

## Review

# Syndemics & syndemogenesis in COVID-19 and rheumatic and musculoskeletal diseases: old challenges, new era

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## Abstract

People with rheumatic and musculoskeletal diseases (RMDs) are facing several challenges during the COVID-19 pandemic, such as poor access to regular health services and drug shortages, particularly in developing countries. COVID-19 represents a syndemic, synergistic condition that interacts with and exacerbates pre-existing diseases such as RMDs, other co-morbidities and social conditions. The emerging evidence on both biological and non-biological factors implicated in worse outcomes in people with RMDs affected by the COVID-19 pandemic, whether infected by the virus or not, calls for the need to use more novel and holistic frameworks for studying disease. In this context, the use of a syndemic framework becomes particularly relevant. We appeal for a focus on the identification of barriers and facilitators to optimal care of RMDs in the context of the COVID-19 pandemic, in order to tackle both the pandemic itself and the health inequities inherent to it.

**Key words:** COVID-19, syndemics, epidemiology, health inequity, comorbidities, social determinants

### Rheumatology key messages

- COVID-19 represents a syndemic that interacts with and exacerbates pre-existing diseases including RMDs.
- A syndemic approach presents a novel theoretical framework for the study of COVID-19 and RMDs.
- The study of syndemics in RMDs can guide more targeted interventions especially during the pandemic.

## COVID-19 and RMDs

The coronavirus disease 2019 (COVID-19) pandemic has caused immense devastation across the globe since its outbreak in December 2019 in Wuhan, China. The

consequences of this pandemic are likely to continue for years, especially for the most vulnerable populations. As of 7 November 2020, >49 million cases of COVID-19 [also known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)] have been confirmed worldwide, with over 1 million deaths recorded across 219 countries [1].

It was suggested right at the outset of the pandemic that people with a compromised immune system, including those with rheumatic and musculoskeletal diseases (RMDs), were at higher susceptibility to COVID-19 and worse outcomes. Associated disease-modifying therapy was also considered to place individuals at additional risk. However, data from the COVID-19 Global Rheumatology Alliance registry (COVID-19 GRA) showed glucocorticoid therapy at prednisone-equivalent doses of 10 mg/day or more was associated with higher odds of hospitalization in people with RMDs whereas an inverse association between anti-TNF therapy and hospitalization was found [2]. Emergent data will be able to

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clarify this further. In addition, people with RMDs suffer from increased co-morbidities that may place them at additional risk of acquiring COVID-19 and related burden.

Advanced age, male gender and the presence of multi-morbidity have been identified as major risk factors for severe COVID-19 disease [3, 4]. Obesity, among other conditions also known to be highly prevalent in RMDs and associated with higher disease activity and worse quality of life [5–8], has been identified as an added risk factor in the context of COVID-19 disease. The underlying chronic pro-inflammatory state of obesity, the excessive oxidative stress responses and impaired immune responses have been implicated in the association between worse COVID-19 outcomes and higher BMI [7]. Raised pro-inflammatory cytokines associated with obesity, including IL-6 and TNF, are centrally implicated in the pathogenesis of RMDs, highlighting these common pathophysiological mechanisms that potentially link these different conditions or states. In rheumatoid arthritis, high levels of adipokines have been associated with inflammation and increased disease activity [9]. Other than excess weight and obesity, other lifestyle factors such as smoking are associated with increased severity of disease and death in hospitalized COVID-19 patients [10]. Similarly, cardiovascular disease, which people with (certain) RMDs have a higher background risk of, appears to be a key risk factor for COVID-19. Also, cardiovascular complications in patients with COVID-19 represent some of the most significant and concerning outcomes [11]. However, evidence is lacking on more in-depth insights into these potential associations. In the COVID-19 GRA registry older age and co-morbidities, including hypertension, cardiovascular disease, lung disease, diabetes and chronic renal insufficiency were associated with higher odds of hospitalization in people with RMDs and COVID-19 [2].

People with RMDs have faced shortages in crucial treatments for the management of their RMDs [12]. Adding to the burden of disease and the broader aspects of having to deal with chronic illness and its consequences, in the context of one of the worst pandemics in recent history, was the imposed need to rapidly adapt to the use of telehealth, self-quarantine/shielding rules and movement restrictions. In cases where the use of telehealth is not an option, people with RMDs have faced limited access to specialized health care and therapy. Significant anxiety, depression and the general trauma of the COVID-19 pandemic have been unsurprisingly prominent [13]. The negative psychological impact, social isolation, loneliness, depression and anxiety are likely to continue to compound people's mental health and social well-being, especially those in the more vulnerable categories, including older age [14].

### Syndemics and syndemogenesis: old concepts, potential new applications

The concept of syndemics is born of the application of anthropology in the area of health, from which the

experience of the disease is described in groups of individuals with different socio-economic, political and historical conditions. This allows comparison across groups providing specific conditions for each one. The central methodology of anthropology is ethnography, which is the description of the results obtained from techniques such as observation, individual and group interviews, the reconstruction of life histories and the review of archives. Ethnography analyses the context in which patients describe the experience of the disease in relation to the community, as well as the relation with health institutions in a political-historical context. From ethnography it is possible to document the interaction between diseases or health conditions and socio-economic factors (bio-social interaction), central to the concept of syndemics (Fig. 1) [15, 16].

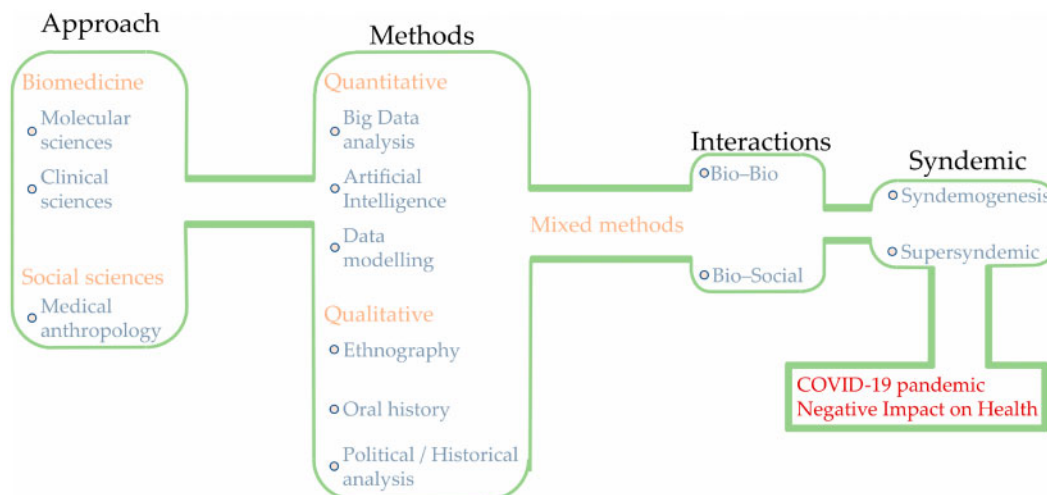
Traditional research focuses on the separate study of biological and non-biological factors in driving disease. In other words, drivers of disease independent of the social contexts of individuals with the disease. This approach, lacks an important attempt to take a more holistic view to the study of disease that would allow the exploration of potential synergistic interactions, with impacts both at the individual and societal level [17]. This is where syndemics and syndemogenesis become relevant.

A syndemic approach focuses on the synergistic interplay between different biological and non-biological factors that drive disease. The non-biological factors focus to a large extent on socio-economic parameters including an individual's social environment that may promote and enhance the negative effects of disease interaction [17]. Syndemics have as components co-occurring diseases or health conditions (disease-disease interaction), adverse biological interactions between those diseases (bio-bio) and socio-economic factors (bio-social) [15]. Syndemogenesis simply refers to the 'process, pathway and stages of syndemic development involving a disease-social context and disease-disease interactions, to acknowledge the health or social conditions that underlie the syndemic-causing illness' [18].

Although syndemics presents an old conceptual challenge and the first syndemic model was described in AIDS back in the 1990s, syndemics remains a fairly novel concept, at least in some disease areas [19]. We have recently advocated the use of a syndemic approach in the study of inflammatory arthritis and other chronic musculoskeletal conditions, to systematically address the social context, biocultural disease interaction and socio-economic characteristics of the setting. This is considered particularly relevant when understanding treatment failure in inflammatory arthritis [20]. Relevant research is currently underway.

Quantitative studies have prevailed in the field of syndemics until now, especially in public health; however, some limitations of classic statistical models for the

Fig. 1 Syndemics and supersyndemics approach



Using different methods to explain bio–bio and bio–social interactions can reveal syndemogenesis and provide information on the negative impact of the COVID-19 pandemic.

study of syndemics have been described [19]. New data modelling techniques focus on the network representation of the individuals in order to provide a cluster analysis of their relationship, namely syndemic and syndemogenesis elements modeler, in the syndemics study of RMDs [21] and in low back pain syndemics [22]. The use of network and cluster analyses have proved to be useful tools for documenting the complexity and the multifaceted impact of syndemics on health in large populations as well as the differences between countries [22].

### Syndemics and syndemogenesis to understand COVID-19 risk in RMDs

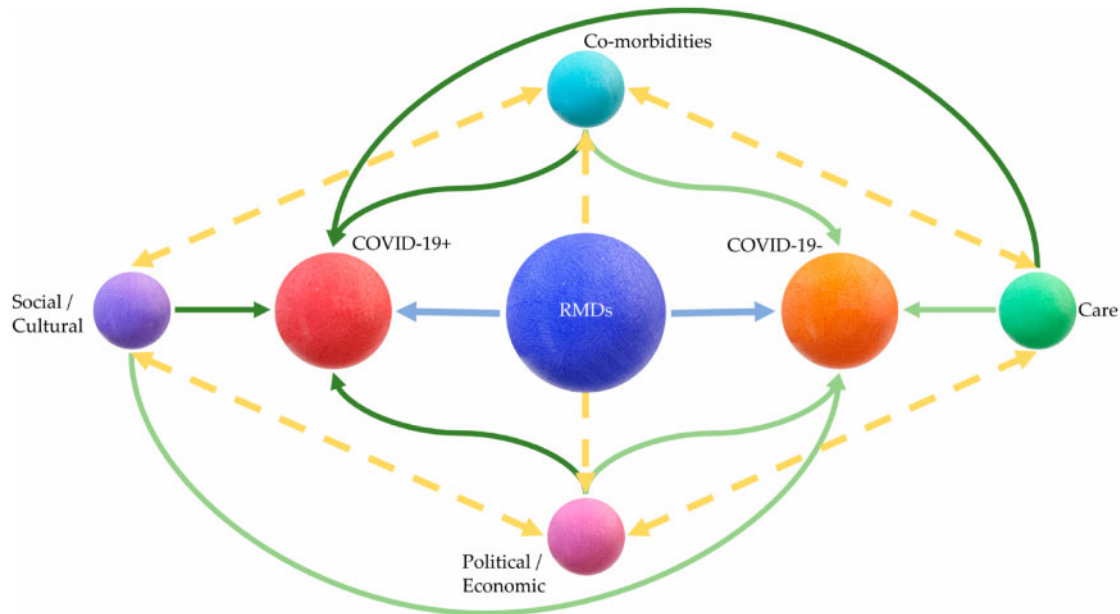
Understanding the risk of COVID-19 in the context of coexisting chronic immune-driven inflammatory diseases, and the growing evidence of the role of coexistent conditions and social determinants of health such as ethnicity, lends itself to syndemics and syndemogenesis. Black, Asian and minority ethnic (BAME) groups have been shown to be at increased fatality risk from COVID-19 [23, 24]. Better understanding of what may drive this higher risk, despite adjustment for geographical region, is expected to reduce health inequities. According to data from the Office of National Statistics (ONS) and Public Health England, occupation and socio-economic deprivation play key roles in the risk of COVID-19 infection and poor outcomes in BAME communities [25, 26]. In Latin America mortality during the COVID-19 pandemic is reported to be higher in low socio-economic status neighbourhoods and rural communities [27, 28]. Limited access to health care, greater social mixing, unemployment, and lower ability to work from home in the vulnerable populations are likely relevant in conferring this increased risk [29]. The COVID-19 GRA reported that

Black and Latin people with RMDs and COVID-19 in the United States had increased odds of hospitalization and requirement of ventilatory support [30].

Anticipated benefits of taking a syndemic approach in the study of COVID-19 and RMDs, include the acquisition of in-depth understanding of complex interactions between biological and non-biological factors [17]. This can help guide more targeted and holistic patient care according to individual and community needs and ultimately reduce health inequities with benefits at both the individual and societal level.

However, to carry out a complete study that enables documentation of the syndemics of RMDs in conjunction with other syndemics such as COVID-19, a new approach is needed, namely supersyndemics [31]. The supersyndemics approach allows the study of two or more previously independent syndemics that come together and significantly impact a population’s health [32]. Supersyndemics of RMDs and COVID-19 could be documented using mixed methods, quantitative Big Data analytics, Artificial Intelligence training and qualitative methods using ethnography (interviews of patients and decision makers, observations of behaviour in the clinical space, analysis of public policy contexts). We hypothesize that the supersyndemic approach, defined as the bio–bio relation of the RMD population with the COVID-19 pandemic, the reported comorbidities that aggravate RMDs (diabetes, obesity, cardiovascular disease including hypertension, mental health problems, among others), and the bio–social relation of social, economic, political and cultural parameters could provide valuable information on the impact of the COVID-19 pandemic (Fig. 2). This could help guide the design of more holistic interventions for the management of people with RMDs in the context of the pandemic, using an inter-transdisciplinary perspective.

**Fig. 2** The supersyndemic approach, defined as the bio–bio relation of RMDs with the COVID-19 pandemic, co-morbidities that aggravate RMDs, and the bio–social relation of social, economic, political and cultural parameters could provide information on the impact of the COVID-19 pandemic on care of RMDs.



## Conclusions and future research agenda

The emerging evidence of both biological and non-biological factors implicated in worse outcomes in people with RMDs affected by the COVID-19 pandemic, whether infected by the virus or not, calls for the need to use more novel and holistic frameworks for studying disease. In this context, the use of a syndemic framework that considers biocultural disease interactions within specific social context and characteristics, becomes particularly relevant. We call for a focus on the identification of barriers and facilitators to optimal care of people with RMDs, including access to specialized health care and treatment, as well as provision of culturally sensitive guidance during the pandemic, which would tackle both the pandemic itself and the health inequities inherent to it. With second COVID-19 pandemic waves looming on the horizon, better public health communications and guidance is necessary, informed by research that covers the unmet need to identify social as well as biological drivers of disease.

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## Data availability statement

Data are available upon reasonable request by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). All data relevant to the study are included in the article.

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