Ageing Research Reviews 73 (2022) 101494

Contents lists available at ScienceDirect

Ageing Research Reviews

journal homepage: www.elsevier.com/locate/arr

Review

# Triple jeopardy in ageing: COVID-19, co-morbidities and inflamm-ageing

Irene Maeve Rea [a,b,c,*], H. Denis Alexander [b]

[a] School of Medicine, Dentistry and Biomedical Science, Queens University Belfast, Belfast, United Kingdom
[b] Northern Ireland Centre for Stratified Medicine, Biomedical Sciences Research Institute, University of Ulster, C-TRIC Building, Altnagelvin Area Hospital, Londonderry, United Kingdom
[c] Meadowlands Ambulatory Care Centre, Belfast Health and Social Care Trust, Belfast, United Kingdom

ARTICLE INFO

*Keywords:*
Ageing
COVID-19
Cytokine storm, inflamm-ageing
Immunosenesence
Co-morbidities
Vaccine efficacy

ABSTRACT

Covid-19 endangers lives, has disrupted normal life, changed the way medicine is practised and is likely to alter our world for the foreseeable future. Almost two years on since the presumptive first diagnosis of COVID-19 in China, more than two hundred and fifty million cases have been confirmed and more than five million people have died globally, with the figures rising daily. One of the most striking aspects of COVID-19 illness is the marked difference in individuals' experiences of the disease. Some, most often younger groups, are asymptomatic, whereas others become severely ill with acute respiratory distress syndrome (ARDS), pneumonia or proceed to fatal organ disease. The highest death rates are in the older and oldest age groups and in people with co-morbidities such as diabetes, heart disease and obesity. Three major questions seem important to consider. What do we understand about changes in the immune system that might contribute to the older person's risk of developing severe COVID-19? What factors contribute to the higher morbidity and mortality in older people with COVID-19? How could immunocompetence in the older and the frailest individuals and populations be supported and enhanced to give protection from serious COVID-19 illness?

## 1. COVID-19 highjacks and controls cells

Early in infection, the SARS-CoV-2 virus targets the nasal and bronchial epithelium and cells of the lung. It uses its viral structural spike protein (S) to bind to the angiotensin-converting enzyme 2 (ACE2) receptor on the host cell surface, where the transmembrane serine protease (TMPRSS2) cleaves ACE2 and activates SARS-CoV-2-S protein, allowing coronavirus to enter the host cells (Hoffman et al., 2020) (Fig. 1A). Neuropilin-1(NRP1), recently identified as a host factor, potentiates the SARS-CoV-2 infectivity (Daly et al., 2020).

COVID-19 uses the internal machinery of the host cell to replicate so that huge numbers of new SARS-CoV-2 viruses emerge into the blood stream. COVID-19 then further replicates itself unrecognised within the host cell by blocking the cell's normal defence molecule – interferon gamma (IFN), that would normally be the primary counter-acting cytokine to initiate an effective immune response, halting the viral invasion.

Similar to infection with other respiratory viruses such as influenza, lymphopenia often develops with COVID-19 illness (Qin et al., 2020; Huang et al., 2020a), which likely contributes to the failure to limit viral replication so that widespread viral dissemination progresses to severe illness (Huang and Pranata, 2020; Tan et al., 2020a). Although T cell depletion in the blood is not well understood, excessive IL-6 production can block lymphopoiesis (Maeda et al., 2005). The SARS-CoV-2 viral-induced inflammatory responses can lead to spleen and lymph node damage inducing secondary lymphopoiesis, and as lymphocytes themselves express ACE2 receptor they may therefore be a direct target of SARS-CoV-2 infection (Tan et al., 2020a; Feng et al., 2020).

In severe COVID-19, fulminant activation of the coagulation cascade, with consumption of clotting factors, can occur with symptoms and findings consistent with disseminated intravascular coagulation (DIC) (Lodigiani et al., 2020; Ackermann et al., 2020). Microthrombi occur in the lungs and thrombotic complications develop in arteries and veins causing deep venous thrombosis, pulmonary embolism, stroke and myocardial infarction.

In later stages, as COVID-19 viral replication increases, the epithelial-endothelial barrier becomes damaged and pulmonary endothelial capillary cells become infected, increasing the inflammatory lung damage (Varga et al., 2020; Channappanar and Perlman, 2017). The evolving inflammation cascade of cytokines, chemokines and necrotic cell debris, causes diffuse thickening of alveolar walls and interstitial mononuclear inflammatory infiltrates (Fig. 3F). As oedema develops,

* Corresponding author at: School of Medicine, Dentistry and Biomedical Science, Queens University Belfast, Belfast, United Kingdom.
*E-mail address:* irene.rea@aol.com (I.M. Rea).

https://doi.org/10.1016/j.arr.2021.101494
Received 11 April 2021; Received in revised form 1 September 2021; Accepted 18 October 2021
Available online 22 October 2021

ground glass opacities present on X-ray computerised tomographic (CT) imaging, visually represent the dysfunctional alveolar-capillary oxygen transmission and impaired oxygen capacity that presents clinically, with silent hypo-oxygenation and critical illness in COVID-19 patients.

The COVID-19 viral sepsis with life-threatening organ dysfunction is caused by a severely dysregulated host response to infection stimulating a systemic cytokine storm which becomes uncontrolled, and further contributes to tissue damage, multi-organ failure and death.

## 2. Is the immune system in older people fit for purpose in its response to COVID-19?

### 2.1. Reduced early T cell progenitors emerge from bone marrow

As age increases, the bone marrow (BM) has a reduced ability to produce hematopoietic stem cells for self-renewal (Kovtonyuk et al., 2016; Latchney and Calvi, 2017) (Fig. 2). There is a skewing towards myeloid cell production with fewer lymphocytes entering the circulation. In BM ablation treatment of haematological cancers, whilst progenitor B cell numbers recover, clinical teams have demonstrated markedly reduced capacity of bone marrow and lymphatic system in older recipients to re-populate their marrow with new naïve T cells (Mackall et al., 1995). We have observed a decreasing ability to restore T cell populations in our patient-recipients of autologous peripheral blood stem cell transplants (ASCT) as treatment for haematological malignancies, with older patients (>55 years) continuing to have CD4+ T cell lymphopenias 4–5 years after transplant (Alexander, 2021).

The reduced capacity of the BM to renew T cell progenitors, puts older people at immune disadvantage when faced with a significant viral infection such as SARS-CoV-2.

### 2.2. Involution of the thymus produces fewer naïve T cells

Human naive T cells are largely produced early in life when the infant thymus is large and functional, whereas with age-related involution, the thymus shows decreased cellularity, with increased adipose tissue (Palmer, 2013; Sun et al., 2012). Age-related changes are associated with reduced numbers of CD4+ naïve cells (Wang et al., 2021a; Strindhall et al., 2013; Rea et al., 1996a) (Fig. 2). Naïve T cells, newly emergent T cells from the thymus, with predefined antigen specificity following rearrangement of T cell receptor genes, circulate between blood and lymphoid tissue. Each CD4+ T cell has a different specificity with potential to respond to novel antigens, such as the SARS-CoV-2 virus. Age-related lower production and response to decreased IFN characterise the impaired immune response to new infections in older people (Molony et al., 2017; Haynes and Eaton, 2005; Rea et al., 1996b).

Without adequate numbers of naïve CD4+ T cells to respond to the unfamiliar SARS-CoV-2 virus, the immune response in older people, is less able to respond quickly and effectively and immunity is impaired.

### 2.3. Tissue resident macrophages ($T_{RM}$s), T-cell and B cell response in the lung in COVID-19

Tissue Resident Macrophages ($T_{RM}$s), if present in the lung tissue, can 'kick start' a prompt, effective IFN-guided immune response in people previously exposed to COVID-19 or related coronavirus (Grau-Expósito et al., 2021). However, $T_{RM}$s may less likely to be present in elderly people, self-isolating during the COVID-19 pandemic, to help generate an efficient immune response. Furthermore, the decreased numbers of CD4+ naïve cells, less effective T helper and B and cell interactions, reduced IFN signalling, contribute to the well-described impaired response after vaccination (Stebegg et al., 2020; Agrawal, 2013;

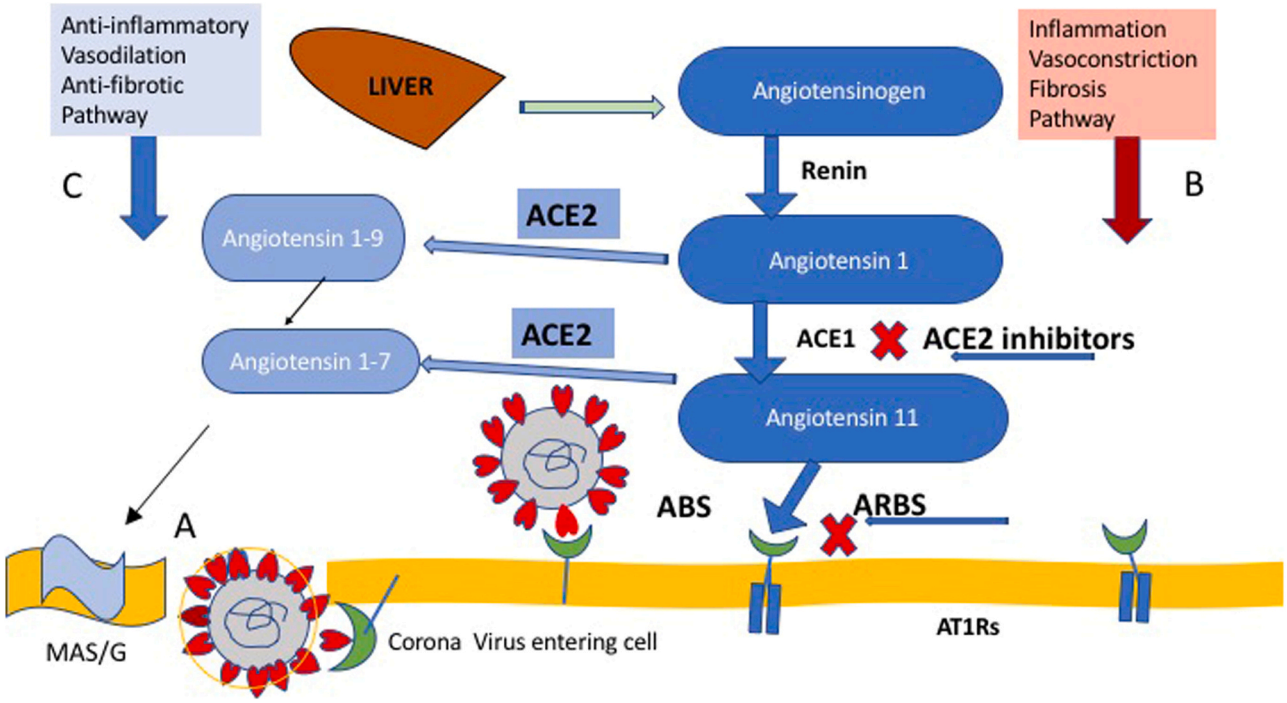


**Fig. 1.** ACE pathway and role of ACE2 in the pathogenesis of COVID-19 and the inflammatory Response. The lung loses ACE2-mediated protection following endocytosis of the enzyme with SARS-CoV-2 virus, as it enters cells in the lung and other organs [A]. The angiotensin-converting enzyme ACE enzyme cleaves Angiotensin I (Ang 1), generating Angiotensin 11 (Ang 11), which acts though the angiotensin 11 receptor (AT1R), to increase vasoconstriction, increase blood pressure and promote inflammation [B]. In the counter-regulatory pathway, ACE2, hydrolyses Ang 11 into heptapeptide angiotensin Ang (1–7), that acts through the ACE2/Ang1–7/MAS/G receptor pathway to downgrade the constrictive proliferative effect of Ang 11, and induce vasodilation, and reduce inflammation and fibrosis [C]. The ACE2 gene influences the renin angiotensin system (RAS) function by modulating blood pressure, sodium and fluid balance and may thereby be important in COVID-19 patients with cardiovascular and renal disease. ACE2, Angiotensin converting enzyme 2; AT1R, Angiotensin 1 Receptor; ACEi, Angiotensin converting enzyme inhibitors; ARBs, Angiotensin converting enzyme receptor blockers; MAS/G receptor, Mas-related g protein-coupled receptor.

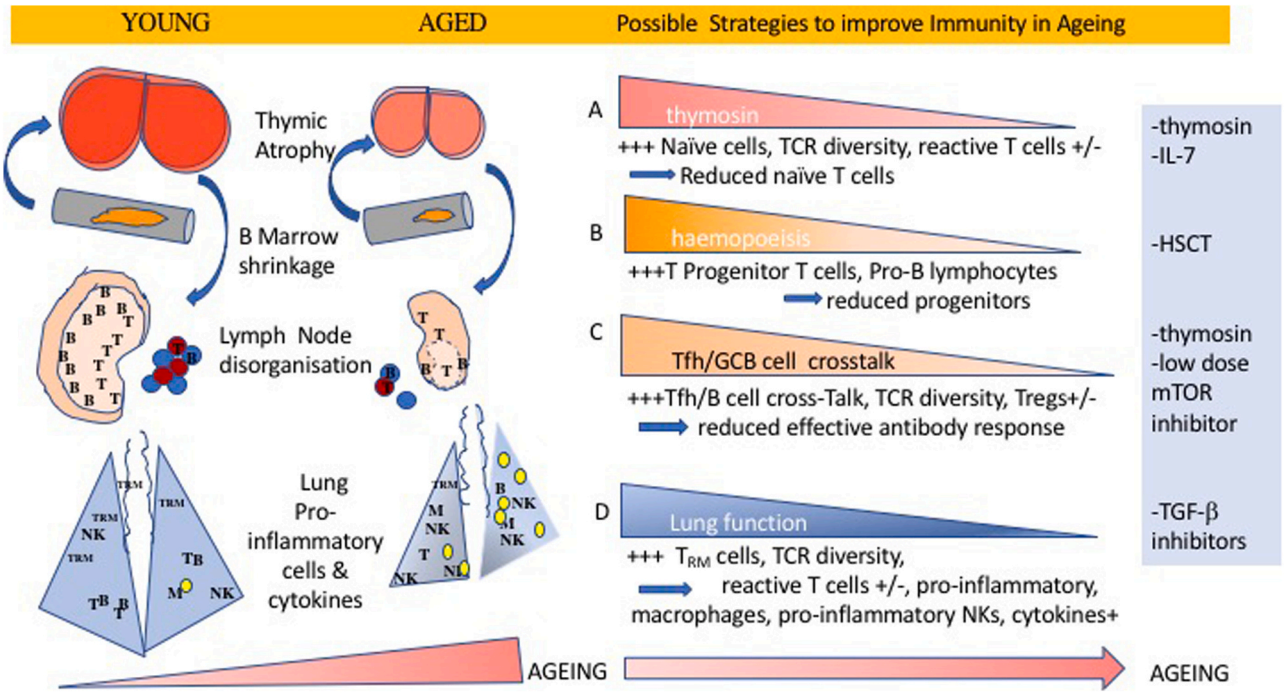


**Fig. 2.** Graphic of immune changes in ageing. A. The thymus atrophies and gets much smaller with age. B. The bone marrow (BM) area producing haematopoietic stem cells reduces with age. A&B Progenitor T cells and pro-B lymphocytes produced in the BM migrate to thymus and complete antigen-independent maturation into functional T cells, such as naïve T cells, and B cells. Thymic involution with ageing, reduces the output of naïve T cells. C. Reduced naïve CD4+ T cells, reduced T cell receptor (TCR) diversity, and disorganisation of lymph nodes with increasing age, results in less effective T follicular helper (TFh)/B cell interaction in germinal centres in peripheral lymph nodes. D. Less effective Tfh/B cell adaptive and specific antibody production in response to SARS-COV-2 virus, results in delayed containment and resolution of SARS-CoV-2 infection in the lungs in older people, often damaged by disease and with reduced respiratory function; therefore, there is increased potential for uncontrolled infection, increased tissue damage, development of cytokine storm and progression to multi-organ failure.

Agrawal et al., 2017) (Fig. 3).

The decreased numbers of CD4+ naïve cells, less effective T helper and B cell interactions, reduced IFN signalling due to impaired dendritic cell (DC) activation, and likely absence of $T_{RM}$ cells, together contribute to a sluggish immune response in the lung in older people during COVID-19 illness, that is critical for effective recovery.

### 2.4. *Is the innate immune system out of control in COVID-19?*

Natural killer cells (NKs) and macrophages are the main innate leucocyte subsets that aim to stop the spread of the SARS-CoV-2 virus when inhaled into the lungs, from air droplets and aerosols of a COVID-19 carrier. $T_{RM}$s if present in lung tissue, sound the alarm, and macrophage and NKs recognise, destroy and engulf the SARS-CoV-2 virus by releasing damaging cytotoxic molecules, that stimulate the inflammasome and trigger pro-inflammatory cytokines. NKs and macrophages to track to the infected lung tissue, guided by chemokines, CCL3, CXCL3 and granulocyte macrophage-cell secreting factor (GM-CSF), secreted by type 11 alveolar cells (Fig. 3C–E).

The active bi-directional crosstalk and interaction between NK and DCs involving the secretion of cytokines (Jost and Altfeld, 2013; Ferlazzo and Moretta, 2014), is regulated by monocytes/neutrophils in a "menage a trois", so that a controlled and modulated production of IFN-γ by NK cells occurs for effective viral control (Wałajtys-Rode and Dzik, 2017). In serious COVID-19 illness, authors have reported fewer NK cells, some displaying an exhausted phenotype (Giamarellos-Bourboulis et al., 2020a; Kuri-Cervantes et al., 2020; Maucourant. et al., 2020), with NK numbers and cytotoxity improving with recovery (Rodriguez et al., 2020). Lower NK numbers may occur because NKs traffic to, and remain in the lungs, contributing further to the local milieu of inflammation injury (Liao et al., 2020; Zhou et al., 2020c). The lower numbers of dendritic cells (DCs) in older age, reduces capacity to produce IFN-γ that is essential to control Phase 1 of the inflammatory response to COVID-19 and stop the damaging SARS-CoV-2 virus replication early in the illness.

In older, healthy age-groups, there is a well-described age-related increase in CD3− CD56+ NK cells and NK-related subsets (Hazeldine and Lord, 2013; Yan et al., 2010; Le Garff-Tavernier et al., 2010; McNerlan et al., 1998). NK cells can produce both pro-inflammatory and anti-inflammatory cytokines, demonstrating that counterbalancing cytokine feedback loops are important during controlled innate immune responsiveness, homoeostasis and repair (Vivier and Ugolini, 2009; Rea et al., 2013) (Fig. 4). The age-related increase in NK and NKT-related cells likely contributes to the pro-inflammatory hyperinflammation and cellular damage seen in older individuals, in early COVID-19 illness.

An important aspect of NK function is the NK, Killer Immunoglobulin-like Receptors (KIRs) that control NK functions and can be classified into A and B haplotypes; A has an inhibitory role, compared to the activating role of B, which produces pro-inflammatory cytokines (Cisneros et al., 2020; Pegram et al., 2011) (Fig. 5). A balance between activating KIR A haplogroup and inhibiting KIR B group KIR genes ensures effective and timely immune surveillance by NK cells; when unregulated, their unbalanced activity contributes to uncontrolled inflammation (Lam and Lanier, 2017; Schmidt et al., 2016). In examining NK cell diversity, Horowitz et al. (2013), suggested that whereas genetics primarily determined inhibitory KIR B receptor expression, pro-inflammatory activating KIR A receptors were likely controlled by environmental factors. Could KIR haplotype A play a role in the social determinants of health such as smoking, obesity or poverty and predict a more activating damaging pro-inflammatory NK response to SARS-COV-2 infection? Furthermore, A and B KIR haplotypes demonstrate different frequencies across different populations, ethnicities and geographical locations, that could contribute to differences in how COVID-19 presents clinically, and with different patient outcomes (Yao et al., 2019; Norman et al., 2001; Guinan et al., 2010).

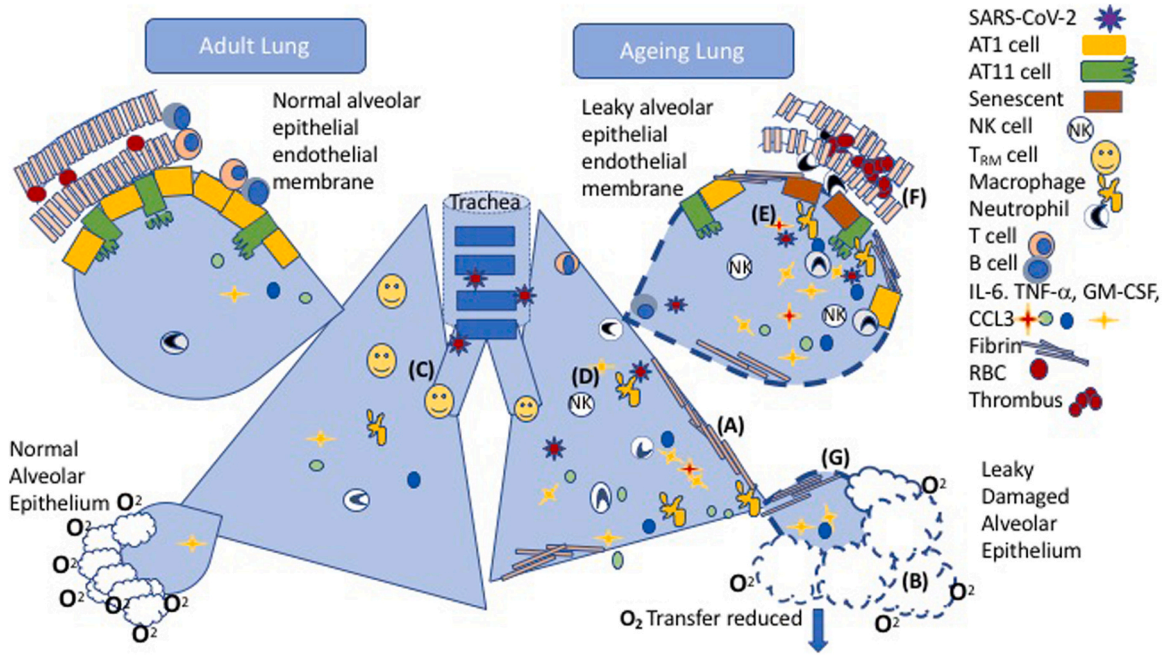


**Fig. 3.** SARS-CoV-2 virus-induced Inflammatory response in the Lung, is accentuated in Ageing. (A) In elderly individuals reduced lung elasticity and respiratory volume, increased fibrosis and inflammation from smoking, environmental toxin exposure, multiple disease pathologies and poorer respiratory function, compromise oxygen and blood gas exchange. (B) Alveolar epithelial cells AT1s, responsible for the integrity of the epithelial-endothelial barrier, are less elastic, the alveolar sacs become baggy, and gas exchange is reduced. (C) $T_{RM}$s holding memory from a SARS-CoV-2 or related-coronavirus infection, can 'kick start' immune response to new SARS-CoV-2 infections, but are unlikely to be present in older people who have spent months isolating during COVID-19 pandemic times. (D) Following SARS-COV-2 infection, NKs and macrophages go to the infected lung tissue, guided by chemokines, CCL3, CXCL3 and GM-CSF, secreted by type 11 alveolar cells (ATII). (E) Macrophages and NK cells recognise, engulf and destroy SARS-CoV-2 virus, and continue to release cytotoxic and cytokine molecules, in an ongoing, continuous cycle of inflammation. (F) In fulminant COVID-19 infection, more common in elderly patients, the epithelial-endothelial barrier becomes damaged and leaky, pulmonary epithelial cells become infected, interstitial oedema develops, and platelet-fibrin microthrombi form in capillaries, with risk of widespread venous and arterial thrombosis. (G) The evolving inflammation cascade causes diffuse thickening and fibrosis of alveolar walls with reduced oxygen diffusion and critical hypo-oxygenation, and multi-organ failure in ill COVID-19 patients. $T_{RM}$s, Tissue Resident Macrophages, NKs, natural killer cells, GM-CSF, granulocyte macrophage-cell secreting factor, AT1, type 1 alveolar cells, AT11, type 11 alveolar cells.

SARS-CoV-2, NK-driven viral destruction has the potential to cause severe self-damage, if phase 1 of the inflammatory response is ineffectively shut down, because of reduced IFN production in older age (Masselli et al., 2020; Jose and Manuel, 2020).

### 2.5. *Adaptive immunity in ageing and in COVID-19 illness*

Adaptive immunity relies on effective transfer of information between T and B cells, so that high quality specific antibodies which recognise surface antigens on the SARS-CoV-2 virus, can neutralise virus-infected cells. Differing subsets of CD4+ T cells, such as CD4 Tregs have a role in helping to damp down and control the NK and CD8+ T effector cells' potentially damaging and exuberant cytotoxic response to SARS-COV-2 virus (Okeke and Uzonna, 2019).

With increasing age, there is a gradual deterioration in the immune system that reduces an effective response to infections and vaccination and has been termed immunosenscence (Franceschi et al., 2000; Cunha et al., 2020; Pietrobon et al., 2020). The age-related changes in the T cell landscape show reduced T cell receptor (TCR) repertoire diversity, increased memory and self-reactive T cells and an accumulation of polyclonal regulatory T (Treg) cells that are associated with an increased background of inflammation called inflamm-geing (Franceschi et al., 2000, 2007; Franceschi and Campisi, 2014).

In age-related investigations in peripheral blood mononuclear cells, derived from healthy donors in a wide range of age-groups, the normal range of changes in the immune system with ageing have been characterised (Hirokawa et al., 2013; Wikby et al., 2008, 2002; Rea et al., 1999; McNerlan et al., 1999). Fluorescence-activated cell sorting and transcriptome sequencing show that lymphopenia occurs quite frequently, with CD4+ naïve T cells decreasing with age (Moro-Garcia et al., 2013; Derhovanessian et al., 2013; Rea et al., 1996), whereas antigen-experienced memory T cells increase with loss of co-stimulation factors CD27+ and CD28+ (Vescovini et al., 2014) (Fig. 6). The loss of CD28+ T cells is more pronounced in cytomegalovirus (CMV) seropositive donors, has been used as a marker of immunosenescence in older populations and together with an inverted CD4/CD8 ratio was identified as a biomarker of frailty and mortality in the OCTO immune study (Pawelec, 2012; Adriaensen et al., 2015; Wikby et al., 1998), though has not replicated in other older cohorts (Li et al., 2019; Rea et al., 2010).

Lymphopenia is a common feature in COVID-19 illness (Huang et al., 2020b), with markedly lower CD4+ and CD8+ T cell counts in patients in Intensive Care Units (ICU) and an age-dependent reduction of T cells in patients $\geq$ 60 years old (Diao et al., 2020). Reduced numbers of CD4+ T cells, CD8+ T cells, B cells and NK cells, irrespective of age have been consistently reported (Lucas et al., 2020; Braun et al., 2020; Grifoni et al., 2020), and would seriously compromise an integrated, effective immune response in the older person presenting with COVID-19 infection (Li et al., 2019; Lin et al., 2016; Rea et al., 1996). In comparing immune differences in COVID-19 patients and healthy individuals, using a systems biology approach, Arunachalam et al. (2020) demonstrated a reduced frequency of plasmacytoid dendritic cells (pDCs), reduced relative frequency of HLA-DR activation and pro-inflammatory cytokines by myeloid cells, together with impaired mTOR-signalling and IFN-α production. De Biasi et al. (2020), demonstrated a severely impaired immune system in COVID-19 patients, with reduced absolute numbers of CD4+ and CD8+ T lymphocytes showing activation or exhaustion/senescence markers, and elevation of pro- and anti-inflammatory cytokines-TNF, IFN-γ, IL-2 and IL-17. Sadeghi et al.

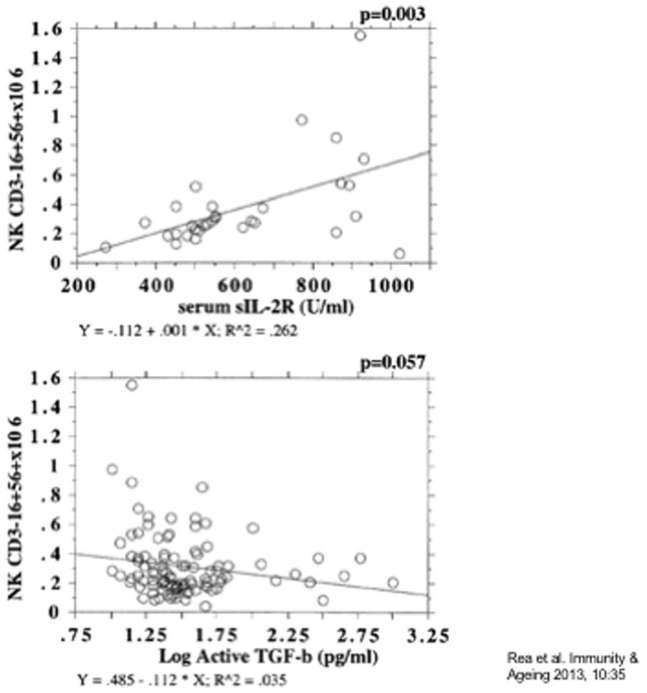


**Fig. 4.** Regression plots showing association for NK counts and pro-inflammatory and anti-inflammatory cytokines, sIL-2R and TGF-β, in Octo/nonagenarians from BELFAST study. (A) Regression plot showing association between NK count and serum IL-2R (A), with increases in NK cell number associated with increases in serum IL-2R, linked with increased inflammation. $r^2 = 0.262$, $p = 0.003$. (B) Regression plots showing association between NK count and log Active TGF-β, showing a negative association between NK count and the anti-inflammatory cytokine TGF-β, linked with resolving inflammation. $r^2 = 0.035$, $p = 0.057$. NKs, natural killer cells, BELFAST, Belfast Elderly Longitudinal Free-living Ageing Study.

(2021), similarly demonstrated elevated IL-17 and TH 17 cell numbers in ICU-SARS-CoV-2-patients.

Community-living older people also show quantitative and qualitative changes in the B lymphocyte pool (Blanco et al., 2018; Dunn-Walters, 2010; Frasca et al., 2011). B cells secrete TNF-α that further inhibits survival of B-cell precursors (Ratliff et al., 2013). The reduced production of B cells in BM, decreased numbers of pro-B and pre-B lymphocytes in blood (Rossi et al., 2003) and reduced numbers of B lymphocyte lead to reduced B cell help to T lymphocytes and less effective antibody response, essential to stamp out the SARS-CoV-2 virus promptly (McElhaney et al., 2020).

Cytokine IL-7 can improve the CD4+ naïve T cell response and has demonstrated effectiveness in sepsis and COVID-19 illness (Laterre et al., 2020; Monneret et al., 2020; Francois et al., 2018; Mackall et al., 2011). Thymosin alpha-1, (Tα 1), a synthetic thymic peptide, used in viral infections as an immune response modifier, reduced mortality of patients with severe COVID-19 illness (Liu et al., 2020; Wang et al., 2021). A clinical trial to treat COVID-19 in elderly patients with Tα1 was approved to commence early 2021. (https://clinicaltrials.gov/ct2/show/NCT04428008). The skewing of cytokine profiles towards the TH17 phenotype in COVID-19 might suggest that IL-17 blockers could provide a potential therapeutic strategy.

The lower numbers of CD4 lymphocytes and B cells in the immune profile in older people, puts them at considerable immune disadvantage and risk of life-threatening illness, when they develop SARS-CoV-2 illness (Cunha et al., 2020).

### 2.6. Dysregulation of cytokine network in ageing

The pro-inflammatory and anti-inflammatory cytokines are key molecular messengers that act immediately to activate an immune response in response to threats from the SARS-CoV-2 virus (Conti et al., 2020a; Mantovani et al., 2019; Rea et al., 2018). In older people, who are not overtly ill, the major pro-inflammatory cytokines such as IL-6, TNF-α, IL-1α and IL-12p40 are increased, with many researchers reporting similar age-related increases in pro-inflammatory cytokines (Franceschi et al., 2007, 2000; Forsey et al., 2003; Rea et al., 2000). Conversely, IL-10 and TGF-β, corresponding anti-inflammatory cytokines, show less consistent age-related change (Salminen et al., 2012; Minciullo et al., 2016; Kubiczkova et al., 2012). The gene and allele profile associated with pro-inflammatory and anti-inflammatory cytokines, is also important in each person's immune response, with alleles of the pro-inflammatory cytokine IL-6, for instance, showing different frequencies and expression depending on geographical location in Europe and globally, whereas the anti-inflammatory cytokine IL-10 and its alleles show differences between male and female nonagenarian subjects and mortality risk (Di Bona et al., 2009; Ross et al., 2003; Lio et al., 2003).

The chronic low-grade, sterile inflammation, characterised by increased levels of pro-inflammatory cytokines and mediators such as IL-6, IL-1β, TNF-α and C-reactive protein (CRP) in the circulation has been called 'inflamm-ageing', a term first coined in 2000 by Claudio Franceschi (Franceschi et al., 2000).

## 3. Why is morbidity and mortality so much higher in older people with COVID-19?

### 3.1. 'Inflamm-ageing' as we age fuels the cytokine storm

Immunosenesence and inflamm-ageing are high risk factors for severe COVID-19 illness in older people. The increased low-grade sterile inflammation, or inflamm-ageing, contributes to many age-related diseases such as atherosclerosis, rheumatoid arthritis, diabetes, neurodegeneration and ageing itself (Liberale et al., 2020; Ferruci and Fabbri, 2018; Rea et al., 2018; Franceschi et al., 2014). However, when SARS-CoV-2 illness co-exists with any or several of these age-related diseases, COVID-19 illness is much more severe and may become life-threatening (Akbar and Gilroy, 2020; Yang et al., 2020b; Bonafè et al., 2020).

Several molecular pathways and pattern-recognition receptors (PRRs) contribute to inflamm-ageing and ageing (Fig. 7). Toll-like receptors (TLRs) and Danger-Associated Molecular Patterns (DAMPs) use various intracellular signalling pathways, resulting in NF-κB activation and overproduction of cytokines, chemokines and IFNs. SARS-CoV-2 is sensed by the RNA-sensing endosomal PRRs, TLR 3, 7 and 8, the cytoplasmic-residing RIG-1-like receptors, and the mitochondrial mitochondrial antiviral-signalling protein (MAVS) signalome, but it interferes with normal production of anti-viral interferons (Wu et al., 2021; Jiang et al., 2020; Lei et al., 2020). Senescent cells and the associated secretome of senescence-associated-secretory-phenotype (SASP) increase with age and contribute to the inflammatory NF-κB pathway (De Francesco et al., 2020; Molony et al., 2017). Autophagy too is slowed up with ageing, causing damaged material to accumulate and trigger several signalling inflamm-ageing pathways (Stead et al., 2019; He et al., 2013).

The NLPR3 inflammasome-dependent response (Zhao and Zhao, 2020; Lee et al., 2020), activated by SARS-CoV-2 endosomal replication, oxidative stress, DNA damage, necrotic cell damage and multiple DAMPs, causes stimulation of the NF-kB- and IL-1β, IL-18, IL-33-mediated inflammatory cascade and adds to the cytokine-mediated hyperinflammation and cytokine storm, by further paracrine activation (Tay et al., 2020; Conti et al., 2020a; Salminen et al., 2012) (Fig. 8).

Although the term 'cytokine storm' has become widely synonymous with the self-perpetuating inflammatory cascade of severe COVID-19 illness, the mechanisms of COVID-19-induced lung injury and pathophysiology are still being clarified (Sinha et al., 2020), and no unifying

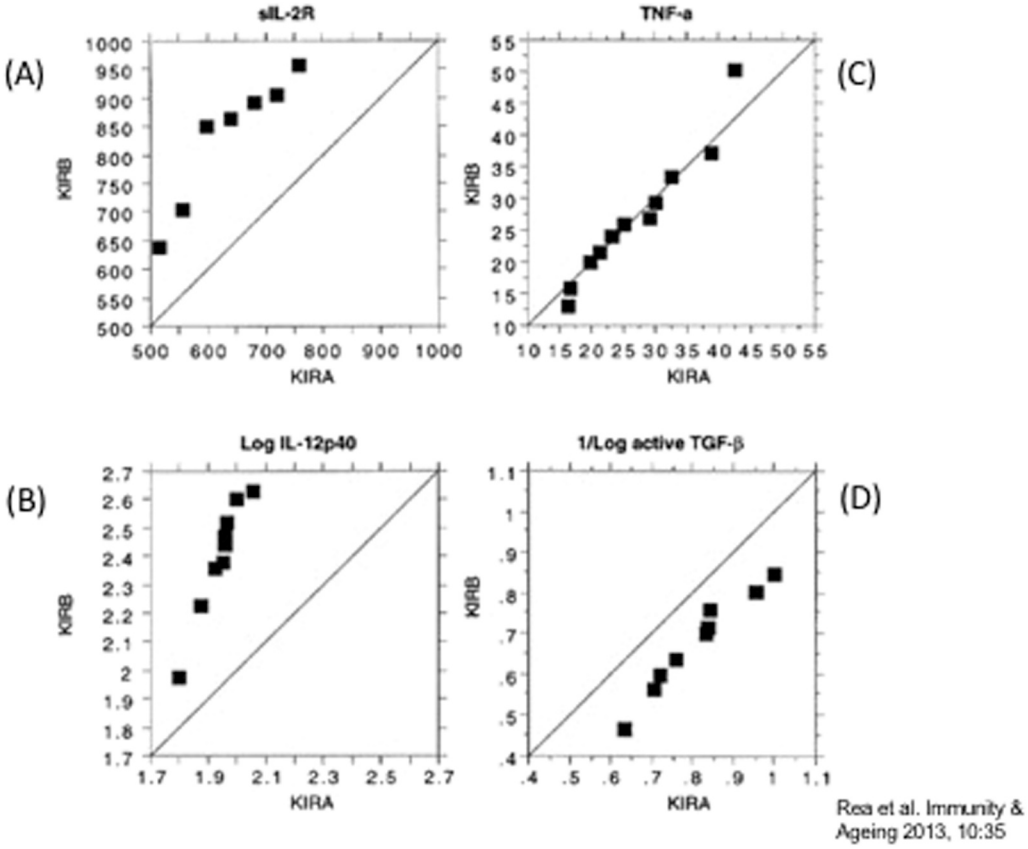


**Fig. 5.** Percentile plots for pro-inflammatory and anti-inflammatory cytokines, grouped by NK-related, Killer Immunoglobulin Receptor Haplotypes A and B (KIR A and KIR B), in Octo/Nonagenarians from BELFAST study. Killer cell Immunoglobulin-like Receptors (KIRs) are genetic markers on NK cells in individuals, that can be grouped into A and B haplotypes; KIR A haplotype has an inhibitory role, compared to the activating role of haplotype B, which produces pro-inflammatory cytokines. (A) shows percentile plot for NK cells grouped by KIR A haplotype on X-axis v KIR B haplotype on Y-axis for percentile values of serum sIL2-R in community-living octo/nonagenarian subjects; findings showing KIR B percentile values to the left of the 45° line, are consistent with KIR B haplotype-grouped NK cells producing sIL-2R, linked with pro-inflammation. (B) shows percentile plot for NK cells grouped by KIR A haplotype on X-axis v KIR B haplotype on Y-axis for percentile values of serum log IL-12p40 in community-living octo/nonagenarian subjects; findings showing KIR B values to the left of the 45° line, are consistent with KIR B haplotype-grouped NK cells producing IL-12p40, a pro-inflammatory cytokine. (C) shows percentile plot for NK cells grouped by KIR A haplotype on X-axis v KIR B haplotype on Y-axis for percentile values of serum TNF-α in community-living octo/nonagenarian subjects; findings showing KIR B values and KIR A values at or on the 45° line, are consistent with TNF-α being a neutral cytokine with respect to KIR A and KIR B haplotype-grouped NK cells. (D) shows percentile plot for NK cells grouped by KIR A haplotype on X-axis v KIR B haplotype on Y-axis for percentile values of log TGF-β in community-living octo/nonagenarian subjects; findings showing KIR B values to the left of the 45° line, are consistent with KIR B haplotype-grouped NK cells producing log TGF-β, with anti-inflammatory effects. NK cells produce both pro-inflammatory and anti-inflammatory cytokines, and balance is important in controlled innate immune responsiveness, homeostasis and repair. NKs, natural killer cells, BELFAST, Belfast Elderly Longitudinal Free-Living Ageing Study.

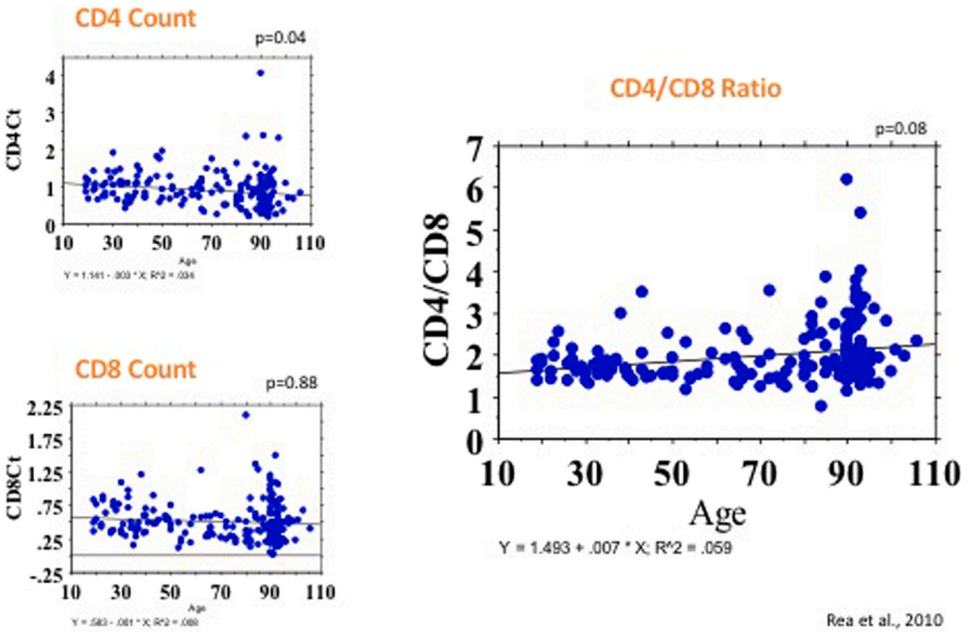


**Fig. 6.** Age-related changes in CD4+, CD8+ T cells counts and CD4/CD8 Ratio in Belfast Elderly Longitudinal Free-Living Ageing STudy (BELFAST). (A) Regression plot showing association for CD4+ T cell count with age, through 20–100 years. $R^2 = 0.034$; $p = 0.04$. (B) Regression plot showing CD8 +T cell count with age, through 20–100 years. $R^2 = 0.019$, $p = 0.88$. (C) CD4+/CD8+ Ratio and Age from 20 to 100 years. $R^2 = 0.059$, $p = 0.08$. All age participants recruited as part of Belfast Elderly Longitudinal Free-living Ageing STudy (BELFAST), were apparently well, community-living, mobilising independently, with no cognition impairment. $P = < 0.0001$ for difference between cell counts and age-related change for CD4+ and CD8+ subsets and age.

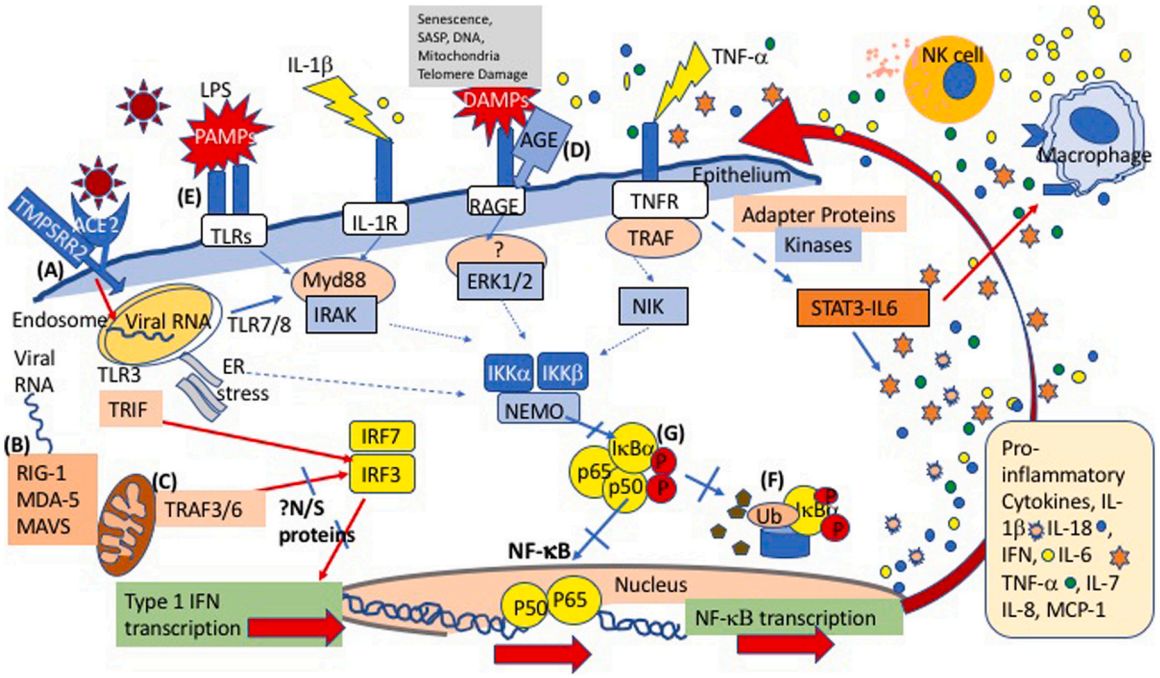


**Fig. 7.** Schematic diagram of molecular cellular pathways potentially involved in the NF-κB and IFN-signalling pathways, in SARS-CoV-2 illness. (A) SARS-COV-2 virus enters the alveolar cell via ACE2 receptor with help of TMPSRR2 protease, moves to the endosome where viral single-stranded DNA signals through TLR 7 and 8, and double-stranded DNA through TLR 3, to activate the NF-kB pathway via NEMO. (B) SARS-CoV-2, DNA, triggers the RIG-1-like receptors that act through interferon response elements, and interferes with normal production of anti-viral IFNs. (C) Viral SARS-COV-2 and ROS acting through mitochondrial MVAS pathway, reduces mitochondrial function and production of anti-viral interferons, possibly by use of its structural proteins. (D) Senescent cells, the associated secretome (SASP) and RAGE-associated-glycated damage join an inflammatory pathway involving the NF-kB, IL-1α, TGF-β, IL-6, that contribute to the pro-inflammatory milieu. (E) Secondary bacterial infections, such as pneumococcus, PAMPs and DAMPs use TLR4 and various intracellular signalling pathways, that result in NF-κB activation and further augmentation and production of cytokines, chemokines and interferons. (F) Autophagy is slowed up, causing damaged material to accumulate and trigger inflamm-ageing pathways. (G) All different signalling pathways join a common downstream signalling pathway that results in phosphorylation of the cytosolic inhibitor IκBα, which triggers its proteasomal degradation, resulting in translocation of NF-κB into the nucleus, with the production of the SARS-COV-2-related pro-inflammatory cytokine cascade. (H) Research trials are investigating repurposed drugs to block the NEMO/NF-κB pathway and proteosome inhibitors to block the autophagy process. TLR4, Toll-Like Receptor, LPS, Lipopolysaccharide; NEMO, NF-kappa B Essential Modulator; RIG-1-like, retinoic acid-inducible gene-I-like receptors; PAMPs, Pathogen Associated Molecular Patterns; DAMPs, Danger Associated Molecular Patterns; NLRs, nucleotide-binding and oligomerization domain receptors; NLRP3, NLR family pyrin domain containing 3; SASP, Senescence-Associated-Secretory-Phenotype; RAGE, Receptor for Advanced Glycation Endproducts; ROS, reactive oxygen species; MAVS, mitochondrial anti-viral signalling protein; TMPRSS2, transmembrane serine protease; BTK, Bruton's tyrosine kinase; NSAID, nonsteroidal anti-inflammatory drugs.

definition of cytokine storm exists. Fajgenbaum and June (2020), have proposed the following criteria: 1) elevated cytokine levels, 2) acute systemic inflammatory symptoms, and 3) secondary organ dysfunction, beyond that which could be attributed to a normal response to a pathogen, if a pathogen is present.

In COVID-19 illness, cytokine profiles stratify patients and likely outcomes (Lucas et al., 2020). Higher pro-inflammatory cytokines IL-1α, IL-1β, IFN-α, IL-17A and IL-12p70 provided a 'core' signature of severe COVID-19 illness, with lower levels of pro-inflammatory cytokines and early tissue repair proteins found in moderate illness. COVID-19 severe illness was further characterised by lymphopenia and the over-expression of molecules of inflammation (Matthew et al., 2020; Song et al., 2020; Tan et al., 2020a). Seriously ill COVID-19 patients showed impaired expression of pro-inflammatory cytokines and diminished mTOR signalling in myeloid cells and reduced IFN-α production by pDCs, both important first defences against viral replication and invasion (Arunachalam et al., 2020). The authors suggested that pDCs, the major producers of type 1 IFNs were impaired in COVID-19-infected patients, replicating findings of others (Sa Ribero et al., 2020; Schulte-Schrepping et al., 2020; Hadjadj et al., 2020; Chen et al., 2020a).

Administration of type 1 IFN has been proposed as a strategy for COVID-19 treatment (Wang et al., 2020a; Sallard et al., 2020; Zhou et al., 2020b; Abdolvahab et al., 2021). Two trials have reported. Monk et al. (2021), in a meta-analysis, demonstrated reduced length of hospitalisation with inhaled or interferon-beta-1α (Synairgen), and Fu et al. (2020) demonstrated good clinical improvement using combined inhaled IFN-γ with TTK, a small peptide that enhances mucosal healing, in COVID-19 patients. Sosa et al. (2021), in a systematic review of evidence, demonstrated reduced length of hospital stay with IFN-β use, in COVID-19 patients.

The production of Type I IFNs, a key defence against COVID-19 is reduced in COVID-19 patients. Clinical improvement and length of hospital stay was reduced in clinical trials, with careful use of type 1 IFN, early in illness.

### 3.2. *The inflammation pathway fails to resolve in COVID-19*

Inflammation is induced when NK cells and macrophages detect infection from protein-associated molecular patterns (PAMPs) associated with the SARS-CoV-2 virus. Danger-associated molecular patterns (DAMPs) are also triggered by host-derived stress signals such as ATP, nuclear proteins and cytokines including the extended IL-1 family of cytokines that amplify the very exuberant damage response stimulated by the host's NK cells response to the SARS-CoV-2 virus (Li et al., 2020b; Tay et al., 2020; Cicco et al., 2020). Pro-inflammatory cytokines, arachidonic acid-derived prostaglandins and leukotrienes increase vascular permeability, allowing macrophages and neutrophils to migrate across venules to sites of SARS-CoV-2 invasion in the lung and continue the cycle of phagocytosis and killing, fibrin deposition and possible capillary thromobosis.

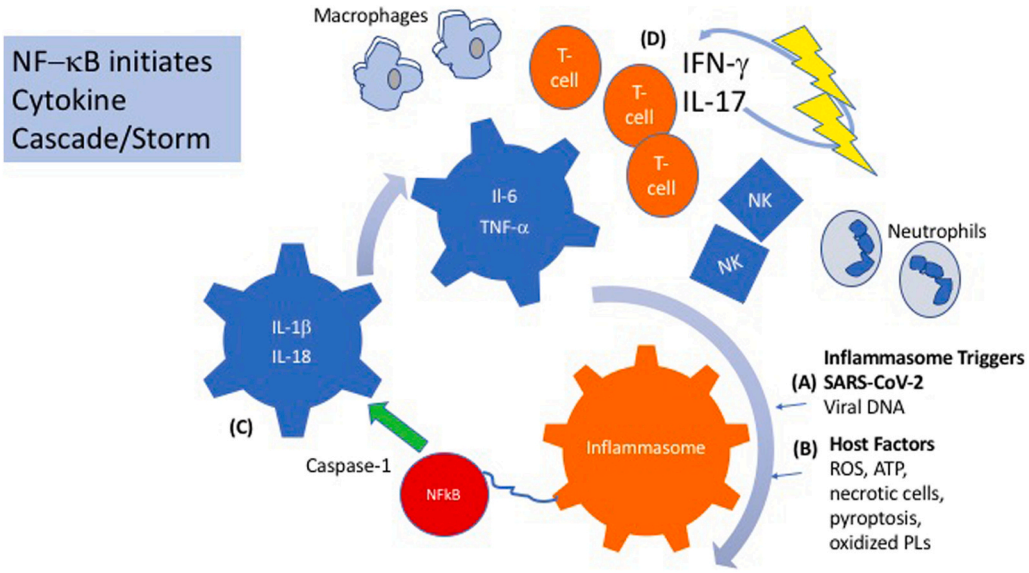


**Fig. 8.** Inflammasome NLRP3 initiates the cytokine cascade/storm using NF-kB pathway. (A) Direct stimulation of inflammasome NLRP3 is triggered by viral protein from SARS-CoV-2 through TLR 3 signalling. (B) Non-direct stimulation occurs through host-intrinsic mechanisms such as DAMPS - oxidation of phospolipids from alveolar epithelial/endothelial membranes, ROS, ATP, necrotic cells and pyroptosis. (C) NLRP3 inflammasome activation induces the production of mature IL-1β and IL-18 from inactive pro-IL-1β and pro-IL-18 precursors by caspase-1, which initiates a cytokine cascade. (D) The pro-inflammatory cytokines including L-6, IL-2, TNF-α, in turn stimulate production of IL-17 and IFN-γ which can activate the JAK-STAT or NF-κB signalling via binding to their receptors expressed on immune cells, to induce more production of pro-inflammatory genes, forming a positive feedback to trigger hyperinflammation and the threshold of cytokine storm. TLR3, Toll-Like Receptor 3; NLRP3, NLR family pyrin domain containing 3, DAMPs, Danger Associated Molecular Patterns; ROS, Reactive Oxygen Species; ATP, Adenosine Triphosphate; PLs, phospholipids; JAK-STAT, Janus kinase-signal transducer and activator of transcription.

In older age, the molecular and cellular processes that normally damp down inflammation, such as the anti-inflammatory cytokine families of IL-10 and TGF-β, soluble receptor antagonists, microRNAs, the resolvin family of bioactive molecules and pro-resolving monocyte-derived macrophages become less ineffective in stopping the inflammatory cascade. Resolution and repair seem to be seriously inadequate in some COVID-19 patients (Fig. 9).

The continuous breakdown of cellular products and DAMPs-related pro-inflammatory molecules produces a constant cycle of entry and re-entry into self-perpetuating and damaging pro-inflammatory cytokine pathways (Fig. 9).

### *3.3. SARS-CoV-2 virus-induced inflammatory response in the lung is accentuated in ageing*

COVID-19 has major effects on the lungs and airways and the lung is at the centre of the SARS-CoV-2 cytokine storm. Advanced age is a leading risk factor for developing acute respiratory distress syndrome (ARDS), a life-threatening event, requiring ICU admission (Hu et al., 2021; Du et al., 2020). In elderly individuals reduced lung volume and elasticity, increased fibrosis and inflammation from smoking, environmental toxin exposure/s, and multiple disease pathologies, result in markedly reduced respiratory function that compromises oxygen blood gas exchange, and make it more difficult for older patients to overcome COVID-19 illness and respond to ICU ventilation (Thomas et al., 2019;

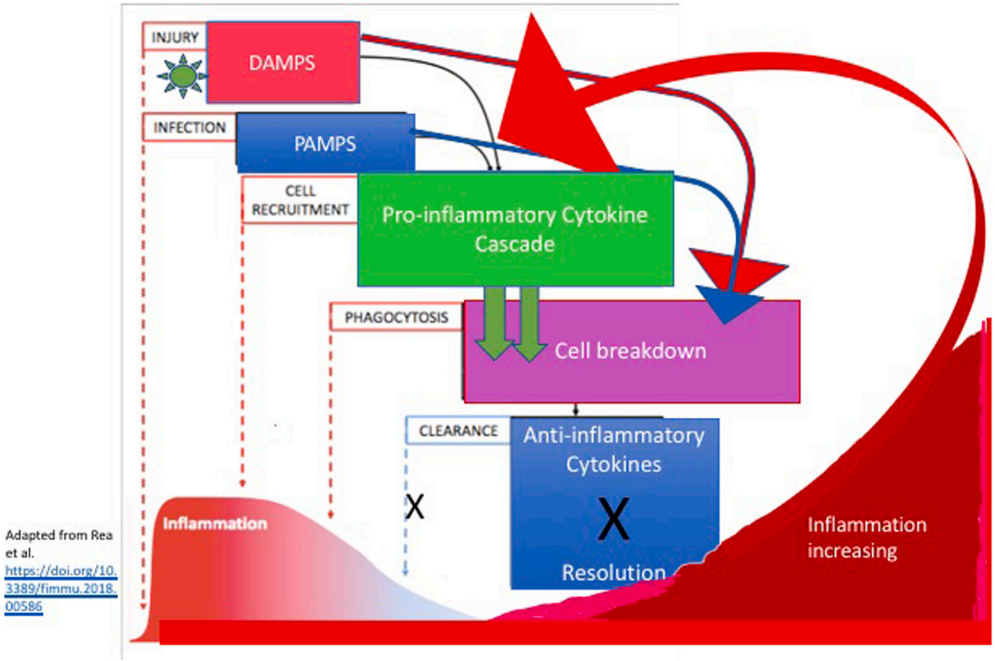


**Fig. 9.** The cycle of non-resolving inflammation leading to self-perpetuating cell breakdown and the cytokine storm. The cycle of injury begins when antigen from the SARS-Cov-2 virus is detected by DAMPS and then by PAMPs which are triggered by host-derived stress molecules, such as damaged nuclear proteins. NK cells' release of cytotoxic materials, together with DAMPs and PAMPs trigger a pro-inflammatory cytokine cascade of the IL-1 family of cytokines and multiple pro-inflammatory molecules. The resolution of inflammation by resolvins and anti-inflammatory cytokines is unable to commence promptly and a cycle of self-perpetuating, self-destructive inflammation is triggered, causing cell and multi-organ damage and possible death. DAMPS, danger -associated molecular patterns; PAMPs, protein-associated molecular patterns; NKs, natural killer cells, SARs-CoV-2.

Turner et al., 2017; Yoon et al., 2019; Kim et al., 2017) (Fig. 3A, B).

### 3.3.1. Alveolar epithelial cells and alveolar macrophages and ageing

Ageing causes senescence and metabolic alterations in AT11 cells that reduce regeneration after acute lung injury, such as COVID-19 (Brandenberger et al., 2018; Yazicioglu et al., 2020). There are age-related changes in alveolar epithelial type 1 (AT1) cells that normally maintain the epithelial-endothelial barrier preventing protein fluid leakage across the alveolar wall into the air spaces, while allowing gases to freely cross the air-blood barrier (Byrne et al., 2015). The lung tissues lose elasticity, risking collapse and alveolar sacs become baggy, both influencing gas exchange and patient outcome in COVID-19, and when receiving ICU ventilation (Fig. 3B). The age-related decrease in alveolar macrophage numbers and function (Linehan et al., 2015) is likely important, as the monocyte infiltration that they recruit, peaks between days 5–7, and could become delayed in the older COVID-19 patient, pausing initiation of an effective immune response.

### 3.3.2. Tissue-resident T cells ($T_{RM}$) in lung

$T_{RMs,}$ holding memory from a previous SARS-CoV-2 or related-coronavirus infection, can 'kick start' immune responses to a new COVID-19 infection (Grau-Expósito et al., 2021; Golpen et al., 2021; Kok et al., 2020) (Fig. 3C). The discrete immunostatic balance between alveolar macrophages, NK and CD8 $T_{RM}$ memory cells can become easily disturbed and overactive in lungs already damaged by chronic disease, with increases in CD8 $T_{RM}$ cells causing augmentation of inflammation, influx of fibrosing fibroblasts, resulting in damaging fibrosis and reduced lung function in the COVID-19-ARDs patient (Mora-Buch and Bromley, 2021; Goplen et al., 2020). In fulminant COVID-19, more common in elderly patients, the epithelial-endothelial barrier becomes damaged and platelet/fibrin microemboli form, with risk of thrombosis and multi-organ damage (Fig. 3D–F).

While TRMs have the potential to augment the hyperinflammatory immune response, in COVID-19 illness, the presence of SARS-CoV-2-N-specific-$T_{RM}$ cells in some patients suggests the possibility of being able to induce stable and highly reactive vaccines.

## 3.4. Reduced type 1 IFN and IFN genetics play a role in COVID-19

Interferon and members of the type I IFN family interfere with viral replication and are essential for an effective antiviral response. Reduced type 1 IFN secretion contributes to weaker immune responses in older people during phase 1 of the immune response (Wells and Coyne, 2018). Research shows there are genetic and antibody explanations for some of the excess mortality among patients with severe COVID-19, and for increased risk in males and older age groups.

Clues into genetic mutations in COVID-19 illness were identified by comparing DNA from brother-pairs, severely ill with COVID-19; there were genetic and gender differences of genes involved in IFN production (van der Made et al., 2020). Inborn errors of TLR3, vital in viral recognition and activation of innate immunity, and IRF7-dependent type-I IFN critical in immunity against viruses, were pin-pointed as DNA markers. In these patients, IFN immune response was insufficient to suppress early COVID-19 infection, allowing SARS-CoV-2 virus to trigger widespread immune reaction and disastrous lung-injuring, inflammatory-collateral damage and death (Blanco-Melo et al., 2020).

The COVID Host Genetic Effort (2020) (https://www.covidhge.com), also reported loss-of-function (LOF) variants, previously known to compromise TLR3- and IRF7-dependent type 1 IFN immunity to influenza and childhood pneumonitis (Casonova et al., 2020; Zhang et al., 2020). The genetic mutations, carried on the X-chromosome affected males and inhibited IFN production directly or indirectly, and although rare, occurred at all ages, including at older ages. A distinct COVID-19 phenotype characterised by absent IFN-β and low IFN-α production and activity and partially driven by the NF-kB cytokine pathway (Hadjadj et al., 2020), explained, in part, how deleterious mutations in the human IRF7-dependent type 1 IFN immunity caused severe COVID-19 illness.

Antibodies to IFN, newly recognised in life-threatening COVID-19 pneumonia in 2.6% of women and 12.5% of men (Bastard et al., 2020), were found at all ages, and the autoantibody abnormality was clinically silent before patients developed COVID-19 (Zhang et al., 2020: Hadjadj et al., 2020). Possible treatment options include blocking/removing damaging antibodies by plasmapheresis or specific inhibition of type 1 IFN-reactive B cells.

Of the six genes identified, by The COVID-19 Host Genetics Initiative (2020a,b) on chromosome 3, SLC6A20 encoded a transporter that interacts with ACE2, the SARS-CoV-2 cell receptor, and others encoded chemokine receptors. A signal at 9q34.2 coincided with ABO blood group locus previously shown to have higher risk for blood group A carriers and a protective effect for blood group O, in non-genetic studies (Zhao et al., 2020). In a further twist, Zeberg and Pääbo (2020), reported that the chromosome 3 gene cluster, found in life-threatening COVID-19, (The Severe COVID-19 GWAS Group 2020), matched chromosome 3 haplogroup in Neanderthals, inherited 50,000 years ago. Today this gene haplotype is carried by ≈ 30% South Asians, 8% Europeans and 4% admixed Americans, but rarely in East Asians and Africans, and is the gene area associated with increased risk of severe COVID-19 (Public Health England, 2020). Heterozygous or homozygous carriers have ≈ 1.5–3 times increased risk compared to non-carriers, which may link with increased COVID-19 severity, in certain present-day populations (Zeberg and Pääbo, 2020).

Genetic research aids understanding about the complex effect that COVID-19 has on the immune system and has focused clinicians to identify vulnerable individuals by screening for IFN-related genes, IFN-related autoantibodies, and to establish trials using type 1 IFNs in selected patients, at different times in the course of SARS-CoV-2 infection. Recent understanding suggests that appropriate and timely interaction between Type 1 and Type 11 IFNs is important in controlling SARS-CoV-2 viral replication and avoiding uncontrolled inflammation and excess tissue death.

## 3.5. The ACE2 doorway

The SARS-CoV-2 virus enters the host cell by using ACE2 as an entry receptor, and two host transmembrane serine proteases TMPRSS2 and neuropilin-1 help prime the SARS-CoV-2 spike (S) protein to allow entry into the host cell (Hoffman et al., 2020; Daly et al., 2020). The renin-angiotensin-aldosterone system (RAAS) is considered to play an important role in the pathogenesis of COVID-19 infection (Ingraham et al., 2020) (Fig. 1A–C). The ACE2 gene influences the renin angiotensin system (RAS) function by modulating blood pressure, sodium and fluid balance and may thereby be important in COVID-19 patients with cardiovascular and renal disease (Narula et al., 2020; Guo et al., 2020; Shi et al., 2020).

### 3.5.1. Hypertension and ACE and ACE2 polymorphisms

Since the start of the COVID-19 pandemic, researchers and clinicians have noticed an increased severity of SARS-CoV-2 disease in patients with cardiovascular disease and hypertension (Clerkin et al., 2019; Bonow et al., 2020). Given the importance of the ACE receptor for SARS-CoV-2 access into the cell, ACE polymorphisms might be important in COVID-19 susceptibility. The DD homozygous allele of the insertion/deletion (I/D) polymorphism of the ACE gene has been previously investigated as a risk factor for hypertension and cardiovascular disease, the outcome in ARDS, and progression of pneumonia in Middle Eastern SARS (Evans et al., 1994; Matsuda et al., 2012; Itoyoma et al., 2004) and was considered a possible risk for severe COVID-19 disease. Yamamoto et al. (2020), reported that SARS-CoV-2 cases and mortality were negatively associated with the ACE II genotype, and that ACE I/D polymorphism may be a genetic marker for SARS-CoV-2 infectivity and pathogenicity, dependent on patient geo-location. The ACE II

homozygote frequency varies widely East to West, with higher frequencies in Japan (48%), Korea and China (41%) compared to Spain (15%) and 18% in Europe. Serum levels of ACE are higher in DD genotype carriers (Rigat et al., 1990) suggesting that normal homoeostasis that is controlled by the functional balance between ACE /ACE 2 genes, may be compromised by SARS-CoV-2's use of the ACE2 receptor, resulting in over-activation of ACE pathway of the RAAS system, causing endothelial dysfunction, microthrombi, pulmonary shut-down, severe critical illness and death (Fig. 1).

Bosso et al. (2020) demonstrated that 12 variants of the ACE2 gene were associated with risk of hypertension and/or cardiovascular disease. Meta-analyses across different populations confirmed hypertension risk in carriers of the rs2285666 polymorphism (Niu et al., 2007; Lu et al., 2012). This polymorphism demonstrated higher allele frequency (0.556) in the China Metabolic Analytics Project (China MAP) populations compared to Mixed American, 0.336; African, 0.211; European, 0.235 and Indian populations (0.6) (Cao et al., 2020a; Srivastava et al., 2020), with similar population findings by (Hou et al., 2020).

ACE inhibitor (ACEi) and angiotensin receptor blockade (ARB) drugs are commonly used medications for high blood pressure and for diabetic patients with co-existing renal disease, leading to concerns that these drugs, would increase susceptibility to SARS-CoV-2 infection (Mogensen et al., 2000; Fang et al., 2020). Several observational studies have not demonstrated any adverse association between medication use and risk of increased mortality, though variations between different ethnic groups did raise the possibility of ethnic-specific effects of ACE inhibitors/ARBs on COVID-19 disease susceptibility and severity (Hippisley-Cox et al., 2020; Straw and Witte, 2020). Current clinical advice is to continue the use of ACEi and ARB medication in COVID-19 patients, as medication may help support the cardiovascular system (Jarcho et al., 2020; Morales et al., 2021).

Both ACE2 and ACE polymorphisms vary across the world (Asselta et al., 2020; Cao et al., 2020a). Taken together, the differences in allele frequencies of ACE and ACE2 variants may compromise the functional balance in the RAAS system and relate to COVID-19 morbidity and mortality across different populations and ethnicities (Lippi et al., 2020).

### 3.6. Obesity and diabetes

COVID-19 death rates are 10 times higher in countries where more than half of the adult population is overweight, compared to countries where populations are within normal weight guidelines (The World Obesity Federation, 2021). In 160 countries, there were linear correlations between a country's COVID-19 mortality and the proportion of overweight adults. The report builds on previous analyses demonstrating that obesity is an independent risk factor of severe illness and death from COVID-19 (Wise, 2021; Popkin et al., 2020; Global Burden of Disease, 2019). The UK OpenSAFELY analysis (Williamson et al., 2020) also demonstrated a dose-response relationship between excess weight and severe COVID-19 after adjusting for age, sex, ethnicity and social deprivation, with studies from Europe, Asia and USA confirming similar findings (Petrilli et al., 2020; Huang et al., 2020b). The prevalence of being overweight and being obese approaches 60–70% in the UK and US and contributes to high blood pressure, type 2 diabetes and heart disease, that associate with the highest morbidity and mortality in SARS-CoV-2 patients, particularly in males (Holman et al., 2020; Li et al., 2020a; Sattar et al., 2020).

Older people, while not necessarily fitting criteria for obesity, do demonstrate disproportionate increases in body fat percentage due to muscle loss because of sarcopenia (Dutra et al., 2017; Batsis et al., 2016). Fat cells contribute to inflamm-ageing and impair the immune system at the molecular level by producing pro-inflammatory cytokines such as TNF-α (Frasca et al., 2017), and also reduce the physiological ability of the lung to clear airway infection, as for example in influenza or COVID-19. The high levels of ACE2 gene expression present in the large number of fat cells in obesity, serve as a hidden reservoir for the SARS-CoV-2 virus, facilitating spread to other organs, causing severe COVID-19 inflammation, multi-organ failure, and increased mortality (Al-Benna, 2020; Kruglikov and Scherer, 2020).

Diabetes, one of the main risk factors associated with COVID-19, is linked with obesity and increases with age. Diabetes doubled the risk of death for those with reduced diabetic control, with similar findings and outcomes in patients with pre-existing type 2 diabetes and COVID-19 (Williamson et al., 2020; Zhu et al., 2020; Yang et al., 2020a). The hazard-ratio increased by 4 times if renal function was markedly reduced. An analysis of the most common co-morbidities of patients in ICUs with COVID-19 were hypertension (23·7%) and diabetes mellitus, further confirmed by data collation of mortality and co-morbidities in 52 ICUs (Guan et al., 2020; Fang et al., 2020). With improved follow-up of COVID-19 patients, new-onset diabetes has been identified as a post-COVID-19 illness and a monitoring group-CoviDIAB Project (covidiab.e-dendrite.com), will investigate the bidirectional relationship between COVID-19 and new-onset diabetes (Rubino et al., 2020; Lim et al., 2021).

Patients with COVID-19, and those with the metabolic syndrome (a combination of obesity, high blood pressure, diabetes), were almost 5 times more likely than their peers to require intensive care and ventilation, and 3–4 times more likely to die from COVID-19 illness (Xie et al., 2021a).

### 3.7. Age and gender

Age and gender are well-established risk factors for morbidity and mortality from SARS-CoV-2 infection. The data from China demonstrated greater numbers of male patients in hospital with SARS-CoV-2 illness, and male sex was an independent risk for disease and death (Zhou et al., 2020a). In Italy, men represented 58% of COVID-19 infected patients and 70% of COVID-19-related deaths (Remuzzi and Remuzzi, 2020). The UK openSAFELY data-analysis demonstrated that 90% of COVID-19-related deaths were in people > 60-years-of -age and 60% were male (Williamson et al., 2020). According to the authors, males have an overall 1.6-fold increased risk of death compared to female patients in the UK, with similar findings globally (Dehingia and Raj, 2021).

The reason for the sex-related increase in COVID-19-related deaths has been much considered. The ACE2 gene, is present on the X gene, and the double 'dose' of ACE2 on XX genes which females carry, may provide some advantage, such as increased ACE2 receptor coverage in the lung where it could protect from ACE-related damage in COVID-19 infection (Gemmati et al., 2020). According to Chen et al. (2020a,b,c), ACE2 expression in the lung was highest in children and young people and increased by oestrogen and androgen; conversely ACE2 expression decreased with age and was lower in hypertension, cardiac hypertrophy and cardiac failure, co-morbidities that increased COVID-19 risk (Luo et al., 2019; Sama et al., 2020; Gebhard et al., 2020).

Females and males differ in incidence, susceptibility, response and disease severity in viral infections (Klein, 2020; Mauvais-Jarvis et al., 2020; Klein and Flanagan, 2016). Males are more vulnerable, across a range of diseases throughout life, including in old age (Hirokawa et al., 2013; Wang et al., 2015; Bonafè et al., 2020). Generally, females mount stronger innate and adaptive immune responses than males, that results in faster clearance of pathogens and greater vaccine efficacy in females than in males. However, contraintuitively, higher innate cytokine responses- IL-18 and IL-8- were demonstrated in response to COVID-19 illness in males, whereas female patients developed higher T cell activation, whichaccording to the authors might explain the sex-related differences in COVID-19 outcome (Takahashi et al., 2020).

Sex hormones influence the immune system (Auerbach and Khera, 2021; Taneja, 2018), fall with age and are decreased by multiple age-related co-morbidities (Traish et al., 2015), with evidence of improvement following hormone replacement treatment (Yassin et al.,

2019; Baillargeon et al., 2019). Sex steroids bind to immune-cell steroid receptors, influence signalling pathways, including NF-κB and interferon regulatory factor (IRF) 1, resulting in production of cytokines/chemokines (Bereshchencko et al., 2018). Sex differences could be caused by imbalanced gene expression encoded on the X and Y chromosomes, mediated by sex differences in the XX gene dose or parental epigenetic imprinting, resulting in incomplete X inactivation (Mauvais-Jarvis et al., 2020).

Male sex was an independent risk for disease and death from COVID-19. Sex differences could be caused by sex hormones and imbalanced gene expression encoded on the X and Y chromosomes.

### 3.8. Behaviour, culture and geography

Behaviour, culture and geography influence COVID-19 infections and the severity of illness. Past and current smoking behaviours, previously higher in men compared to women, have contributed to chronic obstructive pulmonary disease (GBD 2015 Tobacco Collaborators, 2017; Jamal et al., 2016), and increased risk of death in COVID-19 illness (Alqahtani et al., 2020; Khalil et al., 2021). Males have a greater life-time burden of cardiovascular risk compared to females, that also contributes to their differential risks of serious COVID-19 illness compared to females (Walli-Attaei et al., 2020). Females also benefit from the early vascular protection provided by pre-menopausal hormones (EL Khoudary et al., 2020; Aggarwal et al., 2018). Obesity affects both sexes. The World Obesity Federation (2021) report demonstrates population obesity is highly associated with a country's COVID-19 mortality. The evidence calls for vaccination priority related to obesity and for strong government control measures, to stop industry-based-food production, that contributes to population obesity and poor health (Tan et al., 2020b).

Data from Public Health England (PHA) has shown correlation between rates of COVID-19 cases/100,000 residents and average life expectancy, so that cities with lower life expectancy rates also track with higher rates of COVID-19 illness (Public Health England, 2020). The Office for National Statistics (ONS, 2020a,b) reported similar associations between the social determinants of health and COVID-19 illness in 2020. Similar findings were described in the US by van Dorn et al. (2020) writing that "*people's health is directly related to the conditions in which people are born, grow up, work and age and that social injustice is the biggest killer of all*", findings that mirror the frequently re-iterated message in the UK by Marmot et al. (2008), relating to 'social determinants of health'. Similar calls for equity and social justice alongside public health actions are being called for, across continents (Smith and Judd, 2020; Rollston and Galea, 2020).

Altogether, the evidence shows that after adjusting for age, most differences in COVID-19 mortality could be explained by demographic, geographical and socio-economic factors, such as home location and occupation (Golestaneh et al., 2020; Haynes et al., 2020).

### 3.9. Vitamin D

The possibility that vitamin D supplements could reduce susceptibility to and the severity of illness with COVID-19 seems a simple solution, particularly since older people are often vitamin D deficient, but robust and convincing evidence remains elusive. A series of smaller studies have shown relationships between vitamin D deficiency and severity of COVID-19 illness and death (Laird et al., 2020; Ilie et al., 2020; Ali, 2020). Conversely, Hastie et al. (2020) using retrospective Biobank data from half a million people, found no association between vitamin D and COVID-19 infection, with similar findings from the OpenSAFELY data (Williamson et al., 2020), and from an Australian randomised clinical trial, of vitamin D and severity in non-COVID-19 respiratory infections in older people (Pham et al., 2021). An updated meta-analysis (Teshome et al., 2021), found a sufficient Vitamin D level was associated with a decreased risk of COVID-19 infection.

In an interesting approach, lower vitamin D associated with COVID-19 mortality dependent on participant geographical North/South latitude (Whittemore, 2020; Pereira-Santos et al., 2019; Rhodes et al., 2020). People with darker skins, those with excess body fat, older people and carriers of the GC (group-specific component) vitamin D receptor rs4588 AA genotype were also more likely to become vitamin D deficient (Kohlmeier, 2020). The A allele variant of rs4588, particularly common in people with caucasian ancestry, demonstrated 36% lower vitamin D levels in the 8% of the population, who are homozygous carriers (Jiang et al., 2018).

Vitamin D affects the immune system and has been considered to protect against respiratory infections (Martens et al., 2020; Chambers and Vukmanovic-Stejic, 2021; Martineau et al., 2017). It acts through receptors on T and B cells to modulate the adaptive and innate immune response through signalling pathways, by suppressing Th-1 cell proliferation, by decreasing production of pro-inflammatory cytokines, IFN-γ and IL-2 and reducing antigen presentation by DCs (Bscheider et al., 2016; Martens et al., 2020). Overall, vitamin D polarises the adaptive immune system away from Th-1 and towards Th-2-related immune responses. Recent research showed that Vitamin D-deficient, COVID-19 patients had worse outcomes compared with aged-matched, vitamin D-replete patients, with signs of increased cytokine release syndrome (Daneshkhah et al., 2020). and ongoing need for ventilatory support (Baktash et al., 2020).

An updated Cochrane review found inconsistent evidence regarding an association between vitamin D deficiency and COVID-19 severity (Stroehlein et al., 2021). Meanwhile, as the debate continues, current advice has encouraged use of vitamin D3 supplementation of 600 IU daily, at least during the darker, colder days of winter and spring, in keeping with wider clinical opinion (Vimaleswaran et al., 2021; National Institute of Clinical Excellence (NICE), 2020).

## 4. How could immunocompetence in older and frailer populations be strengthened and supported to improve protection from COVID-19 illness?

### 4.1. SARS-CoV-2-reactive T cells

One of the most important questions about COVID-19 infection, is whether SARS-Cov-2 virus stimulates T cell memory, likely to protect people and provide long-term immunity. Immune studies in COVID illness have begun to answer this question.

Weiskopf et al. (2020) demonstrated that SARS-COV-2-reactive T cells were present and increased over time in ventilation-supported, severely ill COVID-19 patients. Further supporting evidence was presented by Braun et al. (2020) who demonstrated S-protein-specific CD4+ T cells in 83% of patients with COVID-19, but also in 34% of seronegative healthy donors. Grifoni et al. (2020) used large-scale testing with HLA class 1 and 11 peptide 'megapools' and identified SARS-CoV-2-specific CD8+ and CD4+ T cells in approximately ≈ 70% seronegative COVID-19 individuals and 100% of convalescent COVID-19 patients respectively, with robust CD4+T cell responses to S spike, the main target of vaccine efforts. The authors suggested that some T cells induced by common cold coronaviruses could cross-react with the SARS-COV-2 viral antigens.

In another series of studies with a different emphasis, Peng et al. (2020) demonstrated a greater breadth and magnitude in memory T cell responses from convalescent individuals in severe, compared to mild cases, for spike S, M, and ORF3, SARS-CoV-2 proteins. Research, by Kusnadi et al. (2021), demonstrated that CD8+ T cells in milder cases showed T cell exhaustion, whereas SARS-CoV-2-reactive cells in severe COVID-19 showed transcripts linked to co-stimulation, pro-survival NF-κB signalling, and antiapoptotic pathways, suggesting robust CD8+ T cell memory. In a longer follow-up, SARS-CoV-2-specific CD4+ and CD8+ memory T cells were present at 7 weeks, and interestingly, SARS-CoV-2-specific memory T-cell were also present in contacts,

exposed to, but not infected by virus Wang et al. (2021b).

Despite studies showing that T cell reactivity to SARS-CoV-2 was present in individuals recovering from COVID-19 infection or in unexposed individuals, perhaps due to cross-reactivity with the common cold coronaviruses, it is not known how long this immunity will last, and if it can continue to influence clinical outcomes in SARS-CoV-2 infection in patients, irrespective of age. Could the mild or asymptomatic presentation of Covid-19 illness in young children be related to their frequent exposure to common cold and respiratory illness during childhood and produce useful cross-reactivity to SARS-COV-2 infection? Research in previous SARS animal models suggested that cross-reactive airway CD4+ T cells might be of value in protective immunity to coronaviruses (Zhao et al., 2016). Similar findings were described by Dan et al. (2021), who demonstrated that pre-existing reactivity against SARS-CoV-2 came from cross-reactive T cells that can specifically recognise a SARS-CoV-2 epitope as well as the similar epitope from common cold human coronaviruses. Le Bert et al. (2020), too, in a comparative study of T cell responses to SARS-CoV-2 structural proteins, between recovering COVID-19 and uninfected subjects, demonstrated increased NSP7 and NSP13 proteins in uninfected patients, similar to those found in animal betacoronaviruses, suggesting cross-reactivity; additionally, the authors demonstrated long-lasting memory T cells, that reacted to the N protein of the previous SARS-CoV virus, and could be detected in recovered SARS patients, 17 years later, providing suggestive evidence that COVID-19 patients would likely develop long-term T cell immunity.

To date, there is increasing evidence that COVID-19 develops SARS-Cov-2-specific-T cell immunity that can last up to 6 months.

### 4.2. Bystander activation linked to vaccination

Live attenuated vaccines given to patients may extend the patient's immunity to other viruses for several months (van Aalst et al., 2017). For years bacille Calmette-Guérin (BCG for tuberculosis) and measles vaccines have been used as a mechanism to reduce all-cause mortality, with evidence that bystander effects of vaccination reduced infectious disease mortality by 40% in neonates (Benn et al., 2020; Moorlag et al., 2019; Biering-Sørensen et al., 2017). In a systematic analysis, Yitbarek et al. (2020) described the incidence and death from acute respiratory infection including COVID-19, was significantly lower in countries with universal BCG vaccination, but called for further evidence. In a related study, Gursel and Gursel (2020), demonstrated that COVID-19 cases/million and deaths/million were significantly lower in countries with, as compared to those without, BCG vaccination programmes, and reported that BCG vaccination-induced, non-specific protective effects could be long-lasting (~ 20 years), with the potential to influence SARS-CoV-2-associated community spread and/or disease severity. A short Israeli study compared SARS-CoV-2 infection rate between previously BCG-vaccinated and non-vaccinated young adults and found no difference in positivity or severity of infection (Hamiel et al., 2020), whereas the Activate randomised clinical trial of BCG-vaccinated, compared to non-BCG-vaccinated elderly people, showed a reduction of ≈ 45% against a range of non-COVID-19 respiratory infections (Giamarellos-Bourboulis et al., 2020a,b).

Influenza has a resemblance to SARS-COV-2 virus, sharing similar approaches to control interferon-stimulated-gene (ISG) responses (Menachery et al., 2014) and the use of ACE2 receptors in the lung (Liu et al., 2014). An analysis, linking recent influenza vaccination and data from 34 countries from the Organisation for Economic Cooperation and Development (OECD) and COVID-19-related mortality, morbidity and case incidence in adults > 65 years, suggested that influenza vaccination (H1N1) appeared protective, with a mortality benefit of ≈ 30% (Arokiaraj, 2020). The author further suggested that *Streptococcus pneumonia* vaccination, with similar mortality benefits, be included in vaccination strategies, for older people where immunity was lower (Brooks and Mias, 2018). Although the cause of this extended immunity to viruses after live-attenuated virus inoculation is not properly understood, activation of the surrounding memory T cells may be beneficial to the immune system as it may prime or strengthen the memory T cell repertoire (Li Causi et al., 2015; Di Genova et al., 2010, 2006) in an immune-related hormesis-type-effect by contributing to immune tolerance/resilience and decreasing the extent of infection-related tissue damage, through possible epigenetic changes (Calabrese, 2016; Weis et al., 2017; Kleinnijenhuis et al., 2012).

Altogether, evidence points to a possible protective and all-cause mortality benefit from the non-specific effects of influenza and/or pneumococcal vaccination in older people, when used as an adjunct strategy to improve protection from serious COVID-19 illness.

### 4.3. Neutralising antibodies and COVID-19 illness

Convalescent plasma, hyperimmune globulin and synthesised monoclonal antibodies are based on the same principle of using natural or manufactured antibody to stop and neutralise the virus. Antibodies, whether human-derived or laboratory-manufactured, last for some weeks and then decline, but they can help hold the seriously ill patient stable, while their own immune system recovers well enough to effectively to deal with the SARS-COV-2 virus threat.

Small studies using convalescent serum for SARS-CoV-2 patients suggested that treatment was well tolerated, reduced viraemia and clinical symptoms (Shen et al., 2020; Duan et al., 2020), whereas the larger RECOVERY Collaborative Group (2021c), testing convalescent plasma as a treatment in life-threatening COVID-19 did not result in significant improvement and was discontinued early. Early clinical donor convalescent studies may not have been consistent with Federal Drug Association (FDA) guidelines (US FDA, 2020), since donor convalescent serum antibodies are higher in males compared to females and after severe COVID-19 illness, and studies may not have been comparable (Klein et al., 2020; Chen et al., 2020b). In an editorial update, Katz (2021), proposed that any use of convalescent plasma should be considered in early infection; whereas an updated meta-analysis reported that convalescent plasma did not provide improved survival or other positive outcomes for COVID-19 patients (Janiaud et al., 2021).

Synthetic monoclonal antibodies have been developed and have been used in the treatment of COVID-19 illness. The apparently successful use of a laboratory-made neutralising antibody in the early days of COVID-19 treatment of a former US President, was followed by the publication of data from a small Regeneron trial. The, two-drug-cocktail, contained casirivimad and imdevimab, both proteins that bind to the surface spike S protein and block the virus attachment to the ACE2 receptor (Baum et al., 2020). In a clinical trial of non-hospitalised people, positive for SARS-CoV-2, treatment with REGN-COV2 showed reduced viral carriage and improved clinical outcomes (Weinreich et al., 2021). Drug concentrations were detected at 29 days in almost all patients and the long half-life of REGN-COV2 treatment suggested passive immunity lasted several months. Another monoclonal antibody LY-CoV555, uses a potent anti-spike neutralising monoclonal antibody that binds to the receptor-binding domain of SARS-CoV-2, (Jones et al., 2020). In a trial, involving outpatients with mild/moderate COVID-19, those who received a single intravenous infusion of neutralising antibody LY-CoV555, had less severe symptoms, reduced viral loads and a lower percentage of COVID-19–related hospitalisation compared with those who received placebo (Chen et al., 2021). Because, the monoclonal antibodies target different parts of the virus, it is possible that administering several together may produce a synergistic effect and may limit the emergence of neutralisation-escape mutants (Pinto et al., 2020; Roodink et al., 2021).

SARS-CoV-2 convalescent-derived antibodies used in clinical trials have given mixed results, whereas monoclonal antibodies demonstrated improvement in non-hospitalised patients, treated early in their illness.

### 4.4. Monoclonal antibodies and drugs in COVID-19 illness

Both IL-6 monoclonal antibody tocilizumab, or its receptor antibody have been prescribed widely in COVID-19 patient clinical care, though with mixed reports on patient hospitalisation and mortality (Salvarani et al., 2021; Stone et al., 2020; Wise, 2020). Two recent trials have added more information for tocilizumab. In the Randomised, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP), patients receiving an IL-6 receptor blocker had improved in-hospital mortality compared with the control group, whereas in the COVACTA randomised controlled trial, mortality at 28 days was not different in either groups (REMAP--CAP Investigators 2021; Rosas et al., 2021). Subgroup non-peer reviewed results in the RECOVERY trial indicated that those receiving glucocorticoids had a survival advantage, interpreted to suggest that glucocorticoid use in addition to tocilizumab, which was more standard in the later REMAP-CAP and RECOVERY trials, as compared to the COVACTA trial, could explain differing results (RECOVERY Collaborative Group, 2021a; Rubin et al., 2021).

Increased levels of pro-inflammatory cytokines IL-1α, IL-1β, IFN-α, IL-17A and IL-12p70 characterise a 'core' signature of severe COVID-19 illness, as compared with lower levels found in moderate illness. IL-1 and IL-1β inhibitors have been used clinically, though results have been mixed, suggesting that patient stratification and timing of use, may be important (Conti et al., 2020a,b; Cavalli and Dagna, 2021). IL-1 inhibition with anakinra in small studies produced rapid reduction of the systemic inflammatory response and improved oxygenation (Ucciferri et al., 2020; Huet et al., 2020), whereas canakinumab did not improve outcomes in patients with mild-to-moderate COVID-19 pneumonia (Aouba et al., 2020; The CORIMUNO-19 Collaborative Group, 2021). Other soluble receptor antagonists, chemokines, microRNAs-MiR-146 and MiR-125 (Lee et al., 2016), and siRNAs also function as inhibitors for pro-inflammatory cytokines and have potential for use in COVID-19 treatment.

Remdesivir is the main anti-viral agent that has demonstrated some benefit in treatment of COVID-19 patients, with faster time to clinical improvement than those receiving placebo, among patients with symptom duration of 10 days or less (Beigel et al., 2020; Wang et al., 2020b). A small Israeli phase 1 clinical trial has reported in the press that moderately ill COVID-19 patients were discharged in 3–5 days, when given a new substance EXO-CD24, containing a protein CD24, and delivered to the lungs by exosomes (Penna, 2020). CD24, expressed by many immune cells, helps rebuild and rebalance the immune system and prevent inflammatory overaction (Chen et al., 2009a; Liu et al., 2009). More clinical studies are urgently needed to assess any new anti-viral agents, anti-inflammatory cytokines or cytokine genotypes that could contribute to reducing the severity of the pro-inflammatory phenotype and 'cytokine storm' seen in seriously ill Covid-19 patients (Al-Beltagi et al., 2021; Cao et al., 2020b).

Dexamethasone, a corticosteroid used in a wide range of conditions for its anti-inflammatory and immunosuppressant effects is effective in COVID-19 and reduces the risk of death by approximately 25% in seriously ill patients at risk of, or requiring mechanical ventilation (RECOVERY Collaborative Group, 2021b; WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, 2020). The benefit effect of glucocorticoids seems to be highly dependent on careful selection of dose, timing and patient clinical status.

Dexamethasone been found to be effective in COVID-19, dependent on dose, timing and patient selection; IL-6 monoclonal antibody tocilizumab, or its receptor antibody and IL-1 inhibition have shown some benefits.

### 4.5. COVID-19 vaccination effectiveness in older people

Numerous studies have shown that vaccine efficacy decreases with age, a reduction that is driven by the age-related decline of innate and adaptive immune responses and characterised by a combination of inflamm-ageing and immunosenescence. This not only puts older people at risk from the SARS-COV-2 virus but also makes it more difficult to produce a vaccine that will provide adequate protection in the oldest age groups. There is heterogeneity in each person's immune system, marked out by sex, age, genetics, ethnicity, lifestyle, and immunobiography (Franceschi et al., 2017; Rea et al., 2018). Yet there is evidence that many older people get good protection from vaccines; for example, at the age 70 the pneumococcal vaccine has an efficacy of about 60% (Djennad et al., 2018) and the adjuvanted herpes zoster shingles vaccine demonstrated a 90% efficacy against shingles in people > 70 years of age (Le et al., 2017; Lal et al., 2015). The influenza vaccine effectiveness varies from one season to the next, and in the UK is estimated by Public Health England (2018), to be between 30% and 60% for adults aged 18–65 years. The challenge has been to produce a COVID-19 vaccine that is safe, with the ability to produce an immune response that is sufficiently protective for people at every age of life.

A large number of vaccines against COVID-19 have been developed and are in use, based on different platforms such as lipid particles, mRNA, DNA, adjuvant proteins, inactivated virus particles and non-replicating viral particles. The BNT162b2 (Pfizer-BioNTech) vaccine began the first ever immunisation programme against the SARS-COV-2 virus in December 2020, < 12 months after SARS-CoV-2 was identified. The vaccine is novel and uses a piece of messenger mRNA from the SARS-CoV-2 spike protein combined with a lipid nanoparticle, to stimulate production of antibodies against the mRNA fingerprint of the SARS-CoV-2 virus. The results showed that the Pfizer vaccine worked with an efficacy of 95% overall, including for older participants (Polack et al., 2020). The Moderna (mRNA-1273) vaccine uses similar mRNA biotechnology (Baden et al., 2021; Anderson et al., 2020) and shows vaccine efficacy of 86% for participants, 71 years or older (Widge et al., 2021). The Moderna and the Pfizer vaccines have documented detecting neutralising antibodies and significant CD4 cytokine Type-1T helper cell responses within several weeks (Polack et al., 2020; Widge et al., 2021), but it has yet to be established that the immune response and antibodies will confer long-lasting, adequate immunity to COVID-19, particularly in those in the > 70s, and those in immunosuppressed 'at risk' groups (Anderson et al., 2020; Walsh et al., 2020).

The adenovirus-vector-based vaccine ChAdOx1 nCoV-19 (AZD1222) (Oxford–AstraZeneca), produced by Oxford Vaccine Group, demonstrated good anti-spike SARS-CoV-2 IgG responses and neutralising antibody titres after a booster dose in both older (>70 years) and young participants (Folegetti et al., 2020; Ramasamy et al., 2020). Overall vaccine efficacy across groups was 70·4%, and an increased 12-week gap between vaccines, improved efficacy (Voysey et al., 2021). However, only 3% of participants were in the > 70s-age-group, and additional confirmation in older people with co-morbidities would be highly valuable (Knoll and Wonodi, 2021).

Both Pfizer and AstraZeneca vaccines produce strong immunogenicity and high short-term efficacy, but antibodies wane over time (Shrotri et al., 2021). However, research is confirming the longer-term presence of SARS-COV-2 memory cells in patients recovered from COVID-19 (Wheatley et al., 2021; Gaebler et al., 2021; Rodda et al., 2021; Doria-Rose et al., 2021), which strongly suggests that immune responses could develop on SARS-CoV-2 re-exposure; the findings are further validated from research demonstrating that vaccination reduces serious illness, hospitalisation and death after COVID-19 re-infection (Amit et al., 2021; Dagan et al., 2021; Vasileiou et al., 2021; Lumley et al., 2021). The emerging reports of breakthrough infections in healthcare workers (Bergwerk et al., 2021), and the surge in cases caused by the Delta-variant have caused countries to look more closely at booster vaccinations; these will likely be required to maintain adequate longer-lasting immunity, particularly in the > 50s age-group and for those in an immunosuppressed 'at risk' group (Callaway, 2021).

Other vaccines have been developed – Sinovac in China and Sputnik in Russia, with thousands of participants being vaccinated. The Sputnik

V Phases 1/2 and 3 trials, using a combination of 2 adenovirus-based vaccines, reported fairly good efficacy and safety, and adequate but lower IgG spike and neutralising titres in participants > 60 years of age (Logunov et al., 2020, 2021). The Johnson/ Johnson/Janssen Ad26COV2 S vaccine, a single shot, normal temp-based, DNA vaccine, has presented data demonstrating good early efficacy, with production of neutralising antibodies against the spike protein with CD4+ T helper Th1 and Th2 cells, present in participants aged 18–65 years (Sandoff et al., 2021).

The rapid spread of the new SARS-CoV-2 variants is concerning, and more mutations are likely to arise. Vaccine teams are keen to reassure the public and politicians that the newly developed vaccines will be able to curb the virus, irrespective of the variants (Callaway, 2021), and that vaccine manufacturing will cover new variant combinations (Xie et al., 2021b). To date virtually all other variants have been driven off by the far more transmissible B.1.617.2 Delta-variant of SARS-CoV-2, which is spreading rapidly across the world. The efficacy of current vaccines against the Delta-variant is moderately good at preventing serious illness, hospitalisation and death, but its high transmissibility is of concern. However, despite reassurances, there is a clear risk that future epidemic waves may be larger, producing a greater burden of transmission, infection, serious illness and death globally. Prospective mapping of mutations during viral surveillance, may enable prediction of the consequences of mutations and allow proactive, prospective vaccine development (Starr et al., 2021).

There is very good early efficacy from new RNA and DNA-related COVID-19 vaccines, but antibody levels wane with time, and boosters will likely be needed in older groups and those in immunosuppressed 'at risk' groups.

### 4.6. *Controlling inflamm-ageing: a possible treatment approach for COVID-19 in older individuals (456)*

Inflamm-ageing, (Franceschi et al., 2000) contributes to many age-related diseases (Fig. 10) (new inflamm-ageing), and is associated with global indicators of poor health status, multimorbidity, and premature death, all factors that increase risk of serious illness from COVID-19 illness. Age-related diseases such as cardiovascular disease, hypertension and diabetes continue to be treated by clinical guidelines and drugs such as anti-hypertensives, aspirin, statins and metformin, during COVID-19, to maximise treatment of patient co-morbidities. However, inflamm-ageing related to cardiovascular disease, diabetes and a range of cancers can be modulated not only by conventional drugs and behaviour change, but by targeting cellular inflammatory pathways, to improve or modulate inflamm-ageing (Ridker et al., 2021; Christoffersen and Tybjaerg-Hansen, 2021; Ferruci et al., 2018; Ruparelia et al., 2017). Several potential mechanisms that might contribute to inflamm-ageing, include genetic susceptibility, central obesity, increased gut permeability, changes to microbiota composition, cellular senescence and SASP, NLRP3 inflammasome activation, oxidative stress, dysfunctional mitochondria, DNA damage and immune cell dysregulation (López-Otín et al., 2013; Kennedy et al., 2014), and researchers are developing re-purposed drugs to improve understanding of cellular signalling pathways involved.

#### 4.6.1. *Metformin*

Central obesity is strongly associated with a pro-inflammatory state and inflamm-ageing (Frasca et al., 2017). Metformin used in type 2 diabetes and obesity help with weight control and appetite (Sanchez-Rangel and Inzucchi, 2017), and acts at the molecular level to damp down inflamm-ageing, regulate the mitochondria and inflammasome (Barra et al., 2020), and reduce activation of the NF-κB signalling pathways. Diabetes increases risk for serious illness and death from COVID-19 (Apicella et al., 2020) and outcomes have been improved by metformin treatment (Dardano and Del Prato, 2021; Sharma et al., 2020). In a retrospective cohort analysis of hospitalised patients with obesity or type 2 diabetes presenting with COVID-19, prior metformin use, reduced mortality by 25%, but more in women compared to men (Bramante et al., 2020). Further trials are planned.

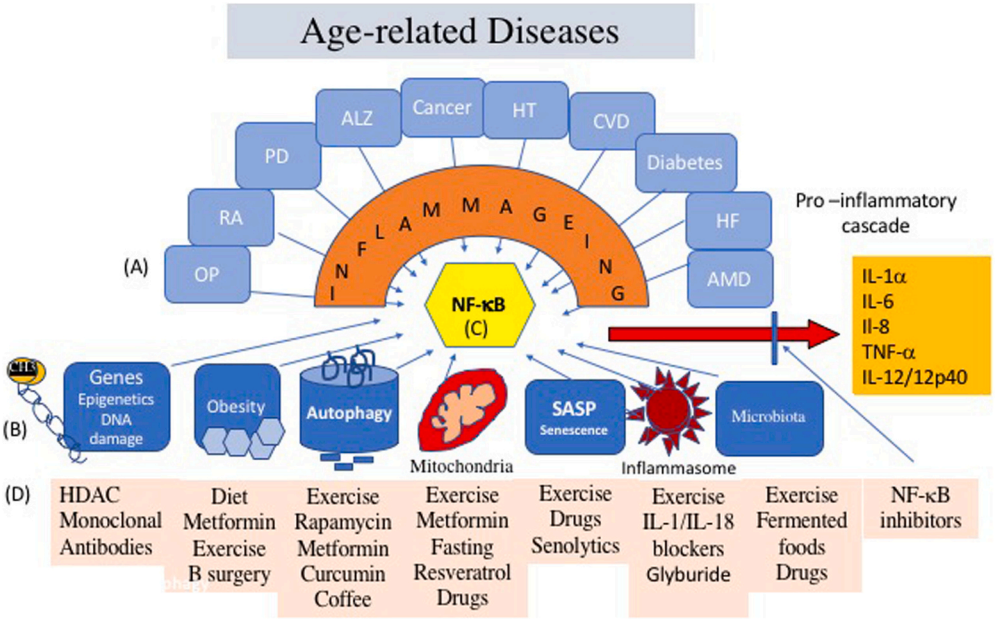


**Fig. 10.** Controlling Inflamm-ageing: a possible treatment approach for COVID-19 in older people. Multiple age-related diseases occur with increasing age. (A) Inflamm-ageing contributes to many age-related diseases for example, atherosclerosis, rheumatoid arthritis, diabetes and Alzheimer's Disease, and is associated with poor health status. (B) Several potential mechanisms that might contribute to inflamm-ageing include genetic susceptibility, central obesity, reduced autophagy, mitochondrial dysfunction, cellular senescence and SASP, inflammasome NLRP3 activation, changes to microbiota, oxidative stress, DNA damage. (C) The signalling pathways that link age-related diseases and inflamm-ageing join a common downstream signalling pathway causing NF-κB to translocate into the nucleus and resulting in activation of a low grade pro-inflammatory cytokine-related, sterile inflammation. (D) Researchers are developing re-purposed drugs and new molecules to improve understanding of the cellular pathways involved in inflamm-ageing. Evidence is becoming available as to how conventional drugs such as metformin used in diabetes and behaviour changes such as exercise, diet or episodic fasting, together with monoclonal antibodies, can be shown to reduce inflamm-ageing and improve disease management. OP, osteoporosis, RA, rheumatoid arthritis, PD, Parkinsons Disease, Alz, Alzheimers Disease, HT, hypertension, CVD, cardiovascular disease, HF, heart failure, AMD, age-related macular degeneration, HDACs, histone deacetylases, B-surgery, bariatric surgery.

#### 4.6.2. Rapamycin

Cellular senescence increases in multiple human tissues and cells with age (Gillispie et al., 2021; Rossman et al., 2017). As senescent cells accumulate, SASP develops secreting interleukins, chemokines, growth factors and metalloproteinases, that spread cellular senescence in neighbouring cells, and activate NF-κB signalling. Inhibition of the mechanistic target of rapamycin complex 1 (mTORC1) with rapamycin, has been shown to delay or reverse many age-related phenotypes, including declining immune function (Chen et al., 2009b; Baker et al., 2011, 2016). Natural senolytics are present in foods such as resveratrol in grapes, quercetin in onion and catechins in tea.

There have been calls for small doses of rapamycin to be used in the treatment of COVID-19, based on evidence from studies showing rejuvenation of the immune system and improved response to influenza vaccination (Bischof et al., 2021).

## 5. Final comments

In the new global reality of living with Covid-19 there are many unanswered questions. The new type of RNA vaccines produced by Pfizer and Moderna, Novavax and the more traditional vaccines of Oxford/Zeneca and Johnston/Janssen have produced good initial antibody results in older people but as with previous knowledge about other vaccinations, immunoprotection begins to wane early, fitting with the well-recognised weaker immune responsiveness in the oldest and frailest people (Andrew et al., 2020; McElhaney et al., 2020; Aspinall and Lang, 2018). Already, Israel, a country with high population vaccination rates has completed a third dose vaccination programme, to people as young as 50 years of age (Mizrahi et al., 2021: Wadman, 2021). A population-level study from Denmark estimated that protection against re-infection with SARS-CoV-2 fell by half in older people, compared to younger people (Hansen et al., 2021). Like the 4 other common coronaviruses in population circulation, seasonal re-exposure and re-infection seem likely to be required, to maintain immunity (Monto et al., 2020). Currently, booster doses are being considered at 12 months or earlier and given with the influenza winter inoculation. Mixing and matching two or even three vaccines, rotating primer and booster doses, adding adjuvant/s or increasing antigen dose, to improve efficacy in older aged groups, are being considered, and some are undergoing testing.

Despite the best efforts of governments, scientists and clinicians, some people will decline or be unable to be vaccinated and that includes health care staff, caring for the oldest and frailest people. Non-uptake of vaccine risks reduces population and global immunity and undermines the hope of ending the COVID-19 pandemic across the world. The unequal supply and sharing of vaccines, puts all countries at risk and could contribute to the further emergence of mutations. Successful population vaccination helps countries move towards herd immunity, but even without herd immunity, vaccination of vulnerable people seems to have reduced hospitalisations and deaths from COVID-19. Continuing with behavioural and non-pharmaceutical interventions are likely to be necessary to keep COVID-19 case numbers down, with high transmissibility of the Delta variant or any new antigenic evolution. Increased understanding of the immunology of COVID-19 illness in the older person has never been more important, and the opportunity never greater, to progress immunological knowledge and skills that are likely to benefit everyone irrespective of age. COVID-19 seems unlikely to disappear any time soon; it can only be hoped that its prominence might begin to wane with better targeted vaccines, and an improved focus on rapid equitable vaccine distribution for global control of the pandemic.

## Ethical issues

There are no ethical issues.

## Author contributions

Both HDA and IMR conceived and designed the outline of the manuscript and both authors contributed to the drafting and revising of the manuscript and its various iterations prior to approving the manuscript prior to submission.

## Conflict of interest statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be considered as a potential conflict of interest.

## Acknowledgements

IMR has received funding from EU funded LSH-2002-2.1.4-1-Genetic Factors of Longevity and Healthy Ageing, EU Socrates Erasmus Programme for Thematic Network, Interfacing Science, Literature and Humanities ACUME2 (227942-CP-1-2006-1IT-ERASMUS-TN2006-2371/001SO2-23RETH), Atlantic Philantropies, Changing Ageing Partnership Grant, Belfast Foundation Trust, United Kingdom (R9158PHM) (IMR), Wellcome Trust Project Grant, United Kingdom, (045519/Z/95/Z) (IMR), Eastern Health and Social Care Board Research Fellowship Grant Belfast, United Kingdom (IMR) and Belfast City Hospital Trust Fund, United Kingdom (Research and Education into Ageing) (0-132) (IMR). We thank all age participants recruited as part of Belfast Elderly Longitudinal Free-living Ageing Study (BELFAST), who willingly participated in the research and acknowledge the help from Dr David Gibson in the preparation of an earlier version of Fig. 9.

## References

Abdolvahab, M.H., Moradi-kalbolandi, S., Zarei, M., Bose, D., Majidzadeh-A, K., Farahmand, L., 2021. Potential role of interferons in treating COVID-19 patients. Int. Immunopharmacol. 90, 107171 https://doi.org/10.1016/j.intimp.2020.107171.

Ackermann, M., Verleden, S.E., Kuehnel, M., Haverich, A., Welte, T., Laenger, F., Vanstapel, A., Werlein, C., Stark, J., Tzankov, A., Li, William, W., Li, V.W., Mentzer, S.J., Jonigk, D., 2020. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. N. Engl. J. Med. 383, 120–128. https://doi.org/10.1056/NEJMoa2015432.

Adriaensen, W., Derhovanessian, E., Vaes, B., Van Pottelbergh, G., Degryse, J.-M., Pawelec, G., Hamprecht, K., Theeten, H., Mathei, C., 2015. CD4:8 ratio >5 is associated with a dominant naive T-cell phenotype and impaired physical functioning in CMV-seropositive very elderly people: results from the BELFRAIL study. J. Gerontol. Ser. A 70 (2), 143–154. https://doi.org/10.1093/gerona/glu018.

Aggarwal, N.R., Patel, H.N., Mehta, L.S., Sanghani, R.M., Lundberg, G.P., Lewis, S.J., Mendelson, M.A., Wood, M.J., Volgman, A.S., Mieres, J.H., 2018. Sex differences in ischemic heart disease: advances, obstacles, and next steps. Circ. Cardiovasc. Qual. Outcomes 11, e004437. https://doi.org/10.1161/CIRCOUTCOMES.117.004437.

Agrawal, A., Agrawal, S., Gupta, S., 2017. Role of dendritic cells in inflammation and loss of tolerance in the elderly. Front. Immunol. 8, 896. https://doi.org/10.3389/f.immu.2017.00896.

Agrawal, A., 2013. Mechanisms and implications of age-associated impaired innate interferon secretion by dendritic cells. A mini review. Gerontology 59, 421–426. https://doi.org/10.1159/000350536.

Akbar, A., Gilroy, D.W., 2020. Aging immunity may exacerbate COVID-19. Science 369 (6501), 256–257 doi:10.1126/science.abb0762.

Al-Beltagi, S., Preda, C.A., Goulding, L.V., James, J., Pu, J., Skinner, P., Jiang, Zhimin, Wang, B.L., Yang, J., Banyard, A.C., Mellits, K.H., Gershkovich, P., Hayes, C.J., Nguyen-Van-Tam, J., Brown, I.H., Liu, J., Chang, K.-C., 2021. Thapsigargin is a broad-spectrum inhibitor of major human respiratory viruses: coronavirus, respiratory syncytial virus and influenza A virus. Viruses 13 (2), 234. https://doi.org/10.3390/v13020234.

Al-Benna, S., 2020. Association of high-level gene expression of ACE2 in adipose tissue with mortality of COVID-19 infection in obese patients. Obes. Med. 19, 100283 https://doi.org/10.1016/j.obmed.2020.100283.

Alexander, H.D., 2021. Personal Communication.

Ali, N., 2020. Role of vitamin D in preventing of COVID-19 infection, progression and severity. J. Infect. Public Health 13, 1373–1380. https://doi.org/10.1016/j.jiph.2020.06.021.

Alqahtani, J.S., Oyelade, T., Aldhahir, A.M., Alghamdi, S.M., Almehmadi, M., Alqahtani, A.S., Quaderi, S., Mandal, S., Hurst, J.R., 2020. Prevalence, severity and mortality associated with COPD and smoking in patients with COVID-19: a rapid systematic review and meta-analysis. PLOS One 15 (5), e0233147. https://doi.org/10.1371/journal.pone.0233147.

Amit, S., Regev-Vochay, G., Afek, A., Kreiss, Y., Lesham, E., 2021. Early rate reduction of SARS-CoV-2 infection and Covid -19 in BNT162b2 vaccine recipients. Lancet 397 (10277), 875–877. https://doi.org/10.1016/S0140-6736(21)00448-7.

Anderson, E.J., Rouphael, N.G., Widge, A.T., Jackson, L.A., Roberts, P.C., Makhene, M., Chappell, J.D., Denison, M.R., Stevens, L.J., Pruijssers, A.J., Mcdermott, A.B., Flach, B., Lin, B.C., Doria-Rose, N.A., O'dell, S., Schmidt, S.D., Corbett, K.S., Swanson, P.A., Padilla, M., Neuzil, K.M., Bennett, H., Leav, B., Makowski, M., Albert, J., Cross, K., Edara, V.V., Floyd, K., Suthar, M.S., Martinez, D.R., Baric, R., Buchanan, W., Luke, C.J., Phadke, V.K., Rostad, C.A., Ledgerwood, J.E., Graham, B. S., mRNA-Study Group, mRNA-1273 Study Group, 2020. Safety and immunogenicity of SARS-CoV-2 mRNA-1273 vaccine in older adults. N. Engl. J. Med. 383, 2427–2438. https://doi.org/10.1056/NEJMoa2028436.

Andrew, M.K., McElhaney, J.E., 2020. Age and frailty in COVID-19 vaccine development. Lancet 396 (10267), 1942–1944 https://doi.org/10.1016/ S0140-6736(20)32481-8.

Aouba, A., Baldolli, A., Geffray, L., Verdon, R., Bergot, E., Martin-Silva, N., Justed, A., 2020. Targeting the inflammatory cascade with anakinra in moderate to severe COVID-19 pneumonia: case series. Ann. Rheum. Dis. 79 (10), 1381–1382. https://doi.org/10.1136/annrheumdis-2020-217706.

Apicella, M., Campopiano, M.C., Mantuano, M., Mazoni, L., Coppelli, A., Del Prato, S., 2020. COVID-19 in people with diabetes: understanding the reasons for worse outcomes. Lancet Diabetes Endocrinol. 8, 782–792. https://doi.org/10.1016/S2213-8587(20)30238-2.

Arokiaraj, M.C., 2020. Considering interim interventions to control COVID-19 associated morbidity and mortality—perspectives. Front. Public Health 8, 444. https://doi.org/10.3389/fpubh.2020.00444.

Arunachalam, P.S., Wimmers, F., Mok, C.K.P., Perera, R.A.P.M., Scott, M., Hagan, T., Sigal, N., Feng, Y., Bristow, L., Tak-Yin Tsang, O., Wagh, D., Coller, J., Pellegrini, K. L., Kazmin, D., Alaaeddine, G., Leung, W.S., Chan, J.M.C., Chik, T.S.H., Choi, C.Y.C., Huerta, C., Paine McCullough, M., Lv, H., Anderson, E., Edupuganti, S., Upadhyay, A.A., Bosinger, S.E., Maecker, H.T., Khatri, P., Rouphael, N., Peiris, M., Pulendran, B., 2020. Systems biological assessment of immunity to mild versus severe COVID-19 infection in humans. Science 369 (6508), 1210–1220. https://doi.org/10.1126/science.abc6261. Epub2020 Aug 11.

Aspinall, R., Lang, P.O., 2018. Vaccination choices for older people, looking beyond age specific approaches. Expert Rev. Vaccin. 17 (1), 23–30. https://doi.org/10.1080/14760584.2018.1411197.

Asselta, R., Paraboschi, E.M., Mantovani, A., Duga, S., 2020. ACE2 and TMPRSS2 variants and expression as candidates to sex and country differences in COVID-19 severity in Italy. Aging 12 (11), 10087–10098. https://doi.org/10.18632/aging.103415 (Albany NY).

Auerbach, J.M., Khera, M., 2021. Testosterone's role in COVID-19. J. Sex. Med. 18, 843–848. https://doi.org/10.1016/j.jsxm.2021.03.004.

Baden, L.R., Sahly, H.M., Essink, B., Kotloff, K., Frey, S., Novak, R., Diemert, D., Spector, S.A., Rouphael, N., Creech, B., McGettigan, J., Khetan, S., Segall, N., Solis, J., Brosz, A., Fierro, C., Schwartz, H., Neuzil, K., Corey, L., Gilbert, P., Janes, H., Follmann, D., Marovich, M., Mascola, J., Polakowski, L., Ledgerwood, J., Graham, B.S., Bennett, H., Pajon, R., Knightly, C., Leav, B., Deng, W., Zhou, H., Han, S., Ivarssson, M., Miller, J., Zaks, T., COVE Study Group, 2021. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N. Engl. J. Med. 384, 403–416. DOI: 10.1056/NEJMoa2035389.

Baillargeon, J., Urban, R.J., Zhang, W., Zaiden, M.F., Javed, Z., Sheffield-Moore, M., Kuo, Y.F., Sharma, G., 2019. Testosterone replacement therapy and hospitalization rates in men with COPD. Chronic Respir. Dis. 16, 1479972318793004 https://doi.org/10.1177/1479972318793004.

Baker, D., Wijshake, T., Tchkonia, T., 2011. Clearance of p16Ink4a-positive senescent cells delays ageing-associated disorders. Nature 479, 232–236. https://doi.org/10.1038/nature1060.

Baker, D.J., Childs, B.G., Durik, M., Wijers, M.E., Sieben, C.J., Zhong, J., Saltness, R.A., Jeganathan, K.B., Verzosa, G.C., Pezeshki, A., Khazaie, K., Miller, J.D., van Deursen, J.M., 2016. Naturally occurring p16Ink4a-positive cells shorten healthy lifespan. Nature 530, 184–189. https://doi.org/10.1038/nature16932.

Baktash, V., Hosack, T., Patel, N., Shah, S., Kandiah, P., Van den Abbeele, K., Mandal, A. K.J., Missouris, C.G., 2020. Vitamin D status and outcomes for hospitalised older patients with COVID-19. Postgrad. Med. J. 97, 442–447. https://doi.org/10.1136/postgradmedj-2020-138712.

Barra, N.G., Henriksbo, B.D., Anhê, F.F., Schertzer, J.D., 2020. The NLRP3 inflammasome regulates adipose tissue metabolism. Biochem. J. 477 (6), 1089–1107. https://doi.org/10.1042/BCJ20190472.

Bastard, P., Rosen, L.B., Zhang, Q., Michailidis, E., Hoffman, H.-H., Zhang, Y., Dorgham, K., 2020. Auto-antibodies against type I IFNs in patients with life-threatening COVID-19. Science 370, 6515. https://doi.org/10.1126/science.abd4585 eabd4585.

Batsis, J.A., Mackenzie, T.A., Jones, J.D., Lopez-Jimenez, F., Bartels, S.J., 2016. Sarcopenia, sarcopenic obesity and inflammation: results from the 1999-2004 National Health and Nutrition Examination Survey. Clin. Nutr. 35 (6), 1472–1483. https://doi.org/10.1016/j.clnu.2016.03.028.

Baum, A., Ajithdoss, D., Copin, R., Zhou, A., Lanza, K., Negron, N., Ni, M., Wei, Y., Mohammadi, K., Musser, B., Atwal, G.S., Oyejide, A., Goez-Gazi, Y., Dutton, J., Clemmons, E., Staples, H.M., Bartley, C., Klaffke, B., Afson, K., Gazi, M., Gonzalez, O., Dick Jr, E., Carrion Jr, R., Pessaint, L., Porto, M., Cook, A., Brown, R., Ali, V., Greenhouse, J., Taylor, R., Andersen, T., Lewis, M.G., Stahl, N., Murphy, A.J., Yancopoulos, G.D., Kyratsous, C.A., 2020. REGN-COV2 antibodies prevent and treat SARS-CoV-2 infection in rhesus macaques and hamsters. Science 1110–1115. https://doi.org/10.1126/science.abe2402.

Beigel, J.H., Tomashek, K.M., Dodd, L.E., Metha, A.K., Zingman, B.S., Kalil, A.C., 2020. Remdesivir for the treatment of Covid-19 — final report. N. Engl. J. Med. 383, 1813–1826. https://doi.org/10.1056/NEJMoa2007764.

Benn, C.S., Roth, A., Garly, M.-L., Fisker, A.B., Schaltz-Buchholzer, F., Timmermann, A., Berendsen, M., Aaby, P., 2020. BCG scarring and improved child survival: a combined analysis of studies of BCG scarring. J. Int. Med. 288 (6), 614–624. https://doi.org/10.1111/joim.13084.

Bereshchencko, O., Bruscoli, S., Ricardo, C., 2018. Glucocorticoids, sex hormones and immunity. Front. Immunol. 9 https://doi.org/10.3389/fimmu.2018.01332.

Bergwerk, M., Gonen, T., Lustig, Y., Amit, S., Lipsitch, M., Cohen, C., Mandelboim, M., Levin, E.G., Rubin, C., Indenbaum, V., Tal, I., Zavitan, M., Zuckerman, N., Bar-Chaim, A., Kreiss, Y., Regev-Yochay, G., 2021. COVID-19 breakthrough infections in vaccinated health care workers. N. Engl. J. Med. 385, 1474–1484. https://doi.org/10.1056/NEJMoa2109072.

Biering-Sørensen, S., Aaby, P., Lund, N., Monteiro, I., Jensen, K.J., Eriksen, H.B., Schaltz-Buchholzer, F., Jørgensen, A., Rodrigues, A., Fisker, A.B., Benn, C.S., 2017. Early BCG-Denmark and neonatal mortality among infants weighing <2500 g: a randomized controlled trial. Clin. Infect. Dis. 65, 1183–1190. https://doi.org/10.1093/cid/cix525.

Bischof, E., Siow, R.C., Zhavoronkov, A., Kaeberlein, M., 2021. The potential of rapalogs to enhance resilience against SARS-CoV-2 infection and reduce severity of COVID-19. Lancet Healthy Longev. 2 (2), E105–E111. https://doi.org/10.1016/S2666-7568(20)30068-4.

Blanco, E., Perez-Andres, M., Arriba-Mendez, S., Contreras-Sanfeliciano, T., Criado, I., Pelak, O., Serra-Caetano, A., Romero, A., Puig, N., Remesal, A., Canizales, J.T., Lopez-Granados, E., Kalina, T., Sousa, A.E., van Zeim, M., van der Burg, M., van Dongen, J.J., Orfao, A., EuroFlow PID Group, 2018. Age-associated distribution of normal B-cell and plasma cell subsets in peripheral blood. J. Allergy Clin. Immunol. 141 (6), 2208–2219. https://doi.org/10.1016/j.jaci.2018.02.017 e16.

Blanco-Melo, D., Nilsson-Payant, B.E., Liu, W.C., Uhl, S., Hoagland, D., Møller, R., Jordan, T.X., Oishi, K., Panis, M., Sachs, D., Wang, T.T., Schwartz, R.E., Lim, J.K., Albrecht, R.A., tenOever, B.R., 2020. Imbalanced host response to SARS-CoV-2 drives development of COVID-19. Cell 181 (5), 1036–1045. https://doi.org/10.1016/j.cell.2020.04.026 e9.

Bonafè, M., Prattichizzo, F., Giuliani, A., Storci, G., Sabbatinelli, J., Olivieri, F., 2020. Inflamm-aging: why older men are the most susceptible to SARS-CoV-2 complicated outcomes. Cytokine Growth Factor Rev. 53, 33–37. https://doi.org/10.1016/j.cytogfr.2020.04.005.

Bonow, R.O., Fonarow, G.C., O'Gara, P.T., Yancy, C.W., 2020. Association of coronavirus disease 2019 (COVID-19) with myocardial injury and mortality. JAMA Cardiol. 5 (7), 751–753. https://doi.org/10.1001/jamacardio.2020.1105.

Bosso, M., Thanaraj, T.A., Abu-Farha, M., Alanbaei, M., Abubaker, J., Al-Mulla, F., 2020. The two faces of ACE2: the role of ACE2 receptor and its polymorphisms in hypertension and Covid-19. Mol. Ther. Methods Clin. Dev. 18, 321–327. https://doi.org/10.1016/j.omtm.2020.06.017.

Bramante, C.T., Buse, J., Tamaritz, L., Palacio, A., Cohen, K., Vojta, D., Liebovitz, D., Mitchell, N., Nicklas, J., Lingvay, I., Clark, J.M., Aronne, L.J., Anderson, E., Usher, M., Demmer, R., Melton, G.B., Ingraham, N., Tignanelli, C.J., 2020. Outpatient metformin use is associated with reduced severity of COVID-19 disease in adults with overweight or obesity. J. Med. Virol. 93, 4273–4279.

Brandenberger, C., Yazicioglu, T., Autilio, C., Huang, C., Bär, C., Thum, T., Perez-Gil, J., Schmiedl, A., Mühlfeld, C., 2018. Aging causes alveolar epithelial type II (AT11) cell dysfunction in acute lung injury with a reduction in AT11 cell number and an increase in stress-related senescence marker p16 in old compared to young mice. Am. J. Respir. Crit. Care Med. 197, A4632.

Braun, J., Loyal, L., Frentsch, M., Wendisch, D., Georg, P., Kurth, F., Hippenstiel, S., Dingeldey, M., Kruse, B., Fauchere, F., Baysal, E., Mangold, M., Henze, L., Lauster, R., Mall, M.A., Beyer, K., Rohmel, J., Voigt, S., Schmitz, J., Miltenyi, S., Demuth, I., Muller, M.A., Hocke, A., Witzenrath, M., Suttorp, N., Kern, F., Reimer, U., Wenschuh, H., Droster, C., Corman, V.M., Giesecke-Thiel, C., Sander, L. E., Thiel, A., 2020. SARS-CoV-2-reactive T cells in healthy donors and patients with COVID-19. Nature 587, 270–274. https://doi.org/10.1038/s41586-020-2598-9.

Brooks, L., Mias, G., 2018. Streptococcus pneumoniae's virulence and host immunity: aging, diagnostics, and prevention. Front. Immunol. 9, 1366. https://doi.org/10.3389/fimmu.2018.01366.

Bscheider, M., Butcher, E.C., 2016. Vitamin D immunoregulation through dendritic cells. Immunology 148 (3), 227–236. https://doi.org/10.1111/imm.12610.

Byrne, A.J., Mathie, S.A., Gregory, L.G., Lloyd, C.M., 2015. Pulmonary macrophages: key players in the innate defence of the airways. Thorax 70, 1189–1196. https://doi.org/10.1136/thoraxjnl-2015-207020.

Calabrese, E.J., 2016. Preconditioning is hormesis part II: How the conditioning dose mediates protection: dose optimization within temporal and mechanistic framework. Pharmacol. Res. 110, 265–275. https://doi.org/10.1016/j.phrs.2015.12.020.

Callaway, E., 2021. Could new COVID variant undermine vaccines? Labs scramble to find out. Nature 589, 177–178. https://doi.org/10.1038/d41586-021-00031-0.

Cao, Y., Li, L., Feng, Z., Wan, S., Huang, P., Sun, X., Wen, F., Huang, X., Ning, G., Wang, W., 2020a. Comparative genetic analysis of the novel coronavirus (2019-nCoV/SARS-CoV-2) receptor ACE2 in different populations. Cell Discov. 6, 11. https://doi.org/10.1038/s41421-020-0147-1.

Cao, B., Wang, Y., Wen, D., Liu, W., Wang, J., Fan, G., Ruan, L., Song, B., Cai, Y., Wei, M., Li, X., Xia, J., Chen, N., Xiang, J., Yu, T., Bai, T., Xie, X., Zhang, L., Li, C., Luan, Y., Chen, H., Li, H., Huang, H., Tu, S., Gong, F., Liu, Y., Wei, Y., Dong, C., Zhou, F., Gu, X., Xu, J., Liu, Z., Zhang, Y., Li, H., Shang, L., Wang, K., Li, K., Zhou, X., Dong, X., Qu, Z., Lu, S., Hu, X., Ruan, S., Luo, S., Wu, J., Peng, L., Cheng, F., Pan, L., Zou, J., Jia, C., Wang, J., Liu, X., Wang, S., Wu, X., Ge, Q., He, J., Zhan, H., Qui, F., Guo, L., Huang, C., Jaki, T., Hayden, F.G., Horby, P.W., Zhang, D., Wang, C., 2020b. A trial of

lopinavir–ritonavir in adults hospitalized with severe COVID-19. N. Engl. J. Med. 382, 1787–1799. DOI:10.1056/NEJMoa2001282.
Casanova, J.L., Su, H.C., 2020. A global effort to define the human genetics of protective immunity to SARS-CoV-2 infection. Cell 181 (6), 1194–1199. https://doi.org/10.1016/j.cell.2020.05.016.
Cavalli, G., Dagna, L., 2021. The right place for IL-1 inhibition in COVID-19. Lancet Respir. Med. 9 (3), 223–224. https://doi.org/10.1016/S2213-2600(21)00035-7.
Chambers, E.S., Vukmanovic-Stejic, M., Turner, C.T., Shih, B.B., Trahair, H., Pollara, G., Tsaliki, E., Rustin, M., Freeman, T.C., Mabbott, N.A., Noursadeghi, M., Martineau, A. R., Akbar, A.N., 2021. Vitamin D3 replacement enhances antigen-specific immunity in older adults. Immunother. Adv. 1 (1), ltaa008. https://doi.org/10.1093/immadv/ltaa008.
Channappanavar, R., Perlman, S., 2017. Pathogenic human coronavirus infections; causes and consequences of cytokine storm and immunopathology. Semin. Immunopathol. 39 (5), 529–539. https://doi.org/10.1007/s00281-017-0629-x.
Chen, G.-Y., Tang, J., Zheng, P., Liu, Y., 2009a. CD24 and Siglec-10 selectively repress tissue damage-induced immune responses. Science 323 (5922), 1722–1725. https://doi.org/10.1126/science.1168988.
Chen, C., Liu, Y., Liu, Y., Zheng, P., 2009b. mTOR regulation and therapeutic rejuvenation of aging haematopoietic stem cells. Sci. Signal. 2 (98), ra75. https://doi.org/10.1126/scisignal.2000559.
Chen, G., Wu, D., Guo, W., Cao, Y., Huang, D., Wang, H., Wang, T., Zhang, X., Chen, H., Yu, H., Zhang, X., Zhang, M., Wu, S., Song, J., Chen, T., Han, M., Li, S., Luo, X., Zhao, J., Ning, Q., 2020a. Clinical and immunological features of severe and moderate coronavirus disease 2019. J. Clin. Investig. 130 (5), 2620–2629. https://doi.org/10.1172/JCI137244.
Chen, X., Pan, Z., Yue, S., Yu, F., Zhang, J., Yang, Y., Li, R., Liu, B., Yang, X., Gao, L., Li, Z., Lin, Y., Huang, Q., Xu, L., Tang, J., Hu, L., Zhao, J., Liu, P., Zhang, G., Chen, Y., Deng, K., Ye, L., 2020b. Disease severity dictates SARS-CoV-2-specific neutralizing antibody responses in COVID-19. Signal Transduct. Target. Ther. 5, 180. https://doi.org/10.1038/s41392-020-00301-9.
Chen, J., Jiang, Q., Xia, X., Liu, K., Yu, Z., Tao, W., Gong, W., Han, J.-D.J., 2020c. Individual variation of the SARS-CoV-2 receptor ACE2 gene expression and regulation. Ageing Cell 19 (7), ee13168. https://doi.org/10.1111/acel.13168.
Chen, P., Nirula, A., Heller, B., Gottlieb, R.L., Boscia, J., Morris, J., Huhn, G., Cardona, J., Mocherla, B., Stosor, V., Shawa, I., Adams, A.C., Van Naarden, J., Custer, K.L., Shen, L., Durante, M., Oakley, G., Schade, A.E., Sabo, J., Patel, D.R., Klekotka, P., Skovronsky, D.M., BLAZE-1 Investigators, 2021. SARS-CoV-2 neutralizing antibody LY-CoV555 in outpatients with Covid-19. N. Engl. J. Med. 384, 229–237. https://doi.org/10.1056/NEJMoa2029849.
Christoffersen, M., Tybjaerg-Hansen, A., 2021. Targeting IL-6 in patient at high cardiovascular risk. Lancet 397 (10289), 2025–2027. https://doi.org/10.1016/S0140-6736(21)00985-5.
Cicco, S., Cicco, G., Racenelli, V., Vacca, A., 2020. Neutrophil extracellular traps (NETs) and damage-associated molecular patterns (DAMPs): two potential targets for COVID-19 treatment. Mediat. Inflamm. 2020, 1–25. https://doi.org/10.1155/2020/7527953, 7527953.
Cisneros, E., Moraru, M., Gomez-Lozano, N., Muntasell, A., Lopez-Botet, M., Vilches, C., 2020. Haplotype-based analysis of KIR-gene profiles in a South European population—distribution of standard and variant haplotypes, and identification of novel recombinant structures. Front. Immunol. 11, 440. https://doi.org/10.3389/fimmu.2020.00440.
Clerkin, K.J., Fried, J.A., Raikhelkar, J., Sayer, G., Griffin, J.M., Masoumi, A., Jain, S.S., Burkhoff, D., Kumaraiah, D., Rabbani, L., Schwartz, A., Uriel, N., 2019. COVID-19 and cardiovascular disease. Circulation 141 (20), 1648–1655. https://doi.org/10.1161/CIRCULATIONAHA.120.046941.
Conti, P., Ronconi, G., Caraffa, A., Gallenga, C.E., Ross, R., Frydas, I., Kritas, S.K., 2020a. Induction of pro-inflammatory cytokines (IL-1 and IL-6) and lung inflammation by coronavirus-19 (Covid 19 or SARs-Cov-2) anti-inflammatory strategies. J. Biol. Regul. Homeost. Agents 34 (2), 327–333. https://doi.org/10.23812/CONTI-E.
Conti, P., Gallenga, C.E., Tetè, G., Caraffe, A., Ronconi, G., Younes, A., Toniato, E., Ross, R., Kritas, S.K., 2020b. How to reduce the likelihood of coronavirus-19 (CoV-19 or SARS- CoV-2) infection and lung inflammation mediated by IL-1. J. Biol. Regul. Homeost. Agents 34 (2), 333–338. https://doi.org/10.23812/Editorial-Conti-2.
The COVID-19 Host Genetics Initiative, 2020a. The COVID-19 host genetics initiative, a global initiative to elucidate the role of host genetic factors in susceptibility and severity of the SARS-COV-2 virus epidemic. Eur. J. Hum. Genet. 28, 715–718. https://doi.org/10.1038/s41431020-0636-6.
Cunha, L.L., Perazzio, S.F., Azzi, J., Cravedi, P., Riella, L.V., 2020. Remodeling of the immune response with aging: immunosenescence and its potential impact on COVID-19 immune response. Front. Immunol. 11, 1748. https://doi.org/10.3389/fimmu.2020.01748.
Dan, J.M., Mateus, J., Kato, Y., Hastie, K.M., Yu, E.D., Faliti, C.E., Grifoni, A., Ramirez, S. I., Haupt, S., Frazier, A., Nakao, C., Rayaprolu, V., Rawlings, S.A., Peters, B., Krammer, F., Simon, V., Saphire, E.O., Smith, D.M., Weiskopf, D., Sette, A., Crotty, S., 2021. Immunological memory to SARS-CoV-2 assessed for up to 8 months after infection. Science 371, 6529 eabf4063 DOI:10.1126/science.abf4063.
Dagan, N., Barda, N., Kepten, E., Miron, O., Perchik, S., Katz, M.A., Hernan, M.A., Lipsitch, M., Reis, B., Balicer, R.D., 2021. BNT162b2 mRNA Covid-19 vaccine in a nationwide mass vaccination setting. N. Engl. J. Med. 384, 1412–1423. February 24, 2021; NEJMoa2101765. doi:10.1056/NEJMoa2101765.
Daly, J.L., Simonetti, B., Klein, K., Chen, K.-E., Williamson, M.K., Antón-Plágaro, C., Shoemark, D.K., Simon-Gracia, L., Bauer, M., Hollandi, R., Greber, U.F., Horvath, P., Sessions, R.B., Helenius, A., Hiscox, J.A., Teesalu, T., Matthews, D.A., Davidson, A. D., Collins, B.M., Cullen, P.J., Yamauchi, Y., 2020. Neuropilin-1 is a host factor for SARS-CoV2 infection. Science 370 (6518), 861–865. https://doi.org/10.1126/science.abd3072.
Daneshkhah, A., Agrawal, V., Eschein, A., Subramanian, H., Roy, H.K., Backman, V., 2020. Evidence for possible association of vitamin D status with cytokine storm and unregulated inflammation in COVID-19 patients. Aging Clin. Exp. Res. 32, 2141–2158. https://doi.org/10.1007/s40520-020-01677-y.
Dardano, A., Del Prato, S., 2021. Metformin, an inexpensive and effective treatment of people with diabetes and COVID-19? Lancet Healthy Longev. 2 (1), E6–E7. https://doi.org/10.1016/S2666-7568(20)30047-7.
De Biasi, S., Meschiari, M., Gibellini, L., Bellinazzi, C., Borella, R., Fidanza, L., Gozzi, L., Iannone, A., Lo Tartaro, D., Mattioli, M., Paolini, A., Menozzi, M., Milić, J., Franceschi, G., Fantini, R., Tonelli, R., Sita, M., Sarti, M., Trenti, T., Brugioni, L., Cicchetti, L., Facchinetti, F., Pietrangelo, A., Clini, E., Girardis, M., Guaraldi, G., Mussini, C., Cossarizza, A., 2020. Marked T cell activation, senescence, exhaustion and skewing towards TH17 in patients with COVID-19 pneumonia. Nat. Commun. 11, 3434. https://doi.org/10.1038/s41467-020-17292-4.
De Francesco, E.M., Vella, V., Belfiore, A., 2020. COVID-19 and diabetes: the importance of controlling RAGE. Front. Endocrinol. 11, 526. https://doi.org/10.3389/fendo.2020.00526 (Lausanne).
Dehingia, N., Raj, A., 2021. Sex differences in COVID-19 case fatality; do we know enough? Lancet Glob. Health 9 (1), E14–E15. https://doi.org/10.1016/S2214-109X(20)30464-2.
Derhovanessian, E., Maier, A.B., Hähnel, K., Zelba, H., de Craen, A.J., Roelofs, H., Slagboom, E.P., Westendorp, R.G., Pawelec, G., 2013. Lower proportion of naïve peripheral CD8+ T cells and an unopposed pro-inflammatory response to human Cytomegalovirus proteins in vitro are associated with longer survival in very elderly people. Age 35 (4), 1387–1399. https://doi.org/10.1007/s11357-012-9425-7 (Dordr.).
Diao, B., Wang, C., Tan, Y., Chen, X., Liu, Y., Ning, L., Chen, L., Li, M., Liu, Y., Wang, G., Yuan, Z., Feng, Z., Zhang, Y., Wu, Y., Chen, Y., 2020. Reduction and functional exhaustion of T cells in patients with coronavirus disease 2019 (COVID-19). Front. Immunol. 11, 827. https://doi.org/10.3389/fimmu.2020.00827.
Di Bona, D., Vasto, S., Capurso, C., Christiansen, L., Deiana, L., Franceschi, C., Hurme, M., Mocchegiani, E., Rea, M., Lio, D., Candore, G., Caruso, C., 2009. Effect of interleukin-6 polymorphisms on human longevity: a systematic review and meta-analysis. Ageing Res. Rev. 8 (1), 36–42. https://doi.org/10.1016/j.arr.2008.09.001.
Di Genova, G., Roddick, J., McNicholl, F., Stevenson, F.K., 2006. Vaccination of human subjects expands both specific and bystander memory T cells but antibody production remains vaccine specific. Blood 107 (7), 2806–2813. https://doi.org/10.1182/blood-2005-08-3255.
Di Genova, G., Savelyeva, N., Suchacki, A., Thirdborough, S.M., Stevenson, F.K., 2010. Bystander stimulation of activated CD4+ T cells of unrelated specificity following a booster vaccination with tetanus toxoid. Eur. J. Immunol. 40, 976–985. https://doi.org/10.1002/eji.200940017.
Djennad, A., Ramsay, M.E., Pebody, R., Fry, N.K., Sheppard, C., Ladhani, S.N., Andrews, N.J., 2018. Effectiveness of 23-valent polysaccharide vaccine and changes in invasive pneumococcal incidence from 2000-2017 in those aged 65 and over in England and Wales. ECinicalMedicine 6, 42–50. https://doi.org/10.1016/j.eclinm.2018.12.007.
Doria-Rose, N., Suthar, M.S., Makowski, M., O'Connell, S., McDermott, A.B., Flach, B., Ledgerwood, J.E., Mascola, J.R., Graham, B.S., Lin, B.C., O'Dell, S., Schmidt, S.D., Widge, A.T., Edara, V.V., Anderson, E.J., Lai, L., Floyd, K., Rouphael, N.G., Zarnitsyna, V., Roberts, P.C., Makhene, M., Buchanan, W., Luke, C.J., Beigel, J.H., Jackson, L.A., Neuzil, K.M., Bennett, H., Leav, B., Albert, J., Kunwar, P., mRNA-Study Group, 2021. Antibody persistence through 6 months after the second dose of mRNA-1273 vaccine for COVID-19. N. Engl. J. Med 384, 2259–2261. https://doi.org/10.1056/NEJMc2103916.
Du, R.H., Liang, L.R., Yang, C.Q., Wang, W., Cao, T.Z., Li, M., Guo, G.Y., Du, J., Zheng, C. L., Zhu, Q., Hu, M., Li, X.Y., Peng, P., Shi, H.Z., 2020. Predictors of mortality for patients with COVID-19 pneumonia caused by SARSCoV- 2: a prospective cohort study. Eur. Respir. J. 55, 2000524 https://doi.org/10.1183/13993003.00524-2020.
Duan, K., Liu, B., Li, C., Zhang, H., Yu, T., Qu, J., Zhou, M., Chen, L., Meng, S., Hu, Y., Peng, C., Yuan, M., Huang, J., Wang, Z., Yu, J., Gao, X., Wang, D., Yu, X., Li, L., Zhang, J., Wu, X., Li, B., Xu, Y., Chen, W., Peng, Y., Hu, Y., Lin, L., Liu, X., Huang, S., Zhou, Z., Zhang, L., Wang, Y., Zhang, Z., Deng, K., Xia, Z., Gong, Q., Zhang, W., Zheng, X., Liu, Y., Yang, H., Zhou, D., Yu, D., Hou, J., Shi, Z., Chen, S., Chen, Z., Zhang, X., Yang, X., 2020. Effectiveness of convalescent plasma therapy in severe COVID-19 patients. Proc. Natl. Acad. Sci. USA 117 (17), 9490–9496. https://doi.org/10.1073/pnas.2004168117.
Dunn-Walters, D.K., Ademokun, A.A., 2010. B cell repertoire and ageing. Curr. Opin. Immunol. 22 (4), 514–520. https://doi.org/10.1016/j.coi.2010.04.009.
Dutra, M.T., Avelar, B.P., Souza, V.C., Bottaro, M., Oliveira, R.J., Nóbrega, O.T., Lima, R. M., 2017. Relationship between sarcopenic obesity-related phenotypes and inflammatory markers in postmenopausal women. Clin. Physiol. Funct. Imaging 37 (2), 205–210. https://doi.org/10.1111/cpf.12287.
El Khoudary, S.R., Aggarwal, B., Beckie, T.M., Hodis, H.N., Johnson, A.E., Langer, R.D., Limacher, M.C., Manson, J.E., Stefanick, M.L., Allison, M.A., American Heart Association Prevention Science Committee of the Council on Epidemiology and Prevention, Council on Cardiovascular and Stroke Nursing, 2020. Menopause transition and cardiovascular disease risk: implications for timing of early prevention: a scientific statement from the American Heart Association. Circulation 2020 (142), e506–e532. https://doi.org/10.1161/CIR.0000000000000912.
Evans, A.E., Poirier, O., Kee, F., Lecerf, L., McCrum, E., Falconer, T., Crane, J., O'Rourke, D.F., Cambien, F., 1994. Polymorphisms of the angiotensin-converting-enzyme gene in subjects who die from coronary heart disease. Q. J. Med. 87 (4), 211–214.

Fajgenbaum, D.C., June, C.H., 2020. Cytokine storm. N. Engl. J. Med. 383 (23), 2255–2271. https://doi.org/10.1056/NEHMra2026131.
Fang, L., Karakiulakis, G., Roth, M., 2020. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? Lancet Respir. Med. 8 (4), e21. https://doi.org/10.1016/s2213-2600(20)30116-8.
Feng, Z., Diao, B., Wang, R., Wang, G., Wang, C., Tan, Y., Liu, L., Wang, C., Liu, Y., Liu, Y., Yuan, Z., Ren, L., Wu, Y., Chen, Y., 2020. The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) directly decimates human spleens and lymph nodes. medRxiv. https://doi.org/10.1101/2020.03.27.20045427. Posted March 31, 2020. Preprint.
Ferlazzo, G., Moretta, L., 2014. Dendritic cell editing by natural killer cells. Crit. Rev. Oncog. 19 (1–2), 67–75. https://doi.org/10.1615/critrevoncog.2014010827.
Ferrucci, L., Fabbri, E., 2018. Inflammageing: chronic inflammation in ageing, cardiovascular disease, and frailty. Nat. Rev. Cardiol. 15 (9), 505–522. https://doi.org/10.1038/s41569-018-0064-2.
Folegetti, P.M., Ewer, K.J., Aley, P.K., Angus, B., Becker, S., Belij-Rammerstorfer, S., Bellamy, D., Bibi, S., Bittaye, M., Clutterbuck, E.A., Dold, C., Faust, S.N., Finn, A., Flaxman, A.L., Hallis, B., Heath, P., Jenkin, D., Lazarus, R., Makinson, R., Minassian, A.M., Pollock, K.M., Ramasamy, Robinsoon, Snape, H., Tarrant, S., Voysey, R., Green, M., Douglas, C., Hill, A.D., Lambe, V.S., Gilbert, T., Pollard, S.C., Oxford, A.J., Vaccine Trial Group, COVID, 2020. Safety and immunogenicity of the ChAdOx1nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2 single-blind, randomised controlled trial. Lancet 396 (10249), 467–478. https://doi.org/10.1016/S0140-6736(20)31604-4.
Forsey, R.J., Thompson, J.M., Ernerudh, J., Hurst, T.L., Strindhall, J., Johansson, B., Nilsson, B.-O., Wikby, A., 2003. Plasma cytokine profiles in elderly humans. Mech. Ageing Dev. 124 (4), 487–493. https://doi.org/10.1016/S0047-6374(03)00025-3.
Franceschi, C., Bonafè, M., Valensin, S., Olivieri, F., De Luca, M., Ottaviani, E., De Benedictis, G., 2000. Inflamm-aging. An evolutionary perspective on immunosenescence. Ann. N. Y. Acad. Sci. 908, 244–254. https://doi.org/10.1111/j.1749-6632.2000.tb06651.x.
Franceschi, C., Capri, M., Monti, D., Giunta, S., Olivieri, F., Sevini, F., Panourgia, M.P., Invidia, L., Celani, L., Scurti, M., Cevenini, E., Castellani, G.C., Salvioli, S., 2007. Inflammaging and anti-inflammaging: a systemic perspective on aging and longevity emerged from studies in humans. Mech. Ageing Dev. 128 (1), 92–105. https://doi.org/10.1016/j.mad.2006.11.016.
Franceschi, C., Campisi, J., 2014. Chronic inflammation (inflammaging) and its potential contribution to age-associated diseases. J. Gerontol. A Biol. Sci. Med. Sci. 69 (Suppl. 1), S4–S9. https://doi.org/10.1093/gerona/glu057.
Franceschi, C., Salvioli, S., Garagnani, P., de Equileor, M., Monti, D., Capri, M., 2017. Immunobiography and the heterogeneity of immune responses in the elderly: a focus on inflammaging and trained immunity. Front. Immunol. 8, 982. https://doi.org/10.3389/fimmu.2017.00982.
Francois, B., Jeannet, R., Daix, T., Walton, A.H., Shotwell, M.S., Unsinger, J., Monneret, G., Rimmele, T., Blood, T., Morre, M., Gregoire, A., Mayo, G.A., Blood, J., Durum, S.K., Sherwood, E.R., Hotchkiss, R.S., 2018. Interleukin-7 restores lymphocytes in septic shock: the IRIS-7 randomized clinical trial. JCI Insight 3 (5), e98960. https://doi.org/10.1172/jci.insight.98960.
Frasca, D., Diaz, A., Romero, M., Landin, A.M., Blomberg, B.B., 2011. Age effects on B cells and humoral immunity in humans. Ageing Res. Rev. 10 (3), 330–335. https://doi.org/10.1016/j.arr.2010.08.004.
Frasca, D., Blomberg, B.B., Paganelli, R., 2017. Aging, obesity, and inflammatory age-related diseases. Front. Immunol. 8, 1745. https://doi.org/10.3389/fimmu.2017.01745.
Fu, W., Liu, Y., Liu, L., Hu, H., Cheng, X., Liu, P., Song, Z., Zha, L., Bai, S., Xu, T., Yuan, S., Lu, F., Shang, Z., Zhao, Y., Wang, J., Zhao, J., Ding, L., Chen, J., Zhang, L., Zhu, T., Zhang, X., Lu, H., Xu, J., 2020. An open-label, randomized trial of the combination of IFN-γ plus TFF2 with standard care in the treatment of patients with moderate COVID-19. EClinicalMedicine 27 (100547), 100547. https://doi.org/10.1016/j.eclinm.2020.100547.
Gaebler, C., Wang, Z., Lorenzi, J.C.C., Muecksch, F., Finkin, S., Tokuyama, M., Cho, A., Jankovic, M., Schaefer-Babajew, D., Oliveira, T.Y., Cipolla, M., Viant, C., Barnes, C. O., Bram, Y., Breton, G., Hägglöf, T., Mendoza, P., Hurley, A., Turroja, M., Gordon, K., Millard, K.G., Ramos, V., Schmidt, F., Weisblum, Y., Jha, D., Tankelevich, M., Martinez-Delgado, G., Yee, J., Patel, R., Dizon, J., Unson-O'Brien, C., Shimeliovich, I., Robbiani, D.F., Zhao, Z., Gazumyan, A., Schwartz, R.E., Hatziioannou, T., Bjorkman, P.J., Mehandru, S., Bieniasz, P.D., Caskey, M., Nussenzweig, M.C., 2021. Evolution of antibody immunity to SARS-CoV-2. Nature 591, 639–644. https://doi.org/10.1038/s41586-021-03207-w.
GBD 2015 Tobacco Collaborators, 2017. Smoking prevalence and attributable disease burden in 195 countries and territories, 1990–2015: a systematic analysis from the Global Burden of Disease Study 2015; GBD 2015 Tobacco Collaborators. Lancet 389 (10082), 1885–1906. https://doi.org/10.1016/S0140-6736(17)30819-X.
Gebhard, C., Regitz-Zagrosek, V., Neuhauser, H.K., Morgan, R., Klein, S.L., 2020. Impact of sex and gender on COVID-19 outcomes in Europe. Biol. Sex Differ. 11, 29. https://doi.org/10.1186/s13293-020-00304-.
Gemmati, D., Bramanti, B., Serino, M.L., Secchiero, P., Zauli, G., Tisato, V., 2020. COVID-19 and individual genetic susceptibility/receptivity: role of ACE1/ACE2 genes, immunity, inflammation and coagulation. Might the double X-chromosome in females be protective against SARS-CoV-2 compared to the single X-chromosome in male? Int. J. Mol. Sci. 21 (10), 3474, 10.3390/ijms21103474.
Giamarellos-Bourboulis, E.J., Netea, M.G., Rovina, N., Akinosoglou, K., Antoniadou, A., Antonakos, N., Damoraki, G., Gkavogianni, T., Adami, M.-E., Katsaounou, P., 2020a. Complex immune dysregulation in COVID-19 patients with severe respiratory failure. Cell Host Microbe 2020 (27), 992–1000 e3.
Giamarellos-Bourboulis, E., Tsilika, M., Moorlag, S., Antonakos, N., Kotsaki, A., Dominguez-Andres, J., Kriazopoulou, E., Gkavogianni, T., Adami, M.-E., Damoraki, G., Koufargyris, P., Karageorgos, A., Bolanou, A., Koenen, H., van Crevel, R., Droggiti, D.-I., Renieris, G., Papadopoulos, A., Netea, M.M., 2020b. Activate: randomized clinical trial of BCG vaccination against infection in the elderly. Cell 183 (2), 315–323. https://doi.org/10.1016/j.cell.2020.08.051 e9.
Gillispie, G.J., Sah, E., Krishnamurthy, S., Ahmidouch, M.Y., Zhang, B., Orr, M.E., 2021. Evidence of the cellular senescence stress response in mitotically active brain cells—implications for cancer and neurodegeneration. Life 11 (2), 153. https://doi.org/10.3390/life11020153.
Global Burden of Disease 2019 Factors Collaborators, 2020. Global burden of 87 risk factors in 204 countries and territories, 1999-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet 396 (10258), 223–1249. https://doi.org/10.1016/S0140-6736(20)30752-2.
Golestaneh, L., Neugarten, J., Fisher, M., Billet, H.H., Gil, M.R., Johns, T., Yunes, M., Mokrzycki, M.H., Coco, M., Norris, K.C., Perez, H.R., Scott, S., Kim, R.S., Belin, E., 2020. The association of race and Covid-19 mortality. EClinicalMedicine 25 (100455). https://doi.org/10.1016/j.eclinm.2020.100455.
Golpen, N.P., Cheon, I.S., Sun, J., 2021. Age-related dynamics of lung-resident memory CD8+ T cells in the age of COVID-19. Front. Immunol. 29 https://doi.org/10.3389/fimmu.2021.636118.
Goplen, N.P., Wu, Y., Son, Y.M., Li, C., Wang, Z., Cheon, I.S., Jiang, L., Zhu, B., Ayasoufi, K., Chini, E.N., Johnson, A.J., Vassallo, R., Limper, A.H., Zhang, N., Sun, J., 2020. Tissue-resident CD8(+) T cells drive age-associated chronic lung sequelae after viral pneumonia. Sci. Immunol. 5, eabc4557. https://doi.org/10.1126/sciimmunol.abc4557.
Grau-Expósito, J., Sánchez-Gaona, N., Massana, N., Suppi, M., Astorga-Gamaza, A., Perea, D., Rosado, J., Falcó, A., Kirkegaard, C., Torrella, A., Planas, B., Navarro, J., Suanzes, P., Álvarez-Sierra, D., Ayora, A., Sansano, I., Esperalba, J., Andrés, C., Antón, A., Ramón Y Cajal, S., Almirante, B., Pujol-Borrell, R., Falcó, V., Burgos, J., Buzón, M.J., Genescà, M., 2021. Peripheral and lung resident memory T cell responses against SARS-CoV-2. Nat. Commun. 12, 3010. https://doi.org/10.1038/s41467-021-23333-.
Grifoni, A., Weiskop, D., Ramiriz, S.I., Mateus, J., Dan, J.M., Moderbacher, C.R., Rawlings, S.A., Sutherland, A., Premkumar, L., Jadi, R.S., Marrama, D., de Silva, A. M., Frazier, A., Carlin, A.F., Greenbaum, J.A., Peters, B., 2020. Targets of T cell responses to SARS-CoV-2 coronavirus in humans with COVID-19 disease and unexposed individuals. Cell 181 (7), 1489–1501. https://doi.org/10.1016/j.cell.2020.05.015 e15.
Guan, W.-J., Ni, Z.-y., Hu, Y., Liang, W.-h., Ou, C.-q., He, J.-x., Liu, L., Shan, H., Lei, C.-l., Hui, D.S.C., Du, B., Li, L.-j., Zeng, G., Yuen, K.-Y., Chen, R.-c., Tang, C.-l., Wang, T., Chen, P.-y., Xiang, J., Li, S.-y., Wang, J.-l., Liang, Z.-j., Peng, Y.-x., Wei, L., Liu, Y., Hu, Y.-h., Peng, P., Wang, J.-m., Liu, J.-y., Chen, Z., Li, G., Zheng, Z.-j., Qiu, S.-q., Luo, J., Ye, C.-j., Zhu, S.-y., Zhong, N.-s., Clinal Medical Treatment Expert Group for COVID-19, 2020. Clinical characteristics of coronavirus disease 2019 in China. N. Engl. J. Med. 382, 1708–1720. https://doi.org/10.1056/NEJMoa2002032.
Guinan, K.J., Cunningham, R.T., Meenagh, A., Dring, M.M., Middleton, D., Gardiner, C. M., 2010. Receptor systems controlling natural killer cell function are genetically stratified in Europe. Genes Immun. 11, 67–78. https://doi.org/10.1038/gene.2009.60.
Guo, T., Fan, Y., Chen, M., Wu, X., Zhang, L., He, T., Wang, H., Wan, J., Wang, X., Lu, Z., 2020. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). JAMA Cardiol. 5 (7), 811–818. https://doi.org/10.1001/jamacardio.2020.1017.
Gursel, M., Gursel, I., 2020. Is global BCG vaccination-induced trained immunity relevant to the progression of SARS-CoV-2 pandemic? Allergy 75, 1815–1819. https://doi.org/10.1111/all.14345.
Hadjadj, J., Yatim, N., Barnabei, L., Corneau, A., Boussier, J., Smith, N., Pere, H., Charbit, B., Boder, V., Chenevier-Gobeaux, C., Breillat, P., Carlier, N., Gauzit, R., Morbieu, C., Pene, F., Marin, N., Roche, N., Szwebel, T.-A., Merkling, S.H., Treluyer, J.-M., Veyer, D., Mouthon, L., Blanc, C., Tharauz, P.-L., Rozenberg, F., Fischer, A., Duffy, D., Rieux-Laucat, F., Kerneis, S., Terrier, B., 2020. Impaired type 1 interferon activity and inflammatory responses in severe COVID-19 patients. Science 369 (6504), 718–724. https://doi.org/10.1126/science.abc6027.
Hamiel, U., Kozer, E., Youngster, I., 2020. SARS-CoV-2 rates in BCG-vaccinated and unvaccinated young adults. JAMA 323 (22), 2340–2341. https://doi.org/10.1001/jama.2020.8189.
Hansen, C.H., Michlmayr, D., Gubbels, S.M., Molbak, K., Ethelberg, S., 2021. Assessment of protection against reinfection with SARS-CoV-2 among 4 million PCR-tested individuals in Denmark in 2020: a population-level observational study. Lancet 397 (19280), 1204–1212. https://doi.org/10.1016/S0140-6736(21)00575-4 online.
Hastie, C.E., Mackay, D.F., Ho, F., Celis-Morales, C.A., Katikireddi, S.V., Niedzwiedz, C. L., Jani, B.D., Welsh, P., Mair, F.S., Gray, S.R., O'Donnell, C.A., Gill, J.M.R., Sattar, N., Pell, J.P., 2020. Vitamin D concentrations and COVID-19 infection in UK Biobank. Diabetes Metab. Syndr. 14 (4), 561–565. https://doi.org/10.1016/j.dsx.2020.04.050.
Haynes, L., Eaton, S.M., 2005. The effect of age on the cognate function of CD4+ T cells. Immunol. Rev. 205, 220–228. https://doi.org/10.1111/j.0105-2896.2005.00255.x.
Haynes, N., Cooper, L.A., Albert, M.A., 2020. At the heart of the matter: unmasking and addressing the toll of Covid-19 on diverse populations. Circulation 142, 105–107. https://doi.org/10.1161/CIRCULATIONAHA.120.048126.
Hazeldine, J., Lord, J.M., 2013. The impact of ageing on natural killer cell function and potential consequences for health in older adults. Ageing Res. Rev. 12 (4), 1069–1078. https://doi.org/10.1016/j.arr.2013.04.003.
He, L.Q., Lu, J.H., Yue, Z.Y., 2013. Autophagy in ageing and ageing-associated diseases. Acta Pharmacol. Sin. 34, 605–611. https://doi.org/10.1038/aps.2012.188.

Hippisley-Cox, J., Young, D., Coupland, C., Channon, K.M., Tan, P.S., Harrison, D.A., Rowan, K., Aveyard, P., Pavord, I.D., Watkinson, P.J., 2020. Risk of severe COVID-19 disease with ACE inhibitor and angiotensin receptor blockers; cohort study including 8.3 million people. Heart 106, 1503–1511, 10.1136/heartjnl-2020-317393.

Hirokawa, K., Utsuyama, M., Hayashi, Y., Kitagawa, M., Makinodan, T., Fulop, T., 2013. Slower immune system aging in women versus men in the Japanese population. Immun. Ageing 10, 19 https://doi.org/10.1186/1742-4933-10-19.

Hoffmann, M., Kleine-Weber, H., Schroeder, S., Kruger, N., Herrler, T., Erichsen, S., Schiergens, T.S., Herrler, G., Wu, N.H., Nitsche, A., Muller, M.A., Drosten, C., Pohlmann, S., 2020. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 181 (2), 271–280. https://doi.org/10.1016/j.cell.2020.02.052.

Holman, N., Knighton, P., Kar, P., O'Keefe, J., Curley, M., Weaver, A., Barron, E., Bakhai, C., Khunti, K., Wareham, N.J., Sattar, N., Young, B., Valabhji, J., 2020. Risk factors for COVID-19-related mortality in people with type 1 and type 2 diabetes in England: a population-based cohort study. Lancet Diabetes Endocrinol. 8 (10), 823–833. https://doi.org/10.1016/S2213-8587(20)30271-0.

Horowitz, A., Strauss-Albee, D.M., Leipold, M., Kubo, J., Nemat-Gorgani, N., Dogan, O. C., Dekker, C.L., Mackey, S., Maecker, H., Swan, G.E., Davis, M.M., Norman, P.J., Guethlein, L.A., Desai, M., Parham, P., Blish, C.A., 2013. Genetic and environmental determinants of human NK cell diversity revealed by mass cytometry. Sci. Transl. Med. 5 (208), 208ra145 doi:10.1126/scitranslmed.3006702.

Hou, Y., Zhao, J., Martin, W., Kallianpur, A., Chung, M.K., Jehi, L., Sharifi, N., Erzurum, S., Eng, C., Cheng, F., 2020. New insights into genetic susceptibility of COVID-19:an ACE2 and TMPRSS2 polymorphism analysis. BMC Med. 18, 216. https://doi.org/10.1186/s12916-020-01673-z.

Hu, C., Li, J., Xing, X., Gao, J., Zhao, S., Xing, L., 2021. The effect of age on the clinical and immune characteristics of critically ill patients with COVID-19: a preliminary report. PLOS ONE 16 (3), e0248675. https://doi.org/10.1371/journal.pone.0248675.

Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., Zhang, L., Fan, G., Xu, J., Gu, X., Cheng, Z., Yu, T., Xia, J., Wei, Y., Wu, W., Xie, X., Yin, W., Li, H., Liu, M., Xiao, Y., Gao, H., Guo, L., Xie, J., Wang, G., Jiang, R., Gao, Z., Ji, Q., Wang, J., Cao, B., 2020a. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 395 (10223), 497–506. https://doi.org/10.1016/s0140-6736(20)30183-5.

Huang, R., Zhu, L., Xue, L., Lui, L., Yan, X., Wang, J., Zhang, B., Xu, T., Ji, F., Zhao, Y., Cheng, J., Wang, Y., Shao, H., Hong, S., Cao, Q., Li, C., Zhao, X.-a., Zou, L., Sang, D., Zhao, H., Guan, X., Chen, X., Shan, C., Xia, J., Chen, Y., Yan, X., Wei, J., Zhu, C., Wu, C., 2020b. Clinical findings of patients with coronavirus disease 2019 in Jiangsu province, China: a retrospective, multi-center study. PLOS Negl. Trop. Dis. 14 (5), e0008280 https://doi.org/10.1371/journal.pntd.0008280.

Huang, I., Pranata, R., 2020. Lymphopenia in severe coronavirus disease-2019 (CoVID-19: systematic review and met-analysis). J. Intensive 8, 36. https://doi.org/10.1186/s40560-020-00453-4.

Huet, T., Beaussier, H., Voisin, O., Jouveshomme, S., Dauriat, G., Lazareth, I., Sacco, E., Naccache, J.-M., Bezie, Y., Laplanche, S., Le Berre, A., Le Pavec, J., Salmeron, S., Emmerich, J., Mourad, J.-J., Chatellier, G., Hayem, G., 2020. Anakira for severe forms of COVID-19: a cohort study. Lancet Rheumatol. 2 (7), E393–E400. https://doi.org/10.1016/S2665-9913(20)30164-8.

Ilie, P.C., Stefanescu, S., Smith, L., 2020. The role of vitamin D in the prevention of coronavirus disease 2019 infection and mortality. Aging Clin. Exp. Res. 32, 1195–1198. https://doi.org/10.1007/s40520-020-01570-8.

Ingraham, N.E., Barakat, A.G., Reilkoff, R., Bezdicek, T., Schacker, T., Chipman, J.G., Tiganelli, C.J., Puskarich, M.A., 2020. Understanding the renin-angiotensin-aldosterone-SARS-CoV-Axis: a comprehensive review. Eur. Respir. J. 56, 2000912 https://doi.org/10.1183/13993003.00912-2020.

Itoyoma, S., Keicho, N., Quy, T., Phi, N.C., Long, H.T., Ha, L.D., Van Ban, V., Ohashi, J., Hijikata, M., Matsushita, I., Kawana, A., Yanai, H., Kirikae, T., Kuratsuji, T., Sasazuki, T., 2004. ACE1 polymorphism and progression of SARS. Biochem. Biophys. Res. Commun. 323, 1124–1129. https://doi.org/10.1016/j.bbrc. 2004.08.208.

Jamal, A., King, B.A., Neff, L.J., Whitmill, J., Babb, S.D., Graffunder, C.M., 2016. Current cigarette smoking among adults—United States, 2005-2015. Morb. Mortal. Wkly. Rep. (MMWR) 65 (44), 1205–1211. https://doi.org/10.15585/mmwr.mm6544a2.

Janiaud, P., Axfors, C., Schmitt, A.M., Gloy, V., Ebrahimi, F., Hepprich, M., Smith, E.R., Haber, N.A., Khanna, N., Moher, D., Goodman, S.N., Ioannidis, J.P.A., Hemkens, L. G., 2021. Association of convalescent plasma treatment with clinical outcomes in patients with COVID-19A SysTematic Review and Meta-analysis. JAMA 325 (12), 1185–1195. https://doi.org/10.1001/jama.2021.2747.

Jarcho, J.A., Ingelfinger, J.R., Hamel, M.B., D'Agostino, R.B., Harrington, D.P., 2020. Inhibitors of the renin-agiotensin-aldosterone system and Covid-19. N. Engl. J. Med. 382, 2462–2464. https://doi.org/10.1056/NEJMe2012924.

Jiang, H.-W., Zhang, H.-N., Meng, Q.-F., Xie, J., Li, Y., Chen, H., Zheng, Y.X., Wang, X.N., Qi, H., Zhang, J., Wang, P.H., Han, Z.G., Tao, S.C., 2020. SARS-CoV-2 Orf9b suppresses type I interferon responses by targeting TOM70. Cell. Mol. Immunol. 17, 998–1000. https://doi.org/10.1038/s41423-020-0514-8.

Jiang, X., O'Reilly, P.F., Aschard, H., Hsu, Y.-H., Richards, J.B., Dupuis, J., Ingelsson, E., Karasik, D., Pilz, S., Berry, D., Kestenbaum, B., Zheng, J., Luan, J., Sofianopoulou, E., Streeten, E.A., Albanes, D., Lutsey, P.L., Yao, L., Tang, W., Econs, M.J., Wallaschofski, H., Volzke, H., Zhou, A., Power, C., McCarthy, M.I., Michos, E.D., Boerwinkle, E., Weinstein, S.J., Freedman, N.D., Huang, W.-Y., Van Schoor, N.M., van der Velde, N., de Groot, L.C.P.G.M., Enneman, A., Cupples, L.A., Booth, S.L., Vasan, R.S., Liu, C.-T., Zhou, Y., Ripatti, S., Ohlsson, C., Vandenput, L., Lorentzon, M., Eriksson, J.G., Shea, M.K., Berry, D.K., Kritchevsky, S.B., Liu, Y., Lohman, K.K., Ferruci, L., Peacock, M., Gieger, C., Beekman, M., Slagboom, E., Deelen, J., van Heemst, D., Kleber, M.E., Marx, W., de Boer, I.H., Wood, A.C., Rotter, J.I., Rich, S.S., Robinson-Cohen, C., den Heijer, M., Jarvelin, M.-R., Cavadino, A., Joshi, P.K., Wilson, J.F., Hayward, C., Lind, L., Michaelsson, K., Trompet, S., Zillikens, C., Uitterlinden, A.G., Rivadeneira, F., Broer, L., Zgaga, L., Campbell, H., Theodoratou, E., Farrington, S.M., Timofeeva, M., Dunlop, M.G., Valdes, A.M., Tikkanen, E., Lehtimaki, T., Lyytikainen, L.-P., Kahonen, M., Raitakari, O.T., Mikkila, V., Ikram, M.A., Sattar, N., Jukema, J.W., Wareham, N.J., Langenberg, C., Forouchi, N.G., Gundersen, T.E., Khaw, K.-T., Butterworth, A.S., Danesh, J., Spector, T., Wang, T.J., Hypponen, E., Kraft, E., Kiel, D.P., 2018. Genome-wide association study in 79,366 European-ancestry individuals informs the genetic architecture of 25-hydroxyvitamin D levels. Nat. Commun. 9, 260. https://doi.org/10.1038/s41467-017-02662-2.

Jones, B.E., Brown-Augsburger, P.L., Corbett, K.S., Westendorf, K., Davies, J., Cujec, T.P., Weithoff, C.M., Blackbourne, J.L., Heinz, B.A., Foster, D., Higgs, R.E., Balasubramaniam, D., Wang, L., Bidshahri, R., Kraft, L., Hwang, Y., Zentelis, S., Jepson, K.R., Goya, R., Smith, M.A., Collins, D.W., Hinshaw, S.J., Tycho, S.A., Pellacani, D., Xiang, P., Muthuraman, K., Sobhanifar, S., Piper, M.H., Triana, F.J., Hendle, J., Pustilnik, A., Adams, A.C., Berens, S.J., Baric, R.S., Martinez, D.R., Cross, R.W., Geisbert, T.W., Borisvich, V., Abiona, O., Belli, H.M., de Vries, M., Mohamed, A., Dittmann, M., Samanovic, M., Mulligan, M.J., Goldsmith, J.A., Hsieh, C.-L., Johnson, N.V., Wrapp, D., McLellan, J.S., Barnhart C., B., Graham, B.S., Mascola, J.R., Hansen, C.L., Falconer, E., 2020. LY-CoV555, a rapidly isolated potent neutralizing antibody, provides protection in a non-human primate model of SARS-CoV-2 infection. bioRxiv. https://doi.org/10.1101/2020.09.30.318972, 1: 2020.09.30.318972. not peer-reviewed. [Prepr.].

Jose, R.J., Manuel, A., 2020. COVID-19 cytokine storm: the interplay between inflammation and coagulation. Lancet Respir. Med. 8 (6), e46–e47. https://doi.org/10.1016/S2213-2600(20)30216-2.

Jost, S., Altfeld, M., 2013. Control of human viral infections by natural killer cells. Annu. Rev. Immunol. 31, 163–194. https://doi.org/10.1146/annurev-immunol-032712-100001.

Katz, L.M., 2021. (A Little) clarity on convalescent plasma for Covid-19. N. Engl. J. Med. 666–668. https://doi.org/10.1056/NEJMe2035678.

Kennedy, B.K., Berger, S.L., Brunet, A., Campisi, J., Cuervo, A.M., Epel, E.S., Franceschi, C., Lithgow, G.J., Morimoto, R.I., Pessin, J.E., Rando, T.A., Richardson, A., Schadt, E.E., Wyss-Coray, T., Sierra, F., 2014. Geroscience: linking aging to chronic disease. Cell 159 (2014), 709–713. https://doi.org/10.1016/j.cell.2014.10.039.

Khalil, A., Dhingra, R., Al-Mulki, J., Hassoun, M., Alexis, N., 2021. Questioning the sex-specific differences in the association of smoking on the survival rate of hospitalized COVID-19 patients. PLOS ONE 16 (8), e0255692. https://doi.org/10.1371/journal.pone.0255692.

Kim, J., Heike, R.L., Reynolds, A.M., Pidaparti, R.M., 2017. Aging effects on airflow dynamics and lung function in human bronchioles. PLOS ONE 12 (8), e0183654. https://doi.org/10.1371/journal.pone.0183654.

Klein, S.L., Pekosz, A., Park, H.-S., Ursin, R.L., Shapiro, J.R., Benner, S.E., Littlefield, K., Kumar, S., Naik, H.M., Betenbaugh, M.J., Shrestha, R., Wu, A.A., Hughes, R.M., Burgess, I., Caturegli, P., Laeyendecker, O., Quinn, T.C., Sullivan, D., Shoham, S., Redd, A.D., Bloch, E.M., Casadevall, A., Tobian, A.A.R., 2020. Sex, age and hospitalization drive antibody responses in a COVID-19 convalescent plasma donor population. J. Clin. Investig. 11, 6141–6150. https://doi.org/10.1172/JCI142004.

Klein, S., Flanagan, K., 2016. Sex differences in immune responses. Nat. Rev. Immunol. 16, 626–638. https://doi.org/10.1038/nri.2016.90.

Kleinnijenhuis, J., Quintin, J., Preijers, F., Joosten, L.A., Ifrim, D.C., Saeed, S., Jacobs, C., van Loenhout, J., de Jong, D., Stunnenberg, H.G., Xavier, R.J., van der Meer, J.W., van Crevel, R., Netea, M.G., 2012. Bacille Calmette-Guerin induces NOD2-dependent nonspecific protection from reinfection via epigenetic reprogramming of monocytes. Proc. Natl. Acad. Sci. USA 109, 17537–17542. https://doi.org/10.1073/pnas.1202870109.

Knoll, M.D., Wonodi, C., 2021. Oxford-AstraZeneca COVID-19 vaccine efficacy. Lancet 397 (10269), 72–74. https://doi.org/10.1016/S0140-6736(20)32623-4.

Kohlmeier, M., 2020. Avoidance of vitamin D deficiency to slow the COVID-19 pandemic. BMJ Nutr. Prev. Health 3, e000096 doi:10.1136/ bmjnph-2020-000096.

Kok, L., Dijkgraaf, F.E., Urbanus, J., Bresser, K., Vredevoogd, D.W., Cardoso, R.F., Perié, L., Beltman, J.B., Schumacher, T.N., 2020. A committed tissue-resident memory T cell precursor within the circulating CD8+ effector T cell pool. J. Exp. Med. 217, e20191711 https://doi.org/10.1084/jem.20191711,11–16).

Kovtonyuk, L.V., Fritsch, K., Feng, X., Manz, M.G., Takizawa, H., 2016. Inflamm-aging of hematopoiesis, hematopoietic stem cells, and the bone marrow microenvironment. Front. Immunol. 7, 502. https://doi.org/10.3389/fimmu.2016.00502.

Kruglikov, I.L., Scherer, P.E., 2020. The role of adipocytes and adipocyte-like cells in the severity of covid-19 infections. Obesity 28 (7), 1187–1190. https://doi.org/10.1002/oby.22856 (Silver Spring).

Kubiczkova, L., Sedlarikova, L., Hajek, R., Sevcikova, S., 2012. TGF-beta – an excellent servant but a bad master. J. Transl. Med. 10, 183. https://doi.org/10.1186/1479-5876-10-183.

Kuri-Cervantes, L., Pampena, M.B., Meng, W., Rosenfeld, A.M., Ittner, C.A.G., Weisman, A.R., Agyekum, R.S., Mathew, D., Baxter, A.E., Vella, L.A., 2020. Comprehensive mapping of immune perturbations associated with severe COVID-19. Sci. Immunol. 5, eabd7114.

Kusnadi, A., Ramírez-Suástegui, C., Fajardo, V., Chee, S.J., Meckiff, B.J., Simon, H., Pelosi, E., Seumois, G., Ferhat, Ay, Vijayanand, P., Ottensmeier, C.H., 2021. Severely ill COVID-19 patients display impaired exhaustion features in SARS-CoV-2-reactive CD8 T cells. Sci. Immunol. 6 (55), eabe4782.

Laird, E., Rhodes, J., Kenny, R.A., 2020. Vitamin D and inflammation: potential implications for severity of COVID-19. Ir. Med. J. 113 (5), 81.

Lal, H., Cunningham, A.L., Godeaux, O., Chlibek, R., Diez-Domingo, J., Hwang, S.-J., Levin, M.J., McElhaney, J.E., Poder, A., Puig-Barbera, J., Vesikari, T., Watanabe, D.,

Weckx, L., Zahaf, T., Heineman, T.C., ZOE-50 Study Group, 2015. Efficacy of an adjuvanted herpes zoster subunit vaccine in older adults. N. Engl. J. Med. 372, 2087–2096. https://doi.org/10.1056/NEJMoa1501184.
Lam, V.C., Lanier, L.L., 2017. NK cells in host responses to viral infections. Curr. Opin. Immunol. 44, 43–51. https://doi.org/10.1016/j.coi.2016.11.003.
Latchney, S.E., Calvi, L.M., 2017. The aging hematopoietic stem cell niche: phenotypic and functional changes and mechanisms that contribute to hematopoietic aging. Semin. Hematol. 54 (1), 25–32. https://doi.org/10.1053/j.seminhematol.2016.10.001.
Laterre, P.F., Francois, B., Collienne, C., Hantson, P., Jeannet, R., Remy, K.E., Hotchkiss, R.S., 2020. Association of interleukin 7 immunotherapy with lymphocyte counts among patients with severe coronavirus disease 2019 (COVID-19). JAMA Netw. Open 3 (7), e2016485. https://doi.org/10.1001/jamanetworkopen.2020.16485.
Le, P., Sabella, C., Rothberg, M.B., 2017. Preventing herpes zoster through vaccination: new developments. Clevel. Clin. J. Med. 84 (5), 359–366. https://doi.org/10.3949/ccjm.84a.16020.
Le Bert, N., Tan, A.T., Kunasegaran, K., Tham, C., Hafezi, M., Chia, A., Chng, M., Lin, M., Tan, N., Linster, M., Chia, W.N., Chen, M.I., Wang, L.F., Ooi, E.E., Kalimuddin, S., Tambyah, P.A., Low, J.G., Tan, Y.J., Bertoletti, A., 2020. SARS-CoV-2-specific T cell immunity in cases of COVID-19 and SARS, and uninfected controls. Nature 584, 457–462. https://doi.org/10.1038/s41586-020-.
Lee, H.-M., Kim, T.S., Jo, E.-K., 2016. MiR-146 and miR-125 in the regulation of innate immunity and inflammation. BMB Rep. 49 (6), 311–318. https://doi.org/10.5483/bmbrep.2016.49.6.056.
Lee, S.J., Channappanavar, R., Kanneganti, T.-D., 2020. Coronaviruses: innate immunity, inflammasome activation, inflammatory cell death, and cytokines. Trends Immunol. 41, 1083–1099. https://doi.org/10.1016/j.it.2020.10.005.
Le Garff-Tavernier, M., Beziat, V., Decocq, J., Siguret, V., Gandjbakhch, F., Pautas, E., Debre, P., Merle-Beral, H., Vieillard, V., 2010. Human NK cells display major phenotypic and functional changes over the life span. Aging Cell 9 (4), 527–535. https://doi.org/10.1111/j.1474-9726.2010.00584.x.
Lei, X., Dong, X., Ma, R., Wang, W., Xiao, X., Tian, Z., Wang, C., Wang, Y., Li, L., Ren, L., Guo, F., Zhao, Z., Zhou, Z., Xiang, Z., Wang, J., 2020. Activation and evasion of type I interferon responses by SARS-CoV-2. Nat. Commun. 11, 3810. https://doi.org/10.1038/s41467-020-17665-9.
Li, B., Yang, J., Zhao, F., Zhi, L., Wang, X., Liu, L., Bi, Z., Zhao, Y., 2020a. Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. Clin. Res. Cardiol. 109 (5), 531–538 doi:10.1007/s00392-020-01626-9.
Li, S., Zhang, Y., Guan, Z., Li, H., Ye, M., Chen, X., Shen, J., Zhou, Y., Shi, Z.-L., Zhou, P., Peng, K., 2020b. SARS-CoV-2 triggers inflammatory responses and cell death through caspase-8 activation. Signal Transduct. Target. Ther. 5, 235. https://doi.org/10.1038/s41392-020-00334-0.
Li, M., Yao, D., Zeng, X., Kasabovski, D., Zhang, Y., Chen, S., Zha, X., Li, Y., 2019. Age related human T cell subset evolution and senescence. Immun. Ageing 16, 24. https://doi.org/10.1186/s12979-019-0165-8.
Liao, M., Liu, Y., Yuan, J., Wen, Y., Xu, G., Zhao, J., Cheng, L., Li, J., Wang, X., Wang, F., Liu, L., Amit, I., Zhang, S., Zhang, Z., 2020. Single-cell landscape of bronchoalveolar immune cells in patients with COVID-19. Nat. Med. 26, 842–844. https://doi.org/10.1038/s41591-020-0901-9.
Liberale, L., Montecucco, F., Tardif, J.-C., Libby, P., Camici, G.G., 2020. Inflamm-ageing: the role of inflammation in age-dependent cardiovascular disease. Eur. Heart J. 41 (31), 2974–2982. https://doi.org/10.1093/eurheartj/ehz961.
Li Causi, E., Parikh, S.C., Chudley, L., Layfield, D.M., Ottensmeier, C.H., Stevenson, F.K., Di Genova, G., 2015. Vaccination expands antigen-specific CD4+ memory T cells and mobilizes bystander central memory T cells. PLOS One 10 (9), e0136717. https://doi.org/10.1371/journal.pone.0136717.
Lim, S., Bae, J.H., Kwon, H.-S., Nauck, M.A., 2021. COVID-19 and diabetes: from pathophysiology to clinical management. Nat. Rev. Endocrinol. 17, 11–30. https://doi.org/10.1038/s41574-020-00435-4.
Lin, Y., Kim, J., Metter, E.J., Nguyen, H., Truong, T., Lustig, A., Ferrucci, L., Weng, N.-P., 2016. Changes in blood lymphocyte numbers with age in vivo and their association with the levels of cytokines/cytokine receptors. Immun. Ageing 13, 24. https://doi.org/10.1186/s12979-016-0079-7.
Linehan, E., Fitzgerald, D.C., 2015. Ageing and the immune system: focus on macrophages. Eur. J. Microbiol. Immunol. 5 (1), 14–24. https://doi.org/10.1556/EUJMI-D-14-00035.
Lio, D., Scola, L., Crivello, A., Colonna-Romano, G., Candore, G., Bonafè, M., Cavallone, L., Marchegiani, F., Olivieri, F., Franceschi, C., Caruso, C., 2003. Inflammation, genetics and longevity: further studies on the prospective effects in men of IL-10-1082 promoter SNP and its interaction with TNF-alpha-308 promoter SNP. J. Med. Genet. 40, 296–299. https://doi.org/10.1136/jmg.40.4.296, 296–209.
Lippi, G., Lavie, C.J., Henry, B.M., Sanchais-Goman, F., 2020. Do genetic variants in angiotensin converting enzyme 2 (ACE2) play a role in corona virus-19 disease (COVID-19). Clin. Chem. Lab. Med. 58, 1415–1422 https//doi.org/10.1515/cclm.2020-0727.
Liu, X., Yang, N., Tang, J., Liu, S., Luo, D., Duan, Q., Wang, X., 2014. Downregulation of angiotensin-converting enzyme 2 by the neuraminidase protein of influenza A (H1N1) virus. Virus Res. 185, 64–71. https://doi.org/10.1016/j.virusres.2014.03.010.
Liu, Y., Chen, G.Y., Zheng, P., 2009. CD24-Siglec G/10 discriminates danger-from pathogen-associated molecular patterns. Trends Immunol. 30 (12), 557–561. https://doi.org/10.1016/j.it.2009.09.006.
Liu, Y., Pan, Y., Hu, Z., Wu, M., Wang, C., Feng, Z., Mao, C., Tan, Y., Liu, Y., Chen, L., Li, M., Wang, G., Yuan, Z., Diao, B., Wu, Y., Chen, Y., 2020. Thymosin alpha 1 reduces the mortality of severe Coronavirus Disease 2019 by restoration of lymphocytopenia and reversion of exhausted T cells. Clin. Infect. Dis. 71, 2150–2157. https://doi.org/10.1093/cid/ciaa630.
Lodigiani, C., Iapichino, G., Carenzo, L., Cecconi, M., Ferrazzi, P., Sebastian, T., Kucher, N., Studt, J.-D., Sacco, C., Bertuzzi, A., Sandri, M.T., Barco, S., Humanitas COVID-19 Task Force, 2020. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. Thromb. Res. 191, 9–14. https://doi.org/10.1016/j.thromres.2020.04.024.
Logunov, D.Y., Dolzhikova, I.V., Shcheblyakov, D.V., Tukhvatulin, A., Zubkova, O.V., Dzharullaeva, A.S., Kovyrshina, A.V., Lubenets, N.L., Grousova, D.M., Erokhova S., A., Botikov G., A., Izhaeva, F.M., Popova, O., Ozharovskaya, T.A., Esmagambetov, I.B., Favorskaya, I.A., Zrelkin, D.I., Voronina, D.V., Shcherbinin, D. N., Semikhin, A.S., Simakova, Y.V., Tokarskaya, E.A., Egorova, D.A., Shmoarov, M. M., Nikitenko, N.A., Gushchin, V.A., Smolyarchuk, E.A., Zyryanov, S.K., Borisevich, S.V., Naroditsky, B.S., Gintsburg, A.L., The Gam-COVID-Vac-Vaccine Trial Group, 2021. Safety and efficacy of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine: an interim analysis of a randomised controlled phase 3 trial in Russia. Lancet 397 (10275), 671–681. https://doi.org/10.1016/S0140-6736(21)00234-8.
Logunov, D.Y., Dolzikova, I.V., Zubkova, O.V., Tukhvatulin, A.I., Shcheblyakov, D.V., Dzharullaeva, A.S., Grousova, D.M., Erokhova, A.S., Kovyrshina, A.V., Botikov, A.G., Izhaeva, F.M., Popova, O., Ozharovskaya, T.A., Esmagambetov, I.B., Favorskaya, I. A., Zrelkin, D.I., Voronina, D.V., Shcherbinin, D.N., Semikhin, A.S., Simakova, Y.V., Tokarskaya, E.A., Lubenets, N.L., Egorova, D.A., 2020. Safety and efficacy of an rAD26 and rAD5 vector-based heterologous prime-boost COVID-19 vaccine in two formulations; two open, non-randomised phase 1/2 studies from Russia. Lancet 396 (10255), 887–897. https://doi.org/10.1016/S0140-6736(20)31866-3.
López-Otín, C., Blasco, M.A., Partridge, L., Serrano, M., Kroemer, G., 2013. The hallmarks of aging. Cell 153, 1194–1217. https://doi.org/10.1016/j.cell.2013.05.039.
Lu, N., Yang, Y., Wang, Y., Liu, Y., Fu, G., Chen, D., Dai, H., Fan, X., Hui, R., Zheng, Y., 2012. ACE2 polymorphism and essential hypertension; an updated meta-analysis involving 11,051 subjects. Mol. Biol. Rep. 39 (6), 6518–6519. https://doi.org/10.1007/s11033-012-1487-1.
Lucas, C., Wong, P., Klein, J., Castro, T.B.R., Silva, J., Sundaram, M., Ellingson, M.K., Mao, T., Oh, J.E., Israelow, B., Takahashi, T., Tokuyama, M., Lu, P., Venkataraman, A., Park, A., Mohanty, S., Wang, H., Wyllie, A.L., Vogels, C.B.F., Earnest, R., Lapidus, S., Ott, I.M., Moore, A.J., Muenker, C., Fournier, J.B., Campbell, M., Odio, C.D., Casanovas-Massana, A., Yale IMPACT Team, Herbst, R., Shaw, A.C., Medzhitov, R., Schulz, W.L., Grubaugh, N.D., DeLa Cruz, C., Farhadian, S., Ko, A.I., Omer, S.B., Iwasaki, A., 2020. Longitudinal analyses reveal immunological misfiring in severe COVID-19. Nature 463–469. https://doi.org/10.1038/s41586-020-2588-y.
Luo, Y., Liu, C., Guan, T., Li, Y., Lai, Y., Li, F., Zhao, H., Maimaiti, T., Zeyaweiding, A., 2019. Association of ACE2 genetic polymorphisms with hypertension-related target organ damages in south Xinjiang. Hypertens. Res. 42 (2019), 681–689. https://doi.org/10.1038/s41440-018-0166-6.
Lumley, S.F., O'Donnell, D., Stoesser, N.E., Matthews, P.C., Howarth, A., Hatch, S.B., Marsden, B.D., Cox, S., James, T., Warren, F., Peck, L.J., Ritter, T.G., de Toledo, Z., Warren, L., Axten, D., Cornall, R.J., Jones, E.Y., Stuart, D.I., Screaton, G., Ebner, D., Hoosdally, S., Chand, M., Crook, D.W., O'Donnell, A.-M., Conlon, C.P., Pouwels, K. B., Walker, A.S., Peto, T.E.A., Hopkins, S., Walker, T.M., Jeffery, K., Eyre, D.W., Oxford University Hospitals Staff Testing Group, 2021. Antibody status and incidence of SARS-CoV-2 infection in health care workers. N. Engl. J. Med. 384, 533–540. https://doi.org/10.1056/NEJMoa2034545.
Mackall, C.L., Fleisher, T.A., Brown, M.R., Andrich, M.P., Chen, C.C., Feuerstein, I.M., Horowitz, M.E., Magrath, I.T., Shad, A.T., Steinberg, S.M., Wexler, L.H., Gress, R.E., 1995. Age, thymopoiesis, and CD4+ T-lymphocyte regeneration after intensive chemotherapy. N. Engl. J. Med. 332 (3), 143–149. https://doi.org/10.1056/NEJM199501193320303.
Mackall, C.L., Fry, T.J., Gress, R.E., 2011. Harnessing the biology of IL-7 for therapeutic application. Nat. Rev. Immunol. 11 (5), 330–342. https://doi.org/10.1038/nri2970.
Maeda, K., Baba, Y., Nagai, Y., Miyazaki, K., Malykhin, A., Nakamura, K., Kincade, P.W., Sakaguchi, N., Coggenshall, K.M., 2005. IL-6 blocks a discrete early step in lymphopoiesis. Blood 106 (3), 879–885. https://doi.org/10.1182/blood-2005-02-0456.
Mantovani, A., Dinarello, C.A., Molgora, M., Garlanda, C., 2019. Interleukin-1 and related cytokines in the regulation of inflammation and immunity. Immunity 50 (4), 778–795. https://doi.org/10.1016/j.immuni.2019.03.012.
Marmot, M., Friel, S., Bell, R., Houweling, T.A.J., Taylor, S., 2008. Closing the gap in a generation: health equity through action on the social determinants of health. Lancet 372 (9650), 1661–1669. https://doi.org/10.1016/S0140-6736(08)61690-6.
Martens, P.-J., Gysemans, C., Verstuyf, A., Mathieu, C., 2020. Vitamin D's effect on immune function. Nutrients 12 (5), 1248. https://doi.org/10.3390/nu12051248.
Martineau, A.R., Joliffe, D.A., Hooper, R.L., Greenberg, L., Aloia, R.L., Bergman, P., Dubnov-Raz, G., Esposito, S., Ganmaa, D., Ginde, A.A., Goodall, E.C., Grant, C.C., Griffiths, C.J., Janssens, W., Laaksi, I., Manaseki-Holland, S., Mauger, D., Murdoch, D.R., Neale, R., Rees, J.R., Simpson, S., Stelmach, I., Kumar, G.T., Urashima, M., Camargo, C.A., 2017. Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data. BMJ 356, i6583. https://doi.org/10.1136/bmj.i6583.
Masselli, E., Vaccarezza, M., Carubbi, C., Pozzi, G., Presta, V., Mirandola, P., Vitale, M., 2020. NK cells: a double edge sword against SARS-CoV-2. Adv. Biol. Regul. 77, 100737 https://doi.org/10.1016/j.jbior.2020.100737.
Matthew, D., Giles, J.R., Baxter, A.E., Oldridge, D.A., Greenplate, A.R., Wu, J.E., Alanio, C., Kuri-Cervantes, L., Pampena, M.B., D'Andrea, K., Manne, S., Chen, Z., Huang, Y.J., Reilly, J.P., Weisman, A.R., Ittner, C.A.G., Kuthura, O., Dougherty, J.,

Nzingha, K., Han, N., Kim, J., Pattekar, A., Goodwin, E.C., Anderson, E.M., Weirick, M.E., Gouma, S., Arevalo, C.P., Bolton, M.J., Chen, F., Lacey, S.F., Ramage, H., Cherry, S., Hensley, S.E., Apostolidis, S.A., Huang, A.C., Vella, L.A., The UPenn COVID Processing Unit, Betts, M.R., Meyer, N.J., Wherry, E.J., 2020. Deep immune profiling of COVID-19 patients reveals distinct immunotypes with therapeutic implications. Science 369 (6508), eabc8511. https://doi.org/10.1126/science.abc8511.

Matsuda, A., Kishi, T., Jacob, A., Aziz, M., Wang, P., 2012. Association between insertion/deletion polymorphism in angiotensin-converting enzyme gene and acute lung injury/acute respiratory distress syndrome: a meta-analysis. BMC Med. Genet. 13, 76. https://doi.org/10.1186/1471-2350-13-76.

Maucourant, C., Filipovic, I., Ponzetta, A., Aleman, S., Cornillet, M., Hertwig, L., Strunz, B., Lentini, A., Reinius, B., Brownlie, D., Cuapio, A., Ask, E.H., Hull, R.M., Haroun-Izquierdo, A., Schaffer, M., Klingstrom, J., Folkessom, E., Buggert, M., Sandberg, J.K., Eriksson, L.I., Rooyackers, O., Ljunggren, H.-G., Malmberg, K.-J., Michaelsson, J., Marquardt, N., Hammer, Q., Stralin, K., Björkström, N.K., The Karolinska COVID-19 Study Group, 2020. Natural killer cell immunotypes related to COVID-19 disease severity. Sci. Immunol. 5 (50), eabd6832. https://doi.org/10.1126/sciimmunol.abd6832.

Mauvais-Jarvis, F., Bairey Merz, N., Barnes, P.J., Brinton, R.D., Carrero, J.J., DeMeo, D. L., De Vries, G.J., Epperson, C.N., Govindan, R., Klein, S.L., Lonardo, A., Maki, P.M., McCullough, L.D., Regitz-Zagrosek, V., Regensteiner, J.G., Rubin, J.B., Sandberg, K., Suzuki, A., 2020. Sex and gender: modifiers of health, disease and medicine. Lancet 396 (10250), 565–582. https://doi.org/10.1016/S0140-6736(20)31561-0.

McElhaney, J.E., Verschoor, C.P., Andrew, M.K., Haynes, L., Kuchel, G.A., Pawelec, G., 2020. The immune response to influenza in older humans: beyond immune senescence. Immun. Ageing 17, 10. https://doi.org/10.1186/s12979-020-00181-1.

McNerlan, S.E., Alexander, H.D., Rea, I.M., 1999. Age-related reference intervals for lymphocyte subsets in whole blood of healthy individuals. Scand. J. Clin. Lab. Invest. 59 (2), 89–92. https://doi.org/10.1080/00365519950185805.

McNerlan, S.E., Rea, I.M., Alexander, H.D., Morris, T.C.M., 1998. Changes in natural killer cells, the CD57CD8 subset, and related cytokines in healthy aging. J. Clin. Immunol. 18, 31–38. https://doi.org/10.1023/A:1023283719877.

Menachery, V.D., Eisfeld, A.J., Schäfer, A., Josset, L., Sims, A.C., Proll, S., Fan, S., Li, C., Neumann, G., Tilton, S.C., Chang, J., Gralinski, L.E., Long, C., Green, R., Williams, C. M., Weiss, J., Matzke, M.M., Webb-Robertson, B.J., Schepmoes, A.A., Shukla, A.K., Metz, T.O., Smith, R.D., Waters, K.M., Katze, M.G., Kawaoka, Y., Baric, R.S., 2014. Pathogenic influenza viruses and coronaviruses utilize similar and contrasting approaches to control interferon-stimulated gene responses. mBio 5, e01174–14. https://doi.org/10.1128/mBio.01174-14.

Minciullo, P.L., Catalano, A., Mandraffino, G., Casciaro, M., Crucitti, A., Maltese, G., Morabito, N., Lasco, A., Gangemi, S., Basile, G., 2016. Inflammaging and anti-inflammaging: the role of cytokines in extreme longevity. Arch. Immunol. Ther. Exp. 64 (2), 111–126. https://doi.org/10.1007/s00005-015-0377-3.

Mizrahi, B., Lotan, R., Kalkstein, N., Peretz, A., Perez, G., Ben-Tov, A., Chodick, G., Gazit, S., Patalon, T., 2021. Correlation of SARS-CoV-2 breakthrough infections to time-from-vaccine; preliminary study. medRxiv. https://doi.org/10.1101/2021.07.29.21261317 this version posted July 31, 2021. preprint (which was not certified by peerreview).

Mogensen, C.E., Neldam, S., Tikkanen, I., Oren, S., Viskoper, R., Watts, R.W., Cooper, M. E., 2000. Randomised controlled trial of dual blockade of renin-angiotensin system in patients with hypertension, microalbuminuria, and non-insulin dependent diabetes: the candesartan and lisinopril microalbuminuria (CALM) study. BMJ 321 (7274), 1440–1444. https://doi.org/10.1136/bmj.321.7274.1440.

Molony, R.D., Nguyen, J.T., Kong, Y., Montgomery, R.R., Shaw, A.C., Iwasaki, A., 2017. Aging impairs both primary and secondary RIG-I signaling for interferon induction in human monocytes. Sci. Signal. 10 (509), eaan2392. https://doi.org/10.1126/scisignal.aan2392.

Monk, P.D., Marsden, R.J., Tear, V.J., Brookes, J., Batten, T.N., Mankowski, M., Gabbay, F.J., Davies, D.E., Holgate, S.T., Ho, L.-P., Clark, T., Djukanovic, R., Wilkinson, T.M.A., On Behalf of the Inhaled Interferon Beta COVID-19 Study Group, 2021. Safety and efficacy of inhaled nebulised interferon beta-1a (SNG001) for treatment of SARS-CoV-2 infection: a randomised, double-blind, placebo controlled, phase 2 trial. Lancet Respir. Med. 9 (2), 192–206. https://doi.org/10.1016/S2213-2600(20)30511-7.

Monneret, G., de Marignan, D., Coudereau, R., Bernet, C., Ader, F., Frobert, E., Gossez, M., Viel, S., Venet, F., Wallet, F., 2020. Immune monitoring of interleukin-7 compassionate use in a critically ill COVID-19 patient. Cell. Mol. Immunol. 17, 1001–1003. https://doi.org/10.1038/s41423-020-0516-6.

Monto, A.S., DeJonge, P.M., Callear, A.P., Bazzi, L.A., Capriola, S.B., Malosh, R.E., Martin, E.T., Petrie, J.G., 2020a. Coronavirus occurrence and transmission over 8 years in the HIVE cohort of households in Michigan. J. Infect. Dis. 222 (1), 9–16. https://doi.org/10.1093/infdis/jiaa161.

Moorlag, S.J.C.F.M., Arts, R.J.W., van Crevel, R., Netea, M.G., 2019. Non-specific effects of BCG vaccine on viral infections. Clin. Microbiol. Infect. 25 (12), 1473–1478. https://doi.org/10.1016/j.cmi.2019.04.020.

Mora-Buch, R., Bromley, S.K., 2021. Discipline in stages: regulating CD8+ resident memory T cells. Front. Immunol. 11, 624199 https://doi.org/10.3389/fimmu.2020.624199).

Morales, D.R., Conover, M.M., You, S.C., Pratt, N., Kostka, K., Duarte-Salles, T., Fernández-Bertolín, S., Aragón, M., DuVall, S.L., Lynch, K., Falconer, T., van Bochove, K., Sung, C., Matheny, M.E., Lambert, C.G., Nyberg, F., Alshammari, T.M., Williams, A.E., Park, R.W., Weaver, J., Sena, A.G., Schuemie, M.J., Rijnbeek, P.R., Williams, R.D., Lane, J., Prats-Uribe, A., Zhang, L., Areia, C., Krumholz, H.M., Prieto-Alhambra, D., Ryan, P.B., Hripcsak, G., Suchard, M.A., 2021. Renin–angiotensin system blockers and susceptibility to COVID-19: an international, open science, cohort analysis. Lancet Dig. Health 3 (2), E98–E114. https://doi.org/10.1016/S2589-7500(20)30289-2.

Moro-Garcia, M.A., Alsonso-Arias, R., Lopez-Larrea, C., 2013. When aging reaches CD4+ T-cells: phenotypic and functional changes. Front. Immunol. 4, 107. https://doi.org/10.3389/fimmu.2013.00107.

Narula, S., Yusuf, S., Chong, M., Ramasundarahettige, C., Rangarajan, S., Bangdiwala, S., van Eikels, M., Leineweber, K., Wu, A., Pigeyre, M., Pare, G., 2020. Plasma ACE2 and risk of death or cardio metabolic diseases; a case-cohort analysis. Lancet 396 (10256), 968–976. https://doi.org/10.1016/s0140-6736(20)31964-4.

National Institute of Clinical Excellence (NICE), 2020. Guidance NG 187. Vitamin D for COVID-19: Evidence Reviews for the Use of Vitamin D Supplementation as Prevention and Treatment of COVID-19. ⟨https://www.nice.org.uk/guidance/ng187/evidence/evidence-reviews-for-the-use-of-vitamin-d-supplementation-as-prevention-and-treatment-of-covid19-pdf-8957587789⟩.

Niu, W., Qi, Y., Hou, S., Zhou, W., Qiu, C., 2007. Correlation of angiotensin-converting enzyme 2 gene polymorphisms with stage 2 hypertension in Han Chinese. Transl. Res. 150 (6), 374–380. https://doi.org/10.1016/j.trsl.2007.06.002.

Norman, P.J., Stephens, H.A.F., Verity, D.H., Chandanayingyong, D., Vaughan, R.W., 2001. Distribution of natural killer cell immunoglobulin-like receptor sequences in three ethnic groups. Immunogenetics 52, 195–205. https://doi.org/10.1007/s002510000281.

Okeke, E.B., Uzonna, J.E., 2019. The pivotal role of regulatory T cells in the regulation of innate immune cells. Front. Immunol. 10, 680. https://doi.org/10.3389/fimmu.2019.00680.

ONS, Office for National Statistics, 2020a. Deaths Involving Covid-19 by Local Area and Socioeconomic Deprivation: Deaths Occurring Between 1 March and 31 July 2020. ⟨https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/bulletins/deathsinvolvingcovid19bylocalareasanddeprivation/deathsoccurringbetween1marchand31july2020⟩. (Accessed 18 March 2021).

ONS, Office for National Statistics, 2020b. Updating Ethnic Contrast in Deaths Involving the Coronavirus (Covid-19), England and Wales: Deaths Occurring 2 March to 28 July 2020. ⟨https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/articles/updatingethniccontrastsindeathsinvolvingthecoronaviruscovid19englandandwales/deathsoccurring2marchto28july2020⟩. (Accessed 18 March 2020).

Palmer, D.B., 2013. The effect of age on thymic function. Front. Immunol. 4, 316. https://doi.org/10.3389/fimmu.2013.00316.

Pawelec, G., 2012. Hallmarks of human 'immunosenescence': adaption or dysregulation? Immun. Ageing 9, 15. https://doi.org/10.1186/1742-4933-9-15.

Pegram, H.J., Andrews, D.M., Smyth, M.J., Darcy, P.K., Kershaw, M.H., 2011. Activating and inhibitory receptors of natural killer cells. Immunol. Cell Biol. 89, 216–224. https://doi.org/10.1038/icb.2010.78.

Peng, Y., Mentzer, A.J., Liu, G., Yao, X., Yin, Z., Dong, D., Dejnirattisia, W., Rostron, T., Supasa, P., Liu, C., Lopez-Camacho, C., Slon-campos, J., Zhao, Y., Stuart, D., Paeson, G., Grimes, J., Antson Bayfield, F., Hawkins, O.W., Ker, D.E.D.P., Turtle, D.-S., Subramaniam, L., Thomson, K., Zhang, P., Dold, P., Ratcliff, C., Simmonds, J., de Silva, P., Sopp, T., Wellington, P., Rajapaksa, D., Chen, U., Salio, Y.-L., Napolitani, M., Paes, G., Borrow, W., Kessler, P., Fry, B., Schwabe, J.W., Semple, N. F., Bailllie, M.G., Moore, K.J., Openshaw, S., Ansari, P.J.M., Dunachie, A., Barnes, S., Frater,J, E., Kerr, G., Goulder, P., Lockett, T., Levin, R., Oxford Immunology Network Covid-19 Response T cell Consortium, Cornall, R.J., Conlon, C., Klenerman, P., McMichael, A., Screaton, G., Mongkolsapaya, J., Knight, J.C., Ogg, G., Dong, T., 2020. Broad and strong memory CD4+ and CD8+ T cells induced by SARS-CoV-2 in UK convalescent individuals following COVID-19. Nat. Immunol. 21 (2020), 1336–1345. https://doi.org/10.1038/s41590-020-0782-6.

Penna, D., 2020. London Telegraph, 5 February 2021. New Israeli Covid Drug Which Cured 30 Cases of Disease Hailed by Scientists as 'Huge Breakthrough'. ⟨https://www.telegraph.co.uk/news/2021/02/05/new-israeli-covid-drug-cured-30-cases-disease-hailed-scientists/⟩.

Pereira-Santos, M., Gomos dos Santos, J.Y., Carvalho, G.Q., Barbosa dos Santos, D., Oliveira, A.C., 2019. Epidemiology of vitamin D insufficiency and deficiency in a population in a sunny country: geospatial meta-analysis in Brazil. Crit. Rev. Food Sci. Nutr. 59 (13), 2102–2119. https://doi.org/10.1080/10408398.2018.1437711.

Petrilli, C.M., Jones, S.A., Yang, J., Rajagopalan, H., O'Donnell, L., Chernyak, Y., Tobin, K.A., Cerfolio, R.J., Francois, F., Horwitz, L.I., 2020. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. BMJ 369, m1966. https://doi.org/10.1136/bmj.m1966.

Pham, H., Waterhouse, M., Baxter, C., Romero, B.D., McLeod, D.S.A., Armstrong, B.K., Ebeling, P.R., English, D.R., Hartel, G., Kimlin, M.G., Martineau, A.R., O'Connell, R., van der Pols, J.C., Venn, A.J., Webb, P.M., Whiteman, D.C., Neale, R.E., 2021. The effect of vitamin D supplementation on acute respiratory tract infection in older Australian adults: an analysis of data from the D-health trial. Lancet Diabetes Endocrinol. 9 (2), 69–81. https://doi.org/10.1016/S2213-8587(20)30380-6.

Pietrobon, A.J., Teixeira, F.M.E., Sato, M.N., 2020. Immunosenescence and inflammaging: risk factors of severe COVID-19 in older people. Front. Immunol. 11, 579220 https://doi.org/10.3389/fimmu.2020.579220.

Pinto, D., Park, Y.J., Beltramello, M., Walls, A.C., Tortorici, M.A., Bianchi, S., Jaconi, S., Culap, K., Zatta, F., De Marco, A., Peter, A., Guarino, B., Spreafico, R., Cameroni, E., Case, J.B., Chen, R.E., Havenar-Daughton, C., Snell, G., Telenti, A., Virgin, H.W., Lanzavecchia, A., Diamond, M.S., Fink, K., Veesler, D., Corti, D., 2020. Cross-neutralization of SARS-CoV-2 by a human monoclonal SARS-CoV antibody. Nature 583, 290–295. https://doi.org/10.1038/s41586-020-2349-y.

Polack, F.P., Thomas, S.J., Kitchin, N., Absalon, J., Gurtman, A., Lockhart, S., Perez, J.L., Perez Marc, G., Moreira, E.D., Zerbini, C., Bailey, R., Swanson, K.A., Roychoudhury, S., Koury, K., Li, P., Kalina, W.V., Cooper, D., Frenck, R.W.,

Hammitt, L.L., Tureci, O., Nell, H., Schaefer, A., Unal, S., Tresnan, D.B., Mather, S., Dormitzer, P.R., Sahin, U., Jansen, K.U., Gruber, W.C., C4591001 Clinical Trial Group, 2020. Safety and efficacy of the BNT162b2 Covid-19 vaccine. N. Engl. J. Med. 383, 2603–2615. https://doi.org/10.1056/NEJMoa2034577.

Popkin, B.M., Du, S., Green, W.D., Beck, M.A., Algaith, T., Herbst, C.H., Alsukait, R.F., Alluhidan, M., Alazemi, N., Shekar, M., 2020. Individuals with obesity and Covid-19. A global perspective on the epidemiology and biological relationships. Obes. Rev. 21 (11), e13128 https://doi.org/10.1111/obr.13128.

Public Health England, 2018. Influenza Vaccine Effectiveness in Adults and Children in Primary Care in the UK: Provisional End of Season Results 2017 to 2018.

Public Health England, 2020. COVID-19: Review of Disparities in Risks and Outcomes, pp. 1–92. ⟨https://www.gov.uk/government/publications/covid-19-review-of-disparities-in-risks-and-outcomes⟩).

Qin, C., Zhou, L., Hu, Z., Zhang, S., Yang, S., Tao, Y., Xie, C., Ma, K., Shang, K., Wang, W., Tian, D.-S., 2020. Dysregulation of immune response in patients with coronavirus 2019 (COVID-19) in Wuhan, China. Clin. Infect. Dis. 71 (15), 762–768. https://doi.org/10.1093/cid/ciaa248.

Ramasamy, M.N., Minassian, A.M., Ewer, K.J., Flaxman, A.L., Folegetti, P.M., Owens, D. R., Voysey, M., Aley, P.K., Angus, B., Babbage, G., Belij-Rammerstorfer, S., Berry, L., Bibi, S., Bittaye, M., Cathie, K., Chappell, H., Charlton, S., Cicconi, P., Clutterbuck, E. A., Colin-Jones, R., Dold, C., Emary, K.R.W., Fedosyuk, S., Fuskova, M., Gbesemete, D., Green, C., Hallis, B., Hou, M.M., Jenkin, D., Joe, C.C.D., Kelly, E.J., Kerridge, S., Lawrie, A.M., Lelliott, A., Lwin, M.N., Makinson, R., Marchevsky, N.G., Mujadidi, Y., Munro, A.P.S., Pacurar, M., Plested, E., Rand, J., Rawlinson, T., Rhead, S., Robinson, H., Ritchie, A.J., Ross-Russell, A.L., Saich, S., Singh, N., Smith, C.C., Snape, M.D., Song, R., Tarrant, R., Themistocleous, Y., Thomas, K.M., Villafana, T.L., Warren, S.C., Watson, M.E.E., Douglas, A.D., Hill, A.V.S., Lambe, T., Gilbert, S.C., Faust, S.N., Pollard, S.J., The Oxford COVID Vaccine Trial Group, 2020. Safety and immunogenicity of ChAdOx1 nCoV-19 vaccine administered in a prime-boost regimen in young and old adults (COV002): a single-blind, randomised, controlled, phase 2/3 trial. Lancet 396 (10267), 1979–1993. https://doi.org/10.1016/S0140-6736(20)32466-1.

Ratliff, M., Alter, S., Frasca, D., Blomberg, B.B., Riley, R.L., 2013. In senescence, age-associated B cells secrete TNFa and inhibit survival of B-cell precursors. Aging Cell 12 (2), 303–311. https://doi.org/10.1111/acel.12055.

Rea, I.M., Alexander, H.D., Crockard, A.D., Morris, T.C.M., 1996a. CD4 lymphopenia in very elderly people. Lancet 347 (8997), 328–329. https://doi.org/10.1016/s0140-6736(96)90504-8.

Rea, I.M., Stewart, M., Campbell, P., Alexander, H.D., Crockard, A.D., Morris, T.C.M., 1996b. Changes in lymphocyte subsets, interleukin 2, and soluble interleukin 2 receptor in old and very old age. Gerontology 42, 69–78. https://doi.org/10.1159/000213775.

Rea, I.M., McNerlan, S.E., Alexander, H.D., 2000. Total serum IL-12 and IL-12 p40, but not IL-12 p70 are increased in the serum of older subjects; relationship to CD3+ and NK subsets. Cytokine 12 (2), 156–159. https://doi.org/10.1006/cyto.1999.0537.

Rea, I.M., 2010. BELFAST nonagenarians: nature or nurture? Immunological, cardiovascular and genetic factors. Immun. Ageing 7, 6. https://doi.org/10.1186/1742-4933-7-6.

Rea, I.M., Maxwell, L.D., McNerlan, S.E., Alexander, H.D., Curran, M.D., Middleton, D., Ross, O.A., 2013. Killer immunoglobulin-like receptors (KIR) haplogroups A and B track with natural killer cells and cytokine profile in aged subjects: observations from octo/nonagenarians in the belfast elderly longitudinal free-living aging study (BELFAST). Immun. Ageing 10, 35 https://doi.org/10.1186/1742-4933-10-35.

Rea, I.M., Gibson, D.S., McGilligan, V., McNerlan, S.E., Alexander, H.D., Ross, O.A., 2018. Age and age-related diseases. Role of inflammation triggers and cytokines. Front. Immunol. 9, 586. https://doi.org/10.3389/fimmu.2018.00586.

RECOVERY Collaborative Group, Horby, P.W., Pessoa-Amorim, G., Peto, L., Brightling, C.E., Sarkar, R., Thomas K., Jeebun V., Ashish, A., Tully R., Chadwick, D., Sharafat, M., Stewart, R., Rudran, B., Baillie, J.K., Buch, M.H., Chappell, L.C., Day, J.N., Furst, S.N., Jaki, T., Jeffery, K., Juszcak, E., Lim, W.S., Montgomery, A., Mumford, A., Rowan, K., Thwaites, G., Mafham, M., Haynes, R., Landray M.J., 2021a. Tocilizumab in patients admitted to hospital with covid-19 (recovery): preliminary results of a randomised, controlled, open-label, platform trial. medRxiv. Preprint not peer reviewed doi: ⟨10.1101/2021.02.11.21249258⟩. ⟨www.medrxiv.org/content/10.1101/2021.02.11.21249258v1⟩).

RECOVERY Collaborative Group, Horby, P., Lim, W.S., Emberson, J.R., Mafham, M., Bell, J.L., Linsell, L., Staplin, N., Brightling, C., Ustianowski, A., Elmahi, E., Prudon, B., Green, C., Felton, T., Chadwick, D., Rege, K., Fegan, C., Chappell, L.C., Faust, S.N., Jaki, T., Jeffery, K., Montgomery, A., Rowan, K., Juszczak, E., Baillie, J. K., Haynes, R., Landray, M.J., 2021b. Dexamethasone in hospitalized patients with Covid-19. N. Engl. J. Med. 384 (8), 693–704 doi:10.1056/NEJMoa2021436.

RECOVERY Collaborative Group, 2021c. Convalescent plasma inpatients admitted to hospital with COVID-19 (RECOVERY: a randomised cotrolled, open-label, platform trial). Lancet 397 (10289), 2049–2059. https://doi.org/10.1016/S0140-6736(21)00897-7.

REMAP-CAP Investigators, Gordon, A.C., Mouncey, P.R., Al-Beidh, F., Rowan, K.M., Nichol, A.D., Arabi, Y.M., Annane, D., Beane, A., van Bentum-Puijk, W., Berry, L.R., Bhimani, Z., Bonten, M.J.M., Bradbury, C.A., Brunkhorst, F.M., Buzgau, A., Cheng, A.C., Detry, M.A., Duffy, E.J., Estcourt, L.J., Fitzgerald, M., Goossens, H., Haniffa, R., Higgins, A.M., Hills, T.E., Horvat, C.M., Lamontagne, F., Lawler, P.R., Leavis, H.L., Linstrum, K.M., Litton, E., Lorenzi, E., Marshall, J.C., Mayr, F.B., McAuley, D.F., McGlothlin, A., McGuinness, S.P., McVerry, B.J., Montgomery, S.K., Morpeth, S.C., Murthy, S., Orr, K., Parke, R.L., Parker, J.C., Patanwala, A.E., Pettilä, V., Rademaker, E., Santos, M.S., Saunders, C.T., Seymour, A.D., Shankar-Hari, M., Sligl, W.I., Turgeon, A.F., Turner, A.M., van de Veerdonk, F.L., Zarychanski, R., Green, C., Lewis, R.J., Angus, D.C., McArthur, C.J., Berry, S., Webb, S.A., Derde, L.P.G., 2021. Interleukin-6 receptor antagonists in critically Ill patients with Covid-19. N. Engl. J. Med. https://doi.org/10.1056/NEJMoa2100433.

Remuzzi, A., Remuzzi, G., 2020. COVID-19 and Italy: what next? Lancet 395 (10231), 1225–1228. https://doi.org/10.1016/S0140-6736(20)30627-9.

Rhodes, J.M., Subramanian, S., Laird, E., Kenny, R.A., 2020. Low population mortality from COVID-19 in countries South of latitude 35 degrees North supports vitamin D as a factor determining severity. Aliment. Pharmacol. Ther. 51 (12), 1434–1437. https://doi.org/10.1111/apt.15777.

Ridker, P.M., Devalaraja, M., Baeres, F.M.M., Engelmann, M., Hovingh, G.K., Ivkovic, M., Lo, L., Kling, D., Pergola, P., Raj, D., Libby, P., Davidson, M., RESCUE Investigators, 2021. IL-6 inhibition with ziltivekimab in patients at high atherosclerotic risk (RESCUE): a double-blind, randomised, placebo-controlled, phase 2 trial. Lancet 397 (10289), 2060–2069. https://doi.org/10.1016/S0140-6736(21)00520-1.

Rigat, B., Hubert, C., Alhenc-Gelas, F., Cambien, F., Corvol, P., Soubrier, F., 1990. An insertion/deletion polymorphism in the angiotensin I-converting enzyme gene accounting for half the variance of serum enzyme levels. J. Clin. Investig. 86, 1343–1346. https://doi.org/10.1172/JCI114844.

Rodda, L.B., Netland, J., Shehata, L., Pruner, K.B., Morawski, P.A., Thouvenel, C.D., Takehara, K.K., Eggenberger, J., Hemann, E.A., Waterman, H.R., Fahning, M.L., Chen, Y., Hale, M., Rathe, J., Stokes, C., Wrenn, S., Fiala, B., Carter, L., Hamerman, J. A., King, N.P., Gale Jr., M., Campbell, D.J., Rawlings, D.J., Pepper, M., 2021. Functional SARS-CoV-2-specific immune memory persists after mild COVID-19. Cell 184 (1), 169–183. https://doi.org/10.1016/j.cell.2020.11.029. Epub 2020 Nov 23. PMID: 33296701; PMCID: PMC7682481.

Rodriguez, L., Pekkarinen, P.T., Lakshmikanth, T., Tan, Z., Consiglio, C.R., Pou, C., Chen, Y., Mugabo, C.H., Nguyen, N.A., Nowlan, K., 2020. Systems-level immunomonitoring from acute to recovery phase of severe COVID-19. Cell Rep. Med. 1, 100078.

Rollston, R., Galea, S., 2020. COVID-19 and the social determinants of health. Am. J. Health Promot. 34 (6), 687–689. https://doi.org/10.1177/0890117120930536b, 697-689.

Roodink, I., et al., 2021. Cornering an ever-evolving coronavirus: TATX-03, a fully human synergistic multi-antibody cocktail targeting the SARS-CoV-2 spike protein with in vivo efficacy. bioRxiv. https://doi.org/10.1101/2021.07.20.452858. ⟨https://www.biorxiv.org/content/10.1101/2021.07.20.452858v1⟩).

Rosas, I.O., Brau, N., Waters, M., Go, R.C., Hunter, B.D., Bhagani, S., Skiest, D., Aziz, M. S., Cooper, N., Douglas, I.S., Savic, S., Youngstein, T., Del Sorbo, L., Gracian, A.C., De La Zerda, D., Ustianowski, A., Bao, M., Dimonaco, S., Graham, E., Matharu, B., Spotswood, H., Tsai, L., Malhotra, A., 2021. Tocilizumab in hospitalised patients with severe Covid-19 pneumonia. N. Engl. J. Med. 2021, 1503–1516. https://doi.org/10.1056/NEJMoa2028700.

Ross, O.A., Curran, M.D., Meenagh, A., Williams, F., Barnett, Y.A., Middleton, D., Rea, I. M., 2003. Study of age-association with cytokine gene polymorphisms in an aged Irish population. Mech. Ageing Dev. 124 (2), 199–206. https://doi.org/10.1016/S0047-6374(02)00132-X.

Rossi, M.I.D., Yokota, T., Medina, K.L., Garrett, K.P., Comp, P.C., Schipul, A.H.Jr, Kincade, P.W., 2003. B lymphopoiesis is active throughout human life, but there are developmental age-related changes. Blood 101 (2), 576–584. https://doi.org/10.1182/blood-2002-03-0896.

Rossman, M.J., Kaplon, R.E., Hill, S.D., McNamara, M.N., Santos-Parker, J.R., Pierce, G. L., Seals, D.R., Donato, A.J., 2017. Endothelial cell senescence with aging in healthy humans: prevention by habitual exercise and relation to vascular endothelial function. Am. J. Physiol. Heart Circ. Physiol. 313 (5), H890–H895 doi:10.1152/ajpheart.00416.2017.

Rubin, E.J., Longo, D.L., Baden, L.R., 2021. Interleukin-6 receptor inhibition in Covid-19-cooling the inflammatory soup. N. Engl. J. Med., e2103108 https://doi.org/10.1056/NEJMe210308.

Rubino, F., Amiel, S.A., Zimmet, P., Alberti, G., Bornstein, S., Eckel, R.H., Mingrone, G., Boehm, B., Cooper, M.E., Del Prato, S., Ji, L., Hopkins, D., Herman, W.H., Khunti, K., Mbanya, J.-C., Renard, E., 2020. New-onset diabetes in Covid-19. N. Engl. J. Med. 383, 789–790. https://doi.org/10.1056/NEJMc2018688.

Ruparelia, N., Chai, J.T., Fisher, E.A., Choudhury, R.P., 2017. Inflammatory processes in cardiovascular disease: a route to targeted therapies. Nat. Rev. Cardiol. 14, 133–144. https://doi.org/10.1038/nrcardio.2016.185.

Sa Ribero, M., Jouvenet, N., Dreux, M., Nisole, S., 2020. Interplay between SARS-CoV-2 and the type I interferon response. PLOS Pathog. 16 (7), e1008737 doi:10.1371/journal.ppat.1008737.

Sadeghi, A., Tahmasebi, S., Mahmood, A., Kuznetsova, M., Valizadeh, H., Taghizadieh, A., Nazemiyeh, M., Aghebati-Maleki, L., Jadidi-Niaragh, F., Abbaspour-Aghdam, S., Roshangar, L., Mikaeili, H., Ahmadi, M., 2021. Th 17 and Treg cell function in SARS-CoV-2 patients compared with healthy controls. JCP 236, 2829–2839. https://doi.org/10.1002/jcp.30047.

Sallard, E., Lescure, F.-X., Yazdanpanah, Y., Mentre, F., Peiffer-Smadja, N., 2020. Type 1 interferons as a potential treatment against COVID-19. Antivir. Res. 178, 104791 doi:10.1016/j.antiviral.2020.104791.

Salminen, A., Ojala, J., Kaarniranta, K., Kauppinen, A., 2012. Mitochondrial dysfunction and oxidative stress activate inflammasomes: impact on the aging process and age-related diseases. Cell Mol. Life Sci. 69 (18), 2999–3013. DOI 10.1007/s00018-012-0962-0.

Salvarani, C., Dolci, G., Massari, M., Merlo, D.F., Cavuto, S., Savoldi, L., Bruzzi, P., Boni, F., Braglia, L., Turra, C., Ballerini, P.F., Sciascia, R., Zammarchi, L., Para, O., Scotton, P.G., Inojosa, W.O., Ravagnani, V., Salerno, N.D., Sainaghi, P.P., Brignone, A., Codeluppi, M., Teopompi, E., Milesi, M., Bertomoro, P., Claudio, N., Salio, M., Falcone, M., Cenderello, G., Donghi, L., Del Bono, V., Colombelli, P.L., Angheben, A., Passaro, A., Seondo, G., Pascale, R., Piazzo, I., Facciolongo, N., Constantini, M., RCT-TCZ-COVID-19 Study Group, 2021. Effect of tocilizumab vs

standard care on clinical worsening in patients hospitalized with COVID-19 pneumonia: a randomized clinical trial. JAMA Intern. Med. 181 (1), 24–31. https://doi.org/10.1001/jamainternmed.2020.6615.

Sama, I.E., Ravera, A., Santema, B.T., van Goor, H., ter Maaten, J.M., Cleland, J.G.F., Rienstra, M., Friedrich, A.W., Samani, N.J., Ng, L.L., Dickstein, K., Lang, C.C., Filippatos, G., Anker, S.D., Ponikowski, P., Metra, M., van Veldhuisen, D.J., Voors, A. A., 2020. Circulating plasma concentrations of angiotensin-converting enzyme 2 in men and women with heart failure and effects of renin–angiotensin–aldosterone inhibitors. Eur. Heart J. 41 (19), 1810–1817. https://doi.org/10.1093/eurheartj/ehaa373.

Sanchez-Rangel, E., Inzucchi, S.E., 2017. Metformin: clinical use in type 2 diabetes. Diabetologia 60, 1586–1593. https://doi.org/10.1007/s00125-017-4336-x.

Sandoff, J., Le Gars, M., Shukarev, G., Heerwegh, D., Truyers, C., de Groot, A.M., Stoop, J., Tete, S., Van Damme, W., Leroux-Roels, I., Berghmans, P.-J., Kimmel, M., de Hoon, J., Smith, W., Stephenson, K.E., De Rosa, S.C., Cohen, K.W., McElrath, M.J., Cromier, E., Scheper, G., Barouch, D.H., Hendriks, J., Struyf, F., Van Hood, J., Schuitemaker, H., 2021. Interim results of a phase 1–2a, trial of ad26.COV2.S covid-19 vaccine. N. Engl. J. Med. 384, 1824–1835. https://doi.org/10.1056/NEJMoa2034201.

Sattar, N., McInnes, I.B., McMurray, J.J.V., 2020. Obesity is a risk factor for severe COVID-19 infection: multiple potential mechanisms. Circulation 142, 4–6. https://doi.org/10.1161/CIRCULATIONAHA.120.047659.

Schmidt, S., Ullrich, E., Bochennek, K., Zimmermann, S.-Y., Lehrnbecher, T., 2016. Role of natural killer cells in antibacterial immunity. Expert Rev. Hematol. 9 (12), 1119–1127 doi:10.1080/17474086.2016.1254546.

Schulte-Schrepping, J., Reusch, N., Paclik, D., Baßler, K., Schlickeiser, S., Zhang, B., Krämer, B., Krammer, T., Brumhard, S., Bonaguro, L., De Domenico, E., Wendisch, D., Grasshoff, M., Kapellos, T.S., Beckstette, M., Pecht, T., Saglam, A., Dietrich, O., Mei, H.E., Schulz, A.R., Conrad, C., Kunkel, D., Vafadarnejad, E., Xu, C.-J., Horne, A., Herbert, M., Drews, A., Thibeault, S., Pfeiffer, M., Hippenstiel, S., Hocke, A., Muller-Redetzky, H., Heim, K.-M., Machleidt, F., Uhrig, A., de Jarcy, L.B., Jurgen, L., Stegemann, M., Glosenkamp, C.R., Volk, H.-D., Goffinet, C., Landthaler, M., Wyler, E., Georg, P., Schneider, M., Dang-Heine, C., Neuwinger, N., Kappert, K., Tauber, R., Corman, V., Raabe, J., Kaiser, K.M., Vinh T., M., Rieke, G., Meisel, C., Ulas, T., Becker, M., Geffers, R., Witzenrath, M., Drosten, C., Suttorp, N., von Kalle, M., Kurth, F., Handler, K., Schultze, J.L., Aschenbrener, A.C., Li, Y., Nattermann, J., Sawitzki, B., Saliba, A.-E., Sander, L.E., Deutsche COVID-19 OMICS Initiative (DECOI), 2020. Severe COVID-19 Is marked by a dysregulated myeloid cell compartment. Cell 182 (6), 1419–1440. https://doi.org/10.1016/j.cell.2020.08.001 e23.

Sharma, S., Ray, A., Sadasivam, B., 2020. Metformin in COVID-19: a possible role beyond diabetes. Diabetes Res. Clin. Pract. 164, 108183 https://doi.org/10.1016/j.diabres.2020.108183.

Shen, C., Wang, Z., Zhao, F., Yang, Y., Li, J., Yuan, J., Wang, F., Li, D., Yang, M., Xing, L., Wei, J., Wang, J., Xiao, H., Yang, Y., Qu, J., Qing, L., Chen, L., Xu, Z., Peng, L., Li, Y., Zheng, H., Chen, F., Huang, K., Jiang, Y., Liu, D., Zhang, Z., Liu, Y., Liu, L., 2020. Treatment of 5 critically ill patients with COVID-19 with convalescent plasma. JAMA 323 (16), 1582–1589. https://doi.org/10.1001/jama.2020.4783.

Shi, S., Qin, M., Shen, B., Cai, Y., Liu, T., Yang, F., Gong, W., Liu, X., Liang, J., Zhao, Q., Huang, H., Yang, B., Huang, C., 2020. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. JAMA Cardiol. 5 (7), 802–810. https://doi.org/10.1001/jamacardio.2020.0950.

Shrotri, M., Navaratnam, A.M.D., Nguyen, V., Byrne, T., Geismar, C., Fragaszy, E., Beale, S., Fong, W.L.E., Patel, P., Kovar, J., Hayward, A.C., Aldridge, R.W., 2021. Spike antibody waning after 2nd dose of BNT162b2 or ChADOx1. Lancet 398 (10298), 385–387. https://doi.org/10.1016/S0140-6736(21)01642-1.

Sinha, P., Matthay, M.A., 2020. Is the cytokine storm relevant to COVID-19. JAMA Intern. Med. 180 (9), 1152–1154. https://doi.org/10.1001/jamainternmed.2020.3313.

Smith, J.A., Judd, J., 2020. COVID-19: vulnerability and the power of privilege in a pandemic. Health Promot. J. Aust. 31 (2), 158–160. https://doi.org/10.1002/hpja.333.

Song, J.W., Zhang, C., Fan, X., Meng, F.-P., Xu, Z., Peng, X., Cao, W.-J., Yang, T., Dai, X.-P., Wang, S.-Y., Xu, R.-N., Jiang, T.-J., Li, W.-G., Zhang, D.-W., Zhao, P., Shi, M., Agrati, C., Ippolito, G., Maeurer, M., Zumla, A., Wang, F.-S., Zhang, J.-Y., 2020. Immunological and inflammatory profiles in mild and severe cases of COVID-19. Nat. Commun. 11, 3410. https://doi.org/10.1038/s41467-020-17240-2.

Sosa, J.P., Ferreira Caceres, M.M., Ross Comptis, J., Quiros, J., Príncipe-Meneses, F.S., Riva-Moscoso, A., Belizaire, M.P., Malanyaon, F.Q., Agadi, K., Jaffery, S.S., Sahajwani, J., Arshia, A., Senatus, A., Verdecia, G., Akano, L., Razzack, A.A., Salam, S., Gadamidi, V.K., Marian, S., 2021. Effects of interferon beta in COVID-19 adult patients: systematic review. Infect. Chemother. 53 (2), 247–260. https://doi.org/10.3947/ic.2021.0028.

Srivastava, A., Pandey, R.K., Singh, P.P., Kumar, P., Rasalkar, A.A., Tamang, R., van Driem, G., Shrivastava, P., Chaubey, G., 2020. Most frequent South Asian haplotypes of ACE2 share identity by descent with East Eurasian populations. PLOS One 15 (9), e0238255. https://doi.org/10.1371/journal.pone.0238255.

Starr, T.N., Greaney, A.J., Addeite, A., Hannon, W.W., Choudhary, M.C., Dingens, A.S., Li, J.Z., Bloom, J.D., 2021. Prospective mapping of viral mutation that escape antibodies used to treat COVID-19. These complete escape maps enable interpretation of the consequences of mutations observed during viral surveillance. Science 371 (6531), 850–854 doi://10.1126.science.abf9302.

Stead, E.R., Castillo-Quan, J.I., Miguel, V.E.M., Lujan, C., Ketteler, R., Kinghorn, K.J., Bjedov, I., 2019. Agephagy – adapting autophagy for health during aging. Front. Cell Dev. Biol. 7, 308. https://doi.org/10.3389/fcell.2019.00308.

Stebegg, M., Bignon, A., Hill, D.L., Silva-Cayetano, A., Krueger, C., Vanderleyden, I., Innocentin, S., Boon, L., Wang, J., Zand, M.S., Dooley, J., Clark, J., Liston, A., Carr, E., Linterman, M.A., 2020. Rejuvenating conventional dendritic cells and T follicular helper cell formation after vaccination. eLife 9, e52473. https://doi.org/10.7554/eLife.52473.

Stone, J.H., Frigault, M.J., Serling-Boyd, N.J., Fernandes, A.D., Harvey, L., Foulkes, A.S., Horick, N.K., Healy, B.C., Shah, R., Bensaci, A.M., Woolley, A.E., Nikiforow, S., Lin, N., Sagar, M., Schrager, H., Huckins, D.S., Axelrod, M., Pincus, M.D., Fleisher, J., Sacks, C.A., Dougan, M., North, C.M., Halvorsen, Y.D., Thurber, T.K., Dagher, Z., Scherer, A., Wallwork, R.S., Kim, A.Y., Schoenfeld, S., Sen, P., Neilan, T.G., Perugino, C.A., Unizony, S.H., Collier, D.S., Matza, M.A., Yinh, J.M., Bowman, K.A., Meyerowitz, E., Zafar, A., Drobni, Z.D., Bolster, M.B., Kohler, M., D'Silva, K.M., Dau, J., Lockwood, M.M., Cubbison, C., Weber, B.N., Mansour, M.K., BACC Bay Tocilizumab Trial Investigators, 2020. Efficacy of tocilizumab in patients hospitalized with Covid-19. N. Engl. J. Med. 10 (383(24)), 2333–2344. https://doi.org/10.1056/NEJMoa2028836.

Straw, S., Witte, K.K., 2020. Observational data during the COVID-19 pandemic: opportunity with uncertainty. Heart 106 (29), 1503–1511 doi:10.1136/ heartjnl-2020-317486.

Strindhall, J., Skog, M., Ernerudh, J., Bengner, M., Löfgren, S., Matussek, A., Nilsson, B. O., Wikby, A., 2013. The inverted CD4/CD8 ratio and associated parameters in 66-year-old individuals: the Swedish HEXA immune study. Age 35, 985–991. https://doi.org/10.1007/s11357-012-9400-3 (Dordr.).

Stroehlein, J.K., Wallqvist, J., Iannizzi, C., Mikolajewska, A., Metzendorf, M.-I., Benstoem, C., Meybohm, P., Becker, M., Skoetz, N., Stegemann, M., Piechotta, V., 2021. Vitamin D supplementation for the treatment of COVID-19: a living systematic review. Cochrane Database Syst. Rev. 5, CD015043 https://doi.org/10.1002/14651858.CD015043.

Sun, L., Brown, R., Chen, S., Zhuge, Q., Su, D.M., 2012. Aging induced decline in T-lymphopoiesis is primarily dependent on status of progenitor niches in the bone marrow and thymus. Aging 4 (9), 606–619. https://doi.org/10.18632/aging.100487 (Albany, NY).

Takahashi, T., Ellingson, M.K., Wong, P., Israelow, B., Lucas, C., Klein, J., Silva, J., Mao, T., Oh, J.E., Tokuyama, M., Lu, P., Venkataraman, A., Park, A., Liu, F., Meir, A., Sun, J., Wang, E.Y., Casanovas-Massana, A., Wyllie, A.L., Vogels, C., Earnest, R., Lapidus, S., Ott, I.M., Moore, A.J., Yale IMPACT Research, T., Shaw, A., Fournier, J. B., Odio, C.D., Farhadian, S., Dela Cruz, C., Grubaugh, N.D., Schulz, W.L., Ring, A. M., Ko, A.I., Omer, S.B., Iwasaki, A., 2020. Sex differences in immune responses that underlie COVID-19 disease outcomes. Nature 588, 315–320. https://doi.org/10.1038/s41586-020-2700-3.

Tan, L., Wang, Q., Zhang, D., Ding, J., Huang, Q., Tang, Y.-Q., Wang, Q., Miao, H., 2020a. Lymphopenia predicts disease severity of COVID-19: a descriptive and predictive study. Signal Transduct. Target. Ther. 5, 33. https://doi.org/10.1038/s41392-020-0148-4.

Tan, M., He, F.J., MacGregor, G.A., 2020b. Obesity and covid-19: the role of the Food Industry. BMJ 369, m2237. https://doi.org/10.1136/bmj.m2237.

Taneja, V., 2018. Sex hormones determine immune response. Front. Immunol. 9, 1931. https://doi.org/10.3389/fimmu.2018.01931.

Tay, M.Z., Poh, C.M., Rénia, L., MacAry, P.A., Ng, L.P.F., 2020. The trinity of COVID-19: immunity, inflammation and intervention. Nat. Rev. Immunol. 20, 363–374. https://doi.org/10.1038/s41577-020-0311-8.

Teshome, A., Adane, A., Girma, B., Mekonnen, Z.A., 2021. The impact of vitamin D level on COVID-19 infection: systematic review and meta-analysis. Front. Public Health 9, 624559, 10.3389/fpubh.2021.624559. PMID: 33748066; PMCID: PMC7973108.

The CORIMUNO-19 Collaborative Group, 2021. Effect of anakinra versus usual care in adults in hospital with COVID-19 and mild-to-moderate pneumonia (CORIMUNO-ANA-1): a randomised controlled trial. Lancet Respir. Med. 9 (3), 295–304 https://doi.org/10.1016/S2213-2600(20)30556-7.

The COVID-19 Host Genetics Initiative, 2020b. The COVID-19 host genetics initiative, a global initiative to elucidate the role of host genetic factors in susceptibility and severity of the SARS-CoV-2 virus pandemic. Eur. J. Hum. Genet. 28 (6), 715–718 doi:10.1038/s41431-020-0636-6.

The Severe COVID-19 GWAS Group, 2020. Genomewide association study of severe COVID-19 with respiratory failure. N. Engl. J. Med. 383 (16), 1522–1534. https://doi.org/10.1056/NEJMoa2020283.

The World Obesity Federation, 2021. Covid-19 and Obesity: The 2021 Atlas. March 2021. ⟨https://www.worldobesityday.org/assets/downloads/COVID-19-and-Obesity-The-2021-Atlas.pdf⟩.

Thomas, E.T., Guppy, M., Straus, S.E., Bell, K.J.L., Glasziou, P., 2019. Rate of normal lung function decline in ageing adults: a systematic review of prospective cohort studies. BMJ Open 9 (6), e028150 doi:10.1136/bmjopen-2018-028150.

Traish, A.M., Zitzmann, M., 2015. The complex and multifactorial relationship between testosterone deficiency (TD), obesity and vascular disease. Rev. Endocr. Metab. Disord. 16, 249–268. https://doi.org/10.1007/s11154-015-9323-2.

Turner, J.M., Mead, J., Wohl, M.E., 2017. Elasticity of human lungs in relation to age. J. Appl. Physiol. 25, 664–671. https://doi.org/10.1152/jappl.1968.25.6.664.

Ucciferri, C., Auricchio, A., Di Nicola, M., Potere, N., Abbate, A., Cipollone, F., Vecchiet, J., Falasca, K., 2020. Canakinumab in a subgroup of patients with COVID-19. Lancet Rheumatol. 2 (8), E457–EE458. https://doi.org/10.1016/S2665-9913(20)30167-3.

US FDA, 2020. Recommendations for Investigational COVID-19 Convalescent Plasma, 2020. ⟨https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/recommendations-investigational-covid-19-convalescent-plasma⟩. (Accessed 21 March 2021).

van Aalst, S., Ludwig, I.S., van der Zee, R., van Eden, W., Broere, F., 2017. Bystander activation of irrelevant CD4+ T cells following antigen-specific vaccination occurs in

the presence and absence of adjuvant. PLOS One 12 (5), e0177365. https://doi.org/10.1371/journal.pone.0177365.
van der Made, C.I., Simons, A., Schuurs-Hoeijmakers, J., van den Heuvel, G., Mantere, T., Kersten, S., van Deuren, R.C., Steehouwer, M., van Reijmersdal, S.V., Jaeger, M., Hofste, T., Astuti, G., Galbany, J.C., van der Schoot, V., van der Hoeven, H., Hagmolen of ten Have, Klijn, W., van den Meer, E., Fiddelaers, C., de Mast, J., Bleeker-Rovers, Q., Joosten, C.P., Yntema, L.A.B., Gilissen, H.G., Nelen, C., van der Meer, M., Brunner, J.W.M., Netea, H.G., van de Veerdonk, M.G., Hoischen, F.L., A, 2020. Presence of genetic variants among young men with severe COVID-19. JAMA 324 (7), 663–673 doi:10.1001.jama.2020.13719.
van Dorn, A., Cooney, R.E., Sabin, M., 2020. Covid-19 exacerbating inequalities in the US. Lancet 395 (10232), 1243–1244. https://doi.org/10.1016/S0140-6736(20)30893-X.
Varga, Z., Flammer, A.J., Steiger, P., Haberecker, M., Andermat, R., Zinkernagel, A.S., Mehra, M.R., Schuepbach, R.A., Ruschitzka, F., Moch, H., 2020. Endothelial cell infection and endothelitis in Covid-19. Lancet 395 (10234), 1417–1418. https://doi.org/10.1016/S0140-6736(20)30937-5.
Vasileiou, E., Simpson, C.R., Shi, T., Kerr, S., Agrawal, U., Akbari, A., Bedston, S., Beggs, J., Bradley, D., Chuter, A., de Lusignan, S., Docherty, A.B., Ford, D., Hobbs, F. R., Joy, M., Katikireddi, S.V., Marple, J., McCowan, C., McGagh, D., McMenamin, J., Moore, E., Murray, J.L., Pan, J., Ritchie, L., Shah, S.A., Stock, S., Torabi, F., Tsang, R. S., Wood, R., Woolhouse, M., Robertson, C., Sheikh, A., 2021. Interim findings from first-dose mass COVID-19 vaccination roll-out and COVID-19 hospital admissions in Scotland: a national prospective cohort study. Lancet 397 (10285), 1646–1657. https://doi.org/10.1016/S0140-6736(21)00677-2. Epub 2021 Apr 23. PMID: 33901420; PMCID: PMC8064669.
Vescovini, R., Fagnoni, F.F., Telera, A.R., Bucci, L., Pedrazzoni, M., Magalini, F., Stella, A., Pasin, F., Medici, M.C., Calderaro, A., Volpi, R., Monti, D., Franceschi, C., Nikolich-Zugich, J., Sansoni, P., 2014. Naïve and memory CD8 T cell pool homeostasis in advanced aging: impact of age and of antigen-specific responses to cytomegalovirus. Age 36, 625–640.
Vimaleswaran, K.S., Forouhi, N.G., Khunti, K., 2021. Vitamin D and covid-19. BMJ 372, n544. https://doi.org/10.1136/bmj.n544.
Vivier, E., Ugolini, S., 2009. Regulatory natural killer cells: new players in the IL-10 anti-inflammatory response. Cell Host Microbe 6 (6), 493–495. https://doi.org/10.1016/j.chom.2009.12.001.
Voysey, M., Clemens, S.A.C., Madhi, S.A., Wechx, L.Y., Folegatti, P.M., Aley, P.K., Angus, B., Baillie, V.L., Barnabas, S.L., Bhorat, Q.E., Bibi, S., Briner, C., Cicconi, P., Collins, A.M., Colin-Jones, R., Cutland, C.L., Darton, T.C., Dheda, K., Duncan, C.J.A., Emary, K.R.W., Ewer, K.J., Fairlie, L., Faust, S.N., Feng, S., Ferreira, D.M., Finn, A., Goodman, A.L., Green, C.M., Green, C.A., Heath, P.T., Hill, C., Hill, H., Hirsch, I., Hodgson, S.H.C., Izu, A., Jackson, S., Jenkin, D., Joe, C.C.D., Kerridge, S., Koen, A., Kwatra, G., Lazarus, R., Lawrie, A.M., Lellliott, A., Libri, V., Lillie, P.J., Mallory, R., Mendes, A.V.A., Milan, E.P., Minassian, A.M., McGregor, A., Morrison, H., Mujadidi, Y.F., Nana, A., O'Reilly, P.J., Padayachee, S.D., Pittella, A., Plested, E., Pollock, K.M., Ramasamy, M.N., Rhead, S., Schwarzbold, A.V., Singh, N., Smith, A., Song, R., Snape, M.D., Sprinz, E., Sutherland, R.K., Tarrant, R., Thomson, E.C., Torok, M.E., Toshner, M., Turner, D.P.J., Vekemans, J., Villafana, T.L., Watson, M.E. E., Williams, C.J., Douglas, A.D., Hill, A.V.S., Lambe, T., Gilbert, S.C., Pollard, A.J., 2021. Safety and efficacy of ChAdOx1nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa and the UK. Lancet 397 (10269), 99–111. https://doi.org/10.1016/S0140-6736(20)32661-1.
Wadman, M., 2021. A grim warning from Israel: vaccination blunts, but does not defeat Delta. Science. https://doi.org/10.1126/science.abl9630. Aug. 16, 2021.
Wałajtys-Rode, E., Dzik, J.M., 2017. Monocyte/macrophage: NK cell cooperation-old tools for new functions. Results Probl. Cell Differ. 62, 73–145. https://doi.org/10.1007/978-3-319-54090-0_5.
Walli-Attaei, M., Joseph, P., Rosengren, A., Chow, C.K., Rangarajan, S., Lear, S.A., AlHabib, K.F., Davletov, K., Dans, A., Lanas, F., Yeates, K., Poirier, P., Teo, K.K., Bahonar, A., Camilo, F., Chifamba, J., Diaz, R., Didkowska, J.A., Irazola, V., Ismail, R., Kaur, M., Khatib, R., Liu, X., Manczuk, M., Miranda, J.J., Oguz, A., Perez-Mayorga, M., Szuba, A., Tsolekile, L.P., Varma, R.P., Yusufali, A., Yusuf, R., Wei, L., Anand, S.S., Yusuf, S., 2020. Variations between women and men in risk factors, treatments, cardiovascular disease incidence, and death in 27 high-income, middle-income, and low-income countries (PURE): a prospective cohort study. Lancet 396 (10244), 97–109. https://doi.org/10.1016/S0140-6736(20)30543-2.
Walsh, E.E., Frenck, R.W.Jr., Falsey, A.R., Kitchin, N., Absalon, J., Gurtman, A., Lockhart, S., Neuzil, K., Mulligan, M.J., Bailey, R., Swanson, K.A., Li, P., Koury, K., Kalina, W., Cooper, D., Fontes-Garfias, C., Shi, P.-Y., Tureci, O., Tompkins, K.R., Lyke, K.E., Raabe, V., Dormitzer, P.R., Jansen, K.U., Sahin, U., Gruber, W.C., 2020. Safety and immunogenicity of two RNA-based COVID-19 vaccine candidates. N. Engl. J. Med. 383, 2439–2450.
Wang, B., Li, D., Liu, T., Wang, H., Luo, F., Liu, Y., 2020a. Subcutaneous injection of IFN alpha-2b for COVID-19: an observational study. BMC Infect. Dis. 20, 723. https://doi.org/10.1186/s12879-020-05425-5.
Wang, Y., Zhang, D., Du, G., Du, R., Zhao, J., Jin, Y., Fu, S., Gao, L., Cheng, Z., Lu, Q., Hu, Y., Luo, G., Wang, K., Lu, Y., Li, H., Wang, S., Ruan, S., Yang, C., Mei, C., Wang, Y., Ding, D., Wu, F., Tang, X., Ye, X., Ye, Y., Liu, B., Yang, J., Yin, W., Wang, A., Fan, G., Zhou, F., Liu, Z., Gu, X., Xu, F., Shang, L., Zhang, Y., Cao, L., Guo, T., Wan, Y., Qin, H., Jiang, Y., Jaki, T., Hayden, F.G., Horby, P.W., Cao, B., Wang, C., 2020b. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet 395 (10236), 1569–1578. https://doi.org/10.1016/S0140-6736(20)31022-9.
Wang, W., Thomas, R., Oh, J., Su, D.M., 2021a. Thymic aging may be associated with COVID-19 pathophysiology in the elderly. Cells 10 (3), 628. https://doi.org/10.3390/cells10030628.
Wang, Z., Yang, X., Zhong, J., Zhou, Y., Tang, Z., Zhou, H., He, J., Mei, X., Tang, Y., Lin, B., Chen, Z., McCluskey, J., Yang, J., Corbett, A.J., Ran, P., 2021b. Exposure to SARS-CoV-2 generates T-cell memory in the absence of a detectable viral infection. Nat. Commun. 12, 1724. https://doi.org/10.1038/s41467-021-22036-z.
Wang, X.-L., Yang, L., Chan, K.-H., Chan, K.-P., Cao, P.-H., Lau, E.H.-Y., Peiris, J.S.M., Wong, C.-M., 2015. Age and sex differences in rates of influenza-associated hospitalizations in Hong Kong. Am. J. Epidemiol. 182 (4), 335–344. https://doi.org/10.1093/aje/kwv068.
Weinreich, D.M., Sivapalasingam, S., Norton, T., Ali, S., Gao, H., Bhore, R., Musser, B.J., Soo, Y., Rofail, D., Im, J., Perry, C., Pan, C., Hosain, R., Mahmood, A., Davis, J.D., Turner, K.C., Hooper, A.T., Hamilton, J.D., Baum, A., Kyratsous, C.A., Kim, Y., Cook, A., Kampman, W., Kohli, A., Sachdeva, Y., Graber, X., Kowal, B., DiCioccio, T., Stahl, N., Lipsich, L., Braunstein, N., Herman, G., Yancopoulos, G.D., Trial Investigators, 2021. REGN-COV2, a neutralizing antibody cocktail, in outpatients with Covid-19. N. Engl. J. Med. 384, 238–251. https://doi.org/10.1056/NEJMoa2035002.
Weis, S., Rubio, I., Ludwig, K., Weigel, C., Jentho, E., 2017. Hormesis and defense of infectious disease. Int. J. Mol. Sci. 18 (6), 1273. https://doi.org/10.3390/ijms18061273.
Weiskopf, D., Schmitz, K.S., Raadsen, M.P., Grifoni, A., Okba, N.M.A., Endeman, H., van den Akker, J.P.C., Molenkamp, R., Koopmans, M.P.G., van Gorp, E.C.M., Haagmans, B.L., de Swart, R.L., Sette, A., de Vries, R.D., 2020. Phenotype and kinetics of SARS-CoV-2–specific T cells in COVID-19 patients with acute respiratory distress syndrome. Sci. Immunol. 5 (48), eabd2071. https://doi.org/10.1126/sciimmunol.abd2071.
Wells, A.I., Coyne, C.B., 2018. Type III interferons in antiviral defenses at barrier surfaces. Trends Immunol. 39 (10), 848–858. https://doi.org/10.1016/j.it.2018.08.008.
Wheatley, A.K., Juno, J.A., Wang, J.J., Selva, K.J., Reynaldi, A., Tan, H.X., Lee, W.S., Wragg, K.M., Kelly, H.G., Esterbauer, R., Davis, S.K., Kent, H.E., Mordant, F.L., Schlub, T.E., Gordon, D.L., Khoury, D.S., Subbarao, K., Cromer, D., Gordon, T.P., Chung, A.W., Davenport, M.P., Kent, S.J., 2021. Evolution of immune responses to SARS-CoV-2 in mild-moderate COVID-19. Nat. Commun. 12 (1), 1162, 10.1038/s41467-021-21444-5. PMID: 33608522; PMCID: PMC7896046.
Whittemore, P.B., 2020. COVID-19 fatalities, latitude, sunlight, and vitamin D. Am. J. Infect. Control 48 (9), 1042–1044. https://doi.org/10.1016/j.ajic.2020.06.193.
WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, 2020. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: a meta-analysis. JAMA 324 (13), 1330–1341. https://doi.org/10.1001/jama.2020.17023.
Widge, A.T., Rouphael, N.G., Jackson, L.A., Anderson, E.J., Roberts, P.C., Makhene, M., Chappell, J.D., Denison, M.R., Stevens, L.J., Pruijssers, A.J., McDermott, A.B., Flach, B., Li, B.C., Doria-Rose, N.A., O'Dell, S., Schmidt, S.D., Neuzil, K.M., Bennett, H., Leav, B., Makowsi, M., Albert, J., Cross, K., Edara, V.-V., Floyd, K., Suthar, M.S., Buchanan, W., Luke, C.J., Ledgerwood, J.E., Mascolsa, J.R., Graham, B. S., Beigel, J.H., mRNA-1273 Study Group, 2021. Durability of responses after SARS-C0V-2 mRNA-1273 vaccination. N. Engl. J. Med. 384, 80–82. https://doi.org/10.1056/NEJMc2032195.
Wikby, A., Maxson, P., Olsson, J., Johansson, B., Ferguson, F.G., 1998. Changes in CD8 and CD4 lymphocyte subsets, T-cell proliferation responses and non-survival in the very old: the Swedish longitudinal OCTO-immune study. Mech. Ageing Dev. 102, 187–198. https://doi.org/10.1016/S0047-6374(97)00151-6.
Wikby, A., Johansson, B., Ferguson, F., 2002. The OCTO and NONA immune longitudinal studies: a review of 11 years studies of Swedish very old humans. Adv. Cell Aging Gerontol. 13, 1–16. https://doi.org/10.1016/S1566-3124(02)13001-X.
Wikby, A., Månsson, I.A., Johansson, B., Strindhall, J., Nilsson, S.E., 2008. The immune risk profile is associated with age and gender: findings from three Swedish population studies of individuals 20-100 years of age. Biogerontology 9 (5), 299–308. https://doi.org/10.1007/s10522-008-9138-6.
Williamson, E.J., Walker, A.J., Bhaskaran, K., Bacon, S., Bates, C., Morton, C.E., Curtis, H.J., Mehrkar, A., Evans, D., Inglesby, P., Cockburn, J., McDonald, H.I., MacKenna, B., Tomlinson, L., Douglas, I.J., Rentsch, C.T., Mathur, R., Wong, A.Y.S., Grieve, R., Harrison, D., Forbes, H., Schultze, A., Croker, R., Parry, J., Hester, F., Harper, S., Perera, R., Evans, S.J.W., Smeeth, L., Goldacre, B., 2020. Factors associated with COVID-19-related death using OpenSAFELY. Nature 584, 430–436. https://doi.org/10.1038/s41586-020-2521-4.
Wise, J., 2020. Critically ill patients treated with arthritis drug tocilizumab show improved outcomes, researchers report. BMJ 371, m4530. https://doi.org/10.1136/bmj.m4530. March 2020.
Wise, J., 2021. Covid-19: highest death rates seen in countries with most overweight populations. BMJ 372, n623. https://doi.org/10.1136/bmj.n623. March 2021.
Wu, J., Shi, Y., Pan, X., Wu, S., Hou, R., Zhang, Y., Zhong, T., Tang, H., Du, W., Wang, L., Wo, J., Mu, J., Qiu, Y., Yang, K., Zhang, L.K., Ye, B.C., Qi, N., 2021. SARS-CoV-2 ORF9b inhibits RIG-I-MAVS antiviral signaling by interrupting K63-linked ubiquitination of NEMO. Cell Rep. 34 (7), 10876. https://doi.org/10.1016/j.celrep.2021.108761.
Xie, J., Zu, Y., Alkhatib, A., Pham, T.T., Gill, F., Jang, A., Radosta, S., Chaaya, G., Myers, L., Zifodya, J., Bojanowski, C.M., Marrouche, N.F., Mauvais-Jarvis, F., 2021a. Metabolic syndrome and COVID-19 mortality among adult black patients in new orleans metabolic syndrome and COVID-19 mortality among adult black adults in New Orleans. Diabetes Care 44 (1), 188–193. https://doi.org/10.2337/dc20-1714.
Xie, X., Zou, J., Fontes-Garfias, C.R., Xia, H., Swanson, K.A., Cutler, M., Cooper, D., Menachery, V.D., Weaver, S., Dormitzer, P.R., Shi P.-Y., 2021b. Neutralization of

N501Y mutant SARS-CoV-2 by BNT162b2 vaccine-elicited sera. bioRxiv. DOI: ⟨https://doi.org/10.1101/2021.01.07.425740⟩. Preprint not peer reviewed.

Yan, J., Greer, J.M., Hull, R., O'Sullivan, J.D., Henderson, R.D., Read, S.J., McCombe, R. S., 2010. The effect of ageing on human lymphocyte subsets: comparison of males and females. Immun. Ageing 7 (4), 1–10. https://doi.org/10.1186/1742-4933-7-4.

Yamamoto, N., Ariumi, Y., Nishida, N., Yamamoto, R., Bauer, G., Gojobori, T., Shimotohno, K., Mizokami, M., 2020. SARS-CoV-2 and COVID-19 mortalities strongly correlate with ACE1 I/D genotype. Gene 758, 144944. https://doi.org/10.1016/j.gene.2020.144944.

Yang, J., Zheng, Y., Gou, X., Pu, K., Chen, Z., Guo, Q., Ji, R., Wang, H., Wang, Y., Zhou, Y., 2020a. Prevalence of comorbidities and its effect in patients infected with SARs-Cov-2: a systemic analysis and meta-analysis. Int. J. Inf. Dis. 94, 91–95. https://doi.org/10.1016/j.ijid.2020.03.017.

Yang, X., Yu, Y., Xu, J., Shu, H., Xi, J., Liu, H., Wu, Y., Zhang, L., Yu, Z., Fang, M., Yu, T., Wang, Y., Pan, S., Zou, X., Yuan, S., Shang, Y., 2020b. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir. Med. 8 (5), 475–481. https://doi.org/10.1016/S2213-2600(20)30079-5.

Yao, Y., Shi, L., Yu, J., Liu, S., Tao, Y., Shi, L., 2019. Distribution of killer-cell immunoglobulin-like receptor genes and combinations of their human leucocyte antigen ligands in 11 ethnic populations in China. Cells 8 (7), 711. https://doi.org/10.3390/cells8070711.

Yassin, A., Haider, A., Haider, K.S., Caliber, M., Doros, G., Saad, F., Garvey, W.T., 2019. Testosterone therapy in men with hypogonadism prevents progression from prediabetes to type 2 diabetes: eight-year data from a registry study. Diabetes Care 2019 (42), 1104–1111. https://doi.org/10.2337/dc18-2388.

Yazicioglu, T., Mühlfeld, C., Autilio, C., Huang, C.K., Bär, C., Dittrich-Breiholz, O., Thum, T., Pérez-Gil, J., Schmiedl, A., Brandenberger, C., 2020. Aging impairs alveolar epithelial type II cell function in acute lung injury. Am. J. Physiol. Lung Cell. Mol. Physiol. 319 (5), L755–L769 doi:10.1152/ajplung.00093.2020.

Yitbarek, K., Abraham, G., Girma, T., Tilahun, T., Woldie, M., 2020. The effect of Bacillus Calmette-Guérin (BCG) vaccination in preventing severe infectious respiratory diseases other than TB: implications for the COVID-19 pandemic. Vaccine 38 (41), 6374–6380. https://doi.org/10.1016/j.vaccine.2020.08.018.

Yoon, Y.S., Jin, M., Sin, D.D., 2019. Accelerated lung aging and chronic obstructive pulmonary disease. Expert Rev. Respir. Med. 13 (4), 369–380. https://doi.org/10.1080/17476348.2019.1580576.

Zeberg, H., Pääbo, S., 2020. The major genetic risk factor for severe COVID-19 is inherited from Neanderthals. Nature 587, 610–612. https://doi.org/10.1038/s41586-020-2818-3.

Zhang, Q., Bastard, P., Liu, Z., Le Pen, J., Moncada-Velez, M., Chen, J., Ogishi, M., Sabli, I.K.D., Hodeib, S., Korol, C., Rosain, J., Bilguvar, K., Ye,Y, Bolze, Bigio, A., Yang, B., Arias, R., Zhou, A.A., Zhang, Q., Onodi, Y., Korniotis, F., Karpf, S., Philippot, L., Chbihi, Q., Bonnet-Madin, M., Dorgham, M., Smith, K., Schneider, N., Razooky, W.M., Hoffmann, B.S., Michailidis, H.-H., Moens, E., Han, L., Lorenzo, J.E., Bizien, L., Meade, L., Neehus, P., Ugurbil, A.-L., Corneau, A.C., Kerner, A., Zhang, G., Rapaport, P., Seeleuthner, F., Manry, Y., Masson, J., Schmitt, C., Schluter, Y., Le Voyer, A., Khan, T., Li, T., Fellay, J., Roussel, J., Shahrooei, L., Alosaimi, M., Mansouri, M.F., Al-Saud, D., Al-Mulla, H., Almourfi, F., Al-Muhsen, F., Alsohime, S. Z., Al Turki, F., Hasanato, S., van de Beek, R., Biondi, D., Bettini, A., D'Angio, L.R., Bonfanti, M., Imberti, P., Sottini, L., Paghera, A., Quiros-Roldan, S., Rossi, E., Oler, C., Tompkins, A.J., Alba, M.F., Vandernoot, C., Goffard, I., Smits, J.-C., Migeotte, G., Haerynck, I., Soler-Palacin, F., Martin-Nalda, P., Colobran, A., Morange, R., Keles, P.-E., Colkesen, S., Ozcelik, F., Yasar, T., Senoglu, K.K., Karebela, S., Rodriguez-Gallego, S.N., Novelli, C., Hraiech, G., Tandjaoui-Labiotte, S., Duval, Y., Laouenan, X., COVID-STORM Clinicians, COVID Clinicians; Imagine COVID Group, French COVID Cohort Study Group, CoV-Contact Cohort, Amsterdam UMC Covid-19 Biobank, COVID Human Genetic Effort, NIAID-USUHS/TAGC COVID Immunity Group, Snow, A.L., Dalgard, C.L., Milner, J.D., Vinh, D.C., Mogensen, T.H., Marr, N., Spaan, A.N., Boisson, B., Boisson-Depuis, S., Bustamante, J., Puel, A., Ciancanelli, M.J., Meyts, I., Maniatis, T., Soumelis, V., Amara, A., Nussenzweig, M., Garcia-Sastre, A., Krammer, F., Pujol, A., Duffy, D., Lifton, R.P., Zhang, S.-Y., Gorochov, G., Beziat, V., Jouanguy, E., Sancho-Shimizu, V., Rice, C.M., Abel, L., Notarangelo, L., Cobat, A., Su, C.H., Casanova, J.-L., 2020. Inborn errors of type I IFN immunity in patients with life-threatening COVID-19. Science, eabd4570. https://doi.org/10.1126/science.abd4570.

Zhao, C., Zhao, W., 2020. NLRP3 inflammasome-a key player in antiviral responses. Front. Immunol. 11, 211. https://doi.org/10.3389/fimmu.2020.00211.

Zhao, J., Yang, Y., Huang, H., Li, D., Gu, D., Lu X., Zhang, Z., Liu, L., Liu, T., Liu, Y., He, Y., Sun, B., Wei, M., Yang, G., Wang, X., Zang, L., Zhou, X., Xing, M., Wang, P.G., 2020. Relationship between the ABO blood group and the COVID-19 susceptibility, medRxiv. Preprint posted 27 March 2020. Not peer reviewed. DOI: ⟨https://doi.org/10.1101/2020.03.11.20031096⟩.

Zhao, J., Zhao, J., Mangalam, A.K., Channappanavar, R., Fett, C., Meyerholz, D.K., Agnihothram, S., Baric, R.S., David, C.S., Perlman, S., 2016. Airway memory CD4+ T cells mediate protective immunity against emerging respiratory coronaviruses. Immunity 44 (6), 1379–1391. https://doi.org/10.1016/j.immuni.2016.05.006.

Zhou, F., Yu, T., Du, R., Fan, G., Liu, Y., Liu, Z., Xiang, J., Wang, Y., Song, B., Gu, X., Guan, L., Wei, Y., Li, H., Wu, X., Xu, J., Tu, S., Zhang, Y., Chen, H., Cao, B., 2020a. Clinical course and risk factors for mortality of adult in patients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 395 (10229), 1054–1062. https://doi.org/10.1016/S0140-6736(20)30566-3.

Zhou, Q., Chen, V., Shannon, C.P., Wei, X.-S., Xiang, X., Wang, X., Wang, Z.-H., Tebbutt, S.J., Kollmann, T.R., Fish, E.N., 2020b. Interferon-α2b treatment for COVID-19. Front. Immunol. 15 (11), 1061. https://doi.org/10.3389/fimmu.2020.01061. Erratum in: Front Immunol (2020) Oct 27;11:615275.

Zhou, Z., Ren, L., Zhang, L., Zhong, J., Xiao, Y., Jia, Z., Guo, L., Yang, J., Wang, C., Jiang, S., Yang, D., Zhang, G., Li, H., Chen, F., Xu, Y., Chen, M., Gao, Z., Yang, J., Dong, J., Liu, B., Zhang, X., Wang, W., He, K., Jin, Q., Li, M., Wang, J., 2020c. Heightened innate immune responses in the respiratory tract of COVID-19 patients. Cell Host Microbe 27 (6), 883–890. https://doi.org/10.1016/j.chom.2020.04.017.

Zhu, L., She, Z.-G., Cheng, X., Qin, J.-J., Zhang, X.-J., Cai, J., Lei, F., Wang, H., Xie, J., Wang, W., Li, H., Zhang, P., Song, X., Chen, X., Xiang, M., Zhang, C., Bai, L., Xiang, D., Chen, M.-M., Liu, Y., Yan, Y., Liu, M., Mao, W., Zou, J., Liu, L., Chen, G., Luo, P., Xiao, B., Zhang, C., Zhang, Z., Lu, Z., Wang, J., Lu, H., Xia, X., Wang, D., Liao, X., Peng, G., Ye, P., Yang, Y., Yuan, Y., Huang, X., Guo, J., Zhang, B.-H., Li, H., 2020. Association of blood glucose control and outcomes in patients with COVID-19 and pre-existing type 2 diabetes. Cell Metab. 31 (6), 1068–1077. https://doi.org/10.1016/j.cmet.2020.04.021 e3–1077.e3.