The molecular regulators of vessel function are identical between mice and humans. Thus, could these mechanisms also be operating in humans? A recent study profiled the concentration of more than 2000 proteins in the circulation over the life span of humans (11). VEGFA is among those molecules whose circulating concentrations are substantially regulated over the life span: A subtle, but continuous increase of circulating VEGFA between 25 and 75 years of age is followed by a sharp increase in circulating amounts after 75 years of age (11). Most intriguingly, VEGFA cooperates with angiopoietin-2, which acts as a contextual agonistic and antagonistic ligand for the receptor tyrosine kinase TIE2 (angiopoietin-1 receptor), which controls vessel maturation. Angiopoietin-2 similarly shows a sharp increase in the circulation after 75 years of age (11).

How can a single vasculotrophic factor exert such diverse effects in different organs? Reducing vascular rarefaction will lead to improved organ perfusion, which alone may be sufficient to positively affect homeostatic organ function. Yet, it remains unknown whether this would be sufficient to explain the multitude of different phenotypes. The most compelling common denominator among the different phenotypes may be a complex systemic metabolic reprogramming that could account for many of the different organ phenotypes observed by Grunewald et al. Similarly, chronic systemic inflammation appears to be an important contributor to organismal aging (called “inflammaging”) and also to cancer development (12). Reducing chronic inflammation through improved vascular VEGFA signaling may be another important common denominator of the observed plethora of phenotypes, including the reduction in tumor burden in these aged mice.

How VEGFA overexpression affects the immune system warrants further investigation. Several aspects of the immune system are associated with aging (13), notably shrinkage of the naïve T cell compartment. T cell production in the thymus declines with age—a process that might be slowed down by reduced vascular rarefaction of the thymus. The brain also relies on vascular health to function correctly, and slowed aging of the brain may underlie ameliorated aging of other bodily tissues (14). Although Grunewald et al. did not assess the impact of VEGFA overexpression on brain health, a role of the brain in determining aging of the body could be an exciting future frontier of research.

Grunewald et al. used a genetic approach of VEGFA overexpression that likely reflects a preventive regimen. The study includes some experiments with induced expression of VEGFA only in adult mice. Yet, it remains unclear whether the effects on life span elicited by low-level systemic VEGFA overexpression from early adulthood could also be elicited in a therapeutic setting when given to aging mice.

An important conceptual question not answered by the study of Grunewald et al. is whether low-dose systemic VEGFA overexpression directly alters the aging process or whether it positively interferes with deficiencies in the environment or in the genetic makeup of the particular mouse strain that lead to aging. This question, often ignored, applies to essentially all experimental longevity studies and warrants careful consideration (7). The relatively short life span of the control mice used in the study makes it likely that interference with deficiencies rather than direct alterations of the aging process may causally be involved in the observed phenotypes. Yet, this may not be a limitation of the study but rather part of its strength, because it emphasizes the idea that blood vessels probably do not affect the aging process per se but enable healthy aging. Maintaining physiological function of blood vessels throughout life may therefore be among the most promising strategies in the long run to achieve maximum human life span and optimize health span. This may possibly be achieved with preventive or therapeutic approaches. Likewise, the effects of lifestyle (for example, exercise) in preventing vascular aging deserve intensified analysis.

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The road to addressing Long Covid

Reporting, recognizing, and researching the chronic effects of COVID-19 will help those affected

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By summer 2020, thousands were joining social media support groups. A common theme started to emerge: lack of recognition by the medical profession. Patients, including doctors, with Long Covid were consulting their health care providers, and their symptoms were commonly minimized, dismissed, or labeled as anxiety (3). A narrative emerged of people struggling to make sense of their symptoms and forming their own groups to understand and research what was happening to them in an international citizen science movement (4). The testimonials of people living with Long Covid demonstrated themes of stigma and discrimination.

Those whose initial disease was characterized as “mild” commonly experience Long Covid. There is some indication that having more symptoms at the start of the illness is linked to the development of Long Covid and more multisystem involvement later (5, 6). The most prevalent symptom of Long Covid is commonly called “fatigue.” This is often mistaken for tiredness, but it is better described as a feeling of utter exhaustion, energy drain, or bodily dysfunction that is not necessarily triggered by exertion and is not always relieved by rest. The prevalence of fatigue is followed closely by symptoms of cognitive dysfunction, including poor memory or concentration, confusion, and “brain fog.” Chest pain or heaviness, breathlessness, headache, muscle aches, dizziness, and palpitations are also common (5). A wide range of other symptoms have also been reported, affecting the cardiopulmonary, neurocognitive, and gastrointestinal systems, as well as effects on skin and eyes, and general pain, making Long Covid a multisystem disease (4, 5). Triggers of symptoms include physical activity, stress, sleep disturbance, and cognitive tasks (5).

Most prevalence estimates to date are based on follow-up of hospitalized patients. Follow-up of discharged COVID-19 patients in Wuhan, China, 6 months after symptom onset showed that 76% were still symptomatic (7). In nonhospitalized COVID-19 patients, prevalence estimates are variable depending on the study design, applied definitions, population sample, and duration of follow-up. A UK community prevalence study of over half a million people [Real-time Assessment of Community Transmission 2 (REACT-2) study] reported a prevalence among those who reported having COVID-19 of 38% (33% in males, 42% in females) with at least one symptom lasting 12 weeks or more, and 15% having at least three symptoms lasting 12 weeks or more (1). The Office for National Statistics (ONS) estimates that in June 2021, almost 1 million people who reported having COVID-19 had symptoms for more than 4 weeks in the UK (1.5% of the population), of which 385,000 were estimated to have had COVID-19 at least a year ago (8). All age groups were affected by Long Covid, including children, with an estimated 33,000 aged 2 to 16 years with Long Covid, of which 26,000 had symptoms for at least 12 weeks and 9000 for at least 1 year (8).

Meeting the need of Long Covid

The public health response to the COVID-19 pandemic needs to adequately address the direct long-term effects of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in the context of the ongoing pandemic. An adequate response should incorporate the 4 Rs: Reporting, Recognition (including Rehabilitation), and Research.

- **Reporting**
  - Universal and frequently updated case definitions
  - Disease registries
  - Follow-up after infection to assess recovery
  - Pandemic and postpandemic morbidity surveillance systems
  - Direct link to prevention policy decisions
  - Informing health and social care planning

- **Recognition**
  - Listening, believing, and avoiding stereotypes.
  - Thorough clinical assessment and investigations
  - Inclusive diagnostic criteria
  - Personalized treatment and rehabilitation
  - Equitable care pathways
  - Multidisciplinary care
  - Employment rights and occupational health

- **Research**
  - Risk factors
  - Prognosis and progression
  - Predictors of recovery
  - Pathophysiology
  - Therapeutics
  - Role of vaccination
  - Reinfection
  - Inequalities and stigma
  - Economic and services burden
  - Long Covid in children

The diagnostic criteria of Long Covid are still not standardized. Indeed, even the name varies by country and institution (e.g., post-COVID-19 syndrome, post-COVID-19 condition, post-acute sequelae of COVID-19). Without universal criteria that do not exclude those without lab-confirmed infection, health and social care systems will not be able to accurately track the prevalence and address the impact of Long Covid. One important issue is whether “Long Covid,” as a label, will include organ pathology diagnosed weeks or months after COVID-19, or whether these cases move out into an alternative diagnostic category, leaving only those with “unexplained” symptoms as having Long Covid. In this scenario, follow-up of Long Covid patients with thorough clinical assessment and investigations if symptoms continue would still be needed to avoid missing treatable pathology and prevent neglect and stigmatization.

Long-term sequelae have been reported with other viral infections. Most relevant day activities (8). It substantially affects not only leisure and social activities, but also being able to self-care, care for children or older adults, and carry out domestic chores (5). Also, it often affects the ability to work, commonly resulting in taking sick leave and losing income (5). This will likely accentuate the socioeconomic disparities that are reflected by rates of SARS-CoV-2 infection and mortality. Both the ONS and REACT-2 data show highest prevalence of Long Covid in those living in the most economically deprived areas (1, 8).

The effect of Long Covid on mental health is also concerning. In this context, anxiety can be caused by multiple factors, including the uncertainty of prognosis and treatment, as well as being denied recognition, employment benefits, and support because of being disbelieved, particularly if there is no lab confirmation of SARS-CoV-2 infection. Anxiety may be secondary to not recovering rather than being the primary manifestation of the illness. Being diagnosed with anxiety with no adequate attention to other symptoms can be isolating and detrimental to the patient’s well-being (3). Health inequalities are likely to widen in such scenarios because some groups who already suffer structural disparities may be stereotyped as less credible in interpreting their own health.

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are other coronavirus diseases, with a quarter to a third of those with SARS and Middle East respiratory syndrome (MERS) having lingering lung function abnormalities, reduced exercise capacity, and psychological manifestations (9). Autonomic dysfunction after viral illness, which has been observed in Long Covid but is also a feature of similar conditions such as myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), can cause disabling syndromes including postural orthostatic tachycardia syndrome (POTS). Exact case definitions of what is collectively termed “postviral syndrome” are needed. Long Covid research may also be applicable to a wider range of chronic illnesses, including ME/CFS, which similarly lack adequate understanding and recognition.

Tissue scarring, and organ damage, could be the cause of persistent symptoms. Patients surviving COVID-19 in the short term have higher rates of organ-specific pathology, including of the heart, liver, kidneys, and pancreas, and higher rates of hospital readmission and mortality a few months after infection (10). This may not fully explain the range of symptoms and disability experienced by many “long-haulers” with no obvious evidence of organ damage. However, mechanisms such as vascular damage, hypercoagulability, and microthrombosis have also been implicated (11). These could go undetected because a clinical diagnosis is dependent on the extent of clinical investigations.

Another potential mechanism involves immune system dysregulation and autoantibodies, consistent with the cyclical nature of the symptoms. People with Long Covid have increased concentrations of cytokines in serum at 8 months after infection, indicating up-regulation of immune and inflammatory mediators (12). Even viral reservoirs as a potential cause of Long Covid cannot currently be excluded. SARS-CoV-2 nucleocapsid protein has been detected in extrapulmonary tissues, including gut, liver, gall bladder, and lymph nodes, up to 6 months after infection (13). Responses to COVID-19 vaccines may help identify the underlying mechanisms. Vaccination could help the immune system tackle residual virus, or, if the mechanism is autoimmunity, immunization might “reset” the immune system (14). Therefore, it is imperative that vaccinated people with Long Covid are systematically followed-up. The mechanisms underlying Long Covid may be different in different groups of patients or may coexist in the same patient. Currently, Long Covid is an umbrella term that may include multiple conditions.

To move forward to a more systematic response to the crisis of Long Covid, better reporting, recognition, and research are needed (15) (see the figure). Reporting involves systems that can measure Long Covid. This can be achieved through agreeing on specific diagnostic criteria, establishing disease registers, and following up those with acute infection or a positive test using contact tracing infrastructures. It is unknown if or when many of those with Long Covid will recover, particularly given the relapsing nature of the illness. Surveillance systems must start assessing recovery and medium-term survival (1, 2, and 5 years after SARS-CoV-2 infection). Without knowing how many people remain ill following acute infection, the pandemic and postpandemic responses will always be deficient because they will not account for the full impact of COVID-19.

Recognition requires listening and believing patient testimonies, thorough clinical assessment and investigations, personalized treatment, and rehabilitation. It must include equitable clinical and social care pathways, addressing financial support, and employment rights. Long Covid is a multi-organ condition that necessitates a multidisciplinary clinical approach (11). Patients should not feel that they have to prove their own lived experience in a doctor-patient context. This includes parents and carers of children with Long Covid. It is not the patient’s duty to convince; it is the doctor’s duty to listen and not prejudice.

Rigorous research to understand the mechanisms, risk factors, prognosis, and subgroup characteristics, and to identify potential therapeutics for Long Covid, is desperately needed.

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