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**Citation for published version:**

MacRae, C, Henderson, D, Guthrie, B & Mercer, SW 2022, 'Multimorbidity and comorbidity patterns in the English National Health Service', *Cell Reports Medicine*, vol. 20, no. 3(12).  
<https://doi.org/10.1016/j.xcrm.2022.100863>

**Digital Object Identifier (DOI):**

[10.1016/j.xcrm.2022.100863](https://doi.org/10.1016/j.xcrm.2022.100863)

**Link:**

[Link to publication record in Edinburgh Research Explorer](#)

**Document Version:**

Peer reviewed version

**Published In:**

Cell Reports Medicine

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**Title: Multimorbidity and comorbidity patterns in the English National Health Service**

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## Abstract

In an observational population-based study including nearly four million participants, Kuan et al<sup>1</sup> examined frequencies of common combinations of diseases and identified non-random disease associations in people of all ages and multiple ethnicities.

## Main text

Multimorbidity (the coexistence of two or more long-term conditions within an individual) is common and of increasing importance to policymakers, clinicians, and researchers. Multimorbidity is associated with increased use of healthcare and social care services,<sup>2</sup> and substantial decrements in quality of life.<sup>3</sup> Research in multimorbidity increasingly focusses on identifying clusters of conditions, as a potential way to answer questions about underlying disease processes, uncover greater detail about which sub-groups of society are at increased risk of specific clusters and associated adverse outcomes, and provide opportunities for targeted interventions. There is emerging evidence that certain condition clusters are associated with worse health outcomes, such as increased use of primary care services,<sup>4</sup> hospitalisation, and mortality.<sup>5</sup> Although these findings are promising, results may not be replicable across different datasets and methods.

The recently published study by Kuan et al<sup>1</sup> examines patterns of conditions in an observational population-based study using electronic health records data for nearly four million patients in England. Network analysis was used to identify pairs of 308 conditions which co-occurred more often than expected by chance. Helpfully, the authors provide the code lists used to define each condition via the Health Data Research UK Phenotype Library.<sup>6</sup> Equally helpfully, given the very large number of such pairs, the authors provide online tools to allow readers to visualise patterns for different conditions stratified by age, sex, and ethnicity.<sup>1</sup>

A higher prevalence of multimorbidity was found in boys (aged 0-9 years) (47·8%) than girls of the same age (40·3%). However, multimorbidity was more common in girls and women than boys and men aged 10 years and over (1 361 232 [80·5%] of 1 690 521 vs 1 161 308 [70·8%] of 1 639 593). White individuals, of any age, were more likely to be multimorbid (2 097 536 [78·7%] of 2 666 234) than black or South Asian individuals (59 339 [60·1%] of 98 815).

The authors show networks for exemplar conditions and describe how these networks vary by age, sex, and ethnicity, highlighting the value of network analysis for hypothesis generation for further explanatory studies. Examples include spinal fractures that were most strongly associated with malignancy in Black

individuals but osteoporosis in white individuals, and hypertension that was most strongly associated with kidney disorders in younger people aged 20-29 years, but dyslipidaemia, obesity, and type 2 diabetes in people aged 40 years and older. Additionally, the online tool allows exploration of the 50 most common condition triads and the most prevalence comorbidities for index conditions, with potentially wide-reaching benefits for multiple stakeholders who seek to understand more about multimorbidity.

Key strengths of the study include use of a large and nationally representative electronic health records dataset and examination of common patterns of conditions stratified by population sub-groups including ethnicity. Given the cross-sectional design of the study, the authors point out that they were unable to identify the sequence of condition accrual. However, the study does stratify common patterns of conditions by age-group, which provides new information about which co-existent conditions occur across the life course and importantly provides additional evidence about multiple conditions in younger people. Using a pairwise, rather than multiple, network analysis looks at condition dyads but does not provide information on the association of multiple concurrent diseases, which is common in those with multimorbidity. As in other studies employing network analysis or other clustering techniques,<sup>7</sup> this study demonstrates that multimorbidity combinations are highly heterogenous and therefore clinical care must be tailored to individuals and their unique circumstances.

The Kuan et al<sup>1</sup> study is an insightful and major contribution to new understanding and the potential for hypothesis generation in the study of multimorbidity, and is one of the largest and most rigorous to date. Many questions remain unanswered, however, including exploration of condition networks stratified by socioeconomic status is important, a limitation the authors themselves highlight. Multimorbidity occurs 10-15 years earlier in more deprived populations contributing to health inequalities,<sup>8</sup> and ongoing existence of the inverse care law in the UK National Health Service further limits the potential benefits of healthcare in reducing or mitigating the effects of health inequalities.<sup>9</sup> A comprehensive list of 308 common mental and physical health conditions were included in this study. The condition list includes double counting of some conditions because some single conditions will have multiple manifestations, such as alcoholic liver disease, cirrhosis, portal hypertension, and oesophageal varices for example. However, examining networks in this way is important because it can be used to understand genetics and mechanisms of serious disease. This study also included acute conditions, for example any previous admission with acute infection, which differs from traditional methods including only chronic conditions in multimorbidity measures. Ethnicity was unknown for 22.2% of the study population and it is unclear whether data were randomly or non-randomly missing, which is a common issue when using routinely collected data. Another issue related to the use of electronic recording of data is that neonatal and childhood conditions are more likely to be present in the young, and there is likely to be under

ascertainment for these conditions in the adult populations. These issues are not necessarily limitations but should be considered by researchers when using results from the study.

This is a challenging topic and further research is needed to improve consensus and phenotyping of conditions, an area developed by a recent Delphi consensus study on the measurement of multimorbidity.<sup>10</sup> Moving from observing combinations of conditions to understanding genetic and mechanisms of disease is needed to validate and understand observed clustering, and thus understand therapeutic targets.

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