Comment

MOTT/NYT/REDUX/EYEVINE

People with diabetes are prone to many other comorbidities.

Map clusters of diseases to tackle multimorbidity

Christopher J. M. Whitty & Fiona M. Watt

Many people now have two or more diseases at once. It is time to rethink funding, research, publishing, training and treatment for this growing problem.

More and more people the world over have two or more long-term diseases at once — known as multimorbidity. This is the case for at least half of Europe's population aged 65 or older (more than 50 million people), for example[1]. And in the United Kingdom, the proportion of the population with multi-morbidity is expected[2] to rise from 54% in 2015 to 68% in 2035. Science, and medicine, have been slow to respond to this change.

One of the things that has limited the ability to address disease co-occurrences is that they are usually seen as random. In reality, diseases often cluster because of a common risk factor. Only a fraction of the many thousands of potential clusters are well known. The canonical example is the link between diabetes and conditions in the skin, peripheral nerves, heart, eyes and brain. Now, advances in statistical methods, electronic medical-record keeping and machine learning could help to identify many more links.

Mapping these clusters, and working out which are non-random, is crucial for three reasons: to uncover new mechanisms for disease; to develop treatments; and to reconfigure services to better meet patients' needs.

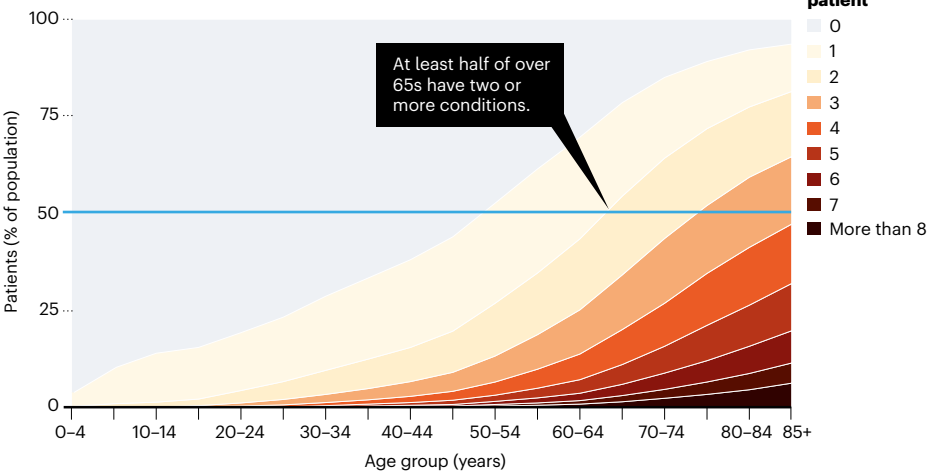
We urge researchers to prioritize the hunt for diseases that occur together because of shared risk factors — biological or environmental.

Multimorbidity has always existed. In

SOURCE: REF. 12

TRIALS OF AGEING

A study of more than one million patients in Scotland, UK, shows the rise in disease clustering as people get older.



all societies studied, people who are less wealthy are more likely to acquire multiple diseases than are those of the same age who have more advantages[3]. In high-income settings, the conditions usually occur in adults and include common cancers, cardiovascular disease and other non-communicable chronic disorders, especially those associated with smoking. In low-income settings, the worst affected tend to be children under five – with clusters related mainly to diet and infection. In rural Tanzania, for instance, children can have malaria, stunting due to malnutrition, anaemia from chronic parasitic infections and a high risk of accidents.

Some clusters vary by region, usually for a combination of socio-economic, cultural or genetic reasons[4]. For example, a higher prevalence of multimorbidity is linked to low educational attainment (see 'The health benefits of learning'). In some low-to-middle income regions, such as parts of South Africa, physical conditions such as anaemia tend to group with infections such as HIV[5]. In rapidly developing Asia, diseases of affluence such as type-2 diabetes and coronary heart disease commonly co-occur with tuberculosis and other diseases of poverty[6].

Mental- and physical-health issues often co-occur, and causation can go in both directions. Those with serious mental-health problems such as major psychotic disease tend to have significantly shorter lives owing to physical health problems[7]. And physical illness can lead to mental-health problems such as depression.

Across all settings, people under 20 with one major condition, such as a genetic or congenital abnormality, often have or acquire others. For example, children with sickle-cell disease can go on to develop infections, visual problems or stroke[8]. Children and adolescents with developmental disorders can be affected by mental-health conditions as well as physical ones[9]. And children with autism spectrum disorder often have comorbidities ranging from dyspraxias[10] to tooth decay[11].

Some diseases cluster in pregnancy. These include infections such as listeriosis; heart disorders such as cardiomyopathy; and autoimmune conditions such as flares of systemic lupus erythematosus.

What's making an already important issue much more important is the strong link with ageing. As we grow old, the probability of developing more than one condition greatly increases[12]. And because the incidence and prevalence of diseases in people younger than 60 has dropped substantially, societies in every continent are projected to have longer lifespans – with east Asian countries such as Japan and Singapore in the lead[13].

In high-income settings, most older people now have either no major conditions or several. A shrinking minority have one significant disease (see 'Trials of ageing'). That's the message of a decade or more of studies and systematic reviews, including a 2018 report from the UK Academy of Medical Sciences[14].

Middle-income countries such as China[6] and South Africa[15], are also seeing a rise in multimorbidity in older people. In fact, the diseases that cluster here arise from the double burden of ageing and poverty, and could well be the most diverse.

Better together

Research, clinical teams and training are organized mainly around single diseases or organ systems. Think coronary heart disease or breast cancer, haematology or gastroenterology. But the cumulative effect of several diseases often involves interactions that make the practical and medical impacts of the combination much greater than the sum of their parts[16].

Because each disease tends to be treated separately, someone with cardiovascular disease, inflammatory bowel disease and asthma, say, might have to attend three clinics to receive treatment from three specialists, with each physician working in isolation.

People with more than one condition tend to be excluded from clinical trials testing potential new drugs. Yet any one drug might have different effects when prescribed to someone with multiple conditions, which could be most of the people it is given to.

Also, interactions that occur when many drugs are used together – known as polypharmacy – can harm patients and increase the complexity of their care[17]. And there are cases in which one drug affects several conditions because they share a common, if unrecognized, biological basis. (Tumour necrosis factor-α inhibitors, for instance, can treat Crohn's disease and psoriasis because both are autoimmune disorders[18].)

In short, opportunities for tackling several problems at once are being missed.

To address this already large, and rapidly growing, problem, clinical epidemiologists and others must first map out disease clusters.

Some associations will occur simply because the component diseases are common. Diabetes and asthma often co-occur, for instance, through random assortment. A shared risk factor or biological interaction is implied only when diseases cluster with a frequency that is greater (or less) than chance alone based on their relative prevalence or incidence.

Historically, the identification of such clusters has depended largely on clinicians simply noting the same groups in multiple patients – often before there was any scientific explanation for the combination. In the early 1980s, for instance, it was clinicians' observations that pneumocystis pneumonia co-occurred with Kaposi's sarcoma in men in San Francisco that led to the identification of HIV/AIDS as the common risk factor[19].

Epidemiologists have helped to flag associations that are too weak or rare for a clinician to spot. In the late 1800s, for example, statistical pioneers such as Florence Nightingale and John Snow identified links between poor sanitation and typhoid, diarrhoeal diseases and hospital-acquired

infections, which led to improved sanitation worldwide. More recently, epidemiologists have established many diseases associated with smoking, including lung cancer, heart disease and chronic obstructive pulmonary disease by following cohorts of smokers and non-smokers[20].

Today, non-random clustering will be much easier to find than it was even five years ago. There are millions of electronic medical records, an ageing population with high rates of multimorbidity, new statistical tools and artificial-intelligence methodologies for pattern recognition. Plus, patients are finding each other online, discovering they share seemingly unrelated problems and flagging these to physicians and researchers.

It should therefore also be possible to identify the sequence in which individual diseases tend to accumulate. This will increase researchers' understanding of mechanisms. It could also allow clinicians to intervene, or to screen people for other conditions when the first disease of the cluster becomes apparent.

Given the thousands of probable clusters[21], such mapping should be done without preconceptions about why conditions might co-occur. Starting with hypotheses about causes — genetic or environmental — could close off possibilities and mean that important links are missed.

Other advances are making it easier to probe the underlying molecular pathology. Already, for example, the global Human Cell Atlas initiative is providing insights into subsets of T cell common to different tissues[22].

Next action

Meeting this new challenge requires action across many fronts, notably funding, training and publishing. At present, few grant-giving panels are equipped to assess proposals that cross disciplinary boundaries. Training tends to be in one disease or organ system. And it is rare to find the best papers addressing multiple conditions in major journals, because editors struggle to find referees who are able to assess them. These are the priorities:

Funding. In the United Kingdom, the National Institute for Health Research and the Medical Research Council are taking steps to actively invest in multimorbidity research (see 'UK steps'). Analogous organizations in other countries need to do so, too. Meanwhile, in clinical trials, it is important to develop ways to include people with more than one disease.

Training. Identifying which conditions co-occur could lead to a rethink of how scientific specialties are defined and medical students are taught. A multi-disease speciality has already been created for diabetes and HIV/AIDS. We need to take a similar approach to training, so that early-career scientists think about diseases that cluster as their principal area of focus (horizontal integration) as well as the vertical integration of a single disease from the basic to the applied sciences (bench to bedside).

Publishing. Journal editors need to proactively identify potentially good papers about disease clusters and adapt the current model of single-disease referees to ensure they are assessed fairly. New fields develop much faster if journals champion them.

Identifying diseases that group together is exciting scientifically and important clinically. It could yield enormous health benefits globally — across all age groups, ethnicities and socio-economic backgrounds. It should now be a priority for medical science.

UK steps

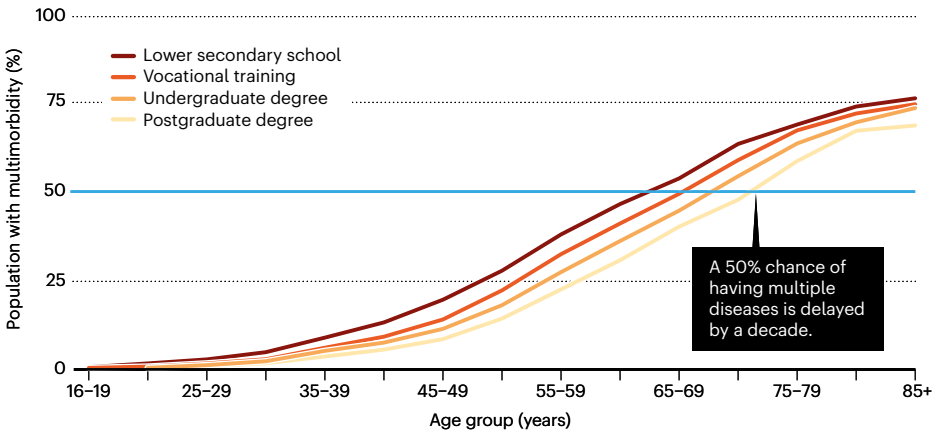
Research funders prioritize the identification of diseases that co-occur.

In the United Kingdom, the National Institute for Health Research and the Medical Research Council are doing four things:

- Calling for proposals for research into multimorbidity. Examples include: strengthening statistical methods to detect clusters; the application of machine learning to large data sets; and the identification of the biological basis of clusters.
- Supporting clinical and public-health research to prevent clusters of disease, and to treat them more effectively (in the UK and globally).
- Supporting work that aims to understand and respond to the needs of people with multiple long-term conditions, as well as the needs of their carers.
- Supporting studies that investigate new approaches to the configuration of health systems to account for clusters of disease and patients' needs.

THE HEALTH BENEFITS OF LEARNING

In Denmark, people with lower levels of education are more likely to develop two or more long-term conditions than are those of the same age with more education, which is often a proxy for income.



SOURCE: REF. 3

The authors

Christopher J. M. Whitty is chief medical officer for England and chief scientific adviser, Department of Health and Social Care, London, UK, and head of the National Institute for Health Research. **Fiona M. Watt** is executive chair, Medical Research Council, London, UK, and a researcher at King's College London.
e-mails: chris.whitty@dhsc.gov.uk; Fiona.watt@mrc.ukri.org

1. Rijken, M. *et al. Eurohealth* **19**, 29–31 (2013).
2. Kingston, A. et al. *Age Ageing* **47**, 374–380 (2018).
3. Schiøtz, M. L., Stockmarr, A., Høst, D., Glümer, C. & Frølich, A. *BMC Publ. Health* **17**, 422 (2017).
4. Afshar, S., Roderick, P. J., Kowal, P., Dimitrov, B. D. & Hill, A. G. *BMC Publ. Health* **15**, 776 (2015).
5. Chang, A. Y. *et al. BMJ Glob. Health* **4**, e001386 (2019).
6. Zhang, R., Lu, Y., Shi, L., Zhang, S. & Chang, F. *BMJ Open* **9**, e024268 (2019).
7. Firth, J. *et al. Lancet Psychiatry* **6**, 675–712 (2019).
8. Dunbar, P. *et al. JAMA Netw. Open* **2**, e197613 (2019).
9. Allerton, L. A., Welch, V. & Emerson, E. *J. Intellect. Disabil.* **15**, 269–278 (2011).
10. Miller, M., Chukoskie, L., Zinni, M., Townsend, J. & Trauner, D. *Behav. Brain Res.* **269**, 95–102 (2014).
11. da Silva, S. N. *et al. Int. J. Paediatr. Dent.* **27**, 388–398 (2017).
12. Barnett, K. *et al. Lancet* **380**, 37–43 (2012).
13. Foreman, K. J. *et al. Lancet* **392**, 2052–2090 (2018).
14. Academy of Medical Sciences. *Multimorbidity: a Priority for Global Health Research* (Academy of Medical Sciences, 2018).
15. Chang, A. Y. *et al. BMJ Glob. Health* **4**, e001386 (2019).
16. Jani, B. D. *et al. BMC Med.* **17**, 74 (2019).
17. Pan, H. H., Li, C. Y., Chen, T. J., Su, T. P. & Wang, K. Y. *BMJ Open* **4**, e004428 (2014).
18. Lis, K., Kuzawińska, O. & Bałkowiec-Iskra, E. *Arch. Med. Sci.* **10**, 1175–1185 (2014).
19. Centers for Disease Control (CDC). *MMWR Morb. Mortal. Wkly Rep.* **30**, 305–308 (1981).
20. Doll, R., Peto, R., Wheatley, K., Gray, R. & Sutherland, I. *BMJ* **309**, 901–911 (1994).
21. Nicholson, K. *et al. Br. J. Gen. Pract.* **69**, e647–e656 (2019).
22. Regev, A. *et al. eLife* **6**, e27041 (2017).