Jana Kornafela ( ginekologia i położnictwo, onkologia)

Przestrzegając w działalności zasad Good Clinical Practice oraz zasad Deklaracji Helsińskiej, po zapoznaniu się z projektem badawczym pt.

„Ocena obciążenia psychicznego pacjentów chorujących na stwardnienie rozsiane w okresie pandemii koronawirusa SARS-CoV-2 – prospektywne badanie obserwacyjne"

zgłoszonym przez **dr hab. Tomasza Pawłowskiego, prof. nadzw.** zatrudnionego w Zakładzie Psychoterapii i Chorób Psychosomatycznych Katedry Psychiatrii Uniwersytetu Medycznego we Wrocławiu oraz złożonymi wraz z wnioskiem dokumentami, w tajnym głosowaniu postanowiła **wyrazić zgodę** na przeprowadzenie badania w Zakładzie Psychoterapii i Chorób Psychosomatycznych Katedry Psychiatrii **pod warunkiem zachowania anonimowości uzyskanych danych**.

Uwaga: Badanie to zostało objęte ubezpieczeniem odpowiedzialności cywilnej Uniwersytetu Medycznego we Wrocławiu z tytułu prowadzonej działalności.

Pouczenie: W ciągu 14 dni od otrzymania decyzji wnioskodawcy przysługuje prawo odwołania do Komisji Odwoławczej za pośrednictwem Komisji Bioetycznej UM we Wrocławiu.

Opinia powyższa dotyczy projektu badawczego realizowanego poza działalnością statutową.
Numer rejestrowy CWN UMW: nie posiada.

Wrocław, dnia 29 czerwca 2020 r.

Uniwersytet Medyczny we Wrocławiu
KOMISJA BIOETYCZNA
przewodniczący
prof. dr hab. Jan Kernafel

KOMISJA BIOETYCZNA
przy
Uniwersytecie Medycznym
we Wrocławiu
ul. Pasteura 1; 50-367 WROCŁAW

# OPINIA KOMISJI BIOETYCZNEJ Nr KB –470/2020

Komisja Bioetyczna przy Uniwersytecie Medycznym we Wrocławiu, powołana zarządzeniem Rektora Uniwersytetu Medycznego we Wrocławiu nr 133/XV R/2017 z dnia 21 grudnia 2017 r. oraz działająca w trybie przewidzianym rozporządzeniem Ministra Zdrowia i Opieki Społecznej z dnia 11 maja 1999 r. (Dz.U. nr 47, poz. 480) na podstawie ustawy o zawodzie lekarza z dnia 5 grudnia 1996 r. (Dz.U. nr 28 z 1997 r. poz. 152 z późniejszymi zmianami ) w składzie:

prof. dr hab. Jacek Daroszewski (choroby wewnętrzne, endokrynologia, diabetologia)
prof. dr hab. Krzysztof Grabowski (chirurgia)
dr Henryk Kaczkowski (chirurgia szczękowa, chirurgia stomatologiczna)
mgr Irena Knabel-Krzyszowska (farmacja)
prof. dr hab. Jerzy Liebhart (choroby wewnętrzne, alergologia)
ks. dr hab. Piotr Mrzygłód, prof. nadzw. (duchowny)
mgr Luiza Műller (prawo)
dr hab. Sławomir Sidorowicz (psychiatria)
prof. dr hab. Leszek Szenborn, (pediatria, choroby zakaźne)
Danuta Tarkowska (pielęgniarstwo)
prof. dr hab. Anna Wiela-Hojeńska (farmakologia kliniczna)
dr hab. Andrzej Wojnar, prof. nadzw. (histopatologia, dermatologia) przedstawiciel Dolnośląskiej Izby Lekarskiej)
dr hab. Jacek Zieliński (filozofia)

pod przewodnictwem
prof. dr hab. Jana Kornafela ( ginekologia i położnictwo, onkologia)

Przestrzegając w działalności zasad Good Clinical Practice oraz zasad Deklaracji Helsińskiej, po zapoznaniu się z projektem badawczym pt.

„Ocena obciążenia psychicznego pacjentów po transplantacji nerki w okresie pandemii koronawirusa SARS-CoV-2"

zgłoszonym przez **prof. dr hab. n. med. Joannę Rymaszewską** zatrudnioną w Katedrze i Klinice Psychiatrii Uniwersytetu Medycznego im. Piastów Śląskich we Wrocławiu oraz złożonymi wraz z wnioskiem dokumentami, w tajnym głosowaniu postanowiła **wyrazić zgodę** na przeprowadzenie badania w Klinice Psychiatrii oraz Klinice Nefrologii i Medycyny Transplantacyjnej Uniwersyteckiego Szpitala Klinicznego im. Jana Mikulicza Radeckiego we Wrocławiu **pod warunkiem zachowania anonimowości uzyskanych danych**.

Uwaga: Badanie to zostało objęte ubezpieczeniem odpowiedzialności cywilnej Uniwersytetu Medycznego we Wrocławiu z tytułu prowadzonej działalności.

Pouczenie: W ciągu 14 dni od otrzymania decyzji wnioskodawcy przysługuje prawo odwołania do Komisji Odwoławczej za pośrednictwem Komisji Bioetycznej UM we Wrocławiu.

Opinia powyższa dotyczy projektu badawczego realizowanego poza działalnością statutową.

Opinia jest ważna do dnia 1 sierpnia 2021 r. (1 rok)

Wrocław, dnia 9 lipca 2020 r.

Uniwersytet Medyczny we Wrocławiu
KOMISJA BIOETYCZNA
przewodniczący
prof. dr hab. Jan Kornafel

KOMISJA BIOETYCZNA
przy
Uniwersytecie Medycznym
we Wrocławiu
ul. Pasteura 1; 50-367 WROCŁAW

# OPINIA KOMISJI BIOETYCZNEJ Nr KB –469/2020

Komisja Bioetyczna przy Uniwersytecie Medycznym we Wrocławiu, powołana zarządzeniem Rektora Uniwersytetu Medycznego we Wrocławiu nr 133/XV R/2017 z dnia 21 grudnia 2017 r. oraz działająca w trybie przewidzianym rozporządzeniem Ministra Zdrowia i Opieki Społecznej z dnia 11 maja 1999 r. (Dz.U. nr 47, poz. 480) na podstawie ustawy o zawodzie lekarza z dnia 5 grudnia 1996 r. (Dz.U. nr 28 z 1997 r. poz. 152 z późniejszymi zmianami ) w składzie:

prof. dr hab. Jacek Daroszewski (choroby wewnętrzne, endokrynologia, diabetologia)
prof. dr hab. Krzysztof Grabowski (chirurgia)
dr Henryk Kaczkowski (chirurgia szczękowa, chirurgia stomatologiczna)
mgr Irena Knabel-Krzyszowska (farmacja)
prof. dr hab. Jerzy Liebhart (choroby wewnętrzne, alergologia)
ks. dr hab. Piotr Mrzygłód, prof. nadzw. (duchowny)
mgr Luiza Müller (prawo)
dr hab. Sławomir Sidorowicz (psychiatria)
prof. dr hab. Leszek Szenborn, (pediatria, choroby zakaźne)
Danuta Tarkowska (pielęgniarstwo)
prof. dr hab. Anna Wiela-Hojeńska (farmakologia kliniczna)
dr hab. Andrzej Wojnar, prof. nadzw. (histopatologia, dermatologia) przedstawiciel Dolnośląskiej Izby Lekarskiej)
dr hab. Jacek Zieliński (filozofia)

pod przewodnictwem
prof. dr hab. Jana Kornafela ( ginekologia i położnictwo, onkologia)

Przestrzegając w działalności zasad Good Clinical Practice oraz zasad Deklaracji Helsińskiej, po zapoznaniu się z projektem badawczym pt.

„Ocena obciążenia psychicznego pacjentów hemodializowanych i dializowanych otrzewnowo w okresie pandemii koronawirusa SARS-CoV-2- prospektywne badanie obserwacyjne"

zgłoszonym przez **prof. dr hab. n. med. Joannę Rymaszewską** zatrudnioną w Katedrze i Klinice Psychiatrii Uniwersytetu Medycznego im. Piastów Śląskich we Wrocławiu oraz złożonymi wraz z wnioskiem dokumentami, w tajnym głosowaniu postanowiła **wyrazić zgodę** na przeprowadzenie badania w Klinice Psychiatrii oraz Klinice Nefrologii i Medycyny Transplantacyjnej Uniwersyteckiego Szpitala Klinicznego im. Jana Mikulicza Radeckiego we Wrocławiu **pod warunkiem zachowania anonimowości uzyskanych danych**.

Uwaga: Badanie to zostało objęte ubezpieczeniem odpowiedzialności cywilnej Uniwersytetu Medycznego we Wrocławiu z tytułu prowadzonej działalności.

Pouczenie: W ciągu 14 dni od otrzymania decyzji wnioskodawcy przysługuje prawo odwołania do Komisji Odwoławczej za pośrednictwem Komisji Bioetycznej UM we Wrocławiu.

Opinia powyższa dotyczy projektu badawczego realizowanego poza działalnością statutową.

Opinia jest ważna do dnia 1 sierpnia 2021 r. (1 rok)

Wrocław, dnia 9 lipca 2020 r.

Uniwersytet Medyczny we Wrocławiu
KOMISJA BIOETYCZNA
przewodniczący
prof. dr hab. Jan Kornafel

## 10.3 Nota biograficzna i dorobek naukowy

**Wykształcenie i przebieg pracy zawodowej:** Mateusz Łuc (urodzony 23.10.1993 r.) ukończył studia na Wydziale Lekarskim Uniwersytetu Medycznego im. Piastów Śląskich we Wrocławiu. W roku 2018 rozpoczął studia doktoranckie w Katedrze Psychiatrii Uniwersytetu Medycznego we Wrocławiu, a w roku 2019 równolegle rozpoczął szkolenie specjalizacyjne w dziedzinie psychiatrii w Klinice Psychiatrii Uniwersyteckiego Szpitala Klinicznego we Wrocławiu (od 12.2019r.).

**Dorobek naukowy:** 13 publikacji z IF; Total IF: 48,778; liczba cytowań łącznie: 113, Total MEiN score: 1406; H-index = 7

**Prace opublikowane z IF:**

1 Łuc M., Pawłowski M., Jaworski A., Fila-Witecka K., Szcześniak D., Augustyniak-Bartosik H., Zielińska D., Stefaniak A., Pokryszko-Dragan A., Chojdak-Łukasiewicz J.: Coping of chronically-ill patients during the COVID-19 pandemic: comparison between four groups, International Journal of Environmental Research and Public Health, 2023, vol. 20, nr 6, art.4814 [14 s.], DOI:10.3390/ijerph20064814, łączna liczba autorów:*14*, 140 punktów, IF(4,614)

2 Cyran A., Łuc M., Szcześniak D., Rymaszewska J.: Nowy obraz objawów psychopatologicznych w dobie pandemii COVID-19 na podstawie pierwszego epizodu depresji psychotycznej , Psychiatria Polska, 2022, vol. 56, nr 5, s. 945-955, DOI:10.12740/pp/141830, 100 punktów, IF(1,596)

3 Lenart-Bugla M., Łuc M., Pawłowski M., Szcześniak D., Seifert I., Wiegelmann H., Gerhardus A., Wolf-Ostermann K., Rouwette E., Rymaszewska J.: What do we know about social and non-social factors influencing the pathway from cognitive health to dementia? A systematic review of reviews, Brain Sciences, 2022, vol. 12, nr 9, art.1214 [22 s.], DOI:10.3390/brainsci12091214, łączna liczba autorów:*20*, 100 punktów, IF(3,333)

4 Łuc M., Woźniak M., Rymaszewska J.: Neuroinflammation in dementia - therapeutic directions in a COVID-19 pandemic setting, Cells, 2022, vol. 11, nr 19, art.2959 [17 s.], DOI:10.3390/cells11192959, 140 punktów, IF(7,666)

5 Seifert I., Wiegelmann H., Lenart-Bugla M., Łuc M., Pawłowski M., Rouwette E., Rymaszewska J., Szcześniak D., Vernooij-Dassen M., Perry M.: Mapping the complexity of dementia: factors influencing cognitive function at the

onset of dementia, BMC Geriatrics, 2022, vol. 22, art.507 [8 s.], DOI:10.1186/s12877-022-02955-2, łączna liczba autorów:*13*, 100 punktów, IF(4,07)

6 Łuc M., Misiak B., Pawłowski M., Stańczykiewicz B., Zabłocka A., Szcześniak D., Pałęga A., Rymaszewska J.: Gut microbiota in dementia. Critical review of novel findings and their potential application, Progress in Neuro-Psychopharmacology & Biological Psychiatry, 2021, vol. 104, art.110039 [13 s.], DOI:10.1016/j.pnpbp.2020.110039, 100 punktów, IF(5,201)

7 Łuc M., Pawłowski M., Kantorska-Janiec M., Rymaszewska J.: Rozlany uraz aksonalny - problem interdyscyplinarny. Stan wiedzy i opis dwóch przypadków klinicznych, Psychiatria Polska, 2021, vol. 55, nr 1, s. 171-180, DOI:10.12740/PP/OnlineFirst/112404, 100 punktów, IF(1,596)

8 Senczyszyn A., Wallner R., Szcześniak D., Łuc M., Rymaszewska J.: The effectiveness of computerized cognitive training combined with whole body cryotherapy in improving cognitive functions in older adults. A case control study, Frontiers in Psychiatry, 2021, vol. 12, art.649066 [13 s.], DOI:10.3389/fpsyt.2021.649066, 100 punktów, IF(5,435)

9 Łuc M., Szcześniak D., Trypka E., Mazurek J., Rymaszewska J.: Pandemia SARS-CoV-2 a populacja osób z otępieniem. Rekomendacje pod patronatem Polskiego Towarzystwa Psychiatrycznego, Psychiatria Polska, 2020, vol. 54, nr 3, s. 421-436, DOI:10.12740/PP/122780, 100 punktów, IF(1,657)

10 Pawłowski M., Fila-Witecka K., Rymaszewska J., Łuc M., Kamińska D., Rymaszewska J.: Quality of life, depression and anxiety in living donor kidney transplantation, Transplantation Reviews, 2020, vol. 34, nr 4, art.100572 [10 s.], DOI:10.1016/j.trre.2020.100572, 70 punktów, IF(3,943)

11 Agrawal S., Woźniak M., Łuc M., Makuch S., Pielka E., Agrawal A., Wietrzyk J., Banach J., Gamian A., Ziółkowski P.: Insulin enhancement of the antitumor activity of chemotherapeutic agents in colorectal cancer is linked with downregulating PIK3CA and GRB2, Scientific Reports, 2019, vol. 9, art.16647 [14 s.], DOI:10.1038/s41598-019-53145-x, łączna liczba autorów:*11*, 140 punktów, IF(3,998)

12 Agrawal S., Łuc M., Winkowski F., Lindner K., Agrawal A., Woźniak M., Sobieszczańska M.: Predictors of mortality in older patients admitted to a geriatric hospital, Geriatrics and Gerontology International, 2019, vol. 19, nr 1, s. 70-75, DOI:10.1111/ggi.13573, 70 punktów, IF(2,022)

13 Łuc M., Woźniak M., Helemejko M., Rymaszewska J.: Tackling Alzheimer's disease: hypothetical synergism between anti-inflammatory and anti-diabetic

agents, Life Sciences, 2019, vol. 231, art.116483 [6 s.], DOI:10.1016/j.lfs.2019.05.039, 70 punktów, IF(3,647)

**Udział w grantach i projektach badawczych:** w latach 2019-2022 zatrudniony na stanowisku badacza w ramach międzynarodowego projektu SHARED Social Health And REserve in the Dementia patient journey - Koncepcja zdrowia społecznego i rezerwy poznawczej w procesie otępiennym (NCBiR JPND.C231.19.001), analizującego czynniki ryzyka, czynniki ochronne oraz trajektorię funkcjonowania poznawczego ze szczególnym uwzględnieniem aspektu zdrowia społecznego. Projekt był finansowany przez JPND/NCBIR i realizowany we współpracy z badaczami z Holandii, Szwecji, Wielkiej Brytanii oraz Australii.